NOVARTIS

Clinical Development

EGF816 (Nazartinib)

Protocol CEGF816X2101 / NCT02108964

A phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816 administered orally in adult patients with EGFRmut solid malignancies

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Amendment 07 (11-Mar-2020)

Amendment rationale

As of the release of this amendment (11-Mar-2020), the study is closed to enrollment. In the phase I part (dose-escalation) of the study, 180 patients were enrolled; 11 patients are ongoing. Forty-five patients were enrolled in Phase 2 part (expansion phase) of this study and 18 patients are ongoing.

Study initiated with capsules and moved to tablets, as it became the Formulated Market Image (FMI) strategy. However, based on the shelf-life superiority of the capsules in comparison to tablets, Novartis has strategically decided to move back to capsules to provide better shelf-life for the market. The main purpose of this amendment is to implement the use of the capsules form again (25 mg / 50 mg / 100 mg) instead of tablets for the ongoing patients promptly upon availability. The decision to switch back from tablet to capsule is based on the following:

- The capsule formulation has a superior stability profile compared to the tablets, allowing the assignment of longer shelf lives
- Statistical analysis showed that exposures between tablet and capsule are comparable with geometric mean ratios of 1.04 and 1.03 for AUCtau and Cmax, respectively, following single 150 mg dose, and 1.06 and 1.12 for AUCtau and Cmax, respectively, following 150 mg QD.

Therefore, based on this rationale, capsules will be used in a timely manner following approval of this amendment for the remainder of this study for all ongoing patients in phase I and phase II parts.

Additionally, the guidelines for some selected toxicities (hepatitis B, skin rash, including maculo-papular rash and Interstitial Lung Disease (ILD)/pneumonitis) have been updated to optimize the patient's safety. These changes are not due to new safety findings but reflects new internal/international clinical guidelines.

Finally, the lists of permitted and prohibited concomitant medications included in Appendix 3 and Appendix 4 have been revised based on periodic update.

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 and tables were changed:

- List of abbreviations – added and updated abbreviations
- Section 2.3 – removed the reference to the use of tablets in the phase II part
- Section 6.1.1 – introduced the implementation of capsules use based on this amendment rationale
- Section 6.2.1– clarification added for the change of drug formulation pertaining to protocol amendment #03
- Sections 6.2.3.2 and 10.4.2.1 – clarification added for the change of drug formulation pertaining to protocol amendment #07

- Section 6.2.3.4 – revised since all patients are on treatment at RP2D with tablets therefore the intra-patient dose escalation switch cannot occur
- Section 6.3.2, Table 6-6, Table 6-7 and Table 6-8 – Guidelines for screening, monitoring and management of HBV/HCV reactivation updated as per new internal/international clinical guidelines
- Table 6-9 - Guidelines for prevention and symptomatic care of rash/skin toxicities updated as per new internal/international clinical guidelines
- Table 6-10 – Management and dose modification for maculopapular rash updated as per new internal/international clinical guidelines
- Table 6-11 - Management and dose modification for other rashes including acneiform rash updated as per new internal/international clinical guidelines
- Section 6.3.4 and Table 6-12 - Guidelines for the management and dose modification of non-infectious pneumonitis/interstitial lung disease updated as per new internal/international clinical guidelines
- Table 7-1 and Table 7-2 – Updated to reflect the change of HBV and HCV monitoring
- Section 13 – Updated with the addition of the reference related to the new clinical guidelines for hepatitis management
- Appendix 3 (Table 14-14) and Appendix 4 (Table 14-15): Permitted concomitant medications requiring caution and prohibited concomitant medications lists revised based on periodic update

In addition, as part of this amendment, minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency, and correction of spelling errors or typographical errors have been 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.

Amendment 06 (07-Apr-2017)

Amendment rationale

As of 31-Mar-2017 in the Phase I part (dose-escalation) of the study, 180 patients have been enrolled with 7 different dose levels at 10 sites in 8 countries; 42 patients were ongoing. During a dose-escalation meeting on 30-Aug-2016, the Investigators and Novartis agreed to declare the Recommended Phase 2 Dose (RP2D) of EGF816 (Nazartinib) capsules and tablets at the dose level of 150 mg QD based on the available safety, pharmacokinetic, efficacy data and on the Bayesian Logistic Regression Model recommendation.

The Phase II part (expansion phase) of this study was originally planned to enroll patients in 6 different groups defined by the prior lines of treatment and the tumor molecular status of the patients. However, the rapid evolving landscape including ongoing trials in this disease setting led to the decision not to start the enrollment of patients who received more than 1 line of prior antineoplastic therapy in Groups 2 to 6. Indeed, it is noteworthy that approval has been granted in different countries to osimertinib (Tagrisso®) for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after prior systemic therapy, including an EGFR-TKI giving patients in this setting access to 3rd generation EGFR-TKI as per FDA and EMA information. Therefore, the Phase II part of the study will continue as a single group of patients, all treated at 150 mg QD Nazartinib.

An Investigator letter dated 07-Dec-2016 informed the investigators about the opening of the Phase II part of the study for enrollment in Group 1 only. This group will now enroll a minimum of 40 treatment-naïve patients instead of 60 patients (Section 10.8.2), who have locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del), have not received any systemic antineoplastic therapy for advanced NSCLC, and are eligible to receive EGFR-TKI treatment. As of 31-Mar-2017, 8 patients have been enrolled in the Phase II part and were ongoing.

In addition, a previous protocol amendment (#4 released on 05-May-2015) introduced the implementation of central laboratories to evaluate the safety of EGF816 (Nazartinib) (e.g., hematology, chemistry, urinalysis, coagulation and pregnancy test) for all 6 groups in the Phase II part; given that only one group will now be opened, the laboratories for screening and safety monitoring will continue to be implemented locally as it is currently being done in the Phase I part.

The main purpose of this amendment is to implement the above-mentioned decisions that were already communicated to all Investigators and submitted to all Ethics Committees and Health Authorities in participating countries.

Furthermore, Amendment 6 implements other substantial changes as follows:

- Provides an update on EGF816 overview based on the most recent version of the Investigator's Brochure (Edition 5, released on 13-Jul-2016 with a data cut-off date 18-Dec-2015)
- Introduces the RP2D that was declared on 30-Aug-2016 during the Phase I part of the study. All patients enrolled in the Phase II will receive the RP2D, i.e. EGF816 150 mg QD. The recommended dose reduction steps starting from the RP2D are also introduced in this amendment.

- Removes the exclusion criterion on fasting plasma glucose > 175 mg/dL (> 9.8 mmol/L) in the absence of evidence of interaction with glucose in light of the most recent available clinical data and according to the latest version of EGF816 Investigator's Brochure (Ed. 5, data cut-off date 18-Dec-2015)
- Updates the exclusion criterion on QTcF threshold from 480 to 470 ms as defined by Morganroth for oncology studies in order to provide a safety margin of 30 ms for QTc > 500, a significant liability for TdP, and a 10 ms safety margin for the second highest QTcF category of >480 and also to ensure patient safety within the context of other factors, related to nausea and vomiting and potentially overt cardiac conditions in the patient population that have not been assessed or diagnosed like left ventricular hypertrophy and subclinical cardiomyopathy
- Updates number of patients required for futility analysis in the Phase II part from 25 to approximately 20 patients. It may allow stopping the enrollment or treatment of patients in case lack of efficacy is concluded. The sample size and the primary analysis in the Phase II are also being revised. The expansion phase will allow to explore the hypothesis that targeting the activating resistance mutants together with the main EGFR resistance mechanism T790M may prevent the acquisition of resistance to EGFR-TKIs. A sample size of 40 patients will provide acceptable operating characteristics to assess the preliminary anti-tumor activity of the study treatment
- Reinstates the collection of CT/MRI scans or other imaging data in the Phase I part of the study for potential retrospective central review.
- Updates to clarify criteria for treatment beyond disease progression of patients as per Investigator's judgment
- Removes in Phase I part for all ongoing patients, the visit on Day 15 during cycles beyond cycle 2 for consistency with the Phase II part of the study and because of the absence of additional or new unexpected safety findings in light of the most recent available clinical data.
- Updates the definition of the end of study to detail study continuation conditions after completion of the primary analysis until all patients are discontinued, or until another clinical trial becomes available for all ongoing patients to be transferred to that clinical study and continue to receive EGF816.
- Adds follow-up requirements for potential QTcF prolongation (in case of QTcF >500 ms, or QTcF prolongation >60 ms from baseline) and potential drug-induced liver injury to align with other Novartis-sponsored study protocols
- Introduces the modalities and conditions for patient re-screening after screen failure, together with screening assessments to be performed again during the new screening phase.
- [redacted]
- [redacted]

- Updates the exclusion criterion related to women of child-bearing potential and the description of imaging efficacy assessments for consistency with other Novartis Oncology sponsored studies.

Other non-substantial changes were made to provide more clarity to the protocol:
- Clarifies the time window for post-dose ECG during the visits with PK sampling.
- Clarifies that the exclusion criterion on the QTc interval value should be based on the Investigator interpretation of the ECG.

Change to the protocol

- Protocol summary:
  - Update purpose and rationale, inclusion and exclusion criteria, data analysis according to the main changes provided the protocol
- Section 1.2.1.2 Clinical experience
  - Updated according to last version of the Investigator's Brochure (Ed. 5, data cut-off date 18-Dec-2015)
  - Update efficacy data based on latest data presented in a poster at ASCO 2016
- Section 2.1: Study rationale and purpose
  - Clarify that the Phase I part will include patients with tumors harboring specific EGFR mutations
  - Clarify that in the Phase II part patients to be enrolled will be in first line of antineoplastic systemic therapy (EGFR TKI and chemotherapy naïve) and whose tumors harbor specific EGFR activating mutations (e.g., L858R and ex19del)
  - Remove the description of the groups 2 to 6 originally planned for the Phase II part
- Section 2.2: Rationale for study design
  - Remove the description of groups originally planned for the Phase II part
- Section 2.6: Risk and Benefits
  - Introduce Risk and Benefits section for consistency with other Novartis Oncology sponsored study protocols
- [redacted]
  - [redacted]
- Section 4.1: Description of study design
  - Update description of patient population and sample size of phase II part
  - Clarify that EGFR mutation status is determined by a local laboratory for patient in Phase II part
- Figure 4-1: Study design, Phase II part
  - Update the Study design of Phase II part following removal of the groups 2 to 6 initially planned
- Table 4-1: Key features of patient population in each of the 6 groups (Phase II)
  - Remove the table entirely as the 6 groups will no longer be applicable for Phase II part

- Section 4.2: Timing for interim analysis and design adaptation
  - Remove all the 6 groups description and clarify the assessment of futility will be based on the calculated Bayesian probability of success (PoS).
- Section 4.3: Definition of end of study
  - Update to clarify that primary analysis will be conducted on Phase I and II patients and end of study definition is applicable for Phase I and II patients
  - Remove the description of the 6 groups
- Section 5: Population
  - Remove the description of the 6 groups and specify that patients in Phase II part must not have received any prior line of systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). However, patients who have failed no more than 1 cycle of antineoplastic therapy in the advanced setting are allowed.
- Section 5.2: Inclusion criteria
  - Update Inclusion criterion 4 to clarify that patients with controlled brain metastases may participate in the trial and must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging.
  - Update inclusion criterion 11 to remove the 6 groups and define the patient population for Phase II (NSCLC with locally documented EGFR mutation L858R and/or ex19del, and must be naïve from any line of systemic antineoplastic therapy in the advanced setting)
- Section 5.3: Exclusion criteria
  - Update exclusion criterion 7 to clarify that patient with QTcF value above 470ms instead of 480ms would be excluded from study provided it was defined as threshold for oncology studies by Morganroth, and it provides a safety margin of 30 ms for QTc>500ms, which constitutes a significant liability for TdP, and a 10 ms safety margin for the second highest QTcF category of >480ms. In addition it was clarified to use the mean QTcF value from triplicate screening ECGs according to Investigator's assessment
  - Update exclusion criterion 11 to clarify minimum time window for patients who have been treated with chemotherapy or biologic therapy or other investigational agent from ≤ 1 week to ≤ 4 weeks prior to the first dose of study treatment
  - Update exclusion criterion 15 to clarify time window for patients who participated in a prior investigational study from within 1 week to within 4 weeks or within 5 half-lives of the investigational product, whichever is longer, prior to first dose of study treatment
  - Update exclusion criterion 12 to remove Fasting Plasma glucose in light of IB ed. 5 data and add editorial updates for ANC, Hemoglobin, Platelets and Creatinine Clearance criteria
  - Update exclusion criteria19 and 20 to provide more clarity on pregnancy/ contraception and clarify when a condom should be used
- Section 6.1.1: Dosing Regimen

- Clarify that for patients in Phase II part, the orally administered film-coated tablet formulation will be treated with RP2D and provided with 2 doses strength of 25 mg and 50 mg.
- Clarify that patients in Phase I part will be continued on capsule or tablets formulations
- Clarify when the dose should be taken on PK days
- Clarify which fruits must be avoided during the treatment period of the study

- Section 6.1.2: Treatment duration
  - Update to remove confirmation of disease progression by BIRC in Phase II
  - Add that patient may continue treatment until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.
  - Section 6.1.2.1: new section added to provide details about treatment beyond disease progression of patients
- Section 6.2.1: Starting dose rationale
  - Add details on EGF816 strength and reference to support the formulation change from capsules to tablets
- Table 6-4: Recommended dose reduction steps for the Phase II part
  - Update the dose reduction steps based on the declared RP2D for Phase I and II patients
- Table 6-5: Criteria for reduction/interruption and re-initiation of EGF816 treatment for adverse drug reactions:
  - Update criteria for Isolated AST/ALT to match with CTCAE and provide guidance based on patient's baseline AST/ALT values and match with new Novartis-sponsored study protocols
  - Ad criteria for Grade 4 QTcF
  - Update to clarify when the dose modifications/interruptions are recommendations or mandatory and also align with other Novartis-sponsored study protocols
- Table 6-8: Guidelines for management of HCV reactivation
  - Update to correct the date of viral reactivation from 22Jan to 01Jan2015
- Table 6-10: Management and dose modification for maculopapular rash
  - Clarify that Grade ≥3 rash should be re-assessed every week and if more than 1 episode of ≥ Grade 3 is developed, patient must be permanently discontinued
  - Clarify that study drug may be resumed although steroids for rash management are still ongoing or being tapered
- Table 6-11: Management and dose modification for other rashes including acneiform rash
  - Clarify that re-assessment should be conducted every 2 weeks instead of after 2 weeks
- Section: 6.3.5: Follow-up for toxicity
  - Add new section 6.3.5.1: follow up on potential QTcF prolongation to align with other Novartis-sponsored study protocols

    - Add new section 6.3.5.2: follow up on potential drug-induced liver injury (DILI) cases to align with other Novartis-sponsored study protocols
- Section 6.4: Concomitant medications
    - Clarify that the use of bisphosphonates is allowed as no drug-drug interaction is expected with EGF816
    - Editorial changes in Section 6.4.2 and 6.4.3
- Section 6.5: Patient numbering, treatment assignment or randomization
    - Clarify that this is a non-randomized trial and Integrated Response Technology (IRT) will only be used for patient registration and drug supply management in the Phase II part
    - Remove the description of treatment assignment of 6 groups originally planned in the protocol
- Section 6.6.1: Study drug packaging and labeling
    - Editorial changes to add more clarity on the packaging difference between Phase I and Phase II
- Table 7-1: Visit Evaluation Schedule (Phase I part)
    - Greyed out Day 15 for all subsequent cycles after cycle 2 to reduce patient's visits for ongoing Phase I patients after protocol amendment 06
    - Add footnote to clarify that EOT tumor assessment doesn't need to be repeated if was performed ≤ 28 days
    - [redacted]
    - Remove Body fluid collection/results as no cytology samples will be collected and only the cytology form needs to be completed
    - Merge Disposition for Screening and Treatment for consistency with Table 7-2 and add Disposition for Disease Progression F/U as this information is collected for Phase I patients
    - Add row for safety follow-up as this assessment is performed for Phase I patients
- Table 7-2: Visit Evaluation Schedule (Phase II part)
    - Greyed out all visits that are no longer applicable for Phase II patients and added the corresponding footnote
    - Update to clarify that EGFR mutation status needs to be confirmed by local testing only
    - Remove all the assessments related to Groups 2 to 6 as they are no longer applicable
    - Move Chest X-Ray (for Japanese Patients Only) from the Tumor assessment section to the Physical examination section for more clarity
    - Provide more details on the imaging data to be collected for tumor assessment per RECIST 1.1 and as per the imaging collection plan in Table 7-4
    - Update to clarify that all phase II patients will now have extensive ECG collection

- [redacted]
- [redacted]
- Remove Body fluid collection/results as no cytology samples will be not collected and only the cytology form needs to be completed and submitted to central imaging CRO

- Section 7.1.1: Molecular pre-screening
  - Remove all the descriptions related to patients in groups 2 to 6
  - Group 1 no longer exists as in phase II only one patient population is required and there is no need to have different groups
  - Clarify that EGFR activating mutation will be confirmed by local lab
- Section 7.1.2: Screening
  - [redacted]
  - Clarify that HBV and HCV tests will be performed by a local laboratory for Phase I and II patients
- Section 7.1.2.1: Eligibility Screening
  - Update eligibility text by adding more details on screening/re-screening procedure and failures for patients enrolled in Phase II part of the study
- Section 7.1.4 : Discontinuation of study treatment
  - Add more details on when the patient “should” and not “must” discontinue the study treatment
  - Add clarification about when patient is considered to have withdrawn from the study and when treatment is continued beyond disease progression
- Section 7.1.5.2: Post-treatment follow-up
  - Add that antineoplastic therapies since discontinuation of study treatment should be collected to match with Tables 7-1 and 7-2
- Section 7.1.5.3: Survival follow-up
  - Add that antineoplastic therapies since discontinuation of study treatment should continue to be collected for Phase II patients for evaluation of overall survival
- Section 7.1.6: Withdrawal of consent
  - Add reasons when patient can withdraw consent and clarify that the Investigator should make every effort to understand the primary reason of this decision
- Section 7.2.1: Efficacy Assessment
  - Clarify that central imaging review will be done by BIRC in an ongoing basis for Phase II and retrospective collection and central review will be conducted for Phase I
  - Editorial changes in Section 7.2.1.1 regarding baseline imaging assessment to align with other Novartis-sponsored study protocols and move the text related to post-baseline imaging assessment in section 7.2.1.2

  - Rename section 7.2.1.2 from Subsequent imaging for response assessment to post-baseline imaging assessment to match with other Novartis-sponsored study protocols
- Section 7.2.1.2: Post-baseline imaging assessment
  - Sub-section renamed to match with other Novartis-sponsored study protocols
  - Repetitive statements removed to add some clarity
- [redacted]
  - [redacted]
- Section 7.2.1.4: BIRC confirmation of disease progression
  - Delete sub-section as BIRC PD confirmation is not required and needed provided the primary efficacy analysis is based on ORR and not on PFS
- Section 7.2.2.1: Physical examination
  - Define the complete and targeted physical examination
- Section 7.2.2.5: Laboratory evaluations
  - Amend to clarify that local lab will be used for patients in Phase I and Phase II and no central lab will be used for patients in Phase II
  - Amend to add Phosphorus to match with inclusion criterion
  - Amend to add Amylase and Lipase in the chemistry panel to allow monitoring of occurring pancreatic AEs
- Section 7.2.2.6.1: Electrocardiogram (ECG)
  - Update to clarify that extensive ECG will be done for all the patients treated in Phase II part provided groups 2 to 6 were removed
  - Clarify that triplicate ECGs should be performed within 15 minutes prior to the collection of PK sample at the matched time-point
  - Update to align wording with other Novartis-sponsored study protocols
- Section 7.2.3: Pharmacokinetics
  - Add dose reference ID prior to PK sampling in Tables 7-9 and 7-10
- Section 7.2.4: Biomarkers
  - Split the biomarker section into 2 sub-sections for Phase I and for Phase II part of the study
  - [redacted]
  - Add reason for biomarker collection and assessments in Phase II part of the study
- Table 7-12: Biomarker sample collection plan for Phase II part
  - Update to remove description for biomarker collection from patients in groups 2 to 6
  - Specify that mandatory tumor samples at screening instead of pre-screening should be collected and block or a minimum of 11 slides instead of 6 slides are required
  - Specify that mandatory tumor samples (if available) at C1D1 instead of screening should be collected and block or additional 5 slides instead of 10 slides are needed

  - Update to clarify that C1D1 optional tumor sample now include either newly obtained tumor biopsy or archival material (3 to 10 slides) if fresh material not available at C1D1
  - Add the possibility to provide optional newly acquired biopsy during the treatment phase for assessing the study drug effect and mechanisms of resistance to EGF816 treatment
  - [redacted]
  - [redacted]
  - [redacted]
  - Add optional on treatment blood sample collection to be paired with on treatment newly acquired biopsy
  - Remove the tissue requirement needed in the companion protocol for phase II patients
- Section 8.1.1: Definitions and reporting
  - Update to clarify AE reporting and align with other Novartis-sponsored study protocols
- Section 8.1.3: Adverse events of special interest
  - New section added to align with other Novartis-sponsored study protocols and define the AESIs to be monitored for EGF816
- Section 8.2.2: Reporting
  - Update the Serious Adverse Event reporting process to allow possible electronic reporting to the Sponsor and name of safety department to Chief Medical Office and Patient Safety (CMO&PS)
- Section 8.3: Pregnancies
  - Replace “Drug Safety and Epidemiology Department” by “Chief Medical Office and Patient Safety (DS&ECMO&PS)”
  - Update: Pregnancy outcomes should be collected for the female partners
- Section 8.5: Data Monitoring Committee
  - Update to remove description regarding groups 2 to 6
- Section 8.7: Blinded Independent Review Committee (BIRC):
  - Reinstate that BIRC review will be performed for patients from Phase I part
  - Remove expedited PD review following local assessment of progression
- Section 9.4: Database management and quality control
  - Update to align with other Novartis-sponsored study protocols
- Section 10: Statistical methods and analysis:
  - Remove description regarding groups 2 to 6
- Section 10.1: Analysis sets
  - Update to remove description regarding groups 2 to 6 and description of the pharmacokinetic analysis set for phase I and II

- Section 10.2: Patient demographics/other baseline characteristics
  - Update to remove description regarding groups 2 to 6
- Section 10.3: Treatments
  - Update to remove description regarding groups 2 to 6
- Section 10.4: Primary objective
  - Remove all the description regarding groups 2 to 6
  - Clarify the interim analysis for futility to be performed when approximately 20 patients have completed at least 4 cycles or discontinued treatment prior to that time.
- Section 10.4.3: Handling of missing values/censoring/discontinuations
  - Add "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"
- Section 10.5.1.2: Adverse events
  - Clarify that Serious adverse events, non-serious adverse events and adverse events of special interest during the on-treatment period will be tabulated
- Section 10.5.1.3: Laboratory abnormalities
  - Clarify that CTCAE grades will be based on observed laboratory values
- Section 10.5.2: Efficacy analysis
  - Clarify that analyses will be based on the FAS
- Section 10.5.2.1: Analysis set and the grouping for analyses
  - Update to confirm phase II part analyses will be summarized for all patients
- Section 10.5.2.2: Secondary efficacy endpoints
  - Add that Best Overall Response (BOR) will be included in the phase I/II secondary efficacy endpoints and BOR will be summarized by phase and group.
- Section 10.5.3: Pharmacokinetics
  - Update to clarify the planned PK analyses
  - Update Table 10-1 to remove Cmin as it could be the concentration at the end of the absorption lag phase.
- Section 10.5.3.2: Data analysis principles
  - Specify which PK plasma concentrations will be included in the analysis
- [redacted]
  - [redacted]
  - [redacted]
- Section 10.7: Interim analysis
  - Remove all group 2 to 6 description
- Table 10-2: Update the table to provide the probabilities of success at the primary analysis based on different numbers of responders observed at the IA
- Section 10.8: Sample Size Calculation
  - Update to remove all the groups 2-6

  - Clarify the number of patients to be enrolled and the number of responders required
- Table 10-3 displays the probabilities to stop for futility at the interim analysis and to declare preliminary anti-tumor activity of the study treatment at the primary analysis (observing at least 22 responses in 40 patients) under different true ORR values
- Section 11.5: update the section regarding the publication of study protocol and results to align with other Novartis-sponsored study protocols
- Section 14.3 – Appendix 3, Table 14-14: Permitted Concomitant Medications requiring caution
  - Update to include last updates from the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: May 2016)
- Section 14.1 – Appendix 1
  - Update to include most recent guidelines for response version 3.2 dated 11-Feb-2016 based on RECIST 1.1
- Section 14.4 - Appendix 4, Table 14-15: Prohibited Concomitant Medications
  - Update to include last updates from the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: May 2016)

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

Amendment 05

Amendment Rationale

As of 23-July-2015, 121 patients have been enrolled in the Phase I part (dose-escalation) of the study at 9 sites in 8 countries in Asia, Europe and North America.

As of 08-July-2015, 2 serious adverse events (SAEs) of viral hepatitis B (HBV) reactivation have been reported in 2 patients participating in the CEGF816X2101 study. One case had a fatal outcome, and the second case was medically significant. The fatal case involved a patient who received EGF816 at 225 mg capsule QD, had HBV infection in the past and was not on antiviral treatment at study entry. The patient developed a HBV reactivation during the study and died due to hepatic failure despite initiation of antiviral treatment after HBV reactivation was confirmed. The second patient also received EGF816 at 225 mg capsule QD, had a history of HBV and was not on antiviral treatment at the time of joining the study; however, HBV reactivation was detected approximately 10 weeks on study. Antiviral treatment was immediately initiated, EGF816 was interrupted and the HBV infection was brought under control. The patient later resumed EGF816 at the same dose of 225 mg QD. The viral reactivation in these two patients was likely due to immunosuppression related to EGF816. Reactivation of HBV and viral hepatitis C (HCV) has been reported with other anticancer therapies that suppress the immune system. To ensure the safety of all patients participating in CEGF816X2101 trial, changes have been made to the protocol to implement the safety measures regarding the reactivation of HBV and HCV.

In addition, early preclinical and clinical findings suggest that EGF816 may have an immunomodulatory effect, related to its ability to inhibit the Tec family of kinases (ITK, TEC, and TXK). While some preclinical and clinical data suggest that Tec kinase inhibition by EGF816 leads to immunosuppression, other preclinical data indicate that it may lead to a shift in differentiation of T cell subtypes that could result in an immunostimulatory effect (Fowell et al., 1999, Sagiv-Barfi et al., 2015). Changes have been made to the protocol to allow sample acquisition at time points at which the presence of such an effect can be evaluated. Clinical data in the context of immune checkpoint inhibition have demonstrated that several months of treatment with an immunomodulatory agent may be necessary before changes in tumor immune infiltrates can be observed. Therefore, to assess changes in tumor immune infiltrates during EGF816 treatment as compared to baseline, the timing of the on-treatment biopsy has been moved to a later time point. In addition, to assess changes in circulating cytokines, additional blood collection for plasma has been added at baseline and on the first day of each cycle.

Based on the rationales for Groups 1-6 in the Phase II part, the protocol has been amended to allow similar patient populations to be enrolled in the Phase I part of the study.

Changes made to the protocol are summarized below and include:

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.

- Updated Section 1.2.1.1.2 to include preclinical results showing inhibition of Tec family kinases by EGF816 and their potential role in EGF816 effects.
- Updated Section 1.2.1.2 Clinical experience with new clinical data and information on the 2 SAEs of the HBV reactivation in patients participating in CEGF816X2101.

- Protocol Sections 2, 4.1, 5, 7.1.1 and 10 were revised to allow NSCLC patients harboring specific EGFR mutations, corresponding to the groups in Phase II part, but with some differences in restrictions on prior lines of therapy, to be included in Phase I part
- Protocol Sections 3, 4 and 7 were revised to be consistent with Companion Sample Collection Protocol languages
- Protocol Sections 3 and 7 were revised that the assessment of progressive disease (PD) with newly obtained tumor samples at screening and C1D15 will be performed up to protocol amendment 05. After that, the on-treatment biopsy will be moved from C1D15 to C4D1, C6D1 (optional), C8D1 (optional) and EOT (optional).
- [redacted]
- [redacted]
- Protocol Section 4.1, 5, Table 6-5, Sections 6.3.2, 7.1, 7.2 and Table 7-6 were revised to add assessment and follow up regarding HBV, HCV testing
- Added exclusion criterion in Section 5.3 to exclude patients who
  - have a history of other malignancies.
  - have undergone a bone marrow or solid organ transplant.
  - have a known history of human immunodeficiency virus (HIV) seropositivity.
  - are receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry.
  - have a history of Torsade de Pointes
- Protocol Section 6.1.2, 7.1.5.2, 7.2.1.3, 7.2.1.4, 8.7 and 10.5.2 were revised to change the imaging assessment from BIRC to investigator assessment for the phase I part
- Updated Section 6.4.2 to include additional permitted concomitant therapies requiring caution and/or action.
- Updated Table 6-10 to recommend consideration of skin biopsy in the event of a maculopapular rash.
- Study phase completion part was removed in Section 7.1.5.3
- Pregnancy assessments were clarified in Section 7.2.2.5.6
- Updated Table 14-14 and Table 14-15 in Section 14.3 Appendix 3.

IRB/IEC/REB Approval

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

Amendment 04

Amendment rationale

As of 16-April-2015, 92 patients have been enrolled in the Phase I part (dose-escalation) of the study from 9 sites in 8 countries. As of 2-February-2015 data cut-off, preliminary efficacy results from 5 dose levels tested have showed an overall response rate (ORR) of 59.5% by Investigator assessment in 25 (11 confirmed and 14 awaiting confirmation) out of 42 evaluable patients. (Note: evaluable patients include those who were ongoing and had at least one post-baseline tumor assessment or who discontinued study treatment as of the data cut-off date.) Based on these response data, changes have been made to the existing groups and two additional groups have been added to the Phase II part in Amendment 4.

The primary purpose of Amendment 4 is to revise the patient populations and/or the number of patients to be enrolled in each group in the Phase II part.

In addition, the number of groups in the Phase II part is revised from 4 groups (as per Amendment 3) to 6 groups (Amendment 4). Each group has a distinctive patient population, determined by the specific EGFR mutations and the number of prior lines of systemic antineoplastic therapy, including prior EGFR TKIs.

Throughout Amendment 4, advanced NSCLC refers to patients with either locally advanced or metastatic NSCLC. Locally advanced NSCLC is defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC.

The table below presents the summary of changes in the groups between Amendment 3 and Amendment 4 and the rationale for those changes.

Summary of the changes in the groups between Amendment 3 and Amendment 4 and the rationale for the changes:

	Amendment 3		Amendment 4		
Group	**Patient population**	**N**	**Patient population**	**N**	**Rationale for the changes**
Group 1	Advanced NSCLC EGFR mutant (L858R and/or ex19del, not T790M) Who are intolerant to an approved EGFR TKI (e.g., erlotinib, gefitinib, afatinib) and/or for whom these drugs are not appropriate	~ 20	Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del) Who have not received any systemic antineoplastic therapy, including EGFR TKI treatment, for advanced NSCLC Note: patients who have received no more than 1 cycle of chemotherapy in the advanced setting are allowed.	60	EGF816 is a 3rd-generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. In preclinical study using tumor model with EGFR ex19del, EGF816 treatment was more efficacious compared to treatment with erlotinib. Other 3rd-generation EGFR TKIs, such as AZD9291, have shown promising preliminary data in this patient population (ESMO 2014); both AZD9291 and CO-1686 have ongoing Phase III clinical trials in the first line setting. Based on the mechanism of action (MoA), EGF816 will likely have similar clinical activity in this patient population. The sample size is increased to approximately 60 patients to have about 81% probability to observe an overall response rate ≥ 60% given the true response rate of this population is 65%.
Group 2	Advanced NSCLC with an acquired EGFR T790M mutation Who have progressed on EGFR TKI (no more than 1 previously approved EGFR TKI)	~ 80	Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del) and an acquired EGFR T790M mutation Who have progressed on 1 and only 1 prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib) No more than 3 prior lines of systemic antineoplastic therapies (including EGFR TKI) in the advanced setting EGFR TKI treatment must be the last prior treatment before study entry.	120	EGF816 is a 3rd-generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. Preliminary efficacy results from the Phase I part in advanced NSCLC patients with both EGFR activating mutation (L858R and/or ex19del) and T790M mutation showed significant antitumor activity of EGF816 that is in line with other 3rd-generation EGFR TKIs, and a tolerable safety profile The increase in sample size will permit a more accurate assessment of overall response rate and a better understanding of the frequency and types of adverse events reported during treatment with EGF816. EGFR TKI treatment is required to be the last prior treatment before study entry to avoid potential “re-challenge” effect.

	Amendment 3		Amendment 4		
Group	**Patient population**	**N**	**Patient population**	**N**	**Rationale for the changes**
Group 3	Advanced NSCLC with a "de novo" EGFR T790M mutation Who have not received prior treatment with an EGFR TKI	~ 80	Locally advanced or metastatic NSCLC with a "de novo" EGFR T790M mutation For purposes of this protocol, "de novo" T790M will be defined as the presence of EGFR T790M mutation in NSCLC patients who have NOT been previously treated with any therapy known to inhibit EGFR. No more than 3 prior lines of systemic antineoplastic therapies in the advanced setting No prior treatment with any therapy known to inhibit EGFR, including EGFR TKI	40	3rd-generation EGFR TKIs, due to their ability to inhibit EGFR T790M mutation, should have antitumor activity in this patient population. Of note, one NSCLC patient with a "de novo" T790M mutation has been enrolled in the Phase I part (dose-escalation) of this study. This patient has been treated with 225 mg of EGF816 and showed a tumor reduction of 41.54% from baseline and continued the study treatment for at least 5 months. The estimated incidence of "de novo" T790M mutation is low (~1%). Thus, the sample size is decreased to 40 patients to allow completion of enrollment within a reasonable timeframe. With a sample size of approximately 40 patients, there is about ≥ 78% probability to observe an overall response rate ≥ 55% given the true response rate of this population is 60%.
Group 4	Advanced solid tumor harboring any EGFR mutation and NOT be otherwise eligible for groups 1-3 No limitation of previous anti-neoplastic therapies in the advanced setting	>10	Locally advanced or metastatic NSCLC whose tumor harbors EGFR exon 20 insertion or deletion No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKI, in the advanced setting	~ 10	The patient population in Group 4 was not well defined under Amendment 3. EGFR exon 20 insertion/deletions are resistant to clinically achievable doses of marketed or investigational EGFR inhibitors, such as gefitinib, erlotinib, neratinib, afatinib, and PF00299804. This group of patients currently represents a high unmet medical need. In a preclinical study, treatment with EGF816 demonstrated promising efficacy and tolerability in an exon 20 insertion model. Thus, EGFR816 may have the potential to provide clinical benefit to this patient population.
Group 5	New group (added under Amendment 4)	-	Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del) AND <u>without</u> an acquired EGFR T790M mutation Who have progressed on 1 and only 1 prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib), or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib) No more than 3 prior lines of systemic	60	Promising clinical activity has been observed in this patient population with treatment of other 3rd-generation EGFR TKIs, such as AZD9291 and CO-1686, with the overall response rates ranging from 21%-36%. Given similar MoA between EGF816 and other 3rd-generation EGFR TKIs, EGF816 may exhibit similar clinical activity in this patient population.

Group	Amendment 3		Amendment 4		Rationale for the changes
	Patient population	**N**	**Patient population**	**N**	
			antineoplastic therapies, including EGFR TKI, in the advanced setting EGFR TKI treatment must be the last prior treatment before study entry.		
Group 6	New group (added under Amendment 4)	-	Locally advanced or metastatic NSCLC with EGFR activating mutations (e.g., L858R or ex19del) and an acquired T790M mutation Who have had treatment with a 1st/2nd-generation EGFR TKI Who have progressed on or are intolerant to a 3rd-generation EGFR TKI (e.g., AZD9291, CO-1686, or ASP8273) No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKIs, in the advanced setting	80	The scaffold of EGF816 is different from those of AZD9291 and CO-1686, thus it is possible that tumors which are resistant to treatment with AZD9291 or CO-1686 may respond to treatment with EGF816. Additionally, the safety profile of EGF816 is different from other 3rd-generation EGFR TKIs; therefore, patients who are intolerant to treatment with those agents may be able to tolerate EGF816 treatment. Patients who have progressed on or are intolerant to a 3rd-generation EGFR TKI represent a population with a significant unmet medical need. Data may provide further understanding of the mechanism of resistance to 3rd-generation EGFR TKIs.

Furthermore, Amendment 4 implements other important changes affecting the **Phase II part** of this trial as follows:

- Implements Interactive Response Technology (IRT) to track patient enrollment, document key eligibility criteria, allocate patients into 6 different groups based on their disease characteristics at study entry, and track EGF816 drug dispensing.
- Implements a Blinded Independent Review Committee (BIRC) for tumor assessment to allow an independent and unbiased evaluation of tumor response for the Phase I part and Phase II part.
- Implements the central laboratories to evaluate the safety of EGF816 (e.g., hematology, chemistry, urinalysis, coagulation and pregnancy test) for all 6 groups. The use of a central laboratory will allow a consistent laboratory assessment and interpretation of the results across a multitude of countries participating in this study.
- Implements the central laboratory to determine the EGFR mutation status for Groups 2 and 5, and only required for Group 3 when the local test does not meet the protocol specified criteria. The use of a central laboratory will allow a consistent determination of the EGFR mutation status across a multitude of countries participating in this study.
- Implements a requirement of ECOG performance status of 0-1 for all patients enrolled in the Phase II part to ensure that patients will be able to receive potential benefit from study treatment. It has been well documented that performance status is among the most important prognostic factors for survival of patients with NSCLC.
- Added overall survival (OS) as a secondary objective to assess clinical benefit and to obtain additional information for the future trial planning.
- [redacted]

In addition, for the Phase I part, BIRC will be implemented retroactively to one of the secondary objectives to evaluate ORR, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR).

Changes to the protocol include:

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.

- Section 1.1 Overview of disease pathogenesis, epidemiology and current treatment
  - Added a sentence to provide the rationale for Group 5.
- Section 1.2.1.1.1 Non-clinical pharmacokinetics and metabolism
  - Removed the restriction on use of concomitant medications which are sensitive substrates of CYP2C8 and CYP2D6.
- Section 1.2.1.2 Clinical experience
  - Added the efficacy and safety summaries of EGF816 based on the data from 2-Feb-2015 (data cut-off date).
  - Added Figure 1-1 to provide EGF816 clinical activity observed at all dose levels tested.
  - Added the description to define the purpose of the Phase II.
- Section 2.2 Rationale for the study design
  - Added descriptions to define the 6 groups of the Phase II part and corresponding rationales.
- Section 2.3 Rationale for dose and regimen selection
  - Deleted the rationale for once daily dosing.
  - Added a sentence to describe that the recommended phase II dose (RP2D) will be based on the efficacy and safety data of the Phase I part.
- Section 3 Objectives and endpoints
  - Separated the Phase I objectives and related endpoints (Table 3-1) from the Phase II objectives and related endpoints (Table 3-2).
  - Added BIRC to one of the secondary objectives for the Phase I part
  - Revised the primary endpoint of Phase II to add overall response rate (ORR) by BIRC
  - Added the secondary objectives and related endpoints for the Phase II part.
  - [redacted]
  - [redacted]
  - Added a sentence to state that patients enrolled in the Phase I part will follow the visit schedule noted in Table 7-1.
  - Moved up the paragraph “Patients may have tumor tissues…once approved and open” and stated it is for the Phase I part.
  - Added the descriptions for the six distinctive groups, corresponding sample size for each respective group and key changes in Amendment 4.
  - Figure 4-1 was revised to reflect the current study design of the Phase II part under Amendment 4.
  - Table 4-1 was added to provide key features of patient population in each of the 6 groups.
  - In Figure 4-2, the sequence of the study visit flow was revised so that the 30 days follow-up period is now before the disease progression follow-up period and the

survival follow-up period was added following the disease progression follow-up period.
    - Created Figure 4-3 for the Phase II part
- Section 4.2 Timing of interim analyses and design adaptations
    - New description was added to describe the updated information for the interim futility analyses. The previous description of the interim analyses for Phase II was deleted.
- Section 4.4 Early study termination
    - Added “discontinued or” and deleted “prematurely” per the guidelines for discontinuation of clinical trial protocol (CTP) elements.
- Section 5 Population
    - Deleted the previous language for describing the different groups in Phase II and added new descriptions for these groups.
    - Added a sentence to define treatment failure.
    - Added “Patients enrolled in the study are not permitted to participate in additional parallel investigational drug or device studies.”
- Section 5.1 Patient population
    - Added clarification that exceptions to the inclusion/exclusion criteria in the Phase II part are not allowed.
- Section 5.2 Inclusion criteria
    - Added the corresponding inclusion criteria for each of the 6 groups in Phase II.
    - Added clarification that an ECOG performance status of 0, 1 or 2 will be required for Phase I and an ECOG performance status of 0 or 1 will be required for Phase II.
- Section 5.3 Exclusion criteria
    - Added the corresponding exclusion criteria for each of the 6 groups in Phase II.
    - In Prior therapies exclusion criterion, remove “phototoxicity” as EGF816 may have photosensitivity.
    - The renal function exclusion criterion was changed to measured or calculated creatinine clearance <45 mL/min.
    - For exclusion criteria, highly effective methods of contraception or condom must be used while taking the study drug and for 3 months after stopping treatment.
- Section 6.1.1 Dosing regimen
    - Added clarification that the 25 mg tablet will be available at the start of Phase II. The 50 mg tablet will be available at a later time during the study.
    - Table 6-4 of Amendment 3 was moved up to this section to better align with the heading. A footnote was added to clarify that the 50 mg tablet will be available at a later time.
- Section 6.1.2 Treatment duration
    - Added new criteria or definitions for treatment discontinuation.
- Section 6.2.1 Starting dose rationale

- Deleted "The highest provisional dose planned (1000 mg, qd) can be dissolved in less than 10 ml of various aqueous solutions tested, far below 250 mg which is the standard volume of water required for the administration of the drug."
- Table 6-2 Provision dose levels: added a row for 100 mg dose.

- Section 6.2.3.2 Change of drug formulation
  - Added clarification that the EGF816 tablet will be used in Phase II.
- Section 6.3.1 Dose modification and dose delay
  - Added the guidelines for the management and dose modification of skin-related toxicities.
  - Added the guidelines for the management and dose modification of non-infectious pneumonitis/interstitial lung disease.
- Section 6.4.1 Permitted concomitant therapy
  - Added clarification that radiotherapy is permitted for patients who develop progressive disease limited to bone in addition to CNS involvement.
- Section 6.5.1 Patient numbering
  - Added a new description about implementation of IRT for Phase II.
- Section 6.5.2 Treatment assignment
  - Revised the description about IRT for the Phase II part.
- Section 6.6 Study drug preparation and dispensation
  - As described above under Section 6.1.1, Table 6-4 was deleted and moved up to Section 6.1.1.
- Section 7.1 Study flow and visit schedule
  - Added the description that written informed consent must be obtained before any study specific assessments are performed.
  - Added clarifications for visit and schedule windows for Phase I and Phase II.
  - Added a separate visit evaluation schedule (Table 7-2) for Phase II.
  - Added clarification that Phase I and Phase II will follow visit evaluation schedule outlined in Table 7-1 and Table 7-2, respectively.
  - Deleted any assessments that are applicable to Phase II from Table 7-1.
  - The Japan only requirement regarding hospitalization during C1 was removed.
- Section 7.1.1 Molecular pre-screening
  - Modified the descriptions for the requirements of the local/central laboratory testing of the EGFR mutation status for the Phase I part and Phase II part.
- Section 7.1.2 Screening
  - Modified the descriptions for the screening period.
- Section 7.1.2.1 Eligibility screening
  - A new section titled "Eligibility screening" was added.
- Section 7.1.2.2 Information to be collected on screening failures

  - Section 7.1.2.1 titled “Information to be collected on screening failures” was revised and is now numbered as Section 7.1.2.2. The eCRF pages to be completed for screening failure patients are listed.
- Section 7.1.2.3 Patient demographics and other baseline characteristics
  - Section 7.1.2.2 titled “Patient demographics and other baseline characteristics” was revised and is now numbered as Section 7.1.2.3. The types of data to be collected are outlined.
- Section 7.1.4 End of treatment visit including study completion and premature withdrawal
  - Section 7.1.4 in Amendment 3 was deleted to better align with the guidelines for discontinuation of CTP elements.
- Section 7.1.4.1 Criteria for premature patient withdrawal
  - Section 7.1.4 in Amendment 3 was deleted to better align with the guidelines for discontinuation of CTP elements.
- Section 7.1.4 Discontinuation of study treatment
  - Section 7.1.4 Discontinuation of study treatment was added to replace Section 7.1.4 Criteria for premature patient withdrawal per the guidelines for discontinuation of CTP elements.
- Section 7.1.4.2 Replacement policy
  - Section 7.1.4.2 Replacement policy in Amendment 3 was moved to a later part of the amendment and is now numbered as Section 7.1.5.5.
- Section 7.1.5 Follow up period
  - Section Disease progression follow-up and Section 30 day safety follow-up were deleted and replaced with Section 7.1.5.1 Follow-up for safety evaluations, Section 7.1.5.2 Post-treatment follow-up, Section 7.1.5.3 Study phase completion and Section 7.1.5.4 Survival follow-up.
- Section 7.1.6 Withdrawal of consent
  - Section 7.1.6 was added per the guidelines for discontinuation of CTP elements.
- Section 7.1.7 Lost to follow-up
  - Section 7.1.7 was added per the guidelines for discontinuation of CTP elements.
- Section 7.2.1 Efficacy assessment
  - Imaging collection plans were separated for Phase I and Phase II.
  - Table 7-4 was added to introduce the imaging collection plan for the Phase II part.
- Section 7.2.1.1 Baseline imaging assessment
  - Additional descriptions were added to this section for imaging requirement at baseline and tumor assessments required at baseline.
- Section 7.2.1.2 Subsequent imaging for response assessment was added.
- Section 7.2.1.3 Transmission of efficacy data to BIRC was added per BIRC implementation.
- Section 7.2.1.4 BIRC confirmation of disease progression was added per BIRC implementation.
- Section 7.2.2.5 Laboratory evaluations

  - Descriptions were added per implementation of central laboratory for safety evaluations.
  - Table 7-6 was relabeled as "Central/local clinical laboratory parameters collection plan."
- Section 7.2.2.6.1 Electrocardiogram (ECG)
  - Table 7-7 was revised with the following changes: 1) Central ECG collection plan for all patients; 2) Triplicates are added for pre-dose timepoints; 3) The requirement for Japan only was removed.
  - Table 7-8 was added for implementation of extensive ECG collection plan at pre-selected sites.
- Section 7.2.3.1 Pharmacokinetic blood sample collection and handling
  - Table 7-10 was revised with the following changes: 1) "scheme 1" was removed from the table title; 2) "first 10 patients in each group" was removed from the table title; 3) the 12 hr timepoint was removed from the table and the dose reference IDs and footnotes were updated accordingly.
  - Table 7-11 was removed as Phase II part PK scheme 2 was not needed.
- [redacted]
- [redacted]
- [redacted]
- Section 8.7 Blinded Independent Review Committee (BIRC) was added per BIRC implementation.
- Section 10.4.2.2
  - Modified the statistical success criterial for Groups 1, 2, and 3, and added statistical analysis and success criterial for Groups 5 and 6.
- Section 10.5.2
  - Clarified the definition of all the efficacy objectives.

[redacted]

- Section 10.7
  - The interim futility analysis for Group 2 (per Amendment 3) was removed due to encouraging preliminary clinical activity observed with EGF816 treatment which is in line with other 3rd-generation EGFR TKIs and better than the current standard-of-care

chemotherapy (ORR of 34% observed for platinum doublet [IMPRESS trial, ESMO 2014]).

- Modified the interim analysis method for Groups 1 and 3, and added the interim analysis method for Groups 5 and 6.

- Section 10.8
  - Modified the sample size rationale for Groups 1, 2, and 3, and added the sample size rationale for Groups 5 and 6.

IRB/IEC/REB Approval

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

Amendment 03

Amendment rationale

In order to create a commercially viable format, tablet is going to be introduced to the study. The main purpose of this amendment is to allow for the possibility of a formulation change during dose escalation from capsule to tablet, and the determination of a MTD and/or RP2D with either formulation.

Additional changes to the protocol:

- Clarification of appropriate methodologies regarding patient selection strategy. Protocol is amended to mandate that T790M positivity be defined by central lab using therascreen EGFR RGQ PCR kits (Qiagen) for Group 2 and Group 3 in phase II part. This change is necessary to minimize the variance in testing methodologies and to meet health authorities standards. The addition of this requirement necessitated several modifications to other specific parts including statistical part in protocol.
- Clarification and modification of inclusion/exclusion criteria regarding previous number of treatments allowable for Groups 1 and Group 4 in phase II part in order to include patients with good performance status but who have received multiple standards of care.
- Clarification and modification of inclusion/exclusion criteria regarding washout time from previous treatments to be aligned with the current standard approach to treat patients with EGFR TKIs and to minimize tumor flare following EGFR TKI withdrawal.
- [redacted]
- Minor changes to address consistencies within protocol

Changes to the protocol include:

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.

Table 3-1 Objectives and related endpoints

[redacted]

Section 4.1 Description of study design

- Added requirement that for patients to be recruited to Group 2 and Group 3, T790M positivity must be defined by therascreen EGFR RGQ PCR kits (Qiagen) at a Novartis-designated central laboratory.

Section 5.2 Inclusion criteria

- Group 1: added "Patients who were found to also have a T790M mutation by local assessment that cannot be confirmed by central Qiagen Therasreen testing will be considered as not having T790M (for purposes of this protocol) and will be eligible for this group."
- Group 2 and Group 3: changed the documentation of EGFR mutational status to be compliant with description of study design.
- Group 2 and Group 3: clarified that only adenocarcinoma patients will be included. Modifications were made in other parts of protocol to be consistent with this change.
- Group 2: removed "according to RECIST v1.1" when defining "acquired T790M mutation following progression on EGFR TKI.

Section 5.3 Exclusion criteria

- Excluded in phase I part patients "previously treated with any investigational EGFR-TKI targeting EGFRmut-T790M".
- Revised to allow "no limitation of previous antineoplastic therapies in the advanced setting" for Group 1 and Group 4 in phase II part.
- Modified washout time frame for previous treatment. In particular, "patients who have been treated with chemotherapy or biologic therapy or other investigational agent ≤ 1 week prior to first dose of study treatment."
- Modified washout time frame for radiation therapy and/or surgery for brain metastases to be consistent with exclusion number 5. And clarified that patients with controlled brain metastases may participate in this trial.

Table 6-1 Dose and treatment schedule

- Added the dose and frequency of tablet and moved the table to Section 6.6.
- Clarified that the administration instruction will be the same as for tablet.

Section 6.2.1 Starting dose rationale

- Added starting dose rationale for tablet.

Section 6.2.3.1 Definition and estimation of MTD/RP2D

- Added "MTD/RP2D for each drug formulation or dosing schedule may be established when appropriate".

Section 6.2.3.2 Dose cohort modification

- Revised wording from “for the purposes of dose escalation decisions, each cohort will consist of 1 to 3 newly enrolled evaluable patients who will be treated at the specified dose level” to “for the purposes of dose escalation decisions, each cohort will consist of 1 to 6 newly enrolled evaluable patients who will be treated at the specified dose level.”
- Added wording to “if significant activity is seen early in the dose escalation, then a recommended dose may be identified and the phase II groups may be initiated without determination of the MTD; therefore fewer than 21 patients may be required.”
- Added wording to allow cohort modification in case of “change of formulation”.

Section 6.2.3.4 Intra-patient dose escalation

- Added “patients still on capsule treatment may switch to tablets at same dose level or following the same intra-patient dose procedure as for capsule”.

Section 6.2.4 Definitions of dose-limiting toxicities (DLTs)

- Clarified that the definition of DLT is for phase I part only.

Table 6-2 Criteria for defining dose-limiting toxicities

- Clarified that definition of grade 3 serum creatinine according to CTCAE.
- Deleted criteria for “pancreas”.

Table 6-3 Criteria for interruption and re-initiation of EGF816 treatment

- Changed guidance for Grade 3 serum creatinine increase and Grade 2 Bilirubin increase.

[redacted]

Section 7.1.1 Molecular pre-screening

- Changed the documentation of EGFR mutational status to be compliant with description of study design.

Section 7.2.1 Efficacy assessments

- Clarified that imagining data will be centrally collected and checked for quality for Group 2 and Group 3 only in Phase II part.

[redacted]

Table 7-6, Table 7-7 and Table 7-8: Schedule of blood sample collections for pharmacokinetics

- Clarified in footnote that “If biopsy is collected on cycle 1 day 15, no unscheduled blood PK sample needs to be collected”.

[redacted]

Section 10.4.2 Statistical hypothesis, model and method of analysis

- Added wording for “change in drug formulation”.

Section 14.2 Operational characteristics of the Bayesian logistic regression mode and hypothetical dose escalation scenarios

- Added specification of the statistical model for tablet and the corresponding hypothetical scenarios.

Added or revised wording regarding optional companion sample collection protocol in Section 4, Table 7-1, Table 7-9, Section 7.2.4, Section 8.2 and Section 9.

Replaced "RDE" with "RP2D" throughout the protocol.

IRB/IEC/REB Approval

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

Amendment 02

Amendment 02 rationale

The rational for the amendment is to address changes requested by health authority (i.e. Japan PMDA) and includes the following:

- Clarify the definition of "women of childbearing potential"
- Add "glucose" into chemistry panel in laboratory parameters

[redacted]

[For Japan only]

- Add a description in the protocol that in Japan, written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.
- Specify that Japanese patients will be hospitalized during Cycle 1, vital signs will be obtained during the first week of hospitalization, chest X-ray will be obtained per cycle with an additional ECG on C1D1 per Japanese standards/concerns regarding EGFR TKI development.

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.

Section 5.3 exclusion criteria

- Added definition of "women of childbearing potential"

Table 7-4 local clinical laboratory parameters collection plan

- Added "glucose" into chemistry panel

Section 7.2.4 biomarker

- Added “Results of biomarker analysis whose clinical reliability has been validated will be communicated back to the investigator, who may discuss them with the patient.”

[For Japan only]

Section 5.2 inclusion criteria

- Added “[For Japan only, written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]”

Section 5.3 exclusion criteria

- Added “[For Japan only: Patients with a current or past history of interstitial lung disease.]”

Table 7-1 visit evaluation schedule, footnote

- Added “[For Japan only, patients are required to be hospitalized in Cycle 1” and “percutaneous oxygen saturation (SpO2) will be measured every time physical examination is performed. In addition, SpO2 and vital signs will be measured on Days 2-7 in Cycle 1]”.

Table 7-1 visit evaluation schedule and section 7.2.5.1 chest X-ray:

- Added “[For Japan only: A 2-view chest X-ray will be performed at screening, Day 15 of cycle1, and on Day1 of cycle 2 and thereafter. If a chest CT scan is performed, a chest X-ray can be skipped except for at screening.]”

Table 7-5 central ECG collection plan

- Added “[For Japan only: triplicate 12-lead ECG at 2 hr post dose (±30 minutes) on C1D1]”

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/IEC/REB Approval

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

Amendment 01

Amendment rationale

The rationale for the amendment is to comply with health authority’s request to add a generic statement to this first-in-man trial: “that all patients participating in this clinical trial must have recurred or progressed following standard therapy, unless no standard therapy exists, is tolerated or appropriate”. The addition of this generic statement however necessitated several modifications to specific inclusion criteria as outlined:

1. Specified that all patients participating in this clinical trial must have recurred or progressed following standard therapy, unless no standard therapy exists, is tolerated or appropriate
2. Revised that Phase I part will recruit NSCLC patients harboring a documented EGFR T790M mutation
3. Revised that the group 1 in Phase II part will recruit patients have advanced NSCLC with EGFR mutation (L858R or ex19del, not T790M) and are intolerant to an approved EGFR TKI (e.g., erlotinib, gefitinib, afatinib); and/or for whom these drugs are not appropriate.

Furthermore, times of blood pressure and time interval of 3 sequential ECGs were deleted to allow sites perform the assessments only to comply with institutional standards.

In addition, this amendment was used to make a few other changes for clarification (please see below Changes to the protocol for details).

Changes to the protocol

Section 2.1 Study rational and purpose

Section 2.2 Rational for study design

Section 4.1 Description of study design

- Revised wording in these 3 sections to be consistent with changes in inclusion criteria

Section 5.2 – Inclusion criteria

- Added one inclusion criteria to specify patient population as stated above
- Revised inclusion criteria for Phase I part as stated above
- Revised inclusion criteria for group 1 in Phase II part as stated above

Section 5.3 – Exclusion criteria

- Revised wording of prior treatment to be consistent with changes in inclusion criteria

Table 6-4 Criteria for interruption and re-initiation of EGF816 treatment

- Deleted “2 of three measures performed five minutes apart under standard conditions” for hypertension

Section 7.2.6.6.1 Electrocardiogram (ECG)

- Time internal requirement (“separated by 10-15 minutes”) was deleted for 3-sequential ECGs

Section 8.7 Warnings and precautions

- Deleted due to duplication with Section 8.4

Section 10.8 Sample size calculation

- Revised wording to be consistent with changes in inclusion criteria

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/IEC/REB Approval

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

Protocol summary

Protocol number	CEGF816X2101
Title	A phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816, administered orally in adult patients with EGFRmut solid malignancies
Brief title	n/a
Sponsor and Clinical Phase	Novartis Phase I/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the Phase I part (dose-escalation) of this study is to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) and to evaluate the preliminary antitumor activity of single-agent EGF816 in adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC harboring a documented EGFR mutation. Based on preclinical data for EGF816 and the known clinical activity of other 3rd-generation epidermal growth factor receptor (EGFR) inhibitors, it is expected that EGF816 would exhibit to significant antitumor activity in non-small cell lung cancer (NSCLC) patients harboring the activating EGFR mutations (e.g., L858R and ex19del) and/or the acquired/resistant “gatekeeper” T790M mutation while sparing wild-type (WT) EGFR. The purpose of the Phase II part is to evaluate the efficacy and safety of single-agent EGF816 in adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC whose tumors harbor specific EGFR mutations. The Phase II part will consist in enrolling treatment naïve patients (i.e. have not received any systemic antineoplastic therapy for advanced NSCLC. Patients who have failed no more than 1 cycle of antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy. Note: throughout this protocol, advanced NSCLC refers to patients with either locally advanced or metastatic NSCLC. Locally advanced NSCLC is defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC.
Primary Objective(s)	**Phase I part (dose-escalation)** • To estimate the MTD or RP2D of EGF816 as assessed by incidence of dose-limiting toxicities (DLTs) during the first 28 days of dosing. **Phase II part** • To evaluate the antitumor activity of EGF816 as measured by overall response rate (ORR) determined by Blinded Independent Review Committee (BIRC) assessment in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
Secondary Objectives	**Phase I part (dose-escalation)** • To characterize the safety and tolerability of EGF816 • To evaluate ORR, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR) by Investigator assessments in accordance to RECIST 1.1 • To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258 • To assess the tumor EGFR signaling inhibition by EGF816 (prior to protocol amendment 05) **Phase II part** • To further characterize the safety and tolerability of EGF816

	• To evaluate ORR by Investigator assessment in accordance to RECIST 1.1 • To evaluate DOR, DCR, PFS and TTR by BIRC and by investigator assessments in accordance to RECIST 1.1 • To evaluate overall survival (OS) • To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258 Note: ORR is defined as the proportion of patients with best overall response of PR+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; DCR is defined as the proportion of patients with best overall response of CR, PR, or SD; PFS is defined as time from date of first dose of study treatment to date of first documented disease progression; TTR is defined as the time from the date of first dose of study treatment to the date of first documented response (CR or PR). OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause.
Study design	This is a Phase I/II, multi-center, open-label study starting with a Phase I part (dose-escalation) followed by a Phase II part. Oral EGF816 will be administered once daily on a continuous schedule until patient experiences unacceptable toxicity, progressive disease (PD), and/or treatment is discontinued at the discretion of the investigator, patient withdrawal of consent, or due to any other reasons. Treatment with EGF816 may be continued beyond RECIST 1.1 defined PD, if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue with the study treatment. A treatment cycle is defined as 28 days.
Population	Adult patients with locally advanced or metastatic NSCLC with specific EGFR mutations. Locally advanced is defined as stage IIIB not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC. For the Phase I part all patients must have locally advanced or metastatic NSCLC harboring specific EGFR mutations. For the Phase II part, treatment naïve adult patients with locally advanced or metastatic NSCLC harboring specific EGFR mutations will be enrolled. Note: Patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy.
Inclusion criteria	**For all patients (unless otherwise specified):** 1. Written informed consent obtained prior to any screening procedures 2. Patient (male or female) ≥ 18 years of age [For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.] 3. Patients must have histologically or cytologically confirmed locally advanced (stage IIIB not amendable to definitive multi-modality therapy including surgery) or metastatic (stage IV) EGFR mutant NSCLC 4. Patients with controlled brain metastases may participate in the trial. If applicable, they must complete any planned radiation therapy and/or surgery > 2 weeks prior to the first dose of study treatment and remain asymptomatic. Patients on steroids must have been on a stable low dose for 2 weeks prior to initiating study treatment. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging. 5. ECOG performance status: Phase I part: 0, 1, or 2; Phase II part: 0 or 1 6. Presence of at least one measurable lesion according to RECIST 1.1 per Investigator assessment. A previously irradiated site lesion may be counted as a target lesion only if there is clear sign of progression since the irradiation (see Section 14.1 Appendix 1) 7. Patients must be screened for HBV. Patients who are either HBsAq positive or HBV-

	DNA positive must be willing to take antiviral therapy 1-2 weeks prior to 1st dose of EGF816 treatment and continue on antiviral therapy for at least 4 weeks after the last dose of EGF816. 8. Patients must be screened for HCV. Patients must have negative hepatitis C antibody (HCV-Ab) or positive HCV-Ab but undetectable level of HCV-RNA. Note patients with detectable HCV-RNA are not eligible to enroll into the study. 9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures 10. **Requirements of EGFR mutation status and prior lines of treatment for Phase I patients** Patients must meet one of the following criteria: • Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del); Who have not received any systemic antineoplastic therapy, including EGFR TKI treatment, for advanced NSCLC; Note: patients who have received no more than 1 cycle of chemotherapy in the advanced setting are allowed. • Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del) AND an acquired EGFR T790M mutation following progression on prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib); No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKI and may not have received any agent targeting EGFR T790M mutation (e.g.,. 3rd generation EGFR TKI) • Locally advanced or metastatic NSCLC with a “de novo” EGFR T790M mutation; For purposes of this protocol, “de novo” T790M will be defined as the presence of EGFR T790M mutation in NSCLC patients who have NOT been previously treated with any therapy known to inhibit EGFR; No more than 3 prior lines of systemic antineoplastic therapies; No prior treatment with any therapy known to inhibit EGFR, including EGFR TKI • Locally advanced or metastatic NSCLC whose tumor harbors EGFR exon 20 insertion or deletion; No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKI • Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del) AND without an acquired EGFR T790M mutation; Who have progressed on prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib), or 2nd-generation EGFR TKI (e.g. afatinib or dacomitinib); No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKI • Locally advanced or metastatic NSCLC with EGFR activating mutations (e.g., L858R or ex19del) and an acquired T790M mutation; Who have had treatment with a 1st/2nd-generation EGFR TKI; Who have progressed on or are intolerant to a 3rd-generation EGFR TKI (e.g., AZD9291, CO-1686, or ASP8273); No more than 3 prior lines of systemic antineoplastic therapies, including EGFR TKIs **11. Requirements of EGFR mutation status and prior lines of treatment for Phase II patients:** • Locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del); Who have not received any systemic antineoplastic therapy, including EGFR TKI treatment, for advanced NSCLC; Note: patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Note: Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy.
Exclusion criteria	**For All patients (unless otherwise specified):** 1. Patients with a history or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e. affecting

	activities of daily living or requiring therapeutic intervention) 2. Patients with unstable brain metastases. 3. Presence or History of another malignancy Exception: Patients who have been disease-free for 3 years, or patients with a history of adequately treated in-situ carcinoma of the uterine cervix, basal or squamous cell carcinoma, non-melanomatous cancer of skin, history of stage IA melanoma that has been cured, are eligible. 4. Undergone a bone marrow or solid organ transplant 5. Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory) 6. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except for control of brain metastases, topical applications, inhaled sprays, eye drops or local injections 7. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures 8. Patients with out of range laboratory values defined as: • Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L (1.5 x 10^3/µL) • Hemoglobin (Hgb) < 9 g/dL (90 g/L) • Platelets < 75 x 10^9/L (75 x 10^3/µL) • Total bilirubin >1.5 x upper limit of normal (ULN). For patients with Gilbert's syndrome total bilirubin >3.0 x ULN) • Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN for patients without hepatic metastasis • AST and/or ALT >5 x ULN for patients with hepatic metastasis • Alkaline phosphatase (ALP) > 5 x ULN • Measured or calculated creatinine clearance < 45 mL/min (0.75 mL/sec) 9. Patients with electrolytes outside the laboratory normal limits that cannot be corrected with supplements during screening: • Potassium • Magnesium • Phosphorus • Total calcium (corrected for serum albumin) 10. Patients receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 and cannot be discontinued 1 week prior to the start of EGF816 treatment and for the duration of the study Additional exclusion criteria are listed in Section 5.3.
Investigational and reference therapy	EGF816 (Nazartinib)
Efficacy assessments	Tumor assessment per RECIST 1.1
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs
Other	Plasma concentration vs. time profiles, plasma PK parameters

assessments	[redacted]
Data analysis	**Phase I part (dose-escalation)** Patients treated during the Phase I part (dose-escalation) with the same dose level, formulation (capsule vs. tablet) and schedule of EGF816 will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group and formulation (unless otherwise specified). Subgroup analyses by mutation type and prior lines of systemic antineoplastic therapy(s) may be performed as appropriate. An adaptive, 2 parameter Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle will be used to make dose recommendations and estimate the MTD/RP2D during the Phase I part study. Phase II part The primary analysis will be performed when patients have completed at least 6 cycles of treatment or discontinued treatment prior to that time. Any additional data for patients continuing to receive study treatment past the data cut-off date for the primary analysis will be reported in the final CSR at the end of the study. One interim futility analysis will be performed when approximately 20 patients have completed at least 4 cycles of treatment or discontinued treatment prior to that time. Primary endpoint: ORR by BIRC assessment will be summarized along with 95% confidence interval.
Key words	NSCLC, EGF816, Nazartinib, EGFR, TKI, T790M+, T790M-, acquired, de novo

List of abbreviations

Ab	Antibody
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
Ag	Antigen
AKT	Also known as Protein Kinase B
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomy Therapeutic Chemical
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
Cmax	Maximum plasma concentration after a single dose
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
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
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
[redacted]	[redacted]
CYP	Cytochrome
DCR	Disease Control Rate

DDS	Dose Determining Set
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration Of Response
DS&E	Drug Safety and Epidemiology
DUSP6	Dual Specificity Phosphatase 6
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGF	Epidermal growth factor
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EOT	End of Treatment
ERKs	Extracellular signal-Regulated Kinases
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin embedded
FMI	Formulated Market Image
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV-DNA	Hepatitis B virus-DNA
HCVAb	Hepatitis C antibody
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus-RNA
hCG	Human Chorionic Gonadotropin
HDL	High-Density Lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hazard Ratio
i.v.	Intravenous(ly)
ICF	Informed Consent Form
ICH	International Council for Harmonization

IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITK	interleukin-2-inducible T-cell kinase
IUD	Intrauterine Device
IUS	Intrauterine System
KLH	Keyhole Limpet Hemocyanin
LC-MS	Liquid Chromatography-Mass Spectrometry
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPLV	Last patient last visit
LPS	Lipopolysaccharide
MAPKs	Mitogen-Activated Protein Kinases
MATE	Multidrug and toxin extrusion transporter
mPFS	Median Progression-Free Survival
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall survival
p.o.	*Oral*
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics or Progressive disease
PET	Positron Emission Tomography
PFS	Progression-free survival
P-gp	p-glycoprotein
PHA	Phytohemagglutinin
PHI	Protected Health Information
PI3K	Phosphoinositide 3-Kinase
PK	Pharmacokinetics
PLT	Platelet

PPOS	Predictive Probability of Success
PR	Partial Response
PT	Prothrombin Time
q.d.	*quaque die*/every day
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RP2D	Recommended Phase II Dose
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease or Standard Deviation
SEC	Safety Event Categories
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
STD10	Severely Toxic Dose in 10% of animal
T1/2	Median terminal elimination half-life
TBIL	Total bilirubin
TEC	Tec protein tyrosine kinase
TKI	Tyrosine Kinase Inhibitor
Tmax	Peak plasma concentration
TT	Tetanus Toxin
TTR	Time to response
TXK	TXK tyrosine kinase
ULN	Upper Limit of Normal
VATS	Video-assisted thoracic surgery
WCLC	World Conference on Lung Cancer
WT	Wild Type

Glossary of terms

Assessment	A procedure used to generate data required by the study
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 dose)
CMO&PS	Chief Medical Office and Patient Safety
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
Locally advanced	Stage IIIB not amenable to definitive multi-modality therapy including surgery
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
Metastatic NSCLC	Stage IV NSCLC
Patient Number (Patient 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 molecular pre-screening, screening, treatment, end 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 the cancer has spread from the original site to other parts of the body
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
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
Treatment group	A treatment group defines the dose and regimen and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Worldwide, lung cancer accounts for 13% (1.6 million) of all total cancer cases and 18% (1.4 million) of cancer deaths. In the US, lung cancer accounts for over 160000 deaths per year (Sangodkar et al 2010; Brawley et al 2011). In Western countries, 10-15% non-small cell lung cancer (NSCLC) patients express epidermal growth factor receptor (EGFR) mutations in their tumors (accounting for 20000 to 30000 new patients per year in the US), and Asian countries have reported rates as high as 30-40%. The predominant oncogenic EGFR mutations (L858R and ex19del) account for about 90% of EGFR NSCLC. This results in the activation of multiple pathways that promote survival, proliferation, angiogenesis and metastasis. Tumor dependence on EGFR signaling has been shown to correlate to tumors with high gene copy number and/or with activating mutations in EGFR (Mendelsohn et al 2000; Hirsch et al 2003; Lynch et al 2004; Paez et al 2004; Pao et al 2004).

EGFR is an established critical therapeutic target for lung cancer. Numerous trials with 1st-generation (i.e. reversible) EGFR tyrosine kinase inhibitors (TKIs) (e.g., erlotinib and gefitinib) and more recently with the 2nd-generation (i.e. irreversible agents that covalently bind to cysteine 797 at the EGFR ATP site; potent on both activating [L858R, ex19del] and acquired T790M mutations in pre-clinical models, but also equally potent on wild-type (WT)) EGFR TKIs (e.g., afatinib and dacomitinib) have been conducted in the EGFR mutant NSCLC population. These trials have consistently demonstrated superior efficacy of EGFR TKIs over chemotherapy in this population (Table 1-1). EGFR TKIs' response rates in EGFR mutant NSCLC patients range from approximately 60 to 80% versus 20 to 30% for the chemotherapy control arms. Similarly, median progression-free survival (mPFS) is prolonged via EGFR TKI treatment on average by 50%; ranging from 8 to11 months, as compared to 4 to 6 months for chemotherapy control arms. However, the improved response rates and increases in mPFS have not been shown to definitively translate into prolonged overall survival.

Table 1-1 Superiority of EGFR TKIs over chemotherapy in EGFRmut NSCLC

Trial	Compound	RR (%)		Median PFS (mo)		Median OS (mo)	
		TKI	Chemo	TKI	Chemo	TKI	Chemo
IPASS (mut+) (Mok et al 2009)	gefitinib	71.2	47.3	9.5	6.3	21.6	21.9
First-SIGNAL (mut+) (Han et al 2012)	gefitinib	84.6	37.5	8.4	6.7	30.6	26.5
WJTOG (Mitsudomi et al 2010)	gefitinib	62.1	32.2	9.2	6.3	30.9	NR
NEJ002 (Inoue et al 2009)	gefitinib	73.7	30.7	10.8	5.4	27.7	26.6
OPTIMAL (Zhou et al 2011)	erlotinib	83	36	13.7	4.6	22.6	28.8
EURTAC (Rosell et al 2012)	erlotinib	58	15	9.7	5.2	19.3	19.5
Afatinib (LUX-Lung 3) (Sequist et al 2013)	afatinib	56.1	23	13.6	6.9	28.1	28.2
Afatinib (LUX-Lung 6) (Wu et al 2014)	afatinib	66.9	23	11	5.6	22.1	22.2

In up to 50% of NSCLC patients harboring a primary EGFR mutation treated with first generation EGFR TKIs, a secondary "gatekeeper" T790M mutation develops. Although T790M is also in the tyrosine kinase domain of EGFR, it likely results in steric hindrance to EGFR TKIs, and restores the affinity for ATP to comparable levels observed for WT EGFR (Yu et al 2013; Kobayashi et al 2005). In addition to being the predominant mechanism of resistance, multiple groups have reported various rates of T790M mutation in pre-treatment specimens, although this could be dependent on the sensitivity of the method of testing and may reflect underlying tumor heterogeneity (Rosell et al 2011; Su et al 2012; Kobayashi et al 2005; Takezawa et al 2012; Bean et al 2007; Engelman et al 2007; Yu et al 2013; Sequist et al 2011). Third-generation (i.e. irreversible; WT EGFR sparing; relative equal potency for activating EGFR mutations [L858R, ex19del] and acquired T790M) EGFR TKIs are beginning to enter clinical development and showing significant initial promise (e.g., CO-1686: ORR of 67% in 28 evaluable T790M+ NSCLC patients treated at the clinical doses (EORTC-NCI-AACR 2014); AZD9291: ORR of 70% (30/43) in T790M+ NSCLC patients treated at the RP2D (ESMO 2014)). In addition, encouraging antitumor activity has been observed for 3rd-generation EGFR TKIs (AZD9291 and CO-1686) in advanced NSCLC patients without an acquired EGFR T790M mutation, who have become resistant to a 1st/2nd-generation EGFR TKI, with the ORRs ranging from 21% to 36% (ESMO 2014, EORTC-NCI-AACR 2014).

Despite the progress and efficacy of EGFR TKIs, a definitive improvement in overall survival has not been demonstrated and there is still a need for better treatment options for patients with EGFR mutant NSCLC. Novel 3rd-generation EGFR therapies, that can target not only the primary activating mutations but also the acquired gatekeeper T790M mutation while sparing WT EGFR inhibition and thus reducing toxicity, are therefore urgently needed.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of EGF816

EGF816 is a targeted covalent irreversible EGFR inhibitor that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. EGF816 has shown significant efficacy in EGFR mutant (L858R, ex19del and T790M) cancer models (*in vitro* and *in vivo*) with no indication of WT EGFR inhibition at clinically relevant efficacious concentrations.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Non-clinical pharmacokinetics and metabolism

The pharmacokinetics (PK) of EGF816 was investigated in the mouse, rat and dog. Following intravenous administration, EGF816 exhibited: moderate plasma clearance, a large volume of distribution and a short terminal half-life (~3 h) in rodents; a high clearance, a high volume of distribution and a relatively long terminal half-life (~13 h) in the dog.

Following single dose oral administration, EGF816 showed good oral bioavailability (>55%) in mouse, rat and dog, with Tmax reached at 1-3 h post-dose. EGF816 is highly permeable across the intestinal membrane as determined in the Caco2 monolayer system. Given the high solubility of EGF816 observed across the pH range and in simulated intestinal fluid for both

fasted and fed state, it is considered a biopharmaceutics classification system (BCS) class I compound with low food effect risk.

EGF816 plasma protein binding is high and averaged 96.4%, 91.9%, 89.9% and 93.8% in mouse, rat, dog and human plasma, respectively. Following administration of ^{14}C-EGF816 in rat, retention of radioactivity in blood was observed with a half-life of 80-90 hours compared to the half-life of 3 hours in plasma. More than 75% of the EGF816 derived radioactivity in blood was covalently bound to red blood cells.

Tissue distribution showed that ^{14}C-EGF816 derived radioactivity was high in limited numbers of tissues. At 24h, colon wall, esophagus, harderian gland, kidney medulla, liver, uveal tract and skin showed higher radioactivity concentration than blood. At 168h, only pituitary gland, pigmented skin and uveal tract showed higher concentration than blood, indicating affinity of EGF816-derived radioactivity to melanin-rich tissues, and the amount of radioactivity associated with blood was 0.04% of the dose. The penetration to brain was minimal with brain to blood ratio of 0.03-0.08.

In rat dosed with ^{14}C-EGF816, the recovery of radioactivity was almost complete (>97%) with only ~1% of the dose remaining in the carcass. The predominant route of elimination was via fecal excretion with renal excretion a minor pathway. The predominant circulating component in rat plasma was the parent compound. The cross-species metabolism comparison in hepatocytes showed that no human specific metabolite was observed, and that the N-demethylation pathway was more predominant in human than that in dog and rat. The N-demethylated metabolite (LMI258) showed similar pharmacological activity to EGF816 *in vitro*. The exposure of LMI258 was 3-9% and 20-40% of the parent exposure in rat and dog 4-week toxicology studies, respectively.

EGF816 is primarily metabolized by CYP3A4. CYP3A inhibitors ketoconazole and azamulin completely inhibited the metabolism of EGF816 in human liver microsomes. EGF816 showed weak to moderate inhibition of CYP2D6 (Ki 3.3 μM, unbound) and CYP2C8 (IC_{50} ~11 μM, unbound) whereas metabolite LMI258 showed relatively strong inhibition of CYP2D6 (Ki 0.41 μM) and weak inhibition of CYP3A4 (IC_{50} 12 μM) *in vitro*. Physiology-based pharmacokinetic (PBPK) predictions performed using SimCYP to further evaluate the DDI potential between EGF816 and a CYP2D6 substrate (dextromethorphan) or CYP2C8 substrate (repaglinide) did not suggest clinically relevant interactions. The predicted change in AUC ratio of dextromethorphan or repaglinide was less than 1.25 and hence a drug-drug interaction is unlikely in the presence of EGF816. EGF816 is a p-glycoprotein (P-gp) substrate with a Km value of 5.0 to 16 μM, and an inhibitor of breast cancer resistance protein (BCRP) with an estimated IC_{50} value of 4.0 μM.

1.2.1.1.2 Pharmacology and toxicology

Non-clinical pharmacology

EGF816 is a potent third generation, irreversible EGFR mutant-selective inhibitor. It covalently links to Cys797 at ATP site of EGFR. In cell-based target modulation assays, EGF816 inhibits both oncogenic (L858R, ex19del) and TKI-resistance (L858R/T790M) lines with single digit nM potency and demonstrates good selectivity (~40-60 fold vs. the least active mutant line) over WT-EGFR cell lines. The potency and WT-selectivity of EGF816 was further confirmed in a receptor occupancy study using ^{14}C-labeled EGF816. Profiling against several large panels

of kinases indicates that EGF816 is highly selective. The confirmed off-target activities are mostly on kinases containing a similarly located cysteine as Cys797 in EGFR.

As evidenced from *in vivo* metabolism studies (see Section 1.2.1.1.1), several metabolic pathways have been identified. The major metabolite, LMI258, has a very similar overall profile as EGF816. It is slightly more active than the parent compound across all cellular assays, while retaining comparable WT-EGFR selectivity.

EGF816 demonstrated strong tumor regressions in several EGFR activating and resistant tumor models *in vivo.* These include HCC827 (ex19del), H3255 (L858R) and H1975 (L858R; T790M) that are representative of the relevant clinical settings. In all of the models EGF816 inhibited tumor growth in a dose-dependent manner and achieved regressions of established tumors at well tolerated doses.

The HCC827 (ex19del activating mutation) mouse xenograft model was very sensitive to EGF816. Even at the lowest tested daily dose of 3 mg/kg, significant tumor regression was achieved. The effect was comparable to erlotinib at 60 mg/kg, a clinically relevant dose, which gave free plasma exposure similar to that observed at clinical efficacious dose. At doses of 10 mg/kg q.d. or above, EGF816 showed maximum regression similar to erlotinib at its maximum tolerated dose (MTD) of 120 mg/kg. EGF816 was very well tolerated, with no body weight loss observed up to 100 mg/kg, while erlotinib at 120 mg/kg showed significant body weight loss (~10%).

In the H3255 (L858R) mouse xenograft model, EGF816 was tested at 30 mg/kg and demonstrated strong tumor regression with no effect on body weight compared to vehicle.

In the H1975 (L858R/T790M) mouse and rat xenograft models, significant tumor regression was achieved at doses ≥ 30 mg/kg. Importantly, EGF816 demonstrated much improved tolerability with superior efficacy as compared to second-generation irreversible pan-EGFR inhibitor afatinib.

Dose-dependent inhibition of pEGFR and its down-stream pharmacodynamics (PD) markers were observed following single oral dose of EGF816 at several dose levels. Sustained inhibition of pEGFR relative to plasma PK was evident in either model, and is consistent with the irreversible binding mechanism of action.

Targeted inhibition of WT EGFR in cells also inhibits dual specificity phosphatase 6 (DUSP6) (Vecchione et al 2011). In an effort to compare the *in vivo* WT EGFR selectivity of EGF816 and afatinib, the DUSP6 gene expression was measured in the skin of treated animals. While afatinib caused significant DUSP6 inhibition, EGF816 had no effect at the efficacious doses.

Together with the *in vitro* data, this indicates EGF816 exhibits antitumor activity in the relevant patient-derived tumor cell lines at well tolerated doses and is predicted to have antitumor activity in humans with known EGFR-driven cancers.

Toxicology

In the 4-week GLP study in rats clinical signs associated with EGF816 were noted at a dose of 75 mg/kg/day in both sexes and included chromorhinorrhea (red secretion from noses), salivation, piloerection, staining of the fur, discolored skin and/or an increased incidence of scab(s)/scratches/abrasions and hair loss. Chromorhinorrhea and scab(s)/scratches/abrasions were also noted in 3 females, as well as an increased incidence of hair loss at a dose of 50

mg/kg/day. The scab(s)/scratches/abrasions were generally noted during the latter part of the dosing period and abated in the majority of animals during the recovery period. Discolored skin was noted during the last week of the dosing period and/or up to recovery day 9. There were no test article-related clinical signs noted at doses ≤ 50 mg/kg/day in males or at 30 mg/kg/day in females.

Hematologic changes reflected the presence of mild, dose-dependent inflammation, characterized by increases in absolute neutrophil, monocyte and/or platelet counts, decreased hemoglobin concentrations and mean corpuscular hemoglobin and increased plasma fibrinogen concentrations. Following compound withdrawal, neutrophil and monocyte counts remained mildly increased in both male and female rats dosed at 75 mg/kg/day, correlating with the skin changes described histologically. In clinical chemistry, mild, reversible decreases in serum triglyceride concentrations were noted in male rats dosed at 75 mg/kg/day and female rats dosed at ≥ 50 mg/kg/day, consistent with mildly decreased food consumption. No changes in urinalysis parameters were noted.

Target organs in the rat included skin/eyelids (inflammation around hair follicles and in epidermis), lungs (foamy macrophages-phospholipidosis), lymphoid organs (cell depletion), vagina (atrophy of epithelium), uterus (atrophy of endometrium), anal (sebaceous) glands (inflammation).

In conclusion the severely toxic dose to 10% of animals (STD10) in rodents was 75 mg/kg/day.

In the 4-week GLP study in beagle dogs, clinical signs associated with EGF816 were noted at a dose of 20 mg/kg/day and included emesis and salivation during the first week of dosing. Clinical signs of fecal changes including decreased/soft feces and diarrhea, absent feces, and feces with apparent blood were noted on 1 or 2 occasions during the dosing period. Discolored urine was noted in one animal on study day 7 and in another animal on 4 occasions between study days 7 and 16; subsequently, this animal was noted to have decreased motor activity intermittently on study days 23 through 30 and was recumbent on study day 23. One male dog had reddened conjunctiva, excessive blinking and/or ptosis intermittently on study day 6 through recovery day 1. During the recovery period at the 20 mg/kg/day dose level, soft feces and diarrhea were noted. Discolored skin, reddened skin and hair loss were noted during the non-dosing period and generally persisted through the end of the recovery period. Skin swelling, scab(s)/scratches/abrasions and reddened ears were also noted. In males at a dose of 8 mg/kg/day, emesis was noted on study day 3 and salivation on 2 occasions in one dog. In females at a dose of 8 mg/kg/day, emesis with apparent compound was noted on one occasion in a single animal. There were no test article-related clinical signs noted in either sex at a dose of 4 mg/kg/day. Test article-related effects on body weight parameters were noted at doses ≥ 8 mg/kg/day in males and females. In all males (5/5) at a dose of 20 mg/kg/day, body weight loss of 0.5 to 0.8 kg (5.3 to 12.8%) was noted between day 1 to 29. During the non-dosing period, body weights rebounded resulting in 6.3 to 7.2% body weight increases from recovery days 1 to 29. In females at a dose of 20 mg/kg/day, body weight loss of 0.6 kg (9.6 to 10.3%) was noted in 2 out of 5 animals. During the recovery period, body weight gains rebounded (0.5 to 0.8 kg) in animals given 20 mg/kg/day resulting in 10.9 to 15.4% body weight increases between recovery days 1 to 29. Mild effects on body weight in males and no effects on body weights in females were observed at a dose of 8 mg/kg/day; no effects were seen for either sex at a dose of 4 mg/kg/day.

Hematology and coagulation changes were noted in male and female dogs dosed at ≥ 8 mg/kg/day when results were compared to those from the pretest period, and included increased neutrophil and monocyte counts (≥ +100%), decreased RBC counts, hemoglobin concentration and hematocrit (≥ -25%), and decreased albumin (≥ -20%) and increased globulins (≥ +25%).

Target organs in the dog included cornea (epithelial thinning), and various glands throughout the organ system (atrophy). The highest non-severely toxic dose (HNSTD) was determined to be 20 mg/kg/day.

EGF816 showed a potential for phototoxicity in the 3T3 NRU *in vitro* assay.

The Ames assay for EGF816 indicated that it was not a potential mutagen and the chromosomal aberration assay in human peripheral blood lymphocytes did not indicate the potential to cause chromosomal aberrations. An *in vivo* evaluation of the bone marrow for the presence of micronuclei was negative in rats. The IC50 for the hERG potassium channel is 6 μM.

The confirmed off-target activities of EGF816 in cellular assays are mostly on Cys-kinases (i.e., kinases containing an analogous cysteine as Cys797 in EGFR). These kinases include Tec family kinases (TEC, ITK, TXK) with IC_{50}=31 nM. EGF816 showed >5 fold selectivity versus Tec family kinases with respect to H3255 (L858R) activity (IC_{50}=5 nM). Because Tec kinases are involved in T cell function, T cell proliferation induced by tetanus toxin (TT) as antigen, lipopolysaccharide (LPS) and phytohemagglutinin (PHA) as mitogens were measured in the absence or presence of EGF816. All stimuli increased T cell proliferation compared to DMSO controls. EGF816 suppressed this T cell proliferation at concentrations of 0.037 μM to 3 μM.

An *in vivo* study that examined the potential immunomodulatory effect of EGF816 was also conducted. Rats were immunized subcutaneously on Days 11 and 21 with keyhole limpet hemocyanin (KLH) antigen during 28 continuous days of oral exposure to EGF816 at 30 or 50 mg/kg or to Prograf at 3 mg/kg as a positive control (an immunosuppressive compound used in transplantation). Serum was collected from all animals and KLH-specific IgM and IgG antibody concentrations were measured by ELISA. Dose-related immunomodulatory responses in EGF816-treated animals following sensitization with KLH immunization were noted when values were compared to concurrent vehicle controls. Recovery following withdrawal of EGF816 treatment was noted, indicating that the EGF816-related decrease of anti- KLH antibody production was reversible. This included both the primary response (anti-KLH IgM), and the isotype switch as measured by secondary anti-KLH IgG production.

In conclusion, EGF816 dampened the antibody response to a neoantigen (KLH) in rats as measured by anti-KLH IgM and IgG antibody titers. This effect was reversed after withdrawal of EGF816. The clinical translation of this effect is not known.

1.2.1.2 Clinical experience

CEGF816X2101 is the first-in-human Phase I/II study of single-agent oral EGF816.

As of the cut-off date of 18-Dec-2015 (cut-off date of the Investigator's Brochure ed. 5) 148 patients have been treated with EGF816 capsules or tablets at seven dose levels: 75 mg QD (N=7), 100 mg q.d. (N=29), 150 mg QD. (N=64), 200 mg QD (N=8), 225 mg QD (N=24), 300 mg QD (N=5) and 350 mg QD (N=11). Eighty-four patients (56.8%) were still receiving treatment and 64 patients (43.2%) had discontinued treatment. Of these 64 patients, reasons for discontinuation were: progressive disease (53 patients), adverse events (3 patients), death (3 patients), subject guardian decision (3 patients), physician decision (2 patients). Of the three

patients who discontinued treatment due to AE, one patient at the 350 mg QD reported Grade 3 maculopapular rash, one patient at the 150 mg daily dose reported Grade 3 interstitial lung disease, and one patient at the 300 mg daily dose reported Grade 3 pulmonary edema. Of the three patients who discontinued treatment due to death, one patient died due to sepsis (considered not related to study treatment), one patient died due to hepatitis B virus (HBV) reactivation (considered related to study treatment), and one patient died due to pneumonia (considered not related to study treatment).

As of 18-Dec-2015, dose-limiting toxicities (DLT) were reported in five patients: one patient at the dose level of 150 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 225 mg capsule reported Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 acute kidney failure and Grade 3 maculopapular rash that resulted in temporary treatment interruption, one patient at the dose level of 350 mg capsule reported Grade 3 maculopapular rash that resulted in permanent discontinuation of treatment, and one patient at the dose level of 350 mg capsule reported Grade 3 enteritis and Grade 3 dehydration that resulted in temporary treatment interruption. The maximum tolerated dose (MTD) has not been determined for EGF816 as a single agent.

As of the data cut-off date of 18-Dec-2015, 142 patients (95.9%) who were treated with EGF816 capsules or tablets experienced at least one AE of any grade, regardless of relationship to the study drug. The most frequent AEs (all CTCAE grades, >10% of patients) regardless of study drug relationship at the seven dose levels were rash (group term) (56.1%), diarrhea (41.9%), maculopapular rash, pruritus (36.5%), fatigue (27.0%), stomatitis (27.0%), dry skin (24.3%), nausea (23.6%), cough (20.9%), decreased appetite (20.3%), vomiting (14.9%), constipation (14.2%), headache (12.8%), anemia (12.2%), paronychia (11.5%), pyrexia (11.5%), dyspnea (10.8%), edema peripheral (10.8%), back pain (10.1%), and upper respiratory tract infection (10.1%).Seventy (47.3%) patients who were treated with EGF816 capsules or tablets at any dose experienced Grade 3 or Grade 4 AEs regardless of relationship to the study drug. Grade 3/4 AEs occurring in ≥ 2% of patients were rash (grouped term) (15.5%), anemia (5.4%), pneumonia (5.4%), diarrhea (4.7%), fatigue (2.7%), dyspnea (2.7%), urticaria (2.7%), hypertension (2.7%), stomatitis (2.0%), decreased appetite (2.0%), hyperuricemia (2.0%), and seizure (2.0%).As of the data cut-off date (18-Dec-2015) SAEs, regardless of study drug relationship, were reported in 48 patients (32.4%) who received at least one dose of single agent EGF816 capsules or tablets.

Of these 48 patients, 15 experienced SAEs that were suspected to be related to study drug, please refer to Investigator's Brochure ed. 5. In summary, the outcome of SAEs suspected to be related to study treatment was recovered or recovering in 12 of 15 patients. One patient died due to hepatic failure secondary to HBV reactivation, one patient was reported as not recovered from Grade 3 maculopapular rash, and one patient was reported as not recovered from Grade 3 anemia.

As of 18-Dec-2015, 2 SAEs of HBV reactivation have been reported in 2 patients participating in the CEGF816X2101 study. One case had a fatal outcome, and the second case was considered medically significant. The fatal case involved a patient who received EGF816 at 225 mg QD, had a history of HBV infection and was not on antiviral treatment at study entry. The patient developed HBV reactivation during the study and died due to hepatic failure despite initiation of antiviral treatment after HBV reactivation had been confirmed. The second patient also received EGF816 at 225 mg QD, had a history of HBV and was not on antiviral treatment at

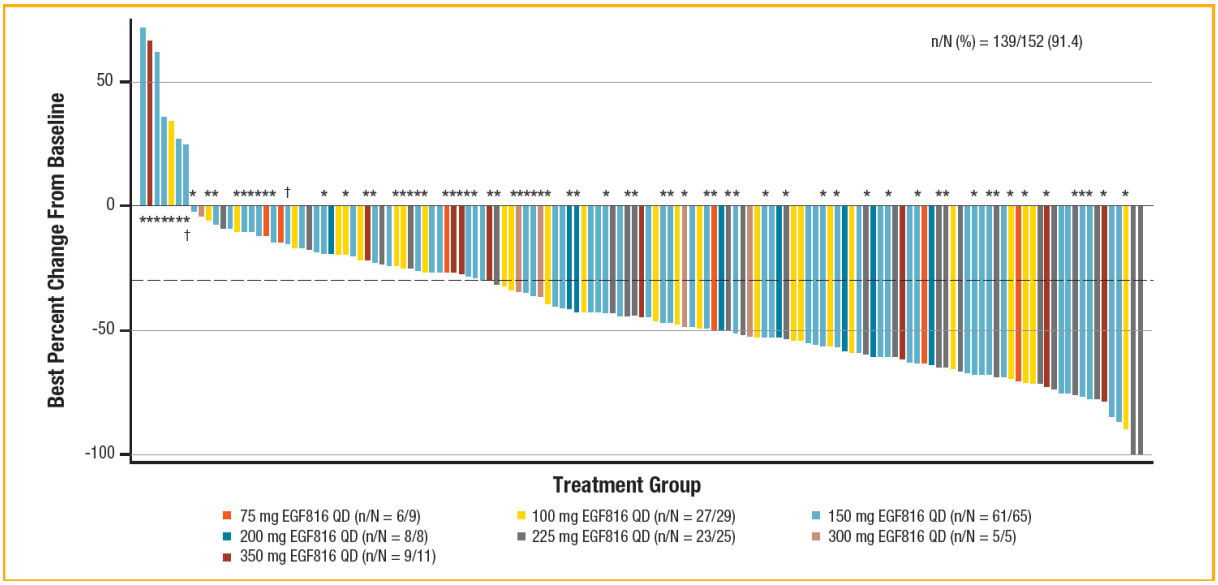
the time of joining the study, HBV reactivation was detected after the patient had been on study for approximately 10 weeks. Antiviral treatment was immediately initiated, EGF816 was interrupted and the HBV infection was brought under control. The patient later resumed EGF816 at the same dose of 225 mg q.d. while continuing on antiviral medication. The viral reactivation in these two patients was likely due to immunosuppression related to EGF816. Reactivation of HBV and hepatitis C virus (HCV) has been reported with anticancer therapies that suppress the immune system.

It should be noted that the maculopapular rash associated with EGF816 treatment appears to be different from the typical EGFR TKI-related rash (e.g., acneiform rash). Its onset was generally in the first 2-3 weeks of study treatment however it could be sporadic. The rash typically appears on the trunk, spreads out to the extremities, and in general spares the palms and soles. EGF816-associated rash was well managed with dose interruption and/or steroid and antihistamine treatments. In most cases, the rash resolved completely or almost completely within 1 week after drug interruption, and patients were able to restart study treatment, at the same dose or a reduced dose, without recurrence of the maculopapular rash.

As of the data cut off of 29-Jan-2016, preliminary efficacy results showed an overall response rate (ORR) of 46.9 % by Investigator assessment in 69 out of 147 evaluable patients treated at all dose levels. Note: evaluable patients include those who were ongoing and had at least one post-baseline tumor assessment or who discontinued study treatment as of the data cut-off date. The antitumor activity of EGF816 is presented in Figure 1-1.

Please refer to the current Investigator's Brochure for more details.

Figure 1-1 Best percentage change from baseline in sum of diameters of target lesions as per investigator by treatment (Capsule) – Full analysis set



*Patient discontinued. † Patient's NSCLC was negative for EGFR T790M.

n: number of evaluable patients responders, N: number of patients enrolled

(Evaluable patients include those who are ongoing with study treatment and have ≥ 1 post-baseline response assessment

or who have discontinued study treatment. This total is used for percentage calculation) (Tan S-W D, Yang C-H J (2016)

As of 14-Sep-2015, data on EGF816 PK parameters are available following treatment with capsules or tablets at 75, 100, 150, 200, 225, 300, and 350 mg/day in patients. For a similar dose, similar exposure was observed with capsules and tablets. Systemic exposure to EGF816 generally increased with the dose, with a median Tmax of 3-6 hr. The steady state was reached by cycle 1 day 15. The terminal half-life T1/2 ranged from 13 to 18 hr. Accumulation of EGF816 following repeated administration is low with an accumulation ratio of up to 2-fold.

2 Rationale

2.1 Study rationale and purpose

Note: throughout this protocol, advanced NSCLC refers to patients with either locally advanced or metastatic NSCLC. Locally advanced NSCLC is defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC.

Inhibitors of EGFR-mutant L858R and ex19del have been well validated as therapeutic agents for advanced NSCLC patients. However, the narrow therapeutic window of currently available EGFR inhibitors limits the potential of this class of drugs. In spite of the proven clinical benefit of 1st- and 2nd-generation of EGFR TKIs, the overall survival has not improved and the dose-limiting toxicities, particularly affecting the skin and gastrointestinal (GI) due to cross-activity with WT EGFR, are frequently reported. Novel EGFR therapies such as 3rd-generation EGFR TKIs that can target not only the primary activating mutations, but also the acquired T790M mutation while sparing WT EGFR, are urgently needed. The sparing of WT EGFR appears to improve the most common toxicities (rash and diarrhea) associated with EGFR TKIs. The 3rd-generation of irreversible EGFR TKIs (e.g., CO-1686 and AZD9291) is entering clinical development and has shown significant initial promise. EGF816 is a 3rd-generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M+), while sparing WT EGFR.

The purpose of the Phase I part (dose-escalation) of this study is to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) and to evaluate the preliminary antitumor activity of single-agent EGF816 in adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. The Phase I part will include patients with tumors harboring specific EGFR mutations (refer to Section 2.2). The purpose of the Phase II part of this study is to evaluate the efficacy and safety of single-agent EGF816 in adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC whose tumors harbor specific EGFR activating mutations (e.g., L858R and ex19del) in first line setting (EGFR TKI and chemotherapy naïve).

Based on the preclinical data of EGF816 and the known clinical activity of other 3rd-generation EGFR inhibitors in advanced NSCLC patients harboring EGFR mutations, it is expected that EGF816 would have significant antitumor activity in NSCLC patients harboring the activating EGFR mutations (e.g., L858R and ex19del) and/or the acquired/resistant “gatekeeper” T790M mutation. While sparing WT EGFR, EGF816 is also expected to be better tolerated than currently available treatment options. Taking into consideration of efficacy and safety, EGF816

treatment should translate into longer sustained responses and improvement in patients' quality of life.

The preliminary results from this study in advanced NSCLC patients with EGFR mutations (L858R and/or ex19del, T790M+) have shown a tolerable safety profile and significant antitumor activity of EGF816 at different dose levels (75 mg, 150 mg, 225 mg and 350 mg) including the lowest dose tested, that is in line with other 3rd-generation EGFR TKIs such as AZD9291 and CO-1686 (see Section 1.2.1.2).

2.2 Rationale for the study design

Phase I part

This open-label, Phase I part (dose-escalation) of the first-in-human study is designed to determine the MTD or RP2D of EGF816 in adult patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC harboring specific EGFR mutations, The acceptable safety profile observed in the patients treated in the Phase I part to date supports the expansion of the eligible Phase I population. The Phase I part will consist of the following:

- Treatment naive patients, who have locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del), have not received any systemic antineoplastic therapy for advanced NSCLC and are eligible to receive EGFR TKI treatment. Note: patients who have received only one cycle of chemotherapy in the advanced setting are allowed.
- Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation AND an acquired T790M mutation (e.g., L858R and/or ex19del, T790M+) following progression on prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKI, and may not have received any agent targeting EGFR T790M mutation (i.e. 3rd-generation EGFR TKI).
- Patients who have locally advanced or metastatic NSCLC with a "de novo" T790M mutation (i.e. no prior treatment with any agent known to inhibit EGFR including EGFR TKI). These patients may not have received more than 3 prior lines of antineoplastic therapy, and may not have received any prior agent known to inhibit EGFR, including EGFR TKIs.
- Patients who have locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion or deletion. These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs.
- Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation AND without an acquired T790M mutation (e.g., L858R and/or ex19del, T790M-) following progression on a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs, and may not have received any agent targeting EGFR T790M (i.e. 3rd-generation EGFR TKI).
- Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation and an acquired T790M mutation (e.g., L858R or ex19del, T790M+) following progression on a prior treatment with a 1st/2nd-generation EGFR TKI, and have progressed

on or are intolerant to a 3rd-generation EGFR TKI (e.g., AZD9291, CO-1686, or ASP8273). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs.

This study will utilize a Bayesian logistic regression model (BLRM) to guide dose escalation and predict the MTD or determine the RP2D for EGF816. The BLRM with escalation with overdose control (EWOC) enables incorporation of available prior information and updates the model parameters based upon new information about observed dose-limiting toxicities seen in the clinical study. The dose recommended by the model at any stage of the trial is based on the entire history of all available DLT information from previous cohorts as opposed to only the number of DLTs observed in the last group of patients. The updated model then provides information on the probabilities of DLTs from the current dose to the next predicted dose level. The use of Bayesian response adaptive models for small datasets has been accepted by EMEA ("Guideline on clinical trials in small populations", February 1, 2007) and endorsed by numerous publications (Babb et al 1998, Neuenschwander et al 2008, Neuenschwander et al 2010), and its development and appropriate use is one aspect of the FDA's Critical Path Initiative. The decision to dose escalate is made by the Investigators and Novartis study personnel and will be based upon the recommendations made by the BLRM, patient tolerability and safety, PK, PD and efficacy information available to date.

Phase II part

The Phase II part will open at the MTD or RP2D using the tablet formulation. The purpose of the Phase II part is to characterize the antitumor activity, safety, tolerability, PK and PD of EGF816 at the selected dose level. The primary objective is to evaluate the antitumor activity of EGF816 in the described patient population. The primary endpoint of antitumor activity is the overall response rate (ORR) per RECIST 1.1 as determined by the Blinded Independent Review Committee (BIRC) to ensure unbiased assessment. A supportive analysis of ORR will be performed based on the Investigators' assessment.

The Phase II part will enroll a minimum of 40 treatment naïve patients, who have locally advanced or metastatic NSCLC with locally documented EGFR activating mutation (L858R, ex19del). The patients will have not received any systemic antineoplastic therapy for advanced NSCLC and will be eligible to receive EGFR TKI treatment. Note: patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy. EGF816 is a 3rd generation irreversible EGFR TKI that selectively inhibits activating and acquired resistance mutants (L858R, ex19del and T790M), while sparing WT EGFR. Inhibitors of EGFR-mutant L858R and ex19del, such as 1st and 2nd generation EGFR TKIs, have been well validated as therapeutic agents for advanced NSCLC patients who are treatment naïve. Novel EGFR therapies such as 3rd generation EGFR TKIs can also target the primary activating mutations. In a preclinical study using tumor model with EGFR ex19del, EGF816 treatment was more efficacious compared to treatment with erlotinib. Other 3rd generation EGFR TKIs, such as AZD9291, have shown promising preliminary data in this patient population (Jänne et al. 2015). AZD9291 has an ongoing Phase III clinical trial in the first line setting. Based on the mechanism of action, EGF816 will likely have similar clinical activity in this patient population.

In the Phase II part, the patients will enter the study in the 1st line setting, i.e. will not have received any prior systemic antineoplastic therapy for advanced disease. Note: patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy

Details of the statistical hypothesis, model and analysis are provided in Section 10.4.2 and sample size is provided in Section 10.8

2.3 Rationale for dose and regimen selection

The human starting dose for EGF816 is 75 mg administered orally on a continuous, once daily dosing schedule. The starting dose was determined based on GLP-toxicology studies using rat as the toxicology species according the regulatory guidance (see Section 6.2.1).

2.4 The recommended phase II dose (RP2D) was determined based on the safety and efficacy data obtained from the Phase I part (dose-escalation) at 150 mg/day on capsules and tablets. Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules, are included in Section 5 and Section 6 of this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.3. The risks to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as close monitoring.

The preliminary results from this study in advanced NSCLC patients with EGFR mutations (L858R and/or ex19del, T790M) have shown a tolerable safety profile and significant antitumor activity of EGF816 at different dose levels (75 mg, 150 mg, 225 mg and 350 mg) including the lowest dose tested, that is in line with other 3rd-generation EGFR TKIs such as AZD9291. All available safety and pharmacokinetic data have been reviewed by participating investigators and Novartis at dose escalation teleconferences of the Phase I after the completion of each cohort. In these dose escalation meetings, all participants have reached a consensus to declare RP2D at 150 mg of EGF816.

As of 18-Dec-2015, there have been 2 reported SAEs of viral hepatitis B reactivation related to EGF816 reported in 2 patients participating in the EGF816 single agent study (CEGF816X2101). One case had a fatal outcome, and the second case was medically significant. The viral hepatitis reactivation is likely related to immunosuppression caused by EGF816 although the exact mechanism of the reactivation is unknown. Reactivation of HBV and HCV has been reported with other anticancer therapies and immunosuppressive agents. To minimize

the risk to all trial subjects and to manage the potential risk of severe liver toxicity associated with hepatitis reactivation, Novartis has amended the protocols for all clinical trials involving EGF816 to provide guidance for patients with evidence of current or prior HBV/HCV infection. However, there may be unforeseen risks with the study treatment which could be serious. Refer to the EGF816 Investigator's Brochure for further information regarding clinical toxicity.

Based on the available pre-clinical and clinical data for EGF816 and the known clinical activity of other 3rd-generation EGFR inhibitors in advanced NSCLC patients harboring EGFR mutations, it is foreseeable that EGF816 will continue to demonstrate significant antitumor activity in NSCLC patients harboring the activating EGFR mutations (i.e. L858R and ex19del) and/or the acquired/resistant "gatekeeper" T790M mutation with better tolerability than the currently available treatment options due to sparing of the WT EGFR. The improved efficacy and tolerability reported with EGF816 treatment should translate into prolonged and sustained responses with improved quality of life.

Therefore evidence and current clinical experience, the overall risk/benefit assessment of EGF816 is predicted to be favorable in treatment naïve patients with advanced NSCLC tumors harboring EGFR activating mutations.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 and Table 3-2 below.

Table 3-1 Objectives and related endpoints (Phase I part)

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To estimate the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of EGF816	Incidence of dose-limiting toxicity (DLT) during the first 28 days of dosing	Refer to Section 10.4
Secondary		Refer to Section 10.5
To characterize the safety and tolerability of EGF816	Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs Tolerability: Dose interruptions and reductions	Refer to Section 10.5.1
To evaluate overall response rate (ORR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and time to response (TTR) determined by Investigator assessments	The following endpoints will be evaluated by Investigator assessments in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1): ORR, DOR, DCR, PFS and TTR*	Refer to Section 10.5.2
To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258	Plasma concentration vs. time profiles, plasma PK parameters	Refer to Section 10.5.3
To assess the tumor EGFR signaling inhibition by EGF816 (prior to Protocol amendment 05)	Pre- and on- treatment immunohistochemistry of EGFR pathway molecules (e.g., p-EGFR, p-AKT, p-ERK) in newly obtained tumor samples	Refer to Section 10.6.2
[redacted]		

Objective	Endpoint	Analysis
[redacted]		

*ORR is defined as proportion of patients with best overall response of PR+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; DCR is defined as the proportion of patients with best overall response of CR, PR, or SD; PFS is defined as the time from the date of first dose of study treatment to the date of first documented disease progression (per RECIST 1.1) or death due to any cause; TTR is defined as the time between date of start of treatment until first documented response (CR or PR).

Table 3-2 Objectives and related endpoints (Phase II part)

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To investigate the antitumor activity of EGF81 6	Overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment in accordance to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)	Refer to Section 10.4
Secondary		Refer to Section 10.5
To further characterize the safety and tolerability of EGF816	Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs Tolerability: Dose interruptions and reductions	Refer to Section 10.5.1
To evaluate ORR	ORR by Investigator assessment in accordance to RECIST 1.1	Refer to Section 10.5.2
To evaluate duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) and time to response (TTR)	The following endpoints will be evaluated by BIRC assessment in accordance to RECIST 1.1: DOR, DCR, PFS and TTR*	Refer to Section 10.5.2
To evaluate DOR, DCR, PFS and TTR	The following endpoints will be evaluated by Investigator assessment in accordance to RECIST 1.1: DOR, DCR, PFS and TTR*	Refer to Section 10.5.2
To evaluate overall survival (OS)	OS	

Objective	Endpoint	Analysis
To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258 for all groups	Plasma concentration vs. time profiles, and plasma PK parameters as appropriate	Refer to Section 10.5.3
[redacted]		

*ORR is defined as proportion of patients with best overall response of PR+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; DCR is defined as the proportion of patients with best overall response of CR, PR, or SD; PFS is defined as the time from the date of first dose of study treatment to the date of first documented disease progression (per RECIST 1.1) or death due to any cause; TTR is defined as the time between date of start of treatment until first documented response (CR or PR); OS is defined as the time from first dose of study treatment to the date of death due to any cause.

4 Study design

4.1 Description of study design

This is a Phase I/II, multi-center, open-label study starting with a Phase I part (dose-escalation) followed by a Phase II part. Oral EGF816 will be administered once daily on a continuous schedule until patient experiences unacceptable toxicity, progressive disease (PD) and/or treatment is discontinued at the discretion of the investigator, patient withdraws consent or due to any other reasons. Treatment with EGF816 may be continued beyond RECIST 1.1 defined PD, if, in the judgment of the investigator, there is evidence of clinical benefit and the patient wishes to continue with the study treatment (see Section 6.1.2 for details).

A treatment cycle is defined as 28 days.

Per protocol definition, advanced NSCLC refers to patients with either locally advanced or metastatic NSCLC. Locally advanced NSCLC is defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC.

Phase I part

In the Phase I part, patients must have locally advanced (stage IIIB) or metastatic (stage IV) NSCLC harboring specific EGFR mutations as described in Section 2.2. An adaptive BLRM with EWOC will guide the dose-escalation to determine the MTD or RP2D. Before the MTD or RP2D can be declared for the study, at least 21 patients should have been treated, with at least six patients treated at the MTD or RP2D (Refer to Section 6.2.3.2).

Patients enrolled in the Phase I part must continue to be evaluated according to the evaluation schedule noted in Table 7-1.

Phase II part

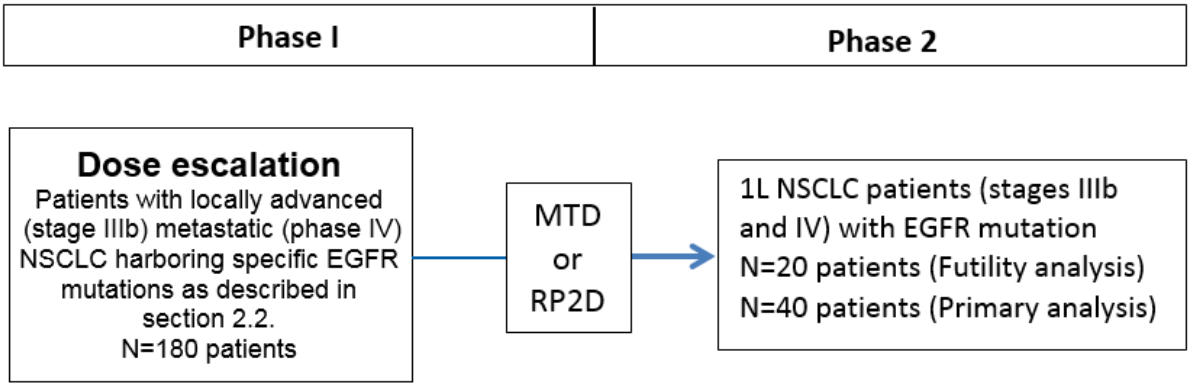
The Phase II part will start when the RP2D in tablet formulation has been identified. A minimum of 40 patients with advanced (stage IIIB) or metastatic (stage IV) NSCLC and documented EGFR activating mutation, who have never received any systemic antineoplastic therapy will be enrolled (Figure 4-1). Note: patients who have received no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed.

The EGFR mutation status is determined by a local laboratory (pre-screening phase). The mutations L858R and exon 19 deletion account for approximately 90% of the EGFR activating mutations and confer sensitivity to the EGFR TKIs. Additionally the other rare mutations such as L861Q, G719S/A/C, and S768I also confer sensitivity to the EGFR TKIs and will also satisfy eligibility criteria.

The EGFR mutation status may be determined from any available tumor tissue. A laboratory report showing evidence of EGFR activating mutation must be available in the source documents.

Details of the sample size calculations leading to the patient numbers are provided in Section 10.8. Patients enrolled in the Phase II part will follow the evaluation schedule noted in Table 7-2.

Figure 4-1 Study design, Phase II part



The study includes different periods as illustrated in Figure 4-2 and Figure 4-3. Refer to Table 7-1 and Table 7-2 for detailed information.

Figure 4-2 Study visit flow (Phase I part)

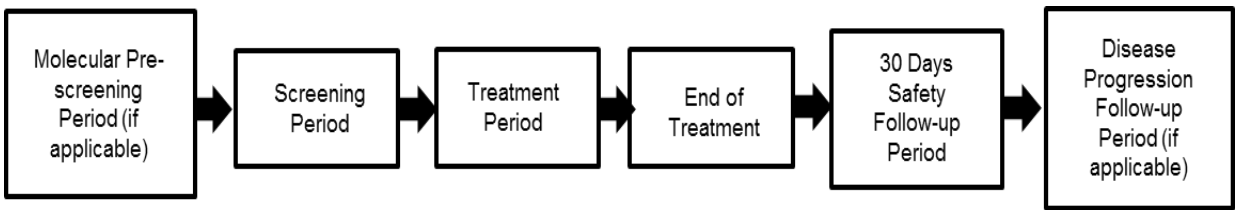
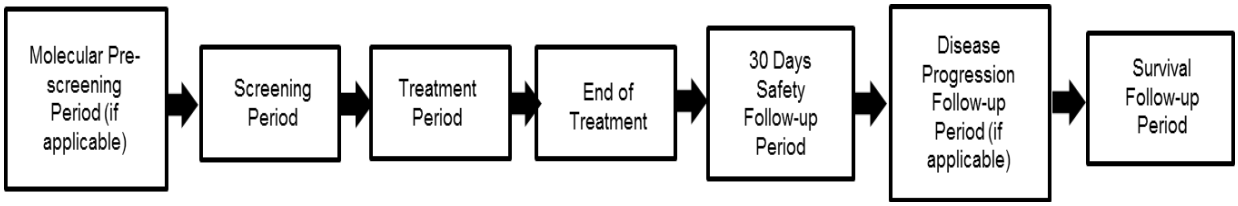


Figure 4-3 Study visit flow (Phase II part)



In the Phase I part, patients may have tumor tissue and blood samples collected at screening and at disease progression to study the mechanisms of drug treatment resistance. For sites that are participating in a Novartis optional companion sample collection protocol to study treatment resistance, the collection of these samples is guided by the companion sample collection protocol and the related informed consent once approved and open.

4.2 Timing of interim analyses and design adaptations

For the Phase I part, no formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.3.

During the Phase II part there will be one interim futility analysis when approximately 20 patients have completed at least 4 cycles of treatment or discontinued treatment prior to that time.

Assessment of futility will be based on the calculated Bayesian probability of success (PoS). The Phase II will be stopped for futility if the PoS is less than 10% at the interim analysis.

If applicable, enrollment of patients into the Phase II part will continue between the time the required data for patients in the interim analysis are observed and the time the results of the interim analysis are available.

Detailed information on the statistical considerations for the interim analysis is provided in Section 10.7 and Section 10.8.

In addition, data from patients in the Phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the MTD/RP2D (Section 8.5).

4.3 Definition of end of the study

The primary analysis will be performed when all patients enrolled have completed at least 6 cycles of treatment or discontinued treatment prior to that time (if not sopped for futility at interim analysis). The primary analysis data will be summarized in the primary clinical study report (CSR) including Phase I and II data.

Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. , Ongoing patients will continue to receive study treatment and be followed as per the schedule of assessments, as long as patients derive benefit from EGF816 or until the **end of study** defined as the earliest occurrence of the following:

- All patients have died or discontinued from the study
- Another clinical study becomes available that can continue to provide EGF816 in this patient population of this study and all patients ongoing are eligible to be transferred to that clinical study

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

Last patient last visit (LPLV) is defined as the date when the last visit is performed by the last patient still on study. The final analysis will occur at the end of the study. All available data from all patients up to LPLV will be 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 for an EOT visit, and the assessments for EOT as described in Section 7 should be performed 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

In this study, EGF816 will be administered as a single agent in adult patients with locally advanced or metastatic NSCLC with specific EGFR mutations. Advanced NSCLC refers to patients with either locally advanced or metastatic NSCLC. Locally advanced NSCLC is defined as stage IIIB NSCLC not amenable to definitive multi-modality therapy including surgery. Metastatic NSCLC refers to stage IV NSCLC.

For the Phase I part all patients must have advanced NSCLC harboring specific EGFR mutations, as described in Section 2.2. The EGFR mutation status may be determined by local or central laboratory testing.

For the Phase II part, adult patients with locally advanced or metastatic NSCLC will be enrolled. The patients must not have received any prior systemic antineoplastic therapy in the advanced setting (NSCLC stage IIIB or IV). However, patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Note: Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy.

The EGFR mutation status for the Phase II part will be determined by local laboratory testing as specified in the inclusion criteria below.

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:

For all patients (unless otherwise specified):

1. Written informed consent must be obtained prior to any screening procedures
2. Patient (male or female) ≥ 18 years of age

[For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]

3. Patients must have histologically or cytologically confirmed locally advanced (stage IIIB not amenable to definitive multi-modality therapy including surgery) or metastatic (stage IV) EGFR mutant NSCLC.
4. Patients with controlled brain metastases may participate in the trial. If applicable, they must complete any planned radiation therapy and/or surgery >2 weeks prior to the first dose of study treatment and remain asymptomatic. Patients on steroids must have been on a stable low dose for 2 weeks prior to initiating study treatment. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on central nervous system imaging.
5. ECOG performance status: Phase I part: 0, 1, or 2; Phase II part: 0 or 1

6. Presence of at least one measurable lesion according to RECIST 1.1 per Investigator assessment. A previously irradiated site lesion may be counted as a target lesion only if there is clear sign of progression since the irradiation. (see Section 14.1 Appendix 1)
7. Patients must be screened for HBV. Patients who are either HBsAg positive or HBV-DNA positive must be willing and able to take antiviral therapy 1-2 weeks prior to 1st dose of EGF816 treatment and continue on antiviral therapy for at least 4 weeks after the last dose of EGF816. Additional management of the patients would be provided by a physician with expertise in management of HBV, if needed.
8. Patients must be screened for HCV. Patients must have negative hepatitis C antibody (HCV-Ab) or positive HCV-Ab but undetectable level of HCV-RNA. Note: patients with detectable HCV-RNA are not eligible for the study.
9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
10. **Requirements of EGFR mutation status and prior lines of treatment for Phase I patients:**

    Patients must have locally advanced or metastatic NSCLC and meet one of the following criteria:

    - Treatment naive patients, who have locally advanced or metastatic NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del), have not received any systemic antineoplastic therapy for advanced NSCLC and are eligible to receive EGFR TKI treatment. Note: patients who have received only one cycle of chemotherapy in the advanced setting are allowed.
    - Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation AND an acquired T790M mutation (e.g., L858R and/or ex19del, T790M+) following progression on prior treatment with a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKI, and may not have received any agent targeting EGFR T790M mutation (i.e. 3rd-generation EGFR TKI). EGFR mutation testing must be performed after progression on EGFR TKI.
    - Patients who have locally advanced or metastatic NSCLC with a “de novo” T790M mutation (i.e. no prior treatment with any agent known to inhibit EGFR including EGFR TKI). These patients may not have received more than 3 prior lines of antineoplastic therapy, and may not have received any prior agent known to inhibit EGFR, including EGFR TKIs.
    - Patients who have locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion or deletion. These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs.
    - Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation AND <u>without</u> an acquired T790M mutation (e.g., L858R and/or ex19del, T790M-) following progression on a 1st-generation EGFR TKI (e.g., erlotinib, gefitinib or icotinib) or 2nd-generation EGFR TKI (e.g., afatinib or dacomitinib). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs, and may not have received any agent targeting EGFR T790M (i.e. 3rd-

generation EGFR TKI). EGFR mutation testing must be performed after progression on EGFR TKI.

- Patients who have locally advanced or metastatic NSCLC with EGFR activating mutation and an acquired T790M mutation (e.g., L858R or ex19del, T790M+) following progression on a prior treatment with a 1st/2nd-generation EGFR TKI, and have progressed on or are intolerant to a 3rd-generation EGFR TKI (e.g., AZD9291, CO-1686, or ASP8273). These patients may not have received more than 3 prior lines of antineoplastic therapy, including EGFR TKIs. A laboratory report demonstrating evidence of EGFR T790M mutation in the tumor prior to treatment with a 3rd generation EGFR TKI must be available in the source documents.

11. Requirements of EGFR mutation status and prior lines of treatment for Phase II patients:

Patients must have advanced NSCLC with locally documented EGFR mutation L858R and/or ex19del (or other rare activating mutations that confer sensitivity to first and second generation EGFR inhibitors (e.g. L861Q, G719A/S/C, S768I)), and must be naïve from any systemic antineoplastic therapy in the advanced setting. Patients who have failed no more than 1 cycle of systemic antineoplastic therapy in the advanced setting are allowed. Treatment failure is defined as documented disease progression or intolerance to treatment. Note: Neo-adjuvant and adjuvant systemic therapies will be counted as 1 prior line of treatment if relapse occurred within 12 months from the end of the neo-adjuvant/adjuvant systemic therapy.

5.3 Exclusion criteria

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

For All patients (unless otherwise specified):

1. Patients with a history or presence of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e. affecting activities of daily living or requiring therapeutic intervention)
2. Patients with unstable brain metastases
3. Presence or history of another malignancy

   Exception: Patients who have been disease-free for 3 years, or patients with a history of adequately treated in-situ carcinoma of the uterine cervix, basal or squamous cell carcinoma, non-melanomatous cancer of skin, history of stage IA melanoma that has been cured, are eligible.
4. Undergone a bone marrow or solid organ transplant
5. Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory)
6. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except for control of brain metastases, topical applications, inhaled sprays, eye drops or local injections
7. Patients with clinically significant, uncontrolled heart disease, such as:
   - Unstable angina within 6 months prior to screening
   - Myocardial infarction within 6 months prior to screening

- Patients with a history of documented congestive heart failure (New York Heart Association functional classification III-IV)
- Patients with uncontrolled hypertension defined as a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive 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
- Patients with a history of congenital long QT syndrome, history of Torsade de Pointes or patients with corrected QT (QTc) >470 msec using Fridericia correction (QTcF) on the screening ECG (using the mean QTcF value from triplicate ECGs) according to Investigator assessment

8. Patients who have received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment 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 the study treatment or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment
9. Patients who have had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study drug 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.
10. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures. Any severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study treatment administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study
11. Prior therapies
    - Patients who have been treated with chemotherapy or biologic therapy or other investigational agent ≤ 4 weeks prior to the first dose of study treatment
    - Unresolved toxicity greater than CTCAE grade 1 from prior anticancer therapy or radiotherapy (excluding neurotoxicity, alopecia, lymphopenia)
    - Note: exceptions to the above are possible, on a case by case basis, following discussion and mutual agreement between investigator and Novartis (**applicable to the Phase I part only**).
12. Patients who have out of range laboratory values defined as
    - Absolute Neutrophil Count (ANC) <1.5 x 10^9/L (1.5 x 10^3/μL)
    - Hemoglobin (Hgb) <9 g/dL (90 g/L)
    - Platelets <75 x 10^9/L (75 x 10^3/μL)

- Total bilirubin >1.5 x upper limit of normal (ULN). For patients with Gilbert's syndrome total bilirubin >3.0 x ULN
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 x ULN for patients without hepatic metastasis
- AST and/or ALT >5 x ULN for patients with hepatic metastasis
- Alkaline phosphatase (ALP) >5 x ULN
- Measured or calculated creatinine clearance <45 ml/min (0.75 mL/sec) using Cockcroft-Gault formula

13. Patients who have the following laboratory values outside of the laboratory normal limits or cannot be corrected to within normal limits with supplements during screening:
    - Potassium
    - Magnesium
    - Phosphorus
    - Total calcium (corrected for serum albumin)
14. Patients who are receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 and cannot be discontinued 1 week prior to the start of EGF816 treatment and for the duration of the study.
15. Participation in a prior investigational study within 4 weeks or within 5 half-lives of the investigational product, whichever is longer, prior to first dose of study treatment

    Note: exceptions to the above are possible, on a case by case basis, following discussion and mutual agreement between investigator and Novartis (**applicable to the Phase I part only**).
16. Patients who have impairment of GI function or GI disease that may significantly alter the absorption of EGF816 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
17. Patients who are receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible
18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study and for 3 months after stopping the study 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, symptomthermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male Partner: male sterilization (at least 6 months prior to screening). For female subjects on the study 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 childbearing 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 childbearing potential.

20. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after stopping treatment; men 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.

6 Treatment

6.1 Study treatment

The study treatment is EGF816.

6.1.1 Dosing regimen

EGF816 will be administered orally once per day on a continuous dosing schedule. The starting dose for the Phase I part first cohort of patients will be 75 mg QD capsule.

For the Phase II part, patients will be treated at the RP2D (150 mg QD) declared on 30-Aug-2016 during Phase I part of the study.

From protocol amendment # 03 dated 21 Aug 2014, an immediate release film-coated tablet was introduced during the dose-escalation phase I and patients were switched from capsules to tablets based on tablets stock availability. As of 07-Mar-2017, 44 patients from Phase I part were ongoing and were receiving capsule or tablet formulations.

Upon the implementation of protocol amendment # 07 dated 11-March-2020, all patients receiving tablets will begin to receive capsules, once the capsule formulation is released and available for dispensation, and will no longer receive tablets.

The dose strength of both capsules and tablets can be found in Table 6-1.

Table 6-1 Dose and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Strength	Frequency and/or Regimen
EGF816	Capsule for oral use	25 mg, 50 mg, 100 mg	Daily
EGF816	Tablet for oral use	25 mg, 50 mg, 200 mg*	Daily

Study treatment	Pharmaceutical form and route of administration	Strength	Frequency and/or Regimen
*200 mg Tablet formulation will be supplied to patients from Phase I and cannot be provided to patients in Phase II (RP2D is 150 mg QD)			

EGF816 (either as capsule or tablet) should be taken as follows:

- Patients should be instructed to take their dose at approximately the same time of day.
- On days when blood for PK samples need to be collected, the patient should take the dose during the clinic visit after the pre-dose PK samples and prior to the post-dose PK samples, when instructed by the site staff.
- Each dose should be taken with a glass of water and swallowed over a short period of time.
- Patients should be instructed to swallow capsules or tablets whole and not to chew or open them.
- Since EGF816 is preliminary BCS class 1 (Section 1.2.1.1.1), EGF816 can be taken with or without food. On days when blood PK samples are collected, the time of the meal before and after the dose need to be recorded on the eCRF.
- Grapefruit or grapefruit juice, seville orange (and juice), pummelos, pomegranate (and juice) star citrus fruits and hybrids of these mentioned fruits must be avoided during the treatment period of the study.
- If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- On days of PK/PD sampling, every effort must be made to capture the time of any vomiting within 4 hours of drug administration.
- If the patient forgets to take his/her daily dose, then he/she should take EGF816 within 6 hours after the scheduled time. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose.
- Patients should inform the investigational site staff of any missed or delayed doses.
- During the whole duration of the treatment with EGF816, the patient is recommended to use precautionary measures against sunlight exposure (refer to Section 6.3.3 and Table 6-9)

6.1.2 Treatment duration

Treatment with EGF816 will continue until:

- Adverse event (based on the recommendations in Table 6-5)
- Death
- Progressive disease
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Technical problems
- Lost to follow-up
- Physician decision
- Subject/guardian decision

Patients who permanently discontinue the study treatment during the treatment phase will continue tumor assessments every 8 weeks until:

- the patient has disease progression or
- the study is terminated by the sponsor, or
- withdrawal of consent for further assessments, or
- the patient is lost to follow-up or
- the patient dies.

Patient may continue treatment with the study treatment until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent.

6.1.2.1 Treatment beyond disease progression

Patients may derive benefit from continuing study treatment despite initial evidence of disease progression therefore patients treated with EGF816 will be permitted to continue study treatment beyond initial disease progression as per RECIST 1.1 criteria provided they meet the following criteria:

- Benefit assessed by the investigator (s)
- No rapid disease progression
- Tolerance of study treatment

The judgment of the investigator should be documented in the Case Report Form as an Investigator comment and the continued evidence of clinical benefit should be updated on a regular basis.In addition, treatment beyond disease progression should not jeopardize critical interventions to treat/prevent severe complications, or prevent patients from receiving adequate care.

Patients who meet above criteria and continue treatment beyond initial disease progression will continue all study procedures as outlined in Section 7. In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Patients with evidence of further disease progression on an imaging assessment or who are no longer deriving clinical benefit will be discontinued.

6.2 Dose-escalation guidelines

6.2.1 Starting dose rationale

The starting dose for EGF816, for patients enrolled in the Phase I part of the trial, is set at 75 mg administered orally on a continuous, once daily schedule. The selection of the starting dose follows the ICH S9 guidelines for choosing a starting dose for a first-in-human trial conducted in patients with cancer.

For selection of the starting dose in the first in human clinical study, standard criteria for an anticancer drug were applied. In the 4-week GLP rat study, the 75 mg/kg dose was considered to approximate the severely toxic dose in 10% of animal (STD_{10}). Expressing 75 mg/kg in the rat based on the body surface area is equivalent to 450 mg/m^2. Applying a safety factor of 10, the starting dose in humans would be 1/10th of the STD_{10} in rats or 1/10th of 450 mg/m^2 = 45.0

mg/m^2. Since 1/10th of the STD_{10} in rat is below the highest non-severely toxic dose (HNSTD) in the dog (20 mg/kg or 400 mg/m^2), this dose is expected to be well-tolerated by the dog. Therefore, the rat is considered an appropriate species for evaluating EGF816 toxicity and the rat STD_{10} was used as the basis for the starting dose calculation. Thus, based on an average body surface area (BSA) of 1.73m^2, the recommended safe starting dose of EGF816 is 77.8 mg/patient (~75 mg/patient/day).

Formulation change from capsule to tablet (based on protocol amendment 03)

An immediate release film-coated tablet will be introduced during the dose-escalation phase.

EGF816 has a high solubility across the pH range of 1 to 6.8. In a Caco-2 cell trans-well study, EGF816 showed high permeability at the concentrations relevant to calculated intestinal lumen concentrations. In addition, EGF816 was almost completely absorbed as demonstrated in the rat radiolabel ADME study. The oral bioavailability of 55% observed in rat was due to the first-pass metabolism. Therefore, based on available data EGF816 is considered a preliminary BCS class 1 compound. The dissolution profile of the capsule formulation was categorized as very rapidly dissolving with > 85% of drug in solution within 15 minutes at pH of 1. The dissolution profile of the tablet formulation was comparable or slightly slower than those for capsule. Therefore, the exposure of EGF816 following the same dose of tablet administration is predicted to be comparable or lower than that for the capsule formulation.

Based on this rationale, EGF816 tablet will be introduced in this study at the highest dose level investigated with EGF816 capsule that has been evaluated in at least 3 patients and shown to satisfy the EWOC principle. In the situation that MTD/RP2D has been reached for capsule formulation, the EGF816 tablet will be introduced at the highest previously tested dose that is lower than the capsule MTD/RP2D, and the MTD/RP2D with the tablet formulation will be established separately. Dose-escalation for the tablet formulation will continue following the procedure specified in Section 6.2.3.

EGF816 will be supplied by Novartis. EGF816 25 mg, 50 mg, 100 mg capsules and 25 mg, 50 mg and 200 mg tablets will be packaged in high-density polyethylene (HDPE) bottles. Similar exposures were observed in the phase I part between capsules and tablets at 150 mg QD (refer to latest Investigator's Brochure Edition).

6.2.2 Provisional dose levels for Phase I part (dose-escalation)

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial. Dose escalation will continue until MTD is reached and/or RP2D is determined. At all decision time points, the adaptive BLRM permits alterations in the dose increments based on the observed DLTs.

Table 6-2 Provisional dose levels for Phase I part (dose-escalation)

Dose level	Proposed daily dose*	Increment from previous dose
-1**	50 mg	-
1 (starting dose)	75 mg	(starting dose)
2	100 mg	33%
3	150 mg	50%
4	300 mg	100%
5	450 mg	50%
6	600 mg	33%
7	800 mg	33%
8	1000 mg	25%

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Dose levels may also be skipped if the safety data and BLRM analyses support a higher increase limited to at most 100% increase in dose level (e.g. a move from 300 mg to 600 mg). Cohorts may be added at any time (either during Phase I and/or during Phase II part) and at any dose level below either the estimated MTD or the RP2D for which safety data exists in order to better understand safety, PK or PD

**Dose level −1 represents a treatment dose for patients requiring a dose reduction from the starting dose level.

6.2.3 Guidance for dose escalation and determination of MTD/RP2D

6.2.3.1 Definition and estimation of MTD/RP2D

The MTD is the highest drug dosage that is unlikely (<25% posterior probability) to cause DLT in more than 33% of the treated patients in the first cycle of EGF816 treatment.

A two-parameter BLRM employing the EWOC principle (Neuenschwander 2008; Babb 1998) will be used during the dose escalation to guide dose level selection and to estimate the MTD. Dose escalation will continue until the MTD is reached or until Novartis and Investigators reach consensus that, based on a review of the totality of the clinical data (e.g., DLT, lower grade AE, PK, [redacted], preliminary antitumor activity etc.) there is no benefit to continue escalation and a lower RP2D is identified (e.g., when PK modeling predicts that further escalation will not result in higher drug exposures).

Estimation of the MTD during the Phase I dose-escalation part of the study will be based upon the estimation of the probability of DLT in cycle 1 in patients in the Dose-Determining Set (DDS). The corresponding statistical methodology is described in Section 10.4.2.

MTD/RP2D for each drug formulation or dosing schedule may be established when appropriate.

6.2.3.2 Dose cohort modification for Phase I part (dose-escalation)

For the purposes of dose-escalation decisions, each cohort will consist of 1 to 6 newly enrolled evaluable patients who will be treated at the specified dose level. The first cohort will be treated with the starting dose of 75 mg QD. When two patients (who may be in different cohorts) have experienced a toxicity of CTCAE grade 2 for which relationship to study drug cannot be ruled out; or when any single patient experiences a DLT or AE of CTCAE grade 3 or greater during Cycle 1, the cohort size will be changed to between 3 and 6 evaluable patients for the current and subsequent cohorts.

Patients must complete a minimum of 1 cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose-escalation decisions. Dose-escalation decisions will occur when the cohort of patients has met these criteria.

Dose-escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information (DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1), PK, and PD data from evaluable patients. The recommended dose for the next cohort of subjects will be guided by the BLRM with EWOC principle (Section 2.2).

The adaptive Bayesian methodology provides an estimate of all dose levels of EGF816 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle (Section 10.4.2). In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose. Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data. If needed to better define the dose-toxicity relationship additional patients may be enrolled to the current dose level, to a preceding dose level, or to an intermediate dose level before proceeding with further dose escalation.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level (see Section 14.2 Appendix 2) that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLT observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose cohort only if the dose still meets the EWOC criteria and as agreed by Investigators and Novartis personnel. Alternatively, if recruitment to the same cohort may not resume, a new cohort of patients may be recruited to a lower dose as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this lower dose to exceed the MTD remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC criteria are satisfied) and Investigators and Novartis personnel agree.

Dose escalation will continue until identification of the MTD or a suitable lower dose for Phase II part. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or
    b. minimum of 21 patients have already been treated on the trial.
3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference.

Note: if significant activity is seen early in the dose escalation, then a recommended dose may be identified and the phase II groups may be initiated without determination of the MTD; therefore fewer than 21 patients may be required.

To better understand the safety, tolerability, PK, PD (paired tumor biopsy) or preliminary activity of EGF816, additional cohorts of one to six patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first cycle of treatment, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

Change of drug formulation:

By protocol amendment 07, the dose escalation decisions were already made and no additional patients were included for BLRM, hence the new change in formulation from tablet to capsule are not expected to impact this part of the study.

Change of schedule:

In the event of a change in dosing schedule, then a new BLRM would have been set up. This new BLRM would have incorporated down-weighted existing dose-escalation data in the prior distribution and a starting dose would have been identified at that time. Subsequent dosing decisions for the new schedule would have followed the same rules defined within the above paragraphs of this section.

6.2.3.3 Implementation of dose-escalation decisions

To implement dose-escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.4 Intra-patient dose escalation for Phase I part (dose-escalation)

Intra-patient dose escalation is not permitted during the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of EGF816 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of EGF816, he or she must have received the lower dose for at least four cycles of therapy without a toxicity ≥ CTCAE grade 2 that is at least possibly related to the study drug. Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation in a dose-escalation meeting and that has not exceeded the MTD estimated by the BLRM.

Any further increases after the initial intra-patient dose escalation are subject to the same rules as for the initial intra-patient escalation except that the patient must have received a minimum of 2 cycles of therapy at the prior current dose before escalation may occur. Consultation with Novartis must occur prior to any intra-patient dose-escalation decision. These changes must be recorded on the Dosage Administration Record eCRF.

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6.2.4 Definitions of dose-limiting toxicities (DLTs) for Phase I part (dose-escalation)

A dose-limiting toxicity (DLT) is defined in the Phase I part as an adverse event or abnormal laboratory value assessed as unrelated to disease, progressive disease, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with EGF816 and meets any of the criteria included in Table 6-3. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Table 6-3 Criteria for defining dose-limiting toxicities in the Phase I part

Toxicity	Any of the following criteria:
Hematology	Any hematologic toxicity = grade 3, lasting for >7 consecutive days
	Any hematologic toxicity ≥ grade 4 (of any duration)
	Febrile neutropenia (ANC < 1.0 x 10^9/L or 1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour.
Renal	Serum creatinine ≥ grade 3 (> 3.0 - 6.0 x ULN or >3.0 x baseline)
Hepatic	total bilirubin ≥ grade 3 (> 3 x ULN)
	AST or ALT = grade 3 (>5.0-20.0 x ULN) for ≥ 7 day AST or ALT = grade 4 (>20.0 x ULN)
	AST or ALT grade 3 and ≥ grade 2 bilirubin
Neurologic	Any neurological abnormality or toxicity ≥ grade 2
Diarrhea	≥ grade 3 despite optimal treatment
Skin and subcutaneous tissue disorders	≥ grade 3 despite 7 days optimal treatment
Other adverse events	Any adverse event ≥ grade 3. Single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycle 1, may be considered to be DLTs by the Investigators and Novartis, even if not CTCAE grade 3 or higher
CTCAE version 4.03 will be used for all grading. Patients may receive supportive care (e.g. transfusion of red blood cells) as per local institutional guidelines, as long as causality can clearly be established that supportive care is to treat disease related events and not related to investigational agent	

6.3 Dose modifications for toxicities

6.3.1 Dose modification and dose delay

If a patient requires a dose interruption of >21 days from the intended day of the next scheduled dose due to EGF816-related toxicity, then the patient must be discontinued from the study treatment unless described otherwise (see Table 6-7 and Table 6-8 for exception).

For patients who do not tolerate the protocol-specified dosing schedule due to drug related toxicities, dose interruptions and/or reductions are recommended in order to allow patients to continue the study treatment.

Table 6-5 provides recommendations for dose modification and dose interruption (i.e., interruption and re-initiation criteria for EGF816 treatment).

Each patient is allowed a maximum of 2 dose reductions. In addition, a patient must discontinue treatment with EGF816, if after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity. Exceptions can be made on a case by case basis after discussion between Novartis Clinical team and Investigator (**applicable to the Phase I part**).

All dose interruptions or modifications must be recorded on the Dosage Administration Record CRF.

In case of study treatment interruption, visit schedule should still be followed and assessments performed as per Table 7-1 (Phase I part) and Table 7-2 (Phase II part).

Refer to Table 6-4 for recommended dose reduction steps for the Phase I and Phase II part of the study.

Table 6-4 Recommended dose reduction steps for the Phase I and II parts

Dose level	Reduction from initial dose for phase I*	Proposed daily dose for phase II
0	0% (current dose)	RP2D = 150 mg
-1	25%-33% reduction from current dose	100 mg
-2	50% reduction from current dose	75 mg
*Note: Since phase I part is exploring dose escalation, the dose reductions in phase I are given as percent of initial dose rather than an absolute number because individual patients may be started on different initial doses.		

Table 6-5 Criteria for dose reduction/interruption and re-initiation of EGF816 treatment for adverse drug reactions

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC <LLN - 1500/mm^3)	Recommendation: maintain dose level
Grade 2 (ANC <1500 - 1000/mm^3)	Recommendation: maintain dose level
Grade 3 (ANC <1000 - 500/mm^3)	Recommendation: omit dose until resolved ≤ Grade 2, then maintain dose level
Grade 4 (ANC <500/mm^3)	Recommendation: omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
Febrile neutropenia (ANC <1.0 x 10^9/L, fever ≥ 38.5°C)	Recommendation: omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT <LLN - 75,000/mm^3)	May maintain dose level
Grade 2 (PLT <75,000 - 50,000/mm^3)	May maintain dose level
Grade 3 (PLT <50,000 - 25,000/mm^3)	Recommendation: omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in >7 days, then ↓ 1 dose level
Grade 4 (PLT <25,000/mm^3)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Investigations (Renal)	
Serum creatinine	
Grade 1 (>ULN - 1.5 x ULN)-	May maintain dose level
Grade 2 (>1.5 – 3,.0 x ULN)	Recommendation: omit dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (>3.0 – 6.0 x ULN	Recommendation: omit dose and discontinue patient from study drug treatment
Grade 4 (>6.0 x ULN)	Recommendation: omit dose and discontinue patient from study drug treatment
Investigations (Hepatic)[b]	
Isolated Total Bilirubin (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
>ULN -1.5 x ULN	Recommendation: maintain dose level
>1.5 - 3.0 x ULN	Recommendation: omit dose. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ 1.5 x ULN ,then: If resolved in ≤14 days, then maintain dose level If resolved in >14 days, then ↓ 1 dose level
>3.0 - 10.0 x ULN[g]	Recommendation: omit dose. Monitor LFTs[c] weekly, or more frequently if clinically indicated until resolved to ≤ 1.5 x ULN, then: If resolved in ≤14 days, then ↓ 1 dose level If resolved in >14 days, then discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin has resolved to baseline or stabilization over 4 weeks.
>10.0 x ULN[g]	Recommendation: Discontinue patient from study drug treatment The patient should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilized over 4 weeks.

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
Isolated AST or ALT	
>ULN - 3.0 x ULN	Recommendation: maintain dose level
>3.0 - 5.0 x ULN	
For patients with baseline value ≤ 3.0 x ULN	Recommendation: maintain dose level. Repeat LFTs[b] 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[b] 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	Maintain dose level
>5.0 - 10.0 x ULN	
For patients with baseline value ≤ 3.0 x ULN	Recommendation: omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, ↓ 1 dose level
For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose level. Repeat LFTsb 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 LFTsb, weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
If AST or ALT > 5 x ULN in patients with baseline AST or ALT ≤ 3 x ULN, or if AST or ALT > 8 x ULN in patients with baseline AST or ALT > 3 x ULN but ≤ 5 x ULN	Immediate testing for viral hepatitis infection or reactivation should be performed, see Section 6.3.4. Patients who have HBV-DNA or HCV-RNA monitoring during the study should be re-tested immediately
> 10.0 - 20.0 x ULN	Recommendation: Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ Grade 1 (or to baseline), then ↓ 1 dose level.
> 20.0 x ULN	
For patients deriving clinical benefit upon investigator's judgement	Recommendation: omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 x ULN (or ≤ 5 x ULN for patients with baseline value > 3.0 -5.0 x ULN), then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 x ULN, discontinue patient from study drug treatment
For all other patients	Discontinue patient from study drug treatment Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
	over 4 weeks. If AST or ALT>20.0 x ULN immediate testing for viral hepatitis infection or reactivation should be performed, see Section 6.3.4. Patients who have HBV-DNA or HCV-RNA monitoring during the study should be re-tested immediately.
Combined[d] elevation of AST or ALT and concurrent Total bilirubin[f]	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[e] OR For patients with elevated baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 xULN]	Mandatory: permanently discontinue study treatment Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Testing for viral hepatitis infection or reactivation should be performed, see Section 6.3.4.
Investigation (metabolic)[h]	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (>ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	May maintain dose level
Grade 3 (>2.0 - 5.0 x ULN)	Recommendation: omit dose until resolved to Grade ≤ 2, then: If resolved in ≤ 14 days, then maintain dose level If resolved in >14 days, then ↓ 1 dose level
Grade 4 (>5.0 x ULN)	Recommendation: Omit dose and discontinue patient from study drug treatment
Note: withhold EGF816 for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
HBV and HCV reactivation Refer to Table 6-6, Table 6-7 and Table 6-8, and Section 6.3.4 for details.	
Cardiac Investigations	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms)	May maintain dose level
Grade 2 (QTc 481-500 ms)	May maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Recommendation: omit dose until QTC is less than 481 ms and then ↓ 1 dose level - Perform an analysis of serum potassium, and if below lower limit of normal, correct with supplements to within normal limits.- Repeat ECG

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
	in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc <481 ms - Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Recommendation : discontinue patient from study treatment
Bradycardia	
Grade 1 or 2	Recommendation: omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of EGF816
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Recommendation: omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume EGF816 at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Recommendation: permanently discontinue EGF816
Vascular disorders	
Hypertension	
CTCAE Grade 3	Recommendation: omit dose until resolved ≤ Grade 1, then ↓ 1 dose level
CTCAE Grade 4	Recommendation: omit dose and discontinue patient from study drug treatment
Gastro intestinal	
Diarrhea[e]	
Grade 1 (despite maximal anti-diarrheal medication)	Recommendation: maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Recommendation: 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 ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea	
Grade 1 or 2	Recommendation: maintain dose level but adjust anti-emetic treatment

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
Grade 3 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting	
Grade 1 (despite standard anti-emetics)	Recommendation: maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Recommendation: omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting.	
Skin and subcutaneous tissue disorders	
Rash/photosensitivity Refer to Table 6-9, Table 6-10 , and Table 6-11 for management and dose modification for rash/skin toxicities	
Pneumonitis/Interstitial lung disease Refer to Table 6-12 for management and dose modification for non-infectious pneumonitis/interstitial lung disease	
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then↓ 1 dose level
Metabolic	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycemia** (glucose > 250 mg/dL) despite optimal anti-hyperglycemic therapy	Omit dose until hyperglycemia is adequately controlled then resume EGF816 at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management permanently discontinue patient from EGF816
Other adverse events	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: omit dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4	Recommendation: omit dose and then discontinue from study treatment.

Dose modifications for EGF816	
Worst toxicity **CTCAE[a] Grade (value) during a cycle of therapy**	
	Note: Recommendation: Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

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

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

[b] If Grade 3 or 4 hyper-bilirubinemia 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.

[c] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin >2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase > 2.0 x ULN) and GGT. For isolated elevations of any grade of alkaline phosphatase and/or gamma-glutamyl transpeptidase (GGT), maintain dose level.

[d] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

[e] "Cholestasis" defined as: ALP elevation (>2xULN and R value< 2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury

[f] 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

[g] 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.

[h] A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.

[i] Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.

6.3.2 Guidelines for screening, monitoring and management of HBV / HCV reactivation

HBV screening tests, on study monitoring, and management of HBV reactivation

1. All patients must be screened with HBV serologic markers: HBsAg, HBsAb, and HBcAb.
2. If HBsAg and/or HBcAb are positive, test for HBV-DNA.
3. Refer to Table 6-6 for actions to be taken based on screening HBV results.
4. If a patient is HBsAg positive or HBV-DNA positive BUT is not on antiviral therapy:
   a. Consult a physician with expertise in managing HBV

b. Initiate antiviral therapy with entecavir 0.5mg QD 1-2 weeks prior to 1st dose of EGF816 treatment. Note: ongoing patients prior to initiation of Amendment 5 follow the Urgent Safety Measure.
c. If a patient cannot take entecavir or if entecavir is not available at your institution, contact Novartis to select an appropriate antiviral therapy.
d. If antiviral therapy cannot be given, the patient is not eligible for EGF816 dosing.
e. During the study, monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated). (Refer to Table 6-7 if there is evidence of viral reactivation on study)
f. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.

5. Patients who are HBsAg positive or HBV-DNA positive at screening and already have been receiving antiviral therapy are eligible provided the patient remains on antiviral treatment.
   a. Identify a consulting physician with expertise in managing HBV who can provide treatment guidance, if required, while the patient is on study.
   b. HBV-DNA should be monitored every 4 weeks (or more frequently if clinically indicated).
   c. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.
6. Refer to Table 6-7 for guidelines of management for HBV reactivation.

Table 6-6 Actions to be taken based on hepatitis B results screening

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	- or + with prior HBV vaccination	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Required actions	* Consult a physician with expertise in managing HBV. After the consultation, antiviral therapy should be started 1-2 weeks prior to 1st dose of EGF816 treatment. Recommended antiviral therapy is entecavir 0.5mg QD. Contact Novartis if a patient cannot take entecavir or if entecavir is not available at your institution. Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated). Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816.		No antiviral therapy. Monitor HBV-DNA every 4 weeks.		No antiviral therapy. HBV-DNA screening not required unless HBsAg and/or HBcAb are positive

Table 6-7 Guidelines for management of HBV reactivation

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
Positive HBV-DNA OR Positive HBsAg	Increase of 1 log in HBV-DNA relative to screening HBV-DNA value OR new appearance of measurable HBV-DNA	Interrupt EGF816 treatment. Assess patient compliance with antiviral therapy. Consult a physician with expertise in managing HBV and consider changing antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 administration until resolution to: • ≤ screening HBV-DNA levels and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed If resolution occurs within ≤ 21 days EGF816 should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816 and is to be further maintained under the surveillance of a physician with expertise in the management of hepatitis B in compliance with international (Terrault NA et al 2018) and local guidelines. If resolution occurs > 21 days Contact Novartis for approval of restarting of EGF816. • If restarting of EGF816 is approved: follow the same guidelines as above. • If restarting of EGF816 is NOT approved: discontinue EGF816 treatment. Continue antiviral therapy for at least 4 weeks after the last dose of EGF816, antiviral treatment is to be further maintained under the surveillance of a physician with expertise in the management of hepatitis B in compliance with international (Terrault NA et al 2018) and local guidelines. Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated).

HBV reactivation (with or without clinical signs and symptoms)*		
Screening test results	**Monitoring test results that define HBV reactivation**	**Actions to be taken**
Negative HBV-DNA AND Negative HBsAg	New appearance of measurable HBV-DNA	Interrupt EGF816 treatment. Consult a physician with expertise in managing HBV. After the consultation, start antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 administration until resolution to: • ≤ baseline HBV-DNA levels and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed. If resolution occurs within ≤ 21 days EGF816 should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. Antiviral therapy should continue for at least 4 weeks after the last dose of EGF816 and is to be further maintained under the surveillance of a physician with expertise in the management of hepatitis B in compliance with international (Terrault NA et al 2018) and local guidelines. If resolution occurs > 21 days Contact Novartis for approval of restarting of EGF816. • If restarting of EGF816 is approved: follow the same guidelines as above. • If restarting of EGF816 is NOT approved: discontinue EGF816 treatment. Continue antiviral therapy for at least 4 weeks after the last dose of EGF816. Monitor HBV-DNA every 4 weeks (or more frequently if clinically indicated).
* All reactivations of HBV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g. for a patient who was HBV-DNA positive on 01-Jan-2015 and whose ALT reached > 5 × ULN on 01-Apr-2015, the date of viral reactivation is 01-Jan-2015).		

HCV screening tests, on study monitoring, and management of HCV reactivation

1. Screen all new patients for HCV-Ab. If HCV-Ab is detected then check HCV-RNA.
2. Only patients with negative HCV-Ab or with positive HCV-Ab but undetectable level of HCV-RNA are eligible to be dosed with EGF816 (assuming all other eligibility criteria are met). Patients with detectable HCV-RNA are not eligible to be enrolled in the study.
3. The following two categories of patients should be monitored every 4 weeks (or more frequently if clinically indicated) with HCV RNA-PCR for HCV reactivation:
   a. Patients with detectable HCV-RNA at screening and were treated until HCV-RNA becomes undetectable (only applicable to patients enrolled prior to amendment 5)
   b. Patients with known history of HCV infection and undetectable HCV-RNA at screening
4. Refer to Table 6-8 for definition of HCV reactivation and the management guidelines.

Table 6-8 Guidelines for management of HCV reactivation

HCV reactivation (with or without clinical signs and symptoms)[1]		
Screening test results	**Monitoring test results that define HCV reactivation**	**Action to be taken**
Knowledge of past hepatitis C infection with no detectable HCV-RNA OR Detectable HCV-RNA at screening and was treated until HCV-RNA becomes undetectable [2]	New appearance of detectable HCV-RNA	Interrupt EGF816 treatment. Consult a physician with expertise in managing HCV. After the consultation, start antiviral therapy. While patient is on antiviral therapy, continue interruption of EGF816 administration until resolution to: • no detectable HCV-RNA and • ≤ grade 1 ALT (or baseline ALT, if > grade 1) if ALT elevation was observed. If resolution occurs within ≤ 21 days EGF816 should be re-started at the same dose level unless dose reduction/interruption is indicated due to any other reason. If resolution occurs > 21 days Contact Novartis for approval of restarting of EGF816. • If restarting of EGF816 is approved: follow the same guidelines as above. • If restarting of EGF816 is NOT approved: permanently discontinue the patient from EGF816 treatment Monitor HCV-RNA every 4 weeks (or more frequently if clinically indicated)

[1.] All reactivations of HCV are to be recorded as serious adverse event (SAE). Date of viral reactivation is the date on which the defined lab results for reactivation were met (e.g., for a patient whose HCV-RNA was detectable on 01-Jan-2015 and ALT reached > 5 x ULN on 22-Jan-2015, the date of viral reactivation is 01-Jan-2015).

[2.] Applicable to ongoing patients only

On study monitoring of liver function test (LFT) for all patients

LFTs should be monitored for all patients as per protocol, or more frequently if clinically indicated.

At any time during the study, if ALT > 5 x ULN in patients with baseline ALT ≤ 3 x ULN, or if ALT > 8 x ULN in patients with baseline ALT > 3 x ULN but ≤ 5 x ULN: immediately

1. Perform test(s) for viral hepatitis infection or reactivation: all patients should be screened with viral hepatitis panel (HAV-Ab-IgM, HBsAg, HBcAb-IgM, and HCV-Ab). In addition
   a. Patients who have HBV-DNA monitoring during the study should be re-tested for HBV-DNA immediately; refer to Table 6-7 for definition and management of HBV reactivation.
   b. Patients who have HCV-RNA monitoring during the study should be re-tested for HCV-RNA immediately; refer to Table 6-8 for definition and management of HCV reactivation.
2. If any of the above tests indicate:
   a. HBV reactivation: refer to Table 6-7 for management guidelines.

b. HCV reactivation: refer to Table 6-8 for management guidelines.
c. New viral infection: immediately interrupt dosing, consult a physician with expertise in managing viral hepatitis and contact Novartis for further discussion.

3. Perform other relevant tests/procedures as clinically indicated.
4. Follow the dosing modification for ALT elevation according to guidelines in Table 6-5.

6.3.3 Guidelines for the management and dose modification of skin-related toxicities

Rash, particularly maculopapular rash or rash pruritic, is an adverse event frequently observed following treatment with EGF816. Patients must be closely monitored for any signs/symptoms related to rash/skin toxicities. Recommended guidelines for management and dose modification of rash/skin toxicities are provided in Table 6-9 , Table 6-10 , and Table 6-11.

Table 6-9 Guidelines for prevention and symptomatic care of rash/skin toxicities

Type of care	Action
Prevention/Prophylaxis Starting from Day 1 for all patients	• Avoid unnecessary exposure to sunlight/ ultraviolet • Apply broad-spectrum sunscreen with SPF≥15 at least twice daily • Use thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body at least twice daily
Symptomatic care*	• Pruritic lesions: cool compresses, topical steroids and oral antihistamine therapies • Desquamation: thick, alcohol-free emollient cream and mild soap • Paronychia: antiseptic bath and topical antibiotics; if no improvement, consult dermatologist • Infected lesions: appropriate topical or systemic antibiotics • Avoid exposure to sunlight/ultraviolet
*Patients who develop rash/skin toxicities should be evaluated by a qualified physician and receive symptomatic and supportive care management.	

Table 6-10 Management and dose modification for maculopapular rash[1, 2]

CTCAE Grade	Adverse Event Management	Action and Dose Modification

Grade 1
Macules/papules covering <10% BSA
	• Initiate appropriate symptomatic care (Refer to Table 6-9)
	• Initiate oral antihistamine treatment (e.g. levocetirizine 5mg qd, desloratadine 5mg qd, or fexofenadine 180 mg qd) maintained for 1 week after resolution of Grade 1 rash
	• Consider steroid use:
	  • Low-dose oral steroid (e.g. prednisolone 5mg-10mg po qd for 3-5 days)
	  • If pruritus with inflammation signs like scaling, erythema and infiltration: Moderate potency topical steroid (e.g. 0.1% momentasone or 0.1% betamethasone valerate cream) on affected areas
	•
	• Re-assess after 1 week until resolution
		Continue study drug at same dose level

CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 2 Macules/papules covering 10-30% BSA	• Initiate appropriate symptomatic care (Refer to Table 6-9) • Consult a dermatologist. • Initiate oral antihistamine treatment (e.g. levocetirizine 5mg qd, desloratadine 5mg qd, or fexofenadine 180 mg qd) maintained for 4 weeks after resolution • Steroid use: • consider initiating oral steroids (e.g. 20mg-40mg po qd for 1-2 weeks) with taper • If pruritus with inflammation signs like scaling, erythema and infiltration: Potent or ultrapotent topical steroid (e.g. 0.025% desoximetasone ointment or 0.05% clobetasol propionate cream) on affected areas • Re-assess after 1 week	Continue study drug at same dose level If no recovery to Grade ≤ 1 within 2 weeks, despite appropriate systemic treatment as per guidelines, interrupt EGF816 for 1 week. • If recovers to Grade ≤ 1, within 1 week of dose interruption restart at same dose • If rash does not recover to Grade ≤ 1 within 1 week of dose interruption, restart EGF816 at reduced dose -1 only after rash has recovered to ≤ Grade 1[3]
Grade ≥3 Macules/papules covering >30% BSA	• Initiate appropriate symptomatic care (Refer to Table 6-9) • Consult dermatologist • Initiate oral antihistamine treatment (e.g. levocetirizine 5mg qd, desloratadine 5mg qd, or fexofenadine 180 mg qd) maintained for 4 weeks after resolution • Steroid Use: • Mid-dose oral steroid (e.g. 20-40mg po qd for 1-2 weeks) with taper • If pruritus with inflammation signs, (scaling, erythema and infiltration), potent or ultrapotent topical steroid (e.g. 0.025% desoximetasone ointment or 0.05% clobetasol propionate cream) on affected areas • Re-assess every week until resolution	Continue EGF816 at same dose level If no recovery to Grade ≤ 1 within 1 week, despite appropriate systemic treatment as per guidelines, interrupt for 1 week • *If recovers to Grade ≤ 1 within 1 week of dose interruption, restart at same dose • *If rash does not recover to Grade ≤ 1 within 1 week, restart EGF816 reduced by 1 dose level only after rash has recovered to ≤ Grade 1

[1] Maculopapular rash (group term) includes the following preferred terms: rash erythematous, rash morbilliform, rash papular, rash maculo-papular, rash rubelliform, rash scarlatiniform, rash macular.

[2] For all grade 2 and 3 of maculopapular rash, consider skin biopsy for pathologic evaluation. Study drug may be resumed although steroids are still ongoing or being tapered.

[3] A maximum of 2 dose reductions is allowed. Patients, who require further dose decrease after 2 dose reductions, should be discontinued from study drug. Escalation by one level to previous dose level may be considered if no rash is evident after 4 weeks of uninterrupted study drug at the reduced dose level. Re-escalation can only be done once.

* Guidelines to be followed even if EGF816 interrupted earlier

Table 6-11 Management and dose modification for other rashes including acneiform rash

CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• Monitor for change in severity and consider symptomatic and/or topical treatment (Refer to Table 6-9)	Continue study drug at same dose level

CTCAE Grade	Adverse Event Management	Action and Dose Modification
	• Re-assess every 2 weeks	
Grade 2	• Initiate appropriate symptomatic care (Refer to Table 6-9) • Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, , topical or systemic antibiotics, topical or systemic antihistamines. • Re-assess every 2 weeks	Continue study drug at same dose level • If no recovery or worsened within 2 weeks, interrupt study drug until rash recovers to ≤ Grade 1 • Once rash recovers to ≤ Grade 1, then restart study drug at one reduced dose level
Grade ≥3	• Initiate appropriate symptomatic care (Refer to Table 6-9) • Depending on the type of rash, a variety of agents can be used including mild to moderate strength steroid creams, low-dose oral steroids, etopical or systemic antibiotics, topical or systemic antihistamines. • Consult dermatologist • Re-assess every 2 weeks	Interrupt study drug until rash recovers to ≤ Grade 1. Once rash recovers to ≤ Grade 1, restart study drug at one reduced dose level • If no recovery to ≤ Grade 2 within 3 weeks, permanently discontinue study drug • Patients who develop more than 1 episode of Grade ≥3 rash will be permanently discontinued from study treatment
*A maximum of 2 dose reductions is allowed. Patients, who require further dose decrease after 2 dose reductions, should be discontinued from study drug. Escalation by one level to previous dose level may be considered if no rash is evident after 4 weeks of uninterrupted study drug at the reduced dose. Re-escalation can only be done once.		

6.3.4 Guidelines for the management and dose modification of non-infectious pneumonitis/interstitial lung disease

Monitor patients for pulmonary symptoms indicative of pneumonitis/ILD. In addition, withhold study treatment for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage. Permanently discontinue study treatment if the diagnosis of ILD is confirmed and initiate appropriate treatment as necessary.

Recommended guidelines for management of non-infectious pneumonitis/interstitial lung disease are provided in Table 6-12 . These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor.

Table 6-12 Management of non-infectious pneumonitis / interstitial lung disease

CTCAE Grade	Required investigations	Management of pneumonitis	Action and dose modification
Grade 1 Asymptomatic, radiographic findings only	• Exclude infectious etiology. 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	No specific therapy is required.	Interrupt study treatment during diagnostic workup for pneumonitis/ILD. Exclude infections and other etiologies. If diagnosis of pneumonitis/ILD is confirmed, permanently discontinue study treatment. In absence of diagnosis of pneumonitis/ILD: restart study treatment at the same dose. If symptoms recur after resumption of study treatment, permanently discontinue study treatment
Grade 2 Symptomatic, not interfering with activity daily living (ADL)	Exclude infectious etiology. CT scan (high resolution with lung windows). • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist Consider pulmonary function testing[a]. . Consider a bronchoscopy with biopsy and /or bronchoalveolar lavage (BAL)[c]. Symptomatic therapy including corticosteroids if clinically indicated (1 to 2 mg/kg/day prednisone or equivalent as clinically indicated)[b]	Symptomatic only. Consider corticosteroids[b] if symptoms are troublesome.	Interrupt study treatment during diagnostic workup for pneumonitis/ILD and until improvement to ≤ Grade 1. Exclude infections and other etiologies. If diagnosis of pneumonitis/ILD is confirmed, permanently discontinue study treatment. In absence of diagnosis of pneumonitis/ILD: if symptoms resolve to ≤ Grade 1 in ≤ 7 days restart the study treatment at one reduced dose level *. If symptoms fail to resolve within 7 days or recur after resumption of study treatment at decreased dose, permanently discontinue study treatment.

CTCAE Grade	Required investigations	Management of pneumonitis	Action and dose modification
Grade 3 Symptomatic, interfering with ADL; O_2 indicated AND Grade 4 Life-threatening; ventilatory support indicated	CT scan (high resolution with lung windows) Clinical evaluation and laboratory work-up for infection Consult pulmonologist Pulmonary function testing[a]. If < normal, repeat every 8 weeks until ≥ normal Bronchoscopy with biopsy and/or BAL[c] if possible Repeat every cycle until return to within normal limits.	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. Oxygen therapy as indicated.	Mandatory: permanently discontinue study drug.

[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.

6.3.5 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last doses of EGF816 as part of the study requirements.

6.3.5.1 Follow-up on potential QTcF prolongation

In case of QTcF >500 ms, (or QTcF prolongation >60 ms from baseline)

- Assess the quality of the ECG recording and the QT value and repeat if needed
- Interrupt study treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.

- Review concomitant medication use for other causes for QT prolongation, and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check study drug dosing schedule and study treatment compliance
- Consider collecting a time-matched PK sample, and record time and date of last study drugs intake.

After confirming ECG reading at site, if QTcF > 500 ms

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 ms:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as clinically indicated, until the QTcF returns to ≤ 480 ms.
- After resolution to ≤480 ms, consider re-introducing study treatment at reduced dose, and increase ECG monitoring:
  - If QTcF remains ≤500 ms after dose reduction, continue planned ECG monitoring during subsequent study treatment
  - If QTcF recurs > 500 ms after dose reduction, recommendation: discontinue patient from trial

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

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

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

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

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

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

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed

history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. 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.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. 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.

6.3.6 Anticipated risks and safety concerns of the study drug

For the Phase I part, appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Prophylactic or supportive treatment for other expected toxicities, including management of other study-drug induced adverse events will be as per institutional guidelines. Refer to preclinical toxicity (Section 1.2.1.1.2) and or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the patient are allowed. Anticoagulation treatment is also allowed if INR has been established within the therapeutic range prior to study entry. PT and PTT ≥ 1.5x ULN are permitted in these cases.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered within 28 days prior to the administration of study treatment and during the study must be listed on the Prior and Concomitant Medications or the Surgical and Medical procedures eCRF.

After discussion with Novartis, patients who develop progressive disease limited to the bone or central nervous system (CNS) may undergo radiotherapy to the bone or CNS and surgical resection of CNS metastases, and remain on study. EGF816 should be held for at least 5 days prior to radiotherapy or surgery. EGF816 may be resumed >3 days after completing radiotherapy or surgery if all procedure-related toxicities have resolved to ≤ Grade 1.

The exception to this is palliative bone radiation, which is permitted throughout the study. However, study treatment should be interrupted on the day of radiotherapy.

The use of bisphosphonates is allowed regardless of indication provided patients have been on stable doses optimally for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the patient should discontinue study treatment.

No drug-drug interaction is expected between EGF816 and bisphosphonates as the drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of EGF816 and do not undergo metabolism in vivo.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Based on the *in vitro* studies, EGF816 is primarily metabolized by CYP3A4. Moderate inhibitors and inducers of CYP3A4 should be used with caution.

EGF816 is a P-gp substrate. Co-administration of EGF816 with P-gp inhibitors may increase systemic exposure and/or alter tissue uptake of EGF816. EGF816 is a moderate inhibitor of BCRP with IC50 value of 4 μM. The exposure of BCRP substrate may increase when co-administered with EGF816. EGF816 is an inhibitor of the human multidrug and toxin extrusion transporter 1 and 2-K (MATE1 and MATE2-K) with an IC50 of 0.70 and 4.6 μM respectively. As a result EGF816 has potential to increase the exposure of co-medications whose clearance is significantly mediated by MATE. In the absence of data confirming whether such an interaction occurs in patients, caution should be exercised when potent P-gp inhibitors and MATE or BCRP substrates are concurrently used.

The patient and the Investigator should be aware of potential signs of overdose of the concomitant medication. In the event of suspected toxicity, administration of either EGF816 or concomitant drugs should be discontinued according to Investigator judgment.

Refer to Section 14.3 Appendix 3 for permitted medications that require caution when concomitantly used with EGF816.

6.4.3 Prohibited concomitant therapy

Concomitant antineoplastic therapy (including radiotherapy and surgery) or other investigational treatment is prohibited except as described in Section 6.4.1.

EGF816 is primarily metabolized by CYP3A4, therefore strong inhibitors and strong inducers of CYP3A4 should not be used concomitantly with EGF816.

Live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) should not be administered while a patient is dosed with EGF816 and for 30 days after the last dose of EGF816.

Refer to Section 14.4 Appendix 4 for a list of prohibited medications. If a patient must use a drug in Section 14.4 Appendix 4, the patient must be discontinued from the study.

6.5 Patient numbering, treatment assignment or randomization

This is a non-randomized trial and Integrated Response Technology (IRT) will only be used for patient registration and study medication management in the Phase II part.

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 molecular pre-screening or screening, as applicable 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 or screening informed consent form, as applicable, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

For the Phase II part, at the molecular pre-screening visit, the investigator or designated staff will contact the Interactive Response Technology (IRT) to provide the requested information for patient registration. 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. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page. IRT must be notified within 2 days that the patient was not enrolled.

6.5.2 Treatment assignment

This is a non-randomized trial. For the Phase I part, the assignment of a patient to a particular group will be coordinated by the sponsor.

For the Phase II part, an IRT will be used to track patient enrollment, document key eligibility criteria, and track individual assignment of EGF816 drug supplies. The IRT will dispense the selected EGF816 dose to each patient participating in this trial.

For each allocated patient, and prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be assigned via IRT an inclusion number. The IRT will also specify medication number of the first bottles of EGF816 study drug to be dispensed to the patient. IRT must be notified within 2 days that the patient was not enrolled.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take EGF816 as per protocol. EGF816 will be dispensed to the patient by authorized site personnel only. Dose strength and treatment schedule are described in Table 6-1. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Study treatment including instructions for administration is dispensed by study personnel. Patients will be provided with adequate supply of EGF816.

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part label (base plus tear-off label). Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the source document (Drug Label Form) for that patient's unique patient number.

In Phase I, responsible site personnel will add the patient number on the label.

For the Phase II part, a unique medication number will also be printed on each part of this label. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s) for the Phase II part. Site personnel will add the patient number on the label.

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.

6.6.2 Drug supply and storage

Study treatment 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, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

Table 6-13 Supply and storage of study treatment

Study treatments	Supply	Storage
EGF816	Centrally supplied by Novartis	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 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.

6.6.4 Disposal and destruction

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

Study treatment destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list all of the assessments for the Phase I part and Phase II part, respectively, and indicate 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 tables indicate which assessments produce data to be entered into database (D) or remain in source documents only (S) ("Category" column).

No CRF will be used as a source document.

Visit and schedule windows

Written informed consent must be obtained before any study specific assessments are performed, including those at molecular screening and screening. Screening/baseline evaluations (including baseline radiological assessment/s) must be performed ≤ 28 days of Cycle 1 Day 1.

For the Phase I part, laboratory assessments performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day.

For the Phase II part, laboratory assessments and height/weight performed as part of the screening evaluations and within 7 days of the first dose of the study treatment will not be required to be repeated on Cycle 1, Day 1.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. All safety assessments (e.g., hematology, chemistry, vitals, etc.) have a +/- 3 days window of the due date of the safety assessment. HBV/HCV results should be available prior to the first dose of EGF816 treatment. On days when PK is collected the window is only +/- 1 day. PK sample of C1D1 (Cycle 1, Day 1) must be collected at the same day of first dose.

Radiological assessments must be performed +/-7 days of the scheduled date of the assessment. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

If a given visit is out of window, the next visit should be performed with reference to the day of the first dose of study treatment in order to get the patient back on schedule.

All assessments required on Cycle 1, Day 1 must be done prior to the first dose of the study treatment unless otherwise specified. The investigator should check the pre-dose laboratory results prior to starting treatment.

Note: Phase I patients will follow the visit schedule outlined in Table 7-1 while Phase II patients will follow the visit schedule outlined in Table 7-2.

Table 7-1 Visit evaluation schedule (Phase I Part)

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Follow-Up	
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EoT)	30-day Safety F/U	Disease progression F/U
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15			
Obtain Molecular Pre-screening Informed Consent (if applicable)	D	7.1.1	X																	
Obtain Main Informed Consent	D	7.1.2		X																
Patient history																				
Demography	D	7.1.2.2	X	X																
Inclusion/exclusion criteria	D	5	X	X																
Current medical conditions at entry	D	7.1.2.2		X																
Diagnosis and extent of cancer	D	7.1.2.2		X																
Prior antineoplastic therapies	D	7.1.2.2		X																
Prior/concomitant medications	D	7.1.2.2		X	Continuously for concomitant medications															

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Follow-Up	
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EoT)	30-day Safety F/U	Disease progression F/U
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15			
Antineoplastic therapies since discontinuation of study treatment	D	7.1.2.2																X	X	X
Tumor progression status	D	7.1.2.2		X																
Physical examination	S	7.2.2.1		X	X		X	X		X	X		X	X	X	X		X		
Vital signs	D	7.2.2.2		X	X		X	X		X	X		X	X	X	X		X		
Height	D	7.2.2.3		X																
Weight	D	7.2.2.3		X	X						X					X		X		
Performance status	D	7.2.2.4		X	X						X					X		X		
Laboratory assessments	D	7.2.2.5																		
Hematology	D	7.2.2.5.1		X	X		X	X		X	X		X	X	X	X		X		
Chemistry	D	7.2.2.5.2		X	X		X	X		X	X		X	X	X	X		X		
Coagulation	D	7.2.2.5.3		X																
Urinalysis	D	7.2.2.5.4		X	X													X		
HBV testing	D	6.3.3 7.2.2.5.5		X	In cases of positive HBV testing, monitor HBV-DNA every 4 weeks, per Table 6-6 and Table 6-7 (or more frequently if clinically indicated).															

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Follow-Up	
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EoT)	30-day Safety F/U	Disease progression F/U
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15			
HCV testing	D	6.3.3 7.2.2.5.5		X	In cases of positive HCV-Ab, monitor HCV-RNA every 4 weeks, per Table 6-8 (or more frequently if clinically indicated).															
Pregnancy test	D	7.2.2.5.6		X	X						X					X		X		
Imaging																				
Tumor evaluation	D	7.2.1		X												X[a]		X[a]		X
Chest X-ray[e]	D	7.2.5.1		X				X			X					X				
ECG	D	7.2.2.6.1		X	X						X					X		X		
Safety																				
Adverse events	D	8	SAE only	Continuously														X		
Biomarkers																				
Collection of archival tumor sample	D	7.1.1 7.2.4	X[b]	X[b]																
Collection of newly obtained tumor from biopsy/resection	D	7.1.1 7.2.4	X[b]	X[b]												X[b]		X[b]		

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Follow-Up	
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2						Subsequent cycles		End of study treatment (EoT)	30-day Safety F/U	Disease progression F/U
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22		Day 1	Day 15			
[redacted]																					

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Follow-Up	
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EoT)	30-day Safety F/U	Disease progression F/U
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15			
End of Phase Disposition	D			X														X		X
Safety follow-up	S	7.1.5.1																	X	
Study Drug administration	D	6.1.1			Continuously															
PK sampling	D	7.2.3.1			X	X	X	X	X		X	X				X[d]				

[a] Tumor assessment every 8 weeks from the start of cycle 3 until progression of disease as per Table 7-3; EOT scan not required if previous scan was done ≤ 28 days

[b] Refer to Section 7.1.1 and Section 7.2.4. For subsequent cycles, newly obtained samples will be collected at C4D1, C6D1 (optional) and C8D1 (optional) and EOT (optional).

[redacted]

[d] Cycle 3 and cycle 4 only

[e] [For Japan only, refer to Section 7.2.5] [For Japan only, percutaneous oxygen saturation (SpO_2) will be measured every time physical examination is performed. In addition, SpO_2 and vital signs will be measured on Days 2-7 in Cycle 1.]

* Collect at screening or anytime thereafter

**Sample will not be collected if a newly obtained tumor sample has already been collected at screening for the purpose of DNA sequencing

***Mandatory if participating in the Companion Sample Collection Protocol. Refer to Companion Sample Collection Protocol for further information

Table 7-2 Visit evaluation schedule (Phase II part)

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
Pre-Screening																						
Obtain Molecular Pre-screening ICF	D	7.1.1	X																			
IRT Registration	D	6.5.1	X	X																		
Confirmation of EGFR mutation status by local testing	D	7.1.1	X																			
Main Screening																						
Obtain Main ICF	D	7.1.2		X																		
Patient history																						
Demography	D	7.1.2.2		X																		
Inclusion/exclusion criteria	D	5.2, 5.3		X																		
Eligibility check	S	7.1.2.1		X																		
Relevant medical history/current	D	7.1.2.2		X																		

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2						Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
medical conditions at entry																							
Diagnosis and extent of cancer	D	7.1.2.2		X																			
Smoking history	D	7.1.2.2		X																			
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.2.2		X																			
Prior/concomitant medications (including OTC meds), procedures and significant non-drug therapies	D	7.1.2.2		X	Continuously for concomitant medications																		
Tumor progression status	D	7.1.2.2		X																			

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
Physical examination																						
Complete physical examination, including neurological exams	S	7.2.2.1		X	Clinically indicated																	
Targeted physical examination	S	7.2.2.1			X						X					X		X				
Vital signs	D	7.2.2.2		X	X						X					X		X				
Height	D	7.2.2.3		X																		
Weight	D	7.2.2.3		X	X						X					X		X				
ECOG Performance status	D	7.2.2.4		X	X						X					X		X				
Chest X-ray[c]	D	7.2.5.1		X				X			X					X						
Laboratory assessments	D	7.2.2.5																				
Hematology	D	7.2.2.5.1		X	X						X					X		X				
Chemistry	D	7.2.2.5.2		X	X						X					X		X				
Coagulation	D	7.2.2.5.3		X	As clinically indicated																	

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase													Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
Urinalysis	D	7.2.2.5.4		X	As clinically indicated																	
HBV testing	D	6.3.3 7.2.2.5.5		X	In cases of positive HBV testing, monitor HBV-DNA every 4 weeks, per Table 6-66 and Table 6-7 (or more frequently if clinically indicated).																	
HCV testing	D	6.3.3 7.2.2.5.5		X	In cases of positive HCV-Ab, monitor HCV-RNA every 4 weeks, per Table 6-8 (or more frequently if clinically indicated).																	
Serum pregnancy test	D	7.2.2.5.6 6		X (within 72 hr)	X[j]													X				
Urine pregnancy test	D	7.2.2.5.6				As clinically indicated																
Tumor assessments RECIST 1.1																						
CT/MRI of chest, abdomen, pelvis	D	7.2.1		X	**Treatment period**: C3D1 and every 8 weeks (±7 days) **End of treatment (EOT):** Scans not required if previous CAP scans were performed within ≤28 days) **Disease Progression Follow Up**: Every 8 weeks (±7 days)																	
Whole body bone scan	D	7.2.1		X	Only if clinically indicated																	
CT/MRI of brain	D	7.2.1		X	C3D1 and every 8 wks (if positive at baseline) or if clinically indicated																	

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
CT/MRI of other metastatic sites (e.g., neck, etc.)	D	7.2.1		X[f]	C3D1 and every 8 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	7.2.1		X[g]	C3D1 and every 8 wks (if positive at baseline) or if clinically indicated																	
Photography (for skin lesions)	D	7.2.1		X[h]	C3D1 and every 8 wks (if positive at baseline) or if clinically indicated																	
Safety assessments																						
Adverse events	D	8	SAE only	Continuously																		X

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
Study drug administration																						
EGF816 dosing	D	6.1			Continuously																	
Biomarkers assessments																						
Collection of archival tumor sample	D	7.2.4		X	X																	
[redacted]																						

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2					Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]	Day 1	Day 15[K]					
Pharmacokinetics and ECG assessments																						
Extensive ECG collection	D	7.2.2.6.1		X	X	X		X			X	X				X[b]		X				
PK sampling	D	7.2.3.1			X	X	X	X			X	X				X[b]						
Post-treatment follow-up																						
Antineoplastic therapies (medications, surgeries, radiotherapies) since discontinuation of study drug	D	7.1.2.2																X (continuous until the last follow-up visit)				
End of Phase Disposition	D			X														X			X	
Safety follow-up	S	7.1.5.1																	X			
Survival	D	7.1.5.1																				X

Visit Name	Category	Protocol Section	Screening Phase		Treatment Phase														Post-treatment Follow-up Phase			Survival Follow-up Phase
			Molecular Pre-screening	Screening	Cycle 1						Cycle 2						Subsequent cycles		End of study treatment (EOT) Visit (within 7d of last dose)	30-day Safety F/U	Disease progression F/U (every 8 wks)	Study Phase Completion	Survival (every 3 months)
				Day -28 to 1	Day 1	Day 2	Day 8	Day 15	Day 16[K]	Day 22[K]	Day 1	Day 2	Day 8[K]	Day 15[K]	Day 22[K]		Day 1	Day 15[K]					

[a] Tumor assessment every 8 weeks from the start of cycle 3 until progression of disease

[b] Cycle 3 and cycle 4 only

[c] [For Japan only, refer to Section 7.2.5][For Japan only, percutaneous oxygen saturation (SpO2) will be measured every time physical examination is performed. In addition, SpO2 and vital signs will be measured on Days 2-7 in Cycle 1]

[d] Patients who permanently discontinue the study treatment without having disease progression will continue tumor assessments every 8 weeks until disease progression.

[e] Refer to Section 7.2.4.1.3

[f] if other metastatic sites

[g] only if lesions on whole body bone scan that are not visible on the CAP scans

[h] only if skin lesions

[I] Cycle 3 Day 1 and day 1 of every 3rd cycle thereafter

[J] Serum pregnancy should be done at screening and/or at C1D1 before the start of EGF816

[K] Visits not applicable for Phase II

Abbreviations: ICF, informed consent form; 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; F/U, follow-up; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD, progressive disease; PK, pharmacokinetics; S, remains in source document only; Tx, treatment; wks, weeks;

*Collect at baseline or anytime thereafter

**Sample will not be collected if a fresh tumor sample has already been collected at baseline for the purpose of DNA sequencing

7.1.1 Molecular pre-screening

All patients entering the pre-screening phase must sign the molecular pre-screening informed consent form (ICF).

In order to be considered eligible for the study, the following sample and testing requirements apply:

For Enrollment in the Phase I part:

Evidence of previously documented EGFR mutation status is acceptable. Alternatively, patients can participate in molecular pre-screening to assess whether or not their tumor harbors specific documented EGFR mutations by either local or central laboratory. Refer to Section 5.2 for specifics regarding the eligible EGFR mutations and required timing (if any) relative to prior treatment of the tumor sample tested.

For enrollment in the Phase II part:

NSCLC patients with EGFR activating mutation (e.g., L858R and/or ex19del), as determined by a local test.

Existing local data and the results of local testing must be captured on the appropriate eCRF upon enrollment onto the study after the patient has signed the study's Informed Consent.

Patients in Phase II will be able to proceed with main informed consent form signature and study specific screening procedures if activating EGFR mutations (e.g. L858R and/or ex19del) analysis results are documented.

During the molecular pre-screening period, the Investigator or designee should start gathering all available supportive screening evaluations (e.g., demography, relevant medical history/current medical conditions, prior antineoplastic therapies etc.) in order to prepare for a potential patient enrollment.

Upon local confirmation of the presence of EGFR activating mutations, patients may advance to the screening period to complete the required study eligibility assessments.

7.1.2 Screening

After the EGFR mutation status has been determined by a local laboratory, patients may begin the screening assessments to determine patient eligibility. All patients must sign and date the study IRB/IEC approved main ICF prior to performing any screening procedures based on the study inclusion and exclusion criteria.

[redacted].

Screening assessments must be completed within 28 days prior to the first dose of study treatment with the exception of pregnancy test, which must be performed within 72 hours before the first dose. Clinical and radiological tumor assessment by RECIST 1.1 (Section 14.1

Appendix 1) should be conducted preferably within 1 week (7 days) prior to the first dose of the study treatment; however tumor assessments up to 4 weeks (28 days) prior to the first dose will be acceptable. The tumor assessment made during the screening phase will provide the baseline tumor measurements, which will be used to determine future responses and/or progression. A complete list of screening evaluations is provided in the visit schedule evaluation tables (Table 7-1 and Table 7-2).

Screening for hepatitis B

Prior to study entry, all patients must be screened with HBV serologic markers: HBsAg, HBsAb, and HBcAb. Check HBV-DNA if HBsAg and/or HBcAb are positive. Refer to Table 6-6 for actions to be taken based on screening HBV results.

Screening for hepatitis C

Screen all patients for HCV-Ab. If HCV-Ab is detected then check HCV-RNA. Only patients who are HCV-Ab negative or HCV- Ab positive with undetectable level of RNA are eligible to be enrolled. Note: patients with detectable HCV-RNA will not be eligible for the study. Patients with HCV-Ab positive or history of hepatitis C infection should be monitored every 8 weeks (or more frequently if clinically indicated) with HCV-RNA.

All screening evaluations will be performed within 28 days prior to Treatment Day 1. HBV/HCV tests will be performed by a local laboratory for the Phase I part and the Phase II part. HBV/HCV test results should be available prior to the first dose of EGF816 treatment.

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 and Table 7-2). Any imaging assessments already completed as 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

For patients enrolled in Phase II part of the study, 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 treatment. 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.

A patient who has a laboratory test result or an ECG finding that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re-test result(s) is/are likely to be within the acceptable range to satisfy the entrance

criteria. If re-tests are performed during the 28-days screening period, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed during the original screening period of 28 days, 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. Patients who met all eligibility criteria but fail to be started on treatment as scheduled may also be re-screened, provided the patient was not registered previously in the CRF as having entered the Treatment Period.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed.

All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study.

Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

If a subject fails screening but is rescreened, the subject must be rescreened using the same subject number.

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 the rescreening is successful, the following information should be collected in the CRF:

- Date the study informed consent was first signed.
- All assessments done during the first screening period.
- All assessments repeated during the re-screening period (e.g. ECG, lab).
- Updated information as per latest status during the re-screening period e.g. Medical history, diagnosis and extent of cancer.
- Adverse events based on the date of re-consent.

7.1.2.2 Information to be collected on screening failures

Patients who signed an ICF 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:

- Screening Phase Disposition
- Demography
- 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 (for patients in Phase II only) 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 mutation status
- Demography (including: date of birth, age, patient initials if permitted, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- Phase assignment
- Smoking history
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis and stage of NSCLC
  - Site of metastatic disease
  - Characteristics of disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and current concomitant medications, surgical and medical procedures
- HBV and HCV status

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 (for patients in Phase II only).

The study treatment will begin on Cycle 1, Day 1 with the first administration of EGF816 and does not have fixed treatment duration. Information on drug exposure will be collected on the Dosage Administration Record eCRF.

A treatment cycle is defined as 28 days (4 calendar weeks) for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 and Table 7-2 for details of the timing of required assessments and Section 7.1 for visit windows.

7.1.4 Discontinuation of Study Treatment

Patients may voluntarily discontinue the study treatment for any reason at any time. If a patient decides to discontinue the study treatment, the investigator should make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. Patients may be considered

withdrawn if they state an intention to withdraw consent, fail to return for visits, or become lost to follow-up for any other reason.

The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being such as the emergence of the severe adverse events, significant laboratory abnormalities or pregnancy. Treatment may also be discontinued due to protocol deviations that result in a significant risk to the patient's safety, deviations from the prescribed dose regimen such as missed doses or prolonged drug interruptions, or use of prohibited medications which are summarized in Appendix 4.

Patients who discontinue study treatment should undergo an end of study visit and then enter the post-treatment follow-up phase. Patients who discontinue study treatment should not be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. In addition, before a new anti-neoplastic therapy is initiated for a patient, it is strongly recommended to perform a tumor assessment. 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 (for patients in Phase II only) to register the patient's discontinuation from study treatment.

In some circumstances patients may be allowed to continue to receive study treatment beyond disease progression as per RECIST criteria (Section 6.1.2.1). These patients will continue assessments as outlined in Section 7, and will complete the EOT visit only after permanent discontinuation of study treatment.

7.1.5 Follow-up period

7.1.5.1 Follow-up for safety evaluations

30-day follow-up

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.

Post-treatment follow-up

Patients who discontinue the study treatment (i.e. EGF816) without a radiological confirmation of disease progression (i.e. patients who discontinue due to clinical disease progression, or unacceptable toxicity, or physician or patient's decision or patient's withdrawal of consent) will continue to have follow-up tumor assessments according to the current tumor assessment schedule or as clinically indicated until radiological confirmation of disease progression by

Investigator assessment (both Phase I and II parts), or withdrawal of consent for further tumor assessments, or loss to follow-up or death. The results of follow-up tumor assessments should be documented in patient's source documents. Scans performed during the tumor follow-up period must be sent promptly to BIRC for an independent tumor assessment. Antineoplastic therapies since discontinuation of study treatment will continue to be collected.

Survival follow-up

As of amendment 4, all patients enrolled in the Phase II part will be followed for survival every 3 months until death, lost to follow-up or withdrawal of consent for survival follow-up. Patient's survival status may be collected via a phone call. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last dose of the study treatment.

7.1.5.2 Replacement policy

Phase I part

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DDS, enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. Enrollment of new patients may be considered until at least the minimum number (1 or 3) or at most the maximum number (3 or 6) of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 6.2.3.

Phase II part

Patients lost to follow-up or withdrawing consent from the study without disease progression will be considered as non-responders for the primary analysis and will not be replaced.

7.1.6 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments should be conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

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 CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Appendix 1) based on RECIST 1.1 (Eisenhauer et al 2009). 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 Contract Research Organization (CRO) designated by Novartis.

Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline imaging data for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding cytology results should be transmitted to the imaging CRO via the Cytology Form for all visits, when applicable, for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

The imaging assessment collection plans are presented in Table 7-3 and Table 7-4 for the Phase I part and Phase II part, respectively.

Table 7-3 Imaging collection plan (Phase I part)

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI with contrast enhancement (Chest and Abdomen)	Mandated	Mandated, every 8 weeks (±7 days)
Whole body bone scan	If clinically indicated	Not applicable
Brain CT or MRI	Mandated	If brain lesions at screening every 8 weeks (±7 days)
Bone X-ray, CT or MRI (bone lesions only)	If lesions on bone scan that are not visible on the chest and abdomen CT/MRI	If bone lesions at screening every 8 weeks (±7 days)
Skin color photography (skin lesions only)	Mandated if skin lesions at screening	If skin lesions at screening every 8 weeks (±7 days)
CT or MRI of other tumor sites (e.g., pelvis)	If clinically indicated	If lesions identified at screening every 8 weeks (±7 days)

For the Phase I part, the imaging data will be retrospectively collected and stored for possible independent review by an imaging CRO designated by Novartis; tumor response will be

determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Section 14.1 Appendix 1). The local investigator's assessment will be used for efficacy analysis and for treatment decision making.

Table 7-4 Imaging collection plan (Phase II part)

Procedure	Screening/Baseline	During Treatment/Follow-up
Computed tomography (CT) or magnetic resonance imaging (MRI) of CAP (Chest, Abdomen, Pelvis) with contrast enhancement	Mandated	Every 8 weeks (±7 days) until PD determined by Investigator and BIRC assessments, End of treatment (EOT) scan not required if previous CAP scan was performed within ≤28 days)
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
Whole Body Bone Scan [e.g. Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride positron emission tomography (NaF PET)]	Mandated	If clinically indicated" (Refer to Section 7.2.1.1).
Brain CT or MRI	Mandated	If brain lesions at screening every 8 weeks (±7 days)
Bone X-ray, CT or MRI (bone lesions only)	If lesions on bone scan that are not visible on the chest and abdomen CT/MRI	Every 8 weeks (±7 days)
Skin color photography (skin lesions only)	Mandated if skin lesion(s) is/are selected as target lesion(s) at baseline	Every 8 weeks (±7 days)

For the Phase II part, imaging data will be centrally collected, checked for quality, and read by BIRC according to the Novartis guideline (Section 14.1 - Appendix 1) based on RECIST 1.1.

7.2.1.1 Baseline imaging assessment

Baseline imaging assessments will be performed within 28 days prior to the first dose of study treatment (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 RECIST 1.1 (Section 14.1 - 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.

- 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.
- Brain CT or MRI with IV contrast, if clinically indicated
    - If brain lesions are documented at screening, 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.
- 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)] required at screening and if clinically indicated on study.
- Whole body bone scans is needed for Phase I if clinically indicated at screening and not required on study.
- Whole body bone scans is required for the Phase II if clinically indicated on study. If indicated, the same methodology as at screening should be used.
- Localized bone CT, MRI or X-rays for any lesions identified on the whole body bone scan, that are not visible on the chest, pelvis and abdomen CT or MRI.
- If skeletal lesions are documented at baseline, scans need to be continued following the same schedule as CT/MRI of chest and abdomen. The same methodology as at screening should be used.
- CT or MRI of other metastatic sites not captured by any of the above listed images (e.g., neck) if clinically indicated.
- If additional sites of disease are documented at screening, 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.
- Color photography for any skin lesions present, if clinically indicated.

- Color photography should be continued following the same schedule as CT/MRI of chest, abdomen and pelvis acquired 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.

Note: chest X-ray and ultrasound must not be used to measure tumor lesions.

7.2.1.2 Post-baseline imaging assessments

Imaging assessments as described in Table 7-3 (Phase I) and Table 7-4 (Phase II) 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 and Table 7-2). Imaging assessments for response evaluation will be performed every 8 weeks (±7 days) until disease progression, death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the first dose date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

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 IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document PD per RECIST 1.1 (Appendix 14.1).

All Phase I retrospective and Phase II prospective study imaging (including any off-schedule imaging studies) performed to evaluate progression or response should be submitted to the designated imaging CRO for quality control and review by the BIRC, promptly after acquisition (as applicable).

7.2.1.3 Transmission of efficacy data to BIRC

All radiological assessments will be read locally and by BIRC. The imaging assessments 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) or by a courier. 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.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessment as well as collection of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination must be performed as indicated in Table 7-1 and Table 7-2 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.

Physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

A targeted (short) physical examination will be performed according to the standards at each institution.

Information about the physical examination must be present in source documentation at the study site. Significant findings that are present prior to signing of informed consent form for the study must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent for the study must be recorded on the Adverse Events eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed as per institutional standards before dosing and as indicated in Table 7-1 and Table 7-2.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.3 Height and weight

Height (screening only) and body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 and Table 7-2.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-1 and Table 7-2.

Table 7-5 ECOG performance status

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

7.2.2.5 Laboratory evaluations

For the phase I and phase II, all laboratory parameters assessed for safety purposes will be evaluated locally, at the site. Refer to Table 7-6 for a summary of the parameters to be evaluated and the frequency of the assessments according to Table 7-1 and Table 7-2 respectively.

Local laboratory assessments may also be performed when an immediate clinical decision needs to be made. In those cases locally unscheduled testing may be performed.

Each time local laboratory results (including unscheduled laboratory assessments) are reported on the 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 central laboratory are provided to investigators in a separate [Laboratory Manual].

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, other)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Gamma-glutamyl transpeptidase (GGT) Calcium, Chloride, Magnesium, Phosphorus (screening in Phase II part only), Potassium, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting at baseline),
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose, bilirubin, ketones, leukocytes, and blood will be performed. Any clinically significant findings on dipstick will be followed up with a microscopic evaluation. (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR),
HBV and HCV	HBsAg, HBsAb, HBcAb, HBV-DNA, HCV-Ab, HCV-RNA

7.2.2.5.1 Hematology

Hematology panel outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.2 Clinical chemistry

Clinical chemistry panel outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.3 Coagulation

Coagulation panel outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.4 Urinalysis

Urinalysis panel outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.5 HBV and HCV testing

HBV tests outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

HCV tests outlined in Table 7-6 will be performed as per the assessment schedule in Table 7-1 and Table 7-2.

7.2.2.5.6 Pregnancy and assessments of fertility

For both Phase I and Phase II parts, a serum pregnancy test is required for women of childbearing potential at screening (within 72 hours) and/or at Cycle 1 Day 1 (prior to dosing) and at the end of the study treatment. During subsequent cycles, for women of childbearing potential urine pregnancy tests will be performed at day 1 of each cycle in the Phase I part, and as clinically indicated in the Phase II part.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12 lead ECGs will be performed as per the assessment schedule in Table 7-7 for Phase I patients and Table 7-8 for Phase II patients.

For all patients in Phase I, 3 sequential 12-lead ECGs must be performed during screening, at pre-dose and at 2 hr post dose (estimated Tmax) on Cycle 1 Day 1 and Cycle 2 Day 1, at pre-dose on Cycle 3 Day 1 and at EOT. Triplicate ECGs will be performed at all time-points during the trial.

Table 7-7 Central ECG collection plan for all patients (for Phase I)

Cycle	Day	Time	
Screening	-28 to -1	Anytime	Triplicate 12 Lead
1	1	Pre-dose	Triplicate 12 Lead
1	1	2 hr post dose	Triplicate 12 Lead
2	1	Pre-dose	Triplicate12 Lead
2	1	2 hr post dose	Triplicate 12 Lead
3	1	Pre-dose	Triplicate 12 Lead
EOT			Triplicate 12 Lead
Unscheduled		Anytime	Triplicate 12 Lead

All patients from the Phase II part will have an extensive ECG collection as shown in Table 7-8.

Table 7-8 Extensive ECG collection plan (for Phase II)

Cycle	Day	Time	
Screening	-28 to -1	Anytime	Triplicate 12 Lead
1	1	Pre-dose	Triplicate 12 Lead
1	1	0.5, 2, 4, 8 and 24 hr	Triplicate 12 Lead
1	15	Pre-dose	Triplicate 12 Lead
1	15	2 hr post-dose	Triplicate 12 Lead

Cycle	Day	Time	
2	1	Pre-dose	Triplicate 12 Lead
2	1	0.5, 2, 4, 8 and 24 hr	Triplicate 12 Lead
3-4	1	Pre-dose	Triplicate 12 Lead
EOT			Triplicate12 Lead
Unscheduled		Anytime	Triplicate12 Lead

Interpretation of the tracing will be made by a central ECG lab. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. New or worsened clinically significant abnormalities occurring after informed consent will be recorded in the AE eCRF page. Clinically significant abnormalities present when the patient signed informed consent at screening should be recorded on the Medical history eCRF page and discussed with Novartis prior to enrolling the patient in the study.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local ECG assessment may also be performed at any time during the study at the discretion of the investigator by a qualified physician and documented on the ECG CRF page.

All ECGs, including unscheduled triplicate safety ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review.

7.2.3 Pharmacokinetics

Serial blood samples will be collected from all patients for the analysis of EGF816 and LMI258 plasma PK. The PK analysis will be performed according to Section 10.5.3.

[redacted]

7.2.3.1 Pharmacokinetic blood sample collection and handling

PK blood samples will be collected in both Phase I and Phase II parts.

For patients treated in the Phase I part, three PK profiles will be collected on Day 1, Day 15 of Cycle 1, and Day 1 of Cycle 2. In addition, trough samples will be taken on Day 8 of Cycle 1, and Day 1 of Cycle 3 and Cycle 4 (Table 7-9).

For patients treated in the Phase II part, two PK profiles will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 in addition to several trough samples as shown in Table 7-10.

Table 7-9 Phase I part: schedule of blood sample collections for pharmacokinetics

Dose reference ID following PK sampling	Dose reference ID prior to PK sampling	Sample number	Cycle	Day	Scheduled time (hours)
1		1	1	1	Pre-dose/0 hr[a]
1		2	1	1	0.5 hr (±10 minutes)

Dose reference ID following PK sampling	Dose reference ID prior to PK sampling	Sample number	Cycle	Day	Scheduled time (hours)
1		3	1	1	1 hr (±10 minutes)
1		4	1	1	2 hr (±10 minutes)
1		5	1	1	3 hr (±15 minutes)
1		6	1	1	4 hr (±15 minutes)
1		7	1	1	6 hr (±30 minutes)
1		8	1	1	8 hr (±1 hr)
1		9	1	1	12 hr (± 1 hr) [b]
2	1	10	1	2	24 hr/pre-C1D2 dose [a]
3	102	11	1	8	Pre-C1D8 dose
4	103	12	1	15	Pre- C1D15 dose/0 hr [a]
4		13	1	15	0.5 hr (±10 minutes)
4		14	1	15	1 hr (±10 minutes)
4		15	1	15	2 hr (±10 minutes)
4		16	1	15	3 hr (±15 minutes)
4		17	1	15	4 hr (±15 minutes)
4		18	1	15	6 hr (±30 minutes)
4		19	1	15	8 hr (±1 hr)
4		20	1	15	12 hr (± 1 hr) [b]
5	4	21	1	16	24 hr/pre-C1D16 dose [a]
6	105	22	2	1	Pre-C2D1 dose/0 hr [a]
6		23	2	1	0.5 hr (±10 minutes)
6		24	2	1	1 hr (±10 minutes)
6		25	2	1	2 hr (±10 minutes)
6		26	2	1	3 hr (±15 minutes)
6		27	2	1	4 hr (±15 minutes)
6		28	2	1	6 hr (±30 minutes)
6		29	2	1	8 hr (±1 hr)
6		30	2	1	12 hr (± 1 hr) [b]
7	6	31	2	2	24 hr/pre-C2D2 dose [a]
8	107	32	3	1	pre-C3D1 dose [a]
9	108	33	4	1	pre-C4D1 dose [a]
		1001+			At the time of newly obtained biopsy on C4D1 (±3 days) and time of progression [d]
--		2001+[c]	NA	NA	Unscheduled

[a] Take samples immediately prior to the administration of EGF816

[b] Optional

[c] Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002,

[d] Time of the dose taken prior to biopsy

If biopsy is collected on Cycle 4 Day 1, no unscheduled blood PK sample needs to be collected

Table 7-10 Phase II part: schedule of blood sample collections for pharmacokinetics

Dose reference ID following PK sampling	Dose reference ID prior to PK sampling	Sample number	Cycle	Day	Scheduled time (hours)
11		101	1	1	Pre-dose/0 hr [a]
11		102	1	1	0.5 hr (±10 minutes)
11		103	1	1	1 hr (±10 minutes)
11		104	1	1	2 hr (±10 minutes)
11		105	1	1	3 hr (±15 minutes)
11		106	1	1	4 hr (±15 minutes)
11		107	1	1	6 hr (±30 minutes)
11		108	1	1	8 hr (±1 hr)
12	11	109	1	2	24 hr/pre-C1D2 dose [a]
13	120	110	1	8	Pre-C1D8 dose
14	130	111	1	15	Pre-C1D15 dose [a]
15	140	112	2	1	Pre-C2D1 dose/0 hr [a]
15		113	2	1	0.5 hr (±10 minutes)
15		114	2	1	1 hr (±10 minutes)
15		115	2	1	2 hr (±10 minutes)
15		116	2	1	3 hr (±15 minutes)
15		117	2	1	4 hr (±15 minutes)
15		118	2	1	6 hr (±30 minutes)
15		119	2	1	8 hr (±1 hr)
16	15	120	2	2	24 hr/pre-C2D2 dose [a]
17	160	121	3	1	pre-C3D1 dose [a]
18	170	122	4	1	pre-C4D1 dose [a]
--		3001+[b]	NA	NA	Unscheduled

[a] Take samples immediately prior to the administration of EGF816

[b] Unscheduled blood samples will be uniquely, sequentially numbered 3001, 3002, …

The exact date and clock times of drug administration and PK blood draw will be recorded on the appropriate eCRF. The timing of meals, before and after the dose on days when PK samples are drawn, should be recorded in the source documents. If vomiting occurs within 4 hours following EGF816 administration on the day of PK blood sampling, the clock time of vomiting should be recorded on the transmittal form, which accompanies the sample.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points, 2 mL blood will be collected into tubes containing K2 EDTA. Refer to the [EGF816X2101 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

7.2.3.2 Analytical method

EGF816 and LMI258 concentrations in human plasma will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Any results below the lower limit of quantification (LLOQ) of 1.0 ng/mL and any missing samples will be labeled accordingly.

7.2.4 Biomarkers

In this study biomarker analyses will be used to investigate the effect of the EGF816 at the molecular and cellular level [redacted] The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the [EGF816X2101 Laboratory Manual].

7.2.4.1 Biomarker assessments for Phase I part

7.2.4.1.1 Pharmacodynamic assessments in newly obtained tumor specimens (For patients enrolled before protocol amendment 5 only (For Phase I part only)

Collection of paired tumor specimens is critical to assess the pharmacodynamic effect of EGF816 on the EGFR pathway. Tumor specimens will be used to assess the phosphorylation state of pathway molecules (e.g. EGFR, AKT, ERK) by immunohistochemistry and genetic abnormalities in the EGFR signaling pathway, other pathways that may interact with the EGFR pathway, or are thought to be important in cancer. Additional markers or methods maybe utilized if indicated by new findings from the literature as well as from Novartis internal data.

7.2.4.1.2 Assessment of tumor immune infiltrates in newly obtained tumor specimens (For Phase I part only)

To assess whether treatment with EGF816 results in a change in tumor immune infiltrates, immunohistochemical analyses of immune cell markers will be performed on newly obtained tumor samples collected at screening/baseline, C4D1, C6D1 (optional) ,C8D1(optional) and EOT (optional). Additional markers or methods maybe utilized if indicated by new findings from the literature as well as from Novartis internal data.

[redacted]

Table 7-11 Biomarker sample collection plan – Phase I part

Sample type	Analysis	Collection visit schedule
Newly obtained tumor samples	Immune infiltrate assessment	Screening/baseline, Cycle 4 Day 1, Cycle 6 Day 1 (optional), Cycle 8 Day 1 (optional) and at EOT (optional)(+/- 28 days for each time point or otherwise as agreed between investigators and Novartis)
[redacted]		

7.2.4.2 Biomarker Assessments for Phase II part

7.2.4.2.1 Biomarker Assessments in Tumor

Archival or newly acquired biopsy are required when a patient enters the screening phase; archival tumor material is requested to assess markers associated with EGFR signaling, EGF816 and cancer with methods including but not limited to Next Generation Sequencing (NGS), immunohistochemistry and fluorescence in-situ hybridization. [redacted]

Table 7-12 Biomarker sample collection plan -Phase II part

Sample Type	Volume	Visit	Time point
Tumor samples			
Mandatory Newly obtained formalin-fixed biopsy or archival tumor block or slides from a formalin-fixed paraffin embedded (FFPE).	Block or minimum of 11 slides (5 microns)	Screening	Screening
Mandatory (if available) Either the remaining archival tumor block or additional 5 slides from same archival biopsy that was provided at molecular screening or the same block used to determine EGFR status locally Additional slides not required if a suitable block (newly acquired or archival) was submitted for molecular screening	Block or additional 5 slides	Cycle 1 Day 1	1Upon enrollment

Sample Type	Volume	Visit	Time point
Optional Newly obtained tumor biopsy or archival material if fresh not available at C1D1	Newly acquired biopsy or archival material, block or 3-10 slides	Cycle 1 Day 1	Pre-dose If a newly obtained tumor biopsy was submitted for screening, this biopsy is not required
	Newly acquired biopsy	EOT	Anytime
Requires separate consent within the main ICF.	Newly acquired biopsy	On treatment	Any time
Sample Type	Volume	Visit	Time point
Blood samples			

[redacted]

[redacted]

7.2.5 [For Japan only] Radiological examinations

7.2.5.1 Chest X-ray

A 2-view chest X-ray will be performed at screening, Day 15 of Cycle1, and on Day1 of Cycle 2 and thereafter. If a chest CT scan is performed, a chest X-ray can be skipped except for at screening.

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

Patients whose EGFR mutation status is known will sign the main study ICF.

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 (or 5 half-lives, whichever is longer) 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 and graded 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 respectively to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather information about any deaths (related to an Adverse Event or not) will also be collected through 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:

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

If the event worsens the event should be reported a second time in the CRF noting the start date when the event 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 (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), 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.

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's Brochure.

The adverse events of special interest to be monitored for EGF816 are diarrhea and gastrointestinal toxicities; pneumonitis/ interstitial lung disease; hepatitis B reactivation; skin adverse events including rash and mucocutaneous dryness; and dry eye disorders.

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

- Serious adverse events considered by the investigator to be possibly related to a biopsy procedure will be indicated as such in the AE eCRF.

8.2.2 Reporting

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

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

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

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

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

Follow-up information is submitted the same way as 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 Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (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 Pregnancies

Study treatment must be stopped if a patient becomes pregnant.

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 Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 Warnings and precautions

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

8.5 Data Monitoring Committee

Phase I part

A data monitoring board will not be used for the Phase I part of this study. Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose-escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first cycle of treatment, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose-escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the Bayesian logistic regression model's (with EWOC) recommendation, and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level (see Section 10.4.2).

Phase II part

This is a single arm trial (i.e. no comparator arm) and there is no apriori information as per the FDA Guidance of "situations in which safety concerns may be unusually high" or the patient population being studied are "potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity." Thus, an independent data monitoring committee will not be constituted for the Phase II part of this study.

The Novartis clinical team will review the safety data on a regular basis. A review of the safety data and assessment of futility based on the calculated Bayesian probability of success (POS) will be performed at the interim analysis by the Novartis clinical trial team and shared with the investigators in a data review meeting.

At the time of the interim analysis, the best overall response for each patient will be derived from the overall lesion response assessments performed by the BIRC . These will be used to calculate the overall response rate for the respective group and a Bayesian analysis will be performed to estimate the POS of the trial given the current data (see Section 10.7 for details).

It is envisioned that the team may make three types of recommendations at the respective interim analysis, namely:

- No safety or efficacy issues, ethical to continue the study group as planned
- POS is too small and the study group is terminated due to lack of significant activity
- Serious safety concerns precluding further treatment in study group, regardless of efficacy.

8.6 Steering Committee

Not applicable.

8.7 Blinded Independent Review Committee (BIRC)

A Blinded Independent Review Committee (BIRC) will review the Phase I and Phase II part radiographic and photographic data to determine tumor response and progression. The designated imaging CRO will be responsible for assembling and managing the BIRC. This and all other imaging procedures will be documented in an independent review charter agreed upon between Novartis and the imaging vendor before initiation of any BIRC reviews.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated 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 CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

9.3 Data collection

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

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood and tumor samples for PK and biomarkers will be collected by sites and sent to a Central laboratory for processing. The Laboratory results will be sent electronically to Novartis database as third party data. Radiological and photography data will be acquired by the sites and interpreted locally. Additionally, radiological and photography data will be transmitted by the sites to the respective vendor designated to undergo quality checks and central review. Details regarding all vendor procedures including collection and shipment of data will be described in the manual provided by the respective vendor.

PK and Biomarker (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 and Biomarker 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.

Biomarker, ECG and central laboratory data obtained by designated central laboratories will be transferred to Novartis database as third party data.

In addition, data entered into the IRT for drug assignment and patient identifiers (i.e. date of birth, gender and Patient ID) will be transferred electronically to Novartis as described in the Data Transfer Specifications for the designated IRT vendor.

If a patient enrolls on a companion sample collection study to evaluate the mechanisms of resistance, data required for the companion sample collection study are collected in the clinical trial database for the treatment protocol. A description of the data to be collected for the study of resistance is provided in the companion sample collection protocol.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel 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 investigational site staff is 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.

PK, biomarker samples, ECG, imaging and IRT data will be processed centrally and the results will be sent electronically to Novartis.

For Phase II patients, data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel.

The occurrence of any protocol violations will be determined.

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

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

10 Statistical methods and data analysis

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

Study data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements.

Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data summary statistics of mean, standard deviation, median, minimum, and maximum will be presented.

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

- **Phase I part**: Patients treated during the Phase I part (dose escalation) with the same dose level, formulation (capsule vs. tablet) and schedule of EGF816 will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group (unless otherwise specified). Subgroup analyses by mutation type and prior lines of systemic antineoplastic therapy(s) may be performed as appropriate.
- **Phase II part**: The primary analysis will be performed when patients enrolled have completed at least 6 cycles of treatment or discontinued treatment prior to that time. Any additional data for patients continuing to receive study treatment past the data cut-off date for the primary analysis will be reported in the final CSR at the end of the study.

10.1 Analysis sets

10.1.1 Phase I part

10.1.1.1 Full analysis set

The full analysis set (FAS) includes all patients who received at least one dose of EGF816. Patients will be analyzed according to the planned treatment (regimen). The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

10.1.1.2 Safety set

The Safety Set includes all patients who received at least one dose of EGF816. Patients will be analyzed according to the study treatment (regimen) they actually received.

A precise definition of "actually received" will be added in the Reporting and Analysis Plan (RAP).

10.1.1.3 Dose-determining set

The dose-determining set (DDS) consists of all patients from the safety set of phase I part who either meet the following minimum exposure criterion and have sufficient safety evaluations, during the first 28 days of dosing or discontinue earlier due to DLT. A patient is considered to have met the minimum exposure criterion if he received at least 75% of the planned doses of EGF816 in the first 28 days of dosing (e.g., 21 of the planned 28 doses on a q.d. schedule).

Patients who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for ≥ 28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements will be regarded as ineligible for the DDS and an additional patient may be recruited (see Section 7.1.4).

10.1.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of EGF816 and have at least one evaluable EGF816 PK sample. Details of PAS definition can be found in the statistical analysis plan.

10.1.2 Phase II part

10.1.2.1 Full analysis set

The full analysis set (FAS) includes all patients who received at least one dose of EGF816. The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

10.1.2.2 Per protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with the requirements of the clinical study protocol. The protocol deviations or conditions leading to exclusion from the PPS will be detailed in the statistical analysis plan.

10.1.2.3 Safety set

The Safety Set includes all patients who received at least one dose of EGF816.

10.1.2.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of EGF816 and have at least one evaluable EGF816 PK sample. Details of PAS definition can be found in the statistical analysis plan.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively by treatment group for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of EGF816 treatment as well as the dose intensity (dose received/duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be listed and summarized by means of descriptive statistics by treatment group for the Safety set.

10.3.2 Concomitant therapies

Use of concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC term by means of contingency tables by treatment group for the Safety set.

10.3.3 Compliance

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

10.4 Primary objective

Phase I part: The primary objective is to determine the MTD and or RP2D of single agent EGF816 when administered orally to adult patients with NSCLC harboring EGFR T790M mutations.

The corresponding primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle (Neuenschwander et al 2008).

Phase II part: The primary objective of the Phase II part is to estimate antitumor activity of EGF816 as measured by overall response rate (ORR) determined by Blinded Independent Review Committee (BIRC) assessment in accordance to RECIST 1.1:

- At least 40 treatment-naïve patients who have advanced NSCLC with EGFR activating mutation (e.g., L858R and/or ex19del)

10.4.1 Variable

10.4.1.1 Phase I part

The primary endpoint is the incidence of dose-limiting toxicities (DLTs) in Cycle 1. Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLT in

Cycle 1 for patients in the DDS. This probability is estimated by the model described in Section 10.4.2.

10.4.1.2 Phase II part

The primary endpoint is the overall response rate, determined as the proportion of patients in FAS experiencing a best overall response of CR or PR per RECIST 1.1 at any time on study by BIRC assessment.

Overall response rate and best overall response are based on confirmed responses only.

10.4.2 Statistical hypothesis, model and method of analysis

10.4.2.1 Phase I part

An adaptive, 2 parameter Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle will be used to make dose recommendations and estimate the MTD/ RP2D during the dose-escalation part of the study.

The dose-toxicity (DLT) relationship in each dose escalation will be described by the following logistic regression model:

$$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*), \quad \alpha>0, \beta>0 \qquad [1]$$

where $\text{logit}(\pi(d))= \ln(\pi(d)/(1- \pi(d)))$, $\pi(d)$ is the probability of a DLT at dose d, where d represents the total daily dose in capsule. Doses are rescaled as d/d* with reference dose d*= 300 mg of EGF816 as total daily dose. As a consequence α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

The Bayesian approach requires the specification of prior distributions for the model parameters. The prior distributions and the process for their derivation based on available pre-clinical data are provided in Section 14.2 Appendix 2, along with examples of hypothetical decisions that may be followed during the dose escalation.

Change in drug formulation

By amendment 07, the dose escalation decisions were already made and no additional patients were included for BLRM, hence the change in formulation doesn't impact this part of the study.

Change in dosing schedule

In the event of a change in dosing schedule, then a new BLRM will be set up. This new BLRM will have the same functional form as equation [1] and will incorporate down-weighted existing dose-escalation data in the prior distribution. For comparability, doses for the new and old models will be normalized to dose in mg per day. The process by which the prior distributions are to be derived for this updated BLRM is described in Section 14.2 Appendix 2.

Dose recommendation

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels are obtained. The results of this analysis are summarized in terms of the estimated probabilities that the true rate of DLT at each dose-level will lie within each of the following intervals:

- [0, 0.16) under-dosing
- [0.16, 0.33) targeted toxicity
- [0.33, 1.00] excessive toxicity

The overdose control criterion mandates that any dose of EGF816 for which the DLT rate has more than a 25% chance of being excessively toxic, i.e. P(DLT) is 0.33 or higher, will not be considered for the next dose cohort. The final estimate of the MTD/ RP2D will also satisfy this condition.

Details of the criteria for dose escalation and the estimation of the MTD/ RP2D are provided in Section 6.2.3.

Listing/ summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, preferred term type of adverse event, and by treatment group. The dose-determining set will be used for these summaries.

10.4.2.2 Phase II part

The primary analysis will be performed when patients enrolled have completed at least 6 cycles of treatment or discontinued treatment prior to that time. Any additional data for patients continuing to receive study treatment past the data cut-off date for the primary analysis will be reported in the final CSR at the end of the study. There will be one interim analysis for futility when approximately 20 patients have completed at least 4 cycles of treatment or discontinued treatment prior to that time.

The primary analysis will be performed using the FAS when all patients enrolled have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

The preliminary anti-tumor activity of the study treatment will be assessed using dual criteria:

- The posterior median ORR is equal to or greater than 55%
- The posterior risk of being in the unacceptable anti-tumor activity is lower than 5%.

An observed ORR $\geq$ 55% based on BIRC assessments will be considered clinically meaningful as this similar with the reported ORRs for 1st-generation EGFR TKI (gefitinib, erlotinib) and 2nd-generation EGFR TKI (afatinib) in similar setting, (Refer to Table 1-1).

The ORR < 40% will be considered as unacceptable anti-tumor activity. This is based on the ORR for carboplatin/paclitaxel-treated patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. (AstraZeneca Pharmaceuticals LP (2015)).

A Bayesian design will be used in order to estimate the ORR and to provide inferential summaries (e.g., mean, median, standard deviation, 90% credible intervals) based on the posterior distribution of ORR in the Phase II part. A minimally informative unimodal Beta distribution (Neuenschwander et al. 2008) will be used as a prior distribution. This prior distribution reflects the current uncertainty about the efficacy of EGF816. For the primary analysis, the posterior distributions of the ORR will be computed using the available data.

Additionally, the ORR and 95% exact CI will be provided.

An interim analysis for futility will be performed when approximately 20 patients have completed at least 4 cycles of treatment or discontinued treatment prior to that time. More details on the interim analysis are presented in Section 10.7.

The sample size calculation and rationale are provided in Section 10.8.

10.4.3 Handling of missing values/censoring/discontinuations

For continuing events (e.g., AEs, concomitant medication, etc.), there will be an indication within listings that the event is continuing.

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

Patients who have missing BOR will be considered as a treatment failure within the interim and final analyses of 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.

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

10.4.4 Supportive analyses

Additional supportive [redacted] analyses will be conducted to support the primary objective if appropriate and details of the analysis will be defined in the RAP.

10.5 Secondary objectives

10.5.1 Safety objectives

10.5.1.1 Analysis set and grouping for the analyses

Listings of all safety data will be provided; these will be based on the FAS. For all safety analyses, the safety set will be used. The overall observation period will be divided into three mutually exclusive periods:

1. Pre-treatment period: From the day of informed consent until the day before first dose of study medication
2. On-treatment period: From the day of first dose of study medication until 30 days after the last dose of study medication
3. Post-treatment period: Starting 31 days after last dose of study medication

All safety data will be listed. Where applicable, a flag indicating into which period observations fall will be provided. Safety summaries will contain only data collected in the On-treatment period, unless otherwise specified. For the phase I part subgroup analyses by mutation type and prior lines of systemic antineoplastic therapy(s) may be performed as appropriate.

10.5.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data

(including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group

Serious adverse events, non-serious adverse events and adverse events of special interest during the on-treatment period will be tabulated.

10.5.1.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, laboratory data will be graded accordingly. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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 by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- 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) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

[redacted]

10.5.1.4 Other safety data

ECG

The following analysis will be performed for ECG:

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

The following analysis will be performed for vital signs:

- shift table baseline to worst on-treatment result

- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.1.5 Tolerability

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

10.5.2 Efficacy objectives

CT/MRI assessments will be used for all efficacy assessments of antitumor activity on study. Best overall response (BOR), overall response rate (ORR), progression-free survival (PFS), disease control rate (DCR), duration of response (DOR) and time to response (TTR) will be defined as per RECIST v1.1 (see Section 14.1). Analyses will performed separately for data based on Investigator assessment for the Phase I part and both BIRC assessment and Investigator assessment for the Phase II part.

The analyses will be based on the FAS.

10.5.2.1 Analysis set and the grouping for analyses

The analyses of all secondary efficacy objectives will be based on FAS.

Phase I part: All secondary efficacy analyses will be summarized by treatment group. Subgroup analyses by mutation type and prior lines of systemic antineoplastic therapy(s) may be performed as appropriate.

Phase II part: All secondary efficacy analyses will be summarized for all patients.

10.5.2.2 Secondary efficacy endpoints

The secondary efficacy endpoints including:

Phase I part: Overall response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) by Investigator assessments in accordance to RECIST 1.1

Phase II part: ORR by investigator assessment, DOR, DCR, TTR, PFS by both BIRC and Investigator assessment in accordance to RECIST 1.1 and overall survival (OS).

Phase I/II secondary efficacy endpoints

Best overall response

BOR is the best response recorded from the start of the treatment until documented radiological disease progression/recurrence. However, any assessments taken more than 28 days after the last dose of study treatment will not be included in the best overall response derivation.

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

BOR will be summarized by phase and group.

Overall response rate (ORR)

ORR is defined as the proportion of patients in FAS with a best overall response of complete response (CR) or partial response (PR) per RECIST 1.1.

ORR will be estimated together with 95% confidence intervals (CIs) based on the exact binomial distribution will be presented.

Duration of response (DOR)

Among patients with a confirmed 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. A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date.

DOR will be described using Kaplan-Meier methods and including estimated median (in months) with 95% CI, 25th and 75th percentiles. Summary statistics of DOR for patients whose best response is CR or PR will be provided for groups with ≤ 5 responders.

Disease control rate (DCR)

DCR is defined as the proportion of patients in FAS with a best overall complete response (CR) or partial response (PR) or stable disease (SD) per RECIST 1.1.

DCR will be estimated together with 95% confidence intervals (CIs) based on the exact binomial distribution will be presented.

Time to response (TTR)

TTR is defined as the time between date of start of treatment until first documented response (CR or PR). For patients who did not achieve a confirmed PR or CR, their TTR will be censored.

TRR will be described using Kaplan-Meier methods and including estimated median (in months) with 95% CI, 25th and 75th percentiles. A summary statistics of TTR for patients whose best response is CR or PR will also be provided.

Progression-free survival (PFS)

PFS is defined as the time from the date of first dose of study treatment to the date of first documented disease progression per RECIST 1.1 or death due to any cause. A patient who has not progressed or died at the date of the analysis will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD.

PFS will be described using Kaplan-Meier methods and including estimated median (in months) with 95% CI, 25th and 75th percentiles.

Phase II only efficacy endpoints

Overall survival (OS)

OS is defined as the time from the date of first dose of study drug to the date of death due to any cause. OS time for patients who are alive at the analysis cut-off date or are lost to follow-up will be censored at the date of last contact. OS analysis will only be performed for phase II part of patients.

OS will be described using Kaplan-Meier methods and including estimated median (in months) with 95% CI, 25th and 75th percentiles.

10.5.3 Pharmacokinetics

The plasma samples from all patients will be assayed for EGF816 and LMI258 concentrations by Novartis or a Novartis-designated facility.

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of EGF816 and LMI258. PK parameters such as listed in Table 10-1 will be derived and reported, as appropriate. PK data generated from this study may be used in conjunction with PK data from other clinical studies for population PK analysis..

Table 10-1 Noncompartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) (amount x time x volume^{-1})
Cmax	Maximum (peak) observed plasma drug concentration (mass x volume^{-1})
Tmax	Time to reach maximum (peak) plasma drug concentration (time)
CL/F	Apparent total body clearance of drug from plasma after oral administration (volume x time^{-1})
Vz/F	Apparent volume of distribution during terminal phase after oral administration (volume)
T1/2, eff	Effective half-life calculated from Racc (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
Racc	Accumulation ratio calculated using AUCtau at steady state divided by AUCtau on C1D1

10.5.3.1 Data handling principles

All concentrations of EGF816 and LMI258 below their respective LLOQs (lower limits of quantification) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters. Any missing PK parameters will not be imputed.

10.5.3.2 Data analysis principles

10.5.3.2.1 Analysis sets

Only PK plasma concentrations with non-missing sampling date and time, and for which the last dose date and time prior to the PK sample draw are non -missing will be included in the PK analysis. Unscheduled samples are not included in any analysis, but these samples will be listed using FAS and flagged in the corresponding concentration listing.

10.5.3.2.2 Tables, figures and listings

Descriptive statistics (n, mean, standard deviation, median, geometric mean, coefficient of variation CV (%), geometric CV (%), minimum, and maximum) will be presented for EGF816 and LMI258 plasma concentrations by treatment group. Corresponding graphical presentation of the plasma concentration profiles will also be provided using the arithmetic mean (+/- SD) and geometric mean values at each scheduled time point for full PK collections. The trough concentration-time profile will also be plotted. PK parameters will be summarized as well using descriptive statistics for EGF816 and LMI258. For Tmax, median values and ranges will be given.

10.5.3.2.3 Dose proportionality and inter- and intra-individual variability

An initial assessment of dose-proportionality and steady-state attainment will be conducted Inter- and intra-individual variability in systemic exposures will be assessed.

[redacted]

[redacted]

10.7 Interim analysis

Phase I part

No formal interim analyses are planned. However, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation part, the next dose will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in Section 6.2.3.

Phase II part

A futility interim analysis (IA) will be performed when approximately 20 patients have completed at least 4 cycles or discontinued treatment prior to that time.

The decision to stop enrollment will be based on the predictive probability of success (PPS), which is the predictive probability that the observed ORR at the end of the study will reach the target 55% (i.e., the probability of a positive conclusion of the study, should the trial be conducted to the maximum planned sample size). Given the interim observed data: x responders among n patients,

PPS = Prob [Final Observed $ORR_{\text{All patients}} \geq 55\%$| x, n]

The enrollment and/or treatment will be stopped at the interim analysis if PPS < 0.10 (i.e., if less than 9 out of the first 20 patients have the best overall response of CR or PR). The criterion (number of responders) will be based on the actual number of patients in the FAS at the time of the interim analysis.

For the purpose of PPS computation, vague prior beliefs about the ORR distribution reflecting the current uncertainty about the efficacy of EGF816 in the study populationwill be summarized in prior distribution. A minimally informative Beta distribution prior (Neuenschwander et al. 2008) with prior mean equal to a clinical threshold for futility on this population (55%) will be used (beta distribution with parameters a = 1 and b = (1 – 0.55)/0.55 = 0.818). At the time of interim analysis, the posterior parameters of the beta distribution of ORR will be computed using the available data. The number of responses in the potential future patients follows a beta-binomial distribution with the same parameters. From this, the probability that the final observed ORRs exceeds a given threshold can be computed.

Table 10-2 Probability of success at the primary analysis based on various numbers of responders observed at the IA

Responders at IA out of 20 evaluable patients at IA	Probability of Success
8/20	0.04
9/20	0.14
10/20	0.33
11/20	0.57
12/20	0.79

10.8 Sample size calculation

10.8.1 Phase I part

Each cohort will consist of 1 to 6 evaluable patients in the Phase I dose-escalation part. At least six patients at the MTD/ RP2D level will be enrolled, as described in Section 6.2.3. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 21 patients are expected to be treated in the dose-escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

10.8.2 Phase II part

The operating characteristics of the statistical design are presented below with the probabilities to stop for futility at the interim analysis and to declare preliminary anti-tumor activity of the study treatment at the primary analysis (observing at least 22 responses in 40 patients) under different true ORR values (see also Table 10-3). The actual total sample size may be greater than 40. The cut-off for the number of responders needed will be determined at the time of the interim analysis based on the actual number of patients who completed up to 4 cycles of study treatment.

Table 10-3 displays the probabilities to stop for futility at the interim analysis and to declare preliminary anti-tumor activity of the study treatment at the primary analysis (observing at least 22 responses in 40 patients) under different true ORR values

Table 10-3 Operating characteristics given sample size of 40 patients and interim analysis at 20 patients

True ORR	Probability to stop for futility at IA	Success probability at primary analysis
0.40	0.596	0.038
0.45	0.414	0.129
0.50	0.252	0.309
0.55	0.131	0.553
0.60	0.057	0.780
0.65	0.020	0.923
0.70	0.005	0.982
0.75	0.001	0.998
0.80	0.000	1.000

With a sample size of 40 patients, the operating characteristics show reasonable characteristics of stopping for futility when the true ORR is below the expected rate of 55% and low probabilities of stopping for cases with ORR in the range of 55% or above. The probability of a positive conclusion at the primary analysis with 40 patients is greater than 0.55 if the true ORR is greater or equal to 55%.

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 if applicable:, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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

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 childbearing 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.

Additional consent form

Companion study will have a separate consent form covering this study. This form will be adapted for each Study based on a standard template used globally for all Studies. These

informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis 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 in a publicly accessible database e.g. such as ...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 upon study completion (i.e., LPLV), and finalization of the study report the results of this study will be either submitted for publication and/or posted in those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (...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.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to ...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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14 Appendices

14.1 Appendix 1 – 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

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 14.1.29 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical 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 14.1.27.

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.
- **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 14.1.27.

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 major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from

conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. 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 new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
- 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.
- **Physical exams**: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound**: When the primary endpoint of the study is overall response rate, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. 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 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.

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]. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and 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 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, 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.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

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[2].

[1] The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of Investigator or central review does prevail and the progression status should be confirmed later on by the review panel (or study chair).
[2] It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned
- 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**' there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- 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 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).

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 14.1.27 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 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)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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

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

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. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

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.

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 PFS2

A recent EMA guidance (EMA, 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

14.1.23 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.

14.1.24 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.

14.1.25 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 14.1.24. 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.

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

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

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.

14.1.27 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 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 non-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.

14.1.28 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 SAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.26, 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

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
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) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
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 14.1.26
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.26.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy

would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

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 SAP documentation.

14.1.29 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).

14.1.30 Study/project specific decisions

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

14.1.31 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
- 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)

Death is a reason which "*must*" lead to discontinuation of patient from trial

14.1.32 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
- Progressive disease
- Study terminated by the sponsor

14.1.33 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment 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), This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) 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 SAP 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.

14.1.34 Programming rules

The following should be used for programming of efficacy results:

14.1.35 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.

14.1.36 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 14.1.26). 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.

14.1.37 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.

14.1.38 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)'.

14.1.39 Study/project specific programming

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

14.1.40 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 14.1.26. 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.

14.1.41 References (available upon request)

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

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

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

EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man

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

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

14.2 Appendix 2 – Operating characteristics of the Bayesian logistic regression mode and hypothetical dose-escalation scenarios

14.2.1 Introduction

An adaptive Bayesian logistic regression model (with 2 parameters) guided by the escalation with overdose control principle will be used to make dose recommendations and estimate the MTD/ RP2D during the escalation part of the study. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

14.2.2 Model specifications

14.2.2.1 Statistical model for capsule formulation in qd schedule

The dose-toxicity (DLT) relationship in the escalation part of the study will be described by the following logistic regression model:

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

where $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, and $\pi_{(d)}$ is the probability of a DLT at dose d in capsule. Doses are rescaled as d/d* with reference dose d^*=300 mg of EGF816. As a consequence α is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

This study uses a weakly informative bivariate normal prior for the model parameters (log(α),log(β)) based on prior guesses (medians) from preclinical data and wide confidence intervals for the probabilities of DLT at each dose, and can be obtained as follows:

- For the purposes of tuning the prior for the model, the median DLT rate at 75 mg qd is assumed to be at 0.1%, and the median DLT rate at 750 mg qd is assumed to be at 25%. For the remaining doses, median DLT rates a priori are assumed linear in the logit-scale as a function of log-dose.
- Based on the above specified medians for the DLT rate at certain dose and wide prior confidence intervals, the optimal parameters of the bivariate normal distribution can be obtained following the procedure described by (Neuenschwander et al 2008).

All the information to derive the prior distributions for the model parameters is provided in Table 14-6. Table 14-7 summarizes the associated prior distribution of the DLT rates. The doses not meeting the overdose criteria are bold in the table, i.e. doses not eligible at the start of the study (under the prior).

Table 14-6 Prior distribution of model parameters

Parameter	Means	Standard deviations	Correlation
log(α), log(β)	-3.068,0.564	2.706,0.728	-0.817

Table 14-7 Summary of prior distribution of DLT rates

EGF816 dose (mg qd)	Prior probabilities that Pr(DLT) is in interval:					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33, 1]	Mean	SD	2.50%	50.00%	97.50%
50	0.871	0.047	0.082	0.075	0.186	0.000	0.002	0.772
75 (starting dose)	0.849	0.055	0.096	0.088	0.199	0.000	0.004	0.808
150	0.794	0.076	0.130	0.119	0.223	0.000	0.013	0.860
300	0.700	0.110	0.190	0.170	0.251	0.000	0.044	0.903
450	0.603	0.147	0.251	0.220	0.267	0.002	0.095	0.923
600	0.485	0.185	0.330	0.280	0.277	0.006	0.170	0.938
800	0.338	0.207	0.455	0.364	0.290	0.014	0.286	0.958
1000	0.237	0.197	0.566	0.439	0.297	0.024	0.398	0.975

Note: bold values indicate doses not meeting the overdose criterion (more than 25% chance of excessive toxicity) with the prior information only.

To check the performance of the model, some hypothetical dose-escalation scenarios were investigated and are summarized in Section 14.2.3.1 below. Details regarding dose recommendation are described in Section 10.4.2 of the protocol.

14.2.2.2 Statistical model for tablet formulation in qd schedule

A new BLRM will be set up for tablet formulation. This new BLRM will have the same functional form as above:

$$\text{logit}(\pi_{T(d)}) = \log(\alpha_T) + \beta_T \log(d/d^*), \quad \alpha_T>0, \beta_T>0$$

where $\text{logit}(\pi_{T(d)})= \ln (\pi_{T(d)}/(1-\pi_{T(d)}))$, and $\pi_{T(d)}$ is the probability of a DLT at dose d in tablet. Doses are rescaled as d/d* with reference dose d^*=300 mg of EGF816. As a consequence α_T is equal to the odds of toxicity at d*. Note that for a dose equal to zero, the probability of toxicity is zero.

The prior distributions for the model parameters ($\log(\alpha_T)$, $\log(\beta_T)$) are the same as those for ($\log(\alpha)$, $\log(\beta)$) in Table 14-6.

Prior to each dose-escalation meeting the available capsule dose-DLT data will be included in the likelihood with a discounted weight w:

$$w = \frac{1}{1 + 2n\tau^2/\sigma^2}$$

In this formula n is the total number of evaluable patients in the DDS of capsule formulation, σ is the "outcome standard deviation" for one observation and set to 2, and τ is the between-formulation standard deviation and set to 0.25 for moderate heterogeneity between capsule and

tablet (Neuenschwander et al. 2010). This choice of τ is based on the similar dissolution profiles of capsule and of tablet as described in Section 6.2.1.

14.2.3 Hypothetical dose-escalation scenarios

In order to show how the Bayesian model reacts, different hypothetical dose-escalation scenarios were investigated. The design should make reasonable dose-recommendations during the clinical trial based on the observed DLTs. During the study, the decision to dose escalate after completion of a given cohort and the actual dose chosen for the subsequent cohort will depend on the recommendation of the BLRM per EWOC principle and medical review of available clinical and laboratory data.

14.2.3.1 Scenarios for capsule formulation in qd schedule

Some scenarios to illustrate the dose escalation up to the fifth dose cohort are listed in Table 14-8. The maximum dose increment allowed in the scenarios did not exceed 100% as per escalation rules defined in Section 6.2.3. The recommended next dose level satisfied the EWOC principle.

Table 14-8 Hypothetical scenarios for capsule on-study decisions (cohort size: 1-6)

	Current capsule status			For next capsule cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
1	75	1	0	150	0.074	0.070	0.009
2	75	2	0	150	0.069	0.042	0.008
3	75	3	1	50	0.255	0.208	0.143
4	75	6	1	150	0.328	0.228	0.183
5	75 150	1 2	0 0	300	0.102	0.057	0.024
6	75 150	1 3	0 1	150	0.296	0.225	0.169
7	75 150 300	1 2 4	0 0 0	600	0.186	0.098	0.078
8	75 150 300	1 2 4	0 0 1	300	0.294	0.110	0.127
9	75 150 300	1 2 4	0 0 2	150	0.314	0.126	0.140

	Current capsule status			For next capsule cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
10	75 150 300	1 2 6	0 0 1	450	0.353	0.171	0.169
11	75 150 300 600	1 2 4 5	0 0 0 0	1000	0.264	0.216	0.152
12	75 150 300 600	1 2 4 5	0 0 0 1	600	0.315	0.082	0.130
13	75 150 300 600	1 2 4 5	0 0 0 2	450	0.314	0.081	0.129
14	75 150 300 600 800	1 2 4 5 4	0 0 0 0 0	1000	0.234	0.082	0.101
15	75 150 300 600 800	1 2 4 5 4	0 0 0 0 1	800	0.345	0.098	0.144
16	75 150 300 600 800	1 2 4 5 4	0 0 0 0 2	600	0.289	0.037	0.117
17	75 150 300 600 800	1 2 4 5 4	0 0 0 0 3	600	0.421	0.101	0.165

Within Table 14-8, P(Target) represents the probability that the true DLT rate for the dose lies in the target interval (16%, 33%) while P(Over) represents the probability that the true DLT rate for the dose exceeds 33%. Note, the actual number of evaluable patients per cohort is variable (see Section 6.2.3) and the recommendations during the study will depend on the number of evaluable patients at each dose level and the observed number of DLT.

For this FIH trial, in early cohort scenarios, the model is showing appropriate behaviors which are conservative but sensitive to data. Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

Similarly, Table 14-9 shows some scenarios with exactly 3 evaluable patients in each cohort.

Table 14-9 Hypothetical scenarios for capsule on-study decisions (cohort size: 3)

	Current capsule status			For next capsule cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
1	75	3	0	150	0.059	0.032	0.006
2	75	3	1	50	0.255	0.208	0.143
3	75	3	2	STOP			
4	75 150	3 3	0 0	300	0.085	0.030	0.050
5	75 150	3 3	0 1	150	0.280	0.130	0.128
6	75 150	3 3	0 2	75	0.358	0.206	0.184
7	75 150 300	3 3 3	0 0 0	600	0.193	0.103	0.080
8	75 150 300	3 3 3	0 0 1	300	0.287	0.103	0.124
9	75 150 300	3 3 3	0 0 2	150	0.308	0.085	0.127
10	75 150 150	3 3 3	0 1 0	300	0.352	0.200	0.182
11	75 150 150	3 3 3	0 1 1	150	0.427	0.199	0.201
12	75 150 150	3 3 3	0 1 2	75	0.424	0.174	0.191

	Current capsule status			For next capsule cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
13	75 150 75	3 3 3	0 2 0	75	0.304	0.071	0.123
14	75 150 75	3 3 3	0 2 1	50	0.400	0.144	0.173
15	75 150 75	3 3 3	0 2 2	STOP			
16	75 50	3 3	1 0	75	0.265	0.101	0.111
17	75 50	3 3	1 1	STOP			
18	75 50 75	3 3 3	1 0 0	150	0.327	0.134	0.147
19	75 50 75	3 3 3	1 0 1	75	0.420	0.166	0.186
20	75 50 75	3 3 3	1 0 2	STOP			
21	75 50 75 150	3 3 3 3	1 0 0 0	300	0.376	0.223	0.196
22	75 50 75 150	3 3 3 3	1 0 0 1	150	0.458	0.188	0.204
23	75 50 75 150	3 3 3 3	1 0 0 2	75	0.456	0.125	0.182

14.2.3.2 Scenarios for tablet formulation in qd schedule

The dose-escalation scenarios for tablet formulation will depend on the available capsule dose-DLT data. Three hypothetical capsule datasets are considered (Table 14-10).

Table 14-10 Hypothetical capsule dose-DLT datasets prior to the first tablet dose-escalation meeting

Capsule dataset	75mg		150mg		300mg		Dose for next capsule cohort	Tablet starting dose
	Npat	Ntox	Npat	Ntox	Npat	Ntox		
1	3	0	3	0	3	0	600mg	300mg
2	3	0	3	0	3	1	300mg	300mg
3	3	0	3	0	3	2	150mg	150mg

Assuming no further capsule data are available, some scenarios to illustrate the tablet dose escalation up to two cohorts based on specific hypothetical capsule datasets are listed in Table 14-11 through Table 14-13. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2. The maximum dose increments allowed in the scenarios do not exceed 100% as per escalation rules defined in Section 6.2.3. The recommended next dose levels satisfy the EWOC principle and other rules specified in Section 6.2.3.2.

Table 14-11 Hypothetical scenarios for tablet on-study decisions (cohort size: 3) using hypothetical capsule dataset 1

Scenario	Current tablet status			For next tablet cohort			
	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
1	300	3	0	600	0.181	0.080	0.075
2	300	3	1	450	0.354	0.185	0.173
3	300	3	2	150	0.232	0.040	0.096
4	300 600	3 3	0 0	800	0.232	0.121	0.105
5	300 600	3 3	0 1	600	0.341	0.145	0.156
6	300 600	3 3	0 2	450	0.350	0.120	0.151
7	300 450	3 3	1 0	600	0.381	0.184	0.182
8	300 450	3 3	1 1	450	0.460	0.232	0.224
9	300 450	3 3	1 2	300	0.479	0.170	0.202
10	300 150	3 3	2 0	300	0.428	0.142	0.181
11	300 150	3 3	2 1	150	0.382	0.072	0.148
12	300 150	3 3	2 2	75	0.320	0.054	0.128

Table 14-12 Hypothetical scenarios for tablet on-study decisions (cohort size: 3) using hypothetical capsule dataset 2

	Current tablet status			For next tablet cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
1	300	3	0	450	0.316	0.126	0.140
2	300	3	1	300	0.412	0.176	0.187
3	300	3	2	150	0.363	0.112	0.152
4	300 450	3 3	0 0	600	0.335	0.141	0.152
5	300 450	3 3	0 1	450	0.438	0.184	0.197
6	300 450	3 3	0 2	300	0.446	0.137	0.184
7	300 300	3 3	1 0	450	0.454	0.249	0.229
8	300 300	3 3	1 1	300	0.497	0.224	0.225
9	300 300	3 3	1 2	150	0.409	0.092	0.160
10	300 150	3 3	2 0	150	0.289	0.038	0.116
11	300 150	3 3	2 1	150	0.492	0.151	0.198
12	300 150	3 3	2 2	75	0.414	0.105	0.165

Table 14-13 Hypothetical scenarios for tablet on-study decisions (cohort size: 3) using hypothetical capsule dataset 3

	Current tablet status			For next tablet cohort			
Scenario	EGF816 dose (mg qd)	Npat	Ntox	EGF816 dose (mg qd)	P(Target)	P(Over)	Median DLT rate
1	150	3	0	300	0.398	0.199	0.193
2	150	3	1	150	0.424	0.158	0.183
3	150	3	2	75	0.393	0.135	0.168
4	150 300	3 3	0 0	300	0.337	0.081	0.137
5	150 300	3 3	0 1	150	0.251	0.029	0.103
6	150 300	3 3	0 2	150	0.419	0.095	0.164
7	150 150	3 3	1 0	150	0.356	0.060	0.139
8	150 150	3 3	1 1	150	0.520	0.194	0.220
9	150 150	3 3	1 2	75	0.445	0.119	0.177
10	150 75	3 3	2 0	150	0.513	0.248	0.240
11	150 75	3 3	2 1	75	0.496	0.177	0.209
12	150 75	3 3	2 2	50	0.492	0.236	0.230

Using hypothetical capsule dataset 1 the model results in Table 14-11 are in agreement with clinical sense and decision making process, i.e. allow dose escalation, stay at the same dose, and dose de-escalation when no, 1 and 2 DLTs are observed, respectively.

Using hypothetical capsule dataset 2 the model results in Table 14-12 have the same behaviors, except for Scenario 10, where the model does not allow dose escalation after observing no DLTs in the second cohort at 150mg. This is due to already 2 DLTs in the first cohort at 300mg.

Using hypothetical capsule dataset 3 the model results in Table 14-13 are more conservative and generally do not allow dose escalation even without observing DLTs, except for Scenario 1. This is due to 2 DLTs at 300mg in the hypothetical capsule dataset.

Overall, the model is showing appropriate behaviors, in agreement with clinical sense and decision making process. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

14.2.4 References

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Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol; 25(31): 4982-6.

14.3 Appendix 3- Permitted Concomitant Medications requiring caution

Table 14-14 Permitted concomitant medications requiring caution

Mechanism of interaction	Drug name
Moderate CYP3A4 inhibitor	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), asafoetida resin (Ferula asafoetida), verapamil
Moderate CYP3A4 inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, lopinavir, modafinil, nafcillin, telotristat, thioridazine
BCRP substrate	atorvastatin daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sulfasalazine, sofosbuvir, topotecan, tenofovir, topotecan, venetoclax
MATE substrate	acyclovir, cephalexin, cimetidine, ganciclovir, fexofenadine, glycopyrronium, metformin, pindolol, pilsicainide, procainamide, ranitidine, topotecan, varenicline, ,
Potent P-gp inhibitor	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clopidrogel, cremophor EL and RH40, curcumin, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, fluvoxamine, fostamatinib, ginkgo (Ginkgo biloba), green tea, isavuconazole, ivacaftor, lapatinib, lopinavir, milk thistle (silymarin, silibinin), mirabegron, nifedipine, nitrendipine, paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rolapitant, saquinavir, Schisandra chinensis extract (wuweizi), simeprevir, survorexant, talinolol, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, vandetanib, velpatasvir, verapamil, voclosporin, vorapaxar
Source: Adapted Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials PK Sciences Internal Memorandum (release date: Jan 2018) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. Please note that this list may not be exhaustive. For the latest information, please refer to the above mentioned database.	

14.4 Appendix 4 - Prohibited Concomitant Medications

Table 14-15 Prohibited concomitant medications

Mechanism of interaction	Drug name
Strong CYP3A4 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, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Strong CYP3A4 inducer	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (Hypericum perforatum)
Live vaccines	e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines
NTI: narrow therapeutic index Source: Adapted from Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials PK Sciences Internal Memorandum (release date: Jan 2018) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. Please note that this list may not be exhaustive. For the latest information, please refer to the above mentioned database.	