NOVARTIS

Novartis Research and Development

INC280

Protocol CINC280X2201 / NCT01737827

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

Document type	Amended Protocol Version
EUDRACT number	2012-003758-10
Version number	v06 (Clean)
Development phase	II
Document status	Final
Release date	16-May-2022

Template version 15-Feb-2012

[redacted]

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List of abbreviations

AE	Adverse Event
[redacted]	[redacted]
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the concentration-time Curve
BCLC	Barcelona-Clinic Liver Cancer
bid	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
Cmax	Maximum concentration
CNS	Central Nervous System
CPC	Child-Pugh Classification
CR	Complete Response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variance
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DDS	Dose-Determining Set
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
CMO&PS	Chief Medical Office and Patient Safety
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EOT	End Of Treatment
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FISH	Fluorescence in situ hybridization
FSH	Follicular Stimulating Hormone
GFR	Glomerular Filtration Rate
GI	Gastro-intestinal
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HV	Healthy volunteer
i.v.	intravenous(ly)

[redacted]

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
LFT	Liver Function Test
LLOQ	Lower Limit Of Quantification
M&S	Modeling and Simulation
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NOAEL	No Observable Adverse Event Effect Level
NRU	Neutral Red Uptake
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow Therapeutic Index
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression Free Survival
PHI	Protected Health Information
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic/Pharmacodynamic
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin time
qd	once a day
Racc	Accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
sCr	Serum Creatinine
SD	Stable Disease
Tmax	Time to reach maximum concentration
TTP	Time To Progression
ULN	Upper Limit of Normal
UNK	Unknown
vs	Versus
WBC	White Blood Cells
γGT	Gamma-glutamyl transferase

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q21 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Patient Number (Patient No.)	A unique identifying number assigned to each patient who enrolls in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Study treatment refers to the investigational treatment.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Protocol summary:

Protocol number	CINC280X2201
Title	A phase II, open label, single arm, multicenter study of INC280 administered orally in adult patients with advanced hepatocellular carcinoma
Brief title	Study of efficacy and safety INC280 in patients with advanced hepatocellular carcinoma.
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To find out if INC280 is safe and has beneficial effects in patients with advanced hepatocellular carcinoma known to have dysregulation of c-MET pathway.
Primary Objective(s) and	**Objective**: To estimate overall clinical activity of INC280 in advanced hepatocellular carcinoma patients with c-MET dysregulation as measured by time to progression.
Secondary Objectives	**Objective 1**: To further assess the clinical activity of INC280 in advanced hepatocellular carcinoma patients with c-MET dysregulation as measured by overall response rate, progression free survival, overall survival and disease control rate. **Objective 2**: To assess the safety and tolerability of INC280 in advanced hepatocellular carcinoma patients. **Objective 3**: To characterize the pharmacokinetics of INC280 in patients with advanced hepatocellular carcinoma.
Study design	Open label, single arm, with a Dose-Determining Part and a Dose Expansion Part.
Population	Approximately 56 male or female, at least 18 years old patients with histologically or cytologically confirmed advanced HCC with c-MET dysregulation who have received no prior systemic therapy. Only patients with Child-Pugh A are included.
Inclusion criteria	Confirmed c-MET pathway dysregulation as defined by: c-MET IHC intensity score 3+ in ≥50% tumor cells, or c-MET IHC intensity score 2+ in ≥50% of tumor cells and in addition MET gene copy number ≥5 by FISH. MET gene copy number ≥5 by FISH and unknown c-MET IHC results or c-MET mutation can be enrolled in the study following discussion and agreement with Novartis. Advanced hepatocellular carcinoma which would not be suitable for treatment with locoregional therapies or has progressed following locoregional therapy. Measurable disease as determined by RECIST version 1.1 Current cirrhotic status of Child-Pugh class A with no encephalopathy ECOG performance status ≤2

[redacted]

Exclusion criteria	Received any prior systemic chemotherapy or molecular-targeted therapy for hepatocellular carcinoma such as sorafenib Previous treatment with c-MET inhibitor or hepatocyte growth factor targeting therapy Previous local therapy completed less than 4 weeks prior to dosing and, if present, any acute toxicity > grade 1 Known active bleeding (e.g. bleeding from gastro-intestinal ulcers or esophageal varices) within 2 months prior to screening or with history or evidence of inherited bleeding diathesis or coagulopathy Clinically significant venous or arterial thrombotic disease within past 6 months History of acute or chronic pancreatitis, surgery of pancreas or any risk factors that may increase the risk of pancreatitis
Investigational and reference therapy	INC280 300 mg (capsule) twice a day for the Dose-Determining Part. The dose for the Dose Expansion Part will be determined after the Dose-Determining Part.
Efficacy assessments	Tumor response assessment as per RECIST v1.1.
Safety assessments	Physical examination Vital signs Weight ECOG performance status Clinical laboratory assessments (hematology, biochemistry, urinalysis, coagulation, hepatitis B and C markers and pregnancy assessments) Cardiac monitoring (12-lead ECGs) Incidence, frequency, and category of qualifying adverse events during the first 28 days of INC280 treatment in the Dose-Determining Part Frequency, duration and severity of adverse events
Other assessments	INC280 pharmacokinetics assessment in plasma samples [redacted]
Data analysis	As the primary analysis, for patients treated at the Expansion Part dose, the distribution of time to progression will be estimated using the Kaplan-Meier method. The median time to progression and quantiles (along with 95% confidence intervals) will be presented. For patients in the Dose-Determining Part (who are not treated at the Expansion Part dose), time to progression will be listed. In the Dose-Determining Part, for the safety analysis, a Bayesian Logistic Regression Model will be used to recommend the Expansion Part dose. For the PK analysis to recommend the Expansion Part dose, systemic clearance of INC280 in hepatocellular carcinoma patients from the Dose-Determining Part will be compared to patients with normal liver function and the 90% confidence interval for the mean ratio of clearance will be reported. A population pharmacokinetic model will be used for this pharmacokinetic analysis.
Key words	INC280, advanced hepatocellular carcinoma, c-MET pathway dysregulation

[redacted]

Amendment 6 (16-May-2022)

Amendment rationale

This amendment has been made to include the following changes:

- The definition of end of study has been revised to include the option for patients still on study treatment and who, in the opinion of the investigator, are still deriving clinical benefit at the time of end of study, to transfer to another study or to use an alternative way to provide study treatment to these patients.
- [redacted]
- In order to mitigate the risks of patient safety and data integrity due to public health emergency (e.g. COVID-19), language related to risk mitigation procedures has been added where applicable.
- To align with the latest available safety information, the INC280 dose modification and study drug-related toxicity management guideline has been updated to include the recommended dose modification and management for ILD/pneumonitis. Additionally, the guidance for follow up evaluations of selected toxicities (renal, hepatic) has been updated.
- To add the duration of the follow-up for pregnancy and newborn.
- The list of permitted concomitant therapy requiring caution and/or action and the list of prohibited concomitant therapy has been updated according to latest available information and in line with other INC280 clinical protocols.

Study status

As of April 2022, 38 patients have been treated with INC280. All of them have discontinued study treatment except for one patient in China who is still receiving treatment with INC280 300 mg BID tablet. The patient is in partial response and has been on treatment for 122 cycles.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

[redacted]

Section 4.3 Definition of end of study: addition of language to account for patients who would transfer into another study or an alternative way to continue provision of study treatment.

Section 4.5: new section “Rationale for Public Health Emergency mitigation procedures” added.

[redacted]

Section 6.2.5 Table 6-5 Recommended dosing guidelines for study drug-related toxicities: added dosing modification and toxicity management guideline for ILD/pneumonitis.

Section 6.2.5 Table 6-6 Follow-up evaluations for selected toxicities: updated the CTCAE grade threshold for serum creatinine increase that requires weekly monitoring until improvement to ≤ CTCAE grade 1 or baseline.

Section 6.2.6 Table 6-9 Follow-up evaluations for hepatic toxicities: added monitoring guidance for combined elevations of ALT and/or AST and total bilirubin.

Section 6.3.2 Permitted concomitant therapy requiring caution and/or action: updated with addition of new classes of drugs.

Section 6.3.3 Prohibited concomitant therapy: drugs with known risk of TdP were removed and added clarification regarding the prohibited use of live vaccines during the study and up to 30 days from the last dose of INC280.

Section 6.5.3.2 Study drug accountability: added clarification on return or destruction of unused study treatment, drug labels and packaging.

Section 7.1 Study flow and visit schedule: added a paragraph to allow that alternative methods of providing continuing care may be implemented by the Investigator during a Public Health emergency situation.

Section 7.1.3 Treatment period: added references to Definition of end of study and Criteria for premature patient withdrawal sections.

Section 7.1.4.1 Criteria for premature withdrawal: addition of language to specify that patients who transfer to another study or to use an alternative way to continue provision of study treatment will complete end of treatment procedures.

Section 7.1.5 Follow-up period: addition of language to specify that patients who transfer into another study or an alternative treatment option to continue provision of study treatment will not complete the safety, disease progression and survival follow-up.

Section 7.2.2 has been revised to include a reference to study visits during public health emergency.

Section 8.2.2 has been revised to indicate that SAE and follow-up should be reported to Novartis immediately, without delay and under no circumstances later than 24h after obtaining knowledge of the event/follow-up.

Section 8.3 Pregnancies: clarification added about duration of pregnancy and newborn follow-up.

[redacted]

Section 14.4 Appendix 4 Tables of drugs prohibited and drugs used with caution: amended Table 14-9 with new class of drugs, made new Table 14-11.

[redacted]

Other minor changes and corrections are made throughout the protocol for consistency and/or clarification.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 5 (04-Aug-2017)

Amendment rationale

In order to alleviate the burden for patients, the primary purpose of this amendment is to reduce assessments, while maintaining access to study treatment and monitoring safety.

The enrollment of this study has been halted since 25-Dec-2016 due to difficulty in identifying patients who met the eligibility criteria of the study. An interim database lock for the primary data analysis was performed on 14-Mar-2017. Since then two patients are ongoing in China and both have been on treatment for over 30 cycles at dose level of 400 mg BID tablet. One of the patients has achieved complete response and the other partial response. As of the cut-off date for the primary CSR, one patient had reported episodes of grade 2 lipase increases which were suspected to be study treatment-related. No suspected treatment-related AEs≥ Grade 2 have been reported in the second ongoing patient.

An additional dose reduction level is added for the tablet formulation in this protocol amendment based on information from other INC280 studies, indicating that 200 mg BID tablet can achieve target inhibition in patients.

INC280 150 mg tablets are also introduced in this protocol amendment to facilitate the dosing schedule of 300 mg BID in case of dose reduction. INC280 is currently supplied as tablets of 50 mg and 200 mg. As the 50 mg tablets will not be extended after expiry date, 150 mg tablets will be supplied for clinical use upon the availability and regulatory approval.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of Abbreviations: Added CMO&PS, Chief Medical Office and Patient Safety.

Section 6.1.1 is updated to include the addition of 150 mg strength of the tablet formulation.

Section 6.2.5 and table 6-4 are updated in the dose modification schedule for INC280 tablet formulation.

Section 7 has been updated as follows:

- Table 7-2 has been added to introduce new assessment schedules.
- Section 7.2.2 has been amended to reduce safety assessments and to inform that no cardiac assessments are required by the protocol.
- Section 7.2.3 has been amended to inform that no pharmacokinetics assessments are required by the protocol.

[redacted]

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 4 (31-Mar-2016)

Amendment Rationale

To optimize the management of liver toxicities and be consistent across the different INC280 studies, this protocol amendment provides additional guidance to investigators for the management of liver toxicities and specifically work-up guidelines for potential Drug Induced Liver Injury (DILI) cases, which were implemented based on the previously described single case of a serious, unexpected, possibly related adverse event of abnormal liver function tests (LFTs) that met the lab criteria of Hy's Law. Patients with increased AST/ALT and total bilirubin values that may be indicative of potential DILI, should be considered as clinically important events; therefore, specific guidance for actions to be taken on the study treatment (e.g. discontinuation) and for monitoring of LFTs have been implemented and clarified.

Furthermore, other updates are being implemented in this protocol amendment as described below:

The dose modification guidelines for elevations in amylase and lipase have been updated to optimize the management of such toxicities and be consistent across the different INC280 studies.

In addition, based on new PK data it is suggested that the concomitant use of Proton Pump Inhibitors (PPIs) is unlikely to impact the efficacy of INC280, therefore the PPI restriction can be removed from this protocol for patients requiring PPI gastric protection treatment. Moreover, requirements on other acid reducing agents (gastric acid modulators and H2 receptor antagonists) can also be removed.

The list of medications prohibited or used with caution has also been updated based on the latest internal DDI guidance and has been modified to include drugs with known risk of causing QTc prolongation.

To ensure consistency of patient selection across all investigational sites, molecular pre-screening for cMET pathway dysregulation is restricted to central laboratory testing only. This change will not affect the conduct of the study since to date no patients had been enrolled based on local pre-screening results.

[redacted]

Other minor clarification changes have been made and are included in the list of changes below.

[redacted]

Changes to the protocol

Section 1.2.1.2.2 Clinical efficacy has been updated based on newly available clinical data.

Section 1.2.1.2.3 Clinical Pharmacokinetics has been updated with new PK data for INC280.

Section 4.1, 5.1 and 7.1.1: Language allowing patients to enter clinical screening with local molecular pre-screening test results have been removed.

Section 5.3 the exclusion criteria 21: Prohibition of treatment with medications that are known CYP2C9, CYP2C19 and CYP2C8 substrates with narrow therapeutic index has been revised based on DMPK/CP data for INC280.

Section 5.3 the exclusion criteria 22: Prohibition of treatment with proton pump inhibitors has been revised based on new PK data.

Section 6.2.5, Table 6-5: The recommended dose modifications for INC280 have been updated for hepatic toxicities and elevations in amylase or lipase.

Table-6.6: Follow-up evaluations for selected toxicities has been updated for hepatic toxicity. Table 6-9 has been added for follow-up evaluations for selected hepatic toxicities. Table 7-3 has been updated to include the required laboratory evaluations for such cases.

Section 6.2.6.1: has been added for follow up on potential drug-induced liver injury (DILI) cases.

Sections 6.3.2 and 6.3.3: Permitted concomitant therapy requiring caution and/or action and prohibited concomitant therapy and Table 14-9, Table 14-10 in Appendix 4: These sections have been updated based on the latest internal DDI guidance and to include drugs with known risk of causing QTc prolongation. Additional updates have been made based on new PK data to remove restrictions on acid reducing agents (proton pump inhibitors, gastric acid modulators and H2 receptor antagonists).

[redacted]

Section 8.1.1 and Section 8.2.2.: have been revised to include language for the electronic reporting of SAEs

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 3

Amendment rationale

This protocol amendment provides additional information and guidance to investigators for the management of liver toxicities. After the cut-off date of the current INC280 Investigator's Brochure (28-Sep-2014), a female patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280

[redacted]

and gefitinib while enrolled in the CINC280X2202 study. This adverse event (AE) met the lab criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. Therefore, clarifications in the dose modification guidelines in case of liver toxicity and updated rules with regards to study treatment discontinuation for events that meet the Hy's Law criteria are added.

Furthermore, other updates are being implemented in this protocol amendment as described below:

Based on the preclinical data which suggest photosensitization potential for INC280, precautionary measures against ultraviolet exposure are being included in this amendment, in addition to the information provided in the current Investigator's Brochure.

The contraception period is being revised based on the half-life of INC280 estimated from the recent studies. Recent pharmacokinetic (PK) data from 3 healthy volunteer (HV) studies (CINC280X2103, CINC280X2107 and CINC280A2101) showed that when sampling PK up to 72 hr, the terminal half-life (T1/2) is longer than the apparent half-life estimated from cancer patients, with the mean terminal T1/2 from HV studies ranged 11.7-19 hr. Therefore, the contraception period for INC280 is extended to 7 days.

A statement that imaging data may be collected for possible central review has been added.

INC280 tablet at 400 mg bid has been evaluated in CINC280X2102, CINC280X1101 and CINC280X2202 studies. Preliminary PK data showed that the mean AUC and Cmax at steady-state following administration of INC280 tablets at 400 mg bid was higher than that following capsules at 600 mg bid (recommended phase II dose [RP2D] in the CINC280X2102 study), but in the range considering the coefficient of variability (CV%). Based on the tablet PK and safety data from these studies, the dosage of INC280 at 400 mg bid in tablet has been declared as RP2D in CINC280X2102 study. Therefore, 400 mg bid is determined to be the dose of tablet formulation in the dose expansion part of this study. When the INC280 tablet formulation is available, patients who are newly enrolled may start at INC280 400 mg bid tablet treatment. Patients who have been treated with INC280 600 mg bid capsules, in compliance with the local regulation, may switch at the beginning of the next scheduled visit to INC280 400 mg bid tablet treatment.

The information of the study formulation (capsule or tablet) have been added throughout the document to increase clarity.

Changes to the protocol

Section 1.2.1.2.1 has been updated with the most recent information based on the current Investigator's Brochure (edition 5.2) including the description of the event of abnormal liver function tests meeting the criteria of Hy's Law.

Section 5.3, exclusion criteria #27 and #28 have been revised to update the duration of the contraception period.

Section 6.1.1 tablets at 100 mg strength have been added.

Section 6.1.1.1 has been updated by adding the instruction during treatment and precautionary measures against ultraviolet exposure.

[redacted]

Section 6.2.4 has been updated with the available information of studies with INC280.

Section 6.2.5, Table 6-4, the dose reductions in the expansion part have been updated with the actual dose.

Section 6.2.5, Table 6-5, the recommended dose modifications for INC280 in case of hepatic toxicities have been updated.

Section 6.2.7 has been updated to increase consistency and clarity.

Section 7.2.1 has been modified by adding possible central imaging review process.

Section 7.2.2.5.6, the status of post-menopausal and not of childbearing potential has been modified to be consistent with that in the exclusion criteria.

Section 14.4, tables of drugs prohibited and drugs used with caution have been updated based on the latest update from the Oncology Clinical Pharmacology Drug-Drug Interaction Database (released date: Apr-2015).

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

[redacted]

Amendment 2

Amendment rationale

The main purpose of this amendment is to update the definition of c-MET positivity as inclusion criteria based on the recent preliminary data from the ongoing clinical studies with INC280.

As of 21 March 2014, in the CIN280X2102 study, 3 out of 6 patients (50%) had a confirmed partial response (PR); all patients had high c-MET status by immunohistochemistry (IHC) (IHC intensity score 3+ ≥50% of tumor cells) or fluorescence in situ hybridization (FISH) (Bang et al 2014).

Moreover, as of 21 March 2014, in the combination study (CINC280X2202) of INC280 plus gefitinib, all responders had high c-MET status (analyzed by IHC or FISH) (Wu et al 2014).

As of 21 August 2014, in this CINC280X2201 study of INC280 single agent with hepatocellular carcinoma (HCC) patients, 1 PR and 2 confirmed stable diseases (SDs) were reported out of 5 patients whose tumors where c-MET high (IHC intensity score 3+ ≥50% of tumor cells) in preliminary efficacy (not validated). Hepatocyte growth factor (HGF) overexpression has been described in almost all liver tissue samples adjacent to HCC tumors (TCGA HCC provisional data, .cbioportal.org/), but in the clinical setting this stimulation alone seems not sufficient for driving the tumor growth especially when the c-MET tumor expression is medium/low.

Based on these preliminary clinical data on the antitumor activity of INC280 as a single agent in NSCLC and HCC patients and in combination with gefitinib in NSCLC patients, the definition of the c-MET positive status in the inclusion criteria in this study will be updated as follow:

- c-MET IHC intensity score 3+ in ≥50% of tumor cells
- or c-MET IHC intensity score 2+ in ≥50% of tumor cells only if they have in addition MET gene copy number ≥5 as detected by FISH
- or MET gene copy number ≥5 by FISH and unknown c-MET IHC results
- or c-MET mutation can be enrolled in the study following discussion and agreement with Novartis

Among the total number of 50 patients as originally planned in the dose expansion part, around 25 to 40 patients can be expected to have the c-MET positive status with the planned enrollment, which can provide reasonable operating characteristics.

Additional modifications have been made:

Clinical safety data including serious adverse events (SAEs) have been updated in Section 1.2.1.2.1.

[redacted]

[redacted]

Renal function will be monitored more carefully by adding creatinine clearance (calculated or directly measured) in the blood chemistry panel since some patients experienced increased blood creatinine and/or renal failure in this HCC study (CINC280X2201).

The prohibited medications and herb/food supplements have been updated for clarification in Section 5.3. Restrictions to the concomitant usage of herb/food supplements are added to prevent potential interactions with INC280 treatment.

Study update: The dose-determining part with the dose level of 300 mg bid in capsule formulation has completed and the dose expansion part has started since December 2013. As of 01 September 2014, 14 patients have been enrolled in the dose expansion part and have been treated with INC280 600 mg bid in capsule formulation.

Changes to the protocol

Section 1.2.1.2 has been updated with newly available clinical data. Clinical safety, efficacy and clinical pharmacokinetics of INC280 have been amended respectively in sections 1.2.1.2.1, 1.2.1.2.2 and 1.2.1.2.3.

[redacted]

Section 4.1 sample size related language has been updated to be consistent with updated Section 10.8.

Section 5.2 the inclusion criteria of c-MET pathway dysregulation has been redefined: c-MET pathway dysregulation confirmed by c-MET IHC intensity score 3+ in ≥50% of tumor cell or by c-MET IHC intensity score 2+ in ≥50% of tumor cell and MET gene copy number ≥5 by FISH. Patients with MET gene copy number ≥5 by FISH and unknown c-MET IHC results or c-MET mutation can be enrolled in the study following discussion and agreement with Novartis.

Section 5.3 the prohibited medications and herb/food supplements have been updated for clarification.

Section 5.3 the exclusion criteria of biochemistry have been modified by adding the criteria of creatinine clearance.

Section 6.2.4 dose determining for tablet formulation has been modified for clarification of the data use from other clinical studies with IN280.

Section 6.2.5 has been updated by adding exceptional situations that study treatment may continue even if the patient experienced one of the treatment stopping rules.

Section 6.3.2 and Section 6.3.3 have been modified for clarification of the use of herbal medications and food products.

Section 7.1 Table 7-1 has been updated based on modifications in Section 7.2.2.6.

Section 7.1.4 and Section 7.1.4.1 exceptional situations of continuance of the study treatment have been added.

Section 7.2.2.1 and Section 7.2.2.2 the “pre-dose” restriction of physical examination and vital signs in Day 1 of Cycle 2 and subsequent cycles have been removed.

[redacted]

Section 7.2.2.5 has been modified by adding creatinine clearance in the blood chemistry panel as it is required for the exclusion criteria.

Section 7.2.2.6 ECGs matched with the PK blood collection will be added and be centrally evaluated by an independent reviewer.

Section 7.2.3 and Table 7-5 have been updated by adding PK blood collections at 2 hours post-morning dose in Cycle 2 and Cycle 3.

Section 7.2.3.1 PK blood collection procedure has been modified for clarification.

Section 10 analyses of efficacy based on the revised definition of c-MET positive, as introduce in Protocol Amendment 2, has been added.

Section 10.4.2 the confidence interval to be presented in the primary analysis of TTP has been changed to one-sided 90% to be consistent with sample size justification.

[redacted]

Section 10.8 sample size justification has been updated based on the c-MET positive patient population. More technical detail has been provided.

Section 13 the corresponding references have been added.

Section 14.4 Appendix 4 the tables 14-9 and 14-10 have been modified based on the updated reference.

Section 14.6 Appendix 6 the calculation method of creatinine clearance (Cockcroft-Gault formula) has been added.

Clarification has been made that INC280 capsule was used in the dose-determining part.

Minor editorial changes have been made and typos have been corrected throughout sections.

[redacted]

Amendment 1

Amendment rationale

The primary purpose of this amendment is to introduce the use of INC280 tablets.

INC280 is currently supplied as capsules of 50 mg. Doses up to 600 mg bid have been tested. To improve the convenience of study drug administration for patients, a tablet formulation with higher dosage strengths (50 mg and 200 mg) has been developed. A relative bioavailability study (INC280X2103) is ongoing to compare the two formulations. If the relative bioavailability is comparable, new patients will be treated with tablets and patients still benefitting from treatment with capsules may be switched to the tablets. If the exposures are significantly different between the two formulations, a dose conversion based on the relative bioavailability may be applied.

Additional modifications and updates to the protocol include:

The section covering the preclinical safety of INC280 has been updated to reflect new findings obtained from additional toxicity studies which have been conducted since the original protocol development. These include the 13-week monkey study, the embryofetal studies in rats and rabbits, and photosensitization potential assay evaluation.

[redacted]

An update to the eligibility criteria for serum creatinine, contraception requirement, permitted and prohibited concomitant medication to align with other INC280 protocols and Novartis standards.

The data analysis plan has been updated to include the consideration of statistical and PK analysis for different study treatment formulations.

Additional editorial changes have been made to sections where previous language was deemed inaccurate or ambiguous.

Changes to the protocol

Section 1.2.1.1.3 has been modified by adding new data and findings from preclinical toxicity studies.

[redacted]

Section 5.3 the typo of exclusion criteria 4 has been amended.

Section 5.3 the exclusion criteria 21 has been amended to exclude patients whose serum creatinine are greater than grade 1.

Section 5.3 the exclusion criteria 24 and 25 were amended to update the contraception requirement to align with other protocols.

Section 4.1 and Section 6.1.1 tablet formulation and strength have been added, and the usage of tablets and capsules has been specified. Moreover, the fasting requirement is now clarified.

[redacted]

Section 6.2.2 and Table 6-1 have been updated to specify how to adjust dose when decreased INC280 exposure is noted during Dose-Determining Part.

Section 6.2.4 has been added to specify the dose determining procedure for INC280 formulation change during Dose Expansion Part.

Table 6-5 has been updated for dose modification of serum creatinine increased to align with other INC280 protocols.

Table 6-8 has been modified to define the criteria of hepatitis C reactivation.

Section 6.3.2 and Section 6.3.3 and Appendix 4 have been updated to clarify permitted and prohibited medication.

Section 7.1 has been modified to define the window day for Day 1 of Cycle 1.

Section 7.1.1.1 and Section 7.1.1.2 have been modified to align with inclusion criteria 1.

Section 7.1.1.3 and Section 7.1.2.1 have been modified to specify the use of Patient Registration Form.

Section 7.1.5 has been modified to comply with Novartis Clinical Data Standards.

Section 7.2.1 has been modified to specify the visit window of each tumor assessments.

Section 7.2.4.2.1 has been modified to specify the collection of fresh tumor biopsy is optional.

Section 7.2.5.5.5 has been modified to remove redundant Hepatitis B serology exams on Day 1 of every cycle from Cycle 2 and EOT.

Section 10 and Section 10.5.3.3 and Section 10.7 have been updated to include the consideration of statistical analysis for the change of study treatment formulation.

Section 10.4.3 has been modified to clarify how to handle missing values/censoring/discontinuations.

Section 10.5.4.1 has been updated to specify the PK analysis method for dose decision.

[redacted]

IRB/IEC

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide and the third leading cause of cancer-related death. In 2008, an estimated 748,000 new cases of liver cancer occurred and approximately 696,000 people died of this cancer worldwide. Over 80% of HCCs occur in developing countries in Sub-Saharan Africa, Southeast Asia, and East Asia, consistent with the fact that about three-quarters of HCCs are attributed to chronic Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections and are often associated with liver cirrhosis (Ferlay 2008, Anzola 2004). Other common etiologies include alcohol consumption, nonalcoholic steatohepatitis, exposure to carcinogens, and the genetic metabolic diseases such as hemochromatosis (El-Serag 2000, Donato 2002, Adams 2005, Turner 2002). Obesity has also been identified as an independent risk factor for developing HCC (Park et al 2010).

Approximately 80% of HCC patients present with advanced or unresectable disease (Ferlay et al 2008). HCC is resistant to conventional chemotherapy, and is rarely amenable to radiotherapy. No single chemotherapy agent or combination has demonstrated convincing survival benefits or improvement in quality of life (Ng 2000, Thomas 2009, Simonetti 1997). Some newer chemotherapy agents have demonstrated some activity, but have had minimal impact on disease stabilizations and overall survival (OS). The 5-year relative survival rate for patients with HCC treated with local or systemic treatment is only 7% (Bosch et al 2004).

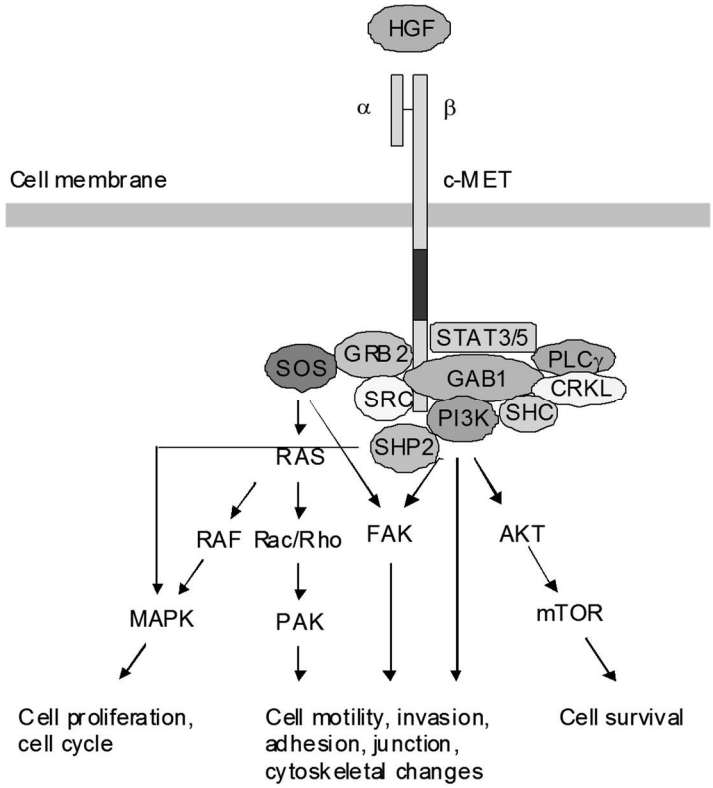
HCCs are phenotypically and genetically heterogeneous tumors with alteration of multiple signaling pathways. Inhibiting multiple targets may be important to optimize and induce durable anti-tumor effects (Whittaker et al 2010). Sorafenib, a multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity, was the first targeted agent to show a statistically significant improvement in OS for patients with advanced HCC across all regions. The results of a phase III randomized placebo-controlled trial (SHARP trial) demonstrated the hazard ratio for OS (sorafenib/placebo) was 0.69 (95% CI 0.55-0.87; p=0.0006). Improvement in OS for the patients randomized to sorafenib in another phase III sorafenib study in Asia-Pacific region was consistent with the SHARP trial as indicated by hazard ratio b for survival of 0.68 (95% CI, 0.5-0.93; p=0.014). The positive results from sorafenib demonstrated the potential for further development of therapeutic agents targeting the molecular pathways involved in HCC. However, the observed OS of 6.5 months in the sorafenib group compared with 4.2 months in the placebo group for the sorafenib Asia-Pacific study compared to that of 10.7 months in the sorafenib group vs 7.9 months in the placebo group for the SHARP study suggest that the patient population in the Asia-Pacific region presented with more advanced disease, the most common etiology being HBV infection (Llovet 2008a, Cheng 2009).

The biological functions of the c-MET-mediated signaling pathway in normal tissues and human malignancies have been well documented (Birchmeier 2003, Christensen 2005, Liu 2008, Liu 2010) (Figure 1-1). Improved knowledge of oncogenic processes and signaling pathways has led to the identification of c-MET pathway as one of the therapeutic targets in HCC. Clinical activities have been observed in NSCLC, medullary thyroid cancer, liver cancer and other tumor types when c-MET pathway was interfered (Peters 2012, Spiegel 2011, Kurzrock 2011, Rimassa 2012, Gherardi 2012, Verslype 2012). Two phase II trials of c-MET

[redacted]

inhibitors in the treatment of HCC were reported recently. The phase II trial of tivantinib for HCC is the first randomized data in HCC showing OS advantage (HR=0.64; p=0.04) with a MET inhibitor and identifying a biological subgroup responding to a target therapy. c-Met positive patients treated with tivantinib experienced significant improvement in time to progression (TTP), 2.9 months vs 1.5 months, and OS, 7.2 months vs 3.8 months, compared to patients who received placebo (Rimassa et al 2012). In another phase II trial of cabozantinib in HCC patients, a median progression-free survival (PFS) of 4.2 months, with 2/36 (5%) confirmed partial response (PR) was reported. The overall disease control rate (DCR = PR+SD) at Week 12 was 68% (Asian subgroup: 73%) (Verslype et al 2012).

Figure 1-1 Signaling and biological functions of the HGF/c-MET pathway



1.2 Introduction to investigational treatment

1.2.1 Overview of INC280

The chemical name for INC280 is 2-fluoro-N-methyl -4-(7-(quinolin-6-ylmethyl) imidazo[1,2b][1,2,4]triazin-2-yl)benzamide dihydrochloride. INC280 is a small ATP competitive, reversible inhibitor of the c-MET receptor tyrosine kinase. The proto-oncogene c-MET, a member of the receptor tyrosine kinase family, encodes the high-affinity receptor for hepatocyte growth factor (HGF), the only ligand for the receptor.

In vitro and in vivo data suggest that INC280 possess potent pharmacological activity against c-MET and supports its clinical development as a potentially effective oral treatment for human cancers.

Please refer to the [INC280 Investigator's Brochure] for more detailed information.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology summary

INC280 possesses potent inhibitory activity against the c-MET kinase in vitro (IC_{50} = 0.13 ± 0.05 nM) and is both ATP competitive and reversible (Liu et al 2011). INC280 is highly specific for c-MET with > 10,000-fold selectivity over a panel of 56 other human kinases tested.

Systematic in vitro dose-response proliferation assays on >500 cancer cell lines showed that INC280-responsive cancer models are characterized by either strong c-MET overexpression due to c-MET gene amplification or by co-expression of c-MET and HGF, leading to autocrine activation.

The pharmacokinetic/pharmacodynamic (PK/PD) relationship of INC280 was characterized in tumor-bearing mice. These experiments probed the potential of INC280 to inhibit phosphorylation of c-MET, as assessed by phospho-c-MET levels in tumors using immunohistochemical or ELISA-based methods. In c-MET/HGF-driven xenograft mouse tumor models, oral dosing of INC280 demonstrated significant in vivo activity in blocking c-MET phosphorylation. Oral administration of INC280 at a dose of 3 mg/kg suppressed > 90% c-MET phosphorylation for at least 7 hours in a mouse xenograft tumor model and this correlated with plasma INC280 levels greater than or equivalent to the human whole blood IC90 of 71 nM.

Previous experiments indicated that HCC cell lines with high c-MET expression are responsive to c-MET inhibition (Zhang et al 2005). These earlier findings were confirmed by testing the anti-tumor efficacy of INC280 in the xenograft HCCLM3 model, which expresses very high c-MET levels due to c-MET amplification. Tumor regression was observed at the dose level of 5mg/kg/day and c-MET phosphorylation was fully suppressed up to 8 hours after dosing. These data indicate that inhibition of c-MET by INC280 could have therapeutic benefit in HCC patients in whose tumors c-MET is activated, for example by gene amplification.

More detailed information can be found in the current INC280 Investigator's Brochure.

Collectively, the data demonstrate that INC280 possesses potent in vitro and in vivo pharmacological activity against c-MET. Together with our epidemiological evidence for pathway activation (Section 1.1) these data support the clinical development of INC280 as a potentially effective oral treatment for hepatocellular carcinoma.

1.2.1.1.2 Nonclinical drug metabolism and pharmacokinetics summary

In preclinical models, INC280 demonstrated high protein binding (>93%) with low apparent volume of distribution. INC280 was predominantly metabolized by CYP enzymes and to a minor extent by cytosolic molybdenum containing oxidases. The major enzyme involved in INC280 metabolism in the liver is CYP3A4. Other enzymes involved include CYP2C9 and 2C19.

Drug-drug interaction (DDI) potential of INC280 has been investigated in in vitro metabolism and transporter systems. INC280 has low potential for CYP3A4 induction. INC280 showed

[redacted]

inhibitory potency for CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5. Time-dependent (irreversible) inhibition by INC280 was observed for CYP1A2 and CYP3A4/5. Potential drug-drug interaction due to inhibition of CYP1A2, 2C8, 2C9, 2C19 and 3A4/5 is possible at clinically relevant doses.

Based on Caco2 in vitro study, DDI with a P-gp substrate is possible at clinically relevant INC280 doses (IC_{50} of 2.9 μM). INC280 displayed inhibition of MDR1/P-gp, MXR/BCRP, OATP1B1 and OATP1B3 with IC_{50} values of 12 μM, 16.4 μM, 6.5 μM and 6.2 μM, respectively in LLCPK1, MDCKII and HEK293 uptake assays, indicating INC280 might result in an increased uptake of co-mediations transported by ABC and SLC-transporters in the gastrointestinal (GI) tract or a decreased elimination into the bile and/or urine at clinical relevant doses of INC280.

For more information, please refer to the most updated the current [INC280 Investigator's Brochure].

1.2.1.1.3 Non clinical toxicology summary

Repeat dose toxicity studies conducted revealed the following target organs or systems: kidneys, pancreas, central nervous system (CNS), and potentially liver. Additionally, embryofetal toxicity / teratogenicity was observed in rats and rabbits, and skin photosensitization potential were also identified.

A potential risk of kidney damage was evidenced in the 28-day toxicology study in cynomolgus monkeys, where mild-to-moderate deposits of crystalline-like material within the renal interstitium and/or tubular lumen were present at the doses of 75 and 150 mg/kg/day. The no observable adverse effect level (NOAEL) for the cynomolgus monkey study is 30 mg/kg/day, and is associated with an average area under the curve (AUC) of 97.6 μM*hr (total) or 3.28 μM*hr (unbound) and Cmax of 34.8μM (total) or 1.17μM (unbound).In the 13-week monkey study, no evidence of kidney toxicity were observed at the doses tested (up to 75 mg/kg/day)

Clinical and histopathological signs indicative of CNS toxicity were observed in rats only. In the 4-week toxicity study, tremors and convulsions upon handling, as well as white matter vacuolation in the thalamus were observed at the high dose groups (60 mg/kg/day for females, and 120 mg/kg/day for males). At the NOAELs for the CNS toxicity (30 mg/kg/day for females, and 60 mg/kg/day for males), the systemic exposure was 144 μM*hr (or 8.0 μM*hr for unbound drug). In a follow up 13-week rat study with a 13-week recovery, the CNS effects and similar brain lesions were observed, and were shown to be reversible.

A finding common to rat and cynomolgus monkey in the 28-day toxicology studies was the increased incidence of pancreatic acinar cell vacuolation and/or apoptosis without inflammation. These findings are reversible in both species.

Findings in serum chemistry liver enzymes observed in several different studies in rats and monkeys after administration of relatively high doses of INC280 were highly variable, minimal-to-mild in nature and lacked a clear dose response. The significance of the elevations is undetermined and there is no histological correlate within the liver in most studies, with the exception of the 13-week monkey study, where minimal to mild subcapsular neutrophilic infiltration associated with single cell necrosis in liver (males only, and reversible) was observed. Routine clinical chemistry evaluations will allow for monitoring of these parameters.

[redacted]

INC280 is not genotoxic. Studies on embryofetal development were conducted in both rats and rabbits. Based on the results of the embryo-fetal development studies, INC280 is teratogenic to rabbits at ≥5 mg/kg/day, and teratogenic to rats at ≥10 mg/kg/day. Fetal malformations of limb muscle and tongue were the major findings in both rats and rabbits. Based on the findings in animal studies, INC280 is considered potentially teratogenic to humans.

INC280 tested positive for phototoxicity in an in vitro 3T3 NRU assay. In the follow up in vivo study in mice (UV-LLNA), INC280 was also tested positive for photosensitization at the dose of 100 mg/kg/day (with NOAEL of 30 mg/kg/day). Based on these results, INC280 is considered to have potential for photosentization.

For more information, please refer to the most updated the current [INC280 Investigator's Brochure].

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety

As of 28-Sep-2014 (cut-off date of the INC280 Investigator's Brochure, edition 5.2), a total of 203 cancer patients have been treated in five clinical trials with INC280 as a single agent and a total of 103 cancer patients have been treated with INC280 in 5 different combination therapies with anti-cancer agents at various doses and in two formulations, capsule and tablet.

Single agent INC280 is generally tolerable (regardless of the dose), with the majority of the reported AEs being of mild or moderate severity (CTCAE grade 1 or grade 2). CTCAE grade 3 or grade 4 AEs suspected to be related to INC280 in single agent studies (regardless of the dose) included hypophosphatemia, peripheral edema, fatigue, increase in AST, ALT, γGT, amylase, blood bilirubin and lipase, vomiting, colitis ulcerative, lung infection, nausea, anemia, neutropenia, hypophagia, decreased appetite, hypoalbuminemia, maculo-papular rash, dehydration and decreased lymphocytes.

In the combination studies, the most frequent AEs suspected to be related to INC280 (regardless of the dose) were nausea and vomiting. CTCAE grade 3 and grade 4 AEs suspected to be related to INC280 (regardless of the dose) included most frequently: asymptomatic increase in amylase, increase in lipase, AST and ALT, nausea and vomiting. One serious adverse event (SAE) with fatal outcome, deteriorated cough and dyspnea, has been reported with a suspected causal relationship to INC280.

After the cut-off date of 28-Sep-2014, a [redacted] patient experienced a serious, unexpected, possibly related AE of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the [CINC280X2202] study. Patient experienced concurrent elevations of total bilirubin >2×ULN and ALT/AST >3×ULN with alkaline phosphatase (ALP) <2×ULN. The patient permanently discontinued study drugs. The liver function alterations were reversible and improved after the discontinuation of both drugs. At the time of the follow-up Investigator Notification (IN), the outcome of the AE of abnormal liver function tests was reported as completely recovered. This patient met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination.

[redacted]

The recommended phase II dose (RP2D) for INC280 as a single agent with capsule formulation has been determined to be 600 mg bid. The RP2D of INC280 monotherapy is 400 mg bid in tablet formulation. The maximum tolerated dose (MTD) for single agent INC280 has not been defined.

1.2.1.2.2 Clinical efficacy

As of 21-March-2014 (clinical data cut-off date), 8 out of 33 (24%) patients in the dose-escalation part of the single agent INC280 study [CINC280X2102] had stable disease. Moreover INC280 showed preliminary anti-tumor activity in the expansion arm of the dose escalation part of the study in patients with NSCLC, 3 out of 6 patients had confirmed PR; all patients were epidermal growth factor receptor (EGFR) wild type and had high c-MET status by IHC or FISH (Bang Y-J et al, 2014). Two of 3 patients had c-MET mutations.

In addition, as of 21-March-2014, in the INC280 plus gefitinib combination study [CINC280X2202], PRs were seen in 8 out of 46 (17%) evaluable NSCLC patients (6 confirmed and 2 unconfirmed PR). All responders had high c-MET status (by IHC or FISH): patients with MET gene copy number ≥5 by FISH demonstrated an ORR of 40% (n = 8/20) and patients with c-MET IHC intensity score 3+ in ≥50% of tumor cells demonstrated an ORR of 33% (n = 7/21). No responses have been observed in patients with c-MET IHC intensity score 2+ in ≥50% of tumor cells or low MET gene copy number (Wu YI et al, 2014).

As of 28-September-2015, in this CINC280X2201 study of INC280 single agent with HCC patients, total 36 patients were enrolled: 8 patients in a dose-determining part (INC280 300mg BID) and 28 patients in dose-expansion part (INC280 600mg BID). In expansion patients, 3 confirmed PRs and 1 SD were reported in preliminary efficacy analysis. All responders have c-MET high status (IHC 3+, IHC 2+ and cMET gene copy number [GCN] ≥ 5 by FISH, or cMET GCN ≥ 5 and unknown IHC).

1.2.1.2.3 Clinical Pharmacokinetics

As of 28 September 2013, INC280 (capsule) single agent steady state pharmacokinetic (PK) data are evaluable in a total of 102 patients from three clinical studies. After oral administration, INC280 was rapidly absorbed. Median time to peak plasma concentration was reached at 1 to 4 hours. The apparent elimination half-life of INC280 is short, with an average of 2.3 to 6.4 hours across studies. The mean plasma exposures (Cmax and AUC) of INC280 were generally increased with dose following qd administration up to 600 mg/day, and following bid dosing up to 600 mg bid. Upon daily dosing, there was minimal accumulation in all dose cohorts, which is in line with the short terminal half-life of INC280. Steady state INC280 exposure is expected to be reached by the third day of consecutive dosing.

INC280 exhibited a pH-dependent solubility profile with a low solubility at high pH level. A study to evaluate the effect of long acting proton pump inhibitor on the PK of a single dose INC280 tablet (600 mg) was completed in healthy volunteers [CINC280A2101]. Daily treatment of 20 mg rabeprazole for 4 days resulted in a modest reduction in the extent of INC280 absorption with a 25.2% decrease in AUCinf and a 37.5% decrease in Cmax. Considering the 42% and 65% variability in AUC observed in patient single agent studies [CINC280X2102] and [CINC280X1101], therefore a decrease of 25% in AUC when administered with PPI is considered not significant. The impact on the 12 hour post-dose concentration of INC280

(defined as trough concentration for BID dosing) was small with ~7% reduction after rabeprazole treatment. Preliminary data in NSCLC patients [CINC280X2202] suggested that anti-tumor activity is correlated more with Ctrough than AUC and Cmax.

For more information, please refer to the most updated version of the [Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

In view of the challenges in management of HCC, with its high mortality and morbidity as well as limited efficacy to the current available therapies, there is an urgent need for better systemic therapy for HCC.

c-MET overexpression has been associated with increased vascular invasion, resistance to chemo- and radiotherapy, and poor clinical outcome (Farazi 2006, Takami 2007, Boix 1994, Suzuki 1994, Kiss 1997, Ueki 1997, Tavian 2000, Akervall 2004, Kaposi-Novak 2006, Lal 2005, Liu 2008). Moreover, paracrine stimulation of cancer cells by HGF originating from non-cancerous liver tissue that could promote growth and metastasis was reported (Wu et al 2006). Interference with the c-MET receptor intracellular sequence has been shown to impair HGF induced angiogenesis, suggesting blocking of receptor site may be a therapeutic strategy to overcome angiogenesis in cancers (Cantelmo et al 2010). Pathological HGF/c-MET pathway deregulation is one of the key events that drive the oncogenesis and tumor maintenance of HCC (Whittaker et al 2010).

INC280, a specific c-MET inhibitor, has shown anti-tumor activity in several pre-clinical models of HCC that are driven either by c-MET gene amplification or by HGF stimulation. Preclinical studies performed at Novartis have shown that HGF overexpression is found in almost all liver tissue samples adjacent to HCC tumors and that c-MET is expressed by the majority of HCC tumors. Thus, INC280 is an attractive c-MET inhibitor for HCC.

We therefore intend to develop INC280 as a potential treatment option for patients with HCC. Based on the available data that demonstrate the involvement of the c-MET pathway in the tumorigenesis of HCC, and poor prognosis of the disease, this study will evaluate INC280 in patients with advanced HCC with dysregulated c-MET pathway.

The recently reported positive results of c-MET inhibitors in the treatment of HCC provided the strongest rationale for the evaluation of c-MET targeted agents in HCC. The phase II trial of tivantinib for HCC demonstrated significant improvements in TTP and OS, particularly in patients with high MET expression level while the interim data from a phase II trial of cabozantinib for HCC reported a median PFS of 4.2 months, with 2 confirmed PR (Rimassa 2012, Verslype 2012).

2.2 Rationale for the study design

This study is designed as a Phase II, single arm, open-label, multicenter study to evaluate the safety and efficacy of INC280 as first-line treatment in patients with advanced HCC who are not eligible for or had disease progression after surgical or locoregional therapies, with c-MET dysregulation.

[redacted]

A single arm trial design was chosen, with an estimated TTP based on the sorafenib study in Asia-pacific region which enrolled similar patient population (patients with advanced HCC, Child Pugh A and no prior systemic therapy), to evaluate the preliminary activity of INC280 in advanced HCC as well as enabling an evaluation of the safety, PK, and other parameters detailed in Section 10.

TTP is the primary endpoint recommended by the American Association for the Study of Liver Diseases (AASLD) expert panel for a Phase II study in HCC. Secondary endpoints include ORR, PFS, OS and disease control rate (DCR). Safety of INC280 in patients with advanced HCC, especially liver AEs in patients with liver dysfunction associated with underlying viral or cirrhotic medical conditions, will be performed to evaluate INC280 exposure in patients with liver dysfunction.

This study is designed to include a Dose-Determining Part and a Dose Expansion Part. The Dose-Determining Part was designed in order to characterize the PK and safety profiles of INC280 in the setting of liver dysfunction, with the aim of identifying the appropriate dose to be used for HCC patients before exposing a larger group of patients to INC280 in the Dose Expansion Part of this study. The Dose Expansion Part will start when the appropriate dose is determined after the dose decision analysis which will be performed at the end of the Dose-Determining Part and, will also incorporate safety and PK data from other ongoing clinical studies (Section 4.1).

2.3 Rationale for dose and regimen selection

In vitro, INC280 is mainly metabolized via liver CYP3A4 enzyme. HCC and underlying liver cirrhosis or the presence of liver metastasis may change the drug metabolism and elimination. Though preliminary analysis didn't show a difference in INC280 drug exposure in HCC patients as compared to patients with other tumor types, predominant metabolism of INC280 via CYP3A4 enzyme and the fact that the PK of INC280 has not been studied exhaustively in patients with liver dysfunction raised the concern if its PK may be altered in patients with hepatic impairment, a major characteristic of the patient population for this study. Thus, the issue is to be addressed via a Dose-Determining Part to evaluate the PK and safety of INC280 in this population and compared with historical data before exposing to a larger group of patients in the Dose Expansion Part, who could be treated at the same, a lower or a higher dose than the Dose-Determining Part dose, based on the dose analysis decision (Section 4.1 and Section 6.2.2).

INC280 300 mg bid (capsule), which is the highest safe dose being evaluated based on the clinical experience from other ongoing studies (Section 1.2.1.2), will be used for the Dose-Determining Part. 300 mg bid is expected to achieve target inhibition. Observed mean C_{trough} concentration on Day15 at 300 mg bid was approximately 13 fold of in vivo IC_{90}. In addition, a bid dosing regimen is potentially more appropriate in fast growing tumors than a qd regimen (Georgieva et al 2012).

The dose and regimen selection for the Dose-Determining Part was based on previous clinical experience from ongoing studies. By the cut-off date of August 15, 2012, INC280 was well tolerated in human up to 300 mg bid (capsule) (Section 1.2.1.2). A total of six HCC patients have been treated at 10 mg qd (n = 1), 50 mg qd (n = 2), 400 mg qd (n = 1) and 100 mg bid (n

[redacted]

= 2). The safety profile in HCC patients was similar to patients with other tumor types and no major liver toxicity was reported in the ongoing INC280 studies. In an exploratory analysis using linear mixed effect model to assess the impact of the disease status on INC280 exposure, neither disease status of HCC nor status of liver metastasis was identified as the significant covariates. Therefore, it is reasonable to select 300 mg (capsule) bid as an appropriate dose for the Dose-Determining Part in HCC patients.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
To estimate overall clinical activity of INC280 in advanced HCC patients with c-MET dysregulation.	Time to progression (TTP) assessed using RECIST version 1.1 (Appendix 1)	
Secondary		Refer to Section 10.5.
To further assess the clinical activity of INC280 in advanced HCC patients with c-MET dysregulation	ORR, PFS, OS and DCR	
To characterize the safety and tolerability of INC280 in advanced HCC patients.	**Safety**: AEs, SAEs, changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs) **Tolerability**: Dose interruptions, reductions and dose intensity	
To characterize the pharmacokinetics of INC280 in patients with advanced HCC.	Plasma concentration vs. time profiles, plasma PK parameters including but not limited to AUC0-t, CL/F, Cmax, Tmax, T1/2 and Racc	

[redacted]

[redacted]

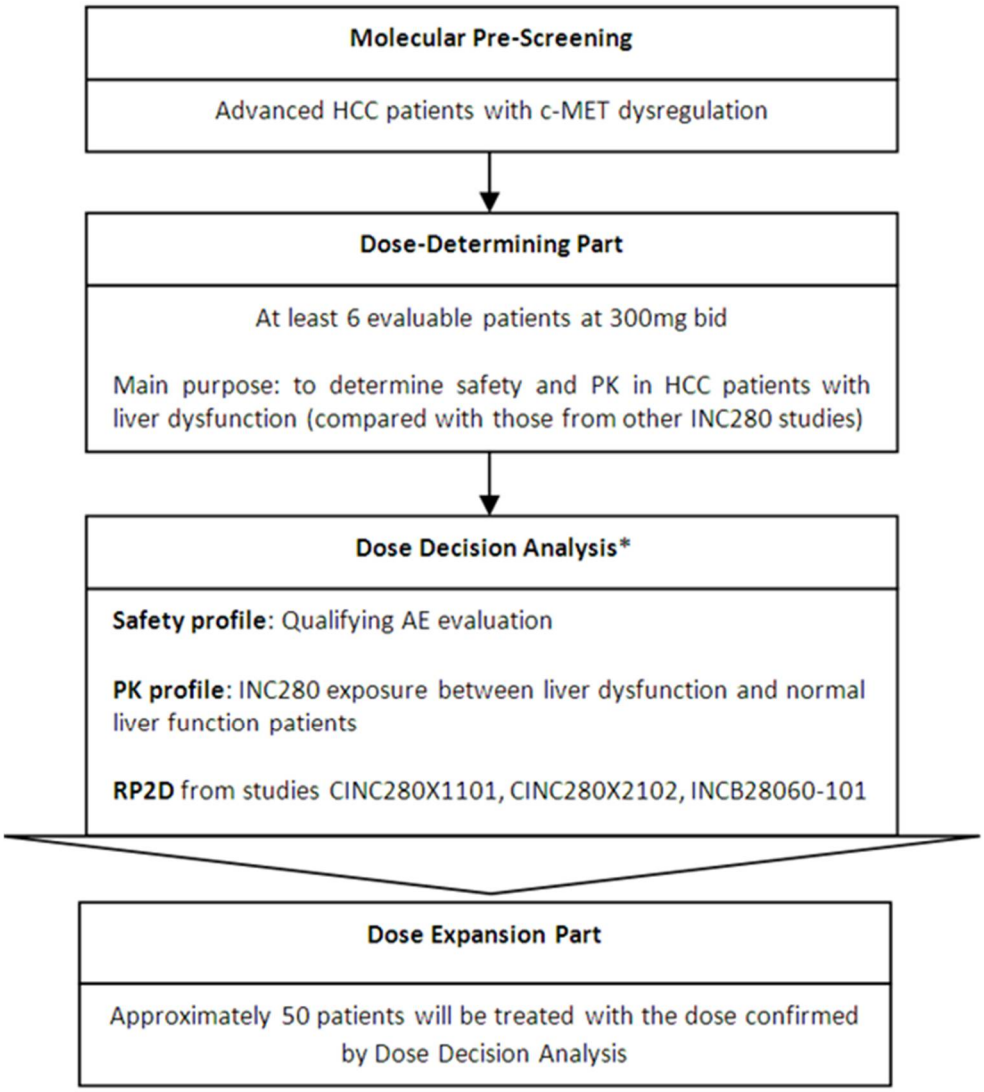
4 Study design

4.1 Description of study design

This is a Phase II, open label, single arm, multicenter study of INC280 administered orally as first-line treatment in patients with advanced HCC. See Figure 4-1 for an overview of the study design.

Patients will be enrolled into the study in 2 parts (Dose-Determining and Dose Expansion parts) where the first Part will allow the assessment of safety and PK profiles prior to initiating a larger second Part.

Figure 4-1 Study design



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

[redacted]

A complete treatment cycle is defined as 21 days of continuous dosing, with the first dose of the INC280 defining Day 1 and the last day of a complete treatment cycle being Day 21. In the Dose-Determining Part, the qualifying AEs for dose determination will be assessed for the first 28 days of treatment for comparability to Cycle 1 safety data observed in previous/ongoing clinical trials.

Molecular pre-screening

Evidence of dysregulation of c-MET pathway is required in order to begin screening activities.

Evidence can be demonstrated by submission of an archival or a newly obtained HCC tumor sample to a central laboratory for analysis. Tissue requirements are found in Section 7.1.1.2.

Patient must sign the molecular pre-screening consent to allow for the collection and submission of samples to the central laboratory for analysis.

If the results of the central analysis meet the criteria for c-MET positivity (Section 5.2), the patient can proceed with the screening procedures. In exceptional cases, patients with a tumor harboring a documented cMET mutation (based on the results of local testing) can be enrolled in the study following discussion and agreement with Novartis.

Screening period

When the required c-MET status is known, patients will sign the Main Informed Consent Form and will be evaluated against study inclusion and exclusion criteria and safety assessments (Table 7-1). Eligible patients will begin study treatment within 14 days of the commencement of the screening assessments.

Dose-Determining Part

During the Dose-Determining Part, at least six patients will be enrolled and treated with INC280 at 300 mg bid (capsule). Safety, full PK profiles of INC280 on Cycle 1, Days 1, 2, 15 and 16, predose PK samples on Cycle 2 Day 1 and Cycle 3 Day 1, demographics and other baseline characteristics will be collected in these patients (Section 7.1.2.3, Section 7.2.2 and Section 7.2.3).

A dose decision analysis based on safety and PK data will be conducted when patients from Dose-Determining cohort have completed 28 days treatment and data from at least 6 patients are evaluable for the dose-determining set (DDS) (see Section 10.1). The analysis will be guided by the medical review of available clinical, laboratory, and PK data, as well as the recommendation from the Bayesian Logistic Regression Model (BLRM) (see Section 6.2.2 for details on the decision process).

Novartis and the principal investigators will have a dose decision meeting to discuss and evaluate the data. At this meeting, Novartis and the principal investigators must reach consensus on the dose level to be used in the Dose Expansion Part. Novartis will prepare minutes from this meeting and circulate them to each investigator for comments prior to finalization. The Expansion Part dose will be communicated to all investigators in writing.

[redacted]

Patients in the Dose-Determining Part who have not experienced a dose reduction will be allowed to switch to the confirmed Expansion Part dose, if different from the Determining Part dose, under consultation from the Investigator with Novartis.

Dose Expansion Part

Once the Expansion Part dose has been confirmed, approximately 50 patients in total will be enrolled, among which around 25 to 40 patients will have the c-MET positive status as specified in the inclusion criteria (Section 5.2).

Detailed information on all patients will be collected and reported (see Section 10 for details).

Follow-up

All patients will be followed-up as described in Section 7.1.5. At minimum, patients must complete the safety follow-up assessments 30 days after the last dose of the study treatment.

All patients will be followed until progressive disease (PD), death or withdrawal of consent regardless of any drug discontinuation. All patients will be followed for OS for a duration of at least 6 months after last patient first dose.

4.2 Timing of dose decision analyses and design adaptations

The safety and PK analysis will be conducted when at least six patients enrolled in the Dose-Determining Part become evaluable for the DDS.

4.3 Definition of end of the study

The end of study will be the earliest occurrence of one of the following:

- completion of the survival follow-up period and the Study Phase Completion page for the last patient treated with INC280
- or the study is terminated early
- or another clinical study becomes available that can continue to provide study treatment in this patient population; all patients ongoing are transferred to that clinical study and all discontinued patients have completed the safety follow-up period. The follow-up for disease progression and survival will not be performed or pursued (See Section 7.1.5)

At the end of the study, every effort will be made to continue provision of study treatment outside this study by an alternative way, to patients who, in the opinion of the investigator, are still deriving clinical benefit.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing IRBs and/or IECs of the early termination of the study.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure patient safety and trial integrity may be implemented; such procedures are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Population

5.1 Patient population

Adult patients with histologically or cytologically confirmed advanced HCC which is not amenable to surgical resection or other loco-regional therapy and who have received no prior systemic therapy, are eligible. Child-Pugh classification (CPC) will be used to assess the severity of impaired hepatic function in patients with liver cirrhosis. Only patients with Child-Pugh A (5-6 point liver function) are included since more severe liver function impairment renders study patients prone to liver decompensation from underlying cirrhosis or reactivation of chronic hepatitis B viral infection potentially leading to uninterpretable study data based on heterogeneity and causality in exposure, mortality, and AEs.

Evidence of c-MET expression must be documented through central laboratory testing (see Section 7.1.1 for further details). Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patients with confirmed c-MET pathway dysregulation at pre-screening as defined by:
   - c-MET IHC intensity score 3+ in ≥50% of tumor cells
   - or c-MET IHC intensity score 2+ in ≥50% of tumor cells only if they have in addition MET gene copy number ≥5 as detected by FISH
   - or MET gene copy number ≥5 by FISH and unknown c-MET IHC results
   - or c-MET mutation can be enrolled in the study following discussion and agreement with Novartis
2. Written informed consent must be obtained prior to any screening procedures.
3. Patients aged ≥ 18 years (male or female).
4. Patients with advanced (unresectable and/or metastatic, stage C based on Barcelona-Clinic Liver Cancer (BCLC) staging classification) hepatocellular carcinoma which would not be suitable for treatment with loco-regional therapies or have progressed following locoregional therapy such as surgical resection, percutaneous hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy.

[redacted]

5. At least one tumor lesion meeting measurable disease criteria as determined by RECIST v1.1. Lesions previously treated with local therapy, such as radiation therapy, hepatic arterial embolization, radiofrequency ablation, and percutaneous interventional therapy should not be selected unless progression is noted at baseline, in which case, these lesions would be considered as non-target lesions.
6. Current cirrhotic status of Child-Pugh class A (5-6 points) (Appendix 2), with no encephalopathy. Slight ascites controlled by diuretics is permitted in this study.
7. Availability of a representative tumor tissue specimen (archival tumor tissue is allowed) at pre-screening.
8. ECOG performance status ≤ 2.
9. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Received any prior systemic chemotherapy or molecular-targeted therapy for HCC such as sorafenib.
2. Previous local therapy completed less than 4 weeks prior to the dosing and, if present any related acute toxicity > grade 1.
3. Previous treatment with a c-MET inhibitor or HGF targeting therapy.
4. Previous treatment with yttrium-90 spheres.
5. Patients with any other malignancies within the last 3 years before study start, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer.
6. History of HCC tumor rupture.
7. Patients who have signs/symptoms attributable to portal hypertension and have not been assessed with upper GI endoscopy to rule out high-risk of variceal bleeding. If varices are identified that require intervention (banding), patient will not be eligible until varices adequately treated.
8. Patients with known active bleeding (e.g. from GI ulcers, esophageal varices) within 2 months prior to baseline/screening visit or with history or evidence of inherited bleeding diathesis or coagulopathy.
9. Clinically significant (CTC grade 3 or 4) venous or arterial thrombotic disease within past 6 months.
10. A history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis.
11. Patients with known brain metastasis or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases.
12. Serious, non-healing wound, ulcer, or bone fracture.
13. History of abdominal fistula, GI perforation, or intra-abdominal abscess within past 6 months prior to study treatment.
14. Clinically significant third space fluid accumulation (i.e., ascites requiring tapping despite use of diuretic or pleural effusion that either required tapping or is associated with shortness of breath).

[redacted]

15. Patients who have undergone major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks of the start of protocol treatment
16. History of a bone marrow or solid organ transplant.
17. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable or unwilling to swallow medication, social/ psychological issues, etc.
18. Unable to undergo either contrast-enhanced magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT).
19. Known history of human immunodeficiency virus (HIV) seropositivity. HIV testing is not required as part of this study.
20. Receiving treatment with medications that are known strong inhibitors or inducers of CYP3A4, and cannot be discontinued 7 days prior to the start of INC280 treatment and during the course of the study (refer to Appendix 4).
21. Receiving treatment with medications that are known CYP3A4 or CYP1A2, substrates with narrow therapeutic index, and cannot be discontinued before start of study treatment (refer to Appendix 4).
22. Unable to stop herbal/food supplements or treatments which are considered to be capable of significantly causing either PK or PD herb/food-drug interactions. From a PK point of view, refer to Appendix 4. From a PD point of view, this definition includes any health authority approved herbal medication for HCC.
23. Have any of the following out-of-range laboratory values:
    - Hematology
        - Hemoglobin ≤ 9g/dL (SI Units: 90g/L)
        - Platelet count < 75 x 10^9/L
        - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
    - Biochemistry
        - Total bilirubin > 2 mg/dL
        - AST/SGOT and/or ALT/SGPT >5 x upper limit of normal (ULN)
        - Serum creatinine > 1.5 x ULN
        - Calculated or directly measured creatinine clearance <45 mL/min (refer to Appendix 6 for the calculation)
        - Asymptomatic serum pancreatic amylase > grade 2
        - Serum amylase grade 1 or grade 2 serum with signs and/or symptoms suggesting pancreatic or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc)
        - Serum lipase > ULN
        - Fasting serum triglyceride level >500 mg/dL
24. Patients who have received any other investigational agents within a period of time that is less than the cycle length used for that treatment or equal to 4 weeks (whichever is shorter) prior to starting study drug and recovered from any side effects to grade 1 or less.

[redacted]

25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after permanently discontinuing INC280 medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device or intrauterine system
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

[redacted]

6 Treatment

6.1 Study treatment

INC280 will be considered as the investigational treatment or the "study drug" for this study.

6.1.1 Dosing regimen

INC280 will be dosed on a flat scale of mg/day and not individually adjusted by body weight or body surface area. Hard gelatin capsules at strength of 50 mg, and film-coated tablets at dosage strengths of 50 mg and 200 mg are available. Tablets at 150 mg strength may be also provided according to local regulations when available.

During the Dose Expansion Part, the INC280 formulation may be changed from capsule to tablet upon its availability.

6.1.1.1 Instructions for administration of INC280

INC280 will be administered orally and continuously on bid dosing schedule. A treatment cycle is defined as 21 days in Dose-Determining and Dose Expansion parts.

Except on the days of full PK profiles sampling, patients should be instructed to take their dose at approximately the same time each day. The second (evening) dose should be taken 12 (±2) hours apart from first morning dose. Patients will self-administer the study medication with a glass of water at about the same time every day. Patients will consume another glass of water approximately 2 hours after dosing. INC280 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal. During fasting period, patients can freely drink water. Patients should avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice and start fruits during the treatment. On the days when PK blood samples are to be collected (Section 7.2.3), patients will be instructed to hold their dose of INC280 until arrival at the study center. The administration of study treatment will be supervised by the study personnel. The same dietary restrictions for dosing will be in place on days with PK sampling.

- If vomiting occurs, no attempt should be made to replace the vomited dose. If any episodes of vomiting occurred within the first 4 hours of INC280 dosing, on PK sampling days, exact time of vomiting should be recorded on the appropriate electronic Case Report Form (eCRF) besides the AE eCRF.
- A missed dose is defined as any time point when a patient forgets to take INC280 within 8 hours after the planned time of dosing or if a patient forgets to take his/her dose for that day. In such cases, the dose should be omitted and the patient should continue treatment with the next scheduled dose.
- On days when PK [redacted] blood samples are to be collected after Cycle 2, study drug will be administered at the site in the morning.

During the entire duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a sunlamp or tanning bed).

[redacted]

6.1.2 Treatment duration

All patients will be treated with INC280 administered orally, beginning on Cycle1 Day1. Each cycle will have 21 days. All patients will continue to receive INC280 until disease progression or unacceptable toxicity occurs, withdrawal of consent, or discontinuation for any other reason.

6.2 Dose modifications guidelines

6.2.1 Starting dose rationale

The selection of the oral dosing schedule had been discussed above Section 2.3.

6.2.2 Implementation of dose decision analysis

To implement dose determination for Dose Expansion Part, the available toxicity information (including AEs and laboratory abnormalities that are not qualifying AEs), the recommendations from the BLRM, and the available PK [redacted] information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during dose decision meeting by teleconference. Drug administration at Dose Expansion Part may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the Dose-Determining Part were evaluated and that it is permissible to proceed to the Dose Expansion Part.

For safety analysis: The tolerability of INC280 will be evaluated by the BLRM based on the incidence of qualifying adverse events during the first 28 days treatment for which relationship to study treatment cannot be ruled out (see Table 6-2 and Section 10.5.3.3 for details). The BLRM will recommend the highest dose which is estimated to be tolerable (as per the Escalation with Overdose Control (EWOC) criteria). The EWOC criteria mandate that any dose that is estimated to have 25% or more chance to be excessively toxic ($\geq$ 33% qualified AE-rate) must not be used until more data is available. At time of the analyses, BLRM will include all available safety data for INC280 from this study and external trials. See Section 10.5.3.3 for details.

For PK analysis: Mean ratio of INC280 systemic clearance will be calculated based on the data from HCC patients in the Dose-Determining Part and pooled historical data from cancer patients who had normal liver function (NCI-ODWG criteria) (Patel et al 2004). If INC280 exposure in Dose-Determining Part is comparable to the historical data, as indicated by mean ratio of the systemic clearance, Expansion Part dose will be recommended as recommended phase 2 dose (RP2D). If INC280 exposure at Dose-Determining Part dose is higher, Expansion Part dose as per PK analysis will be the RP2D proportionally reduced by the decreased mean ratio. If INC280 exposure in lead-in Dose-Determining Part is lower, Expansion Part dose as per PK analysis will be the RP2D proportionally increased by the increased mean ratio taking into consideration the toxicity and feasibility. For details of PK analysis and PK specific criteria for choosing a dose, please refer to Section 10.5.4.1.

The rules for dose recommendation for the Dose Expansion Part will be followed as listed in Table 6-1. The Expansion Part dose can be the same, lower or higher than the Dose-Determining Part dose.

[redacted]

Table 6-1 Rules for dose recommendation for the Dose Expansion Part

Consideration of both safety and PK data based on the following scenarios		Recommended Expansion Part Dose
Safety	**INC280 exposure (PK profile)**	
Tolerable	Comparable	RP2D/MTD/maximum tested dose that is determined to be safe, from dose escalation studies CINC280X1101, CINC280X2102 and/or INCB28060-101
	Increase in exposure	Proportional reduction of RP2D; if the reduced dose is lower than the Dose-Determining Part dose, use the Dose-Determining Part dose for Dose Expansion Part.
	Decrease in exposure	Proportional increase of RP2D by taking into consideration the toxicity and feasibility.
Intolerable	Comparable	Highest dose recommended by BLRM safety analysis
	Increase in exposure	The lower of the dose following recommendation from PK and safety analysis: - Proportional reduction of the Dose-Determining Part dose - Highest dose recommended by BLRM safety analysis
	Decrease in exposure	Highest dose recommended by BLRM safety analysis

6.2.3 Adverse events criteria for dose decision analysis

As mentioned in Section 4.1 and Section 10.5.3.3, a two-parameter BLRM will be used for the safety analysis. This safety analysis (to be performed during the dose decision analysis after the Dose-Determining Part as well as to confirm the Expansion Part dose) will be based on data (occurrence/ absence) of certain AEs within 28 days treatment. The qualifying AEs are defined as an adverse event or abnormal laboratory value that is assessed by the investigator as related to therapy with INC280 and unrelated to disease progression, intercurrent illness, or concomitant medications and meets any of the criteria in Table 6-2. The qualifying AEs will be considered in the safety analysis

Table 6-2 Criteria for qualifying AEs to be considered for the dose decision analysis

Toxicity	Any of the following criteria:
Hematology	Any grade 3 hematologic toxicity, lasting for > 7 consecutive days Grade 3 thrombocytopenia with bleeding Any grade 4 hematologic toxicity (of any duration) Febrile neutropenia (ANC < 1.0 x 10^9/L or 1000/mm^3 and a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour.
Renal	Serum creatinine ≥ grade 3 (≥3.0 x baseline or >3.0 - 6.0 x ULN)
Hepatic	≥ CTCAE grade 3 total bilirubin (> 3 x ULN) AST or ALT grade 3 (>5.0 -20.0 x ULN) for ≥ 7 consecutive days AST or ALT grade 4 (>20.0 x ULN) Reactivation of Hepatitis B or/and C
Pancreas	Asymptomatic ≥ CTCAE grade 3 serum amylase or lipase (>2.0 × ULN) occurring for > 14 consecutive days Symptomatic serum amylase or lipase elevation, medical intervention required
Neurologic	Any neurological abnormality or toxicity ≥ grade 2
Cardiac	≥ CTCAE grade 3

[redacted]

Toxicity	Any of the following criteria:
Other AEs	Any other AE ≥ grade 3 Grade 3 fatigue, lasting for > 7 consecutive days Grade 3 nausea, vomiting, diarrhea if in setting of optimal, anti-emetic and anti-diarrheal therapy
CTCAE version 4.03 will be used for all grading. Patients may receive supportive care (e.g. transfusion of red blood cells) as per local institutional guidelines.	

6.2.4 Dose determining for tablet formulation

A relative bioavailability study in HVs, CINC280X2103 study, was conducted to compare the relative bioavailability of INC280 tablet to INC280 capsule. The results of this study showed that following a single oral administration of 600 mg INC280 in healthy subjects, both formulations had similar Tmax; tablets however provided higher systemic exposures (Cmax and AUC) and lower inter-subject variability. The exposure geometric mean ratios (tablet vs. capsule) were around 2 to 3. As of 3-Nov-2014, preliminary tablet PK data are available from 16 patients of tablet cohorts at different doses in various INC280 studies (i.e., 200 and 400 mg bid single agent in CINC280X1101 study, 200 mg bid in combination with gefitinib in CINC280X2202 study, and 400 mg bid single agent in CINC280X2102 study). INC280 tablet showed generally lower inter-subject variability than capsule (CV% typically <50% for tablet, whereas >50% for capsule). Based on the limited data, mean AUC and Cmax at steady-state following administration of INC280 tablets at 400 mg bid was higher than that following capsules at 600 mg bid (RP2D in CINC280X2102 study), but in the range considering the CV%. Based on the tablet PK and safety data from these studies, the dosage of INC280 at 400 mg bid in tablet has been declared as RP2D in CINC280X2102 study, and is further evaluated in CINC280X1101 study and CINC280X2202 study. Therefore, 400 mg bid is determined to be the dose of tablet formulation in the dose expansion part of this study. When the INC280 tablet formulation is available, patients who are newly enrolled may start at INC280 400 mg bid tablet treatment. Patients who have been treated with INC280 600 mg bid capsules, in compliance with the local regulation, may switch at the beginning of the next scheduled visit with INC280 400 mg bid tablet treatment.

6.2.5 Dose modification and delay

For patients who do not tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03). Once a dose reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with INC280. In addition, in the Dose Determining Part, a patient must discontinue treatment with INC280 if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity. In the Dose Expansion Part, a patient must discontinue treatment with INC280 if, after treatment is resumed at the lowest allowed dose (200 mg BID, tablet), the toxicity recurs with the same or worse severity. All interruptions or modifications to study drug administration must be recorded on the Dose Administration Record eCRF.

If a dose delay of >21 days is required, then the investigational treatment with INC280 must be discontinued. Table 6-3, Table 6-4, Table 6-5, Table 6-7 and Table 6-8 provide the guidelines to be followed for dose modification of the study drug in the event of toxicities. Included are

[redacted]

also instructions for re-initiation of study treatment once sufficient recovery of toxicity is seen. **Any dosing modifications that are not in accordance with the guidelines in Table 6-3, Table 6-4, Table 6-5, Table 6-7 and Table 6-8** (Andrew et al 2010) **must be discussed with Novartis.** Any dose change to the study drug must be recorded on the eCRF. The study visit schedule should be followed irrespective of any study drug interruption.

In exceptional situations, study treatment may continue even if there is a dose interruption of >21 days or the patient experienced disease progression. The decision to allow for continuation of treatment will be made on a case-by-case basis following discussion between Novartis and the investigator. Situations that may allow for continuation of treatment include the following:

- A dose delay of >21 days has occurred but the patient is clearly benefiting from study treatment (i.e., SD, PR, or CR) and it is the investigator's opinion that no safety concerns are present.
- A patient with disease progression may be allowed to continue study treatment if it is in the best interest of the patient to continue treatment. Examples of situations that may allow for continuation of therapy include cystic lesions, mixed responses, and new brain metastases that are treatable with stereotactic radiotherapy or surgery.

Table 6-3 and Table 6-4 describe respectively for the Dose-Determining Part and Dose Expansion Part, the starting dose and the study drug dose modification to be followed in case of study drug related toxicities. For each patient in Dose Expansion Part treated with INC280 tablets, a maximum of 2 dose level modifications is allowed after which the patient must be discontinued from treatment. The lowest dose allowed, 200 mg BID in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations ([CINC280X1101], [CINC280X2202], n=6) were above the concentration associated with full cMET inhibition in xenograft mice models (EC90, 120 nM total concentration).

Table 6-3 Dose-Determining Part study drug dose reductions

Dose level	Dose and schedule (capsule)	Increment from previous dose
-1	200 mg bid	-33% of starting dose
0	300 mg bid	Starting dose for Dose-Determining Part

Table 6-4 Dose Expansion Part study drug dose reductions

Dose level	Dose and schedule (capsule)	Increment from previous dose
−1	450 mg bid (capsule)	−25% of starting dose
0	600 mg bid (capsule)	Starting dose for Expansion Part

Dose level	Dose and schedule (tablet)	Increment from previous dose
−2	200mg bid (tablet)	-50% of starting dose
−1	300 mg bid (tablet)	−25% of starting dose
0	400 mg bid (tablet)	Starting dose for Expansion Part

[redacted]

Table 6-5 Recommended dosing guidelines for study drug-related toxicities

Recommended dose modifications of INC280	
Worst toxicity CTCAE v4.03 grade	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Hematologic	
ANC decreased (Neutropenia)	
Grade 1 (LLN - 1500/mm^3 or LLN – 1.5x10^9/L)	Maintain dose level
Grade 2 (< 1500 - 1000/mm^3 or <1.5 – 1.0x10^9/L)	Maintain dose level
Grade 3 (< 1000 - 500/mm^3 or < 1.0 – 0.5x10^9/L)	Discontinue dose until resolved to ≤ grade 1 or baseline, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (< 500/mm^3 or < 0.5x10^9/L)	Discontinue dose and patient from study treatment.
Febrile neutropenia ANC < 1.0 x 10^9/L or 1000/mm^3 and a single temperature of >38.3°C (101 °F) or a sustained temperature of >=38 °C (100.4 ° F) for more than one hour.	Discontinue dose until resolved, then: If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level. If resolved in > 7 days, then discontinue dose and patient from study treatment
Platelet count decreased (Thrombocytopenia)	
Grade 1 or 2 (< LLN – 50x10^9/L)	Maintain dose level
Grade 3 (<50 – 25x10^9/L)	Discontinue dose until resolved to ≤ grade 1 or baseline, then: If resolved in ≤7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (<25x10^9/L)	Discontinue dose until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level
Renal	
Serum creatinine	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Discontinue dose until resolved to ≤ grade 1 or baseline, then maintain dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ grade 1 or baseline.
Grade 3 or 4 (> 3.0 x ULN)	Discontinue dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ grade 1 or baseline. If grade 4 event recurs at any point during participation, discontinue study treatment.

[redacted]

Recommended dose modifications of INC280	
Worst toxicity CTCAE v4.03 grade	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Hepatic	
Isolated Total Bilirubin[a]	
Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level with liver function tests (LFTs)* monitored
Grade 2 (>1.5 - 3.0 × ULN)	Omit/delay dose until resolved to ≤ grade 1 or baseline, then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit/delay dose until resolved to ≤ grade 1 or baseline, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, discontinue patient from study treatment
Grade 4 (> 10.0 x ULN)	Discontinue dose and patient from study treatment.
Isolated AST or ALT	
Grade 1 or 2 (> ULN - 5.0 x ULN)	Maintain dose level with liver function tests (LFTs)* monitored
Grade 3 (> 5.0 – 20.0 x ULN)	Omit/delay until resolved to ≤ grade 1 or ≤ grade 2 if grade 2 elevation at baseline, then: If resolved in ≤ 7 days, maintain dose level of INC280 If resolved in > 7 days, ↓ 1 dose level of INC280
Grade 4 (>20.0 x ULN)	Discontinue dose and patient from study treatment.

[redacted]

Recommended dose modifications of INC280	
Worst toxicity CTCAE v4.03 grade	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Combined[b] elevations of AST or ALT, and Total Bilirubin	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[c] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN] combined with [total bilirubin >2x baseline AND >2.0 xULN	Discontinue study treatment permanently. Repeat LFTs as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs*, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.2.6 for additional follow-up evaluations as applicable.
Reactivation of HBV or HCV	Please refer to Table 6-7, Table 6-8.
*LFTs include albumin, ALT, AST, GGT, total bilirubin (fractionated [direct and indirect] if total bilirubin > 2.0 x ULN) and ALP (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN). Refer to Section 6.2.6 for additional follow-up evaluations.	
Pancreatic[d]	
Asymptomatic grade 1 or 2 amylase or lipase increased (>ULN – 2.0 x ULN) Asymptomatic grade 3 or greater amylase or lipase increased (> 2.0 - > 5.0 x ULN)	Maintain dose level Omit/delay dose until resolved to ≤ G2, then: If resolved in ≤ 7 days, maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Asymptomatic grade 4 (> 5.0 x ULN)	Discontinue does and patient form study treatment
Symptomatic elevations of any grade	Discontinue does and patient form study treatment

[redacted]

Recommended dose modifications of INC280	
Worst toxicity CTCAE v4.03 grade	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Neurologic	
Any Neurological Toxicity Grade 2	 Discontinue study treatment. Neurological assessments must be repeated at least twice a week until resolution to < CTCAE grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may be performed to monitor for physiological changes in brain activity.
Cardiac	
Cardiac general Grade 1 or 2 Grade 3 Grade 4	 Maintain dose level Discontinue dose until resolved to ≤ grade 1, then ↓ 1 dose level Discontinue dose and patient from study treatment
ILD / pneumonitis	
Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold INC280 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt INC280 during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue INC280. Only in the absence of a diagnosis of ILD/Pneumonitis, INC280 may be restarted at the same dose. If it recurs after resumption of study drug, permanently discontinue INC280.

[redacted]

Recommended dose modifications of INC280	
Worst toxicity CTCAE v4.03 grade	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing**
Grade 2	Mandatory: Interrupt INC280 dose during diagnostic workup for ILD/pneumonitis until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue INC280. Only in the absence of a diagnosis of ILD/Pneumonitis, INC280 may be restarted following these guidelines: · If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level · If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue INC280.
Grade 3 and Grade 4	Mandatory: Permanently discontinue INC280. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Discontinue study treatment
[a] If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level of INC280, and continue treatment at the discretion of the Investigator [b] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction [c] "Cholestasis" defined as: ALP elevation (>2xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note : The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R≤2), hepatocellular (R≥5), or mixed (R>2 and <5) liver injury [d] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase or lipase.	

[redacted]

Table 6-6 Follow-up evaluations for selected toxicities

Toxicity	Follow-up evaluation
Hematology	If febrile neutropenia of any duration occurs, the patient must be followed until resolution. If ≥ CTCAE grade 3 hematologic toxicity occurs, the parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 and then at least weekly until either initiation of retreatment or until stabilization.
Renal	If serum creatinine ≥ CTCAE grade 2 has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline, and then at least weekly until either initiation of re-treatment or until stabilization. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
Hepatic	In case of isolated elevations in total bilirubin, AST or ALT, additional follow-up evaluations are recommended as outlined in Table 6-9.
Pancreatic	If serum amylase or serum lipase ≥ CTCAE grade 3, follow until resolution to grade 2 or less.
Neurologic	If any neurological abnormality or toxicity ≥ grade 2 has been demonstrated, neurological assessments must be repeated at least twice a week until resolution to ≤ CTCAE grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may also be performed to monitor for physiological changes in brain activity.
Cardiac	Monitor toxicity until resolution to grade 1 or baseline. If applicable, monitor electrocardiograms (ECGs) twice weekly until normalization or stabilization.
Non-laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, until stabilization of the toxicity, or until study completion.

[redacted]

Table 6-7 Guidelines for the management of hepatitis B reactivation

HBV-DNA OR HBsAg in baseline result	Definition of reactivation	Treatment
+	Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value	Provide antivirus treatment * AND Interrupt study drug administration until: ≤ baseline HBV-DNA levels If resolution occurs within ≤ 21 days, study drug should be restarted at one dose lower, if available (see Table 6-2 and Table 6-3 for dose level available). If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. If resolution occurs >21 days, patients should discontinue study drug but continue antiviral therapies at least 4 weeks after last dose of study drug.
-/ HBsAb (+) (with no prior history of vaccination against HBV or HBcAb(+)	New appearance of measurable HBV-DNA	Provide antivirus treatment* AND Interrupt study drug administration until resolution: ≤ undetectable (negative) HBV-DNA levels If resolution occurs within ≤ 21 days, study drug should be restarted at one dose lower, if available (see Table 6-2 and Table 6-3 for dose level available). If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. If resolution occurs >21 days, patients should discontinue study drug but continue antiviral therapies at least 4 weeks after last dose of study drug.

*Antivirus treatment will be provided under discretion of investigator according to local clinical practice.

All reactivations of HBV are to be recorded as grade 3 (CTCAE version 4.03 Infections and infestations/Hepatitis viral), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA criteria was recorded.

Table 6-8 Guidelines for the management of hepatitis C reactivation

HCV Reactivation*	
For patients with baseline results : Detectable HCV – RNA Reactivation is defined as : ALT elevation to > 5x ULN Increase of 1 log in HCV-RNA relative to baseline HCV-RNA value	Discontinue INC280
For patients with baseline results : Knowledge of past hepatitis C infection with no detectable HCV – RNA Reactivation is defined as : New appearance of detectable HCV – RNA	Discontinue INC280

* All reactivations of HCV are to be recorded as grade 3 (CTCAE Version 4.03 - Infections and infestations/Hepatitis viral), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HCV-RNA (and ALT) criteria was recorded.

[redacted]

6.2.6 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All patients must be followed up for AEs and SAE for 30 days following the last doses of INC280.

Table 6-9 Follow-up evaluations for Hepatic Toxicities*

Toxicity	Follow-up evaluation
Isolated total bilirubin elevation	
CTCAE Grade 1	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 2	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN
CTCAE Grade 3	Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN. If resolved in > 7 days, after discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
CTCAE Grade 4	After discontinuing the patient from INC280 permanently, the patient should be monitored weekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 week
Isolated AST/ALT elevation	
CTCAE Grade 2 For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN	Monitor LFTs per protocol or more frequently if clinically indicated
CTCAE Grade 3 -For elevation > 5.0 - 10.0 x ULN: For patients with baseline value ≤ 3.0 x ULN	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
For patients with baseline value > 3.0 - 5.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
CTCAE Grade 3 For AST/ALT elevation > 10.0 - 20.0 x ULN:	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to ≤ baseline
CTCAE Grade 4	Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	

Toxicity	Follow-up evaluation
Combined elevations of AST or ALT and total bilirubin	After discontinuing the patient from INC280 permanently, repeat core LFTs as soon as possible, preferably within 48 hr from awareness of the abnormal results, then with weekly monitoring of LFTs, or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)
*Note: this table refers only to the evaluation schedule to monitor hepatic toxicities. Refer to Table 6-5 for dose modifications required for applicable toxicities.	

6.2.6.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g., biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.

[redacted]

- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

6.2.7 Anticipated risks and safety concerns of the study drug

Based upon the preclinical data set for INC280, the clinical experience from the three ongoing INC280 single agent studies, the overall risk-benefit assessment of INC280 is considered favorable. The AEs that have been reported, irrespective of relationship to study drug, have been manageable and generally mild or moderate in severity. As of the cut-off date of August 15, 2012, there have been no SAEs or fatal events with a suspected causal relationship with INC280. For further information, please refer to the current version of the [Investigator's Brochure].

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

Patients are permitted to use the following medications while taking INC280:

- Antivirus medications to manage HBV or HCV infection and/or prevent reactivation (e.g. lamivudine); supportive care.
- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea.
- Growth factors for low hemoglobin levels (should only be used if hemoglobin is less than 10g/dL and the patient is symptomatic).
- Pain medication to allow the patient to be as comfortable as possible.
- Localized radiotherapy and treatment with bisphosphonates for pre-existing, painful bone metastases is permitted only if evidence of radiological progression is not present.
- Nutritional support or appetite stimulants (e.g. megestrol).
- Oxygen therapy and blood products or transfusions.

6.3.2 Permitted concomitant therapy requiring caution and/or action

Medications, herbal remedies and food products that are moderate inducers or inhibitors of CYP3A4 are not prohibited but should be administered with caution.

The following medications should be used with caution when concomitantly used with INC280 treatment in this study:

- **Strong CYP3A inhibitors:** Coadministration of INC280 with a strong CYP3A inhibitor (itraconazole) increased INC280 AUC_{inf} by 42%. There was no change in INC280 C_{max}.

[redacted]

Closely monitor patients for adverse reactions during coadministration of INC280 with strong CYP3A inhibitors.

- **Moderate CYP3A inducers:** Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of INC280 with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in INC280 $AUC_{0\text{-}12h}$ and 34% decrease in C_{max} at steady-state compared to administration of INC280 alone. Caution should be exercised during concomitant use of INC280 with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during coadministration with INC280.
- **CYP1A2 substrates with narrow therapeutic index (NTI):** INC280 is a moderate CYP1A2 inhibitor. Coadministration of INC280 increased sensitive CYP1A2 probe substrate (caffeine) AUCinf by 134%. Avoid coadministration of INC280 with CYP1A2 substrateswhere minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- **P-gp and BCRP substrates:** Coadminstration of INC280 increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively). Avoid coadministration of INC280 with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- **Proton pump inhibitor :** Coadministration of INC280 with proton pump inhibitor (rabeprazole) decreased INC280 AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of INC280 with proton pump inhibitors.

H_2-receptor antagonists and antacids: As an alternative to proton pump inhibitors, H_2-receptor antagonist or antacid can be taken. INC280 should be administered at least 3 hours before or 6 hours after an H_2-receptor antagonist. INC280 should be administered at least 2 hours before or 2 hours after an antacid.

Refer to Appendix 4 for a list of the medications that require caution when concomitantly used with INC280.

6.3.3 Prohibited concomitant therapy

INC280 is moderately metabolized by CYP3A4 *in vitro*. Strong inhibitors or inducers of CYP3A4/5 (including medications, herbal remedies and food products) shall be discontinued 7 days prior to the start of INC280 treatment and are prohibited during the course of the study. INC280 is an irreversible inhibitor of CYP1A2 and CYP3A4/5. All agents that are metabolized mainly by CYP1A2 or CYP3A4/5 and have a narrow therapeutic window are prohibited during this study.

Therapeutics or supplements with herbal-origination for the purpose of hepatic protection or supportive care of liver diseases, which are particularly considered as common practices in Asia, are also prohibited during the INC280 treatment.

[redacted]

The use of live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, TY21a typhoid vaccines) is not allowed during the study and up to 30 days from the last dose of INC280 treatment.

The prohibited medications are listed in Appendix 4.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the first informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator.

6.4.2 Treatment assignment

The assignment of a patient to a particular treatment will be coordinated by the sponsor.

This is an open-label, non-randomized, single arm, multicenter study.

6.4.3 Treatment blinding

This is an open label study.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.5.1 Study drug packaging and labeling

The study medication packaging has a two-part label. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and batch number but no information about the patient.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated

[redacted]

site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

In case that unexpected circumstances interfere with the patient's compliance and/or protocol procedures, the visits can be rescheduled within a ±3-day window except for Day 1 of Cycle 1 unless otherwise specified in any other section of this protocol. There is -1 day window for all evaluations scheduled on Cycle 1 Day 1 except for the PK sampling.

No CRF will be used as a source document.

Following approval by Authorities of protocol amendment 5, the ongoing patients will follow a reduced schedule of safety and efficacy assessments as detailed in Table 7-2. The assessments in Table 7-1 will no longer be applicable. The table indicates which assessments produce data

to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Other assessments may be performed at the Investigator's discretion following standard of care at the site.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1				Cycle 2		≥Cycle 3	End of treatment (EOT)	Follow-up (FU)		
													Disease progression	30-day follow-up	Survival Every 3 Weeks
Day of cycle(D)				**-14 to -1**	**1**	**2**	**15**	**16**	**1**	**8**	**1**				
Obtain molecular pre-screening informed consent	D	7.1.1.1	X												
c-MET screening on fresh or archival tumor biopsy	D	7.1.1.2	X												
Obtain Informed Consent	D	7.1.2		X											
Patient history															
Demography	D	7.1.2.3	X	X											
Inclusion/ exclusion criteria	D	5.2 & 5.3		X											
Relevant medical history/current medical conditions, etiology of HCC	D	7.1.2.3		X											
Diagnosis, extent and stage of HCC	D	7.1.2.3		X											
Child-Pugh and BCLC classification	D	7.1.2.3		X											
Prior antineoplastic therapy	D	7.1.2.3		X											
Physical examination	S	7.2.2.1		X	X		X		X	X	X	X			
Vital signs	D	7.2.2.2		X	X		X		X	X	X	X			
Weight / Height	D	7.2.2.3		X	X				X		X	X			

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1				Cycle 2		≥Cycle 3	End of treatment (EOT)	Follow-up (FU)		
													Disease progression	30-day follow-up	Survival Every 3 Weeks
Day of cycle(D)				**-14 to -1**	**1**	**2**	**15**	**16**	**1**	**8**	**1**				
ECOG performance status	D	7.2.2.4.		X	X				X		X	X			
Hematology	D	7.2.2.5.1		X	X		X		X	X	X	X			
Biochemistry	D	7.2.2.5.2		X	X		X		X	X	X	X			
Urinalysis	D	7.2.2.5.3		X								X			
Coagulation	D	7.2.2.5.4		X	X		X				X	X			
Hepatitis markers	D	7.2.2.5.5		X					X		X	X			
Serum Pregnancy	D	7.2.2.5.6		X								X			
Urinary Pregnancy	D	7.2.2.5.6							X		X				
[redacted]															
Tumor Response Assessment per RECIST– i.e., CT/MRI	D	7.2.1		X(-21 to -1)					X		X (every other cycle starting C4D1)	X	X (every 6 weeks)		
12-lead ECG	D	7.2.2.6		X	X				X		X (Cycle 3 only)	X			
Blood for PK Profile – Dose-Determining Part		7.2.3.1			X	X	X	X	X		X (Cycle 3 only)				
Blood for PK Profile – Dose Expansion Part	D	7.2.3.1			X		X		X		X (Cycle 3 only)				
[redacted]															

[redacted]

	Category	Protocol Section	Molecular pre-screening	Screening	Cycle 1				Cycle 2		≥Cycle 3	End of treatment (EOT)	Follow-up (FU)		
													Disease progression	30-day follow-up	Survival Every 3 Weeks
Day of cycle(D)				**-14 to -1**	**1**	**2**	**15**	**16**	**1**	**8**	**1**				
[redacted]															
Antineoplastic therapy after discontinuation of study drug	D	7.1.5											X	X	
Study Drug Administration	D	7.1.3			Twice Daily										
AEs	D	8	X	X	Continuous									X	
Prior/concomitant medications	D	6.3		X	Continuous									X	
Survival contact	D	7.1.5													X

[redacted]

Table 7-2 Visit evaluation schedule (applicable upon local IRB/EC approval of protocol amendment 5)

	Category	≥Cycle 3 (every 12 weeks)	End of treatment (EOT)	Follow-up (FU)		
				Disease progression	30-day follow-up	Survival (every 12 Weeks)
Day of cycle(D)		1				
Physical examination	S	X	X			
Hematology	D	X	X			
Biochemistry*	D	X	X			
Coagulation	D	X	X			
Hepatitis markers	D	X	X			
[redacted]						
Tumor Response Assessment per RECIST–i.e., CT/MRI	D	X	X	X (every 12 weeks)		
Antineoplastic therapy after discontinuation of study drug	D			X	X	
Study Drug Administration	D	Twice Daily				
AEs	D	X			X	
Concomitant medications	D	X			X	
Survival contact	D					X

* Albumin, ALP, ALT (SGPT), AST (SGOT), amylase, creatinine, lipase, total bilirubin, direct bilirubin are mandatory for each visit. The additional parameters may be measured at the discretion of the investigator.

7.1.1 Molecular pre-screening

7.1.1.1 Molecular pre-screening informed consent

Molecular pre-screening consent must be obtained from all patients to permit the collection, shipment and testing of archival or fresh tumor sample prior to the planned clinical screening.

7.1.1.2 c-MET pre-screening on fresh or archival biopsy

To be eligible to participate in this study, evidence of c-MET pathway dysregulation in HCC patients must be available. Tumor biopsy samples (archival or fresh tumor samples) must be submitted to a Novartis designated central laboratory for molecular pre-screening.

Please refer to Section 7.2.4.1 for the collection of tumor samples.

[redacted]

7.1.1.3 Eligibility for clinical screening

When the patient is considered eligible for clinical screening, the investigator or designee should complete the Patient Registration Form and send it to Novartis.

7.1.2 Screening

The clinical screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of study entry. Screening assessments have to be done within 14 days prior to the first dose of INC280. Patients' demographics and other characteristics data to be collected include: general demography, relevant medical history/current medical conditions, diagnosis of HCC, extent of cancer (using BCLC staging classification-Appendix 3) for study eligibility evaluation, and prior antineoplastic therapies (medication, radiation and surgery), CPC (Appendix 2), physical examination, height and weight, vital signs, ECOG performance status, cardiac assessment, safety laboratory assessments including hematology, biochemistry, coagulation and pregnancy tests. Other assessments will include the special laboratory assessments such as hepatitis markers. Clinical and radiological tumor assessment by RECIST (Appendix 1) should be conducted preferably within 1 week (7 days) prior to the first dose of the study drug; however tumor assessments up to 3 weeks (21 days) prior to the first dose will be acceptable. During screening, the disease must be staged. The tumor assessment made during the screening phase will provide the baseline tumor measurements, which will be used to determine future responses and/or progression. A complete list of screening evaluations is provided in the visit of assessments table (Table 7-1).

7.1.2.1 Eligibility screening

When the patient is considered eligible for study treatment, then the investigator or designee should complete the Patient Registration Form.

7.1.2.2 Information to be collected on screening failures

Patient who signed an Informed Consent Form but failed to begin taking INC280 for any reason will be considered a screen failure. Patients who signed a molecular pre-screening ICF but who did not meet the molecular pre-screening criteria, and those patients who did not meet screening eligibility criteria will be considered as screening failures. The data from all screening failure will be handled in the same manner.

The molecular pre-screening failure or screening failure information will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported (i.e., SAEs that are assessed as not related will not be reported).

[redacted]

7.1.2.3 Patient demographics and other baseline characteristics

Data collected will include general patient demographics, relevant medical history and current medical confirmations, diagnosis and extent of tumor (BCLC staging classification), CPC and details of prior and current anti-neoplastic treatments.

7.1.3 Treatment period

INC280 will be dosed continuously on 21-day (3 calendar weeks) cycles beginning on Day 1 of cycle 1. A treatment cycle is defined as 21 days (3 calendar weeks) for the purposes of scheduling procedures and evaluations. There will be no scheduled break between cycles.

Cycles begin on Day 1 of Cycle 1. Visits will occur on Days 1, 2, 15, and 16 of Cycles 1. Days 1 and 8 of Cycles 2. Beginning with Cycle 3 Day 1, scheduled visits will occur every 21 days.

Patients will be treated until one of the following criteria is met:

- Documented disease progression according to RECIST (Appendix 1)
- Unacceptable/intolerable toxicity
- Death or discontinuation from study treatment for any other reason as described in Section 7.1.4.1 and Section 4.3.

Safety and efficacy monitoring should continue as per visit schedule (see Table 7-1 and Table 7-2). Dose adjustments of study drug (reduction, interruption or) according to safety findings will be allowed. Tumor assessments will be performed at screening, C2D1(±7 days), then on Day 1 (±7 days) of every other cycle after C2D1 until disease progression. PR and Complete Response (CR) should be confirmed at the next scheduled tumor assessment (and no sooner than 4 weeks after the initial response).

7.1.4 End of treatment visit including study completion and premature withdrawal

An EOT visit should be conducted within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study drug. If the patient discontinues from the study at a scheduled visit, the EOT assessment can be performed on that day. An End of Treatment Phase Completion eCRF page should be completed to include the date and reason for discontinuing INC280.

If the patient experiences INC280 dose delay >21 days (refer to Section 6.2.5 for exceptional situations), the EOT assessment should be performed within 30 days of the last dose of INC280.

7.1.4.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be withdrawn from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- AE(s)
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision

[redacted]

- Pregnancy
- Progressive Disease (refer to Section 6.2.5 for exceptional situations)
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Patient/guardian decision
- Death

Patients who transfer into another study or an alternative way to continue provision of study treatment will perform the end of treatment procedures.

7.1.4.2 Replacement policy

Dose-Determining Part :

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of new patients may be considered until at least the minimum number of 6 evaluable patients is achieved within the Dose-Determining Part.

Dose Expansion Part:

During the Dose Expansion Part, no replacements will be needed.

7.1.5 Follow up period

30-day follow up

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such in the source documents. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Disease progression follow up

Any patient who discontinues from INC280 for any reason (except for death, disease progression, lost to follow-up, or study termination) will continue to have tumor assessments performed every 6 weeks in the follow-up period until disease progression or start of new anticancer therapy. Patients who withdraw consent to take study treatment but still agree to be followed will continue to have all protocol-specific procedures.

Survival follow up

Upon completion of the 30-day follow up or disease progression follow up, all patients, except those who died, withdrew consent for follow-up as a result of patient decision or were lost of follow-up, will be followed for survival every 3 weeks until death or at least 6 months after last patient first dose.

[redacted]

For patients who transfer to another clinical study or an alternative way to continue provision of study treatment, as described in Section 4.3, the follow-up for safety, disease progression and survival will not be performed.

7.2 Assessment types

7.2.1 Efficacy assessments

Evidence of clinical efficacy will be evaluated based on radiographic tumor assessments. Tumor response will be evaluated using RECIST version 1.1. (See Appendix 1 for complete details) including the additional modifications described later in this section.

Tumor assessments are required for screening purposes to determine baseline disease at study entry. Both measurable and non-measurable lesions must be assessed and target lesions identified at the baseline visit. Scans performed within 21 days of treatment start can be used as the baseline assessments.

Schedule of tumor assessments

The scheduled tumor assessments are as follows:

- At screening (preferably 7 days prior to 1st dose, however, scans within 21 days of 1st dose are acceptable).
- Day 1 (± 7 days) of every other cycle starting from C2D1, (i.e C2D1, C4D1, C6D1, etc).
- At the EOT if a scan was not conducted within 30 days prior to EOT.

Tumor assessments at baseline/screening

The following tumor assessments are to be performed at baseline/screening:

- Chest, abdomen and pelvis CT or MRI scan, including dual-phase imaging of the entire liver
- Brain CT or MRI scan (only if clinically indicated to exclude CNS metastases)
- If bone metastases are suspected, a whole body bone scan (e.g., Tc99m bone scan, NaF positron emission tomography (PET) or whole body bone MRI). Any skeletal lesions identified on the bone scan at baseline that are not visible on the chest, abdomen and pelvis CT or MRI scan, should be imaged with localized CT, MRI or x-ray at baseline.
- Color photography if skin lesions are present (it is recommended to include a ruler to estimate the size of the lesion).

Tumor assessments after baseline/screening

The following tumor assessments are to be performed after baseline/screening:

- Chest, abdomen (including dual-phase imaging of the entire liver), pelvis CT or MRI scan
- Any skeletal lesions identified at baseline that are not visible on the chest and/or abdomen and/or pelvis CT or MRI scan, should be imaged with localized CT, MRI or x-ray at subsequent visits. Whole body bone scans need not be repeated after baseline unless clinically indicated

[redacted]

- Color photography if skin lesions were identified at baseline (it is recommended to include a ruler to estimate the size of the lesion).
- Additional tumor assessments may be performed if there is symptomatic evidence suggesting the possibility of disease progression based on clinical symptoms or physical exam.

PR and CR should be confirmed at the next scheduled tumor assessment (and no sooner than 4 weeks later).

Chest x-ray or ultrasound should not be used for tumor response assessments in this study.

All patients discontinuing from the study for PD must have their disease progression documented by radiologic evaluation. In cases of clinically-evident disease progression, all efforts should be made to perform a radiologic evaluation.

Methods of tumor assessments

All scans should be performed with intravenous (i.v.) contrast administration. If a patient cannot tolerate i.v. contrast for either CT or MRI at baseline, the patient may not participate in the study. If a patient develops a contraindication to CT i.v. contrast during the study, MRI (preferably with i.v. contrast if tolerated) may be performed instead. CT without i.v. contrast is not recommended unless MRI cannot be performed.

The same method of assessment and the same technique should be used throughout the study to characterize each identified and reported lesion at baseline and during follow-up.

It is mandatory to obtain dual-phase imaging of the liver throughout the study (if there is liver involvement at baseline). Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. The timing of the contrast administration should also be kept consistent across timepoints for a patient.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media and provided acquisition of a dual-phase CT scan, as previously described.

Reporting and recording of tumor assessments

Each center should have a designated radiologist responsible for the interpretation of scans and the response evaluation according to RECIST 1.1 (Appendix 1). Preferably, a single radiologist should perform all evaluations for an individual patient.

Tumor assessments will be recorded in the eCRF RECIST pages.

All patients should have at least one measurable lesion on contrast enhanced CT or contrast enhanced MRI per RECIST 1.1(Appendix 1).

Tumor assessments during follow-up

If study drug discontinuation is not due to disease progression, death, lost to follow-up, or starting a new cancer therapy, patients will continue to have tumor assessments every 6 weeks

[redacted]

(±7 days), until the patient has documented disease progression, begins a new cancer therapy (if started before disease progression was documented) or until the completion of study evaluation for any other reason. Tumor assessments during the follow-up phase should be scheduled from the last scans.

Central assessment

In addition to local radiological assessments, Novartis may collect imaging data for storage and possible future central review by a Novartis designated central imaging contract research organization (CRO). The radiologist performing the reading at the central imaging CRO would remain blinded to the results of the local assessment and to the treatment the patient has received. Investigator sites may be requested to submit results of any cytological evaluations performed during the study (e.g., to investigate ascites or pleural/pericardial effusions) along with the radiological studies to the central imaging CRO. Additionally, the central imaging CRO may collect information regarding baseline conditions like prior loco-regional therapies (e.g., surgical resection, percutaneous hepatic arterial embolization, radiofrequency ablation, percutaneous interventional therapy, etc.) directly from the sites to be made available to the central reader.

7.2.2 Safety and tolerability assessments

Safety will be monitored using the following assessments: safety labs, 12-lead ECG, physical examination, vital sign, height and weight, ECOG performance status, laboratory evaluations, liver function assessment, [redacted] HBV and HCV testing. In addition, AEs and concomitant medications will also be collected at every visit. For details on AE collection and reporting, refer to Section 8.

All safety assessments performed on Cycle 1 Day 1 pre-dose will provide the baseline safety assessments. For safety assessments not carried out on Cycle 1 Day 1 prior to dosing, screening assessment will be used as baseline.

Following approval of protocol amendment 5, assessments for vital signs, height and weight, performance status are not required by the protocol.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the patient´s health status until it is safe for the patient to visit the site again.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological assessments.

A complete physical examination must be performed:

- Screening
- Cycle 1 Day 1 pre-dose
- Day 15 of Cycle 1

[redacted]

- Day 1 and 8 of Cycle 2
- Day 1 of Cycle 3 and subsequent cycles
- EOT

Information about the physical examination must be present in source documentation at the study site.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (blood pressure, pulse and body temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection. Vital signs are usually taken with the physical examination but may be taken within a window period of ± 72 hours from the physical examination.

Vital signs will be performed at:

- Screening
- Cycle 1 Day 1 pre-dose
- Day 15 of Cycle 1 (blood pressure and pulse only)
- Cycle 2 Day 1
- Day 8 of Cycle 2 (blood pressure and pulse only)
- Day 1 of Cycle 3 and subsequent cycles
- EOT

Additional results from vital sign evaluations should be recorded on the appropriate Unscheduled visit eCRF page.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured and recorded at the screening visit only.

Body weight (to the nearest 0.1 kilogram) will be measured in indoor clothing and without shoes; weight will be measured and recorded:

- Screening
- Day 1 of all cycles (before first dose on Cycle 1 Day 1)
- EOT

Additional results from weight evaluations should be recorded on the appropriate unscheduled visit eCRF page.

[redacted]

7.2.2.4 Performance status

ECOG performance status will be documented at:

- Screening
- Day 1 of all cycles (before first dose on Cycle 1 Day 1)
- EOT

Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is being held.

Table 7-3 ECOG Performance status

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

7.2.2.5 Laboratory evaluations

The local site laboratory will be used for the following standard clinical laboratory assessments: hematology, chemistry, coagulation, urinalysis and serum pregnancy test. All analyses for these tests will be performed locally and the results will be based on local laboratory normal ranges. Creatinine clearance will be calculated using Cockcroft-Gault formulation for Glomerular Filtration Rate (GFR) estimation (Appendix 6).

Table 7-4 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Complete blood count, including total White blood cells (WBC) with differentials (neutrophil count), hemoglobin (Hb), hematocrit, platelet count.
Chemistry	Albumin, ALP, ALT (SGPT), AST (SGOT), Amylase, Bicarbonate, Calcium, Chloride, Creatinine, glucose, lipase, inorganic phosphorus, magnesium, potassium, sodium, Direct Bilirubin, Total Bilirubin, Total Cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid.
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel (Red Blood Cells, WBC, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR)
Hepatitis markers	HBV-DNA, HBsAg, HBcAb, HBsAb, HCV RNA-PCR
Tests for hepatotoxicity follow-up (if clinically indicated for INC280)	LFTs: albumin, ALT, AST, GGT, total bilirubin, direct and indirect bilirubin, ALP, ALP fractionated (quantification of isoforms) Creatine kinase, prothrombin time (PT)/INR Testing for acute hepatitis A, B, C or E infection, other hepatotropic viral infection and autoimmune hepatitis as clinically indicated (refer to Section 6.2.6.1)
[redacted]	[redacted]

[redacted]

7.2.2.5.1 Hematology

Hematological tests will be performed at:

- Screening
- Cycle 1 Day 1, before first dose, unless screening samples were collected within 72 hours prior to the Cycle 1 Day 1 visit.
- Day 15 of Cycle 1
- Days 1 and 8 of Cycle 2
- Day 1 of Cycle 3 and subsequent cycles
- EOT

More frequent hematology testing may also be performed as medically necessary. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate Unscheduled Visit eCRF.

In the event of ≥ grade 3 hematological toxicities that require study drug dose modifications or interruptions, hematological tests must be repeated until recovery to the baseline value or ≤ grade 1.

7.2.2.5.2 Clinical chemistry

Clinical chemistry will be performed at:

- Screening
- Cycle 1 Day 1, before first dose, unless screening samples were collected within 72 hours prior to the Cycle 1 Day 1 visit
- Day 15 of Cycle 1
- Day 1 and 8 of Cycle 2
- Day 1 of Cycle 3 and subsequent cycles
- EOT

More frequent clinical chemistry testing may also be performed as medically necessary. Additional results from unscheduled clinical chemistry lab evaluations should be recorded on the appropriate Unscheduled Visit eCRF.

In the event of ≥ grade 3 clinical chemistry toxicities that require study drug dose modifications or interruptions, clinical chemistry tests must be repeated until recovery to the baseline value or ≤ grade 1 (refer to Table 6-5)

7.2.2.5.3 Urinalysis

Urinalysis will be performed at screening and EOT visit.

Microscopic urinalysis will be performed only if macroscopic urinalysis result is abnormal.

7.2.2.5.4 Coagulation

The same coagulation test (PT or INR) will be used at each time point where the evaluation is conducted.

[redacted]

A coagulation profile must be performed:

- Screening
- Cycle 1 Day 1, before first dose, unless screening samples were collected within 72 hours prior to the Cycle 1 Day 1 visit
- Day15 of Cycle 1
- Day 1 of Cycle 3 and subsequent cycles
- EOT

7.2.2.5.5 Hepatitis markers assessments

During the screening period, all patients must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

Hepatitis B:

At screening, all patients will be tested for:

- HBV-DNA level
- Hepatitis B surface antigen (HBsAg)
- Hepatitis B core antibody (HBcAb)
- Hepatitis B surface antibody (HBsAb)

Monitoring for HBV –DNA on Day 1 of every cycle from Cycle 2 and EOT is required for:

- Patients known to have a history of HBV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)
- Patients positive for viral load on HBV DNA-PCR test at screening.
- Patients positive for any of the serology at screening.

Hepatitis C:

All patients will be tested for quantitative HCV RNA-PCR at the screening visit.

Monitoring for HCV RNA-PCR levels of Day 1 of every cycle from Cycle 2 and EOT is required for:

- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)
- Patients positive for viral load on HCV RNA-PCR test at screening.

7.2.2.5.6 Pregnancy and assessments of fertility

All females of childbearing potential should have a serum pregnancy test (hCG) performed ≤ 72 hours prior to the first administration of INC280 and at EOT visit.

In addition, a urinary pregnancy test should be completed Day 1 at Cycle 2 and on Day 1 of subsequent cycles.

[redacted]

Women who are of non-childbearing potential do not require a pregnancy test, but must fulfill the conditions for the non-childbearing status given in Section 5.3.

Please refer to Section 8.4 for information on reporting any pregnancies that occur while the patient is on study.

[redacted]

7.2.2.6 Cardiac assessments

12-lead ECGs will be performed in triplicate, separated by 1 minute. ECGs will be transmitted to a central laboratory and reviewed by an independent reviewer. Any original ECG not transmitted to a central laboratory will be forwarded for central review. At screening, ECGs will be performed locally. ECGs will be performed at the following timepoints:

Local laboratory

- Screening

Central laboratory

- Cycle 1 Day 1 pre-morning dose and at 2 hours post-morning dose
- Cycle 2 Day 1 pre-morning dose and at 2 hours post-morning dose
- Cycle 3 Day 1 pre-morning dose and at 2 hours post-morning dose
- EOT
- As clinically indicated

For local laboratory, interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

Following local IRB/EC approval of protocol amendment 5, no cardiac assessments are required by the protocol.

7.2.3 Pharmacokinetics

During the Dose-Determining Part, full PK blood samples of INC280 will be collected on Days 1, 2, 15 and 16 of Cycle 1 and trough concentrations will be collected on Cycle 2, Day 1 and Cycle 3, Day 1 (Table 7-5). The rationale to collect full PK profiles during Cycle 1 is to closely monitor potentially increased exposure of INC280 in HCC patients who usually have impaired liver function.

[redacted]

During the Dose Expansion Part of the study, sparse PK samples will be collected for all patients based on a sparse "window" sampling scheme on Cycle 1, Days 1 and 15. In addition, blood samples of pre-morning dose and at 2 hours post-morning dose will be collected on Cycle 2 Day 1 and Cycle 3 Day1 to match central triplicate ECG collection for potential exposure-QT analysis (Table 7-6).

For Dose-Determining Part and Dose Expansion Part, an additional PK sample will be taken with post treatment tumor biopsy (within 30 min after tumor biopsy completion).

Following approval of protocol amendment 5, no pharmacokinetic assessments are required by the protocol.

[redacted]

7.2.3.1 Pharmacokinetic blood collection and handling

Table 7-5 Timepoints of blood collection for PK assessment during Dose-Determining Part

PK sample No	Cycle	Day	Scheduled time relative to dosing	Description	Dose Reference ID	Blood volume
1	1	1	0 h [a]	Pre-dose	1	3 mL
2			0.5 h (± 5 min)	Post-dose	1	3 mL
3			1 h (± 10 min)	Post-dose	1	3 mL
4			2 h (± 15 min)	Post-dose	1	3 mL
5			4 h (± 20 min)	Post-dose	1	3 mL
6			6 h (± 30 min)	Post-dose	1	3 mL
7			8 h (± 30 min)	Post-dose	1	3 mL
8		2	0 h [a]	Sample will be collected prior to the morning dose of Cycle 1 Day 2	2/3002[d]	3 mL
9		15	0 h [a]	Sample will be collected prior to the morning dose of Cycle 1Day 15	3/3003[d]	3 mL
10			0.5 h (± 5 min)	Post-dose	3	3 mL
11			1 h (± 10 min)	Post-dose	3	3 mL
12			2 h (± 15 min)	Post-dose	3	3 mL
13			4 h (± 20 min)	Post-dose	3	3 mL
14			6 h (± 30 min)	Post-dose	3	3 mL
15			8 h (± 30 min)	Post-dose	3	3 mL
16		16	0 h [a]	Sample will be collected prior to the morning dose of Cycle 1 Day 16	4/3004[d]	3 mL
17	2	1	0 h [a]	Sample will be collected prior to the morning dose of Cycle 2 Day 1	5/3005[d]	3 mL
18	3	1	0 h [a]	Sample will be collected prior to the morning dose of Cycle 3 Day 1	6/3006[d]	3 mL
Total volume						54 mL
2001+ [b]	Unscheduled			Unspecified	NA	3 mL
1001	1	Coinciding with tumor biopsy [c]			NA	3 mL

All measurement times are relative to dose of INC280 unless otherwise specified.
[a] Take PK sample immediately prior to the morning administration of INC280.
[b] Sample numbers for any unscheduled blood collection for INC280 will start with 2001, and then coded by 2002, 2003 etc.
[c] PK sample should be collected within 30 min after tumor biopsy completion.
[d] The first Dose Reference ID is for the current dose, while the second Dose Reference ID is for last dose the subject received prior to the collection of the PK sample.

[redacted]

Table 7-6 Timepoints of blood collection for INC280 PK assessment during Dose Expansion Part

PK sample No	Cycle	Day	Scheduled time relative to dosing	Description	Dose reference ID	Blood volume
101	1	1	0 h [a]	Pre-dose	101	3 mL
102			2 h (± 1 h)	Post-dose	101	3 mL
103			6 h (± 2 h)	Post-dose	101	3 mL
104			12 h (± 3 h)	Post-dose	101	3 mL
105		15	0 h [a]	Sample will be collected prior to the morning dose of Cycle 1 Day 15	102/5001[d]	3 mL
106			2 h (± 1 h)	Post-dose	102	3 mL
107			6 h (± 2 h)	Post-dose	102	3 mL
108			12 h (± 3 h)	Post-dose	102	3 mL
109	2	1	0 h [a]	Sample will be collected prior to the morning dose of Cycle 2 Day 1	103/5002[d]	3 mL
111			2 h (± 1 h)	Post-dose	103	3 mL
110	3	1	0 h [a]	Sample will be collected prior to the morning dose of Cycle 3 Day 1	104/5003[d]	3 mL
112			2 h (± 1 h)	Post-dose	104	3 mL
Total volume						36 mL
7001+ [b]	Unscheduled			Unspecified	NA	3 mL
6001	1	Coinciding with tumor biopsy [c]			NA	3 mL

All measurement times are relative to dose of INC280 unless otherwise specified.
[a] Take PK sample immediately prior to the morning administration of INC280.
[b] Sample numbers for any unscheduled blood collection for INC280 will start with 7001, and then coded by 7002, 7003 etc.
[c] PK sample should be collected within 30 min after tumor biopsy completion.
[d] The first Dose Reference ID is for the current dose, while the second Dose Reference ID is for last dose the subject received prior to the collection of the PK sample.

Detailed instructions for the processing, handling, storage and shipment of the PK samples will be provided in a separate laboratory manual at the time of study initiation.

The exact collection date and time of all samples must be documented on the PK blood collection CRF pages. The date and exact time of drug administration as well as the date and exact time of blood sampling must be recorded on the CRF.

All blood samples will be taken by either direct venipuncture or venous catheter or indwelling cannula inserted in a forearm vein. 3 mL blood will be drawn per sample at series time points Samples should be processed to obtain plasma and labeled as detailed in the [Laboratory Manual]. All samples should be stored frozen at ≤ −70°C within 90 minutes of venipuncture at the site until sample shipment.

[redacted]

[redacted]

7.2.3.2 Analytical method

Concentration of INC280 will be measured in plasma by a validated liquid chromatography-tandem mass spectrometry assay with a lower limit of quantification (LLOQ) of 1 ng/mL. Any results below the LLOQ and missing samples will be labeled accordingly. [redacted]

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients whose c-MET status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study

[redacted]

procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the AE CRF.

Patients whose c-MET status is known will sign the main study ICF.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

AEs that begin or worsen after informed consent should be recorded in the AEs CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. AE monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

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

If CTCAE grading does not exist for an AE, 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 criteria; rather, information about deaths will be collected though a Death form.

The occurrence of AEs should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. AEs also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. The severity Grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a SAE is defined as in Section 8.2.1, and which seriousness criteria have been met.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of

[redacted]

any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a SAE.

AEs separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AEs CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an AE and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

SAE is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as SAEs:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a SAE

8.2.2 Reporting

For patients with unknown c-MET status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known c-MET status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 hours of learning of its occurrence (Note: if more stringent, local regulations regarding reporting timelines prevail).

Any SAEs experienced after this 30 days period (or 5 half-lives, whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report i.e. reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 hours of learning of its occurrence (Note: if more stringent, local regulations regarding reporting timelines prevail). Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

[redacted]

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS)department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification, to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy follow up in this study will end after birth or after any adverse pregnancy outcome associated with the end of the pregnancy. In case of live birth the newborn will be followed up until 12 months of age to detect any developmental issue or abnormality that would not be seen at birth. Pregnancy outcomes should also be collected for the female partners of any males who received study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (subject initials and exact date of birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated Contract Research Organization (CRO)) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. This includes clinical data from safety assessments but also all information as described in the protocol regarding PK, [redacted] imaging, etc.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted] PK samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

All statistical analysis will be performed under the direction of Novartis personnel. Any data analysis carried out independently by the investigator should be submitted to Novartis prior to publication or presentation.

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK [redacted] measurements.

[redacted]

The study data will be analyzed and reported based on all patients' data of the Dose-Determining and Dose Expansion parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. 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 once all patients have discontinued the study (Section 4.3).

If the dose used in the Dose-Determining and Dose Expansion parts is the same, patients will be pooled into a single treatment group within all analyses unless otherwise specified. If the dose used in the Dose-Determining and Dose Expansion parts differ, then patients will be reported by part.

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

All data collected for patients in the Dose-Determining part will be reported at the initial Dose-Determining dose level, irrespective of whether a patient undergoes intra-patient escalation to a higher dose level.

The statistical analyses will take into account the study treatment formulation as appropriate.

Details of the statistical analysis and data reporting will be provided in the Novartis Report and Analysis Plan (RAP) document finalized prior to database lock.

10.1 Analysis sets

All analysis sets will be identified prior to database lock.

10.1.1 Full Analysis Set

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

10.1.2 Safety Set

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

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

10.1.3 Per-Protocol Set

The per-protocol set (PPS) consists of all patients in the FAS who are in compliance with the protocol in the following ways:

- diagnosis corresponds to that defined in inclusion criteria
- stage of disease corresponds to that defined in inclusion criteria
- prior treatment corresponds to that defined in inclusion criteria

[redacted]

Patients will be evaluable for efficacy if they have at least one response assessed differently from 'unknown' or 'not assessed' under RECIST (Appendix 1). A patient who discontinued the study prior to being evaluated for the primary efficacy variable for a reason(s) other than AE, PD or death will not be included in the per-protocol set.

10.1.4 Dose-determining analysis set

The DDS consists of all patients from the safety set (who are in the Dose-Determining Part) who either meet the minimum exposure criterion and have sufficient safety evaluations (as determined by the Investigators and Novartis), or who have experienced a qualifying AE during the first four weeks of treatment (see Table 6-2).

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

10.1.5 Pharmacokinetic analysis set

The PK analysis set (PAS) consists of all patients set who have at least one sample providing evaluable PK data.

The PAS will be used for summaries of PK data (tables and listings) as well as for listings of derived parameters.

Note: patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analysis.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients in the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of INC280, as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) will be listed and summarized by means of descriptive statistics in the clinical study report (CSR). Categories for relative dose intensity of INC280 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9

[redacted]

- < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment, for cycle 1 alone and for overall treatment duration. The FAS will be used.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC term by means of contingency tables. The FAS will be used.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized.

10.4 Primary objective

The primary objective of this study is to estimate the overall activity of INC280 in advanced HCC patients with c-MET dysregulation. Please refer to Table 3-1 for the primary objective.

10.4.1 Variable

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

10.4.2 Statistical hypothesis, model, and method of analysis

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

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

For patients treated at the Expansion Part dose, the distribution of TTP will be estimated using the Kaplan-Meier method. The median TTP and quantiles (along with one-sided 90% confidence intervals) will be presented. The Kaplan-Meier curve will be presented graphically. TTP rate estimates (along with one-sided 90% CI) at 3 months, 6 months, 9 months and 1 year will presented, as given by the Kaplan-Meier analysis.

10.4.3 Handling of missing values/censoring/discontinuations

If a patient has not experienced a radiological disease progression or death due to underlying cancer, TTP will be censored at the date of the last adequate tumor assessment, defined as the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before a censoring reason occurred, or the date of first dose of INC280 if no post-baseline assessments are available (See RECIST v1.1).

[redacted]

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

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

10.4.4 Supportive analyses

Using the PPS, the TTP analysis may be re-run for patients treated with the Expansion Part dose.

10.5 Secondary objectives

Please refer to Section 3 for the secondary objectives.

10.5.1 Efficacy objective(s)

The efficacy objective of this study is to further assess the clinical activity of INC280 in advanced HCC patients with c-MET dysregulation.

The tumor response will be evaluated based on RECIST V1.1., ORR, DCR, PFS and OS in patients with advanced HCC will be assessed. ORR is defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or PR at any time on study per RECIST. DCR is defined as the proportion of patients with a BOR of CR, PR or SD at any time on study per RECIST. PFS is defined as the time from date of first study treatment intake to the date of the first radiologically documented progression or death due to any cause or initiation of new antineoplastic therapy. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment. OS is defined as the time from date of first study treatment intake to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

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

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

10.5.2 Other secondary objectives

Please refer to Section 10.5.3 for the analyses of safety data.

Please refer to Section 10.5.4 for the analysis of PK data.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

A listing of all AEs will be provided based on the FAS. For all safety analyses, the safety set will be used unless otherwise specified.

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 dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

All AEs recorded during the study will be summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by primary system organ class, severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) current edition version 4.03, type of AE, and relationship to the study drug by study Part. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by primary system organ class, type of AE, and study Part.

Qualifying AEs will be separately listed by primary system organ class, worst grade based on the CTCAE current edition version 4 and type of AE. The DDS will be used.

Any other information collected (e.g. start/end dates and duration of AE, severity or relatedness to study medication) will be listed as appropriate. For patients undergoing intra-patient escalation to doses other than their initially received dose level, data up to the first intra-patient escalation will be summarized and all post-escalation data will only be listed.

10.5.3.3 Analysis of qualifying AEs within first four weeks of treatment

An adaptive BLRM guided by the EWOC principle will be used to guide the dose recommendation for the Dose Expansion Part of the study. Doses available for consideration as the Expansion Part dose will be those estimated under the modeling for which the risk that the true rate of qualifying AE in the first four weeks of treatment (Table 6-2) exceeds 33% is less than 25%. Subsequently, the PK data will be used to assess if the highest of these doses is acceptable for use in the Dose Expansion Part, or whether a lower dose is appropriate based of increased exposure within the HCC patients.

A two-parameter BLRM will be fitted on the qualifying AE data (i.e. absence or presence during the first four weeks of treatment) accumulated throughout the Dose-Determining Part of the study. All information currently available about the dose-AE relationships of single agent INC280 will be summarized in prior distributions.

The DDS will be used for these analyses.

The dose-toxicity relationship in will be described by the following Bayesian logistic regression model:

[redacted]

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0,$$

where $\text{logit}(\pi_{(d)})= \ln (\pi_{(d)}/(1-\pi_{(d)}))$, $\pi_{(d)}$ is the probability of patient experiencing a qualifying adverse event within the first four weeks of treatment at dose d (mg BID). Doses are rescaled as d/d* with reference dose $d^*= 400$ mg bid (total 800mg/day) of INC280. As a consequence α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

The Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions and the process for their derivation based on available pre-clinical data are provided in Appendix 5.

Dose recommendation

Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credibility interval, and the probability that the true AE-rate (as defined by Table 6-2) for each dose lies in one of the following categories :

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

Following the principle of EWOC, at the end of Dose-Determining Part, a range of doses will be recommended for the Dose Expansion Part. The highest dose level in that dose range will be the highest dose that satisfies the overdose criterion that there is less than 25% chance of excessive toxicity. If the recommended Dose Expansion Part dose as per the PK analysis (Section 10.5.4.1 and Section 6.2.2) is higher than the dose allowed by the BLRM, the highest dose allowed by the BLRM will be used for the Dose Expansion Part. Summaries of the posterior distribution of model parameters and posterior distribution of AE rates based on the AE data from all patients in the DDS will be presented.

10.5.3.4 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g. hematology, biochemistry, etc.) a listing of laboratory values will be provided by laboratory parameter, patient and treatment group. The frequency of notable lab abnormalities will be displayed by parameter, cycle and treatment group. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE version 4.03 grade experienced and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or 4 laboratory toxicities). Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE version 4.03 allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

Laboratory data will also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

[redacted]

10.5.3.5 Other safety data

Data from other tests (e.g., ECG or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.3.6 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions by study Part. Reasons for dose interruption and dose reductions will be listed by patient and study Part and summarized by Part.

10.5.4 Pharmacokinetics

PAS will be used in all INC280 PK data analysis and PK descriptive statistics.

PK parameters summarized in Table 10-1 will be estimated by non-compartmental analysis of individual INC280 plasma concentration versus time data using WinNonlin (WinNonlin version 5.2 or above, or Phoenix; Pharsight Corporation, Moutain View, California). Descriptive statistics will be calculated for PK parameters by treatment group and scheduled days.

Concentration data collected in the Dose Expansion Part will be listed. Summary tables by time point (as described earlier) will be presented as well.

Table 10-1 Noncompartmental pharmacokinetic parameters

AUC0-t	The AUC from time zero to time t (t=12 hours dosing interval for twice daily dosing) post dose (ng*h/mL)
AUCinf	The AUC from time zero to infinity (ng*h/mL)
AUClast	The AUC from time zero to the last quantifiable concentration point (ng*h/mL)
Cmax	The maximum (peak) observed plasma drug concentration (ng/mL)
Tmax	The time to reach maximum (peak) plasma drug concentration after single dose administration (h)
Lambda_z	Terminal elimination rate constant, calculated as the slope of linear regression of the terminal phase of the logarithmic concentration-time profile(hr^{-1})
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve. Determined as Ln (2)/Lambda z (h).
CL/F	Apparent drug clearance from the plasma (L/hr), as calculated by dose/AUCinf or dose/steady state AUC0-t following extravascular administration.
Vz/F	The apparent volume of distribution during terminal elimination phase (L)
Racc	Accumulation ratio of drug exposure, calculated by AUC0-t on Day 15 divided by AUC0-t on Day 1.

10.5.4.1 Dose-Determining Part

PK will be assessed for patients treated in the Dose-Determining Part on Cycle 1, Day 1 and 15. Patients with at least one evaluable full PK profile will be included in PK analysis.

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

[redacted]

with concentration mean and standard deviation by time point and treatment dose will be presented as well.

The following PK parameters from Dose-Determining Part will be summarized:

Cycle 1, Day 1: AUC0-t, Cmax, T1/2, Tmax, CL/F, and Vz/F.

Cycle 1, Day 15: AUC0-t, Cmax, T1/2, Tmax, CL/F, Vz/F and Racc.

PK parameters other than Tmax will be summarized by number, arithmetic mean, standard deviation, CV%, median, range (minimum and maximum), geometric mean and geometric CV%. Number, median and range (minimum and maximum) will be presented for Tmax.

At the dose decision analysis, systemic clearance of the HCC patients from the Dose-Determining Part as well as from study CINC280X2102 will be assessed in comparison with the cancer patients from historical studies (INCB028060-101, CINC280X1101 and CINC280X2102) who had normal liver function (NCI-ODWG criteria) using non-compartmental analysis. 90 percent confidence interval for the systemic clearance mean ratio of the two populations will be calculated and compared to the no effect boundary of 80% to 125%. If 90 percent confidence interval for the mean ratio falls between the no effect boundary, it indicates the drug exposure is comparable in the two populations. Recommended Expansion Part dose (as per PK analysis) will be RP2D. If lower drug clearance is observed in HCC patients from the Dose-Determining Part, recommended Expansion Part dose is the RP2D proportionally reduced by decreased mean ratio of systemic clearance. For example, if mean ratio of systemic clearance is 0.7, which indicates a 30% increase in drug exposure in HCC patients from the Dose-Determining Part, recommended Expansion Part dose will be 0.7 times RP2D (Section 6.2.2). If INC280 exposure in lead-in Dose-Determining Part is lower, Expansion Part dose as per PK analysis will be the RP2D proportionally increased by the increased mean ratio taking into consideration of the toxicity and feasibility. Drug exposure of the HCC patients from the Dose-Determining Part, including AUC0-t and Cmax will also be compared to the historical studies at the same dose level.

In addition, the recommended Expansion Part dose as per PK analysis will not be higher than the dose recommended by the safety analysis (Section 10.5.3.3).

10.5.4.2 Dose Expansion Part

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

[redacted]

[redacted]

10.5.4.4 Data handling principles

All concentrations of INC280 below their respective LLOQs (lower limits of quantification) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters.

[redacted]

10.7 Interim analysis

No formal interim analysis of the primary efficacy variable (TTP) has been planned. However, a safety analysis and PK analysis will be done when at least six patients evaluable for the DDS is available at the 300 mg dose level (capsule) in the Dose-Determining Part to evaluate which dose level is to be used for the Expansion Part dose (Section 6.2.2).

10.8 Sample size calculation

Dose-Determining Part

It is expected that between 6 and 10 patients will be enrolled in order to obtain data on occurrence or absence (within first four weeks of treatment) of qualifying AE (Table 6-2) for at least 6 patients evaluable for the DDS.

Dose expansion Part

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

- in general the median TTP for patients treated with sorafenib has been established to be 2.8 months (Cheng et al 2009); for the c-MET high patients it has been estimated to be 2.2 months (Santora et al 2013)
- the required improvement to be seen on treatment with INC280 in the Dose Expansion Part is an increase in median TTP to approximately 4 months in patients with advanced

[redacted]

HCC with high c-MET status and preserved liver function of Child Pugh class A with 5-6 point

- therefore a successful outcome will be indicated by an observed median TTP of ≥4 months, and a one-sided 90% lower confidence limit for median TTP of ≥2.2 months
- It is assumed that on average 1.5 patients are enrolled per month; the primary analysis is conducted 6 months after enrolment of the final patient
- Data is simulated from the exponential distribution with true mTTP = 2.2, 4, 5 and 6 months
- a 30% risk of loss to follow up per patient per year is assumed ; this corresponds to loss to follow up of approximately 15% patients given an assumed true mTTP = 4 months; censoring time is simulated from the exponential distribution with rate parameter = -log(1-0.30)/12

Kaplan-Maier method is used to estimate the median TTPs and provide the Brookmeyer-Crowley CIs in simulated event data. Table 10-2 presented the expected numbers of observed events at primary analysis, the probability that the observed mTTP is ≥4 months, the probability that the lower limit of one-sided 90% CI is >2.2 months provided the observed mTTP ≥4 months, and the probability of study success (i.e. the probability that the lower limit of one-sided 90% CI is >2.2 months and the observed mTTP is ≥4 months), given different true values of TTP and sample sizes. Therefore, with the planned enrollment, if the true median TTP is 6 months a successful outcome is expected with high probability. Conversely, a successful outcome is highly improbable if the true median TTP is as low as 2.2 months.

Table 10-2 Design operating characteristics when the number of patients is 25, 30, 35 and 40, respectively

True TTP (months)	Expected number of observed events	P(observed mTTP ≥4m | true TTP)	P (lower CI >2.2m | observed mTTP ≥4m, true TTP)	P (lower CI >2.2m and observed mTTP ≥4m | true TTP)
N = 25				
2.2	22	0.01	0.76	0.01
4	19	0.52	0.95	0.49
5	18	0.77	0.97	0.75
6	16	0.90	0.99	0.89
N = 30				
2.2	27	0.01	0.81	0.01
4	24	0.50	0.97	0.49
5	22	0.79	0.98	0.78
6	20	0.92	0.99	0.92
N = 35				
2.2	31	0.01	0.82	0.00
4	28	0.51	0.98	0.50
5	26	0.81	0.99	0.80
6	24	0.94	1.00	0.93
N = 40				
2.2	36	0.00	0.93	0.00

[redacted]

True TTP (months)	Expected number of observed events	P(observed mTTP ≥4m | true TTP)	P (lower CI >2.2m | observed mTTP ≥4m, true TTP)	P (lower CI >2.2m and observed mTTP ≥4m | true TTP)
4	32	0.50	0.99	0.50
5	30	0.82	0.99	0.82
6	28	0.95	1.00	0.95

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

[redacted]

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source

[redacted]

documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient

included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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14 Appendices

14.1 Appendix 1: RECIST 1.1

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

List of Contributors

Authors (Version 3):	[redacted]
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Authors (Version 1):	[redacted]
Document type:	TA Specific Guideline
Document status:	Version 3: Final, October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002

[redacted]

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.13 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.14 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.24 of this guideline describes data handling and programming rules. This section is to be referred to in the analysis plan(s) to provide further details needed for programming.

As for a usual Novartis template, comments are written in italic font. The protocol authors must take these comments into consideration and provide project or study specific details in the protocol. Specifically, definitions highlighted in red must be discussed, defined and then documented in the study protocol. Any deviations to the guideline must be clearly specified in the protocol with justification.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.3.1 Disease measurability

In order to evaluate tumors throughout a study definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.22.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions.

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- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10mm and <15mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (longest diameter <10 mm with CT scan or pathological lymph nodes with ≥ 10 to < 15 mm short axis), e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

14.1.3.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the ORR. Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.22.

14.1.4 Methods of tumor measurement - general guidelines

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (eg. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

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- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PT at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PT at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, [redacted] LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the ULN they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or SD. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and SD (an effusion may be a side effect of the treatment) or PD (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions,

[redacted]

documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.5 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination) should be at least 10mm in longest diameter. See Section 14.1.3.1.
- **Nodal target:** See Section 14.1.3.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastasis). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.6 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameter for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.7 Follow-up & recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion

evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.7.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are patient to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

When a tumor does not disappear completely and shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.7.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

If a nodal lesion shrinks to less than the slice thickness a default value should be assigned depending on the slice thickness. With 5 mm contiguous slice thickness, the default value will be 5 mm. Similarly, for a 7 mm slice thickness, the default value will be 7 mm. Actual measurement should be given for all lesions larger than the default value.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

14.1.8 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
CR:	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
PR:	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
PD:	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
SD:	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions

[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10mm in size. In this case, the target lesion response is CR

[3.] Methodology change See Section 14.1.4.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as PD
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline). Proper documentation should be available to support this decision.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed the target lesion response would be UNK.

[redacted]

- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the CRF, the diameter of the "merged lesion" should b recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10mm are considered normal a CR for target lesion response should be assigned when nodal target lesions shrink to less than 10mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if the absolute sum of the remaining nodal target lesions increases by at least 5mm **and** at least one of those remaining lesions are at least 10mm in size. i.e. if the short axis of a remaining nodal target lesion increases from 5 mm to 10 mm or from 7 mm to 12.5 mm this is called PD, but if it increases from 7 mm to 10 mm it does not qualify for PD.

When both nodal and non-nodal lesions are still present there may be rare occasions when a PD for target lesion response is primarily due to increases in size of nodal lesions but where the target lymph nodes are still all less than 10mm in size. This kind of rare anomaly is acceptable since otherwise the rules for determining target lesion response would become too complex.

[redacted]

14.1.9 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
CR:	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
PD:	Unequivocal progression of existing non-target lesions.[1]
Incomplete Response/SD:	Neither CR nor PD
UNK	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1.] Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Incomplete response/Stable disease**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. Even in cases where there is no measurable disease at baseline, in order for a PD to be assigned on the basis of non-target lesions the increase in the extent of the disease must be substantial. In studies where the overall non-target lesion response is not recorded but instead the individual status of individual lesions (Absent, Present or Worsened) is determined, if there is unequivocal progression of non-target lesions then at least one of the non-target lesions must be assigned a status of "Worsened". Similarly, an individual non-target lesion should only be assigned a "Worsened" status if there is unequivocal progression of non-target lesions overall.
- Where possible, similar rules to those described in Section 14.1.8 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

14.1.10 New lesions

The appearance of a new lesion is always associated with PD and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion1
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.11).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of PD if the short axis increases in size to ≥ 10mm for the first time in the study plus 5mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.4.

14.1.11 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Incomplete response/SD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline.

[2.] Once confirmed PR was achieved, all these assessments are considered PR.

[3.] As defined in Section 14.1.6.

If there are no baseline scans taken at all at baseline then the overall lesion response at each assessment should be considered UNK.

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

[redacted]

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.12 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.22 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.13 Best overall response

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The BOR will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of BOR and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 28 days after the last dose of study therapy will not be included in the BOR derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the BOR determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination then this should be described and justified in the protocol.

Where a study requires a response PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

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

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

If PD in a different follow-up period is considered overall response=’PD’, this must be specified in the protocol.

[redacted]

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which PFS is primary endpoint should consider only documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

- Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

If the patient progressed but continues study medication, further assessments are not considered for the determination of BOR.

Note: these cases may be described as a separate finding in the CSR but not included in the BOR rate.

The BOR for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the BOR will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

[redacted]

Specify which determination of BOR will be considered primary (and delete the other terms in the text). If a central blinded review is used (e.g. in an open-label study in which response is the primary endpoint), the BOR evaluated by the central blinded review will always be considered the primary response.

Based on the patients' BOR during the study, the following rates are then calculated:

ORR is the proportion of patients with a BOR of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

DCR is the proportion of patients with a BOR of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with PD within 8 weeks of the start of treatment.

14.1.14 Time to event variables

14.1.15 Progression-free survival

PFS is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

14.1.16 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, survival will be censored at the date of last contact.

14.1.17 Time to progression

TTP is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, TTP is censored at the date of last adequate tumor assessment.

14.1.18 Time to treatment failure

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.19 Duration of response

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

[redacted]

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall CR: For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for TTP.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or an SD the start and end date as well as censoring is defined the same as that for TTP.

14.1.20 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the ORRs, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.19. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a responders only descriptive analysis is presented. Where an inferential statistical comparison is required then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS is the worst possible outcome as it means the patient that the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall CR is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

Indicate in the protocol whether a subgroup analysis of responders only will be performed in addition to the full population analysis (which should be included as default).

14.1.21 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is

[redacted]

CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from, e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

For all "time to event" variables, other than the duration of responses, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of responses the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as PD.

When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.19).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then corresponds to 9 months.

[redacted]

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last contact date from that survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.22 Handling of patients with non-measurable disease only at baseline

It is possible that patients with just non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

The protocol should state clearly whether patients with non-measurable disease only at baseline will be allowed into the study. If patients with non-measurable disease only are allowed to be enrolled then the statistical section should describe clearly how data from these patients will be incorporated into the primary analysis and main analyses of the key secondary endpoints. In studies where presence or otherwise of measurable disease is expected to have a relatively large impact on the primary endpoint, this factor can even be considered as a stratification factor in the randomization process.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

For studies which specifically exclude patients with non-measurable disease only at baseline the pre-specified analysis plan should describe how to handle data from these types of patients if they are enrolled by error. It is recommended for these types of studies that patients with non-measurable disease identified through the local site evaluation be included in the list of protocol violations. However, decisions on exclusion from a per protocol analysis should relate to whether the patient has measurable disease according to the primary data source. For example, if the primary data source is from a central independent review then patients with non-measurable disease only according to this central review should be excluded from the relevant per protocol analyses.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

[redacted]

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.1.6.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for BOR patients with just non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders". Study teams may also want to perform sensitivity analyses excluding patients from the analysis of ORR (e.g. possibly as part of a per-protocol type analysis). Similar considerations should be given to other endpoints which rely on a clear distinction being made between a PR and an SD response.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with just non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients

14.1.23 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well is addressing the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.21, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation	Options for end-date (progression or censoring?)[1] (1) = default unless specified differently in the protocol or analysis plan	Outcome

[redacted]

A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 14.1.21.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.21.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

[redacted]

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.24 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.25 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.26 Treatment and study completion CRFs

If study drug is discontinued, the **End of Treatment Page** is to be completed with a visit date reflecting the date the discontinuation decision was made, and with the 'Last known date patient took study drug' and one of the following reasons:

- AE(s)
- Abnormal laboratory value(s)
- Abnormal test procedure results(s)
- Protocol violation
- Patient withdrew consent
- Lost to follow-up
- Administrative problems

[redacted]

- Death
- Disease progression
- Treatment duration completed as per protocol *(optional, to be used if only a fixed number of cycles is given)*

For reasons other than progression (and death) it should be checked if this was not in fact progression (especially reasons AEs, Abnormal laboratory value (s), Abnormal test procedure result and patient withdrew consent). Also it should be checked if patient withdrew consent because of safety issues, in which case reasons AEs, Abnormal laboratory value (s), Abnormal test procedure result should be used. In such cases where the reason for discontinuation is AE, the adverse event CRF page must be consistent with the EOT reason provided.

All patients who discontinued study drug will be followed for post a treatment evaluation until progression or until a new anticancer therapy is initiated. Patients who discontinued study drug for reasons other than documented progression, death or lost to follow-up will be followed for progression thereafter (patients who withdrew consent might not be followed with regular tumor assessments at the study site, but should ideally be followed until progression outside the study site). Ideally, all patients who discontinued study drug for progression without documented progression will still be followed with regular tumor assessments (e.g. in case of central radiology review).If patient withdraws consent, it must be clearly stated if patient is also withdrawing consent from post treatment evaluations and/or post treatment follow-up assessments. During that evaluation period, usually only tumor measurements (and/or response status) and survival data are collected. In some protocols, the subsequent anti-cancer therapies may also be recorded.

14.1.27 Study evaluation completion

At the end of the study evaluation period, the **study evaluation completion page** is filled out with the following options:

- Patient withdrew consent
- Lost to follow-up
- Administrative problems *(when follow-up for progression has met protocol required events, e.g. follow-up stopped at certain number of events or certain time)*
- Death
- New cancer therapy *(optional, to be used when follow-up for progression is stopped in this case)*
- Disease progression

Thereafter, patients will be followed for survival using the survival follow-up pages. If information on death becomes available for patients who were lost to follow-up or withdrew consent, this may also be entered in the database. The reason for death must be documented (and will be coded using MedDRA); it must be also stated if death was due to ‘Study indication’ or ‘Other’ reason.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the

[redacted]

patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

Until the specified cut-off point has been reached, the goal is to collect tumor assessments until disease progression for all patients regardless of whether the patients are still receiving study drug. If patients are not followed for progression, e.g. in a Phase I or II study mainly evaluating safety, the evaluation is completed when study drug is completed (in this case only the first completion page is used).

14.1.28 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator response assessment will never be overruled.

If Novartis elect to invalidate an evaluation of overall lesion response upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.29 Programming rules

The following should be used for programming of efficacy results:

14.1.30 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

[redacted]

14.1.31 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.21). 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 a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.32 Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.33 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.34 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.35 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*

[redacted]

- New cancer therapy added *(optional; only if the protocol specified that PFS/TTP will be censored at that date)*

* Adequate assessment is defined in Section 14.1.21. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:-

- This may be when there has been a definite decision to stop evaluation (e.g. reason='Administrative problems' on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used for censor in case of no baseline assessment.

14.1.36 References (available upon request)

Dent S, Zee (2001). application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009). New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008). Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988). Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck S, Eisenhauer E, et al (2000). New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

[redacted]

14.2 Appendix 2: Child-Pugh classification of severity of liver disease

Child-Pugh classification system

The CPC is used to assess the severity of impaired hepatic function in patients with liver cirrhosis (Child 1964, FDA guidance 2003). In general, it is used to determine the risk to a patient with regard to the treatment(s) (e.g. surgery, transplant, medication), and, to suggest the perceived survival of the patient over a period of time.

Hepatocellular carcinoma patients who have Child-Pugh grade A score (5 - 6 points) at the baseline screening are eligible for participating in Study CINC280X2201, provided that the patients meet all other eligibility criteria.

Calculation and interpretation for Child-Pugh scores

The severity of liver disease is based on the CPC criteria, which will be calculated based on clinical findings and laboratory results during the screening period. Five variables are considered (severity of ascites, hepatic encephalopathy, abnormality in serum bilirubin, serum albumin and clotting times).A score (between 1 and 3) is accordingly assigned to each of these factors (Table 14-6). The sum of the scores provides the Child-Pugh score, which corresponds to a Child-Pugh grade (or Child's grade) of A, B or C (Table 14-7).

Table 14-6 Child-Pugh score calculation

Variables	Points assigned			Units
	1	2	3	
Total Bilirubin	< 2 (<34)	2-3 (34-50)	> 3 (>50)	mg/dL (µmol/L)
Serum Albumin	> 35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)	g/L (g/dL)
PT (or INR)	< 4 (< 1.7)	4-6 (1.7-2.30)	> 6 (>2.30)	sec (no unit)
Ascites	Absent	Slight	Moderate	no unit
Hepatic Encephalopathy*	None	Grade 1-2	Grade 3-4	no unit

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
*Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
*Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
*Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
*Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Table 14-7 Child-Pugh score interpretation

Severity (grade)	Child-Pugh Score
A	5 - 6
B	7 - 9
C	10 - 15

References (available upon request)

Child CG, Turcotte JG (1964). Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders:50-64

FDA Guidance for industry (2003). pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling

[redacted]

14.3 Appendix 3: Hepatocellular carcinoma staging systems

Staging systems

Clinical staging is crucial for risk stratification during cancer management. For HCC, a number of clinical staging systems have been developed mainly from HCC patients of different etiologies and extent of disease. The following three staging systems : the BCLC system are most widely studied and will be assessed at screening for all patients participating in this study:

For more information on patient eligibility, please refer to the core text of the study protocol.

Barcelona-Clinic Liver Cancer system

The BCLC staging system (Table 14-8) was developed based on the combination of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms. (Llovet et al 2008b)

Table 14-8 Barcelona-Clinic Liver Cancer system

BCLC stage	PS	Tumor Features	Liver Function
Stage A* (early HCC)			
A1	0	Single < 5 cm	No portal HTN** and normal bilirubin
A2	0	Single < 5 cm	Portal HTN, normal bilirubin
A3	0	Single < 5 cm	Portal HTN, abnormal bilirubin
A4	0	Up to 3 tumors < 3 cm	Child-Pugh class A - B
Stage B (intermediate HCC)	0	Large multinodular	Child-Pugh class A - B
Stage C (advanced HCC)	1 - 2	Vascular invasion or extrahepatic spread	Child-Pugh class A - B
Stage D (end-stage HCC)	3 - 4	Any of the above	Child-Pugh class C

* Stages A1, A2, A3 and A4 will be considered “Stage A” for data collection.
** HTN = Hypertension

Only BCLC Stage C HCC patients are eligible for participating in this study, provided that the patients meet all other eligibility criteria.

References (available upon request)

Chan S, Mo F, Johnson P, et al (2010). Prospective validation of the CUPI and Comparison with other staging systems for hepatocellular carcinoma in Asian population. Journal of Gastroenterology and Hepatology, “Accepted Artcle”; doi: 10.111/j.1440-1746.2010.06329.x

Llovet J, Sergio R, Mazzaferro V, et al (2008). Sorafenib in advanced hepatocellular carcinoma. N Engl J Med; 359: 378-390

The Cancer of the Liver Italian Program (CLIP) investigators (1998). A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology; 28(3): 751-755

[redacted]

14.4 Appendix 4: Tables of drugs prohibited and drugs used with caution

If a medication that is listed in both Table 14-9 and Table 14-10, more stringent practice shall be applied (that is, the medication shall be prohibited as in Table 14-9).

Based on available data, INC280 is not expected to have any clinically relevant effect on QTc (INC280 Investigator's Brochure); drugs with known risk of Torsade de Pointes (TdP) were therefore removed from the list of INC280 prohibited concomitant medications.

The use of live vaccines is not allowed during the study and up to 30 days from the last dose of INC280 treatment.

Table 14-9 Prohibited concomitant medications

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies"	

Table 14-10 Permitted concomitant medications requiring caution

Mechanism of Interaction	Drug Name
Strong CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, eltegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate CYP3A inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates [1]	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan,

Mechanism of Interaction	Drug Name
	maraviroc, mirabegron, moxifloxacin, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, phenytoin, posaconazole, pravastatin, proguanil, quinidine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates [1]	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned databases for latest information. NTI: narrow therapeutic index [1] If coadministration with capmatinib is unavoidable and minimal concentration changes of the drug listed may lead to serious adverse reactions, decrease dosage in accordance with the approved prescribing information.	

14.5 Appendix 5: The Bayesian logistic regression model and dose recommendations in hypothetical scenarios

An adaptive Bayesian logistic regression model (with 2 parameters) guided by the escalation with overdose control principle will be used to make dose recommendations for the Dose Expansion Part at the end of the Dose-Determining Part.

The dose-toxicity relationship will be described by the following logistic regression model:

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*), \qquad \alpha>0, \beta>0$$

where $\text{logit}(\pi_{(d)})= \ln (\pi_{(d)}/(1-\pi_{(d)}))$, $\pi_{(d)}$ is the probability of a patient experiencing a qualifying AE within the first four weeks of treatment at dose d (mg BID). Doses are rescaled as d/d* with reference dose d^*= 400 mg BID (800mg total in a day) of INC280. As a consequence α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

Prior specifications

Prior for (log(α), log(β)):

Step 1: Weakly informative bivariate normal prior for the model parameters (log(α),log(β)) is elicited based on prior guesses (medians) from preclinical data and wide confidence intervals for the probabilities of DLT at each dose, and can be obtained as follows:

- For the purposes of tuning the prior for the model *a priori* the median DLT rate at 10 mg BID is assumed to be low (1%) and the MTD is surmised to be 300 mg BID (33% DLT rate) based on preclinical studies (BSA-based projection to human dose). For the remaining doses, median DLT rates *a priori* are assumed linear in the logit-scale as a function of log-dose.
- Based on the above specified medians for the DLT rate at each dose and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by (Neuenschwander et al 2008).

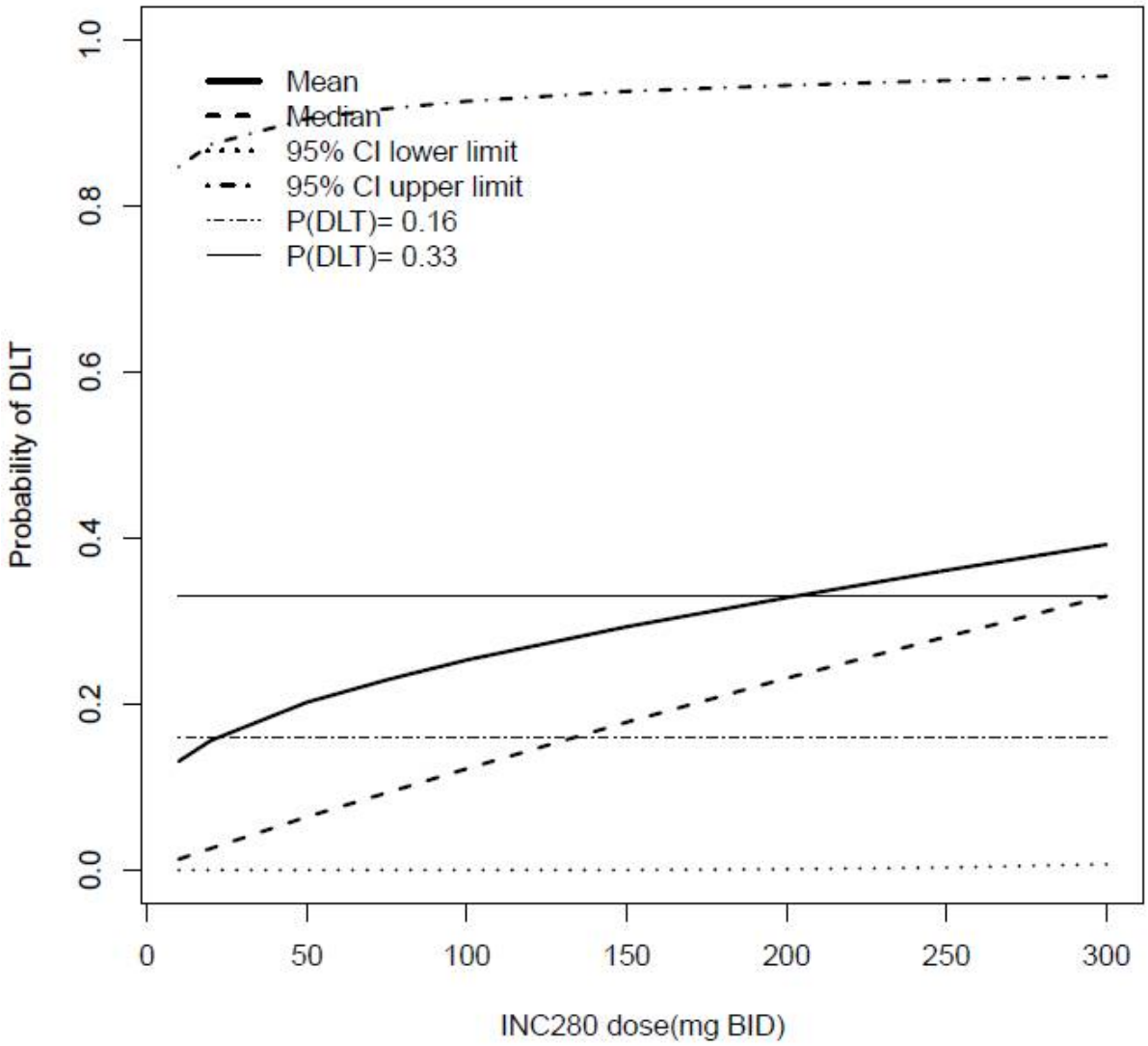
The parameters of the weakly informative prior distributions of model parameters and the assigned weights are presented in Table 14-11. Figure 14-1 illustrates the resulting prior distribution of qualifying AE-rate derived from the prior given in Table 14-11.

Table 14-11 Weakly-informative prior parameters for bivariate normal distribution of model parameters

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-0.308, 0.011)	(1.835, 0.949)	-0.310

[redacted]

Figure 14-1 Probability of qualifying AE according to the weakly informative prior distribution in Table 14-11



Step 2: Given the weakly informative prior obtained in Step 1 above, data available (at the time of developing the study plan of the present trial) from the ongoing trials of INC280 is then used to compute a posterior that serves as informative prior. Table 14-12, Table 14-13 and Table 14-14 summarizes the information available from the ongoing trial. Because there are both qd and bid dosing schedule in the INCB28060-101 trial, when deriving the informative priors, a Bayesian logistic regression model with a covariate that represents the dosing schedule is used to take the dosing schedule into account. The model parameter for the covariate is γ, which is assumed to have a weakly informative normal prior distribution with mean of 0.693 and standard deviation of 0.541.

[redacted]

Table 14-12 DLT information (cut-off date 15AUG 2012) from ongoing trial INCB28060-101 in patients with advanced malignancies used to derive informative prior

Dose (mg/day)	Regimen	FIH study (Prot No. INCB28060-101)	
		No. of evaluable patients	No. of DLT(s)
10	QD	3	0
20	QD	3	0
50	QD	6	1
70	QD	3	0
100	BID	3	0
150	QD	3	0
200	QD	3	0
300	QD	4	0
400	QD	4	0
400	BID	4	0
600	BID	4	0

Table 14-13 DLT information (cut-off date AUG2012) from ongoing trial INC280X1101 used to derive informative prior

Dose (mg QD)	FIH study (Prot No. INC280X1101)	
	No. of evaluable patients	No. of DLT(s)
100	3	0
200	3	0
400	3	0

Table 14-14 DLT information (cut-off date 15AUG 2012) from ongoing trial INC280X2102

Dose (mg BID)	FIH study (Prot No. INC280X2102)	
	No. of evaluable patients	No. of DLT(s)
100	4	0

The parameters of the informative prior distributions of all model parameters are provided in Table 14-15. The weakly informative prior (Table 14-11) was updated using the data in the above trials separately to derive the informative priors presented in Table 14-15.

[redacted]

Table 14-15 Posterior (based on data in Table 14-12, Table 14-13 and Table 14-14) parameters for bivariate normal distribution of model parameters for ongoing/previous trials

Parameters	Means	Standard deviations	Correlation
log(α), log(β) – INCB28060-101	(-2.226, -0.393)	(0.825, 0.627)	0.1833
log(α), log(β) – INC280X1101	(-1.961, 0.406)	(1.286, 0.900)	-0.107
log(α), log(β) – INC280X2102	(-1.358, 0.476)	(1.476, 0.859)	0.056

Step 3: For the deriving the predictive distribution of the model parameters, the between trial variability was captured by the prior distributions of standard deviations of (log(α),log(β)), denoted by τ_1 and τ_2. Both τ_1 and τ_2 are assumed to follow log-normal distributions with mean log(0.70) and standard deviation 0.01, assuming substantial between-trial variability (Neuenschwander et al 2010). The resulting prior (see Table 14-16 and Figure 14-2) may be updated again (based on new data from [INC280X1101], [INC280X2102] and INCB28060-101) before the safety analysis at the end of the Dose-Determining Part. If such an update is made, the new prior (and the corresponding summary of qualifying AE-rates) will be presented in the meeting to discuss dose adjustment for the Dose Expansion Part and will be reported in the statistical appendix to the CSR as well.

[redacted]

Figure 14-2 Probability of DLT according to the predictive prior distribution in Table 14-15

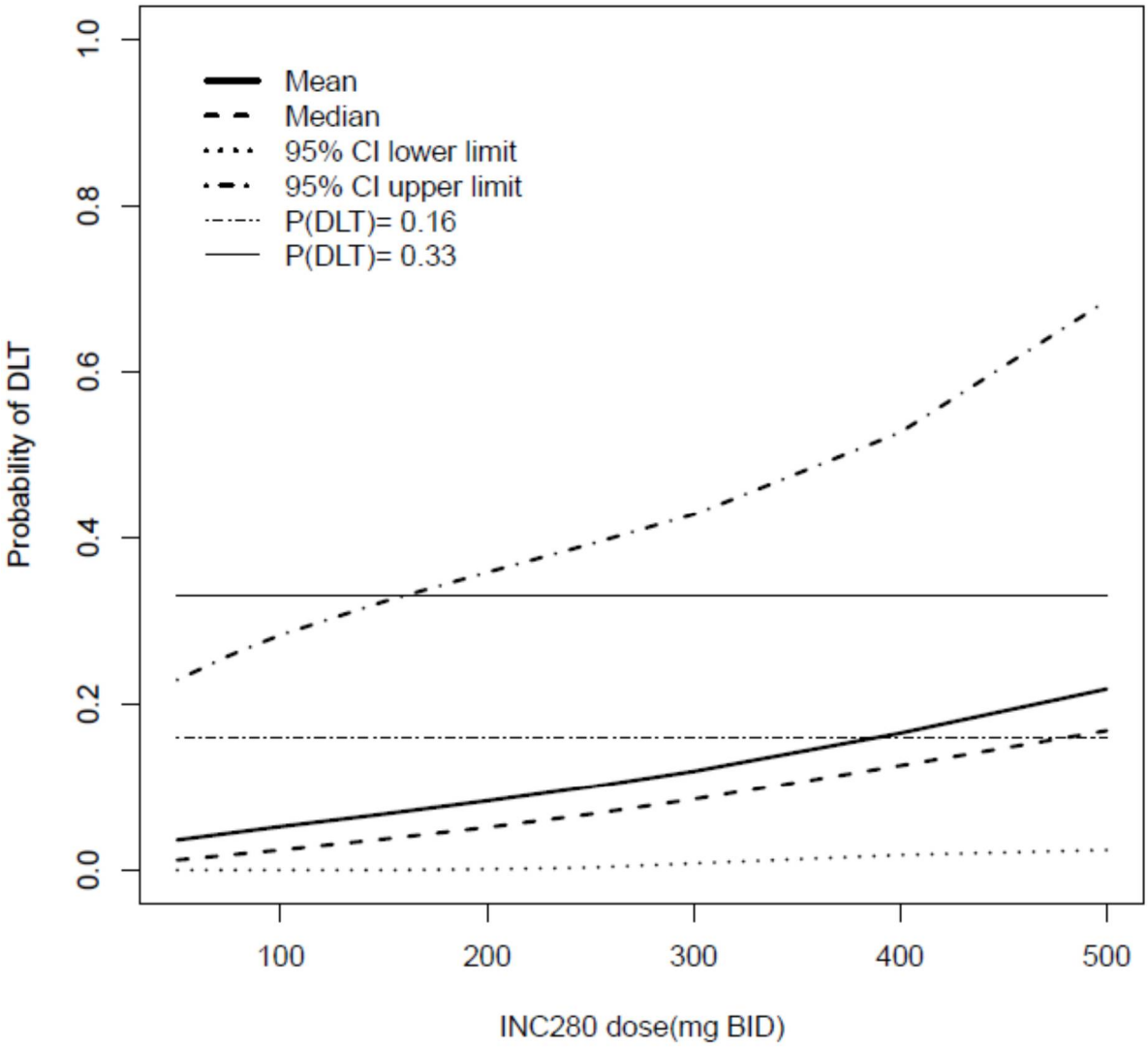


Table 14-16 Predictive distribution of model parameters

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-1.940, 0.092)	(1.040, 0.926)	0.043

[redacted]

Table 14-17 Prior probabilities of under, targeted and over dosing (derived from mixture of priors in Table 14-12

Dose (mg BID)	Prior probabilities that Pr(DLT) is in interval:			Mean	Sd	Quantile		
	0-0.16	0.16-0.33	0.33-1.0			2,5%	50%	97.5%
50	0.953	0.037	0.011	0.036	0.066	0	0.012	0.229
75	0.938	0.048	0.014	0.044	0.073	0	0.018	0.258
100	0.924	0.059	0.017	0.052	0.078	0	0.024	0.283
150	0.893	0.083	0.024	0.067	0.087	0	0.037	0.323
200	0.855	0.113	0.031	0.083	0.095	0.001	0.051	0.358
250	0.809	0.149	0.042	0.1	0.103	0.003	0.067	0.392
300	0.752	0.191	0.057	0.119	0.111	0.008	0.085	0.428
400	0.607	0.276	0.117	0.165	0.134	0.018	0.126	0.527
500	0.48	0.31	0.21	0.218	0.174	0.024	0.168	0.685

Hypothetical dose escalation scenarios

The design should make reasonable decisions during a study based on the observed toxicities. After completion of the first 28 days in all evaluable patients in the Dose-Determining Part, the decision to adjust the dose will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data.

Some scenarios to illustrate the dose adjustment are listed in Table 14-18 using the 2-parameter BLRM. It is assumed that the Dose-Determining Part has exactly 6 evaluable patients. It is also assumed that the RP2D from other INC280 studies will be 600mg bid (in practice, the RP2D can be different).

Table 14-18 Possible scenarios in study CINC280X2201 in the Dose-Determining cohort with 6 evaluable patients

Scenario number	Dose History (mg bid) – Cohort	No. AEs / No. Pat	Dose recommended (mg bid) for Dose Expansion Part *
1	300 - 1	0/6	600
2	300 - 1	1/6	500
3	300 - 1	2/6	300
4	300 - 1	3/6	200
5	300 - 1	4/6	100
6	300 – 1	5/6	50 mg bid too toxic
7	300-1	6/6	50mg bid too toxic

* Please note that the recommendation presented in this table is based on the BLRM only. The actual dose will be determined after a comprehensive review of all available data, including PK analysis as mentioned in the protocol.

[redacted]

Discussion

The BLRM enables us to incorporate the pre-clinical and clinical information, as well as to update the recommended dose based on emergent safety data in the study.

On-study recommendations based on the model are consistent with the clinical decision making process regarding the Dose Expansion part dose should be made in conjunction with other available clinical information by the Novartis Clinical Trial Team and Study investigators in deciding the dose-levels to be tested in the Dose Expansion Part.

References (available upon request)

Neuenschwander B, Capcun–Niggli G, Branson M, et al (2010). Summarizing Historical Information on Controls in Clinical Trials. Clin Trials; 7(1): 5-18

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

[redacted]

14.6 Appendix 6: Cockcroft-Gault formula for GFR estimate

Calculation

a. Indications: Stable kidney function
    1. Older patients
    2. General screening
b. Male GFR = (140 − age) × (weight) / (sCr × 72)
c. Female GFR = (140 − age) × (weight) × 0.85 / (sCr × 72)
d. Annotation
    1. Where GFR is Glomerular Filtration Rate in ml/min
    2. Where age is in years
    3. Where weight is Lean Body Mass in kilograms
    4. Where sCr is Serum Creatinine in mg/dl
e. Efficacy
    1. As accurate as 24 hour urine in most cases
    2. Exceptions: See 24 hour CrCl indications below

Should be altered in the following: Calculating GFR in specific cohorts

1. Overweight (GFR >25 kg/m^2)
    - Calculate based on adjusted body weight
    - Adjusted body weight = wtKgIdeal + 0.4 × (wtKgActual - wtKgIdeal)
2. Underweight
    - Use actual weight
    - Do not round up to Serum Creatinine (significantly underestimates GFR)
3. Elderly
    - Do not round up to Serum Creatinine (significantly underestimates GFR)
4. Amputation
    - Measure 24 hour Creatinine Clearance

Reference

Wallach JB (2007) Interpretation of Diagnostic Tests. 8th ed; Lippincott Williams & Wilkins.

[redacted]