NOVARTIS

Clinical Development

INC280 (capmatinib)

Clinical Trial Protocol CINC280A2201 / NCT02414139

A phase II, multicenter, study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC)

Authors [redacted]

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Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of appendices

List of figures

List of tables

[redacted]

[redacted]

List of abbreviations

ADME	Absorption Distribution Metabolism Excretion
AE	Adverse Event
ALKP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
AUCinf	Area under the plasma concentration versus time curve from time zero to infinity
BID	*bis in diem* / twice a day
BLRM	Bayesian Logistic Regression Model
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
BSC	Best Supportive Care
CxDx	Cycle x Day x
CDx	Companion Diagnostics
CEP7	Centromere of chromosome 7
Cmax	Maximum (peak) concentration of drug
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRF/ eCRF	Case Report/Record Form/ electronic Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed Tomography
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP	Cytochrome P450 isoenzyme
DCR	Disease Control Rate
DILI	Drug Induced Liver Injury
DOR	Duration of Response
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FDG-PET	FluoroDeoxyGlucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridization
FFPE	Formalin Fixed Paraffin Embedded
GCN	Gene Copy Number
Hgb	Hemoglobin
[redacted]	[redacted]
IB	Investigator Brochure
i.v.	intravenous(ly)

[redacted]

IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NOAEL	No-observed-adverse-effect level
NSCLC	Non-Small Cell Lung Cancer
NTI	Narrow therapeutic index
o.d./QD	*omnia die* / quaque die / once a day
ORR	Overall response rate
OS	Overall Survival
PD	Progressive Disease
POS	Probability of Success
PFS	Progression Free Survival
p.o.	*per os* / by mouth / orally
PHI	Protected Health Information
PK	Pharmacokinetics
PPI	Proton Pump Inhibitor
PR	Partial Response
PS	Performance Status
QT interval	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electric cycle
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Friderica's correction
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RoW	Rest of the World
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SD	Stable Disease
SDH	Sorbitol Dehydrogenase
SOP	Standard Operating Procedure
TBIL	Total Bilirubin
TKI	Tyrosine Kinase Inhibitor
Tmax	Time of occurrence for maximum (peak) drug concentration
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
US	United States
wt	Wild-type

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e., treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.,: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
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	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason

[redacted]

Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g., premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 6 (28-Feb-2019)

Amendment rationale

As of 21-Feb-2019, a total of 327 patients have been enrolled in the study.

Cohort/ Sub-cohort 1b, 2 and 3 were closed for futility. Cohort/Sub-cohort 1a, 4 and 5b are fully enrolled and closed for recruitment. Enrollment in Sub-cohort 5a has been discontinued and in scope of this protocol amendment. Cohort 6 is open for enrollment of patients with cMET mutations regardless of cMET GCN.

The purpose of this amendment is to:

1. Implement a new expansion Cohort 7 for the enrollment of approximately additional 27 treatment-naïve patients with advanced NSCLC harboring cMET exon 14 skipping mutations (regardless of cMET GCN). The eligibility criteria for the new Cohort 7 will match those of the completed Sub-Cohort 5b. The new Cohort 7 will allow to generate additional supportive safety and efficacy data in this first line patient population, which currently accounts for the patients enrolled in Sub-cohort 5b of this study.

   As of 9-Aug-2018 data cut-off date, preliminary data showed promising activity of INC280 in treatment-naïve cMET mutated NSCLC patients (n=25, Sub-cohort 5b): ORR by BIRC was 72.0% (95% CI 50.6–87.9).

   INC280 safety profile assessed in 302 patients enrolled across all the study cohorts confirmed to be manageable and no new safety signals were observed (Wolf et al 2018), [Investigator's Brochure edition 10].
2. Close the recruitment of GCN $\geq$ 10 NSCLC patients in Sub-cohort 5a and Cohort 6 due to enrollment hurdles and to very low prevalence of patients with GCN$\geq$ 10.

   Therefore, as of 25-Jan-2019 prescreening for cMET GCN $\geq$ 10 NSCLC patients and central FISH (Fluorescence In Situ Hybridization) testing for cMET GCN eligibility has been discontinued. Enrollment in Cohort 6 will continue for patients with cMET mutated NSCLC, regardless of GCN. Patients already identified with cMET GCN$\geq$10 NSCLC without cMET mutations prior to 25-Jan-2019 and not ready yet to enter the study, will be allowed to start main screening and treatment in Cohort 6, if deemed eligible per protocol.

[redacted]

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.

The following sections of the protocol were changed:

Updated the List of abbreviations

[redacted]

Updated Glossary of terms

Protocol Summary: Updated to align with the amended protocol

Section 1.2.1.2.1 Clinical Safety and tolerability

- Updated to reflect changes in IB version 10.0 (November 2018)

Section 1.2.1.2.2 Clinical Efficacy

- Updated to include the study preliminary efficacy data in cMET mutated NSCLC patients (Wolf et al 2018)

Section 1.2.1.2.4 Clinical pharmacokinetics

- Updated to reflect latest PK data on studies CINC280A2108 and CINC280A2101 based on final analyses

Section 2.2 Rationale for the study design

- Updated to include a new Cohort 7 with treatment-naïve patients with cMET mutations regardless of cMET GCN and rationale

Section 2.2.2 Rationale for cMET mutation cohorts

- Updated rationale with the most recent published data

Section 2.2.3 Rationale for treatment-naïve cohort with cMET dysregulation

- Updated rationale with the most recent published data

Section 2.2.5 Rationale for additional Cohort 7 in treatment-naïve NSCLC with cMET mutation

- Added to provide rationale for new Cohort 7

Section 3 Objectives and Endpoints

[redacted]

Section 4.1 Description of study design

- Updated the overall patient sample size from 429 to 456
- Updated to reflect the addition of a new Cohort 7 with changes made to the description of the study design to reflect this addition
- Updated to include additional analyses planned due to the inclusion of Cohort 7

Figure 4-1 Overall study Design

- Updated to reflect the addition of new Cohort 7
- Update of the footnote to clarify interim analysis purpose (for futility)
- Correction of a typo on number of patients in Cohort 6

Section 4.1.1 Molecular pre-screening

- Updated to include the discontinuation of central pre-screening by FISH testing for eligibility as of 25-Jan-2019.

Section 4.2 Timing of interim analysis and design adaptations

- Updated to clarify interim analysis purpose

[redacted]

- Updated to reflect addition of new Cohort 7

Section 5.1 Patient population

- Updated to reflect the addition of Cohort 7 treatment-naïve patients with cMET mutations regardless of cMET GCN

Section 5.2 Inclusion criteria

- Updated Criterion #3 to reflect the inclusion of treatment-naïve patients with cMET mutations regardless of cMET GCN in Cohort 7
- Fixed a topographical error introduced with Protocol Amendment 5 which leads to renumbering of Inclusion Criteria

Section 6.1.1 Dosing regimen

- Updated to reflect that similarly to Cohort 6, there will be no food restriction for patients enrolled in Cohort 7

Section 6.4 Concomitant medications

- Updated presentation of concomitant medications to be listed in only one table with the most stringent practice of use

Section 6.4.2 Permitted concomitant therapy requiring caution and/or action

- Updated to reflect latest PK data on studies CINC280A2108 based on final analysis
- Table 6-5 updated to reflect general change on concomitant medications listed in only one table with the most stringent practice

Section 6.4.2 Prohibited concomitant therapy

- Table 6-6 updated to remove note and align with general change on concomitant medications use
- Table 6-7 updated to remove note and align with general change on concomitant medications use

Section 6.5.2 Treatment assignment

- Updated to reflect new Cohort 7 with inclusion of treatment-naïve patients with cMET mutations regardless of cMET GCN

Table 7-1 Visit Evaluation Schedule

- Updated tumor biopsy requirement at pre-screening
- Updated to correct the missing collection of diagnosis and extent of cancer at molecular pre-screening

[redacted]

Section 7.1.1.1 Tumor sample requirement

- Updated to reflect use of tumor biopsy for amplification and/or mutation status
- Updated to include a possible request of additional tumor tissue retrospectively, if available, for development of future NGS companion diagnostic

[redacted]

Section 7.1.2 Screening

- Updated to change wording from Central laboratory to Novartis-designated central Laboratory for consistency in the section

Section 7.1.2.1 Eligibility screening

- Updated to add references to ECG Tables 7-5 and 7-6

Section 7.1.6 Withdrawal of consent

- Updated the Withdrawal of consent language in alignment with the most recent Novartis guidelines regarding personal data

Section 7.2.2.5 Laboratory evaluations

- Updated to change wording from Central laboratory to Novartis-designated central Laboratory

Section 7.2.2.6 Cardiac assessments

- Updated Table 7-6 to add Cohort 7 ECG collection

Section 7.2.3 Pharmacokinetics

- Updated Table 7-8 to add Cohort 7 PK collection

[redacted]

Section 8.1.3 Adverse events of special interest

- Updated list of AE of special interest to be monitored for INC280

Section 10 Statistical methods and data analysis

- Updated to clarify purpose of interim analysis
- Updated to include Cohort 7 in primary analysis
- Updated to reflect the additional supportive analyses that may be performed

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Updated language of efficacy response for clarity and adding Cohort 7
- Updated to add that no hypothesis testing is planned for Cohort 6

Section 10.4.4 Supportive analyses

- Updated to clarify analysis for Cohort 6
- Updated to reflect addition of Cohort 7 and additional analyses planned

Section 10.5.2 Other secondary efficacy objectives

[redacted]

- Updated to clarify PFS definition and censoring
- Updated to add that Cohort 7 may also be combined with Sub-cohort 5b

Section 10.5.5.1 Outline of the data analysis

- Updated to remove IHC assessments and related analysis

Section 10.5.5.3.2 Basic tables, figures and listings

- Updated to remove IHC assessments and related analysis

Section 10.7 Interim Analysis

- Updated to clarify that no interim analysis "for futility" is planned for Sub-cohorts 5a and 5b, Cohort 6 and 7

Section 10.8 Sample size calculation

- Updated to reflect increase in overall patient sample size from 429 to 456 based on new Cohort 7 and add number of patients in Cohort 7
- Updated Table 10-9 to add Operating Characteristics for Cohort 7
- Updated wording to include the utility of Cohort 6

Section 13 References

- Updated for new references used in updated sections

Additional revisions including editorial changes were made throughout the protocol.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (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.

Amendment 5 (13-Feb-2018)

Amendment rationale

As of 09-Feb-2018, a total of 269 patients have been enrolled in the study [54/69 patients in Sub-cohort 1a [cMET gene copy number (GCN) ≥10]; 42/69 patients in Sub-cohort 1b (cMET GCN ≥ 6 and < 10); 54/69 patients in Cohort 2 (cMET GCN ≥ 4 and < 6); 30/69 patients in Cohort 3 (cMET GCN < 4); 64/69 patients in Cohort 4 (cMET mutations regardless of cMET GCN); 6/27 patients in Sub-cohort 5a (treatment naïve and cMET GCN≥10); and 19/27 patients in Sub-cohort 5b (treatment naïve and cMET mutations regardless of cMET GCN)].

Cohort 3 (as of 31-Aug-2016) and Sub-cohort 1b/Cohort 2 (as of 17-Nov-2016) have been closed due to futility based on the planned interim analyses as outlined in the protocol.

As of 05-Dec-2017 Sub-cohort 1a and Cohort 4 have successfully passed the planned interim analysis for futility and enrollment is continuing as planned.

The main purpose of this amendment is:

1. To update the exclusion criteria, the list of prohibited medications, the list of medications to be used with caution and the criteria for dose modifications based on the latest INC280 clinical data as per [Investigator's Brochure edition 9] with primary focus on:
   - Pneumonitis/ILD events that have been reported with INC280 monotherapy
   - Results from the Clinical Pharmacology Drug-Drug-Interaction studies [CINC280A2102], [CINC280A2103] and [CINC280A2105]
2. To introduce a new expansion Cohort 6 for enrollment of approximately additional 30 patients with advanced NSCLC pretreated with one prior line of systemic therapy harboring either cMET amplification (GCN≥10) or cMET mutations (irrespective of cMET GCN). The aim is to generate supportive safety and efficacy data in this second line patient population, which currently accounts for the majority of patients enrolled in the respective Sub-Cohort 1a and Cohort 4 and therefore Cohort 6 is considered representative of the overall eligible patient population of pretreated cMET high amplified and mutated NSCLC.

   In light of the food effect study [CINC280A2108] preliminary results, which showed no positive food effect of high fat meal on INC280 exposure, INC280 will be given to patients enrolled in Cohort 6 irrespective of the food intake. The enrollment in this new expansion cohort will only start upon enrollment completion of the respective Sub-cohort 1a or Cohort 4.

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.

The following sections of the protocol were changed:

Protocol Summary: Updated to align with the amended protocol

[redacted]

Section 1.2.1.1 Non-clinical experience

- Updated "Nonclinical pharmacokinetics (PKs) and metabolism" and "Safety pharmacology and toxicology" with the most up to date information

Section 1.2.1.2 Clinical experience

- Updated "Clinical safety and tolerability", "Clinical pharmacodynamics" and "Clinical pharmacokinetics" with the most up to date information following the release of [Investigator's Brochure edition 9]

Section 2.2 Rationale for the study design

- Updated to reflect the implementation of Cohort 6

Section 4.1 Description of study design

- Updated the patient sample size to 429 from 399 and made changes to the description of the study design to reflect the inclusion of Cohort 6
- Updated to include a clarification regarding the availability of EGFR and ALK status for treatment naïve patients potentially eligible for Sub-cohort 5a and 5b
- Updated to include additional analyses planned due to the implementation of Cohort 6

Figure 4-1 Overall study Design

- Updated to reflect the implementation of Cohort 6

Section 4.2 Timing of interim analyses and design adaptations

- Clarified that no interim analysis will be performed for Cohort 6

Section 5.1 Patient population

- Updated to reflect the implementation of Cohort 6 which is to enroll patients who have failed 1 prior line of systemic therapy for advanced/metastatic disease

Section 5.2 Inclusion Criteria

- Inclusion Criterion #3 – Updated to reflect the implementation of Cohort 6 (inclusion of patients with either cMET GCN $\geq$ 10 without cMET mutation or cMET mutation regardless of cMET GCN). Also included a clarification regarding the availability of EGFR and ALK status for treatment naïve patients.
- Inclusion Criterion #4 – Clarified that to be eligible for Cohort 6, patients must have failed one prior line of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC).

Section 5.3 Exclusion Criteria

- Exclusion Criteria #11 – Updated to remove restriction for strong and moderate inhibitors of CYP3A4 based on the recent data from Clinical Pharmacology DDI studies.
- Exclusion Criteria #16 – Updated to include Cohort 6
- Exclusion Criteria #22 – Added a new eligibility criterion to exclude patients with presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

[redacted]

Section 6.1.1 Dosing regimen

- Updated to allow administration of INC280 with or without food for patients enrolled in Cohort 6 only

Table 6-3 Criteria for interruption and re-initiation of INC280 treatment

- Updated to mandate discontinuation of study drug treatment for some adverse events with specified severity
- Updated to include a section for Respiratory Disorders with more specific guidance on management of Interstitial Lung Disease (ILD)/Pneumonitis

Table 6-4 Follow-up evaluations for selected toxicities

- Updated to include a section on Respiratory Disorders with more specific guidance on follow up of ILD/Pneumonitis

Section 6.4 Concomitant medications

- Updated to further stress out that for medications listed in more than one table the more stringent practice is to be applied (that is, the medication is prohibited). Drugs that appear in more than one table are underlined and bolded.

Section 6.4.2 Permitted concomitant therapy requiring caution and/or action

- Updated permitted concomitant therapy based on most recent data
- Table 6-5 Drugs to be used with caution while on study - Updated the list of drugs based on most recent data

Section 6.4.3 Prohibited concomitant therapy

- Updated section based on most recent data
- Table 6-6 Drugs prohibited while on study - Updated the list of drugs based on most recent data
- Table 6-7 Drugs with a known risk of Torsades des Pointes - Updated the list of drugs based on most recent data

Section 6.5.2 Treatment assignment

- Updated to reflect the addition of Cohort 6

Section 7.1.2 Screening

- Updated to clarify re-testing and re-screening

Table 7-6 ECG collection plan for remaining patients, including patients in Cohort 6

- Updated to include Cohort 6

Table 7-8 Pharmacokinetic blood collection log for remaining patients, including patients in Cohort 6

- Updated to include Cohort 6

[redacted]

[redacted]

Section 8.1.3 Adverse events of special interest

- Updated to include adverse events of special interest to be monitored in alignment with the recently released [Investigator's Brochure edition 9]

Section 10 Statistical methods and data analysis

- Updated to reflect the inclusion of Cohort 6
- Clarified that no interim analysis is planned for Cohort 6

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Provided clarification regarding the null hypothesis rejection

Section 10.4.4 Supportive analyses

- Updated to reflect the additional analysis as result of inclusion of Cohort 6

Section 10.5.2 Other secondary efficacy objectives

- Updated to reflect the additional analysis as result of inclusion of Cohort 6

Section 10.8 Sample size calculation

- Updated the patient sample size to 429 from 399 to reflect the inclusion of Cohort 6
- Updated to include Cohort 6 samples size

Section 13 References

- Updated the reference list

Additional revisions including editorial changes were made throughout the protocol.

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 4 (17-Nov-2016)

Amendment rationale

As of 15-Nov-2016, a total of 157 patients have been enrolled in the study [19 patients in Cohort 1a (GCN≥10); 42 patients in Cohort 1b (GCN ≥ 6 and < 10); 54 patients in Cohort 2 (GCN ≥ 4 and < 6); 30 patients in Cohort 3 (GCN < 4); and 12 patients in Cohort 4 (cMET exon 14 skipping mutated)].

As of 30-Aug-2016, Cohort 3 has been suspended due to futility based on the planned interim analyses as outlined in the protocol. No new safety signal for INC280 has been observed.

The main purpose of this amendment is to implement a new Cohort 5 to investigate the safety and antitumor activity of INC280 in treatment-naïve patients for advanced/metastatic disease (stage IIIB or IV) NSCLC harboring cMET exon 14 skipping mutations (regardless of cMET amplification) or very high cMET gene amplification (GCN ≥ 10 without cMET mutations).

Increasing data confirm that cMET dysregulations such as cMET exon 14 skipping mutations and high cMET amplification are emerging as independent molecular drivers and predictors of response to cMET inhibition in NSCLC patients, irrespective of the number of prior lines of therapy including some preliminary evidence in the treatment-naïve setting (Frampton 2015, Jenkins 2015, Mendenhall 2015, Paik 2015, Waqar 2015, Liu 2015, Schuler 2016, Drilon 2016).

Promising activity with INC280 in cMET dysregulated (either cMET amplified or cMET exon 14 skipping mutated) advanced NSCLC has been observed in the phase I study [CINC280X2102] (Schuler 2016). In patients with cMET amplified (GCN ≥6) NSCLC, a 47% Overall Response Rate (ORR) and a median Progression Free Survival (PFS) of 7.4 months were reported.

While these promising results were obtained mainly in pretreated patients, three patients (who declined chemotherapy) were enrolled as treatment-naïve. Two of these patients harbored cMET exon 14 skipping mutation (one had concurrent cMET amplification). Both patients gained benefit from INC280 treatment (tumor shrinkage -53.3% and -48.5%), one achieving confirmed response. This result was consistent with the overall benefit gained by the other two cMET mutated patients enrolled in the study (pretreated with 1 and 3 prior lines of systemic therapy, respectively) with 3 out of 4 in cMET mutated patients achieved confirmed partial responses. Overall, INC280 was well tolerated in both treatment-naïve and pretreated NSCLC patients.

Additional preliminary activity in NSCLC patients harboring cMET mutations, including in the treatment-naïve setting, has been reported with another cMET inhibitor (crizotinib). Overall 21 cMET mutated patients have been treated and 8 out of 18 evaluable patients (44%) achieved a confirmed partial response, including at least 1 of the 3 treatment-naïve patients enrolled (Drilon 2016).

While the data are still preliminary, cMET exon 14 skipping mutations and/or high cMET gene amplification are emerging as independent tumor drivers. Patients harboring such cMET dysregulations can benefit from treatment with cMET inhibitors such as INC280, irrespective

of prior lines of therapy, and including treatment-naïve patients, with acceptable safety profile. This concept was successfully confirmed in the treatment-naïve advanced NSCLC setting with other targeted agents directed against established molecular drivers such as EGFR mutation, ALK and ROS1 translocation, which demonstrated greater efficacy when compared with platinum-doublet chemotherapy (Rosell 2012, Sequist 2013, Solomon 2014). These data also confirmed that the safety profile of such targeted agents does not differ in the treatment-naïve setting compared to the pretreated setting.

There is no cMET inhibitor currently approved for cMET dysregulated NSCLC and the activity of platinum-based chemotherapy in patients with treatment-naïve advanced NSCLC harboring cMET exon 14 skipping mutations and/or high level of cMET amplification (GCN ≥10) is unknown.

In the current [CINC280A2201] study design, NSCLC patients with very high cMET amplification (GCN ≥ 10) or cMET exon 14 skipping mutations (regardless of GCN) are eligible for enrollment in Cohort 1 (Sub-cohort 1a) and Cohort 4 (respectively), only if previously treated with 1 or 2 prior lines of systemic therapies. Therefore, to ensure a proper assessment and adequate representation of treatment-naïve NSCLC patients in advanced setting harboring very high cMET amplification (GCN ≥10) and/or cMET mutation, an additional cohort (Cohort 5) is being implemented as follows:

Cohort 5: Treatment-naïve patients with cMET dysregulation

- Sub-cohort 5a: Patients with a cMET GCN ≥10 (without cMET mutations)
- Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN

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.

The following sections of the protocol were changed:

Protocol Title: updated to reflect the new study design

Protocol Summary: Updated to align with the amended protocol

Section 2.2 Rationale for the study design

- Updated to include rationale for changes in study design: the implementation of Cohort 5 for inclusion of patients who are treatment-naïve for advanced/metastatic disease in 2 Sub-cohorts (5a - patients with cMET GCN of ≥10, 5b - patients with cMET mutations regardless of cMET GCN)

Table 3-1 Objectives and related endpoints

- Updated Other secondary objective #4 to align with the inclusion of treatment-naïve patients

Section 4.1 Description of study design

- Updated the patient sample size to 399 from 345 and made changes to the description of the study design to reflect the inclusion of treatment-naïve patients for advanced/metastatic disease in Cohort 5 with the 2 Sub-cohorts (5a - patients with cMET GCN of ≥10 and 5b - patients with cMET mutations regardless of cMET GCN)

[redacted]

- Updated to include an option for central pre-screening by NGS, if assay becomes available
- Updated to clarify that EGFR wt must be documented in the patient source documents before patient can be consented for molecular pre-screening, except if performed by NGS at central laboratory and local status is not available
- Updated to clarify that patients with previously determined cMET mutation or amplification by a Novartis designated central laboratory (as detected by a validated NGS assay), will be allowed to enter the screening phase of the INC280A2201 study
- Added that all efficacy analyses for Cohort 5 will also be performed separately for each of the 2 Sub-cohorts, similar to Cohort 1
- Added that no interim analysis will be performed for Cohort 5
- Simplified language on when primary analysis will be performed
- Updated to include the ORR that will be considered sufficiently efficacious in treatment-naïve setting (Cohort 5) and included 2 hypotheses testing for Sub-cohorts 5a and 5b

Figure 4-1 Overall study Design

- Updated to reflect the implementation of Cohort 5 with Sub-cohorts 5a and 5b

Section 4.2 Timing of interim analyses and design adaptation

- Clarified that no interim analysis will be performed for Cohort 5

Section 5.1 Patient Population

- Clarified that for eligibility in Cohort 5, patients should not have received systemic therapy for advanced/metastatic disease

Section 5.2 Inclusion Criteria

- Inclusion Criterion #3 – Updated to reflect the implementation of Cohort 5 to allow inclusion of treatment-naïve patients for advanced/metastatic disease as 2 Sub-cohorts (5a - patients with cMET GCN of ≥10, 5b - patients with cMET mutations regardless of cMET GCN). Updated to clarify that EGFR wt must be documented in the patient source documents before patient can be consented for molecular pre-screening, except if performed by NGS and local status is not available
- Inclusion Criterion #4 – Updated to include criteria for eligibility of the treatment-naïve patients for advanced/metastatic disease
- Exclusion Criterion #16 – update to clarify that this criterion will apply only for patients in Cohorts 1-4

Section 6.5.2 Treatment assignment

- Updated to reflect the implementation of Cohort 5 for treatment-naïve patients for advanced/metastatic disease as 2 Sub-cohorts (5a - patients with cMET GCN of ≥10, 5b - patients with cMET mutations regardless of cMET GCN)

Table 7-1 Visit evaluation schedule

- Updated to clarify that information on prior local testing for cMET amplification and cMET mutation may include prior central NGS results, if applicable

[redacted]

[redacted]

Section 10 Statistical methods and data analysis

- Updated to reflect the inclusion of Cohort 5 with 2 Sub-cohorts 5a and 5b
- Clarified that no interim analysis is planned for Cohort 5.

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Updated to reflect the inclusion of Cohort 5 with 2 Sub-cohorts 5a and 5b
- Updated to include the ORR that will be considered sufficiently efficacious in treatment-naïve setting (Cohort 5) and included 2 testing hypotheses for Sub-cohorts 5a and 5b with references

Section 10.8 Sample size calculation

- Updated to reflect the inclusion of Cohort 5 with Sub-cohorts 5a and 5b
- Updated Table 10-5 Title to "Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in each Cohort/Sub-cohort 1a, 1b, 2, 3 and 4" to clarify that this table does not apply to Cohorts 5a and 5b
- Added Table 10-6 "Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in each Sub-cohort 5a and 5b" with calculations for Sub-cohort 5a and 5b
- Updated table numbers to reflect the addition of Table 10-6
- Added Table 10-9 "Operating Characteristics for Sub-cohort 5a and 5b"

Section 11.5 Publication of study protocol and results

- Updated to align with the latest Novartis publication guidelines

[redacted]

Section 13 References

- Updated the reference list

Additional revisions including editorial changes were made throughout the protocol.

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 3 (28-Jul-2016)

Amendment rationale

As of 20-Jul-2016, a total of 148 patients have been enrolled in the study.

The main purpose of this amendment is to:

- Further investigate and better characterize the optimal GCN as predictor of response to INC280 by implementing two sub-cohorts within the high cMET amplified Cohort 1 [gene copy number (GCN) ≥ 6]
- Remove the restrictions on the use of proton pump inhibitors (PPIs) as concomitant medications

Changes to implement two sub-cohorts within the high cMET amplified Cohort 1

Emerging data from the ongoing phase I study [CINC280X2102] firmly supports that there is activity of single agent INC280 in cMET dysregulated NSCLC, especially in NSCLC patients with high cMET amplification and cMET exon 14 skipping mutations (Schuler 2016).

In the 15 patients with cMET GCN ≥6, who had at least one post baseline tumor assessment or who had discontinued study treatment early, confirmed partial responses were seen in 7/15 patients [Overall Response Rate (ORR) 47%, Disease Control Rate (DCR) 80% and Kaplan–Meier median Progression Free Survival (PFS) 7.39 months (95% CI 3.84–22.11)]. Three out of these 7 confirmed responders per local assessment had very high cMET gene amplification (GCN ≥10); however, 2 of these responders also harboured a concurrent cMET exon 14 skipping mutation. Therefore, based on this data generated from the [CINC280X2102] study, the single contribution of the very high cMET amplification to the response of INC280 still remains to be elucidated and further optimization of appropriate GCN cut off is warranted.

Currently in the CINC280A2201 study, patients with high cMET amplified NSCLC defined as GCN ≥ 6 are being enrolled in Cohort 1, while NSCLC patients harboring cMET exon 14 skipping mutations (irrespective of the level of cMET amplification) are enrolled in Cohort 4. While detailed epidemiology data are still lacking, the prevalence of cMET amplification in NSCLC is known to diminish with the increase in GCN (Schildhaus 2014). With the emerging data, the assumption that patients with higher GCN may derive greater benefit from cMET inhibition with higher chance of response to treatment require further more robust exploration. To ensure an adequate representation and proper assessment of NSCLC patients with very high amplified disease and to avoid the uneven enrichment in the lower GCN range of this cohort, the following 2 sub-cohorts are being implemented within Cohort 1:

Cohort 1: Patients with a cMET GCN of ≥ 6

- Sub-cohort 1a: Patients with a cMET GCN of ≥ 10, or
- Sub-cohort 1b: Patients with a cMET GCN of ≥ 6 and <10

Each of the two sub-cohorts will be tested independently. This change will allow to adequately assess the individual contribution of the two GCN ranges to the activity of INC280 in Cohort 1 patients and to assess the likelihood of differential response at the high amplified range as previously suggested by Camidge (2014).

[redacted]

The category of GCN ≥ 10 has been recently used to identify the cMET amplified cases in the most extensive analysis ever conducted in 11,205 lung cancer specimens (Ou 2016). Interestingly, in this study the overlap of amplification with cMET exon 14 skipping mutation, which is still a matter of debate, was lower at the GCN ≥ 10 range compared with the one observed at the lower GCN cut offs (Awad 2016, Tong 2016). Similarly, very high cMET amplified tumor samples are expected to be mutually exclusive to RTK/RAS/PI3K driver events (Tong 2016).

Removing restrictions on the concomitant use of proton pump inhibitors (PPIs)

Current clinical data supports the concomitant administration of INC280 with PPIs.

INC280 is known to exhibit a pH-dependent solubility profile with a low solubility at high pH levels (Section 3.1 in the current INC280 Investigator's Brochure). A study to evaluate the effect of a proton pump inhibitor on the PK of a single dose of 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 patients treated in single agent studies [CINC280X2102] and [CINC280X1101], respectively, a decrease of approximately 25% in AUC of INC280 when administered with a proton pump inhibitor (PPI) is not considered clinically significant. Preliminary data in NSCLC patients [CINC280X2202] indicated that maintaining plasma trough concentrations above certain threshold over time was required for efficacy. In the proton pump inhibitor DDI study, the impact on the 12-hour post-dose concentration of INC280 (defined as trough concentration for BID dosing) was minimal with only a ~7% reduction after rabeprazole treatment. Therefore, the concomitant use of PPIs is unlikely to have an impact on the efficacy of INC280, and the PPI restriction as a concomitant medication can be removed from this protocol for patients requiring PPI gastric protection treatment.

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 underlined for insertions.

The following sections of the protocol were changed:

List of abbreviations: Updated to align with the amended protocol

Protocol Summary: Updated to align with the amended protocol

Section 1.2.1.1.2 Nonclinical Pharmacokinetics (PKs) and metabolism

- Update to include the brain to blood ratio of approximately 0.1

Section 1.2.1.2.1: Clinical Safety and Tolerability

- Updated to align with the current INC280 Investigator's Brochure

Section 1.2.1.2.2 Clinical Efficacy

- Updated to align with most recent data as of 15-Mar-2016 from the INC280X2102 study

Section 1.2.1.2.4: Clinical Pharmacokinetics:

[redacted]

- Updated with the most recent PK data available as of 28-Sep-2015
- Updated with the most recent available clinical data from CINC280A2101 detailing the effect of PPIs on the PK of a single dose of INC280
- Updated with the most recent available clinical data from CINC280X2107 detailing the food effect on the rate and extent of INC280 exposure.

Section 2.2. Rational for the study design

- Updated to include rationale for the changes in study design: the implementation of 2 sub-cohorts within Cohort 1 (1a - cMET GCN ≥ 10, 1b - cMET GCN ≥ 6 and < 10)

Table 3-1 Objectives and Endpoint

- Updated objectives to include sub-cohorts (where applicable)

Section 4.1 Description of Study Design

- Updated the patient sample size to 345 patients from 276 patients and made changes to the description of the study design to reflect the implementation of Sub-cohorts 1a and 1b within Cohort 1
- Clarified that separate efficacy analyses for Sub-cohort 1a and 1b will be performed
- Clarified that the primary analysis for any cohort that was stopped for futility may be combined with the primary analyses for other cohorts that were not stopped for futility
- Updated hypothesis testing to 5 from 4 to reflect the implementation of Sub-cohorts 1a and 1b within Cohort 1

Figure 4-1 Overall study Design

- Updated to reflect the implementation of Sub-cohort 1a and 1b within Cohort 1

Section 4.2 Timing of interim analyses and design adaptations

- Updated to reflect the implementation of Sub-cohort 1a and 1b within Cohort 1

Section 5.1 Patient Population

- Clarified that for eligibility in Cohort 1-4, patients must have failed (versus received) one or two prior lines of systemic therapy

Section 5.2 Inclusion Criteria

- Inclusion Criterion #3 – Updated to include Sub-cohort 1a and 1b within Cohort 1
- Inclusion Criterion #4 – clarified that patients must have failed (versus received) 1 or 2 lines of prior therapy and added “Treatment failure is defined as documented disease progression or intolerance to treatment”
- Inclusion Criterion #7 –corrected the conversion of glucose 175mg/mL from 9.8mmol/L to 9.7mmol/L.

Section 5.3 Exclusion Criteria

- Exclusion Criterion #7 – removed the exception that was allowing patients enrollment with indolent malignancies that currently do not require treatment
- Exclusion Criteria #11 – removed proton pump inhibitors (PPI) from the list of prohibitive medications

[redacted]

- Exclusion Criteria #16 – added the following clarification: "If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent before first dose of INC280."

Section 6.1 Study Treatment

- Updated to include the addition of the 150 mg tablet formulation

Table 6-3 Criteria for interruption and re-initiation of INC280 treatment

- Made correction in the guidance for Grade 3 Fatigue/Asthenia (General disorders and administration site condition) due to inconsistency
- Included guidance for Peripheral Edema

Table 6-4 Follow-up evaluations for selected toxicities

- Included guidance for Peripheral Edema

Section 6.4.2 Permitted concomitant therapy requiring caution and/or action

- Removed language on the concomitant use of short acting gastric acid modulators as no longer applicable.

Section 6.4.3 Prohibited concomitant therapy

- Updated to remove PPIs as prohibited concomitant therapies

Table 6-6 Drugs prohibited while on study

- Change CYP3A4 to CYP3A to reduce specificity in referencing CYP enzymes
- Removed PPIs and pomegranate as prohibited concomitant therapies
- Added Fluindione as a prohibited concomitant therapy

Section 6.5.2 Treatment Assignment

- Updated to reflect the implementation of Sub-cohorts 1a and 1b within Cohort 1

Table 7-1 Visit evaluation schedule

- Updated to include collection of information on local testing for cMET amplification and cMET mutation prior to patient consideration for this study

[redacted]

Section 7.1.2

- Updated to reflect the implementation of Sub-cohorts 1a and 1b within Cohort 1

Section 7.1.2.2 Information to be collected on screening failures

- Updated to include collection of information on local testing for cMET amplification and cMET mutation prior to patient consideration for this study and the diagnosis and extend of disease

Section 7.1.2.3 Patient demographics and other baseline characteristics

- Updated to include collection of information on local testing for cMET amplification and cMET mutation prior to patient consideration for this study

[redacted]

[redacted]

Section 8.1.1 Definitions and reporting

- Updated to align with the latest Novartis process on AE reporting

Section 8.2.2 Reporting

- Updated to align with the latest Novartis process on SAE reporting

Section 10 Statistical methods and data analysis

- Updated to reflect the implementation of Sub-cohort 1a and 1b within Cohort 1
- Clarified that all of the efficacy analyses will be performed separately for each of the two sub-cohorts
- Clarified that the primary analysis for any cohort that was stopped for futility may be combined with the primary analyses for other cohorts that were not stopped for futility
- Updated to 5 hypothesis testing as follows: (H_{i0} and H_{i1} correspond to Cohort i where i=1a, 1b, 2, 3 or 4)

Section 10.7 – Interim Analysis

- Added as new table "Number of Responders for Various Number of Evaluable Patients at Interim Analyses by Required Probability of Success for Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4" and re-numbered all of the following tables accordingly

Section 10.8 Sample size calculation

- Updated the patient sample size to 345 patients from 276 patients to reflect the implementation of Sub-cohorts 1a and 1b within Cohort 1

Section 13 References

- Updated the reference list

Additional revisions including editorial changes were made throughout the protocol.

IRB/EC

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 2

Amendment rationale

As of 21-Aug-2015, a total of 5 patients have been enrolled in the study with first patient treated on 16-Jul-2015.

The main purpose of this amendment is to implement a fourth cohort (Cohort 4) to the study design in light of the emerging data showing that NSCLC patients harboring cMET mutations can benefit from the treatment with cMET inhibitors. Moreover the amendment will also provide an update on INC280 safety data aligning with the most current edition of the Investigator's Brochure.

Changes to the study design

Since the release of the last Amendment 1, cMET mutations leading to exon 14 deletion [referred to as cMET mutation(s) hereafter] have been identified as an additional actionable target for cMET inhibition in NSCLC and promising preliminary efficacy data have been published with cMET inhibitors, including INC280, in this setting (Paik 2015, Jenkins 2015, Waqar 2015, Mendenhall 2015, Frampton 2015, Liu 2015). With this Amendment 2, Cohort 4 is added to the study design to allow patients with cMET mutations to be enrolled in the study. Prior to enrollment, the cMET mutation status of all patients must be determined at a Novartis-designated central laboratory along with their cMET amplification status. Patients with cMET mutations will be enrolled in Cohort 4, irrespective of their cMET amplification status, while patients without cMET mutations will be enrolled in Cohorts 1-3 based on their cMET amplification status. For patients already enrolled in the study prior to the implementation of this amendment, the cMET mutation status will be determined retrospectively; however these patients will remain in the cohort to which they were initially enrolled. Sensitivity analysis on the primary endpoint where patients with cMET mutations will be excluded from Cohorts 1, 2 and 3 may also be performed.

Changes related to INC280 safety

Concurrent elevation of ALT and/or AST and total bilirubin: After 28-Sep-2014 (cut-off date of the current [Investigator's Brochure, edition 5.2]), a [redacted] patient experienced a serious, unexpected, possibly related adverse event of abnormal liver function tests during treatment with a combination of INC280 and gefitinib while enrolled in the study [CINC280X2202]. The investigator assessed the adverse event suspected to be related to the combination of INC280 and gefitinib. This adverse event met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination.

The protocol is therefore being amended to modify the existing dose modifications guidelines for hepatotoxicity in regard to discontinuing study medication(s) with concurrent elevation of ALT and/or AST > 3 × ULN and total bilirubin > 2 × ULN with ALP < 2 × ULN, in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury [e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.]. Specific work-up guidelines for potential Drug Induced Liver Injury (DILI) cases have also been added to the protocol. The dose modification rules as well as the follow-up evaluations for hepatic toxicities have also been updated accordingly.

[redacted]

Photosensitization: based on the preclinical data which suggests photosensitization potential of INC280, precautionary measures against ultraviolet exposure are being included in alignment with [Investigator's Brochure edition 5.2].

In addition, the clinical overview of INC280 was updated to align both with the Investigator's Brochure edition 5.2 (cut-off date 28-Sep-2014) and with the more recent efficacy data obtained with INC280 single agent in EGFR wt NSCLC patients (cut-off date 30-Jan-2015).

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 underlined for insertions.

The following sections of the protocol were changed:

Protocol Title: updated to "…four-cohort study…" to reflect the new study design

List of abbreviations: Updated to align with the amended protocol

Protocol Summary: Updated to align with the amended protocol

Section 1.1 Overview of disease pathogenesis, epidemiology and current treatment:

- Added Section 1.1.3.2 on cMET mutations as an oncogenic driver in NSCLC
- Updated Section 1.1.3.3 with the cMET mutations background information

Section 1.2.1.2.1 Clinical safety and tolerability:

- Updated with the most current available clinical information, including the Hy's Law case, from [Investigator's Brochure, edition 5.2]

Section 1.2.1.2.2 Clinical efficacy:

- Updated with recent efficacy data obtained with INC280 single agent in EGFR wt NSCLC patients

Section 1.2.1.2.4 Clinical pharmacokinetics:

- Updated with the recent data from study CINC280X2102 and CIN280X1101 that identifies CMN288 as a major metabolite

Section 2.2 Rationale for the study design

- [redacted]
- [redacted]

Table 3-1 Objectives and related endpoints:

- Added characterization of CMN288 metabolite in the pharmacokinetics objective
- [redacted]

Section 4.1 Description of study design:

[redacted]

[redacted]

- Changed the sample size to 276 patients from 207 patients
- Added definition of cohort 4 and updated the primary analyses

Figure 4.1 Overview of study design:

- Modified figure to reflect the addition of cohort 4 and cMET mutation

Section 4.1.1 Molecular Prescreening:

- Added text to allow retention of a small amount of tissue material from all patients (including pre-screen and screen failures) for the development of an additional companion diagnostic test with methods such as Next Generation Sequencing (NGS).

Section 4.2 Timing of interim analyses and design adaptations:

- Updated to add cohort 4

Section 4.3 Definition of end of the study:

- Updated to simplify definition of end of study

Section 5.2 Inclusion Criteria

- Inclusion criterion #3: added cohort 4 for eligibility of patients with cMET mutations regardless of GCN
- Inclusion criterion #7: updated to remove the exception for patients with Gilbert's syndrome

Section 5.3 Exclusion Criteria

- Exclusion criterion #8: updated to align with the new Novartis internal guidelines on the QTcF limit, that also differentiate between male and female measurements
- Exclusion criterion #18: updated to specify the exclusion of patients known to have active hepatitis B and C
- Exclusion criteria #19, 20 and 21: updated to align with the new Novartis internal guidelines on the female pregnancy and contraception.

Section 6.1.1 Dosing Regimen

- Added recommendation for precautionary measures against ultraviolet exposure during the treatment with INC280

Table 6-3 Criteria for interruption and re-initiation of INC280 treatment:

- Updated criteria with respect to metabolic toxicity, hepatic toxicity and the table footnotes for hepatic and gastrointestinal toxicity

Table 6-4 Follow-up evaluations for selected toxicities

- Updated criteria with respect to hepatic toxicity

[redacted]

Section 6.3.4.1 Follow-up on potential drug-induced liver injury (DILI) cases:

- Added this section to provide guidance on follow-up for potential DILI cases

Section 6.4.1 Permitted concomitant therapy:

- Updated to provide guidance on the use of radiotherapy for analgesic purposes or for lytic lesions at risk of fracture

Table 6-5 Drugs to be used with caution while on study

- Updated with additional medications per the most recent Novartis Oncology Clinical Pharmacology internal memo

Section 6.4.3 Prohibited concomitant therapy:

- Corrected the time from which the prohibited drugs must be discontinued prior to first dose of INC280 from "at least 3 days" to "at least 1 week"
- Added the statement that drugs with known risk of causing QTc prolongation are prohibited.

Table 6-6 Drugs prohibited while on study

- Updated with additional medications per the most recent Novartis Oncology Clinical Pharmacology internal memo

Table 6-7 Prohibited medications causing QTc prolongation

- Updated with new medication according to the new source/reference and removed the ordering in "drug classes"

Section 6.5.2 Treatment assignment

- Updated for the addition of cohort 4 and the eligibility of patients with cMET mutations

Table 7-1 Visit evaluation schedule

- [redacted]
- [redacted]
- Added the following assessments at C1D15 to improve patients safety monitoring: targeted physical examination, vital signs, hematology and chemistry assessments.

Section 7.1.1.1 Tumor sample requirement

- [redacted]
- [redacted]
- Updated the number of slides required upon enrollment

[redacted]

[redacted]

Section 7.1.2 Screening

- Updated to include cMET mutation status and to clarify the possibility of patient re-screening.

Section 7.1.2.2 Information to be collected on screening failures

- Updated with additional information to be collected from screening failures

Section 7.1.4 Discontinuation of study treatment

- Updated language to align with new Novartis internal guideline.

Section 7.2.2.4 Performance status

- Replaced WHO with ECOG

Section 7.2.3.1 Analytical method

- Updated for analysis of metabolite CMN288

[redacted]

Section 10 Statistical methods and data analysis

- Updated data analysis to include cohort 4

Section 10.4.2 Statistical hypothesis, model, and method of analysis

- Updated to reflect the addition of cohort 4 and the implications on analysis. Four hypotheses corresponding to 4 cohorts were added respectively.

Section 10.4.4 Supportive analyses

- Updated to include the possibility to perform sensitivity analysis

Section 10.5.4 Pharmacokinetics

- Updated to clarify that summary statistics that will be reported on a range of PK parameters.

Table 10-1 Noncompartmental pharmacokinetic parameters

[redacted]

- Updated to remove 1 and add 3 PK parameters

Section 10.5.5.1 Outline of the data analysis

[redacted]

Section 10.8 Sample size calculation

- Updated for the addition of cohort 4. Sample size updated to 276 from 207 to include additional 69 patients for cohort 4

Section 13 References:

- Updated and corrected reference list to align with the appropriate "Harvard citation format" and citation updates throughout the document

Additional revisions including editorial changes and clarifications were made throughout the protocol.

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 1

Amendment rationale

As of the release date of this amendment, no patients have been screened or treated in this study.

This amendment has been implemented to indicate that assessment of ALK rearrangement determined with a validated test should be part of the non-squamous NSCLC patient's standard of care, such as the EGFR mutation testing.

Therefore along with the EGFR molecular status, also the ALK rearrangement status should be documented in the source document of all patients enrolled in this study. The inclusion criterion 3 has been amended to include ALK-negative rearrangement status and an exclusion criterion has been added to exclude patients with documented ALK-positive rearrangement status. If no ALK testing is available locally, the ALK rearrangement status must be determined at a Novartis-designated central laboratory.

Changes to the protocol

The following sections of the protocol were changed:

Protocol Summary Table, Section 2.2, Section 4.1, Section 5.1, Section 5.2, Section 5.3, Table 7-1, Section 7.1 and Section 7.2.

Section 2.2, updated to indicate that ALK-negative rearrangement patients should be enrolled and that crizotinib and ceritinib are approved in ALK-positive rearrangement NSCLC patients.

Section 2.3, updated to provide clarification on difference in exposure between tablet and capsule formulation in alignment with the IB.

Section 4.1, updated to indicate that ALK-negative rearrangement patients should be enrolled, ALK rearrangement status should be documented and if ALK testing is not available, the status will be determined centrally with a validated test along with their cMET amplification status.

Figure 4-1, updated to add that ALK-negative rearrangement patients will enter molecular pre-screening and that EGFR wt is for exon 19 deletions and exon 21 L858R substitution mutation.

Section 4.1.1, updated to indicate that if ALK testing is not available for a patient, the status will be determined centrally with a validated test along with their cMET amplification status.

Section 4.1.2, updated to indicate that the ALK rearrangement status will be determined centrally, as applicable.

Section 5.1, updated to indicate that patients with ALK-negative rearrangement should be enrolled.

Section 5.2, inclusion criterion 3 updated to include that patients with ALK-negative rearrangement should be enrolled and ALK rearrangement status should be documented and if

local ALK testing is not available, the status will be determined centrally with a validated test along with the cMET amplification status.

Section 5.3, exclusion criterion 4 added to indicate that patients with ALK-positive rearrangement are excluded.

Table 7-1, updated to indicate that confirmation of ALK-negative rearrangement status is required at pre-screening and to clarify sample requirement for ALK testing, as applicable.

Section 7.1.1.1, tumor sample requirement added for ALK testing, as applicable.

Section 7.1.2.3, data collection updated to include that ALK rearrangement status will be collected.

Section 7.2.4.1, tumor sample requirement added for ALK testing, as applicable.

Table 7-9, updated to indicate sample requirement for ALK testing, as applicable.

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 underlined for insertions.

IRB

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]

Protocol summary

Protocol number	CINC280A2201
Title	A phase II, multicenter study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC)
Brief title	Study of oral cMET inhibitor INC280 in patients with EGFR wild-type (wt), advanced non-small cell lung cancer (NSCLC)
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Currently, there is no approved therapy for tumors with cMET dysregulations (mutations/amplification/overexpression). INC280 is an orally bioavailable, highly potent and selective cMET inhibitor in biochemical and cellular assays and capable of blocking cMET activation. Pre-clinical and early clinical data showed single-agent antitumor activity with a manageable safety profile in NSCLC with cMET mutations and/or amplification and/or overexpression.
Primary Objective(s) and Key Secondary Objective	Primary objective: To demonstrate the antitumor activity of INC280, as measured by overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment, by cohort/sub-cohort Key secondary objective: To evaluate duration of response (DOR) as assessed by BIRC, by cohort/sub-cohort
Secondary Objectives	Objective 1: To evaluate ORR and DOR by investigator assessment, by cohort/sub-cohort Objective 2: To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort/sub-cohort Objective 3: To evaluate overall survival (OS), by cohort/sub-cohort Objective 4: To evaluate INC280 safety profile as monotherapy in NSCLC patients with advanced/metastatic disease Objective 5: To characterize the pharmacokinetics of INC280
Study design	This is a prospectively designed, multicenter, open-label, phase II study of single-agent INC280. Patients with stage IIIB or IV EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations) and ALK-negative rearrangement NSCLC will be pre-screened for cMET amplification and mutation status. Enrolled patients will be assigned to seven cohorts. All patients in Cohorts 1, 2, 3, and 4 must have failed 1 or 2 prior lines of systemic therapy for advanced/metastatic disease. Patients enrolled in Cohort 5 and Cohort 7 must be treatment-naïve for advanced/metastatic disease. Patients enrolled in Cohort 6 must have failed 1 prior line of systemic therapy for advanced/metastatic disease. Patients with cMET mutations will be enrolled in Cohort 4, Sub-cohort 5b, and Cohort 7 irrespective to their cMET GCN. Patients without cMET mutations will be enrolled in Cohorts 1-3 and Sub-cohort 5a, based on their cMET GCN. Cohort 6 will enroll patients with advanced NSCLC harboring either cMET amplification (GCN≥10) or cMET mutations (irrespective of cMET GCN). Patients will be eligible for enrollment in Cohort 6 only upon enrollment completion of the respective Sub-cohort 1a or Cohort 4. **Study cohort summary:** Cohort 1: Pre-treated patients with cMET gene copy number (GCN) ≥ 6, including: • Sub-cohort 1a: Patients with a cMET GCN ≥10, or • Sub-cohort 1b: Patients with a cMET GCN ≥ 6 and < 10, or Cohort 2: Pre-treated patients with cMET GCN ≥ 4 and < 6, or Cohort 3: Pre-treated patients with cMET GCN < 4, or Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or Cohort 5: Treatment-naïve patients with cMET dysregulation, including: • Sub-cohort 5a: Patients with a cMET GCN ≥10, or

[redacted]

	• Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or Cohort 6: Pre-treated patients with either cMET GCN ≥ 10 without cMET mutations or cMET mutations regardless of cMET GCN, or Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN Primary diagnostic of cMET amplification (and ALK rearrangement, if applicable) will be performed using fluorescence in situ hybridization (FISH). Primary diagnostic of cMET mutation will be performed using Reverse Transcription Polymerase Chain Reaction (RT-PCR). Next Generation Sequencing (NGS) may be used as primary diagnostic, if assay becomes available. [redacted] Patients will be consented for a pre-screening visit. If a patient is being treated with systemic therapy for their NSCLC, pre-screening for cMET amplification and mutation status (and for ALK rearrangement status, if applicable) may be performed during this treatment. However, the patient can only be screened for the main study once the patient has discontinued the last prior systemic treatment due to either disease progression or intolerance. Enrolled patients will be treated with INC280 tablets at 400 mg twice daily (BID). Treatment with INC280 will continue until patient experiences any of the following: disease progression according to RECIST 1.1 as determined by investigator and confirmed by BIRC, unacceptable toxicity that precludes further treatment, treatment is discontinued at the discretion of the Investigator or patient, lost to follow-up, or death. Treatment with INC280 may be continued beyond RECIST 1.1-defined PD (as determined by investigator and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment. The efficacy data for each cohort/sub-cohort will be analyzed separately and one (or more) of the cohorts/sub-cohorts 1-4 may be stopped for futility according to the criteria described for the Interim Analysis for Futility Assessment in the Data Analysis Section below. No interim analysis for futility is planned for Sub-cohorts 5a and 5b, Cohort 6 or for Cohort 7. Approximately 30 enrolled patients at selected sites, regardless of cohort assignment, will have full PK samples and ECGs collected and the rest of the patients will have sparse PK samples and ECGs collected. [redacted]
Population	Approximately 456 patients (69 patients per each cohort/sub-cohort in Cohorts 1-4, 27 patients per each Sub-cohorts 5a and 5b, approximately 30 patients in Cohort 6 and approximately 27 patients in Cohort 7), male and female, aged 18 or over with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations) and ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC who have failed one or two prior lines of systemic therapy (Cohorts 1-4) for advanced/metastatic disease, who are treatment-naïve for advanced/metastatic disease (Cohort 5 and Cohort 7) or who have failed one prior line of systemic therapy (Cohort 6).
Inclusion criteria	• Age ≥ 18 years • Stage IIIB or IV NSCLC (any histology) at the time of study entry • Histologically or cytologically confirmed diagnosis of NSCLC that is: • EGFR wt. This should have been assessed as part of the patient standard of care by a validated test for EGFR mutations, as per the Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors from College of American Pathologists, International

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	Association for the Study of Lung Cancer, and Association for Molecular Pathology (Lindeman et al 2013). The EGFR wild-type status (for exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification and cMET mutation status (except for patients who are treatment-naïve potentially eligible for Sub-Cohorts 5a, 5b and Cohort 7 or if molecular pre-screening will be performed by NGS and local status is not available). Patients with NSCLC of pure squamous cell histology can enter pre-screening without EGFR mutation testing or result; however patients with pure squamous cell histology and are known to have EGFR mutations in exons 19 or 21 will be excluded, • AND ALK rearrangement negative. This should have been assessed as part of the patient standard of care by a validated test. The ALK rearrangement negative status must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification, except for patients who are treatment-naïve potentially eligible for Sub-Cohorts 5a, 5b and Cohort 7; if local ALK testing is not available, patient status will be determined centrally along with the cMET status. Patients with NSCLC of pure squamous cell histology can enter pre-screening without ALK testing or result, however patients with pure squamous cell histology that are known to have ALK rearrangement will be excluded. • AND (as determined by central assessment at a Novartis designated laboratory) either: Cohort 1: Pre-treated patients with cMET GCN ≥ 6, including: • Sub-cohort 1a: Patients with cMET GCN ≥ 10, or • Sub-cohort 1b: Patients with cMET GCN ≥ 6 and < 10, or Cohort 2: Pre-treated patients with cMET GCN ≥ 4 and < 6, or Cohort 3: Pre-treated patients with cMET GCN < 4, or Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or Cohort 5: Treatment-naïve patients with cMET dysregulation, including: • Sub-cohort 5a: Patients with cMET GCN ≥ 10, or • Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or Cohort 6: Pre-treated patients with either cMET GCN ≥ 10 without cMET mutations or cMET mutations regardless of cMET GCN Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN cMET (and ALK, if applicable) testing may be performed while patient is still receiving anti-cancer therapy. However, the patient can only be screened for the main study once the patient has discontinued the last prior systemic treatment due to either disease progression or intolerance. • To be eligible for Cohorts 1-4, patients must have failed one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). To be eligible for Cohort 6, patients must have failed one prior line of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Treatment failure is defined as documented disease progression or intolerance to treatment. Maintenance therapy given after 1st line chemotherapy will be considered as part of the 1st line if given to patients with documented response or stable disease before starting the maintenance therapy. Neo-adjuvant and adjuvant systemic therapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy. To be eligible for Cohort 5 and Cohort 7, patients must not have received any systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies will not count as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

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	• At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
	• Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with any grade of alopecia are allowed to enter the study.
	• Patients must have adequate organ function including the following laboratory values at the screening visit:
	  • Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L without growth factor support
	  • Platelets ≥ 75 x 10^9/L
	  • Hemoglobin (Hgb) > 9 g/dL
	  • Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
	  • Total bilirubin ≤ 1.5 x ULN
	  • Aspartate transaminase (AST) ≤ 3 x ULN, except for patients with liver metastasis, who may only be included if AST ≤ 5 x ULN
	  • Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastasis, who may only be included if ALT ≤ 5 x ULN
	  • Alkaline phosphatase (ALP) ≤ 5 x ULN
	  • Asymptomatic serum amylase ≤ grade 2. Patients with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
	  • Serum lipase ≤ ULN
	  • Fasting plasma glucose ≤ 175 mg/dL (≤ 9.7 mmol/L)
	  • Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
	  • Potassium
	  • Magnesium
	  • Phosphorus
	  • Total calcium (corrected for serum albumin)
	• ECOG performance status (PS) of 0 or 1
	• Willing and able to comply with scheduled visits, treatment plan and laboratory tests

Exclusion criteria	• Prior treatment with crizotinib, or any other cMET or HGF inhibitor
	• Patients with known hypersensitivity to any of the excipients of INC280 (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes)
	• Patients with characterized EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 mutations
	• Patients with characterized ALK-positive rearrangement
	• Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms
	• Presence or history of carcinomatous meningitis
	• Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type
	• Clinically significant, uncontrolled heart diseases such as:
	  • Unstable angina within 6 months prior to screening
	  • Myocardial infarction within 6 months prior to screening

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	• History of documented congestive heart failure (New York Heart Association functional classification III-IV) • Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening • Ventricular arrhythmias • Supraventricular and nodal arrhythmias not controlled with medication • Other cardiac arrhythmia not controlled with medication • QTcF ≥ 450 ms (male patients), ≥ 460 ms (female patients) on the screening ECG (as mean of triplicate ECG) • Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting INC280 is allowed • Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting INC280 or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure • Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study: • Strong inducers of CYP3A4 • Impairment of GI function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome) • Unable or unwilling to swallow tablets as per dosing schedule • Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of INC280 • Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of INC280, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible • Applicable to Cohorts 1-4 and Cohort 6 only: Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is longer) before first dose of INC280. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of INC280. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent before the first dose of INC280 • Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results • 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 (including active hepatitis B and C), inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc. • Pregnant or nursing (lactating) women • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during

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	the study and for 7 days after stopping treatment • Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid • Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
Investigational and reference therapy	INC280
Efficacy assessments	Tumor assessment by RECIST 1.1 performed every 6 weeks (i.e., every 2 cycles) from the first day of treatment with INC280 until disease progression as determined by investigator and confirmed by Blinded Independent Review Committee (BIRC). Patients who continue on study treatment beyond RECIST-defined PD (determined by investigator and confirmed by BIRC) will continue to have tumor assessments as per regular visit schedule.
Safety assessments	• Hematology, coagulation, serum chemistry, urinalysis, pregnancy test (females only) • ECG • Performance status • Physical examinations • Vital signs, weight • Adverse events, Serious adverse events
Other assessments	[redacted] • INC280 PK [redacted]
Data analysis	**Data analysis to address the primary objective:** In Cohorts 1 and 5, all of the efficacy analyses will be performed separately for each of the two sub-cohorts. In Cohorts 1, 2, 3 and 4, treatment with INC280 would be considered to have clinically relevant efficacy in a cohort/sub-cohort if an ORR of ~35% (per RECIST 1.1 by BIRC assessment) is observed in that cohort/sub-cohort for the corresponding primary analysis. In addition, 5 hypotheses will be tested as following for all cohorts/sub-cohorts (H_{i0} and H_{i1} correspond to cohort/sub-cohort i where i=1a, 1b, 2, 3 or 4): H_{i0}: ORR ≤ 25% In favor of the alternative H_{i1}: ORR > 25% For Sub-cohorts 5a, 5b and Cohort 7, treatment with INC280 would be considered to have clinically relevant efficacy if an ORR of ~55% (per RECIST 1.1 by BIRC assessment) is observed in that cohort for the corresponding primary analysis. In addition, 3 hypotheses will be tested as following for the cohorts/sub-cohorts (H_{i0} and H_{i1} correspond to sub-cohort i where i=5a, 5b or 7): H_{i0}: ORR ≤ 35% In favor of the alternative H_{i1}: ORR > 35% The tests will be performed based on the exact CI for ORR in each cohort using a one sided α= 0.025 level. The primary analysis will be performed by cohort/sub-cohort in which the patients are enrolled. In addition, for Sub-cohorts 1a and 1b, Cohort 2 and Cohort 3, sensitivity analysis on the primary endpoint may be performed excluding patients with cMET mutations. No hypothesis testing is planned for Cohort 6.

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	Data Analysis to Address Other Objectives: ORR will be analyzed per investigator assessment by cohort/sub-cohort. Other secondary efficacy assessments (DOR, TTR, DCR, PFS) will be analyzed as per investigator assessment and as per BIRC by cohort/sub-cohort. Confirmation of response is required for all response endpoints, as per RECIST 1.1. DOR, PFS and OS will be described by cohort using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. **Interim analysis for futility assessment:** In Cohort 1, the interim analysis will be performed separately for each of the two sub-cohorts. Interim analyses for each cohort/sub-cohort are planned when at least 28 patients in each of Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4 and 20 patients in Cohort 3 have completed at least 6 cycles of treatment (18 weeks) or have discontinued treatment earlier. The decision to stop for futility for the respective cohort/sub-cohort at interim will be based on the probability of success (POS) at the end of the study. POS is the probability of a positive conclusion of the study if the study continued beyond interim, (i.e., until the final analysis), given the interim observed data. The respective cohort/sub-cohort will be stopped for futility at the interim analysis if the respective POS is less than 10%. All evaluable patients at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the POS criteria. The interim analysis will be performed by cohort/sub-cohort in which the patients are enrolled. In addition, for Sub-cohorts 1a and 1b, and Cohort 2 and Cohort 3, sensitivity analysis on the primary endpoint may be performed excluding patients with cMET mutations. **Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4** With 28 evaluable patients for interim analysis in each of the Sub-cohorts 1a and 1b, and Cohorts 2 and 4, if ≤ 7 responses are observed then the respective cohort/sub-cohort will be stopped for futility. If at the time when the 28th patient is enrolled a minimum of 8 responders have not yet been observed, accrual in the cohort/sub-cohort may be temporarily suspended until either the minimum number of 8 responders is observed or results of the interim analysis allow the cohort/sub-cohort to continue. **Cohort 3** With 20 evaluable patients for interim analysis in Cohort 3, if ≤ 5 responses are observed then the respective cohort will be stopped for futility. If at the time that the 20th patient is enrolled a minimum of 6 responders have not yet been observed, accrual in the cohort may be temporarily suspended until either the minimum number of 6 responders are observed or results of the interim analysis allow that cohort to continue. No interim analysis for futility is planned for Sub-cohorts 5a and 5b, Cohort 6 and Cohort 7. **Sample size:** Approximately 456 patients (69 patients per Cohort/Sub-cohort 1-4; 27 patients per Sub-cohort 5a and 5b; approximately 30 patients in Cohort 6, approximately 27 patients in Cohort 7) will be enrolled in the study if none of the cohorts/sub-cohorts is stopped for futility at the time of the interim analysis. For Cohort 2 (cMET GCN ≥ 4 and < 6), the study targets to have at least 40% of patients with cMET GCN ≥ 5 and < 6 at the time of the interim analysis, and if Cohort 2 continues to full enrollment, also at the final analysis. With 28 evaluable patients in each of the Sub-cohorts 1a and 1b, and Cohort 2 and Cohort 4 for interim analysis, there is a > 50% probability of stopping either cohort/sub-cohort for futility when the true ORR is < 25%. When the true ORR is 35%

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	then the probability of positive conclusion at the final analysis based on 69 patients is ≥ 44%. If the true ORR is > 45% or higher, the probability of positive conclusion at the final analysis is more than 90%. For Sub-cohorts 1a and 1b, Cohorts 2 and 3, sensitivity analysis on the primary endpoint may be performed excluding patients with cMET mutations. With 20 evaluable patients in Cohort 3 for interim analysis, there is a > 90% probability of stopping the cohort for futility when the true ORR is 10%. When the true ORR is 20%, then the probability of stopping for futility at the interim analysis is > 80% and the probability of positive conclusion at the final analysis is < 1%. No interim analysis for futility is planned for Cohort 5, Cohort 6 or Cohort 7. In expansion Cohort 6, approximately 30 pre-treated patients with cMET GCN of ≥ 10 and cMET mutations regardless of cMET GCN are expected to be enrolled. Data from Cohort 6 will help to further characterize the safety and efficacy of INC280 in the pre-treated Sub-Cohort 1a and Cohort 4. In addition to presenting the efficacy data of Cohort 6, analysis may also be carried out combining the patients with a cMET GCN of ≥ 10 from Sub-cohort 1a and Cohort 6 to further evaluate the precision of the efficacy estimates. Similar analysis may be carried out for pre-treated patients with cMET mutations regardless of cMET GCN combining the patients from Cohort 4 and Cohort 6. In expansion Cohort 7, approximately 27 treatment-naïve patients with cMET mutations regardless of cMET GCN are expected to be enrolled. Data from Cohort 7 will help to further characterize the safety and efficacy of INC280 in the treatment-naïve patient group with cMET mutations regardless of cMET GCN. Analysis may be carried out combining the patients from Sub-cohort 5b and Cohort 7.
Key words	cMET, NSCLC, INC280

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC)

Lung cancer has been the most common cancer in the world for several decades. In 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers worldwide. It was also the most common cause of death from cancer, with 1.6 million deaths representing 19.4% of the total deaths from cancer (Globocan 2012). For 2014, approximately 160,000 deaths are expected in the US (Siegel et al 2014) and 273,000 in the European Union (Malvezzi et al 2014).

The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers; 47% in NSCLC) is the most common type of lung cancer seen in the United States and is also the most frequently occurring cell type in nonsmokers (NCCN Guidelines 2014).

One reason for the high mortality rate of lung cancer is the advanced stage at diagnosis; only 25-30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery (Nguyen et al 2012). The majority of patients are diagnosed with locally advanced or metastatic disease and they are not candidates for surgery.

Platinum-based combination therapy is superior to best supportive care in patients with advanced, incurable disease. Platinum-doublet chemotherapy (i.e., cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) has been the standard first-line treatment for patients with locally advanced or metastatic NSCLC (Ettinger 2010, NCCN Guidelines 2014) unless a patient has a known “druggable” mutation, and is a candidate for a targeted therapy (as discussed below). Overall response rate (ORR) with chemotherapy in first line has achieved a plateau and most platinum based regimens yield an ORR of 25-35% (NCCN Guidelines 2014). For NSCLC patients with non-squamous histology, pemetrexed-based platinum doublet therapy is a well-established standard first-line treatment option. In a phase III, non-inferiority trial of chemotherapy-naïve patients with Stage IIIB or IV NSCLC, pemetrexed plus cisplatin (P/C) has shown to be non-inferior and better tolerated than gemcitabine/cisplatin (G/C) with a median overall survival (OS) of 10.3 months for both combinations (Scagliotti et al 2008). However, with respect to OS in the various histological subtypes, P/C was superior to G/C in the subset of patients with adenocarcinoma and large-cell carcinoma.

In recent years maintenance therapy has emerged as an approach to try to improve the OS rates in patients with advanced NSCLC with tumor response or stable disease after first line therapy. Several types of maintenance therapy are available (i.e., continuation with the non-

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platinum portion of the platinum doublet until disease progression or switching to a different regimen) and its selection depends on tumor histology, presence of gene mutations or rearrangements, and patient performance status. Maintenance therapy is not considered the standard of care for all patients (Horn 2014). Outcomes of treatment of advanced/metastatic NSCLC in the first-line setting with standard platinum-doublet chemotherapy (with or without maintenance) remain poor, with median progression free survival (PFS) and OS of 5-7 months and 10-16 months, respectively (Scagliotti 2008, Ciuleanu 2009, Ettinger 2010, Paz-Ares 2012).

Docetaxel, pemetrexed, erlotinib, or platinum doublets are recommended as second-line therapy regimens for unselected patients who have experienced disease progression during or after first-line therapy (NCCN Guidelines 2014). The reported response rates to second-line chemotherapy have generally been less than 10%, with median PFS and OS generally below 3 and 8 months respectively (de Marinis 2008, Weiss 2013). Upon progression after second-line chemotherapy, patients may be candidates for further treatment, although randomized evidence is scarce and most data come from phase II trials or retrospective analyses. Pemetrexed, docetaxel, gemcitabine or erlotinib are recommended in third line if they have not been already given. Patients have often limited response to third line therapy, although it may have a useful palliative effect (Shepherd 2005, de Marinis 2008, Eccles 2011, NCCN Guidelines 2014, Reck 2014, Besse 2014).

Overall, current treatments are not considered satisfactory for most NSCLC patients and the prognosis continues to be poor despite chemotherapy treatment, with a 5-year overall survival rate of only 15% (Nguyen et al 2012).

1.1.2 Targeted therapies in NSCLC

During the last few years, improved knowledge of NSCLC biology has led to the identification of aberrant molecular events crucial for malignant transformation and cancer cell survival. These aberrant molecular events are critical oncogenic drivers and represent potential therapeutic targets (Gettinger and Lynch 2011). As a result, "molecular subsets" of NSCLC patients who may be candidates for targeted therapy were defined and new targeted treatment options are available. In particular, activating mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocations are strong predictors of improved efficacy of EGFR and ALK Tyrosine Kinase Inhibitors (TKIs) when compared with standard chemotherapy in patients harboring EGFR activating mutations and ALK translocations, respectively, and represent a new paradigm in the treatment of NSCLC (Fukuoka 2011, Zhou 2011, Sequist 2013, Shaw 2013a, Shaw 2013b). Importantly, due to the high oncogenic addiction to the molecular abnormality during the course of the disease, the efficacy of these targeted therapies seem to be independent of line of treatment and high response rates are still observed in patients who received several treatments (generally excluding therapies targeting the same pathway) before receiving the given targeted therapy (Camidge et al 2012).

The success of EGFR and ALK TKIs, highlights the importance of identifying specific molecular drivers of NSCLC to appropriately direct targeted agents in specific patient populations. The landscape of NSCLC treatment is changing and the treatment paradigm of "one size fits all" is switching to a personalized therapy.

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1.1.3 cMET in NSCLC

cMET is a receptor tyrosine kinase involved in embryogenesis, organogenesis and tissue damage repair (Birchmeier 1998, Birchmeier 2003). cMET-pathway dysregulation through genomic amplification, receptor overexpression, mutations, autocrine or paracrine secretion of its ligand (hepatic growth factor [HGF]) has shown to be oncogenic, promoting cell-cell detachment and metastasis, epithelial-mesenchymal transition, invasion, angiogenesis, proliferation and survival (Christensen et al 2005).

1.1.3.1 cMET amplification as an oncogenic driver in NSCLC

cMET dysregulation, in particular gene amplification, leading to increased cMET signaling driving cell proliferation and survival, was reported in several human cancers, including lung, breast, ovarian and gastrointestinal malignancies. Preclinical findings suggested that lung cancer cell lines harboring cMET gene amplification are dependent on cMET for growth and survival (Lutterbach et al 2007) and significant growth inhibition and apoptosis are observed in cMET overexpressing cell lines when exposed to compounds blocking the cMET pathway (Christensen 2005, Liu 2008). Both cMET amplification and overexpression are linked to acquired resistance to EGFR inhibitors (EGFRi) in lung cancer in preclinical models and the clinical setting (Bean 2007, Engelman 2007, Cappuzzo 2009a). cMET amplification seems to correlate with poor prognosis in several tumor types including lung cancer, where it was associated with higher grades at diagnosis and poor survival (Cappuzzo et al 2009b). In a large retrospective series of 435 surgically resected NSCLC patients, cMET amplification by FISH (MET/CEP7 ratio $\geq$ 2.2 - average ratio of cMET gene to chromosome 7 centromere signals) was reported in ~4% of the patients (Cappuzzo et al 2009b).

cMET amplification is reported in ~4% of NSCLC (TCGA web portal 2015, Schildhaus 2014). cMET amplification appears to be mutually exclusive with all other oncogenic drivers in NSCLC (Cancer Genome Atlas Research Network 2014). Gene amplification is recognized to be the main oncogenic driver in NSCLC (Cappuzzo et al 2009a).

1.1.3.2 cMET mutation as an oncogenic driver in NSCLC

cMET mutations leading to exon 14 deletion [referred to as cMET mutation(s) hereafter] have been identified as an additional actionable target for cMET inhibition in NSCLC (Kong-Beltran et al 2006). The loss of exon 14 deletes the region of the protein required for the Cbl E3 ligase to bind to cMET and target it for degradation. This results in extended cMET occupancy at the membrane and ultimately activation of the receptor. Based on the limited epidemiology data currently available cMET mutations can be detected in 2-4% of NSCLC with adenocarcinoma histology and in ~1% of NSCLC with other histologies and the overlap between high cMET amplification (GCN>6) and cMET mutations is still to be determined; notably no overlap between cMET mutations and either EGFR mutations or ALK translocation is expected (TCGA web portal 2015, internal Novartis data). Promising efficacy data have been published with cMET inhibitors, including INC280, in this setting (Frampton 2015, Jenkins 2015, Mendenhall 2015, Paik 2015, Waqar 2015, Liu 2015, Schuler 2016, Drilon 2016).

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1.1.3.3 cMET inhibitors in NSCLC

Recent clinical studies suggest that inhibitors of cMET may provide a valuable therapeutic option in the treatment of NSCLC and other diseases linked with dysregulated cMET signaling. Anti-tumor activity of this class of agents has recently been reported in patients with locally advanced or metastatic NSCLC whose tumors contain cMET amplification. In a study with crizotinib (inhibitor of ALK and cMET), 5 responses were reported (1 complete and 4 partial responses) in 12 patients with cMET FISH intermediate (MET/CEP7 ratio > 2.2 and < 5) and highly (MET/CEP7 ratio ≥ 5) amplified NSCLC (Camidge 2014). However, 2 other anti-cMET compounds (onartuzumab and tivantinib) failed to demonstrate any clinical benefit when combined with EGFR TKIs in recently reported phase III trials, presumably at least in part due to the lack of proper patient selection (Cappuzzo 2014). In the onartuzumab phase III study, cMET positive patients were defined as IHC 2+ or 3+ for cMET overexpression (Spigel 2014) and in the tivantinib study there was no selection for cMET dysregulation (Scagliotti 2015).

Current clinical data on the activity of cMET inhibitors in cMET-mutated NSCLC are still very limited as this has not been assessed in any prospective clinical studies. Single institution series and single case reports have been published showing preliminary promising efficacy in NSCLC patients with cMET mutations irrespective of the histology when treated with either crizotinib (9 cases), cabozantinib (1 case) and INC280 (2 cases): 10 patients showed PR, 1 showed SD and only 1 case experienced PD (even if in the context of a mixed response). Activity was observed irrespective of the histology and of the line of therapy. (Frampton 2015, Jenkins 2015, Mendenhall 2015, Paik 2015, Waqar 2015; Liu 2015).

1.2 Introduction to study treatment

1.2.1 Overview of INC280

The chemical name of INC280 drug substance is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide dihydrochloride monohydrate.

INC280 dihydrochloride monohydrate is a slightly hygroscopic light yellow powder. The solubility of INC280 dihydrochloride at 25°C is approximately 3.47 mg/mL in water; 0.08 mg/mL in pH 6.8 and 0.72 mg/mL in pH 3.0 buffer.

INC280 is an orally bioavailable highly potent and selective cMET inhibitor capable of blocking cMET activation. In preclinical studies, INC280 treatment induces regression of tumors in lung cancer models with cMET amplification and/or overexpression. Activity in these tumor models correlates with inhibition of cMET pathway signaling, as measured by phospho-cMET levels. Encouraging early clinical activity has been observed with INC280 as single agent in an ongoing phase I trial in patients with metastatic NSCLC (unpublished data summarized below).

These data suggest that INC280 represents a promising therapeutic option in the treatment of NSCLC with dysregulated cMET signaling.

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

[redacted]

1.2.1.1 Non-clinical experience

1.2.1.1.1 *In vitro* and *in vivo* pharmacology

INC280 possesses potent inhibitory activity against the cMET kinase *in vitro* [inhibitory concentration (IC)50 = 0.13 ± 0.05 nM], and is highly specific for cMET with > 10,000-fold selectivity over several other human kinases tested. Potent activity of blocking cMET activation has been observed in cell-based biochemical and functional assays that measure c-MET-mediated signal transduction, as well as cMET-dependent cell proliferation, survival, and migration.

In cMET–dependent mouse tumor models (including lung cancer models), INC280 exhibits dose-dependent antitumor activity and causes tumor regression at well tolerated doses that exceeded IC90 coverage (Liu et al 2011). Importantly, plasma levels of INC280 correlates with both the dose administered and the extent of tumor growth inhibition *in vivo*.

In cMET/HGF-driven tumor models grown as xenografts in mice, oral dosing of INC280 demonstrated significant *in vivo* activity in blocking both c-MET phosphorylation and tumor growth. Activation of cMET in such responsive models is either due to strong cMET overexpression (mostly as a consequence of gene amplification, e.g. in gastric or hepatocellular carcinoma) or HGF secretion resulting in an autocrine loop (e.g. in glioblastoma).

Collectively, the data suggest that INC280 possesses potent *in vitro* and *in vivo* biological and pharmacologic activities, and further support its clinical development as a potentially effective oral treatment for human cancers with cMET dysregulation.

1.2.1.1.2 Nonclinical pharmacokinetics (PKs) and metabolism

INC280 was absorbed rapidly in rats, dogs and monkeys. The absolute oral bioavailability following a single low dose was low in dogs (28%), and moderate to complete in rats and monkeys (> 66%). Single and multiple dose toxicokinetic studies in rats and monkeys showed increase in plasma maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) values of INC280 with increased dose, but the increases were not always dose-proportional.

INC280 plasma protein binding was moderate to high across species, and was 96% in humans with no concentration dependency. The *in vitro* blood-to-plasma ratio in humans was 1.5 (concentration range of 10-1000 ng/mL). After oral dose of [^{14}C]-INC280 in male pigmented and albino rats, INC280 and/or its metabolites were widely and rapidly distributed to all tissues. Melanin containing structures such as eye (choroid) and eye (ciliary body) appeared to show specific uptake and prolonged retention of drug related material. The presence of total radiolabeled components in those tissues was at least partly reversible. INC280 can penetrate across the blood-brain barrier with a brain to blood ratio of approximately 0.1.

Systemic clearance (CL) was low- to-moderate in mice, rats, dogs and monkeys. The estimated terminal half-life (T1/2) was short in mice, rats and dogs but long in monkeys. Metabolism is the predominant mechanism of elimination of INC280 in rats and monkeys after oral administration. The hydroxylated metabolite M8 and the imidazo-triazinone (lactam) M16 were main metabolites observed in plasma and excreta of rats and monkeys. After single

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oral administration of [^{14}C]INC280 to rats and monkeys, the majority of the radioactivity was excreted at the end of the observation period. The major portion of administered radioactivity was recovered in feces and only a minor fraction in urine. Direct renal excretion of INC280 was negligible and biliary excretion/intestinal secretion contributed only to a minor extent to the overall elimination of INC280.

INC280 is predominantly metabolized by cytochromes P450 (CYP) 3A4 with a contribution by aldehyde oxidase. INC280 showed inhibitory potency in vitro against CYP1A2, 2C8, 2C9, 2C19 and 3A4/5. INC280 also displayed inhibition of multidrug resistant 1/Permeability glycoprotein (P-gp), multi-xenobiotic resistance (MXR)/breast cancer resistant protein (BCRP), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 mediated substrate efflux or uptake. Therefore, at clinically relevant doses, potential drug-drug interactions are possible due to inhibition of CYP1A2, 2C8, 2C9, 2C19 and 3A4/5 metabolic enzymes, and/or due to inhibition of P-gp, BCRP, and OATP1B1/1B3 transporters. The clinical DDI study results are presented in Section 1.2.1.2.4.

For more detailed information refer to the current [INC280 Investigator's Brochure].

1.2.1.1.3 Safety pharmacology and toxicology

A series of preclinical safety studies were completed to support human clinical trials with INC280, including safety pharmacology studies, genetic toxicology studies, general toxicology studies (single- and repeat-dose studies) in the mouse, rat, and Cynomolgus monkey (in rats and monkeys up to 13 weeks in duration), and embryofetal developmental studies in rats and rabbits. Additionally, photosensitization potential was also assessed.

Safety pharmacology studies indicate that INC280 had no significant effects on central nervous system (CNS) and respiratory functions in rats, and no effects on cardiovascular function in monkeys. INC280 inhibited hERG potassium current by 50% at 18.7 μM.

Repeat-dose toxicity studies in animals reveal that kidneys, pancreas, CNS/brain, and potentially the liver may constitute the target organs or systems.

Kidney toxicity was observed in the 28-day monkey study where mild-to-moderate deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen were present in the 75 and 150 mg/kg/day, but not in the 30 mg/kg/day groups. It was noted that the results from the 13-week monkey study did not reveal any kidney toxicity at doses up to 75 mg/kg/day. INC280 inhibits renal transporter MATE1 and MATE2K with a Ki of 0.28 μM in vitro. A small portion of creatinine could be cleared via active tubular secretion by renal transporters such as MATE and OAT (Lepist et al 2014).

The findings in pancreas were observed in rats and monkeys in the 28-day and 13-week studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation, and elevations of amylase or lipase. In the 28-day monkey study, a dose of 30 mg/kg/day was identified as a NOAEL because of the low grade and reversible pancreatic findings present at that dose. In the 28-day rat study, the mid-dose groups (60 mg/kg/day in males and 30 mg/kg/day in females) also showed reversible low-grade pancreatic changes. Reversibility has been clearly demonstrated in both species. Similarly, in the 13-week rat study, reversible pancreatic acinar cell vacuolation was observed at the doses of ≥ 60 mg/kg for males and ≥ 30

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mg/kg for females. In the 13-week monkey study, no histopathology findings in the pancreas were detected. However, elevation of lipase was observed in one animal at the dose of 75 mg/kg.

Clinical signs indicative of CNS toxicity (such as tremors and/or convulsions), and histopathological findings of white matter vacuolation in thalamus were observed in rats of high-dose groups (60 mg/kg/day for females, and 120 mg/kg/day for males) in 28-day toxicity study. Additionally, results from the 13-week rat toxicity study reproduced the CNS effects and histopathological findings in the brain and also demonstrated that the CNS effects and brain lesions were reversible. Neither CNS signs nor brain lesions were observed in Cynomolgus monkey studies.

Changes in serum chemistry liver enzymes (ALT, AST, and/or SDH) were observed in several different studies in rats and monkeys. These changes were restricted to highly variable, minimal-to-mild elevations lacking a clear dose response. The significance of elevations of liver enzymes remains undetermined because of the high degree of individual variability, and the absence of any histological correlate within the liver, with the exception of the 13-week monkey study, where in the males given INC280 at 75 mg/kg/day, there was reversible minimal to mild subcapsular neutrophilic infiltration associated with single cell necrosis in the liver (without liver enzyme changes).

In vitro and *in vivo* genetic toxicology studies indicate that INC280 did not induce mutations or cause chromosome aberrations.

Embryo-fetal studies in rats and rabbits indicate that INC280 is teratogenic to both species and the teratogenicity is consistent with the mechanism of action by cMET inhibition, thus INC280 should be considered potentially teratogenic to humans.

With regard to potential photosensitivity, INC280 tested positive for phototoxicity in an in vitro 3T3 Neutral Red Uptake assay. In the follow-up *in vivo* study in mice (UV-Local Lymph Node Assay), 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 be with potential for photosensitization.

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

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

As of the cut-off date of 28-Sep-2018, a total of 1253 cancer patients and 236 non-cancer subjects have received INC280. A total of 709 patients with solid tumors have been treated with INC280 as a single agent, and 544 patients have been treated with INC280 in combination therapies. Fourteen [redacted] 6 patients in single agent studies and 13 in combination studies. For more information, please refer to the current INC280 [Investigator's Brochure].

Overall INC280 has been well tolerated by patients and the majority of the adverse events (AEs) reported with INC280 single agent have been of mild or moderate severity. The most

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frequent AEs suspected to be related to INC280 of any grade reported in the [CINC280A2201] study, which remains as the reference study for the safety profile of INC280 monotherapy, were edema peripheral (122 patients, [40.4%]), nausea (99 patients, [32.8%]), blood creatinine increased (58 patients, [19.2%]), vomiting (58 patients, [19.2%]), decreased appetite (40 patients, [13.2] and fatigue (40 patients, [13.2%]) and diarrhea (35 patients, [11.6]) and the majority were Grade 1/2. The Grade 3/4 AEs suspected to be related to INC280 in the [CINC280A2201] study included edema peripheral (19 patients, [6.3]) and lipase increased (15 patients, [5.0%]), fatigue (10 patients, [3.3%]), alanine aminotransferase increased (12 patients, [4.0%]), vomiting (6 patients, [2.0%], nausea and hypophosphatemia (each in 5 patients, [1.7%], aspartate aminotransferase (5 patients, [1.7%]).

The safety profile of INC280 (capmatinib) has been confirmed to be manageable across all cohorts in INC280A2201 and no new safety signals have been observed.

Pneumonitis and ILD have been reported from both INC280 single agent and combination studies with the EGFR TKIs, including events with fatal outcome. Investigators are advised to carefully monitor patients for signs and symptoms of pneumonitis and implement dose modification and follow up evaluations described in the protocol in all INC280 studies, both single agent and in combination studies.

The maximum tolerated dose (MTD) for INC280 capsules or tablets as single agent was not reached. The RP2D for INC280 as a single agent has been determined to be 600 mg BID in capsule formulation and 400 mg BID in tablet formulation. For latest and more information, please refer to the current [INC280 Investigator's Brochure].

1.2.1.2.2 Clinical efficacy

Based on available data as of 15-Mar-2016, from study [INC280X2102] preliminary clinical activity has been observed with INC280 as single agent therapy in NSCLC. Confirmed partial responses were observed in 11/55 (ORR 20%) evaluable NSCLC patients (defined as those with at least one post-baseline tumor assessment or have discontinued treatment at the time of the data cut-off) enrolled in the 2 expansion phases (treated at the RP2D of 400 mg BID tablet or 600 mg BID capsule) and DCR was 51%. In evaluable patients with cMET IHC 3+ (regardless of GCN), confirmed partial responses were seen in 9/37 patients (ORR 24%) and DCR was 60%, while in evaluable patients with *cMET* GCN ≥6 (IHC 3+, except 2 patients with IHC 2+), confirmed partial responses were seen in 7/15 patients (ORR 47%) and DCR was 80%. Kaplan–Meier median PFS was 3.55 months (95% CI 1.84–7.33) in the total NSCLC population (n=55), while in patients with cMET GCN ≥6 median PFS was extended to 7.39 months (95% CI 3.84–22.11). Four NSCLC patients with cMET exon 14 mutations were identified by retrospective NGS analysis: all 4 were IHC3+ and 3/4 had a GCN ≥10, while the GCN was missing in 1 patient; confirmed PR was achieved in 3 patients (2 with GCN >10 and 1 with unknown GCN), while one achieved unconfirmed PR (Schuler et al 2016). ALK status was available for 51/55 patients and all 51 (100%) were negative for ALK rearrangement. EGFR status was available in 50/55 patients and 49 (98%) were EGFR wt.

Thus, the preliminary efficacy data suggest that patients with NSCLC whose tumors are EGFR wt and have cMET amplification and/or mutations may obtain therapeutic benefit from treatment with single-agent INC280. Based on these preliminary but promising results, a more

thorough investigation of the activity of INC280 in patients with EGFR wt NSCLC with varying degrees of cMET amplification and/or cMET mutations is warranted in order to determine those individuals most likely to benefit from treatment with single-agent INC280.

Promising activity in cMET mutated NSCLC patients with INC280 as single agent therapy with INC280 400 mg BID, both in pretreated (Cohort 4) and particularly in treatment naïve (Sub-cohort 5b) setting was observed as of 09 Aug 2018 cut-off date: ORR by BIRC was 39.1% (95% CI 27.6–51.6) in 2/3 line patients (n=69, Cohorts 4) and 72.0% (95% CI 50.6–87.9) in treatment naïve patients (n=25, Sub-cohort 5b) (Wolf et al 2018).

1.2.1.2.3 Clinical pharmacodynamics

In study [CINC280X2102] (with single-agent INC280 in patients with cMET-dependent advanced solid tumors), pharmacodynamic effect (inhibition of the phosphorylation of cMET in paired biopsies) was observed in one colorectal cancer patient treated at 450 mg BID in capsules.

1.2.1.2.4 Clinical pharmacokinetics

As of 28-Sep-2018, INC280 (capsule and tablet) single agent steady state pharmacokinetic (PK) data are available from five clinical studies ([CINC280X2101T], [CINC280X2102], [CINC280X1101] [CINC280A2201] and [CINC280X2201]), and from four combination studies, INC280 plus gefitinib [CINC280X2202], INC280 plus cetuximab [CINC280X2104], INC280 plus EGF816 [CINC280X2105C] and INC280 plus BKM120 (buparlisib) [CINC280X2204]. After oral administration, INC280 was rapidly absorbed with the median time to reach maximum drug concentration (Tmax) ranging from 1 to 2 hours for tablets and from 1 to 4 hours for capsules. The elimination half-life estimated from [CINC280X1101] ranged from 3.5 to 6.3 hours across the cohorts. Accumulation in INC280 exposure following repeated administration of 400 mg BID tablets is low, with geometric mean accumulation ratio of 1.4-fold in the single agent [CINC280A2201] study. Steady state INC280 exposure is expected to be reached by the third day of consecutive BID dosing. The mean plasma exposures (Cmax and AUC) for INC280 generally increased with dose up to 600 mg QD and 600 mg BID administration with capsule formulation. The mean plasma exposure increase is roughly dose proportional for INC280 tablet from 200 to 400 mg BID.

A relative bioavailability study [CINC280X2103] was conducted to compare the INC280 MF (market form) tablet formulation to INC280 capsule formulation. The outcome of this study showed that tablets provided higher systemic exposures (Cmax and AUC) and lower inter-subject variability following a single oral administration of 600 mg INC280 in healthy subjects. Tablet PK data are available in cancer patients at different doses (150 mg to 400 mg BID) in various INC280 studies. In the study [CINC280X2102], the INC280 MF tablet at 400 mg BID (N=8) provided comparable mean AUC0-12h,ss (1. 05-fold) and slightly higher Cmax,ss (1. 44-fold) compared with the INC280 capsule at 600 mg BID (RP2D, N=45) in the limited subjects tested. In the ongoing phase 2 [CINC280A2201] study with FMI tablet, the exposures (both Cmax and AUC) were comparable to what was observed in [CINC280X2102] study at 400 mg BID. Based on the tablet PK and safety data from these studies, the dosage of INC280 at 400 mg BID in tablet form has been declared as the RP2D for the single agent studies.

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The effect of food on the rate and extent of INC280 exposure was assessed after a single oral dose administration of 600 mg INC280 tablet in healthy subjects [CINC280X2107]. Compared to fasting conditions, a low fat meal increased AUCinf and Cmax by 1.20- and 1.11-fold, respectively; and a high fat meal increased AUCinf and Cmax by 1.46- and 1.15-fold, respectively. Pharmacokinetics data from study [CINC280A2108] in which INC280 tablet was administered with food in cancer patients, indicated no clinically relevant food effect. At 400 mg BID dose, steady state AUC was similar to the exposure observed in study [CINC280A2201], therefore INC280 can be administered without regard to food.

INC280 displayed pH-dependent solubility *in vitro*. A study to evaluate the effect of a long acting proton pump inhibitor on the PK of a single dose of INC280 tablet was completed in healthy volunteers [CINC280A2101]. Daily treatment with 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. Similarly, PK data from patients on the concurrent use of PPI compared to those without PPI (Proton Pump Inhibitor) use from the study [CINC280A2108] showed a ~30% lower AUC0-12 at steady state , therefore caution is advised on the use of PPI when INC280 is taken with no regards of food.

A study to evaluate the effect of INC280 on the PK of CYP3A4 substrate (midazolam) and CYP1A2 substrate (caffeine) in patients with MET dysregulated solid tumors was completed [CINC280A2103]. Multiple doses of INC280 tablets at 400 mg BID did not lead to clinically significant increase of CYP3A4 substrate (midazolam) exposure. However, AUC of CYP1A2 substrate (caffeine) increased by 135%. Therefore, INC280 is not a CYP3A4 inhibitor, but a moderate CYP1A2 inhibitor.

A study to evaluate the effect of INC280 on the PK of Pgp substrate (digoxin) and BCRP substrate (rosuvastatin) in patients with MET dysregulated solid tumors was completed [INC280A2105]. Multiple doses of INC280 tablets at 400 mg BID led to a 74% increase in digoxin Cmax and a 47% increase in AUC. Rosuvastatin Cmax and AUC increased 204% and 108%, respectively. Therefore, INC280 is an inhibitor of P-gp as well as BCRP transporters, with clinically relevant DDI potential.

A study to evaluate the effect of itraconazole (strong CYP3A4 inhibitor) and rifampicin (strong CYP3A4 inducer) on the single-dose pharmacokinetics of INC280 in healthy subjects was completed [CINC280A2102]. When co-administered with itraconazole, INC280 AUC increased by approximately 40%. There was no change in Cmax. When co-administered with rifampicin, INC280 AUC and Cmax decreased by approximately 66% and 56%, respectively. The result indicated that INC280 is not a sensitive CYP3A4 substrate. Given that the reduction in exposure by strong CYP3A4 inducers could potentially compromise the efficacy, the concurrent use of strong CYP3A4 inducers with INC280 should be avoided.

INC280 does not show a risk of QT prolongation. Preliminary analysis on 110 patients in study [CINC280A2201] showed that no patients had new post-baseline QTcF values greater than 500 ms. Changes from baseline (ΔQTcF) greater than 60 ms were not observed and changes greater than 30 ms and below 60 ms were observed in 4 patients (4/110, 3.6%). The observed mean QTcF changes from baseline around Tmax (2 hours post-dose) were 5.21 ms on Cycle 1 Day 1 and -0.54 ms on Cycle 1 Day 15. Based on the PK/QT analysis, the estimated mean ΔQTcF (upper one-sided 95% CI) at mean steady state INC280 concentration

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2 hours post-dose (4584 ng/mL) was 0.11 ms (1.85 ms) at the recommended phase 2 dose of 400 mg BID with tablets. The upper one-sided 95% CIs for the estimated mean ΔQTcF at clinically relevant INC280 concentrations are below the regulatory threshold of 10 ms. For more information, please refer to the current INC280 [Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

cMET dysregulation (amplification, overexpression and mutations) constitutes an oncogenic driver in several tumor types, including lung cancer. Currently, there is no approved therapy for tumors with cMET dysregulations and therefore there is a high unmet medical need to develop therapy capable of cMET inhibition for the treatment of these tumors. INC280 is a highly potent and selective cMET inhibitor in biochemical and cellular assays and capable of blocking cMET activation. Overall, the emerging preclinical and clinical data suggest that INC280 may have a favorable benefit-risk ratio for the treatment of cMET dysregulated advanced lung cancer. The definition of cMET amplification and the activity in cMET amplified and/or cMET mutated NSCLC is based on limited clinical data and exploration of INC280 activity in patients with different levels of gene amplification and with mutation is warranted.

2.2 Rationale for the study design

This is a prospectively designed, multicenter, open-label, phase II study to evaluate the efficacy and safety of single-agent INC280 in patients with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations) and ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC harboring cMET amplification and/or cMET mutations with advanced/metastatic disease. Patients with cMET mutations will be enrolled in Cohort 4, Sub-cohort 5b and Cohort 7, irrespective to their cMET GCN. Patients without cMET mutations, will be enrolled in Cohorts 1-3 and Sub-cohort 5a, based on their cMET GCN. All patients in Cohorts 1, 2, 3, and 4 must have failed 1 or 2 prior lines of systemic therapy for advanced/metastatic disease, while patients enrolled in Cohort 5 and expansion Cohort 7 must be treatment-naïve for advanced/metastatic disease. Expansion Cohort 6 will be opened for both cMET high amplified (GCN≥10) and cMET mutated NSCLC patients who have failed 1 prior line of systemic therapy for advanced/metastatic disease.

The primary objective is to evaluate the antitumor activity of INC280 in the described patient population. The primary measure of antitumor activity is ORR according to RECIST 1.1 and as determined by blinded independent review committee (BIRC) to ensure unbiased assessment of response rate. A supportive analysis will be performed to assess the ORR based on investigator assessment. Response rate is an appropriate primary endpoint that can be adequately assessed and may predict clinical benefit in the context of this single-agent, phase II trial in NSCLC patients with cMET amplification and/or mutations. The suitability of such design and ORR end point has been demonstrated by the Health Authorities' approvals of crizotinib and ceritinib in ALK-positive rearrangement NSCLC in studies with similar design. Data on ORR will be supplemented with data on duration of response (DOR) and time to response (TTR).

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The study design will incorporate a Bayesian interim monitoring for Cohorts 1, 2, 3 and 4, based on pre-specified response criteria (see Section 10.7) for a decision on whether to continue enrollment or stop for futility each of the respective study cohorts.

The study will also monitor and assess safety of INC280 as monotherapy, the disease control rate (DCR), progression-free survival (PFS), overall survival (OS) [redacted] of INC280 treatment. These endpoints are considered to be important supportive endpoints to better assess the potential clinical benefit of INC280.

2.2.1 Rationale for cMET GCN cohorts

In terms of GCN, any value above 2 can be considered as amplified compared to normal tissue when looking across a population of cells. Gene copy numbers in the range of 4-5 are commonly considered low level amplification, whereas gene copy numbers of 6 and above are considered high (Schildhaus 2014). The use of GCN ≥ 6 as a cut- off to determine high amplification is an accepted and routinely used cut-off in pathology labs to determine high gene copy number in several settings (Schildhaus 2014). For cMET in NSCLC, of the initial 5 responders observed on the phase I study [CINC280X2102], 3 had GCN higher than 6 while 2 had no FISH result available (Ma et al 2015).

More recent data from the same study [CINC280X2102] firmly support that there is activity of INC280 in patients with cMET amplified NSCLC with cMET GCN ≥6 where confirmed partial responses were seen in 7/15 evaluable patients (ORR 47%), DCR was 80% and Kaplan–Meier median PFS was 7.39 months (95% CI 3.84–22.11) (Schuler 2016). Of these 7 responders, 3 patients had a GCN ≥10, however, 2 of these confirmed responders with a GCN ≥10 also harboured a concurrent cMET exon 14 skipping mutation. Therefore, the contribution of the very high cMET amplification to the response of INC280 still remains to be elucidated and further optimization of appropriate GCN cut off is warranted. The GCN ≥10 cut-off has been recently used to identify the cMET amplified cases in the most extensive analysis ever conducted in 11,205 lung cancer specimens (Ou 2016).

Preliminary efficacy data has also been observed with crizotinib in NSCLC patients with MET/CEP7 ratio of > 2.2 (Camidge 2014). Four out of six patients with MET/CEP7 ratio of > 5 achieved response, five responses out of 12 patients with MET/CEP7 ratio of > 2.2 were observed and no responses were seen in 2 subjects with low level amplification of (MET/CEP7 ratio ≤ 2.2) suggesting a differential gradient of response at higher level of amplification.

While detailed epidemiology data are still lacking, the prevalence of cMET amplification in NSCLC is known to diminish with the increase in GCN (Schildhaus 2014). With the emerging data, the assumption that patients with higher GCN may derive grater benefit from cMET inhibition with higher chance of response to treatment require further more robust exploration. To characterize the efficacy of INC280 in NSCLC patients with very high amplified disease and to ensure an adequate representation of patients with GCN ≥10, 2 sub-cohorts will be implemented in the high amplified Cohort 1 (cMET GCN of ≥ 6) that will enroll either patients with a cMET GCN of ≥ 6 and <10 or patients with a cMET GCN of ≥ 10. This will allow for adequate and robust characterization of the individual contribution of the two GCN ranges to the activity of INC280 in high amplified patients and to assess the

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likelihood of differential responses in the 2 ranges as previously suggested by Camidge 2014. Interestingly, very high cMET amplified tumor samples are expected to be mutually exclusive to RTK/RAS/PI3K driver events (Tong 2016) and with lower overlap with cMET exon 14 skipping mutation (Ou 2016).

[redacted]

In order to confirm that a GCN ≥ 6 is the optimal cut-off, two other cohorts including patients with lower level of amplification (GCN ≥ 4 and < 6 and GCN < 4), will be enrolled. Based on the relatively low prevalence of GCN ≥ 5 and < 6 patients versus GCN ≥ 4 and < 5, Cohort 2 targets to have at least 40% of patients with 5 ≤ cMET GCN < 6 to ensure adequate representation of this population. There are several publications suggesting that low amplification (between 3 and 5 copies) are a marker of poor prognosis (Okuda 2008, Cappuzzo 2009a, Go 2010, Chen 2011, Kowalczuk 2014). [redacted] Thresholds employed also varied. However, taken together the data suggests that on balance a lower cut-off using a GCN between 3 and 5 appears to define a group of patients with a poor prognosis in terms of overall survival and disease free survival. In this study we have defined two cohorts (one with GCN ≥ 4 and < 6 and one with GCN < 4) in order to span this amplification range and enable us to determine accurately the most appropriate threshold for cMET amplification as related to response to INC280. It is noted that, although not an enrollment criteria to this study, there is the potential for NSCLC patients in this population to be cMET dysregulated due to overexpression in the absence of amplification. Thus there is the potential for patients in the GCN < 4 cohort to be responsive to cMET inhibition by virtue of either low level amplification or another mechanism.

Overall, these data suggest that activity of cMET inhibitors across the range of cMET amplification warrants further exploration.

2.2.2 Rationale for cMET mutation cohorts

cMET mutations leading to exon 14 deletion have been identified as an actionable target for cMET inhibition in NSCLC (Kong-Beltran et al 2006, Salgia 2017, Despcarpetries 2018). Based on the data available, the overlap between high cMET amplification (defined as FISH GCN ≥ 6) and cMET mutations, although possible, has not been elucidated yet (TCGA web portal 2015, internal Novartis data) and no overlap between cMET mutation and either EGFR mutations or ALK translocation is expected (TCGA web portal 2015). Growing clinical data on the activity of cMET inhibitors in cMET-mutated NSCLC have been published showing promising efficacy, irrespective of the histology, making cMET mutations an attractive molecular target in advanced NSCLC (Frampton 2015, Jenkins 2015, Mendenhall 2015, Paik 2015, Waqar 2015, Liu 2015, Awad et al 2016, Jorge et al 2015, Lee et al 2015, Mahjoubi et al 2016, Drilon et al 2016, Drilon et al 2017, Felip et al 2018, Wolf et al 2018).

[redacted]

There is a growing body of clinical evidence that shows that cMET mutation, in particular, is a predictor of response to cMET inhibitors irrespective of the line of treatment (Frampton et al 2015, Schuler et al 2016, Drilon et al 2016, Awad et al 2017, Drilon et al 2017, Felip et al 2018, Wolf et al 2018).

Based on these emerging data, the activity of cMET inhibitors warrants further exploration also in cMET-mutated NSCLC.

2.2.3 Rationale for treatment-naïve cohort with cMET dysregulation

Increasing data confirms that cMET dysregulations such as cMET exon 14 skipping mutations and high cMET amplification are emerging as independent molecular drivers and predictors of response to cMET inhibition in NSCLC patients, irrespective of the number of prior lines of therapy including some preliminary evidence in the treatment-naïve setting (Frampton 2015, Jenkins 2015, Mendenhall 2015, Paik 2015, Waqar 2015, Liu 2015, Schuler 2016, Drilon 2016, Felip et al 2018, Drilon et al 2017, Wolf et al 2018).

Promising activity with INC280 in cMET dysregulated (either cMET amplified or cMET exon 14 skipping mutated) advanced NSCLC has been observed in the phase I study [CINC280X2102] (Schuler 2016). In patients with cMET amplified (GCN ≥6) NSCLC a 47 % ORR and median PFS of 7.4 months was reported. While these promising results were obtained mainly in pretreated patients, three patients (who declined chemotherapy) were enrolled as treatment-naïve. Two of these patients harbored cMET exon 14 skipping mutation (one had concurrent cMET amplification). Both patients gained benefit from INC280 treatment (tumor shrinkage -53.3% and -48.5%) achieving confirmed and unconfirmed partial responses, respectively. This result was consistent with the overall benefit gained by the other two cMET mutated patients enrolled in the study (pretreated with 1 and 3 prior lines of systemic therapy, respectively), leading to an ORR of 75% in cMET mutated patients (3 out of 4 patients achieved confirmed and durable partial responses). Overall, INC280 was well tolerated in both treatment-naïve and pretreated NSCLC patients.

While the data are still preliminary, cMET exon 14 skipping mutations and/or high cMET gene amplification are emerging as independent tumor drivers and patients harboring such cMET dysregulations can benefit from treatment with cMET inhibitors such as INC280, irrespective of prior lines of therapy and including treatment-naïve patients with acceptable safety profile. This concept was successfully confirmed in the treatment-naïve advanced NSCLC setting with other targeted agents directed against established molecular drivers such as EGFR mutation, ALK and ROS1 translocation which showed greater efficacy when compared with platinum-doublet chemotherapy (Rosell 2012, Sequist 2013, Solomon 2014). These data also confirmed that the safety profile of such targeted agents does not differ in the treatment-naïve setting compared to the pretreated setting.

There is no cMET inhibitor currently approved for cMET dysregulated NSCLC and the activity of platinum-based chemotherapy in patients with treatment-naïve advanced NSCLC harboring cMET exon 14 skipping mutations and/or high level of cMET amplification (GCN ≥10) is unknown.

[redacted]

2.2.4 Rationale for additional Cohort 6 in pretreated NSCLC with cMET dysregulation

While enrollment in the pretreated cohorts with cMET amplification less than 10 GCN (Sub-cohort 1b, Cohort 2 and Cohort 3) was stopped following the preplanned interim analyses for futility, Sub-cohort 1a (GCN ≥10) and Cohort 4 (cMET mutations) passed the futility criteria and enrollment is continuing until completion for these 2 cohorts.

In expansion Cohort 6, approximately additional 30 patients with advanced NSCLC pretreated with one prior line of systemic therapy harboring either cMET amplification (GCN≥10) or cMET mutations (irrespective of cMET GCN) will be enrolled after enrollment of the respective Sub-cohort 1a/Cohort 4 is completed.

The main purpose of this additional cohort is to generate supportive safety and efficacy data in this second line patient population (which currently accounts for the majority of patients enrolled in the respective Sub-cohort 1a and Cohort 4). Therefore Cohort 6 is considered representative of the overall targeted patient population of pretreated cMET high amplified and mutated NSCLC.

2.2.5 Rationale for additional Cohort 7 in treatment-naïve NSCLC with cMET mutation

In light of the promising data generated in cMET mutated NSCLC in treatment naive setting in Sub-cohort 5b (Wolf et al 2018 - see Section 1.2.1.2.2), the main purpose of Cohort 7 is to generate additional supportive safety and efficacy data in this is first line patient population, which currently accounts for the patients enrolled in Sub-cohort 5b of this study.

2.3 Rationale for dose and regimen selection

As of 28-Sep-2014, the cut-off date of the IB available at the time of preparation of the original protocol, a total of 203 patients have been treated with INC280 as a single agent with either the capsule formulation (N=192) or tablet formulation (N=11). Five DLTs were experienced with INC280 as a single agent with the capsule formulation and no DLTs were observed with the tablet formulation (see Table 2-1).

Table 2-1 DLTs experienced with single agent INC280 as of 28-Sep-2014

Study and Treatment	N	Dose Limiting Toxicities
Study CINC280X1101		
INC280 capsules:		
100 mg QD	3	None
200 mg QD	4	None
400 mg QD	3	None
500 mg QD	4	None
600 mg QD	4	None
800 mg QD	4	None
400 mg BID	4	None
600 mg BID	3	Grade 2 malaise and suicidal ideation
INC280 tablets:		
200 mg BID	3	None

[redacted]

Study and Treatment	N	Dose Limiting Toxicities
400 mg BID	3	None
Study CINC280X2101		
INC280 capsules:		
10 mg QD	3	None
20 mg QD	4	None
50 mg QD	6	Grade 3 AST and ALKP increase
70 mg QD	4	None
50 mg BID	3	None
150 mg QD	3	None
200 mg QD	4	None
300 mg QD	4	None
400 mg QD	6	None
200 mg BID	4	None
300 mg BID	4	None
Study CINC280X2102		
INC280 capsules:		
100 mg BID	4	None
200 mg BID	5	Grade 3 fatigue
250 mg BID	4	Grade 3 blood bilirubin increased
350 mg BID	3	None
450 mg BID	9	Grade 3 fatigue
600 mg BID escalation	8	None
600 mg BID expansion	53	None
INC280 tablets:		
400 mg BID	5	None

Based on the data from study [CINC280X2102], and the observation that exposure did not further increase from 600 mg to 800 mg QD dosing, the RP2D of INC280 monotherapy in adults (in capsules) is 600 mg BID. Single-agent INC280 is generally tolerable at this dose when given twice daily on a continuous dosing schedule, with most adverse events (AEs) being manageable and of grade 1 and grade 2 severity.

As of 28-Sep-2014 ([Investigator's Brochure edition 5.2] data cut-off date), preliminary PK data were available from 10 patients treated with the INC280 tablet formulation as single agent at 200 mg or 400 mg BID dose. Based on the limited data, mean Cmax at steady-state following administration of INC280 tablets at 400 mg BID was 41% higher than that following capsules administration at 600 mg BID. Considering the 67% variability (CV%) observed with the capsule formulation at 600 mg BID, tablets at 400 mg BID (CV%= 30%) provided exposures within the range of exposures observed with capsules at 600 mg BID (the RP2D in study [CINC280X2102]).

In study [CINC280X2101] (single agent capsules), dose-dependent inhibition of phospho-cMET was observed across 11 dose cohorts (10 mg QD up to 400 mg QD or 300 mg BID) and complete inhibition was observed at trough concentration on Day 15 at 200 mg BID single agent capsules. In addition, complete inhibition of tumor cMET phosphorylation in patients was observed at 450 mg BID single agent capsules in study [CINC280X2102] and at 400 mg BID capsules in combination with gefitinib in study [CINC280X2202]. Based on the observed 400 mg BID tablet exposure, which appears to be higher in mean level but within

[redacted]

the range of 600 mg BID capsule exposure, the 400 mg BID tablet dose and regimen is expected to provide high enough inhibition levels to be efficacious. For details, refer to Section 1.2.1.2.4 and [Investigator's Brochure edition 5.2].

Based on the available tablet PK and safety data, the dosage of INC280 at 400 mg BID in tablet formulation was found to be tolerable in patients and has been declared as the RP2D and is being further evaluated in the ongoing INC280 studies.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

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		
To evaluate the antitumor activity of INC280, as measured by overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment, by cohort/sub-cohort	ORR, proportion of patients with a best overall response defined as complete response or partial response (CR+PR) by BIRC assessment per RECIST 1.1	Refer to Section 10.4
Key secondary		
To evaluate duration of response (DOR) as assessed by BIRC, by cohort/sub-cohort	DOR, calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for patients with PR or CR	Refer to Section 10.5.1
Other secondary		
1. To evaluate ORR and DOR by investigator assessment, by cohort/sub-cohort	ORR (CR+PR) and DOR per RECIST 1.1 by investigator assessment	Refer to Section 10.5.2
2. To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort/sub-cohort	All calculated per RECIST 1.1, both by BIRC and investigator: • TTR, calculated as the time from first dose of INC280 to first documented response (CR+PR) for patients with PR or CR • DCR, calculated as the proportion of patients with best overall response of CR, PR, or SD • PFS, defined as time from first dose of INC280 to progression or death due to any cause	Refer to Section 10.5.2
3. To evaluate overall survival (OS), by cohort/sub-cohort	OS, defined as time from first dose of INC280 to death due to any cause	Refer to Section 10.5.2
4. To evaluate INC280 safety profile as monotherapy in NSCLC patients with advanced/metastatic disease	Incidence of adverse events and serious adverse events, change in vital signs, laboratory results (hematology, blood chemistry, and urinalysis) and ECG.	Refer to Section 10.5.3
5. To characterize the pharmacokinetics of INC280 and metabolite CMN288	Plasma concentration-time profiles and pharmacokinetic parameters estimated by non-compartmental analysis or population PK modeling	Refer to Section 10.5.4

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a prospectively designed, multicenter, open-label, phase II study to evaluate the efficacy and safety of single-agent INC280 in patients with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC harboring cMET amplification and/or mutations.

Approximately 456 male and female patients aged 18 or over will be enrolled in this study in 7 separate cohorts [138 in Cohort 1 (69 patients per each Sub-cohort 1a and 1b) and 69 patients in each Cohorts 2, 3, and 4; 54 patients in Cohort 5 (27 patients per each Sub-cohort 5a and 5b); approximately 30 patients in Cohort 6; approximately 27 in Cohort 7] depending on their cMET amplification and/or mutation status and prior treatment status. A Bayesian interim monitoring for Cohorts 1, 2, 3 and 4, based on pre-specified response criteria is used (see Section 10.7) for a decision on whether to continue enrollment or stop for futility in the respective cohort. Due to the promising data for the treatment naïve patients from [INC280X2102] study, drug tolerability as observed in the other cohorts, and the outcome of the futility interim analyses in Sub-cohort 1a and Cohort 4, as well as the small sample size of Sub-cohorts 5a and 5b, interim analyses for futility are not being implemented in the treatment naïve Sub-cohorts, Cohort 6 and Cohort 7.

For patients with NSCLC, EGFR mutation and ALK rearrangement status should have been assessed as part of the patients standard of care using a validated test as per the Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors from College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (Lindeman et al 2013). The EGFR wt status (for exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the patient source documents before patient can be consented for cMET amplification and mutation pre-screening (except for patients who are treatment-naïve potentially eligible for Sub-cohort 5a and 5b or if molecular pre-screening will be performed by NGS and local status is not available). ALK rearrangement status, if known, should also be documented in the patient's source documents prior to cMET testing, except for patients who are treatment-naïve potentially eligible for Sub-cohorts 5a, and 5b and Cohort 7. If ALK testing is not available for a patient, their ALK status will be determined centrally with a validated test along with their cMET amplification and cMET mutation status. Patients with NSCLC of pure squamous cell histology can enter pre-screening without EGFR mutation or ALK testing or result, however patients with pure squamous cell histology and are known to have EGFR mutations in exons 19 and 21 or ALK-positive rearrangement will be excluded.

Patients will be pre-screened for cMET amplification based on GCN (and ALK rearrangement status, if applicable) by FISH and for cMET mutations by RT-PCR at a Novartis-designated central laboratory following the signing of the molecular pre-screening Informed Consent Form (ICF). Next Generation Sequencing (NGS) may be used as primary pre-screening diagnostic, if assay becomes available. Patients with previously determined cMET mutation or amplification by a Novartis designated central laboratory (as detected by the same

[redacted]

validated NGS assay used in this protocol) who have consented for the use of those results, will be allowed to enter directly the screening phase of the INC280A2201 study. For patients coming from another Novartis study using the same central lab or being rescreened, repeat tumor biopsy or additional archival tumor may not be required provided the central laboratory confirms adequate tumor tissue remains for the required study analyses.

All patients in Cohorts 1, 2, 3, and 4 must have failed 1 or 2 prior lines of systemic therapy, while patients enrolled in Cohorts 5 and 7 must be treatment-naïve for advanced disease. Patients enrolled in Cohort 6 must have failed 1 prior line of systemic therapy for advanced/metastatic disease.

Patients with cMET mutation will be enrolled based on the prior therapy status in Cohort 4 or Sub-cohort 5b or Cohort 7, irrespective of their cMET GCN. Patients without cMET mutations, will be enrolled in Cohort 1 (Sub-cohorts 1a or 1b), Cohort 2, and Cohort 3 and Sub-cohort 5a, based on their cMET GCN and prior treatment status. Patients enrolled in Cohort 6 can be either with cMET GCN $\geq$10 without cMET mutations or with cMET mutation irrespective to their cMET GCN. The enrollment in this Cohort 6 will only start upon enrollment completion of the respective Sub-cohort 1a or Cohort 4.

Only the cMET amplification and mutation test results from the pre-screening analysis performed by the Novartis-designated laboratory will be used to assign patients into the following 7 cohorts:

- Cohort 1: Pre-treated patients with cMET GCN $\geq$ 6, including:
  - Sub-cohort 1a: Patients with a cMET GCN of $\geq$ 10, or
  - Sub-cohort 1b: Patients with a cMET GCN of $\geq$ 6 and < 10, or
- Cohort 2: Pre-treated patients with cMET GCN $\geq$ 4 and < 6, or
- Cohort 3: Pre-treated patients with cMET GCN < 4, or
- Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or
- Cohort 5: Treatment-naïve patients with cMET dysregulation, including:
  - Sub-cohort 5a: Patients with a cMET GCN $\geq$10, or
  - Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or
- Cohort 6: Pre-treated patients with either cMET GCN $\geq$ 10 without cMET mutations or cMET mutations regardless of cMET GCN or,
- Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN

For the interim and final analyses in Cohort 2 (cMET GCN $\geq$ 4 and < 6), the study targets to have at least 40% of patients with cMET GCN $\geq$ 5 and < 6. Enrollment in each cohort will be controlled via Interactive Response Technology (IRT) system.

Each cohort/sub-cohort of the study will enroll patients in parallel. Patients in all cohorts will be treated with 400 mg INC280 twice daily (BID) using the tablet formulation, administered orally on a continuous dosing schedule.

Efficacy assessment of tumor response and progression will be performed every 6 weeks (i.e., every 2 cycles) from the first day of treatment with INC280 until RECIST 1.1 disease progression as determined by investigator and confirmed by Blinded Independent Review Committee (BIRC). This schedule must be followed regardless of dose interruptions.

[redacted]

Confirmation of response is required for all response endpoints, as per RECIST 1.1. All radiological assessments obtained at screening/baseline, during treatment and during the follow-up phase should be performed using the same modality (method) and will be submitted to the designated independent imaging vendor for review by BIRC.

Approximately 30 enrolled patients at selected sites (regardless of cohort assignment) will have full PK samples and ECGs collected. The rest of the patients will have sparse PK samples and ECGs collected (see Table 7-6 and Table 7-7). At the time of eligibility confirmation, the IRT system will inform the site about which PK and ECG schedule should be followed by the patient.

In Cohort 1 and Cohort 5, all of the efficacy analyses will be performed separately for each of the two sub-cohorts.

Interim analyses for futility will be performed separately for Sub-cohorts 1a and 1b and Cohorts 2 and 4 when there are at least 28 evaluable patients in each cohort/sub-cohort. Interim analyses for futility for Cohort 3 will be performed when there are at least 20 evaluable patients in Cohort 3. Evaluable patients are defined as those patients who have completed at least 6 cycles of treatment (18 weeks) or have discontinued the study treatment earlier. The decision to stop for futility at interim will be based on the probability of success (POS) which will be calculated based on the evaluable patients in each cohort/sub-cohort. One (or more) of the cohorts/sub-cohorts will be stopped for futility if the respective POS is less than 10% at the interim analysis. In each of Sub-cohorts 1a and 1b and Cohorts 2 and 4, if 7 or fewer responses are observed in 28 evaluable patients at interim analysis, then the respective cohort/sub-cohort will be stopped for futility. If at the time when the 28th patient is enrolled a minimum of 8 responders have not yet been observed, accrual in the cohort/sub-cohort may be temporarily suspended until either the minimum number of 8 responders is observed or results of the interim analysis allow the cohort/sub-cohort to continue. In Cohort 3, if 5 or fewer responses are observed in 20 evaluable patients at interim analysis, then this cohort will be stopped for futility. If at the time when the 20th patient is enrolled a minimum of 6 responders have not yet been observed, accrual may be temporarily suspended in the cohort until either the minimum number of 6 responders is observed or results of the interim analysis allow the cohort to continue. No interim analysis for futility is planned for Cohort 5, Cohort 6 and 7.

The primary analysis will be conducted when all treated patients in their respective cohort/sub-cohort (if not stopped for futility at interim analysis) have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier. Due to the expected difference in enrollment rate for each cohort/sub-cohort, the primary analysis for the different cohorts/sub-cohorts may occur at different times. The primary analysis for any cohort that was stopped for futility may be combined with the primary analyses for other cohorts.

In Cohorts 1, 2, 3 and 4, treatment with INC280 would be considered to have clinically relevant efficacy if an ORR of ~35% is observed in that cohort/sub-cohort for the corresponding primary analysis. In addition, 5 hypotheses will be tested as following for the cohorts/sub-cohorts (H_{i0} and H_{i1} correspond to cohort/sub-cohort i where i=1a, 1b, 2, 3 or 4):

H_{i0}: ORR $\leq$ 25%

[redacted]

In favor of the alternative

H_{i1}: ORR > 25%

For Sub-cohorts 5a, 5b and Cohort 7, treatment with INC280 would be considered to have clinically relevant efficacy if an ORR of ~55% is observed in that cohort for the corresponding primary analysis. In addition, 3 hypotheses will be tested as following for the cohorts/sub-cohorts (H_{i0} and H_{i1} correspond to sub-cohort i where i=5a, 5b or 7):

H_{i0}: ORR $\leq$ 35%

In favor of the alternative

H_{i1}: ORR > 35%

The tests will be performed based on the exact CI for ORR in each cohort/sub-cohort using a one-sided α= 0.025 level.

Data from Cohort 6 will help characterize the safety and efficacy of INC280 in pre-treated Cohorts 1a and 4. Efficacy and safety data will be presented for Cohort 6 alone and also may be analyzed by combining the patients with a cMET GCN of $\geq$ 10 from Sub-cohort 1a and Cohort 6 to further evaluate the precision of the efficacy estimates. Similar analysis may be carried out for pre-treated patients with cMET mutations regardless of cMET GCN combining the patients from Cohort 4 and Cohort 6. No hypothesis testing is planned for Cohort 6.

Data from Cohort 7 will help to further characterize the safety and efficacy of INC280 in treatment-naïve group with cMET mutations regardless of cMET GCN. Efficacy and safety data will be presented for Cohort 7 alone and also in combination with the patients from Sub-cohort 5b to further evaluate the precision of the efficacy estimates. Cohort 7 efficacy data may be pooled with Sub-cohort 5b once Cohort 7 enrolment is closed and when all treated patients in Cohort 7 have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier.

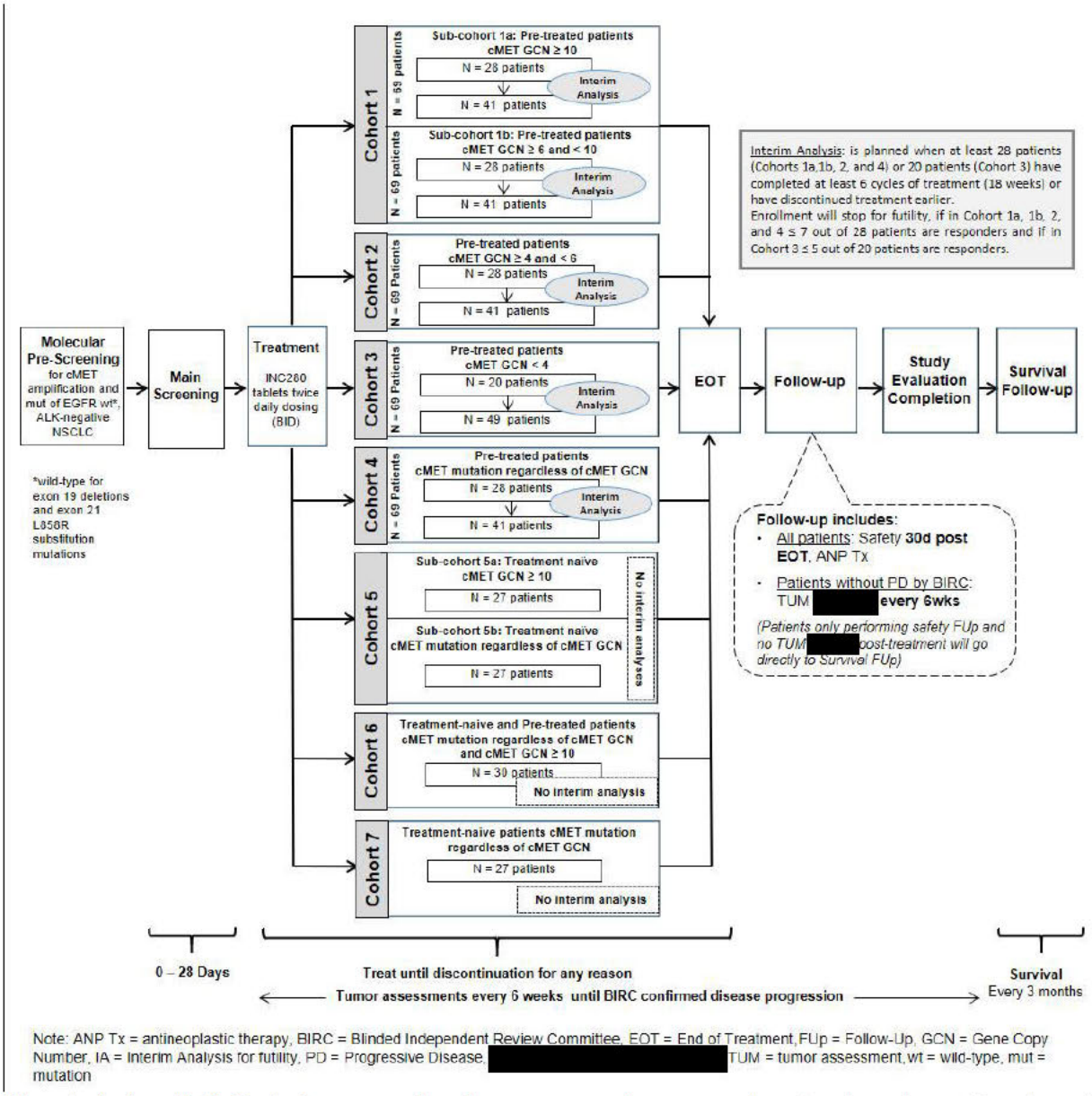
In addition to the imaging vendor conducting the BIRC review, the study will be supported by a Central Laboratory for the routine safety assessment (i.e., hematology, chemistry, coagulation, and urinalysis), a central vendor for ECG assessments and by interactive web or voice response system (IRT) for patient registration and drug supply. For details on study assessments, refer to Section 7.

[redacted]

Refer to Figure 4-1 for an overview of the study design.

[redacted]

Figure 4-1 Overall study design



Note: ANP Tx = antineoplastic therapy, BIRC = Blinded Independent Review Committee, EOT = End of Treatment, FUp = Follow-Up, GCN = Gene Copy Number, IA = Interim Analysis for futility, PD = Progressive Disease, [redacted] TUM = tumor assessment, wt = wild-type, mut = mutation

The study has 5 distinct phases: molecular pre-screening, screening, treatment, post-treatment follow-up (safety and tumor) and survival follow-up.

4.1.1 Molecular pre-screening

Patients will be pre-screened to test for their cMET amplification and mutation status. If ALK testing is not available for a patient, their ALK rearrangement status will be determined centrally with a validated test along with their cMET amplification and mutation status. All patients must sign a molecular pre-screening ICF and register into the IRT system before a sample is sent for testing to the Novartis-designated central laboratory.

The test will be performed using either a newly obtained tumor biopsy (preferred) or archival tumor tissue of a formalin fixed paraffin embedded (FFPE) tumor block or slides. cMET

[redacted]

amplification and mutation testing must be performed by a Novartis-designated central laboratory to determine eligibility. If a patient's cMET amplification and/or mutation status is known via a local result, confirmation of their status via a Novartis-designated central laboratory is required to confirm eligibility. A small amount of tissue material will be retained from all patients (including pre-screen and screen failures) by Novartis, to allow the development of additional companion diagnostic test such as NGS.

Complete information on the molecular pre-screening process, including sample requirements and methodology, may be found in the [Laboratory Manual].

If any cohort/sub-cohort is closed to enrollment then only patients with the cMET amplification or mutation status required for the open cohort(s)/sub-cohort(s) will be eligible for main screening for study enrollment. Similarly, enrollment of patients with cMET GCN $\geq$ 4 and $<$ 5 in Cohort 2 may be stopped when the target of 60% patients is reached in order to ensure that the target of at least 40% patients with cMET GCN $\geq$ 5 and $<$ 6 at IA will be met.

As of 25-Jan-2019, pre-screening for cMET amplification by FISH for eligibility based on GCN has been be discontinued. Eligibility for Cohort 6 and Cohort 7 will be solely based on the presence of cMET mutations leading to exon 14 deletion.

4.1.2 Main screening

After the Novartis-designated laboratory's result determines cMET amplification and cMET mutation status (and ALK rearrangement status, as applicable), patients may enter the main screening to assess eligibility. All patients must provide a signed main ICF prior to performing any screening procedures to determine patient eligibility. Patients will be evaluated against all study inclusion and exclusion criteria. Baseline evaluations must be performed within 4 weeks ($\leq$ 28 days) prior to the first dose of study drug.

[redacted]

When all screening procedures are completed and once the patient's eligibility has been checked and confirmed **(i.e., all inclusion/exclusion criteria have been verified)**, the key eligibility criteria checklist will be completed prior to Day 1 of Cycle 1 (first dose of INC280) in the IRT system by the investigator or designee.

For details of screening assessment, refer to Table 7-1.

4.1.3 Treatment

The treatment period begins on Day 1 of Cycle 1. Treatment cycle is defined as 21 days. The first dose of INC280 will be administered at the study center. All patients will be treated with 400 mg INC280 twice daily (BID) using tablet formulation, administered orally on a continuous dosing schedule.

Treatment with INC280 will continue until patient experiences any of the following: disease progression according to RECIST 1.1 as determined by investigator and confirmed by BIRC, unacceptable toxicity that precludes further treatment, treatment is discontinued at the discretion of the Investigator or patient, or death, or lost to follow-up, etc. Treatment with INC280 may be continued beyond RECIST1.1-defined PD (as assessed by the investigator

[redacted]

and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment. Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment.

When the patient discontinues from study treatment, an End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of INC280.

4.1.4 Follow-up

Regardless of the reason for discontinuation from study treatment, patients will be contacted for a safety follow-up 30 days after the last dose of INC280. At this time, the investigator will record any AEs/SAEs that may have occurred after discontinuation of study treatment and/or follow on resolution of ongoing AEs.

All patients who discontinue treatment with INC280 for any reason other than disease progression according to RECIST 1.1 as determined by investigator and confirmed by BIRC, death, withdrawal of consent for further assessments or lost to follow-up will continue to have tumor assessments as per their current schedule until disease progression is confirmed by BIRC, death, withdrawal of consent for further assessments, or lost to follow-up. [redacted]

When the patient completes all follow-up assessments as required per protocol, a Study Evaluation Completion eCRF must be completed.

Information on new anticancer therapies initiated since discontinuation of study treatment will be collected.

4.1.5 Survival follow-up

Patients will be contacted and followed for survival every 3 months until death, loss to follow-up, withdrawal of consent to survival follow-up, or the end of the study (as defined in Section 4.3). Survival follow-up may be obtained via a phone call.

4.2 Timing of interim analyses and design adaptations

In Cohort 1, the interim analysis will be performed separately for each of the two sub-cohorts. Interim analyses for futility assessment are planned for each cohort/sub-cohort when at least 28 patients in each of Sub-cohorts 1a and 1b, and Cohorts 2 and 4, and 20 patients in Cohort 3 have completed at least 6 cycles of treatment (18 weeks) or have discontinued treatment earlier. The decision to stop for futility at interim will be based on the probability of success (POS) and will be calculated based on the actual number of evaluable patients at the interim analysis. A cohort/sub-cohort will be stopped for futility if the respective POS is less than 10% at the interim analysis. With 28 evaluable patients for interim analysis in each of the Sub-cohorts 1a and 1b, and Cohorts 2 and 4, if 7 or fewer responses are observed, then the cohort/sub-cohort will be stopped for futility. If at the time that the 28th patient is enrolled a minimum of 8 responders have not yet been observed, accrual in the cohort/sub-cohort may be temporarily suspended until either the minimum number of 8 responders are observed or results of the interim analysis allow the cohort/sub-cohort to continue.

[redacted]

With 20 evaluable patients for interim analysis in Cohort 3, if 5 or fewer responses are observed then the respective cohort will be stopped for futility. If at the time that the 20th patient is enrolled a minimum of 6 responders have not yet been observed, accrual in the cohort may be temporarily suspended until either the minimum number of 6 responders are observed or results of the interim analysis allow the cohort to continue.

No interim analysis for futility assessment is planned for Cohort 5,Cohort 6 and Cohort 7.

All evaluable patients at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the POS criteria. The futility boundary will be calculated according to the actual number of evaluable patients in the interim analysis.

The statistical considerations for the interim analysis can be found in Section 10.7.

4.3 Definition of end of the study

Following the cut-off date for the primary analysis reported in the primary Clinical Study Reports (CSR)(s), the study will remain open. After all of the primary analyses for the different cohorts have been conducted, ongoing patients will continue to receive INC280 treatment and be followed as per the schedule of assessments, as long as patients derive benefit from INC280 or until the end of study defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide INC280 in this patient population and all patients ongoing are eligible to be transferred to that clinical study
- INC280 is commercially available and ongoing patients are able to obtain reimbursement of commercial supply

The final analysis will occur at the end of the study. All available data from all patients up to this cut-off date will be analyzed and summarized in a final CSR.

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 7.1.5 for a discontinued or 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 ECs of the early termination of the trial.

5 Population

5.1 Patient population

This study will enroll adult male and female patients with EGFR wt (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-negative rearrangement, advanced (stage IIIB or IV) NSCLC who have failed one or two prior lines of systemic therapy (Cohorts 1-4),

[redacted]

who have failed one prior line of systemic therapy (Cohort 6), or who have received no systemic therapy (Cohort 5 and Cohort 7) for advanced/metastatic disease.

Treatment failure is defined as documented disease progression or intolerance to treatment.

Patients enrolled in the 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:

Written informed consent must be obtained prior to any screening procedures

1. Age ≥ 18 years
2. Stage IIIB or IV NSCLC (any histology) at the time of study entry
3. Histologically or cytologically confirmed diagnosis of NSCLC that is:
   a. EGFR wt. This should have been assessed as part of the patient standard of care by a validated test for EGFR mutations, as per the Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors from College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (Lindeman et al 2013). The EGFR wt status (for exon 19 deletions and exon 21 L858R substitution mutations) must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification and cMET mutation status (except for patients who are treatment-naïve potentially eligible for Sub-Cohort 5a, 5b and Cohort 7 or if molecular pre-screening will be performed by NGS and local status is not available). Patients with NSCLC of pure squamous cell histology can enter pre-screening without EGFR mutation testing or result, however patients with pure squamous cell histology and are known to have EGFR mutations in exons 19 or 21 will be excluded,
   b. AND ALK rearrangement -negative. This should have been assessed as part of the patient standard of care by a validated test. The ALK rearrangement-negative status must be documented in the patient source documents before the patient can be consented for pre-screening for cMET amplification and cMET mutation status, except for patients who are treatment-naïve potentially eligible for Sub-Cohorts 5a, 5b and Cohort 7; if local ALK testing is not available, patient status will be determined centrally along with the cMET status. Patients with NSCLC of pure squamous cell histology can enter pre-screening without ALK testing or result, however patients with pure squamous cell histology that are known to have ALK rearrangement will be excluded.
   c. AND (as determined by central assessment at a Novartis designated laboratory) either:
      - Cohort 1: Pre-treated patients with cMET GCN ≥ 6, including:
        - Sub-cohort 1a: Patients with cMET GCN of ≥10, or
        - Sub-cohort 1b: Patients with cMET GCN of ≥ 6 and < 10, or

[redacted]

- Cohort 2: Pre-treated patients with cMET GCN ≥ 4 and < 6, or
- Cohort 3: Pre-treated patients with cMET GCN < 4, or
- Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or
- Cohort 5: Treatment-naïve patients with cMET dysregulation, including:
  - Sub-cohort 5a: Patients with cMET GCN of ≥10, or
  - Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or
- Cohort 6: Pre-treated patients with either cMET GCN ≥ 10 without cMET mutations or cMET mutations regardless of cMET GCN, or
- Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN

cMET (and ALK, if applicable) testing may be performed while patient is still receiving anti-cancer therapy. However, the patient can only be screened for the main study once the patient has discontinued the last prior systemic treatment due to either disease progression or intolerance.

4. To be eligible for Cohorts 1-4, patients must have failed one or two prior lines of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). To be eligible for Cohort 6, patients must have failed one prior line of systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Treatment failure is defined as documented disease progression or intolerance to treatment. Maintenance therapy given after first line chemotherapy will be considered as part of the first line if given to patients with documented response or stable disease before starting the maintenance therapy. Neo-adjuvant and adjuvant systematic therapies will count as one prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.

   To be eligible for Cohort 5 and 7, patients must not have received any systemic therapy for advanced/metastatic disease (stage IIIB or IV NSCLC). Neo-adjuvant and adjuvant systemic therapies will not count as one prior line of treatment if relapse occurred > 12 months from the end of the neo-adjuvant or adjuvant systemic therapy.
5. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
6. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03). Patients with any grade of alopecia are allowed to enter the study.
7. Patients must have adequate organ function including the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L without growth factor support
   - Platelets ≥ 75 x 10^9/L
   - Hemoglobin (Hgb) > 9 g/dL
   - Calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 45 mL/min
   - Total bilirubin ≤ 1.5 x ULN

[redacted]

- Aspartate transaminase (AST) ≤ 3 x ULN, except for patients with liver metastasis, who may only be included if AST ≤ 5 x ULN
- Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastasis, who may only be included if ALT ≤ 5 x ULN
- Alkaline phosphatase (ALP) ≤ 5 x ULN
- Asymptomatic serum amylase ≤ grade 2. Patients with grade 1 or grade 2 serum amylase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
- Serum lipase ≤ ULN
- Fasting plasma glucose ≤ 175 mg/dL (≤ 9.7 mmol/L)
- Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
  - Potassium
  - Magnesium
  - Phosphorus
  - Total calcium (corrected for serum albumin)

8. ECOG performance status (PS) of 0 or 1.
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. Prior treatment with crizotinib, or any other cMET or HGF inhibitor
2. Patients with known hypersensitivity to any of the excipients of INC280 (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
3. Patients with characterized EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 mutations.
4. Patients with characterized ALK-positive rearrangement.
5. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms
6. Presence or history of carcinomatous meningitis
7. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type
8. Clinically significant, uncontrolled heart diseases.
   - Unstable angina within 6 months prior to screening
   - Myocardial infarction within 6 months prior to screening

[redacted]

- History of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
- Ventricular arrhythmias
- Supraventricular and nodal arrhythmias not controlled with medication
- Other cardiac arrhythmia not controlled with medication
- QTcF ≥ 450 ms (male patients), ≥ 460 ms (female patients) on the screening ECG (as mean of triplicate ECG)

9. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting INC280 is allowed
10. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting INC280 or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥ 1 week after the procedure
11. Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study:
    - Strong inducers of CYP3A4
12. Impairment of GI function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
13. Unable or unwilling to swallow tablets as per dosing schedule
14. Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of INC280
15. Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of INC280, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible
16. Applicable to Cohorts 1-4 and Cohort 6 only: Previous anti-cancer and investigational agents within 4 weeks or ≤ 5 x half-life of the agent (whichever is longer) before first dose of INC280. If previous treatment is a monoclonal antibody, then the treatment must be discontinued at least 4 weeks before first dose of INC280. If previous treatment is an oral targeted agent, then the treatment must be discontinued at least 5 x half-life of the agent before the first dose of INC280.

[redacted]

17. Other severe, acute, or chronic medical or psychotic conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results
18. 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 (including active hepatitis B and C), inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
19. Pregnant or nursing (lactating) women
20. 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 stopping treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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), total 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). The vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

    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), total 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
21. Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
22. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational treatment" or "study drug" refers to INC280. The dose and treatment schedule are listed in Table 6-1.

The orally administered film-coated tablet formulation will be provided in up to three strengths of 100 mg, 150 mg and 200 mg (if available) free base equivalent. For the list of excipients, please refer to current [Investigator's Brochure].

6.1.1 Dosing regimen

INC280 tablet will be administered orally on a continuous twice daily (BID) dosing schedule, on a flat scale of mg/day and not individually adjusted by weight or body surface area. A complete cycle of treatment is defined as 21 days of twice daily treatment with INC280. The investigator must instruct the patient to take the study drug exactly as prescribed.

- Except on days of PK sampling, patients should take 400 mg INC280 tablets twice daily (BID) at approximately the same time each day starting at Cycle 1 Day 1.
- Each dose of INC280 is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).
- Patients should be instructed to swallow the tablets whole and not to chew them.
- INC280 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. The morning dose should be taken the same time each morning. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced
- Only for Cohort 6 and 7, INC280 can be administered with or without food.
- On days when PK blood samples are to be collected, patients will be instructed to hold their dose until arrival at the study center. INC280 will be administered at the site in the morning prior to the PK blood draws supervised by a member of the research team. The exact time of drug administration should be recorded in the appropriate eCRF. If a patient vomits within 4 hours of INC280 dosing, the time of vomiting should be recorded on the eCRF.
- Patients should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole 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 solarium).

[redacted]

The investigator should instruct the patient to take INC280 exactly as prescribed. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC280	Tablet for oral use	400 mg (4 x 100 mg or 2 x 200 mg, if available, or 2 x 150 mg + 1 x 100 mg, if applicable)	Twice Daily (BID)

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines for dose modification of treatment, refer to Section 6.3.

6.1.5 Treatment duration

Patients may be discontinued from treatment with INC280 earlier due to:

- Disease progression according to RECIST 1.1 as determined by investigator and confirmed by BIRC. Patients may continue treatment with INC280 beyond RECIST 1.1-defined PD (as determined by investigator and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment.
- Unacceptable toxicity that precludes further treatment
- Discontinued treatment at the discretion of the investigator or the patient
- Death
- Patient is lost to follow-up

6.2 Dose escalation guidelines

Not Applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). Any changes must be recorded on the Dosage Administration Record eCRF page.

[redacted]

General guidelines for dose modifications are presented in Table 6-3.

Unless otherwise indicated in Table 6-3, for grade 1 and tolerable grade 2 treatment-related toxicities, patients may continue full doses of study treatment. For intolerable grade 2 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by either dose reduction or re-initiation at the same dose level, depending on the type of toxicity as described in Table 6-3. For any grade 4 toxicity, patients should interrupt study treatment until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer to Table 6-3).

Any planned variance from the guidelines in Table 6-3, in view of patient safety (unless there is an urgent need for action) when in the opinion of the investigator the patient continues to experience clinical benefit, must first be discussed and approved by the Novartis Medical Lead or designee.

A patient must discontinue treatment with INC280 if, after treatment is resumed at the lowest allowed dose (200 mg BID), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management. All interruptions or change to study drug administration must be recorded on the Dose Administration Record eCRF page.

6.3.2 Dose reduction and re-escalation

An INC280 dose reduction will follow the dose reduction steps described in Table 6-2. For each patient, a maximum of 2 dose level modifications is allowed after which the patient must be discontinued from treatment with INC280. 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 (IC90, 120 nM total concentration).

Dose re-escalation of study treatment to the previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.

Table 6-2 Dose reduction steps for INC280

INC280 dose levels*			
	Starting dose level - 0	Dose level - 1	Dose level - 2
INC280	400 mg BID	300 mg BID	200 mg BID

*Dose reduction should be based on the worst toxicity demonstrated at the last dose.

**Dose reduction below 200 mg is not allowed.

[redacted]

Table 6-3 Criteria for interruption and re-initiation of INC280 treatment

To be considered recommended dose modifications, unless otherwise specified as mandatory in this Table 6-3. Refer to Table 6-4 for follow-up evaluations as applicable.

Refer to Table 6-4 for follow-up evaluations as applicable.

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3; < 50 - 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓1 dose level
Febrile neutropenia (ANC < 1000/mm3 (< 1.0 x 10^9/L), fever > 38.3°C)	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level Mandatory: If resolved in > 7 days, discontinue patient from study drug treatment

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
Hemoglobin decreased (Anemia)	
Grade 1 (Hgb < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level Mandatory: If toxicity recurs, discontinue patient from study drug treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Mandatory: Permanently discontinue patient from study drug treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1, 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 dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, discontinue INC280 permanently
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue patient from study drug treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
	If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	For patients with clinical benefit from INC280 upon investigator's judgement: • Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline), then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed; if this AE reoccurs at Grade 3 or above, discontinue INC280 permanently. For all other patients: • Mandatory: Permanently discontinue patient from study drug treatment
Combined elevations of AST or ALT and Total Bilirubin[b,d]	
For patients with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN 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 > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, **combined with** [total bilirubin > 2 x baseline AND > 2.0 x ULN]	Mandatory: Permanently discontinue patient from study drug treatment
METABOLIC	
Asymptomatic amylase and/or lipase elevation (If symptomatic elevations of any grade, discontinue INC280 permanently)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN)	Omit the dose until resolved to ≤ grade 2, then If resolved in ≤ 14 days, resume treatment at the same dose level If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN)	Mandatory: Permanently discontinue patient from study drug treatment

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms) and Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Mandatory: Permanently discontinue patient from study drug treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue patient from study drug treatment
Diarrhea**	
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity* **	
Grade 1	Maintain dose level.
Grade 2	Maintain dose level.
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then ↓ resume treatment at 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4, despite skin toxicity therapy	Mandatory: Omit dose and discontinue patient from study drug treatment
RESPIRATORY DISORDERS	
Interstitial Lung Disease (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 absence of diagnosis of ILD/Pneumonitis, study drug may be restarted at the same dose. If it recurs after restarting of study drug, permanently discontinue INC280.
Grade 2	Mandatory: Interrupt INC280 dose during diagnostic workup for ILD 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 absence of diagnosis of ILD/Pneumonitis, study drug 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 recurs after resumption of study drug at decreased dose, permanently discontinue INC280
Grade 3 and Grade 4	Mandatory: Permanently discontinue study drug

[redacted]

Recommended dose modifications for INC280	
Worst toxicity CTCAE Grade[a]	During a cycle of therapy
	Treat with IV steroids as clinically indicated. Oxygen therapy as indicated.
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Peripheral edema	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Grade 4	Omit dose and then discontinue from study drug treatment

All dose modifications should be based on the worst preceding toxicity.

a Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03).

b “Combined” defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

c “Cholestasis” defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

d 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

* Note: 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 and continue treatment at the discretion of the investigator.

** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

*** During the whole duration of treatment with INC280, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively.

6.3.3 Treatment interruption and treatment discontinuation

If the administration of INC280 is temporarily interrupted for reasons other than toxicity, then treatment with INC280 may be resumed at the same dose. If the treatment with INC280 is withheld due to toxicity, the dose modification guidelines in Table 6-3 should be followed. In any case, scheduled visits and all assessments (including tumor assessments) should continue to be performed, as described in Table 7-1.

If the treatment with INC280 is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then INC280 should be permanently discontinued. Under exceptional circumstance, when the investigator believes that continuing treatment may still derive clinical benefit for the patient, study treatment may be resumed. However, the investigator must discuss and receive approval from Novartis Medical Lead or designee prior to continuing INC280 treatment.

Patients who discontinue the study due to a study drug related AE or an abnormal laboratory value must be followed as described in Section 6.3.4.

6.3.4 Follow-up for toxicities

All patients will be followed for safety until 30 days after the last dose of INC280. Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

An unscheduled assessment should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments. Subsequent monitoring must be performed as per the regular visit schedule.

All patients should receive best supportive care (BSC) as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the investigator believes to be in the patient's best interest, but excluding other anti-neoplastic treatments (with the exception of radiotherapy for control of bone metastases – see Section 6.4.1).

Table 6-4 Follow-up evaluations for selected toxicities*

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 2. Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL Serum creatinine ≥ CTCAE grade 2	Test weekly (or more frequently if clinically indicated) until ≤ CTCAE grade 1 or baseline. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
HEPATIC Isolated total bilirubin elevation	**Total bilirubin CTCAE Grade 1:** Monitor LFTs per protocol or more frequently if clinically indicated **Total bilirubin CTCAE Grade 2:** Weekly monitoring of LFTs, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN **Total bilirubin 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 **Total bilirubin 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 weeks
Isolated AST/ALT elevation	**AST/ALT CTCAE Grade 2 elevation:** 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 **AST/ALT CTCAE Grade 3 elevation:** For AST/ALT 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 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 **AST/ALT CTCAE Grade 4 elevation:** 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.
HEPATIC **Combined AST or ALT and total bilirubin elevation**	**Combined elevations of AST or ALT and total bilirubin:** After discontinuing the patient from INC280 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. 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.)

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
METABOLIC Asymptomatic amylase or lipase ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
CARDIAC ≥ CTCAE grade 3 QTcF ≥ 501 ms (CTCAE grade 3)	Test weekly (or more frequently) until ≤ CTCAE grade 2. When QTcF ≥ 501 ms (CTCAE grade 3), perform the following: • Call the study's central ECG review laboratory immediately and request an immediate manual read of the ECG. • Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. • Review concomitant medication usage for the potential to inhibit CYP3A4/5 (Table 6-5) and/or to prolong the QT-interval (Table 6-6). • Check compliance with correct dose and administration of INC280. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. • If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all patients who had therapy interrupted due to QTcF ≥ 501 ms. • If QTcF of ≥ 501 ms recurs, repeat ECGs as described above. Notes: • The investigator should contact the Novartis Medical Lead or designee regarding any questions that arise if a patient with QTcF prolongation should be maintained on study. • If the central ECG report shows a QTcF ≥ 501 msec (not previously documented on the site machine), contact the patient and instruct him/her to suspend INC280 and return for a repeat ECG as soon as possible. The central ECG reader should be called for a manual read of the repeat ECG immediately, and the above guidance followed.

TOXICITY	FOLLOW-UP EVALUATION
GASTROINTESTINAL Diarrhea	Initiate anti-diarrhea treatment after first signs of abdominal cramping, loose stools or overt diarrhea. Consider/Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example: • For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. • For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
SKIN TOXICITY (rash and photosensitivity)	
CTCAE grade 1	Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids)
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids).
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
Peripheral edema	
≤ CTCAE grade 2	Consider to initiate conservative measures such as leg elevation, compression stockings, and dietary salt modification as clinically indicated
≥ CTCAE grade 3	Initiate/intensify conservative measures
RESPIRATORY DISORDERS **ILD /Pneumonitis**	
CTCAE Grade 1	CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression - re-image at least every 3 weeks Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection Monitoring of oxygenation via pulse oximetry recommended Consultation of pulmonologist recommended
CTCAE Grade 2	CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests [a] - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended [c] • Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated) [b]
CTCAE Grade 3 and Grade 4	CT scan (high-resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function tests[a] - if < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL if possible[c] Treat with IV steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours)[b]. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication

*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 6-3 for dose modifications required for applicable toxicities

**Note: except if the patient is Grade 2 at baseline in which case: it is ≥ CTCAE grade 3

[a] PFT (Pulmonary function tests) to include: diffusing capacity corrected for hemoglobin (DLCO); spirometry; resting oxygen saturation

Guideline for significant deterioration in lung function: Decrease in spirometry and/or DLCO of 30% and/or O_2 saturation ≤ 88% at rest on room air.

[b] Duration and dose of course of corticosteroids will vary according to circumstances but should be as limited as possible. Consider tapering dosage at end.

[c] If bronchoscopy is performed, bronchoalveolar lavage (BAL) should be done where possible to exclude alveolar hemorrhage, opportunistic infections, cell count + determination lymphocyte CD4/8 count where possible.

[redacted]

6.3.4.1 Follow up on potential drug-induced liver injury 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 values; 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], whichever is lower, 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 (ALT/ALP in x ULN) < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

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 (eg, 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.
- 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.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.5 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e.,

[redacted]

nausea, vomiting and diarrhea are provided in Section 6.3 and Section 6.4. Refer to preclinical toxicity and or clinical data found in the most current [Investigator's Brochure].

6.4 Concomitant medications

Drugs in Table 6-5 and Table 6-6 are presented by mechanism of interaction. Table 6-7 presents drugs known to cause Torsades des Pointes.

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g. such as anti-emetics, anti-diarrhea) is permitted (see Section 6.4.1), except when specifically prohibited (see Section 6.4.3).

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 (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of INC280 through 30 days after the last dose of INC280 will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients
- No anticancer agents other than the study medication (INC280) should be given to patients.

6.4.1 Permitted concomitant therapy

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

- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors, etc.) are allowed per the investigator's judgement and per local guidelines.
- Treatment with bisphosphonates for pre-existing bone metastases is permitted, if clinically indicated, and following existing local guidelines. Treatment with bisphosphonates should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented; i.e. "pre-existing, non-progressing, bone metastases").
- Oxygen therapy and blood products or transfusions
- Nutritional support or appetite stimulants
- Pain medication
- Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion.

6.4.2 Permitted concomitant therapy requiring caution and/or action

- INC280 is a moderate CYP1A2 inhibitor. Co-administration of INC280 increased sensitive CYP1A2 probe substrate (caffeine) AUC by 135% (see Section 1.2.1.2). The dose of CYP1A2 substrates with narrow therapeutic index may need to be reduced when used concurrently with INC280 as INC280 may increase their exposure. Consult the product information of concomitant drug for dose adjustment.
- Co-administration of INC280 increased Pgp substrate (digoxin) exposure (AUC and Cmax by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC and Cmax by 108% and 204%, respectively) (see Section 1.2.1.2). Monitor patients closely for symptoms of increased exposure to Pgp or BCRP substrates. Consult the concomitant Pgp or BCRP substrate product information when considering dose adjustment.
- Co-administrating INC280 with strong CYP3A4 inhibitor (itraconazole) increased INC280 AUC by 40%. There is no change in INC280 Cmax. Execute caution when using a strong CYP3A4 inhibitor concurrently with INC280.
- In healthy subjects, co-administration of PPI decreased INC280 AUC_{inf} by 25% and C_{max} by 38%. In cancer patients [CINC280A2108], ~30% lower AUC,ss was observed in patients with concomitant use of PPI compared to that in patients without PPI use. The decrease in exposure imposes caution on the use of PPI when INC280 is taken.
- Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken with caution. However, it is recommended to take these drugs at least 1 hour before or 2 hours after administration of INC280.
- H2 receptor antagonists should be used with caution. If patients are using H2 receptor antagonists during the course of this study, INC280 should be administered at least 3 h before or 6 h after an H_2-receptor antagonist.
- INC280 is a weak to moderate inhibitor of CYP2C8, CYP2C9 and CYP2C19 *in vitro*. Substrates of CYP2C8, CYP2C9 and CYP2C19 with a narrow therapeutic index should be administered with caution

Refer to Table 6-5 below for a list of the medications that require caution when concomitantly used with INC280.

Table 6-5 Drugs to be used with caution while on study

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, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, , posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
CYP1A2 substrate with NTI	theophylline, tizanidine
CYP2C9 substrate with NTI	warfarin
CYP2C19 substrate with NTI	(S)-mephenytoin
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin,

[redacted]

Mechanism of Interaction	Drug Name
	losartan, maraviroc, mirabegron, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole, atorvastatin, docetaxel, fentanyl, fexofenadine, linezolid, loperamide, nadolol, nevirapine, paclitaxel, proguanil, ritonavir, simvastatin, sofosbuvir, tacrolimus
BCRP substrates	Atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
Short acting gastric acid modulator and H2 receptor antagonist	ranitidine, nizatidine, famotidine, cimetidine, aluminum hydroxide, aluminum carbonate, calcium hydroxide, calcium carbonate, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" This may not be an exhaustive list, will be updated periodically. NTI: narrow therapeutic index	

6.4.3 Prohibited concomitant therapy

- Co-administrating INC280 with strong CYP3A4 inducer (rifampicin) decreased INC280 AUC by 66% and Cmax by 56%. Concurrent use of strong CYP3A4 inducers is prohibited as decreased INC280 exposure may lead to reduced efficacy.
- Drugs with a known risk of Torsades des Pointes (TdP) are prohibited. For identification of drugs with known risk of TdP please refer to qtdrugs.org (refer to Table 6-7).

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment.

The prohibited medications are listed in the Table 6-6 and Table 6-7 below.

Table 6-6 Drugs prohibited while on study

Mechanism of Interaction	Drug Name
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" This may not be an exhaustive list, will be updated periodically.	

Table 6-7 Drugs with a known risk of Torsades des Pointes prohibited while on study

Class of medication	Drug Name
With Known risk of Torsades des Pointes	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone,

[redacted]

Class of medication	Drug Name
	droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
This may not be an exhaustive list. Check: crediblemeds.org/healthcare-providers/drug-list for the most updated list.	

6.5 Patient numbering and treatment assignment

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for pre-screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject 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 molecular pre-screening informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

At the molecular pre-screening visit, the investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

6.5.2 Treatment assignment

At the main screening visit, the investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills the molecular pre-screening criteria. Prior to dosing he/she or delegate will call or log on to the IRT again (at the C1D1 visit) to confirm that the patient fulfills all main screening inclusion/exclusion criteria and that the patient can initiate study treatment. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page.

IRT must be notified within 2 days if the patient did not start treatment.

The assignment of a patient to a particular cohort will be coordinated by Novartis via IRT based on cMET GCN and cMET mutation pre-screening and prior treatment status results either:

- Cohort 1: Patients with cMET GCN ≥ 6, including:
  - Sub-cohort 1a: Patients with cMET GCN of ≥ 10, or
  - Sub-cohort 1b: Patients with cMET GCN of ≥ 6 and < 10, or
- Cohort 2: Pre-treated patients with cMET GCN ≥ 4 and < 6, or
- Cohort 3: Pre-treated patients with cMET GCN < 4, or
- Cohort 4: Pre-treated patients with cMET mutations regardless of cMET GCN, or
- Cohort 5 treatment-naïve patients with cMET dysregulation, including:

[redacted]

- Sub-cohort 5a: Patients with cMET GCN of ≥10, or
- Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN, or

- Cohort 6: Pre-treated patients with either cMET GCN ≥ 10 without cMET mutations or cMET mutations regardless of cMET GCN, or
- Cohort 7: Treatment-naïve patients with cMET mutations regardless of cMET GCN

In addition, in Cohort 2 (if not stopped for futility at the IA), the study enrollment target of ~40% of patients (i.e. at least 11 patients for the IA and 28 patients for the final enrollment) with GCN ≥ 5 and < 6 at the time of both the interim and the final analysis will be managed via IRT. To achieve this target, the IRT system may close the enrollment of patients with GCN ≥ 4 and < 5 when the target of 60% (i.e. at least 17 patients for the IA and 41 patients for the final enrollment) of the patients with GCN ≥ 4 and < 5 is reached.

All patients will receive the same treatment regimen regardless of the cohort to which they are allocated.

6.5.3 Treatment blinding

Not applicable.

6.6 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 eCRF.

Table 6-8 Preparation and dispensing

Study treatments	Dispensing	Preparation
INC280	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part 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 the medication number but no information about the patient.

Table 6-9 Packaging and labeling

Study treatments	Packaging	Labeling
INC280	Tablets in bottles	Medication labels comply with the legal requirements of each country and will be printed in the local language. They will supply no information about

[redacted]

Study treatments	Packaging	Labeling
		the patient. The storage conditions for the study drug will be described on the medication label.

6.6.2 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 site personnel have access. Upon receipt, INC280 should be stored according to the instructions specified on the drug labels and in the current [Investigator's Brochure].

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Data for all doses of study medication will be recorded on the Dosage Administration eCRF page.

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.

6.6.3.2 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.

At study close-out, and, as appropriate during the course of the study, 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

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

The drug supply can also be destroyed at the site if permitted by local regulations and authorized by Novartis in a prior agreement.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all 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. The table indicates which assessments produce data to be entered into the database (D) or remain in the source documents only (S) ("Category" column). The eCRF will not be used as a source document.

Written informed consent must be obtained before any study specific assessments are performed, including those at molecular screening and screening. Main screening evaluations and baseline radiological tumor assessments should be performed within 28 days of treatment start.

Each treatment cycle is 21 days (the 21 days cycle length is fixed regardless of whether the dose of INC280 is withheld).

All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol.

After screening:

- All assessments have a ±3 day window unless otherwise indicated
- Radiological tumor assessments may be performed within a ±4 day window, unless otherwise indicated
- If a given visit is out of window, the next visit should be performed with reference to the day of first dose in order to get the patient back on schedule
- If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule
- Laboratory assessments and height/weight performed as part of the screening evaluations and within 7 days of the first dose of study drug, will not be required to be repeated on Cycle 1, Day 1
- All assessments on Cycle 1, Day 1 must be done prior to the first dose unless otherwise specified. It is recommended that the investigator checks the pre-dose laboratory results prior to starting treatment
- Patients who discontinue INC280 treatment must have EOT visit performed ≤ 7 days after stopping study drug
- Permitted contact windows for survival follow-up: +/- 7 days

Additional assessments may be performed as clinically indicated.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase						Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
Pre-Screening													
Confirmation of EGFR wild-type & ALK-negative rearrangement status	D	5.2	X										
Obtain Molecular Pre-Screening ICF	D	7.1.1	X										
Newly obtained tumor biopsy (preferred) or archival tumor sample to confirm ALK-negative rearrangement status, only if ALK local testing not available	D	7.1.1.1	X										
Newly obtained tumor biopsy (preferred) or archival tumor sample to confirm cMET amplification and/or mutation status	D	7.1.1.1	X										
Main Screening													
Obtain Main ICF	D	7.1.2		X									
IRT Registration	S	6.5.1	X	X	X					X			

[redacted]

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase						Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
Patient History													
Demography	D	7.1.2.3		X									
Information on prior local testing for cMET amplification and cMET mutation including prior central NGS result, if applicable	D	7.1.2.3		X									
Inclusion/exclusion criteria	D	5.2; 5.3		X									
Eligibility check	S	7.1.2.1		X									
Relevant medical history/current medical conditions	D	7.1.2.3		X									
Smoking History	D	7.1.2.3		X									
Diagnosis and extent of cancer	D	7.1.2.3		X									
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.2.3		X									
Prior and current concomitant medications (including OTC meds); procedures and significant non-drug therapies	D	7.1.2.3		Continuous until ≥ 30 days after the last dose of INC280									

[redacted]

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase						Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
Physical Examination													
Complete physical examination, *including neurological exams*	S	7.2.2.1		X	If clinically indicated								
Targeted physical examination	S	7.2.2.1			X	X	X	X	X	X			
Height	D	7.2.2.3		X									
Weight	D	7.2.2.3		X	X		X	X	X	X			
ECOG Performance status	D	7.2.2.4		X	X		X	X	X	X			
Vital signs	D	7.2.2.2		X	X	X	X	X	X	X			
Laboratory assessments													
Hematology	D	7.2.2.5		X	X	X	X	X	X	X			
Chemistry	D			X	X	X	X	X	X	X			
Coagulation	D			X	If clinically indicated								
Urinalysis (dipstick) with micro-analysis	D			X	If clinically indicated								
Serum pregnancy test (if applicable)	D			X	X		X	X	X	X			
Tumor assessments RECIST 1.1													
CT scan or MRI of chest, abdomen, pelvis *(EOT scan not required if previous scan was performed within ≤28*	D	7.2.1		X				X	C5D1 and every 6 wks	X	X (every 6wks)		

[redacted]

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase						Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
days)													
Whole body bone scan	D			X	Only if clinically indicated								
CT scan or MRI of brain	D			X				C3D1 and every 6 wks (if positive at baseline) or if clinically indicated					
CT scan or MRI of other metastatic sites (e.g., neck, etc)	D			X (if other metastatic sites)				C3D1 and every 6 wks (if positive at baseline) or if clinically indicated					
Localized bone CT scan, MRI or X-ray (for any lesions identified on the whole body bone scan that are not visible on the chest/abdomen/pelvis CT scan or MRI)	D			X (only if lesions on whole body scan that are not visible on the CAP scans)				C3D1 and every 6 wks (if positive at baseline) or if clinically indicated					
Photography (for skin lesions)	D			X (only if skin lesions)				C3D1 and every 6 wks (if positive at baseline) or if clinically indicated					
Safety assessments													
Adverse events	D	8.1	Continuous until ≥ 30 days after the last dose of INC280										

[redacted]

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase					Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
[redacted]													
Study drug administration													
INC280 dosing	D	6.1			Continuous twice daily dosing (BID)								
[redacted]													

[redacted]

	Category	Protocol Section reference	Molecular pre-screening and Main Screening Phases		Study Treatment Phase						Post-treatment Follow-Up phase (safety follow-up within 30d of last dose for all patients and efficacy follow-up every 6 weeks until BIRC-confirmed disease progression)		Survival Follow-up Phase
					Cycle 1 (21 days)		Subsequent cycles (21 days per cycle)			End of study treatment (EOT)			
Visit Name			Molecular pre-screen	Screening Visit (D-28 to D-1)	C1 D1	C1 D15	C2 D1	C3 D1	C4D1 C5D1 etc…	EOT Visit (within 7d of last dose)	Tumor Follow-Up (every 6 wks)	Study Evaluation Completion	Survival Follow-Up (every 3 mo)
[redacted]													
Pharmacokinetics and ECG assessments													
12-Lead ECG	D	7.2.2.6		X	X	X		X		X			
Blood for INC280 PK	D	7.2.3			X	X		X					
Other													
Antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study drug	D	7.1.4								X (continuous until last follow-up visit)			
End of Phase Disposition	D	4.1		X						X		X	
Safety Follow-Up	D	7.1.5.1									X		
Survival *(survival information can be obtained via telephone contact)*	D	4.1.5											X

Abbreviations: C, cycle; CAP, chest/abdomen/pelvis; CT, computed tomography; D, entered into database; d, day; ECG, electrocardiogram; EOT, end of treatment; EOS, end of study; FUp, follow-up; i.v., intravenous; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD, progressive disease; PK, pharmacokinetic; S, remains in source document only; Tx, treatment; wks, weeks;

[redacted]

7.1.1 Molecular pre-screening

7.1.1.1 Tumor sample requirement

The patient must sign the molecular pre-screening ICF before the tumor sample can be provided to a Novartis-designated central laboratory for molecular screening. A newly obtained tumor biopsy (preferred) or archival tumor tissue (block or slides) should be submitted to test cMET amplification and/or cMET mutation status. Archival tumor tissue obtained at the time of diagnosis of NSCLC or any time since is acceptable and may consist of a formalin fixed paraffin embedded (FFPE) tumor block tumor or slides; if more than one archival tissue sample (block or slides) is available, tissue from most recent archival sample is preferred. Samples obtained from bone metastases are not acceptable. Amplification and mutation status will be determined centrally at a Novartis designated laboratory.

Additionally, a portion of these samples will be retrospectively analyzed by NGS for targets including amplification and mutation of cMET. [redacted]

If a tumor block or new biopsy is provided, the remaining tissue from pre-screen failure samples will be returned to the site. However, a small amount of any remaining tissue will be retained from all patients, under the control of Novartis, to support the development of future companion diagnostic test(s) with a method such as NGS. If patient is enrolled, the remaining block will be sent to Novartis-designated vendor. Only if the site requests the sample to be returned, approximately 3 slides will be cut prior to sending the remaining block back to the site. Additional tissue may be requested, retrospectively, if available, to support the development of future NGS companion diagnostics if the remaining tissue sample is insufficient for analysis.

If ALK testing is not available locally, confirmation of ALK-negative rearrangement status at a Novartis-designated central laboratory using a validated ALK testing is required to confirm patient's eligibility. In this case, the tumor sample provided, either as newly obtained tumor biopsy (preferred) or archival tumor tissue (block or slides preferably from the same tumor) will be used to determine cMET amplification and mutation status as well as ALK rearrangement status.

The cMET amplification, cMET mutation and ALK rearrangement status where analyzed will be communicated to the site within approximately 5 working days of receipt of the sample at the central laboratory. Results of the analysis must be received before any additional tests can be performed to determine the patient's eligibility for the study.

Instructions for tumor sampling, preparation and packing/shipping are described in a separate laboratory manual.

If a patient's cMET amplification and/or mutation status is known via a local result, confirmation of their status via a Novartis-designated central laboratory is required to confirm eligibility.

[redacted]

Please refer to Section 6.5 for patient numbering, IRT procedures and cohort assignment.

7.1.2 Screening

Once the cMET amplification and mutation status (and ALK rearrangement status, if applicable) is confirmed by the central designated laboratory performing the molecular pre-screening analysis, patients may enter the screening phase. Written informed consent must be obtained before any study specific procedure is performed. Screening assessments to confirm eligibility into the main study should be performed as per the schedule of assessments between Day-28 and Day-1. Laboratory assessments performed as part of the screening evaluations will not require to be repeated prior to dosing if performed within 7 days prior to the first dose of study treatment. Only laboratory results from the Novartis-designated central Laboratory can be used to determine patient's eligibility for the study. The cardiac eligibility criteria should be assessed with the central ECG report. [redacted]

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated within the 28-day screening period. In these cases, the patient is not required to sign another ICF and must retain the same Subject No. In the event that the laboratory test(s) cannot be performed within the 28 days of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study. A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, however, the Subject No will remain the same.

Patients who fail screening due to laboratory parameters (inclusion criterion # 7) or baseline tumor assessment (inclusion criterion # 5) may be re-screened. Patients who met all eligibility criteria but fail to be started on treatment as scheduled may be also re-screened, provided the patient was not registered previously in IRT as having entered the Treatment Period. Re-screening of a patient must be performed within the 28-day re-screening period, and is allowed only once per patient. All required screening activities must be performed when the patient is re-screened for participation in the study.

All eligibility criteria must be re-checked, based on the most recent data available, and met prior to enrollment of the patient into the study.

If any cohort/sub-cohort is closed to enrollment, then only patients with the cMET amplification or mutation status required for the open cohort(s)/sub-cohort(s) will be eligible for main screening for study enrollment. Enrollment of patients with GCN ≥ 4 and < 5 in Cohort 2 may be stopped when the target of 60% (i.e. at least 17 patients for the IA and 41 patients for the final enrollment) with GCN ≥ 4 and < 5 is reached.

7.1.2.1 Eligibility screening

The main screening period commences as soon as the patient signs the main ICF and ends when the patient fails screening or starts treatment. Evaluations will be performed within 4 weeks (i.e., within 28 calendar days) prior to the first dose of study drug, unless otherwise noted. All screening assessments, including laboratory assessments, must be performed as described in the protocol (Table 7-1). Any imaging assessments already completed as

[redacted]

patient's standard of care within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after first dose cannot be considered baseline images. [redacted]

Eligibility Check

In order to determine and confirm the eligibility of the patient, once all screening procedures are completed, an eligibility checklist must be completed via IRT by the investigator or designee prior to receiving the first dose of study drug (Section 4.1.2). Please refer to and comply with the detailed guidelines in the IRT manual.

After the eligibility has been checked and confirmed that the patient is eligible for the trial, then the patient can be enrolled into the study.

Approximately 30 enrolled patients at selected sites (regardless of cohort assignment) will have full PK samples and ECGs collected. The rest of the patients will have sparse PK samples and ECGs collected (see Table 7-5, Table 7-6, Table 7-7 and Table 7-8). At the time of eligibility confirmation, the IRT system will inform the site which PK and ECG schedule should be followed by the patient.

Patients who fail to be started on treatment may be re-screened (see Section 7.1.2), provided the patient was not registered previously in IRT as having entered the Treatment Period. In this situation, the Subject No. which was previously assigned to the patient will be re-applied to the same patient throughout his/her entire study participation.

7.1.2.2 Information to be collected on screening failures

Patients who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure. Both patients who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as patients who are found not eligible after signing the main study consent will be considered as screening failures, and data will be handled in the same manner. The reason for not satisfying eligibility criteria and not being enrolled will be entered on the Screening Phase Disposition eCRF Page. The following eCRF pages must be completed for screening failure patients:

- EGFR molecular status
- ALK rearrangement status
- Information on local testing for cMET amplification and cMET mutation prior to patient consideration for this study, if available
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis and stage of NSCLC
  - Site of active disease
  - Characteristics of disease
- Tumor samples collection for cMET and ALK (if local ALK status is not available)
- Screening Phase Disposition
- Demography

[redacted]

- Informed consent
- Inclusion/Exclusion Criteria
- Withdrawal of consent (if applicable)
- Death (if applicable)

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event 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.

If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected include:

- EGFR molecular status
- ALK rearrangement status
- Information on local testing for cMET amplification and cMET mutation prior to patient consideration for this study, if available.
- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- Smoking history
- Cohort/sub-cohort assignment
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis and stage of NSCLC
  - Site of active disease
  - Characteristics of disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and current concomitant medications, surgical and medical procedures

Note: All other medications taken within 28 days before the first dose of study treatment is administered must be recorded on the Prior and current concomitant medication eCRF page and updated on an ongoing basis if there is new change to the medication.

7.1.3 Treatment period

Following completion of screening procedures and confirmation of patient eligibility, the patient will be enrolled via the IRT in one of the cohorts based on the cMET amplification status. At the time of eligibility confirmation, the IRT system will inform the site about which PK and ECG schedule should be followed by the patient.

The study treatment will begin on Cycle 1, Day 1 with the first administration of INC280 and does not have fixed treatment duration. Information on drug exposure will be collected on the Dosage Administration Record eCRF.

[redacted]

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Emergence of specific adverse events or laboratory abnormalities under some circumstances as outlined in Section 6
- Pregnancy (pregnancy will be followed for outcome)
- Use of prohibited treatments (refer to Section 6.4.3)
- Any protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue INC280 treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

Patients who become pregnant must cease all tumor assessments regardless of whether or not they developed Progressive Disease according to BIRC.

Patients who discontinue INC280 should be scheduled for an EOT visit as soon as possible and within 7 days of the last dose of INC280, at which time all of the assessments listed for the EOT visit will be performed. If a patient is discontinued from treatment at a study visit, the assessments performed at that visit will be considered as EOT assessments and do not need to be repeated. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping treatment.

Patients who discontinue study treatment should enter either the survival follow-up period or continue tumor assessments, when appropriate.

Patients who have RECIST-defined Progressive Disease as determined by investigator and confirmed by the BIRC, but who, in the judgment of the investigator have evidence of continued clinical benefit from INC280 and the patient wishes to continue on the study treatment may continue to receive the study drug. These patients will continue assessments as detailed in Table 7-1. In such cases, patients must complete the EOT visit only after permanent discontinuation of INC280. An End of Treatment Phase Disposition eCRF page should be completed, specifying the date of the subject's last treatment and reason for stopping study treatment.

[redacted]

7.1.5 Follow-up-period

7.1.5.1 Follow-up for Safety Evaluations

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

At the end of this period, the investigator should assess and discuss with the patient any AE observed/concomitant medication taken since discontinuation of study treatment. This can be done via a phone contact.

Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page.

Patients whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization.

7.1.5.2 Post-Treatment follow-up

All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or disease progression as determined by investigator and confirmed by BIRC (Section 7.1.4) should not be considered withdrawn from the study and should continue with tumor [redacted] assessments every 6 weeks from EOT as per Table 7-1 until disease progression is confirmed per BIRC, withdrawal of consent from tumor assessments, lost to follow-up, death or study terminated by Sponsor. Once the patient ceases tumor follow-up [redacted], the End of Post Treatment Disposition (Study Phase Completion) eCRF page should be completed. Antineoplastic therapies since discontinuation of study treatment will continue to be collected. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the survival status of the patient.

7.1.5.3 Survival follow-up

All patients who had PD determined by investigator and confirmed by BIRC or withdrew consent from further study assessments will subsequently be followed for survival information every 3 months until death, lost to follow-up or withdrawal of consent for survival. The investigator or his designee will collect this survival information and any new anti-neoplastic therapies for all patients until the final survival analysis.

Follow-up can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last dose of the study treatment.

7.1.5.4 Replacement policy

Patients lost to follow-up or withdrawing consent from the study without observed BIRC confirmed PD will be censored for the primary analysis and will not be replaced.

[redacted]

7.1.6 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally and by BIRC according to the Novartis guideline version 3.1 (Appendix 1) based on RECIST 1.1 (Eisenhauer et al 2009). Patients should have at least one documented measurable lesion at study entry as per RECIST 1.1. The imaging

[redacted]

assessment collection plan is presented in Table 7-2. Details of the central review process will be described in the independent review charter.

Imaging data will be centrally collected and checked for quality by an imaging vendor designated by Novartis. The results of the central BIRC evaluations will be used for primary analysis purposes. The local investigator's assessment will be used for treatment decision making.

Table 7-2 Imaging collection plan

Procedure	Screening/Baseline	During Treatment/Follow-Up
CT or MRI (chest, abdomen, pelvis) with i.v. contrast	Mandated	Mandated until PD determined by investigator and confirmed by BIRC, every 6 weeks
CT or MRI of other metastatic sites (e.g., neck, etc.), if applicable	Only if other metastatic sites are suspected	Mandated if patient has other metastatic sites at baseline (following the same schedule as CT/MRI of chest/abdomen/pelvis) or otherwise, only if clinically indicated
CT or MRI of brain with i.v. contrast	Mandated	Mandated if positive at baseline (following the same schedule as CT/MRI of chest/abdomen/pelvis), or otherwise, only if clinically indicated
Whole body bone scan [e.g., Tc-99 bone scan, whole body bone MRI, fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF)-PET]	Mandated	If clinically indicated
Localized bone CT, MRI or X-ray	Only if clinically indicated (for any lesions identified on the whole body bone scan that are not visible on the CT/MRI of chest/abdomen/pelvis)	Mandated if positive at baseline (following the same schedule as CT/MRI of chest/abdomen/pelvis), or otherwise, only if clinically indicated
Color photographs with a metric ruler (only if skin lesions are present)	Only if other skin metastases are present	Mandated if patient has skin lesions at baseline (following the same schedule as CT/MRI of chest/abdomen/pelvis) or otherwise, only if clinically indicated

7.2.1.1 Baseline imaging assessment

Imaging assessments will be performed at screening/baseline Day -28 to Day -1 prior to Cycle 1 Day 1.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after first dose cannot be considered baseline images.

Imaging requirements at baseline

- Patients must have measurable disease as per RECIST 1.1 (Appendix 1). Measurable ("target") lesions include lytic or mixed (lytic + blastic) bone lesions with an identifiable soft tissue component that meets the measurability criteria per RECIST 1.1 (Appendix 1).
- Patients with only non-measurable lesions are not eligible.

[redacted]

- If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable ("non-target") lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

All measurable lesions up to a maximum of 5 nodal and/or non-nodal lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

Tumor assessments required at baseline

The following assessments will be performed:

- Computed Tomography (CT) with IV contrast or Magnetic Resonance Imaging (MRI) of chest, abdomen and pelvis.
  - The preferred radiologic technique is CT with intravenous (IV) contrast. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.
- A whole body bone scan according to institutional guidelines [e.g. Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride positron emission tomography (NaF PET)].
  - After screening, whole body bone scans is not required, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- Localized CT, MRI or X-rays of any skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, pelvis and abdomen CT/MRI.
  - If skeletal lesions are documented at baseline, scans need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis. The same methodology as at screening should be used.
- Brain CT with IV contrast or MRI scan.
  - If brain lesions are documented at baseline, scans need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis. The same methodology as at screening should be used. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.
- Color photographs, if skin lesions are present, using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.
  - If skin lesions are documented at baseline, photographies need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis.
- CT or MRI of any other site of disease not captured by any of the above listed images (e.g., neck).

- If additional sites of disease are documented at baseline, scans need to be continued following the same schedule as CT/MRI of chest, abdomen and pelvis. The same methodology as at screening should be used.

Chest x-ray or ultrasound must not be used to measure tumor lesions.

7.2.1.2 Subsequent imaging for response assessment

Imaging assessments as described in Table 7-2 should be performed at the timepoints specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1). Imaging assessments for response evaluation will be performed every 6 weeks starting from Day 1 of cycle 1 (+/- 4 days window).

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, if necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

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 IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document PD per RECIST 1.1 (Appendix 1).

All study imaging (including any off-schedule imaging studies) performed to evaluate progression or response should be submitted to the designated imaging vendor for quality control and review by the BIRC, promptly after acquisition.

7.2.1.3 Transmission of efficacy data to BIRC

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging vendor designated by Novartis. Rapid image transmission to the central imaging vendor will be accomplished by transferring the images acquired by the investigator electronically in a secured website (e.g.: via the internet). In all instances, the process at the imaging vendor will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review.

7.2.1.4 Timepoints without locally determined progression

All imaging timepoints without locally determined progression will be read on an ongoing non-expedited basis as detailed in the imaging manual to be provided by the designated imaging vendor and independent review charter. However expedited review may be required at the time of the interim analysis. Results of these readings will not be communicated to the sites.

[redacted]

7.2.1.5 Timepoints at which progression is determined locally

All patients who have disease progression determined by the local investigator require an expedited tumor response review by the BIRC. If PD has been determined locally at a timepoint, the investigator must seek an expedited review and indicate this request to the imaging vendor on a designated form or by alternative means identified by the imaging vendor. The imaging vendor will ensure that the BIRC reviewers are blinded to BIRC reading requests.

Rapid image transmission to the central imaging vendor may be accomplished by uploading all digital images acquired by the Investigator to the secure website provided by the imaging vendor. The imaging will undergo expedited central review (within 5 business days from the time of the receipt of images at the imaging vendor) and the results of the central review will be communicated to the site. While the investigator is awaiting the results of the central review, it is preferable that the patient continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

If the central review determines disease progression, then the patient may discontinue study treatment and subsequent follow-up tumor assessments are no longer required. Treatment with INC280 may be continued beyond RECIST 1.1-defined PD determined by the investigator and confirmed by BIRC, if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue on the study treatment.

If the central review does not determine disease progression, the patient should continue receiving the study treatment unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy per the investigator's clinical judgment.

Patients will continue to have imaging performed as per protocol (Table 7-1) until the central review determines disease progression.

Note: If an investigator would like to discuss the central review results, there will be an independent physician at the imaging vendor who is not part of the central review pool for this study. This independent physician will be able to discuss the central review findings with the investigator. The central reviewers are completely excluded from such discussion. The contact at the imaging vendor can arrange such a discussion, as specified in the manual provided by the designated imaging vendor.

7.2.2 Safety and tolerability assessments

Safety will be monitored using the following clinical and laboratory assessments: hematology, chemistry, coagulation parameters, urinalysis, 12-lead ECG, pregnancy test as well as collecting of the adverse events and concomitant medications at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

[redacted]

7.2.2.1 Physical examination

A complete physical examination must be performed at screening and later as clinically indicated and 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 targeted (short) physical exam will be performed as per schedule in Table 7-1 and will include the examination of general appearance and vital signs (blood pressure and pulse).

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 include body temperature, blood pressure and pulse measurements and will be performed as per schedule in Table 7-1. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only (Refer to Table 7-1).

7.2.2.4 Performance status

Assessment of ECOG performance status (Table 7-3) will be performed as per the assessment schedule in Table 7-1, even if study treatment is being interrupted. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-3 ECOG performance status scale

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

7.2.2.5 Laboratory evaluations

Novartis-designated central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 7-4). The frequency of the assessments is indicated in Table 7-1. Dipstick urinalysis

[redacted]

will be performed locally, except in the case of any significant findings, a urine sample will be sent to central laboratory for further microscopic analysis. Laboratory values obtained prior to treatment from central laboratory will be used to assess patient's eligibility. Only laboratory results from the Novartis-designated central Laboratory can be used to determine patient's eligibility for the study. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Local laboratory assessments may only be performed when an immediate clinical decision needs to be made. In those cases locally unscheduled testing may be performed. However samples should also be sent to the central lab. In such cases, local laboratories values should be recorded on the local laboratory eCRFs as unscheduled visits only if a severity grade differs from a severity grade reported by the central laboratory.

Each time local laboratory results are reported on the unscheduled local laboratory eCRF page, the study monitor will collect and submit promptly the local laboratory normal ranges and local laboratory certification.

Details on the collection, shipment of samples and reporting of results by the Novartis-designated central laboratory are provided to investigators in a separate [Laboratory Manual].

Table 7-4 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells, Differentials (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT, Amylase, AST, Calcium, Creatinine, Creatinine Clearance, Total Bilirubin, Direct Bilirubin (*only if total bilirubin is ≥ grade 2*), GGT, Lipase, Magnesium, Sodium, Potassium, Phosphate (inorganic phosphorus), fasting Glucose (*non-fasting allowed post-baseline*), Blood Urea Nitrogen (BUN) or Urea Bicarbonate, Chloride and Uric Acid: at screening and thereafter if clinically indicated
Urinalysis (at screening and thereafter if clinically indicated)	Macroscopic panel (dipstick) (bilirubin, blood, glucose, WBC, pH, protein, specific gravity) Microscopic panel (RBC, WBC, casts)
Coagulation (at screening and thereafter if clinically indicated)	International normalized ratio (INR) and Prothrombin time (PT), or Quick Test (QT)

7.2.2.5.1 Hematology

Hematology assessments of the parameters listed in Table 7-4 will be tested as per the schedule of assessments (Table 7-1). 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.

7.2.2.5.2 Clinical chemistry

Blood chemistry assessments of the parameters listed in Table 7-4 will be tested as per the schedule of assessments (Table 7-1).

[redacted]

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.

Note: Creatinine clearance should be calculated (e.g Cockcroft-Gault formula) at screening and need to be repeated on Cycle 1 Day 1 before first dose, unless screening assessment was performed within 7 days prior to the Cycle 1 Day 1 visit.

7.2.2.5.3 Urinalysis

Dipstick measurements will be performed as per Table 7-4 and according to the schedule of assessments (Table 7-1). Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 7-4 and recorded on the appropriate eCRF page. Dipstick urinalysis will be performed locally. In the case of any out of range parameters are noticed on local urinalysis, urine sample will be sent to central laboratory for further analysis.

7.2.2.5.4 Pregnancy and assessments of fertility

All women of childbearing potential must complete a serum pregnancy test as per the schedule of assessments (Table 7-1). Central laboratories will be used for the analysis of serum pregnancy tests.

Women who are determined not to be of child bearing potential before the study will only be tested at screening.

For postmenopausal women to be considered “of non-childbearing potential”, patient should meet the criteria as outlined in Section 5.3.

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

If a pregnancy test is performed in between study visits by the patient and the result is positive, the patient must immediately notify the investigator.

7.2.2.5.5 Coagulation

International normalized ratio (INR) and prothrombin time (PT) or Quick Test will be measured according to the schedule of assessment.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed as outlined in Table 7-5 and Table 7-6.

Table 7-5 ECG collection plan for approximately 30 enrolled patients at selected sites

Cycle	Day	Time	ECG Type	Number of ECGs
Screening		Anytime	12 Lead	3

[redacted]

Cycle	Day	Time	ECG Type	Number of ECGs
1	1	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
1	15	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
3	1	Pre-dose (within 15 min prior to PK)	12 Lead	3
EOT		Anytime	12 Lead	3
Unscheduled ECG		Anytime if clinically indicated	12 Lead	3

Table 7-6 ECG collection plan for remaining patients, including patients in Cohort 6 and Cohort 7

Cycle	Day	Time	ECG Type	Number of ECGs
Screening		Anytime	12 Lead	3
1	1	Pre-dose	12 Lead	3
1	15	Post-dose 2 h (within 15 min prior to PK)	12 Lead	3
3	1	Pre-dose	12 Lead	3
EOT		Anytime	12 Lead	3
Unscheduled ECG		Anytime if clinically indicated	12 Lead	3

Baseline is defined as the pre-dose assessment on Cycle 1 Day 1 before study drug administration.

All ECG assessments will be performed in the supine position. Detailed instructions regarding the ECG collection will be provided to the investigators in a separate manual prior to the start of the study. INC280 pharmacokinetic evaluation will be conducted in parallel to cardiac evaluations (see Section 7.2.3). All ECGs should be performed within 15 minutes prior to the collection of PK sample. The triplicate ECGs should be taken approximately 2-4 minutes apart. An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated.

All ECGs recorded for each time point will be transmitted electronically to a central laboratory and will be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review. Review of all ECGs from a particular patient should be performed by a single reader. The ECG lead for interval duration measurements should be pre-specified. Baseline and all subsequent ECGs should be based on the same lead.

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, ECG nominal day and time, ECG actual date and time (using a 24-hour clock, record up to second), ECG replicate number, measured variables (QT, RR, PR, QRS), derived variables

[redacted]

(QTcB, QTcF, and HR), ECG lead 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 Novartis 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.

7.2.3 Pharmacokinetics

Blood samples for PK evaluation will be collected from all enrolled patients participating in the study. Time points of blood sample collection for full and sparse PK analyses are outlined in Table 7-7 and Table 7-8, respectively.

The study will consist of sparse PK sampling as detailed in Table 7-8 in the majority of the patients who receive INC280 treatment. Separate from this, a minimum of 30 patients at selected sites will be required to participate in full PK sampling for population PK analysis as detailed in Table 7-7.

Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose prior to the sampling, should be obtained on all sampling days and recorded on the PK eCRF and/or CRO requisition form(s).

An additional unscheduled PK blood sample will be collected if a patient experiences an AE suspected to be related to study treatment that results in an unscheduled visit or fits the criteria of an SAE (unless patient has interrupted INC280 for 7 days or more).

PK parameters will be estimated from each individual plasma concentration-time profile using appropriate methods and software, if possible. A table of PK parameters to be evaluated (e.g., Cmax, Tmax, AUC) is to be included in the statistical and data analysis Section 10.5.4 of the protocol.

Table 7-7 Pharmacokinetic blood collection log for approximately 30 enrolled patients at selected sites

Cycle	Day	Scheduled Time Point	Dose Reference ID		PK Sample No	Sample Volume (mL)
1	1	Pre-dose/0h	1		1	3
1	1	Post-dose 0.5h (± 5min)	1		2	3
1	1	Post-dose 1h (± 10min)	1		3	3
1	1	Post-dose 2h (± 10min)	1		4	3
1	1	Post-dose 4h (± 20min)	1		5	3
1	1	Post-dose 6h (± 20min)	1		6	3
1	1	Post-dose 8h (± 20min)	1		7	3
1	15	Pre-dose/0h	2	201[a]	8	3
1	15	Post-dose 0.5h (± 5min)	2		9	3
1	15	Post-dose 1h (± 10min)	2		10	3
1	15	Post-dose 2h (± 10min)	2		11	3
1	15	Post-dose 4h (± 20min)	2		12	3
1	15	Post-dose 6h (± 20min)	2		13	3
1	15	Post-dose 8h (± 20min)	2		14	3
3	1	Pre-dose/0h	3	301[a]	15	3

[redacted]

Cycle	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Sample Volume (mL)
Unscheduled		Anytime		1001+	3
Total scheduled					45

[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample

Table 7-8 Pharmacokinetic blood collection log for remaining patients, including patients in Cohort 6 and Cohort 7

Cycle	Day	Scheduled timepoint	Dose reference ID		PK Sample No	Sample volume [mL]
1	1	Pre-dose/0h	11		101	3
		Post-dose 2h (± 10min)	11		102	3
1	15	Pre-dose/0h	12	211[a]	103	3
		Post-dose 2h (± 10min)	12		104	3
3	1	Pre-dose/0h	13	311[a]	105	3
Unscheduled		N/A	N/A		1001+	3
Total scheduled						15

[a]Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample

At the specified time points detailed in Table 7-7 and Table 7-8, 3 mL of blood (per sample) will be collected for the measurement of the plasma concentrations of INC280 and metabolites. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Complete instructions for sampling processing, handling and shipment will be provided in the [Laboratory Manual]. All samples should be packed carefully as per the instructions in the separate [Laboratory Manual], ensuring sufficient dry ice is used to keep samples frozen during shipment. Sample labels will include the following information: protocol number, subject number, study day, actual date and time of blood collection, aliquot/matrix. Additional information may be added.

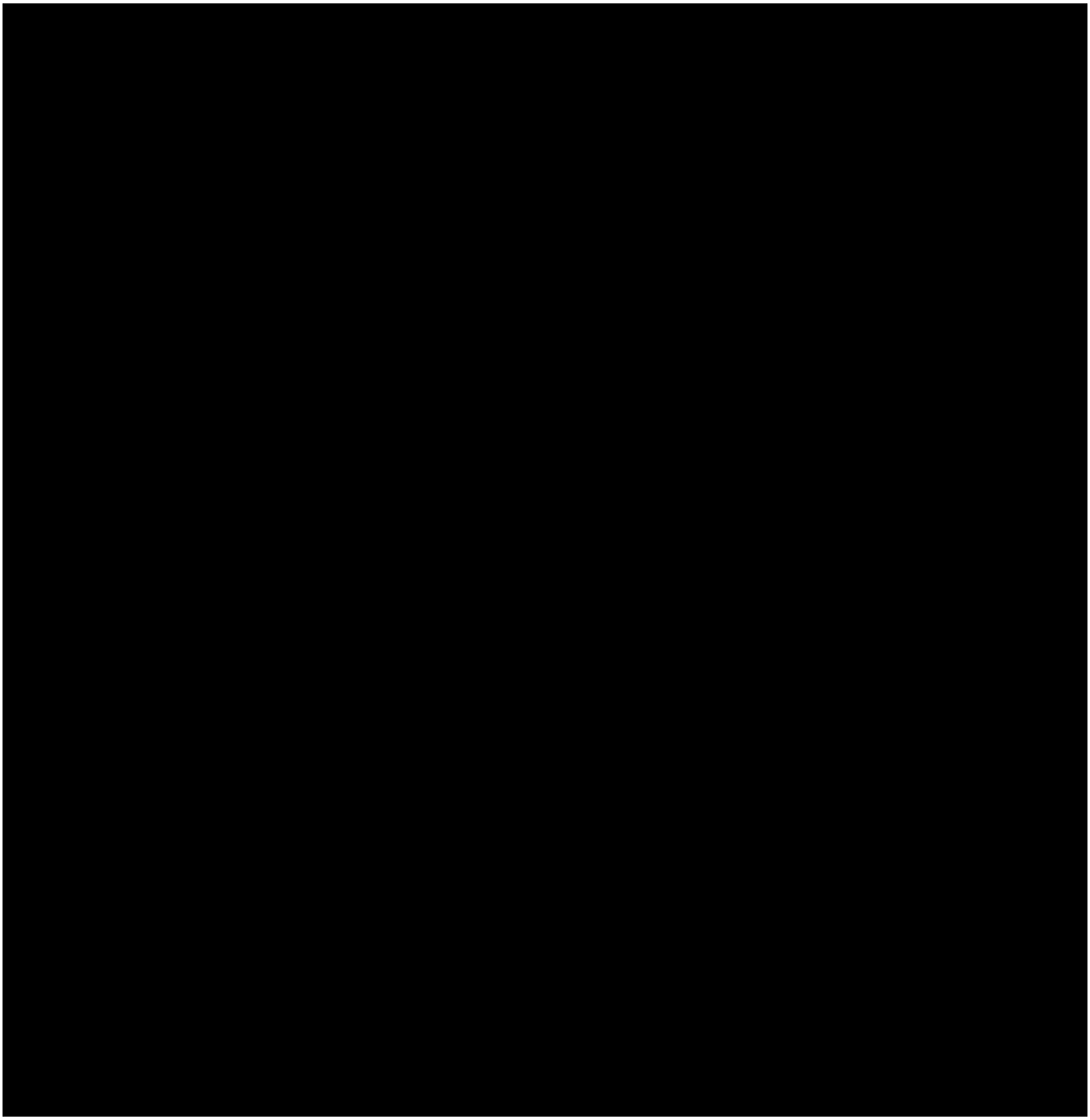
A list of samples, including the date, subject number, and the time of sampling should be included in the shipment. Any missing samples should be indicated on the list. Refer to the [Laboratory Manual] for detailed instructions for specific sample shipment information.

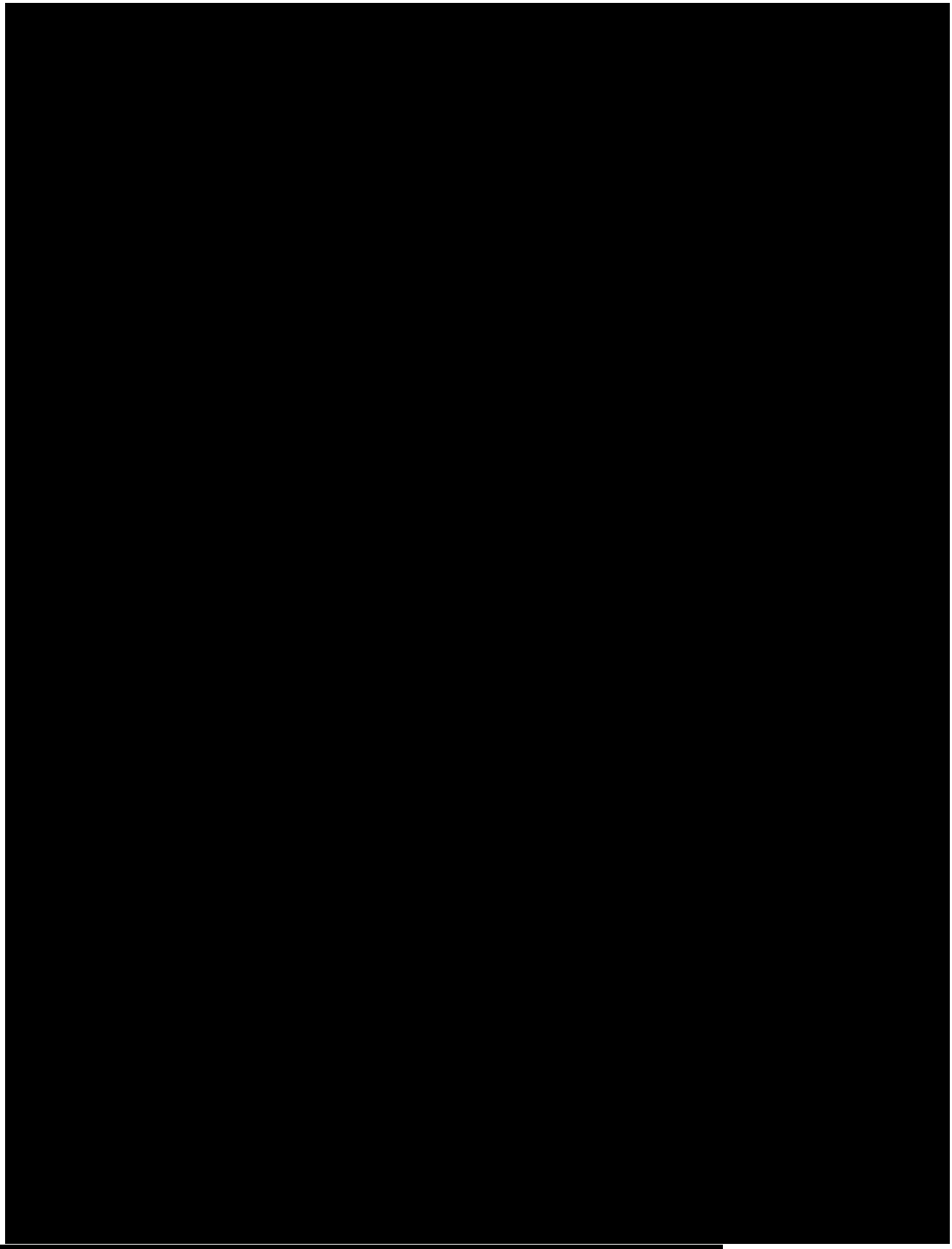
7.2.3.1 Analytical method

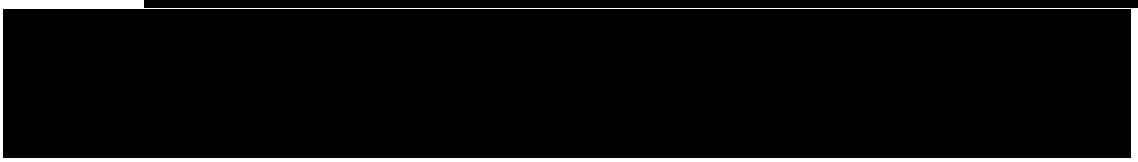
Plasma concentrations of INC280 and CMN288 will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LOQ) of approximately 1.00 ng/mL for both analytes. Residual plasma samples from PK analysis may be used to explore other metabolites of INC280.

[redacted]

[redacted]







8 Safety monitoring and reporting

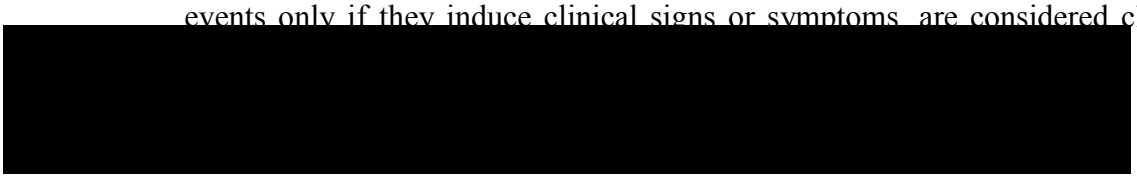
8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event 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 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 8.2.2 and are reported to be causally related with study 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 Adverse Event eCRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events 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).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (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 Adverse Event.

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

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; but is collected as a seriousness criteria; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events 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. Adverse events 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 adverse event should be evaluated to determine:

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

If the event worsened, the event should be reported a second time in the CRF noting the start date when the even worsens in toxicity. For Grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event 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 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 (RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events 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 Adverse event 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 Adverse Events eCRF. 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 Adverse Events 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 adverse event, 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 adverse event, should not be reported as adverse events. 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 adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

8.1.3.1 Definitions and reporting

Adverse events of special interest to be monitored for capmatinib (INC280) include:

- Hepatotoxicity
- Renal dysfunction
- ILD/Pneumonitis

[redacted]

- Central nervous system toxicity
- Phototoxicity
- Teratogenicity
- Pancreatitis
- Drug-drug interactions with strong CYP3A4 inhibitors
- QTc interval prolongation

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (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 serious adverse events:
  - 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
  - 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 serious adverse event.

8.2.2 Reporting

For patients 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 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 the main informed consent and until at least 30 days after the patient has

[redacted]

stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

Any SAE experienced after this 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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. Instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site. 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 to Novartis

Follow-up information is submitted in the same way as the original SAE Report. 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.

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 Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), 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 Emergency unblinding of treatment assignment

Since this study is an open-label study, there is no need for treatment unblinding instructions or unblinding codes.

8.4 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 should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). 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 must 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.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 7 days after INC280 treatment has been stopped. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

8.5 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.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

A Steering Committee (SC) will be formed prior to initiation of the trial and will be appointed by Novartis. It will consist of investigators participating in the trial and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

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

[redacted]

- 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 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, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs 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 eCRF 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated

[redacted]ents, Investigator site

staff will not be given access to the Electronic Data Capture (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 is complete, accurate, and that entry and updates are performed in a timely manner.

Blood and tumor samples for laboratory data, PK [redacted] will be collected by sites and sent to a central laboratory for processing. The laboratory results will be sent electronically to Novartis.

Radiological, ECG, and photography data will be acquired by the sites and interpreted locally. Additionally, radiological, ECG and photography data will be transmitted by the sites to the respective CRO designated to undergo quality checks and central review. Details regarding all CRO procedures including collection and shipment of data will be described in the manual provided by the respective CRO. [redacted].

PK [redacted] (blood and tissue) samples drawn during the course of the study will be collected from the Investigator sites and analyzed by a Novartis assigned laboratory or contracted central laboratories. The site staff designated by the Investigator will enter the information required by the protocol onto the PK [redacted] Sample Collection eCRFs, respectively, as well as the designated laboratory's requisition forms that will be printed on 2-part paper. One copy of the requisition form will be forwarded to the central laboratory along with the corresponding samples with required information (including study number, subject ID, etc.) and the other copy will be retained by the site. The field monitor will review the relevant eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancies as required. The field monitor will also review the requisition forms for completeness.

[redacted]

9.4 Database management and quality control

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 adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

[redacted]

[redacted] The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

The data from all participating centers in this protocol will be combined.

For Cohorts/Sub-cohorts 1-4, the efficacy data for each cohort/sub-cohort will be analyzed separately at the time of the interim analysis and one (or more) of the cohorts/sub-cohorts may be stopped for futility according to the criteria described in the Interim Analysis Section (Section 10.7). No interim analysis for futility is planned for Cohort 5, Cohort 6 and Cohort 7.

The primary analysis will be conducted when all treated patients in their respective cohort/sub-cohort from Cohorts 1-5 and 7 (if not stopped for futility) have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier. Due to the expected difference in enrollment rate for each cohort/sub-cohort, the primary analysis for the different cohorts/sub-cohorts may occur at different times. The primary analysis for any cohort/sub-cohort that was stopped for futility may be combined with the primary analyses for other cohorts/sub-cohorts. The primary efficacy analysis will be performed as defined in Section 10.4.2. These primary analysis results will be summarized in the primary CSR(s). Any additional data for patients continuing to receive study treatment past the data cut-off date for the primary analysis in each of the cohorts/sub-cohorts will be reported in the final CSR at the end of the study as specified in Section 4.3.

Supportive analyses may be carried out combining:

- patients with a cMET GCN of $\geq$ 10 from Sub-cohort 1a and Cohort 6
- patients with cMET mutations from Cohort 4 and Cohort 6 or
- patients from Sub-cohort 5b and Cohort 7,

The supportive analysis will be conducted when all treated patients in their respective cohort/sub-cohort have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier. Due to the expected difference in enrollment rate for each cohort/sub-cohort, the supportive analysis for the groups may occur at different times.

[redacted]

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who receive at least one dose of INC280.Unless otherwise specified the FAS will be the default analysis set used for all analyses, including the primary analysis.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of INC280. All safety data will be analyzed using the Safety Set.

The FAS and Safety Set in this study are identical.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of patients in the FAS who have no major protocol deviations, who have an adequate tumor assessment at baseline and have a follow-up tumor assessment > 5 weeks after starting treatment (unless PD is observed before that time).

All major protocol deviations leading to exclusion from the PPS will be detailed in the Reporting and Analysis Plan (RAP).

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of INC280 and had at least one evaluable post-baseline INC280 concentration measurement.

A PK sample is considered as non-evaluable if it is collected after a patient has vomited within 4 hours post-dose.

The definition of an evaluable PK concentration profile will be further specified in the RAP.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by cohort/sub-cohort based on the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

The actual dose and duration in days of INC280 as well as the dose intensity (computed as the ratio of total 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 cohort/sub-cohort. Dose reductions and dose interruptions (including the reasons for these) will be listed and summarized by cohort/sub-cohort.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by cohort/sub-cohort.

[redacted]

10.4 Primary objective

The primary objective is to demonstrate the antitumor activity of INC280, as measured by overall response rate (ORR) to INC280 by Blinded Independent Review Committee (BIRC) assessment, by cohort/sub-cohort.

10.4.1 Variable

The primary variable used to evaluate the anti-tumor activity of INC280 is the overall response rate (ORR), defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by BIRC.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) provided by cohort/sub-cohort.

In Cohorts 1-4, treatment with INC280 would be considered to have clinically relevant efficacy in a cohort/sub-cohort if an ORR of ~35% is observed in that cohort for the corresponding primary analysis.

In addition, 5 hypotheses will be tested as following for the cohorts/sub-cohorts respectively (H_{i0} and H_{i1} correspond to cohort/sub-cohort i where i=1a, 1b, 2, 3 or 4)

H_{i0}: ORR $\leq$ 25%

In favor of the alternative

H_{i1}: ORR > 25%

For Sub-cohorts 5a, 5b and Cohort 7, treatment with INC280 would be considered to have clinically relevant efficacy if an ORR of ~55% is observed in that cohort for the corresponding primary analysis. In addition, 3 hypotheses will be tested as following for the cohorts/sub-cohorts (H_{i0} and H_{i1} correspond to Sub-cohort i where i=5a, 5b or 7):

H_{i0}: ORR $\leq$ 35%

In favor of the alternative

H_{i1}: ORR > 35%

The tests will be performed based on the exact CI for ORR in each cohort/sub-cohort using a one-sided α= 0.025 level. Based on historical data, as referred in Section 1.1.1, a 25% ORR is a reasonable threshold to be considered as clinically relevant in this specific setting of second and third line advanced NSCLC patients (de Marinis 2008, Weiss 2013, NCCN Guidelines 2014) in Cohorts/Sub-cohorts 1a, 1b, 2, 3 and 4. Similarly, a 35% ORR is a reasonable threshold to be considered as clinically relevant in the treatment-naïve setting for advanced NSCLC patients (Zhou 2015, Scagliotti 2008) in Sub-cohorts 5a, 5b and Cohort 7. Since a one sided α =0.025 is used for a particular hypothesis testing, the testing will be conducted based on two-sided 95% exact confidence interval. The null hypothesis will be rejected if the lower bound of the two-sided 95% exact CI is >25% in Cohorts/Sub-cohorts 1a, 1b, 2, 3 and 4. And

[redacted]

the null hypothesis will be rejected in Sub-cohorts 5a and 5b if the lower bound of the two-sided 95% exact CI is >35%.

No hypothesis testing is planned for Cohort 6.

10.4.3 Handling of missing values/censoring/discontinuations

Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response.

Patients with a best overall response (BOR) of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR.

Patients who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of efficacy endpoints.

10.4.4 Supportive analyses

The primary analysis on FAS will also be repeated on the PPS.

For Sub-cohorts 1a and 1b, and Cohorts 2 and 3, sensitivity analysis on the primary endpoint may be performed excluding patients with cMET mutations.

Data from Cohort 6 will help further characterize the safety and efficacy of INC280 in the pre-treated Sub-cohort 1a and Cohort 4. Efficacy and safety data will be presented for Cohort 6 alone and may also be analyzed for pre-treated patients with cMET GCN $\geq$ 10 by combining the patients from Sub-cohort 1a and Cohort 6. Similar analysis may be carried out for pre-treated patients with cMET mutations regardless of cMET GCN combining the patients from Cohort 4 and Cohort 6.

Data from Cohort 7 will help further characterize the safety and efficacy of INC280 in the treatment-naïve group with cMET mutations regardless of cMET GCN. Efficacy and safety data may also be combined with the patients from Sub-cohort 5b to further increase the precision of the efficacy estimates. These analyses will be performed once Cohort 7 enrolment is closed and when all treated patients in Cohort 7 have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment earlier.

10.5 Secondary objectives

All secondary analyses will be performed on the FAS, unless otherwise specified.

10.5.1 Key secondary objective(s)

The key secondary objective is to evaluate duration of response (DOR) as assessed by BIRC, by cohort/sub-cohort.

Among patients with a confirmed response (PR or CR) per RECIST 1.1, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. If a patient has not had an event, DOR is censored at the date of last adequate tumor assessment. DOR will be described in tabular and graphical

[redacted]

format, by cohort, using Kaplan-Meier methods. The Kaplan-Meier estimate of the distribution function will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25^{th} and 75^{th} percentiles will be reported.

10.5.2 Other secondary efficacy objectives

ORR by investigator assessment, by cohort/sub-cohort: The evaluation of ORR will be also conducted based on investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort/sub-cohort.

DOR by investigator assessment, by cohort/sub-cohort: The evaluation of DOR will be conducted based on investigator assessment. DOR will be analyzed as described above for the analyses based on BIRC assessment.

Overall survival (OS), by cohort/sub-cohort: OS is defined as the time from the date of first dose of INC280 to the date of death due to any cause. If the patient is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cut-off date. OS will be described in tabular and graphical format, by cohort/sub-cohort, using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized.

The following secondary efficacy objectives will be assessed separately based on investigator assessment and BIRC assessment per RECIST 1.1:

Time to response (TTR), by cohort/sub-cohort: Time to overall response of CR or PR (TTR) is defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients with a confirmed CR or PR.

TTR will be summarized in 6-week intervals, by cohort/sub-cohort, using descriptive statistics.

Disease control rate (DCR), by cohort/sub-cohort: DCR is defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST 1.1. DCR will be estimated and the binomial exact 95% CI will be provided by cohort/sub-cohort.

Progression-free survival (PFS), by cohort/sub-cohort: PFS is defined as the time from the date of first dose of INC280 to the date of first radiologically documented disease progression per RECIST 1.1 or death due to any cause. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1 documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of the new cancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. PFS will be described in tabular and graphical format, by cohort/sub-cohort, using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized.

Additional analysis of all secondary efficacy objectives in pre-treated patients with a cMET GCN of ≥ 10 may be carried out combining the patients with a cMET GCN of ≥ 10 from Sub-

[redacted]

cohort 1a and Cohort 6 to further evaluate the precision of the efficacy estimates. Similar analysis will be carried out for pre-treated patients with cMET mutations regardless of cMET GCN combining the patients from Cohort 4 and Cohort 6. Cohort 7 may also be combined with Sub-cohort 5b.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort/sub-cohort for all patients.

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- Post-treatment period: starting at day 31 after last dose of study medication.

The safety summary tables will include only data collected during the on-treatment period. However, all safety data will be listed with data collected during the pre-treatment and post-treatment period flagged.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs observed during the on-treatment period. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and after the on-treatment period will be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/ or preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment by cohort/sub-cohort. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and cohort/sub-cohort.

Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

For each specified category, number and percentage of patients with at least one event per category will be summarized by cohort/sub-cohort.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Further details will be specified in the reporting analysis plan (RAP). Grade 5 will not be used.

[redacted]

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests by cohort/sub-cohort:

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be generated.

A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).

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

10.5.3.4 Other safety data

Data from other tests (including ECGs and vital signs) will be summarized and listed by cohort/sub-cohort. Notable values will be flagged, and any other information collected will be listed as appropriate. Definitions of notably abnormal results will be provided in the RAP.

10.5.3.5 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption due to an AE by cohort/sub-cohort.

10.5.4 Pharmacokinetics

The PAS will be used in all pharmacokinetic data analysis and PK summary statistics. Summary statistics of plasma concentration of INC280 and its relevant metabolites will be reported by visit for all patients that provided at least one evaluable PK sample. Summary statistics include n, arithmetic mean, median, SD, geometric mean, coefficient of variation (CV) (%) and geometric CV (%), minimum and maximum. PK parameters as listed in Table 10-1 will be derived using non-compartmental analysis with the aid of WinNonlin Pro (Version 5.0 or higher) and reported, if feasible. Graphical presentation will be provided on mean concentration at each scheduled time point for PK sub-population where the full PK profile is available. In addition, summary statistics on PK parameters will be reported for PAS.

Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV. Any missing PK parameter data will not to be imputed.

Table 10-1 Noncompartmental pharmacokinetic parameters

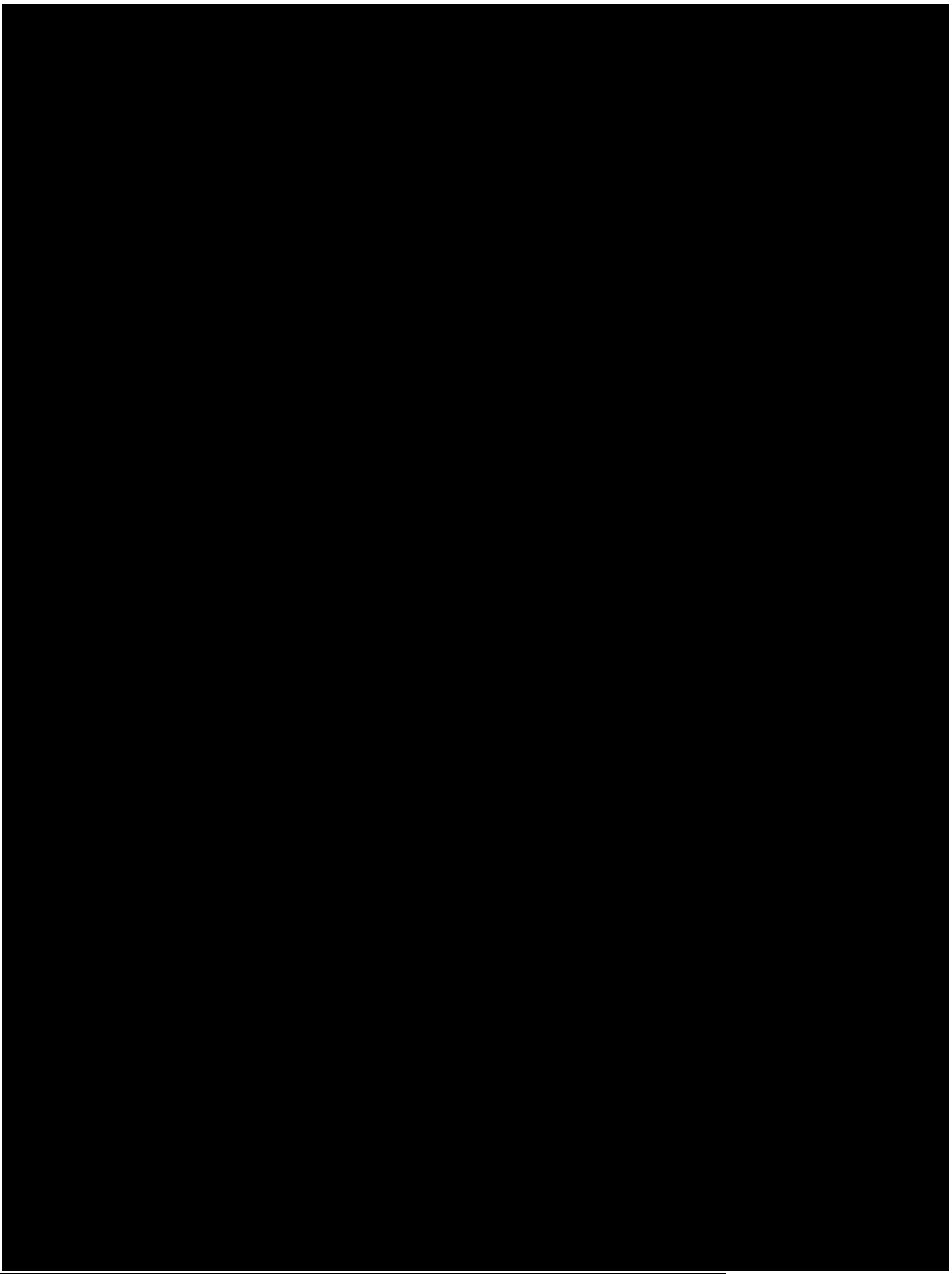
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUC0-t	The AUC from time zero to defined time t (mass x time x volume-1)

[redacted]

AUCtau	The AUC within the dosing interval (τ) (mass x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The apparent total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)
Racc	Accumulation ratio

[redacted]

[redacted]



[redacted]

10.5.6 Resource utilization

Not applicable.

[redacted]

10.7 Interim analysis

In Cohort 1, the interim analysis will be performed separately for each of the two sub-cohorts. Interim analyses for each cohort/sub-cohort are planned when at least 28 patients in each of Sub-cohorts 1a and 1b, Cohorts 2 and 4, and 20 patients in Cohort 3 have completed at least 6 cycles of treatment (18 weeks) or have discontinued treatment earlier. For the interim analysis and the final analysis in Cohort 2 (cMET GCN ≥ 4 and < 6), the study targets to have at least 40% of patients with cMET GCN ≥ 5 and < 6.

No interim analysis for futility is planned for Sub-cohorts 5a and 5b, Cohort 6 and Cohort 7.

The decision to stop for futility for the respective cohort/sub-cohort at interim will be based on the probability of success (POS). POS is the probability of a positive conclusion of the

[redacted]

study if the study continued beyond interim, (i.e., till the final analysis), given the interim observed data (x) and success among n patients. Thus,

POS = Prob[Final observed ORR ≥ 35% | x,n]

Minimally informative Beta distribution prior (Neuenschwander et al 2008) with prior mean equal to 25% will be used, i.e., the prior distribution will be Beta (0.3333, 1) for the POS calculations at the interim analysis.

The respective cohort will be stopped for futility at the interim analysis if the respective POS < 10%. The interim analysis will be performed by cohort in which the patients are enrolled. In addition, for Sub-cohort 1a and 1b, Cohorts 2 and 3, sensitivity analysis on the primary endpoint may be performed at interim analysis excluding patients with cMET mutations.

All evaluable patients at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the POS criteria. The futility boundary will be calculated according to the actual number of evaluable patients in the interim analysis.

Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4

With 28 evaluable patients for interim analysis in each of the Sub-cohorts 1a and 1b, Cohorts 2 and 4, if ≤ 7 responses (POS =0.0543) are observed then the respective cohort/sub-cohort will be stopped for futility. Further details of POS are provided in With 28 evaluable patients for interim analysis in each of the Sub-cohorts 1a and 1b, Cohorts 2 and 4, if ≤ 7 responses (POS =0.0543) are observed then the respective cohort/sub-cohort will be stopped for futility. Further details of POS are provided in Table 10-2. For each of the Sub-cohorts 1a and 1b, Cohorts 2 and 4, if at the time that the 28th patient is enrolled a minimum of 8 responders have not yet been observed, accrual in the cohort/sub-cohort may be temporarily suspended until either the minimum number of 8 responders are observed or results of the interim analysis allow that cohort/sub-cohort to continue.

Table 10-2 Probability of Success at the Final Analysis Based on Various Number of Responders Observed at IA for Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4

Responder at IA out of 28 evaluable patients at IA	Probability of Success
≤ 5	< 0.01
6	0.0164
7	0.0543
8	**0.1398**
9	0.2863
10	0.4794
11	0.6766
≥ 12	> 0.83

Table 10-3 Number of Responders for Various Number of Evaluable Patients at Interim Analyses by Required Probability of Success for Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4

Number of Evaluable patients at IA	Responders at IA	Probability of Success
26	6	0.0368
26	7	0.1050

[redacted]

Number of Evaluable patients at IA	Responders at IA	Probability of Success
27	7	0.0765
27	8	0.1829
28	7	0.0543
28	**8**	**0.1398**
29	7	0.0377
29	**8**	**0.1044**
30	8	0.0760
30	**9**	**0.1792**
31	8	0.0540
31	**9**	**0.1369**
32	8	0.0373
32	**9**	**0.1020**
33	9	0.0740
33	**10**	**0.1739**
34	9	0.0523
34	**10**	**0.1323**
35	10	0.0980
35	**11**	**0.2152**

Cohort 3

With 20 evaluable patients for interim analysis in Cohort 3 if ≤ 5 responses (POS=0.0999) are observed then the cohort will be stopped for futility. All evaluable patients at the time of the data cut-off for the interim analysis will be used to obtain the futility boundary using the POS criteria. Further details of POS are provided in Table 10-4. If at the time that the 20th patient is enrolled a minimum of 6 responders have not yet been observed, accrual in the cohort may be temporarily suspended until either the minimum number of 6 responders are observed or results of the interim analysis allow the cohort to continue.

Table 10-4 Probability of Success at the Final Analysis Based on Various Number of Responders Observed at IA for Cohort 3

Responder at IA out of 20 evaluable patients at IA	Probability of Success
1	0.0001
2	0.0009
3	0.0066
4	0.0309
5	0.0999
6	**0.2379**
7	0.4382
8	0.6533

10.8 Sample size calculation

Approximately 456 patients (69 patients per Sub-cohort in Cohort 1 and 69 patients per cohort in Cohorts 2-4, 27 patients per each Sub-cohort in Cohort 5,approximately 30 patients in Cohort 6 and approximately 27 in Cohort 7) will be enrolled in the study if none of the four cohorts (Cohort 1-4) is stopped for futility at the time of the interim analysis. The exact 95% CIs for various sample sizes and observed ORRs in each cohort/sub-cohort are shown in

[redacted]

Table 10-5 for Sub-cohorts 1a and 1b and Cohorts 2, 3 and 4, and in Table 10-6 for Sub-cohorts 5a, 5b and Cohort 7.

Table 10-5 Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in each Cohort/Sub-cohort 1a, 1b, 2, 3 and 4

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)	
65	23	35.4	23.9	48.2
66	24	36.4	24.9	49.1
67	24	35.8	24.5	48.5
68	24	35.3	24.1	47.8
69	**25**	**36.2**	**25.0**	**48.7**
70	25	35.7	24.6	48.1
71	25	35.2	24.2	47.5
72	26	36.1	25.1	48.3

Table 10-6 Exact Binomial 95 percent Confidence Intervals for Various Sample Sizes and Observed ORRs in each Sub-cohort 5a, 5b and Cohort 7

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)	
25	14	56.0	34.9	75.6
26	15	57.7	36.9	76.6
27	**15**	**55.6**	**35.3**	**74.5**
28	16	57.1	37.2	75.5
29	16	55.2	35.7	73.6

The operating characteristics (with 69 subjects per cohort/Sub-cohort 1a, 1b, 2, 3 and 4) are shown in Table 10-7 and Table 10-8. The tables show probability of stopping at interim, probability for positive conclusion (i.e., not stopped at IA for futility and success criteria met at final analysis) and negative conclusion (i.e., not stopped at IA for futility but success criteria not met at final analysis) under different underlying true ORR. The operating characteristics (with 27 subjects per Sub-cohort in 5a, 5b and Cohort 7) are shown in Table 10-9. The table shows the probability of meeting the success criteria under different underlying true ORR.

Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4

The operating characteristics at this sample size have > 50% probability of stopping the trial for futility when the true ORR is < 25%. Also, when the true ORR is 35% then the probability of positive conclusion at the final analysis with 69 patients is ≥ 44%. If the true ORR is 45% or higher, the probability of positive conclusion at the final analysis with 69 patients is > 90%.

Table 10-7 Operating Characteristics for Sub-cohort 1a, Sub-cohort 1b, Cohort 2 and Cohort 4

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability for positive conclusion in final analysis for a cohort (%)	Probability for negative conclusion in final analysis for a cohort (i.e. not stop at IA* and success criterion not met at final analysis) (%)
10	99.50	0.00	0.50

[redacted]

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability for positive conclusion in final analysis for a cohort (%)	Probability for negative conclusion in final analysis for a cohort (i.e. not stop at IA* and success criterion not met at final analysis) (%)
20	81.82	0.12	18.06
25	59.97	2.34	37.68
30	36.48	15.01	48.51
35	18.21	44.00	37.79
40	7.40	75.38	17.22
45	2.42	93.11	4.47
50	0.63	98.73	0.64

*Assuming interim analysis at 28 evaluable patients

Cohort 3

The operating characteristics at this sample size have > 60% probability of stopping the trial for futility when the true ORR is < 25%. With 69 patients and 20 evaluable patients for interim analysis, when the true ORR is 10% then the probability of stopping for futility at the interim analysis is > 90%. If the true ORR is 20%, the probability of stopping for futility at the interim analysis is > 80% and the probability of positive conclusion at the final analysis is < 1%.

Table 10-8 Operating Characteristics for Cohort 3

True ORR (%)	Probability of a cohort to stop at IA* (%)	Probability of positive conclusion in final analysis for a cohort (%)	Probability of negative conclusion in final analysis for a cohort (i.e., not stop at IA* and success criterion not met at final analysis) (%)
10	98.87	0	1.13
20	80.42	0.11	19.47
25	61.72	2.17	36.12
30	41.64	13.98	44.39
35	24.54	41.41	34.05
40	12.56	71.99	15.45
45	5.53	90.46	4.01
50	2.07	97.36	0.57

*Assuming interim analysis at 20 evaluable patients

Sub-cohort 5a, 5b and Cohort 7

The operating characteristics at this sample size of 27 have < 36% probability of the trial meeting the success criteria when the true ORR is ≤50%. If the true ORR is ≥60%, the probability of the trial meeting the success criteria is ≥ 75%.

Table 10-9 Operating Characteristics for Sub-cohort 5a, 5b and Cohort 7

Sample size (N)	True ORR (%)	Probability (%) that ORR>=55% with lower 95% CI>35%
27	40	7.4
27	45	18.1
27	50	35.1

[redacted]

Sample size (N)	True ORR (%)	Probability (%) that ORR>=55% with lower 95% CI>35%
27	55	55.6
27	60	75.0
27	65	88.9

Cohort 6

In expansion Cohort 6, patients with either cMET GCN ≥ 10 without cMET mutations or cMET mutations regardless of cMET GCN will be enrolled. Based on the rarity of this patient population and considering recruitment within a reasonable timeframe, approximately 30 patients are expected to be enrolled in Cohort 6.

Data from Cohort 6 will help further characterize the safety and efficacy of INC280 in the pre-treated population (from Sub-cohort 1a and Cohort 4).

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

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.

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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.

[redacted]

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 is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

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For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

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 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.

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[redacted]

14 Appendices

14.1 Appendix 1: Harmonization of efficacy analysis of solid tumor studies (RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

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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 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 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 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

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

14.1.4 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 14.1.26.

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, if the soft tissue component meets the definition of measurability.
- 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 ≥10 mm and <15 mm 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.

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- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 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 Overall Response Rate (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 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

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 5 mm 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 have a medical contraindication to CT contrast or develops a contraindication 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 (e.g. 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.
- **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-PET 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-PET 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, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit 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

[redacted]

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 stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (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, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 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, photography) should be at least 10 mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

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 metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameters 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.

14.1.9 Follow-up and 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.

14.1.10 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 subject 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.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

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.

14.1.11 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.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

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]

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (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]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (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].
Stable Disease (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 <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.1.6.

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 progressive disease
- 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 with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- 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 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However,

[redacted]

in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- **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 case report form, the diameter of the "merged lesion" should be 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 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm 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 any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (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)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (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. < 10 mm). 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 '**Non-CR/Non-PD**' 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. 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 even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (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 lesion.
- 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

[redacted]

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 14.1.15).

- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 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	Non-CR/Non-PD[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 14.1.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (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.

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

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

14.1.17 Best overall response

The best overall response 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 best overall response 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 best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response 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 confirmation of 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.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response 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).
- 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

[redacted]

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.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

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

Based on the patients' best overall response during the study, the following rates are then calculated:

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

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

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 progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

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 known date patient alive.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

[redacted]

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, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

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.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

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. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

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.

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 complete response (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 time to progression.

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

14.1.24 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 overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. 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 event is the worst possible outcome as it means 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 complete response (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.

14.1.25 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 CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the

[redacted]

assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

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

For the calculation of duration of response 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 progressive disease.
- 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 14.1.26).

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 correspond to 9 months.

- 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 known date patient alive from the 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.

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

It is possible that patients with only 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

[redacted]

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.

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.

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.

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
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.1.8.

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 best overall response patients with only 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".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only 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 with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses 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 RAP 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.

[redacted]

Based on definitions outlined in Section 14.1.25, 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 RAP	Outcome
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 14.1.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[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

[redacted]

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.

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.

14.1.28 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).

14.1.29 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).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee 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.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.32 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

[redacted]

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' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader 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.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 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.

14.1.35 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 14.1.25). 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.

14.1.36 Incomplete dates for last known date patient alive 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.

[redacted]

14.1.37 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)'.

14.1.38 Study/project specific programming

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

14.1.39 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)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. 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="Sponsor decision" 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 to censor in case of no baseline assessment.

[redacted]

14.1.40 References (available upon request)

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