TITLE PAGE

Trial Statistical Analysis Plan

c04649761-01

BI Trial No.:	1200.217
Title:	An open label, single-arm phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an EGFR mutation (Del19 or L858R) who have failed first-line treatment with platinum-based chemotherapy
Investigational Product:	Afatinib
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Date of statistical analysis plan:	22 September 2015 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse event
BRPM	Blinded report planning meeting
CR	Complete response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
eCRF	Electronic case report form
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EoT	End of treatment
ES	Enrolled set
ICH	International Conference on Harmonisation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
N	Denotes number of patients
NSCLC	Non-small cell lung cancer
IPV	Important protocol violation
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
REP	Residual effect period
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class

Term	Definition / description
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 or a newer version will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

- Confirmation requirement of PR and CR has been specified in Section 7.4 as per RECIST 1.1 (1).

- *Time to objective response*, *duration of objective response*, *best overall response* has been defined with analyses specified in Section 7.4.

- *Duration of disease control* has been defined with analysis specified in Section 7.5.2.

- *Proteinuria* which is mentioned in Section 7.3.3 of CTP, is not included in Section 7.8.2 of TSAP because it is not collected in the study.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

- Objective response (CR, PR) assessed by investigator review according to RECIST 1.1.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

There are no key secondary endpoints.

5.2.2 Other secondary endpoints

- Progression free survival (PFS) assessed by investigator review according to RECIST 1.1.

- Disease control (CR, PR, SD) assessed by investigator review according to RECIST 1.1.

5.3 FURTHER ENDPOINTS

There are no further endpoints.

5.4 OTHER VARIABLES

- [redacted]

- Safety endpoints as specified in CTP Section 5.2.1.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

Eligible patients will receive afatinib once daily treatment until progression or until other criteria for stopping medication are met. The following study periods based on actual start and stop dates of study treatment administration are defined:

The following study periods based on key visit dates and actual start and stop dates of study treatment administration are defined:

- Screening: day of informed consent to day prior to starting study treatment. The day of informed consent is defined as the day of consent to tissue analysis if such analysis is required, or the day of consent to study participation otherwise.
- On-treatment: From day of first administration of study treatment to the day of last administration of study treatment.
- Residual effect period: From day after last administration of study treatment to the 28th day after last administration of study treatment.
- Post-study: From 29th day after last administration of study treatment onwards.

For safety summaries data recorded up to 28 days after last administration of study treatment will be considered as on-treatment (i.e. the actual on-treatment and residual effect period periods defined above will be combined into one ‘on-treatment’ analysis period).

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol analysis will be performed for this study; however patients with potentially important protocol violations (IPVs) will be documented. The following list of potentially IPVs will be used; note that this is a working list and may not be finalised until the final Blinded Report Planning Meeting (BRPM) prior to database lock.

Table 6.2: 1 Important protocol violations

Category / Code		**Description**	**Requirements**
A		Entrance Criteria Not Met	
	A1	Diagnosis of NSCLC questionable (or incorrect disease stage/no measureable disease).	Refers to IN 1, 3 and 4, also check oncological history and baseline tumour measurement details from investigator
	A2	Prior treatment for NSCLC does not meet entrance criteria	Refers to EX 1, 2, 3, 4, 5, 6, and 7 also check previous therapy details.
	A3	Genotypic tumour characteristics do not meet entrance criteria	Refer to IN 2 also check tumour biopsy details.
	A4	Laboratory values do not meet entrance criteria	Refers to IN 7, also check against screening laboratory values.
	A5	Chronic diarrhoea or other pre-existing event that might exacerbate expected Afatinib events	Refers to EX 8 and 16 also check baseline conditions.
	A6	Other deviation from entrance criteria	Refers to IN 5, 6, 8 and 9 and EX 9, 10, 11, 12, 13, 14, 15, 17, 18, 19, and 20. Also check baseline demographics, oncological history, pregnancy test, ECOG score and baseline conditions.
B		Informed Consent	
	B1	Patient's written informed consent not available	Refers to IN10. Date of written informed consent must be available. The day of informed consent is defined as the day of consent to tissue analysis if such analysis is required, or the day of consent to study participation otherwise.
	B2	Patient's written informed consent too late	Date of written informed consent to tissue analysis must be on or before Screening Visit 1. Date of written informed consent to study participation must be on or before Screening Visit 2.

Table 6.2: 1 Important protocol violations (cont.)

C		Trial medication and randomisation	
	C1	Incorrect trial medication taken	Incorrect starting dose or incorrect route of administration; Dose reduction not performed when indicated by the protocol (note that if dose reduction if performed when not indicated, this is not considered an IPV as it does not affect patient safety).
	C2	Non-compliance	Check medication compliance details for extreme non-compliance only.
D		Concomitant medication	
	D1	Prohibited medication use	Review concomitant medications for prohibited medication use, refer to Section 4.2.2 of the CTP.
E		Trial specific	
	E1	Procedure not performed according to protocol	Procedure performed prior to written informed consent and not part of routine clinical assessments

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations.

6.3 PATIENT SETS ANALYSED

Enrolled set (ES)

The enrolled set consists of all patients who signed informed consent at screening Visit 2.

Treated set (TS)

All planned analyses will be based on the Treated set (TS) which includes all patients who were dispensed trial medication and are documented to have taken at least one dose of investigational treatment (afatinib).

6.4 SUBGROUPS

There are no subgroup analyses planned for this study.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates").(2)

For efficacy data, the following rules will apply:

- For PFS, duration of tumour response and duration of disease control, if a patient is known to have progressed, but the date of progression is not attainable, but the date of visit with the disease progression recorded as the physician's assessment, then the date of the visit will be used as the progression date. If the assessment is recorded as disease progression, but both progression and the visit (when the assessment was made) dates are missing, the last date when the patient was assessed will be used as progression (even if the assessment was not a disease progression at that time). If the assessment is recorded as disease progression, both progression and visit dates are missing and a patient has no previous visit dates recorded, then the date of first administration of study medication will be used as the date of disease progression

In addition, time since diagnosis of NSCLC will be calculated from the date of diagnosis and the date of the start of the study. As the date of diagnosis is likely to be partial in many cases, the following rules will be used

- If day is missing but month and year are present, impute to first day of the month and combine with date of Screen Visit 2 to calculate time since diagnosis
- If only year is present, set to January 1st and combine with date of Screen Visit 2 to calculate time since diagnosis

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Where a baseline value is required, this will be the Screening Visit 2 value.

Nominal visit numbers as recorded in the eCRF will be used where required and there will be no windowing. Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'; therefore 'Day 0' will not exist.

For presentation of tumour response data which will follow a calculated visit approach based on the protocol specified tumour assessment schedule at Week 8, 16, 24, 32, 40, 48, 56, and in 12-weekly intervals thereafter; images will be assigned to corresponding visits (i.e., Week 8, 16, 24, 32, 40, 48, 56, …, etc.) based on their study day and using a ±4 or ±6 week window as appropriate (images taken within the first 4 weeks from treatment start will be assigned to Week 8). In case two or more images for a patient are assigned to one interval then the last assessment will be used to ensure progressive disease is not missed.

7. PLANNED ANALYSIS

Unless otherwise stated, for EoT tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group, unless otherwise stated. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Subject Data Listings will be presented for the Treated Set except for

- Disposition (based on Enrolled Set)

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic data collected and to be presented include:

- Age [years]
- Age class *(<65, ≥65 years)*
- Gender *(Male, Female)*
- Race (as defined in the eCRF)
- Ethnicity (as defined in the eCRF)
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/100)^2)
- Body surface area [m^2] (defined as: 0.007184*(height$^{0.725}$)*(weight$^{0.425}$))
- Smoking status *(Never-smoked, Ex-smoker, Current smoker)*
- Baseline ECOG score (0, 1)
- Common EGFR mutation type (Yes, No)
- Oncology history
- Previous therapies:
    - Systemic chemotherapies
    - Other anti-cancer therapies
    - Radiotherapies
- Previous surgeries for trial disease

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. This will include concomitant therapies for rash and diarrhoea only.

7.3 TREATMENT COMPLIANCE

There is no analysis planned for treatment compliance.

7.4 PRIMARY ENDPOINT

Objective response according to RECIST 1.1

Each patient will be assigned to one of the following categories of the *Tumour response*:

1. Complete response (CR)

2. Partial response (PR)

3. Stable disease (SD)

4. Progressive disease (PD)

5. Not evaluable for response, reasons to be specified (e.g. early death, tumour assessments incomplete, etc.)

Objective Response is defined as having a complete or partial response according to RECIST 1.1.

The proportion of patients in each response category will be tabulated by each week (with confirmation of response required). The total number of patients assessed at the week will be used as denominator.

For patients with objective response, *time to objective response* is defined as the time from the start of treatment to the date of the first objective response. Cumulative frequencies will be calculated for time to objective response by 8-week periods.

Duration of objective response is measured from the time of first objective response to the time of progression or death (or date of censoring for PFS, i.e., patients will be censored as for the PFS analysis). Kaplan-Meier estimates and 95% confidence intervals for the 25 th, median, and 75th percentiles of the survival distribution will be calculated for duration of objective response. Kaplan-Meier curves will be produced without confidence intervals.

Best overall response is defined as the best individual response including: CR, PR, SD, PD, Not evaluable from the date of the first administration until the earliest recording of PD, death or end of treatment (as long as no other anti-cancer therapy has been given). Two-sided 95% Clopper-Pearson confidence intervals will be given for the calculated best response rate.

As per RECIST 1.1 guideline, confirmation of CR and PR is required to ensure responses identified are not result of measurement error in non-randomised trials where response is the

primary endpoint, that is, CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In case of SD, measurements must have met SD criteria at least once after study entry at a minimum interval of 6 weeks.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 Other secondary endpoints

The secondary endpoint will be analysed as described below:

Progression-free survival (PFS) according to RECIST 1.1

Progression-free survival is the time from start of treatment to the date of disease progression or date of death, whichever comes first (or the date of censoring for PFS).

For patients with known date of progression:

Progression-free survival [days] = date of progression (or of death if no earlier progression) – (date of start of treatment) + 1

For patients that are known to have progressed, but with unknown date of progression, refer to Section 6.6 for more detail.

Censoring
For patients known not to have progressed, i.e., those remaining on trial drug:

Progression-free survival (censored) [days] = date of last assessment showing no disease progression or death - (date of start of treatment) + 1.

Patients with unknown progression status (no progression reported) will be censored at the date of last assessment, where the assessment was: stable disease, partial response or complete response. If a disease progression was not reported and all tumour assessments are missing or "not evaluable", patient will be censored for PFS at date of first administration of afatinib.

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75^{th} percentiles of the survival distribution will be calculated for progression-free survival. Kaplan-Meier curves will be produced without confidence intervals.

Disease control according to RECIST 1.1

Patients whose best assessment is SD, PR, or CR will be considered to have achieved disease control. *Duration of disease control* is defined as the time from the start of treatment to the

date of progression or death (or date of censoring for PFS), but is restricted to patients who achieve disease control.

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for duration of disease control. Kaplan-Meier curves will be produced without confidence intervals.

7.6 FURTHER ENDPOINTS

There are no further endpoints.

7.7 EXTENT OF EXPOSURE

Total treatment time (days and number of courses) will be calculated for each patient; off-drug periods due to non-compliance or toxicity prior to permanent discontinuation will be included as treatment time. Standard descriptive summaries of these data will be provided for the treated set of patients. Summary of exposure by dose level will also be provided.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

The adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (3)

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake until 28 days after last drug intake will be assigned to be treatment-emergent. All AEs occurring outside of this period will be handled according to the treatment definition period definitions detailed in Section 6.1 and will only be listed unless stated otherwise.

An overall summary of adverse events will be presented. This summary will include the first 5 categories from the list below and AEs by highest Common Terminology Criteria (CTC) grade.

The frequency of patients with adverse events will be summarised by highest CTC grade (grades 3, 4, 5 and all grades including also grade 1 and 2), primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- Any AEs,

- Drug related AEs,
- AEs leading to dose reduction,
- AEs leading to treatment discontinuation,
- Serious AEs,
- Drug related AEs leading to treatment discontinuation,
- Drug related serious AEs,
- AEs leading to death,
- Drug related AEs leading to death.

All tables will be sorted by SOC according to the standard sort order specified by the European Medicines Agency (EMA); PTs will be sorted by frequency (within SOC).

In order to most accurately characterize those adverse events related to different mechanism, MedDRA SMQ and HLT (with some modification) will be used to group MedDRA PT for rash/acne, stomatitis, ocular effects, lip effects, nail effects and fatigue. As a first step in the analysis of grouped AE, all constituent PT will be presented in a separate table for each grouped AE. The first 5 standard tables will be supplemented with tables using the grouped AE. Grouping will follow the project standard and details are defined in the technical TSAP. In these tables the grouped AEs will replace the original PTs for all AEs that are included within the grouped term. The grouped AE categories will then be tabulated along with all remaining MedDRA PTs, sorted by descending frequency. A reference table presenting all project defined groupings and MedDRA PTs within each grouping will also be produced.

Additional AE tables will be prepared to describe the frequency, intensity, clinical consequences for patients who are identified as having experienced any of the following AE:

- Gastrointestinal events (vomiting, nausea, diarrhea)
- Skin reaction (rash, acne)

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [see DM&SM: Display and Analysis of Laboratory Data (4)]. CTC grades will be applied to laboratory parameters using the current BI oncology standard as detailed in the document 'Conversion of laboratory parameters to CTCAE grades within BI' (5).

Descriptive statistics of all laboratory values by visit will be provided including changes from baseline. Frequency tables of transitions relative to the reference range and of possible clinically significant abnormalities will be produced. For those parameters that have CTC grading possible clinically significant abnormalities are defined as those laboratory values with a CTC grade ≥ 2 that have had an increase of ≥ 1 grade from baseline. For those parameters for which no CTC grade has been defined standard BI project definitions will be

used to decide on clinical significance. Further frequency tables will show the transition of CTC grade from baseline to worst value and last value on treatment.

Summaries will be produced of laboratory data recorded prior to treatment, on-treatment and 28 days after last study drug intake.

The focus of the laboratory data analysis will be on the following laboratory parameters:

- Low values: haemoglobin, leukocyte (total WBC), neutrophils, lymphocyte, platelet count, potassium.
- High values: aPTT, creatinine, AST, ALT, total bilirubin, alkaline phosphatase.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Only the date of the tracing is collected. Abnormalities will be recorded with Baseline Conditions or Adverse Events as appropriate.

7.8.5 Others

Not applicable.

8. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247 [R09-0262].

2. 001-MCG-156_RD-01, 'Handling of missing and incomplete AE dates', current version; IDEA for CON.

3. 001-MCG-156, 'Handling and summarisation of adverse event data for clinical trial reports and integrated summaries', current version; IDEA for CON.

4. 001-MCG-157, 'Display and Analysis of Laboratory Data', current version, IDEA for CON.

5. BI Guidance document 'Conversion of laboratory values to CTCAE grades within Boehringer Ingelheim'.

9. Additional sections

Not applicable.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	22-Sep-15	[redacted]	None	This is final TSAP without any modification