NOVARTIS

Clinical Development

EGF816/nazartinib

CEGF816X2101 / NCT02108964

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

Statistical Analysis Plan (SAP)

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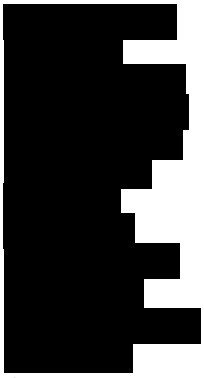
Document type:	SAP Documentation
Document status:	Amendment 3.0
Release date:	14-Jun-2018
Number of pages:	54

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-Aug-2016	Prior to DB lock	Creation of final version	N/A - First version	NA
14-Jul-2017		Addition of phase II and update as per protocol amendment version 6	Amendment 1.0	Entire document
27-Apr-18		Changes due to data availability, feasibility, and project level interest	Amendment 2.0	Section 2.1.1: Efficacy population for phase I was specified Section 2.2.1: subgroup analysis plan was updated to include specification for brain mets Section 2.3: brain and bone grouping for disease history were added Section 2.5.4: analyses for per protocol set was deleted as total number of patients are small Section 2.8.1: Rash subgroup analysis was added. Section 2.9: exposure endpoint was updated and PK covariate alaysis was removed Section 2.10.1: PK endpoint was updated

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.10.3: PK-efficacy analyses was deleted as this will be done in a separate report Section 2.10.4: PK-safety analyses was updated as some of analyses will be done in a separate report  Section 5.3: lab values with special character derivation rules were added
14 –Jun-2018		Change due to clarification	Amendment 3.0	Imputation rules for missing death dates lab parameters were updated in appendix. Definition of trough sample and steady state were added in section 2.2 Adverse event special interest grouping flag in the data was added in section 2.8.1.2

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BCS	Biopharmaceutics Classification System
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CI	Confidence Interval
Cmax	Maximum plasma concentration after a single dose
CR	Complete Response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DDS	Dose Determining Set
DLT	Dose-Limiting Toxicity
DOR	Duration Of Response
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
EGF	Epidermal growth factor
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EOT	End of Treatment
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	[redacted] Progressive disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
Tmax	Peak plasma concentration
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data that will be presented in the Clinical Study Report (CSR) of study CEGF816X2101, a phase I/II, multicenter, open-label study of EGFRmut–TKI EGF816, administered orally in adult patients with EGFRmut solid malignancies. This SAP will cover the primary and final CSR(s) where applicable regardless of study phases.

The content of this SAP is based on protocol CEGF816X2101 amendment 6.0. All decisions regarding analyses as defined in the SAP document, have been made prior to database lock of the study data.

At the time of the finalization of the SAP, the following versions of study documents referred to were in place:

- CEGF816X2101 Study specification document (SSD): version 15.0 dated 16-Apr-2018
- Oncology Guidance for Safety Analyses Final V1.0 (09-Jun-2016)
- Oncology Standard Outputs: Oncology safety TFLs v3.1 (03-Aug-2017), OSO General rules TFL3.0 (17-Jun-2016), Oncology TFLs for CSR v2.0 03Jul2012_reformatted, Oncology TFLs for CP v3.1 (11-Jul-2017), [redacted]

1.1 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 (dose-expansion). Oral EGF816 will be administered once daily on a continuous schedule until subject experiences unacceptable toxicity, progressive disease (PD), treatment is discontinued at the discretion of the investigator, subject 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 subject wishes to continue with the study treatment. A treatment cycle is defined as 28 days.

Phase I part

In the Phase I part, subjects must have locally advanced (stage IIIB) or metastatic (stage IV) NSCLC harboring specific EGFR mutations. An adaptive Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) will guide the dose-escalation to determine the maximum tolerable dose (MTD) or recommended phase 2 dose (RP2D). Before the MTD or RP2D can be declared for the study, at least 21 subjects should have been treated, with at least six subjects treated at the MTD or RP2D.

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 treatment group in the dose-escalation part, the next dose will be chosen depending on the observed data.

Phase II part

The Phase II part will start when the RP2D in tablet formulation has been identified. Subjects with locally advanced or metastatic NSCLC harboring specific EGFR mutations will be enrolled.

This is a single-arm Phase II, multi-center study evaluating safety and efficacy of EGF816 in subjects with locally advanced or metastatic NSCLC harboring specific EGFR mutations and must be naïve from any line of systemic antineoplastic therapy in the advanced setting (Note: Subjects who have failed one cycle of systemic antineoplastic therapy in the advanced setting are allowed). Approximately 40 subjects will be enrolled in the phase II part.

The interim analysis will be performed when approximately 20 subjects have completed at least 4 cycles of treatment or discontinued treatment prior to that time from phase II.

Phase I/II part

The primary analysis will be performed when all subjects from both phases enrolled have completed at least 6 cycles of treatment or discontinued treatment prior to that time. The final analysis will be performed at the end of the study defined in the protocol section 4.3.

1.2 Study objectives and endpoints

Objectives and related endpoints for phase I and II parts are described respectively in Table 1-1 and Table 1-2 below:

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

Objective	Endpoint
Primary	
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
Secondary	
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
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*
To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258	Plasma concentration vs. time profiles, plasma PK parameters
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
[redacted]	[redacted]

[redacted]

Table 1-2 Objectives and related endpoints (Phase II part)

Objective	Endpoint
Primary	
To investigate the antitumor activity of EGF816	Overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment in accordance with Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
Secondary	
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
To evaluate ORR	ORR by Investigator assessment in accordance with RECIST 1.1
To evaluate BIRC-assessed 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 with RECIST 1.1: DOR, DCR, PFS and TTR*
To evaluate investigator-assessed DOR, DCR, PFS and TTR	The following endpoints will be evaluated by Investigator assessment in accordance with RECIST 1.1: DOR, DCR, PFS and TTR
To evaluate overall survival (OS)	OS
To characterize the pharmacokinetics (PK) properties of EGF816 and metabolite LMI258	Plasma concentration vs. time profiles, and plasma PK parameters as appropriate
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4 or above, and for Bayesian modeling, R version 2.13.2 and WinBUGS version 1.4.3 (or newer compatible version). PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.2 (or newer compatible version).

Data from participating centers in this study protocol will be combined, so that an adequate number of Subjects will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) [redacted] measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

A treatment group is defined by the dose level of EGF816, formulation (capsule or tablet) and by phase.

For summaries and figures, subjects treated with the same dose of capsule or tablet are pooled together, and then sorted by dose and phase, unless otherwise specified. This tablet and capsule data pooling is conditioning on the results from tablet and capsule PK comparison described in section 2.9.

For listings, the ordering of treatment group is sorted first by formulation (capsule or tablet) then by dose unless otherwise specified..

Data included in the analysis

The analysis cut-off date for the interim (only for phase II) will be established after approximately 20 subjects have completed at least 4 cycles, and for primary analyses of study data analysis cut-off date will be when all enrolled subjects have completed at least 6 cycles of treatment or have discontinued study, respectively.

The final analysis will be performed at the end of the study as defined in the protocol section 4.3.

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

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

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis and no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to EGF816 only. The term investigational treatment may also be referred to as ***study treatment (=study drug)*** which is used throughout this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) eCRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Study day

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

The study day is defined as:

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

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

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

Time unit

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

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment unless otherwise stated under the related assessment section.

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

For safety parameters (e.g ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected, then the last value should be considered as baseline.

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

On-treatment assessment/event and observation periods

For On-treatment assessment/event reporting, the overall observation period will be divided into three mutually exclusive segments:

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

Note: If a clear assignment to the pre-, on-, or post-treatment period cannot be made, e.g., in case of specific incomplete dates, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data, which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize ECOG, PK, vital signs, ECG, lab data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Last contact date

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
- Tumor (RECIST) assessment date - For non-RECIST studies, any specific efficacy assessment date if available	Evaluation is marked as ‘done’.
Laboratory/PK/[redacted] collection dates	Sample collection marked as ‘done’.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status

Source data	Conditions
Start/End dates of AE	Non-missing verbatim term

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

The last contact date will be used for censoring of subjects in the analysis of overall survival.

Efficacy analysis for Phase I

For the efficacy reporting including tables, figures, and listings, analyses will be done for subjects that are EGFR T790M+ and did not receive prior third generation of TKI therapies.

2.2 Analysis sets

For each analysis set, outputs will be presented as follows unless otherwise specified:

Tables and figures based on the Full analysis set, Safety set and Per-protocol set are presented for all subjects and by treatment group and phase.

Tables and figures based on Dose-determining set are presented by treatment (tablet and capsule data are not combined).

Tables and figures based on the Pharmacokinetic analysis set are presented by actual treatment received.

All listings are presented by treatment group.

Full analysis set (FAS)

The FAS includes all subjects who received at least one dose of EGF816. Subjects will be analyzed according to the planned treatment group. The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

Safety set

The Safety Set includes all subjects who received at least one dose of EGF816. Subjects will be analyzed according to the study treatment group they actually received, which is defined as:

a. The first treatment assigned if it was received at least once during cycle 1 (the first 28 days of dosing);
b. Or the first study treatment received if the first treatment assigned was never received.

Dose-determining set (DDS):

The DDS consists of all subjects 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 have experienced a DLT during cycle 1. This constitutes an evaluable

subject for the determination of MTD. A subject 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). Subjects 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. Subjects who do not meet these minimum exposure criteria and safety evaluation requirements will be regarded as non-evaluable for the DDS.

Per-Protocol Set (phase II)

The Per-Protocol Set (PPS) consists of a subset of the phase II patients in the FAS who have an adequate tumor assessment at baseline and have a follow-up tumor assessment > 7 weeks after starting treatment (unless PD is observed before that time) and compliant with the requirements of the clinical study protocol. Protocol deviations leading to exclusion from the PPS are detailed in Table 2-2.

Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) consists of all subjects who provide at least one evaluable PK concentration. For a concentration to be evaluable, subjects are required to:

- take at least one dose of EGF816
- take the same dose of EGF816 for at least 5 consecutive days prior to sampling on or after cycle 1 day 15
- do not vomit within 4 hours after the dosing of EGF816 prior to sampling;
- for trough samples, have the sample collected 20 to 28 hrs. after the last dose administration and before the next dose administration (trough sample: predose samples after dose, steady state: any samples collected after Cycle 1 Day 8)

The Full Pharmacokinetic analysis set (Full PAS):

Full PAS includes all PAS subjects who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatment doses
- Subject provides at least one PK parameter of AUCtau or Cmax on either Cycle 1 Day 1, Cycle 1 Day 15 (phase I only) or Cycle 2 Day 1

Only PK parameters and concentrations, which are not flagged for exclusion programmatically or by the pharmacokineticist (e.g. due to conmeds, high concentration despite dose modification, etc.), will be used for figures and summaries. All values will be listed with excluded values flagged in the listings.

Subject Classification:

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

Table 2-2 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent (INCL01)	Not meeting FAS definition in Section 2.2 Not evaluable for efficacy: subjects who are not ongoing with study treatment and have no post-baseline response assessment
Safety set	No written inform consent (INCL01)	Not meeting Safety set definition in Section 2.2
DDS	No written inform consent (INCL01)	Not meeting DDS definition in Section 2.2
PAS/Full PAS	No written inform consent (INCL01). strong inhibitors or inducers of CYP3A4/5 taken within 1 week prior to the start of EGF816 treatment and for duration of study. (EXCL26) enzyme-inducing anticonvulsant taken within 1 week prior to the start of EGF816 treatment and for duration of study. (EXCL29)	Not meeting PAS/Full PAS definition in Section 2.2
PPS	No written inform consent (INCL01). Patient (male or female) < 18 years of age. (INCL02) [For Japan only: if written consent is not otained from the patient and his/her legal representative if he/she is under 20 years] (INCL03) Patient does not 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. (INCL04) Patient does not have controlled brain metastases as described in protocol. (INCL05) Patient has an ECOG performance status > 1 (INCL07)	Not meeting PPS definition in Section 2.2

	Patient does not have at least one measurable lesion according based on Investigator assessment according to RECIST 1.1. (INCL08) Patients must have EGFR activating mutation (e.g., L858R and/or ex19del or other EGFR mutations such as G719X and L861Q also considered activating/sensitizing mutations) as determined by a local laboratory. (INCL13) Treatment naive patients, who have locally advanced or metastatic NSCLC, 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. (INCL14) Patient received an antineoplastic therapy while receiving study treatment. (COMD01) The brain CT/MRI is not available or was not performed at baseline.(PROC04)	

Withdrawal of Informed Consent

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

[redacted]

2.2.1 Subgroup of interest

The subgroup analyses for efficacy endpoints will be done for following subgroups. The minimum number of subjects required in each subgroup is subject to change at the time of reporting.

1) the subjects with brain mets at baseline: for phase I, the analysis will be done for the subjects that are EGFR T790M+ and did not receive prior third generation TKI therapies

Derivation rule for T790M+ and 3rd generation TKI for phase I

Exclude subjects with the 3rd generation EGFR TKI are “AZD9291”, “Osimertinib”, “Tagrisso”.

Subjects may have both local and central assessments avaialble. Unless central assessments are not avialble, central assessments will be prioritized for the analysis. Central assessments can be identified using the data load flag (DATLDFL) = “LOADED” and [redacted] vendor name (B1NAM) = ”NAVIGATE” for phase I. Data from the “FOUNDATION MEDICINE” (B1NAM =”FOUNDATION MEDICINE”) will not be included as assessments from this lab were considered not accurate for phase I.

The following criteria are used to select relevant records from [redacted] panel, B1 domain:

1. B1CAT = MOLECULAR
2. B1SCAT = MUTATION
3. B1TEST not equal INTERPRETATION
   Note: It would be “GENETIC CHANGE CODED” or “GENETIC CHANGE OTHER” for local assessment and “GENETIC CHANGE ENTERED” for central assessment.
4. B1ORRES = T790M+
5. “Subject Identifier for the Study” matches with patients who have been treated, i.e. drop cases of screen failure.

Patients with brain metastasis

Additionally, the listing and summary of lesion assessments for brain metastases (target lesion, non-target lesion, and new lesion) are to be generated. Brain metastasis is identified by searching lesion location containing one of the following values as in Table 2-2:

Table 2-2 Brain lesion location and metastatic sites and analyses

Brain group search	Lesion location (ZILOC in ZI panel) at “baseline”	Metastatic Sites (MTSI in ZC panel)
	"BRAIN", "CEREBELLUM", "CNS - NOT OTHERWISE SPECIFIED", "CNS: SUPRATENTORIAL", "LEPTOMENINGEAL", "CNS: INFRATENTORIAL", "BRAIN STEM", "CEREBRAL CORTEX", "PITUITARY", "WHOLE BRAIN", "FRONTAL", "PARIETAL", "OCCIPITAL", "TEMPORAL", "THALAMUS", "PONS",	Same for ZI panel

Brain group search	Lesion location (ZILOC in ZI panel) at “baseline”	Metastatic Sites (MTSI in ZC panel)
	"CORPUS CALLOSUM", "SPINAL CORD", “CEREBRUM"	
Analysis	Analysis based on ZI - Analysis of brain lesion presenting responses on target lesions and non-target lesions - Best overall response - PFS - DOR - Waterfall plot For assessment by investigator, identification of brain metastasis at baseline will be done using investigator review. For assessment by BIRC, identification of brain metastasis at baseline will be done using BIRC review for ZILOC using imaging vendor (imgvnd in ZI panel), where missing information of vendor will be considered as local.	Analysis based on ZC - Disease history

The summary tables and figures for ORR, PFS as well as waterfall plot of tumor size for these subgroups will be generated (see section 2.5.4). Responses on the brain lesions also be summarized for BIRC review as well as investigator assessment.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: <65, 65-85, >=85, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]^2) using weight at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, time since initial diagnosis of primary site, time

since first recurrence/progression, time since most recent relapse/progression, tumor histology/cytology, histological grade, stage at initial diagnosis, stage at time of study entry. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page . Brain and bone metastatic sites are grouped to summarized for presence/absence (refer Table 2-2 for brain grouping). Bone groupings will be done by searching the word conatining 'bone' from the metastatic sites.

Medical history

Medical history and ongoing conditions entered on eCRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment group. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline including childbearing potential will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened subjects, as well as for the FAS. The number (%) of subjects included in the FAS will be presented. The number (%) of screened and not-treated subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS subjects):

The following will be tabulated:

- Number (%) of subjects who are still on-treatment (based on non-completion of the 'End of Treatment disposition' page not completed),
- Number (%) of subjects who discontinued the study treatment phase (based on the 'End of Treatment disposition' page),
- Primary reasons for study treatment discontinuation (based on the 'End of Treatment disposition' page),
- Number (%) of subjects who did not enter the post-treatment follow-up
- Number (%) of subjects who have entered the post-treatment follow-up and are still ongoing at the time of the data cut-off date for the analysis (based on the 'End of Treatment Phase disposition' page);
- Number (%) of subjects who have discontinued from the post-treatment follow-up (based on the End of Post-treatment follow-up phase disposition page);
- Primary reasons for discontinuation from the post-treatment follow-up (based on End of Post-treatment follow-up phase disposition page);

- Number (%) of subjects who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page, only for phase II).
- Number (%) of subjects who entered the survival follow-up and are ongoing (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page and the 'Survival information' page)
- Number (%) of subjects who entered the survival follow-up and discontinued (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page and the 'Survival information' or 'Death' page)

Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan, DHP) for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated. All protocol deviations will be listed.

Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.3) will be summarized.

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

2.4.1 Study treatment / compliance

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

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

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

Duration of exposure to study treatment

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

Summary of duration of exposure to study treatment will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using time units weeks, respectively. The following time intervals will be presented: <=4, 4-8, 8-12, 12-16, 16-24, 24-32, 32-52, >52 weeks.

Cumulative dose

Cumulative dose (unit of g) of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for the study treatment.

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

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

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the treatment period and the planned cumulative dose is the planned starting dose summed over the same treatment period.

Dose intensity and relative dose intensity

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

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

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

Planned dose intensity (PDI) is defined as follows:

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

Relative dose intensity (RDI) is defined as follows:

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

DI and RDI will be summarized.

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

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

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

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

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

reductions will be derived programmatically based on the change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), setting (e.g. adjuvant, metastatic, etc.) also by lowest ATC class, preferred term and treatment group.

Summaries will include for medications, total number of regimens (where a regimen can comprise more than one medication), setting at last medication (last medication is defined based on the last end date of all prior regimen components), number of subjects who received/did not receive prior EGFR TKI, number of subjects for whom EGFR TKI is/is not the last regimen prior to start of study, number of patients who received treatment in adjuvant setting, number of patients who received treatment in neoadjuvant setting, relapse within 12 months from the end of adjuvant/neoadjuvant therapy, relapse more than 12 months after the end of adjuvant/neoadjuvant therapy.For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.
Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term (medication only) by means of frequency counts and percentages using FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using

frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study drug but no later than 30 days after start of last dose of study drug and
2. Medications starting prior to start of study drug and continuing after the start of study drug.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the 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 subjects with NSCLC harboring EGFR T790M mutations. The corresponding primary analysis is based on an adaptive BLRM guided by the EWOC criteria (Neuenschwander, et al. 2008; Neuenschwander, et al. 2014) using the methodology described in detail in Section 2.5.2.1.

At the end of this study, the final recommended doses for future development will be based on considerations of the MTD/RP2D estimated by the BLRM, and on an overall clinical assessment of all available safety, tolerability, PK [redacted] data from all cycles at all different dose levels tested, in both parts of the trial. If it is determined that treatment at doses lower than the MTDs established during the dose escalation of the trial are better tolerated, and have a better [redacted] or efficacy profile based on clinical considerations, then those doses may be recommended and used in further development.

Phase II part

The primary objective is to demonstrate the antitumor activity of EGF816 as measured by ORR by BIRC assessments in subjects with EGFRmut solid malignancies.

2.5.1 Primary endpoint

Phase I part

Incidence of dose-limiting toxicity (DLT) during the first cycle (28 days) of dosing.

Phase II part

The primary endpoint is the overall response rate, defined as the proportion of subjects in FAS experiencing a best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST 1.1(see Appendix 14.1 of the study protocol) by BIRC assessment.

ORR will be calculated based on the FAS using BIRC review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR.

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

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Phase I part

An adaptive, 2 parameter BLRM guided by the EWOC 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 protocol [Section 14.2 Appendix 2], along with examples of hypothetical decisions that may be followed during the dose escalation.

Change in drug formulation

A new BLRM will be set up for tablet. This new BLRM will have the same functional form as equation [1] and will incorporate down-weighted existing dose escalation from the capsule formulation. The down-weighting process is described in protocol [Section 14.2 Appendix 2].

Dose recommendation

After each treatment group of subjects, 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 treatment group. 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 protocol Section 6.2.3.

Listing/summary of DLTs

DLTs will be listed and their incidence summarized by primary system organ class, preferred term and treatment group. The posterior distributions at applied and selected provisional doses will be summarized and depicted. The dose-determining set will be used for these summaries and listing.

2.5.2.2 Phase II part

The primary analysis will be performed using the FAS when all subjects 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 ≥ 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 (e.g. afatinib) in similar setting, (Refer to protocol Table 1-1).

The ORR < 40% will be considered as unacceptable anti-tumor activity. This is based on the ORR for carboplatin/paclitaxel-treated subjects 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.

2.5.3 Handling of missing values/censoring/discontinuations

Phase I part

As specified in protocol [Section 7.1.4.2], if a subject is considered as non-evaluable for the DDS, enrollment of a new subject to the current treatment group will be considered if there is less than the required number of evaluable subjects.

Phase II part

Subjects with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR.

For the computation of ORR, these subjects will be included in the FAS and will be counted as 'failures'.
Other missing data will simply be noted as missing on appropriate tables/listings.

2.5.4 Supportive analyses

Subgroup analysis for the primary end point

The primary endpoint of ORR will be summarized for the subgroups specified in Section 2.1 based on the primary analysis source (BIRC) and local investigator's assessment, and use the same conventions as for the primary analysis. (see section 2.5.2)
In addition, waterfall plot to depict the anti-tumor activity and PFS by BIRC and local investigator's assessment are also be presented (see section 2.7.2)

For each of the subgroups, the proportion of subjects with overall response will be summarized. The minimum number of subjects required to each subgroup is subject to change at the time of reporting.

Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of treatment effect.

Reasons for "Unknown" BOR

Subjects with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early
- PD too late

Note 1: A SD is considered as "SD too early"' if the SD is documented within first 7 weeks after treatment start date.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 17 weeks after treatment start date with no qualifying CR, PR or SD in between.

Note 3: Special (and rare) cases where BOR is "unknown" due to both too early SD and too late PD will be classified as "SD too early".

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

Phase I part

The secondary efficacy objective is to evaluate 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 with RECIST 1.1.

Phase II part

The secondary objective is to evaluate ORR by investigator assessment, DOR, DCR, TTR, PFS by both BIRC and Investigator assessment in accordance with RECIST 1.1 and overall survival (OS).

CT/MRI assessments will be used for all efficacy assessments of antitumor activity on study. BOR, ORR, DCR, TTR, DOR and PFS will be defined as per RECIST v1.1 (protocol [Section 14.1]) and summarized.

2.7.1 Secondary efficacy endpoints

Phase I/II secondary efficacy endpoints

Overall response rate (ORR)

ORR as defined in primary endpoint will be estimated together with 95% confidence intervals (CIs) based on the exact binomial distribution.

Duration of response (DOR)

Among subjects with a confirmed PR or CR per RECIST 1.1, DOR is defined as the time from first documented response of PR or CR (i.e., the start date of response, not the date when response was confirmed), to the date of first documented disease progression or death due to any cause. A subject who has not progressed or died at the cut-off date 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.

Disease control rate (DCR)

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

Time to response (TTR)

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

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for subjects who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other subjects.

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 subject who has not progressed or died at the cut-off date 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.

Phase II part only

Overall survival (OS)

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

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 BOR/ORR/DCR

Phase I/II part

A summary table of investigator assessment will be presented with count and percentage of each BOR category (CR, PR, SD, PD, Unknown), point estimate and the 95% confidence interval (CI) based on the exact binomial distribution for ORR and DCR. A listing will be presented with overall responses at all assessment timepoints, with percentage change from nadir or baseline, and BOR per subject.

Phase II part only

An assessment of the concordance between BIRC assessment and local investigator's assessment of the Best Overall Response for each subject will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both Independent Reviewer and Investigator Assessments): Percent Agreement = (Number of matched responders + Number of matched non-responders) / total number of subjects assessed.

2.7.2.2 TTR/DOR/PFS/OS

Phase I/II part

TTR, DOR and PFS by investigator assessment will be estimated using Kaplan-Meier methods, only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case. For each endpoint a figure for all subjects across treatment groups will be presented. A summary table with estimated median (in months), 25^{th} and 75^{th} percentiles with corresponding 95% CIs will be presented.

Date of PD, last date free of PD, date of death, principle cause of death and last date know alive for all subjects will be listed.

Phase II part only

For the Phase II part, the Kaplan-Meier plots for PFS (BIRC) will be produced. The Kaplan-Meier plots for DOR and TTR (BIRC) will also be produced and the median DOR/TTR will be estimated.

The survival distribution of OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians intervals will be presented for each treatment group.

2.7.2.3 Waterfall plot to depict anti-tumor activity

Waterfall plot will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each subject. Only subjects with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will not be considered for display as bars in the graph, since the percentage change in the sum of diameters of target lesions reflects the non-PD target lesion response, but the overall lesion response is PD. A subject with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be excluded from the waterfall plots. Subjects without any valid assessments will be completely excluded from the graphs.

The total number of subjects displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of subjects with tumor shrinkage and tumor growth. A footnote will explain the reason for excluding some subjects (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-3.

Table 2-3 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
Case	Target response	Overall lesion response	Include in waterfall graph?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes but as ✶ only	PD	any
2	CR/PR/SD	PD	Yes but as ✶ only	any	Yes
3	UNK	UNK or PD	No	any	any
4	CR/PR/SD	UNK	No	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD	No
6	PD	PD	Yes as a bar	any	any

2.7.3 Handling of missing values/censoring/discontinuations

ORR

Subjects with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these subjects will be included in the FAS and will be counted as 'failures'.

TTR

For subjects who did not achieve a confirmed PR or CR, their TTR will be censored.

DOR: A subject who has not progressed or died at the date of the analysis 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.

PFS

PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR, or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the start date of treatment will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-4 for censoring and event date options and outcomes for PFS.

Table 2-4 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Start Date of treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed

Situation	Date	Outcome
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression (*including subjects who crossover from the control to the treatment group.*)	Date of last adequate assessment on or prior to starting new anti-cancer therapy (or crossover treatment)	Censored
Death before first PD assessment	Date of death	Progressed

Censoring pattern of PFS

Number of subjects with a PFS event and number of subjects censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments:

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. 'Ongoing',
2. 'New cancer therapy added',
3. 'Withdrew consent',
4. 'Lost to follow-up',

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate tumor assessment date and the PFS

event date is larger than the interval of 2 missing tumor assessments then the subject will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator and BIRC.

Censoring pattern of OS (only for phase II)

The pattern of censored data will be examined between the treatment groups: reasons for censoring ('Alive' or 'Lost to follow-up') and death cause will be summarized. In addition, survival status, reason for censoring and death cause will be listed. Subjects not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than the protocol specified interval between the survival follow-up assessments plus 2 weeks, 12 weeks for this study.

2.8 Safety analyses

All safety analyses will be based on the safety set.

2.8.1 Adverse events (AEs)

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

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the all subjects column. The rash subgroups defined in the most updated case retrieval strategy (CRS) form will be included in the summaryies along with preferred tem.

Incidence of rash, rash subgoups as well as time to first rash will be summarized separately.

Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables will be provided by SOC and PT based on the safety set:

- on-treatment AEs which are not SAEs with an incidence greater than 5%
- on-treatment SAEs and SAEs suspected to be related to study treatment.

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

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

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

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

2.8.1.1 AEs adjusted for subject exposure time

Not applicable.

2.8.1.2 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound EGF816. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. SPPFL flag in ADAERISK data will be used for special interest groups.

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.

The above rash special interest group terms will be updated annually as needed by safety group and will be included in case retrieval strategy (CRS) form, if a CRS is developed for EGF816 already at time of reporting.

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

Summaries of these AESIs will be provided (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

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

2.8.2 Deaths

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

All deaths will be listed and post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

The summaries will include all assessments available for the lab parameter collected no later then 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade version 4.03 (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of subjects with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized using the following categories:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN *(potential Hy's law)*

A figure displaying worst ALT or AST vs. total bilirubin for on treatment measurements will be displayed in the Safety Set.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses. If a subject has more than one post-baseline measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

The average of triplicate (if available) ECG records at each timepoint (scheduled/unscheduled) will be used in this analysis. ECG time will be the first of any triplicate records (regardless if there are more than 3 or less than 3 triplicates at that timepoint) will be recorded.

Data analysis

12-lead ECGs including PR, QRS, QT, QTcF, QTcB, and RR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally. The number and percentage of subjects with notable ECG values will be presented.

- QT, QTcF, or QTcB
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

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

The listed analysis will be done by excluding subjects taking concomitant medication with known QT prolongation within 7 days prior to ECG assessments on treatment period (see Table 5-3). This will be done in a retrospective way by creating the QT prolonged drug exclusion flag manually.

2.8.4.2 Vital signs

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

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	≤ 35.0

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

A listing of all vital sign assessments will be produced and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Additional Analyses

Safety Graphics

Individual plot will be generated for AST, ALT, Bilirubin for subjects with Hy's law case. Total bilirubin versus worst ALT or AST also be plotted for subjects with Hy's law cases.

2.9 Pharmacokinetic endpoints

For the summaries and figures with PK endpoints, subjects treated with capsule and tablets are pooled as well as phase I and phase II for same dose, unless stated otherwise.

PK parameters

The PK parameters of EGF816 and LMI 258 listed in Table 2-6 will be determined using the non-compartmental methods implemented in Phoenix WinNonlin® software version 6.2 (or newer compatible version).

Table 2-6 Non-compartmental PK parameters for EGF816 and LMI258

AUCtau*	The area under plasma concentation-time curve calculated to the end of the dosing interval tau(ng*hr/mL)
Cmax	Maximum (peak) observed plasma drug concentration (ng/mL)
Tmax	Time to reach maximum (peak) plasma drug concentration (hr)
CLss/F	Apparent total body clearance of drug at steady-state after oral administration (L/hr)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (hr).
T1/2,eff	The effective half-life at steady state.
Racc	Accumulation ratio calculated using AUCtau at steady state divided by AUCtau on day 1 of cycle 1

*AUCtau will be AUC0-24 for QD dosing.

Summary statistics:

Descriptive statistics (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for Full Pharmacokinetic analysis set for all PK parameters defined in Table 2-6 except Tmax, where only n, median, minimum and maximum will be presented for EGF816 and LMI258.

All individual PK parameters for EGF816 and LMI258 will be listed by formulation, dose and phase for the Safety set.

Inferential statistics:

In addition, a formal statistical analysis will be performed separately at 100mg and 150mg, to compare the PK parameters (AUCtau and Cmax) of EGF816 between tablet (test) and capsule (reference), on Day 1 and on Day 15, respectively, using Full PAS. This analysis will be based on phase I data only.

A linear mixed model will be fitted to the log-transformed PK parameters (AUCtau and Cmax) to assess the difference of pharmacokinetics of capsule and tablet of EGF816. The model will include formulation as a fixed factor and subjects as a random factor. A point estimate and the corresponding two-sided 90% confidence interval (CI) for the formulation differences (tablet as test vs. capsule as reference) will be calculated. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean ratio on the original scale.

The difference of Tmax for EGF816 will be compared between tablet (test) and capsule (reference). Median difference will be estimated by means of the Median Scaling method based on a stratified Hodges-Lehmann estimator and its respective two-sided asymptotic 90% confidence interval.

Correlation between PK parameters

Correlation between Ctrough and Cmax as well as between Ctrough and AUCtau at Cycle 2 Day 1 will be explored by presenting the pearson correlation. This will be done for both phases combined data as relationship would not differ by phase.

Dose proportionality

Dose-proportionality will be explored for EGF816 AUCtau and Cmax, after a single dose (Cycle 1 Day 1) and at steady state (Cycle 1 Day 15 (only phase I) and Cycle 2 Day1), respectively, by fitting a power model (Smith, 2000). The power model translates into a linear model of the form:

$$ln(PK) = \alpha + \beta\, ln(dose) + error$$

The log-transformed PK parameters (AUCtau and Cmax) will be analyzed by a linear mixed effects model to account for correlation between repeated measurements for a given patient.

The estimate and 90% confidence intervals (CI) for β will be reported and compared to the target dose-proportionality range of β, which is calculated by the following formula (Smith, 2000):

Lower bound of target dose-proportionality range of β: 1 + ln(0.8)/ln(dose range)

Upper bound of target dose-proportionality range of β: 1 + ln(1.25)/ln(dose range)

In these formula, the dose range is the upper dose/lower dose ratio.

The 90% CI for ß will be compared with the target region defined above, then dose proportionality can be claimed.

Intra-patient variability

Based on the power model from dose proportionality at steady state, a table will be generated to report the intra-patient variability (CV%) for EGF816 AUCtau and Cmax.

EGF816/LMI258 concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for EGF816 concentration will be presented at each scheduled time point by treatment and by phase for the Pharmacokinetic analysis set.

Individual concentration-time profiles for EGF816 concentrations with median will be displayed graphically by treatment and by phase for Safety analysis set on the semi-log view. In addition, the arithmetic mean (+/- SD) and geometric mean concentration-time profiles for EGF816 by treatment and by phase will be displayed graphically for the Pharmacokinetic analysis set on the linear and semi-log view.

All individual plasma EGF816 concentration data will be listed by formulation, dose and phase for the Safety set. The analyses listed above will be repeated for LMI258.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) (<1.0 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

2.10 PK/PD analyses

The minimum number of subjects/events required for each analysis in this section is subject to change at the time of reporting.

2.10.1 PK endpoints for PK [redacted] analyses and general definitions

PK inclusion criteria for a given [redacted] event for analysis:

Geometric mean of AUCtau starting from Cycle 1 Day 2 up to the event, for PK-safety analyses, is defined as

- For patients with an event, the geometric mean of all AUCtau values on and before the date of event .
- For patients without an event, the geometric mean of all AUCtau values on and before the earliest of the date of cut-off or end of study.

Steady state definition would follow the PAS definition (take the same dose of EGF816 for at least 5 consecutive days prior to sampling on or after cycle 1 day 15).

Models may be compared using the AIC to select the most appropriate model. Model fit and residuals will be assessed to determine if any transformation (such as log-transformation) or non-linear model (such as emax model) is necessary for each analysis.

[redacted] Standalone SAP/TFLs also be prepared.

2.10.1.1 PK-QTc analysis

The analysis will be done by excluding subjects taking concomitant medication with known QT prolongation (see Table 5-3) within 7 days prior to ECG assessments on treatment period.

Valid PK-ECG data will be defined as

1) sample time of ECG must be at most 60 minutes prior to the PK collection.
1) If there are multiple records within the 60 minutes range, the closest match will be chosen.

A linear mixed effects model will be used to explore the relationship between change in QTcF from baseline (ΔQTcF) and EGF816 concentration . In the model, $\Delta QTcF_{ij}$ is the change from baseline QTcF value, and $concentration_{ij}$ is the EGF816 plasma concentration, for the i^{th} patient at the j^{th} time point ($i = 1,\ldots n$; $j = 1,\ldots..,n_i$).

$$\Delta QTcF_{ij} = (\beta_0 + b_{0i}) + (\beta_1)(concentration_{ij}) + \varepsilon_{ij}$$
$$where\ \ b_{0i} \sim N(0, \sigma_0^2);\ \ \varepsilon_{ij} \sim N(0, \sigma^2)$$

In this model, b_{0i} is the random component of the intercept for the random patient effect to account for the repeated measures within each patient,. Additional covariates may be added as appropriate. A compound symmetry covariance structure is assumed for the repeated measures within a patient. However, other covariance structure will be explored if convergence is not achieved and/or model's fit is improved.

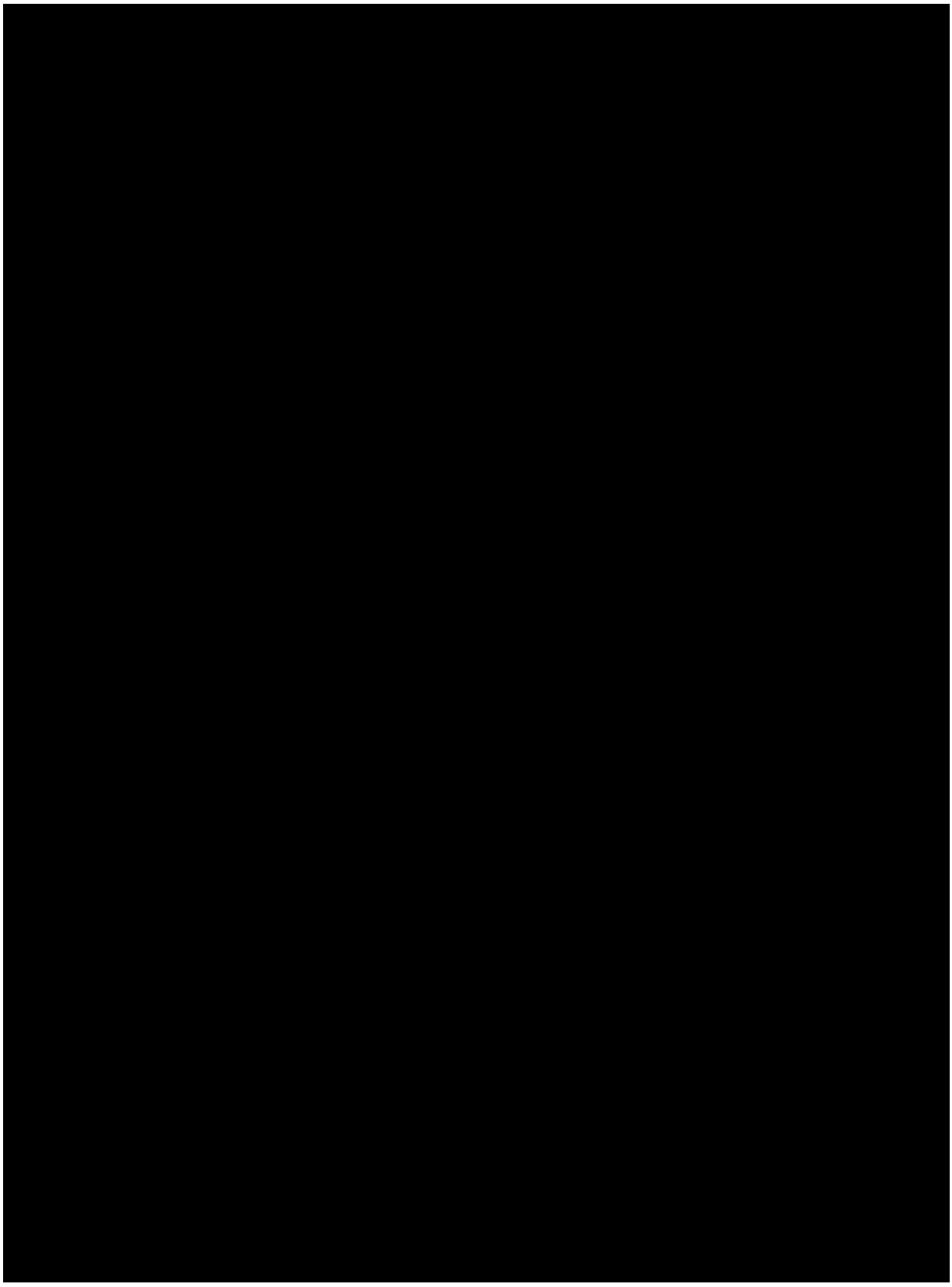
Model parameter estimates, and standard errors (SE) associated with each one of the variables included in the model based on the Type III tests will be presented.

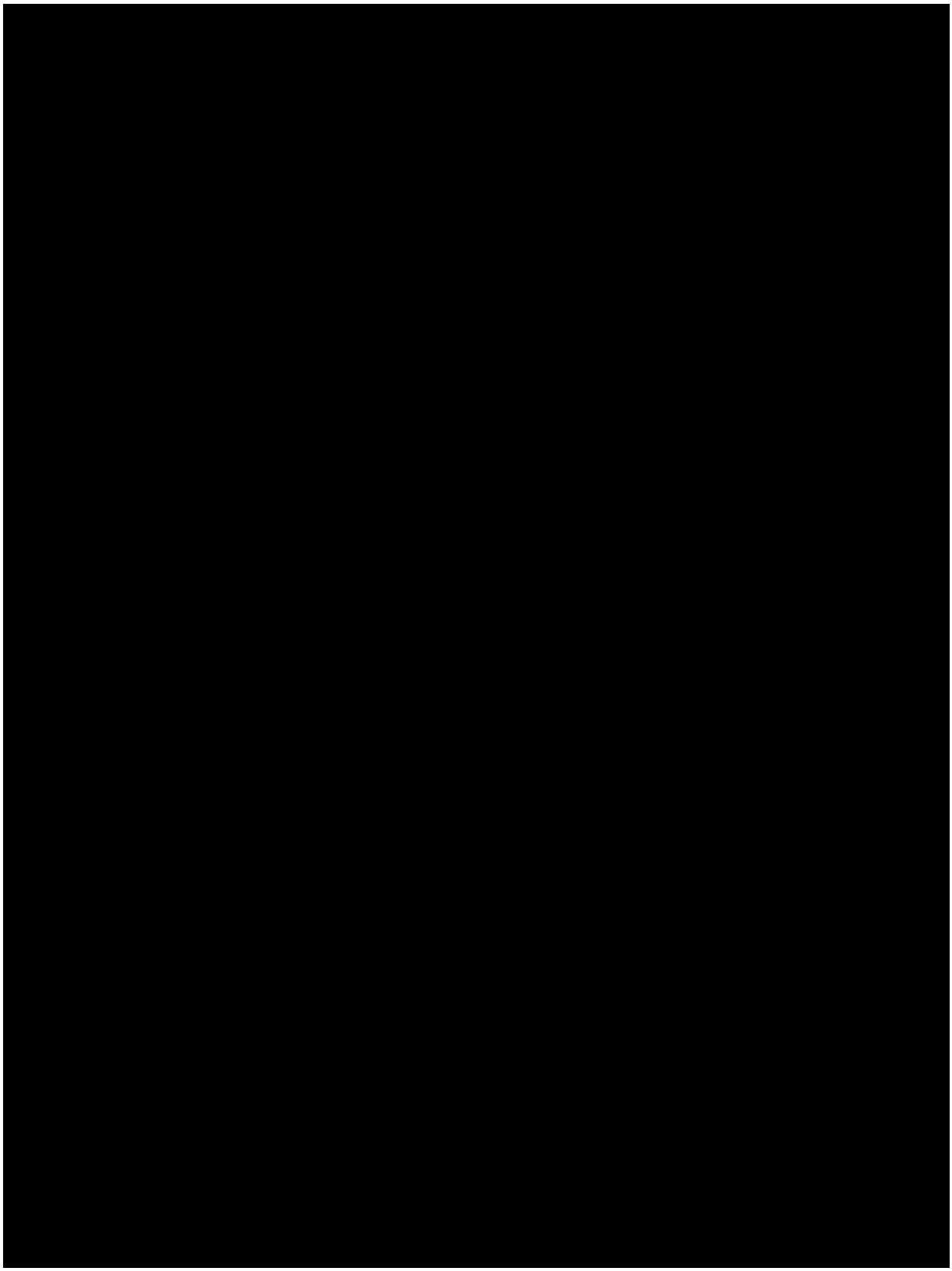
Based on the final model, the estimated average ΔQTcF will be summarized for different concentration thresholds (geometric mean, median, 25th, and 75th percentile of steady state Ctrough and steady state Cmax of 100mg, 150mg and 350mg dose level regardless of formulation) .

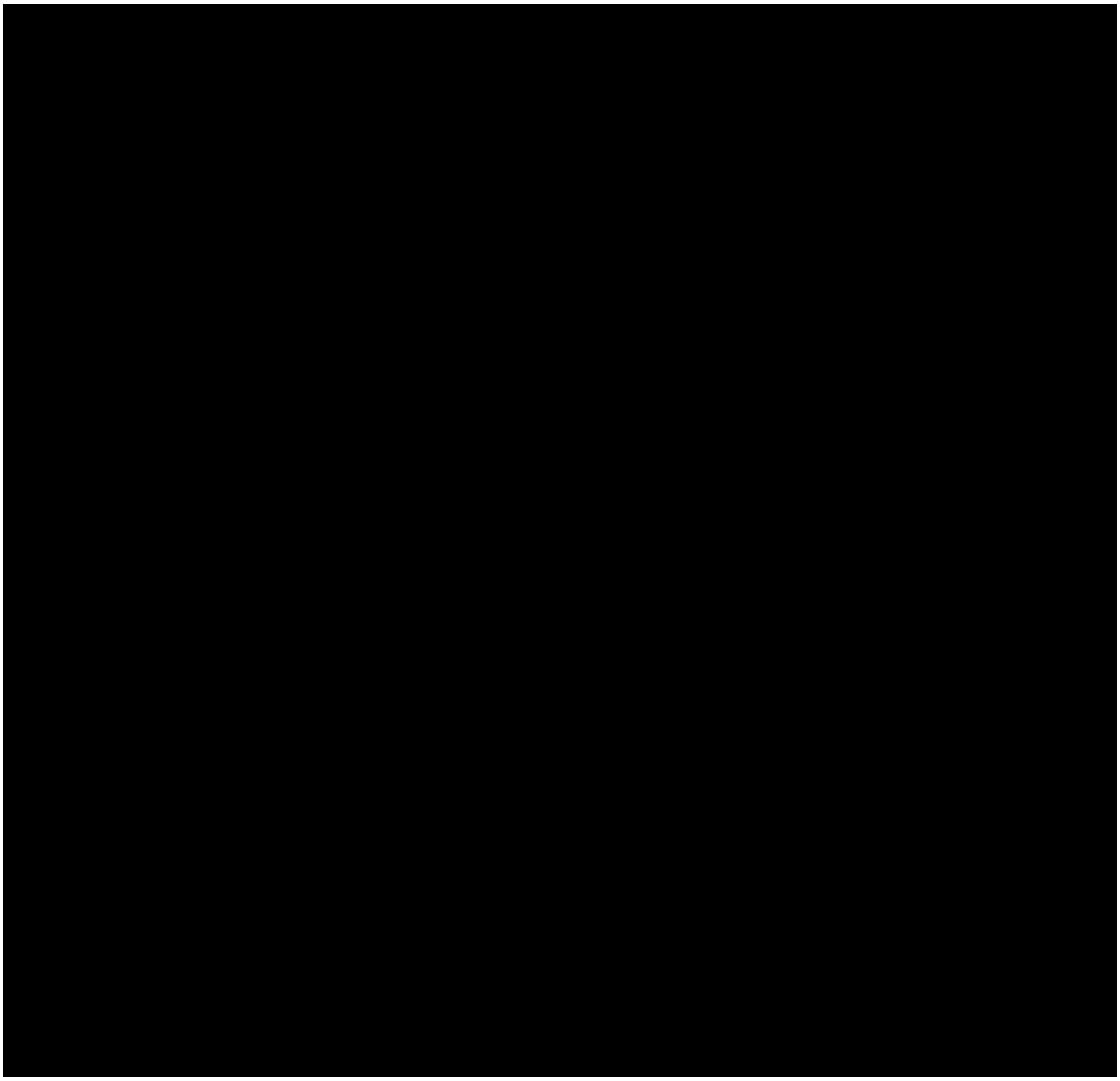
The relationship between ΔQTcF and EGF816 concentration as well as the relationship between QTcF and RR will be illustrated graphically.

2.11 Patient-reported outcomes

Not applicable.







2.14 Interim analyses

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 treatment group 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 the protocol Section 6.2.3.

Phase II part

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

with FAS will be done using the FAS who have an adequate tumor assessment at baseline and have a follow-up tumor assessment > 7 weeks after starting treatment (unless PD is observed before 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 subjects,

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

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

The following Table 2-9 provides the probabilities of success at the primary analysis based on different numbers of responders observed at the IA.

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

Responders at IA out of 20 evaluable subjects 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

Estimation of the final ORR

Various methods (adjusted and unadjusted) have been proposed in the literature to adjust the ORR estimate at the primary (final) analysis to take into account the results of the interim analysis. These include Bayesian estimates, MLE, UMVUE, and more recent proposals like the optimal compatible estimator (Kunzmann and Kieser, 2016). Depending on the underlying sampling space, there is even conflicting advice about the direction of adjustment; for example, Jung and Kim (2004), and Guo and Liu (2008) suggest upward adjustments. The Bayesian point estimate (posterior median) is very similar to the MLE since a minimally informative Beta prior

is used. The unadjusted estimate will therefore be used as it complies with the likelihood principle, and the bias is typically small.

Dissemination of information and decisions based on interim results

An independent data monitoring committee will not be constituted for the Phase II part of this study. This is a single arm trial and there is no a priori information as per the FDA Guidance of 'situations in which safety concerns may be unusually high' or the subject 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.'

The assessment of futility, based on the calculated Bayesian probability of success, and the review of safety data at the interim analysis will be performed by the internal Novartis clinical trial team. It is foreseen to share the results with the investigators in a data review meeting.

It is envisioned that the team may make three types of recommendations at the 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 the study group, regardless of efficacy.

If futility is concluded, the enrollment may be stopped.

Planned analyses

The interim analysis will include a subset of the efficacy, safety and PK analyses described for the CSR. These will comprise basic baseline characteristics, the primary endpoint and selected analyses of the secondary endpoints (BOR, DOR, TTR, PFS) including graphical presentations based on investigator as well as BIRC assessment, safety analyses comprising exposure, adverse events, deaths, lab parameters as well as PK summaries. Outputs related to these will be further detailed in the TFL document.

3 Sample size calculation

Phase I part

Each treatment group will consist of 1 to 6 evaluable subjects in the Phase I dose-escalation part. At least six subjects at the MTD/ RP2D level will be enrolled, as described in protocol [Section 6.2.3]. Multiple treatment groups may be sequentially enrolled to the same dose level. Additional treatment groups of 1 to 6 subjects 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 subjects are expected to be treated in the dose-escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

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 subjects) under different true ORR values (see also Table 3-1). 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 subjects who completed up to 4 cycles of study treatment.

Table 3-1 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 subjects) under different true ORR values.

Table 3-1 Operating characteristics given sample size of 40 subjects and interim analysis at 20 subjects

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 subjects, 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 subjects is greater than 0.55 if the true ORR is greater or equal to 55%

4 Change to protocol specified analyses

Per protocol set in section 2.2, eligibility criteria of “subjects who have an adequate tumor assessment at baseline and have a follow-up tumor assessment > 7 weeks after starting treatment (unless PD is observed before that time)” was added to exclude subjects who do not have a chance to get the first scheduled tumor assessment.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

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

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

Scenario 1 should not applicable for final CSR. All subjects should have EOT page complete before the Database lock for Final CSR

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

Note: The date of assessment on EOT CRT might be very different from last date of dose.

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

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

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

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

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

If because of this imputation the chronology of the events is altered then the imputation should be made to the minimum value up to where chronology remains unchanged. E.g. if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

Incomplete assessment dates for tumor assessment

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

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

Incomplete or missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute the 15th day of the month and year of death
- If both day and month are missing, then impute 01Jul of the year of death

Prior therapies date imputation

- Start dates
  The same rule which is applied to the imputation of AE/concomitant medication start dates will be used with the following exception:
  - If month and day are missing and the available year = year of study treatment start date, then impute with study treatment start date − 1
- End dates
  - If day is missing, imputed date = min(reference end date, last day of the month)
  - If month and day are missing, imputed date = min(reference end date, 31Dec)

Reference end date will be the start date of study treatment.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies date imputation

- Start date
  The same rule which is applied to the imputation of AE/concomitant medication start dates will be used with the following exception:

- If month and day are missing and the available year = year of study treatment start date, then impute with study treatment start date − 1

- End date
  - If day is missing, imputed date = min(reference end date, last day of the month)
  - If month and day are missing, imputed date = min(reference end date, 31Dec)

Reference end date will be the start date of study treatment.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.2 AEs coding/grading

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

The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

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

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

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

Imputation Rules

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

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

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

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

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

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

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

CTC grades for the corrected calcium will be assigned as described above for grading.

5.4 Statistical models

Kaplan-Meier estimates

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

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Confidence interval for response rate

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

Calculation of posterior predictive probability of success for ORR

The posterior predictive probability of success for ORR at the end of study, i.e. Predictive Probability (ORR_{final} <= *xx%*|$ORR_{interim}$<=*yy%*) < *0.z* will be calculated as supportive information at the time of futility interim analysis.

The following sections provide the calculation of posterior predictive probability in a general framework.

Let θ denote ORR and a minimally informative unimodal Beta prior [Neuenschwander et al. 2008] for true ORR centering at xx% (or clinical threshold for futility), i.e. Beta (0.25, 1), will be used.

At the time of futility analyses the posterior parameters of the beta distribution of ORR will be computed using the available data. The number of responses in the potential future subjects 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.

The posterior distribution of x successes observed in n_1 subjects is beta-binomial (x, n_1, a, b):

$$\Pr(x) = \frac{n_1!}{x!(n_1-x)!}\frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\frac{\Gamma(a+x)\Gamma(b+n_1-x)}{\Gamma(a+b+n_1)} \qquad x = 0,1,...,n_1$$

For the number of events y* in n* subjects, after having seen x events in n_1 subjects:

$$\Pr(y^* \mid x) = \frac{n^*!}{y^*!(n^*-y^*!)}\frac{\Gamma(a+b+n_1)}{\Gamma(a+x)\Gamma(b+n_1-x)}\frac{\Gamma(a+x+y^*)\Gamma(b+n_1-x+n^*-y^*)}{\Gamma(a+b+n_1+n^*)}$$

5.5 Drugs with a known risk of QT prolongation

Table 5-3 Drugs with a known risk of QT prolongation

amiodarone, anagrelide, arsenic trioxide, astemizole (off us mkt), azithromycin, bepridil off us mkt), chloroquine, chlorpromazine, cilostazol, cisapride (off us mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on us mkt), donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off mkt worldwide), mesoridazine (off mkt worldwide), methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol (off mkt worldwide), procainamide (oral off us mkt), propofol, quinidine, sevoflurane, sotalol, sparfloxacin (off us mkt), sulpiride (not on us mkt), terfenadine (off us mkt), thioridazine, vandetanib

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EGF816X2101 study protocol version 6 (2017)