Boehringer Ingelheim

Trial Statistical Analysis Plan

c02331303-02

BI Trial No.:	1200.66
Title:	An open label, multicenter, single-arm trial to assess the safety of afatinib for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) Including Protocol Amendment 1 [U13-3195-02] Including Protocol Amendment 2 [c02368116-01]) Including Protocol Amendment 3 [c09028632-0.4]) Including Protocol Amendment 4 [c14890504-01])
Investigational Product(s):	**Giotrif®/ Gilotrif™ (**afatinib)
Responsible trial statistician(s):	
	Phone: Fax:
Date of statistical analysis plan:	28 MAR 2017SIGNED
Version:	Revised
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2.   LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
BRPM	Blinded report planning meeting
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
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
HEP C	Hepatitis C
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IPV	Important protocol violation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum
N	Denotes number of patients
NSCLC	Non-small cell lung cancer
PD	Progressive disease
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class

Term	Definition / description
TKI	Tyrosine kinase inhibitor
TS	Treated set
TSAP	Trial statistical analysis plan
TTSP	Time to symptomatic progression

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 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 will be used for all analyses.

4.   CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The definition of time to symptomatic progression (TTSP) has been clarified in Section 7.5.2.

5.   ENDPOINT(S)

This is an open-label, multi-centre, non-randomised, uncontrolled, single arm trial designed to evaluate the safety, tolerability and efficacy of afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI. After the initial screening visit, patients will enter the open-label treatment period with safety visits at approximately every 28 days until the end of the trial. The trial objective is to evaluate the safety and tolerability of afatinib (Giotrif®) in this cohort of patients. Of main interest are adverse events, collected throughout the study.

No specific tumour measurements are required in this program. Data regarding tumour assessments are performed at clinic visits as per local standard of care for NSCLC.

5.1   PRIMARY ENDPOINT

- Number of patients with serious adverse events (SAEs).

5.2   SECONDARY ENDPOINTS

5.2.1   Key secondary endpoint

There are no key secondary endpoints.

5.2.2   Secondary endpoints

- Number of patients with drug related adverse events.
- Time to symptomatic progression (TTSP)

6.   GENERAL ANALYSIS DEFINITIONS

6.1   TREATMENT

There is only one treatment in this study, which is afatinib. The starting dose for all patients is 40 mg with an option to reduce the dose to 30 mg or 20 mg based on individual tolerability. Unless otherwise stated, for all analyses, treated patients will be presented under the starting dose.

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

*   Screening: From day of informed consent to day prior to starting study treatment.

    Special handling rule:
    If informed consent date = date of first administration of active treatment in the trial, derive start of screening phase on the day of informed consent – 1 day.

*   On-treatment: From day of first administration of study treatment to the day of last administration of study treatment.
*   Residual effect period (REP): From day after last administration of study treatment to the 28th day after last administration of study treatment.
*   Follow-up: After the residual effect period and up to the last per protocol contact.
*   Post-study: After the last per protocol contact but entered in the database before database lock.

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 REP periods defined above will be combined into one 'on-treatment' analysis period).

Safety data recorded after follow-up period will be listed as post-study events but not tabulated.

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	Comment/Example	Efficacy / Safety
A		Entrance Criteria Not Met		
	A1	Inclusion Criteria Not Met		
	A1.1	Not locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC)	Inclusion criteria IN1 not met	E
	A1.2	No presence of Epidermal Growth Factor Receptor (EGFR) mutation in tumour biopsy.	Inclusion criteria IN2 not met or EGFR mutation negative	E
	A1.3	Male or female patients age <18 years	Inclusion criteria IN3 not met or patient's age <18 years	E/S
	A1.4.1	Inadequate organ function as defined in protocol version 2.	Inclusion criteria IN4 not met	E/S
	A1.4.2	Inadequate organ function as defined in protocol version 3.	Inclusion criteria IN4 not met	E/S
	A1.5	ECOG score not between 0 – 2	Inclusion criteria IN5 not met, or baseline ECOG score not between 0-2.	E/S
	A2	Exclusion Criteria Met		
	A2.1	Prior treatment with an EGFR tyrosine kinase inhibitor (TKI)	Exclusion criteria EX1 met	E
	A2.2.1	hormonal anti-cancer treatment within 2 weeks prior to start of trial treatment as defined in protocol version 2.	Exclusion criteria EX2 met	E
	A2.2.2	Use of anti-cancer treatment within 2 weeks prior to start of trial treatment as defined in protocol version 3.	Exclusion criteria EX2 met	E
	A2.3.1	Radiotherapy within 14 days prior to drug administration as defined in protocol version 2.	Exclusion criteria EX3 met	E
	A2.3.2	Radiotherapy within 4 weeks prior to drug administration as defined in protocol version 3.	Exclusion criteria EX3 met	E
	A2.4	Major surgery within 4 weeks from day 1 of first dose of afatinib, or minor surgical procedures including placement of an access device or fine needle aspiration within 7 days, or diagnostic or palliative video-assisted thoracoscopic surgery (VATS) within 14 days.	Exclusion criteria EX4 met	E/S
	A2.5	Known hypersensitivity to afatinib or any of its excipients	Exclusion criteria EX5 met	S
	A2.6	History or presence of clinically relevant cardiovascular abnormalities or myocardial infarction within 6 months prior to starting trial treatment	Exclusion criteria EX6 met	S

Category / Code		Description	Comment/Example	Efficacy / Safety
	A2.7.1	Women of Child-Bearing Potential or man who is able to father a child, unwilling to be abstinent or use adequate contraception prior to trial entry, for the duration of trial participation and for at least 2 weeks after treatment has ended as defined in protocol version 2.	Exclusion criteria EX7 met	S
	A2.7.2	Women of Child-Bearing Potential or man who is able to father a child, unwilling to be abstinent or use adequate contraception prior to trial entry, for the duration of trial participation and for at least 4 weeks after treatment has ended as defined in protocol version 3.	Exclusion criteria EX7 met	S
	A2.8	Childbearing potential who: a. are nursing or b. are pregnant or c. are not using an acceptable method of birth control, or do not plan to continue using this method throughout the trial and/or do not agree to submit to pregnancy testing required by this protocol	Exclusion criteria EX8 met	S
	A2.9	Any history of or co-existing condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the trial or interfere with the evaluation of safety for the trial drug	Exclusion criteria EX9 met	E/S
	A2.10	Previous or concomitant malignancies at other sites, except effectively treated nonmelanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.	Exclusion criteria EX10 met	E/S
	A2.11	Requiring treatment with any of the prohibited concomitant medications that cannot be stopped for the duration of trial participation	Exclusion criteria EX11 met	E
	A2.12	Known pre-existing interstitial lung disease	Exclusion criteria EX12 met	S
	A2.13	Presence of poorly controlled gastrointestinal disorders that could affect the absorption of the trial drug based on investigator assessment	Exclusion criteria EX13 met	E
	A2.14	Known active hepatitis B infection, active Hepatitis C (HEP C) and/or known Human Immunodeficiency Virus (HIV) carrier.	Exclusion criteria EX14 met	S
	A2.15	Meningeal carcinomatosis	Exclusion criteria EX15 met	E/S
	A2.16	Symptomatic brain metastases	Exclusion criteria EX16 met	E/S
B		Informed Consent		
	B1	Informed consent not given	Inclusion criteria IN6 not met or consent date is missing	S
	B2	Informed consent given too late	Inclusion criteria IN6 not met	S
	B3	Re-consent for updated informed consent form not given or given too late	IPV if the change affects the safety and right of the patient	S

Category / Code		Description	Comment/Example	Efficacy / Safety
C		On Study		
	C1	Incorrect trial medication dose affecting the safety of the patient		S
	C2	Local lab test not done affecting the safety of the patient		S
	C3	Expired IP taken by patient and confirmed by CTSU as not suitable for administration		E/S
	C4	Other PV affecting efficacy		E
	C5	Other PV affecting safety		S

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations. All the potential IPVs listed in the table will be identified programmatically.

6.3   PATIENT SETS ANALYSED

Enrolled set (ES)

The enrolled set consists of all patients who signed informed consent.

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).

6.5   POOLING OF CENTRES

This section is not applicable because there will be no pooling of centres or countries and no modelling thereof.

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").[1]

For efficacy data, the following rules will apply:

In addition, time since first diagnosis of NSCLC will be calculated from the date of diagnosis and the date of the start of the study treatment. 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.
- If only year is present, set to January 1st.

For partial treatment discontinuation date, the following logic is applied:
If month and year are known but day is missing, then use date of death if within the same month for a patient who died. Otherwise use last day of the month.

6.7   BASELINE, TIME WINDOWS AND CALCULATED VISITS

Where a baseline value is required, this will be defined as the last non-missing value prior to first administration of afatinib.

The time windows for subsequent clinic visits is 28 -7/+2 days. The end of treatment (EoT) visit can be anything up to a maximum of 14 days after the last trial drug intake and the follow-up visit should be between 28 and 35 days after the EoT visit.

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.

7.   PLANNED ANALYSIS

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

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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.

7.1   DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristic parameters collected and to be presented include

- Age [years]
- Age class *(<65, ≥65 years and <75,≥75 years)*
- Gender *(Male, Female)*
- Race and ethnicity(as defined in the eCRF)
- Country
- 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)*
- Smoking history [pack-years]
- Baseline ECOG score
- EGFR mutation type *(common, uncommon only)*
- Oncology history
- Previous therapies:
    - Systemic chemotherapies
    - Other anti-cancer therapies
    - Radiotherapies
- Previous surgeries for trial disease

This section will include a summary of all the subgroup variables detailed in Section 6.4.

7.2   CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Only concomitant therapies for rash and diarrhoea were collected on the CRF and will be summarised.

For baseline conditions and signs and symptoms of the trial disease also only descriptive statistics will be presented.

7.3 TREATMENT COMPLIANCE

There is no analysis planned for treatment compliance.

7.4 PRIMARY ENDPOINT

Refer to Section 7.8.

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 Secondary endpoints

The secondary endpoints will be analysed as described below:

Number of patients with drug related adverse events

Refer to Section 7.8.

Time to symptomatic progression (TTSP)

Defined as the time (number of days) from first administration of afatinib to the date of first documented clinically significant symptomatic progression that required stopping afatinib according to investigator's assessment.

Patients will be considered to have clinically significant symptomatic progression if the reason for termination of trial medication is recorded as 'progressive disease' or 'worsening or AE of underlying cancer disease', on the termination of trial medication eCRF page.

Therefore TTSP will be derived as:

TTSP [days] = date of last administration of trial drug (where 'progressive disease' or 'worsening or AE of underlying cancer disease' selected on the termination of trial drug eCRF page) – (date of start of treatment) + 1

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for TTSP. Greenwood's standard error estimate will be used. Kaplan-Meier curves will also be produced.

Censoring rules for TTSP:

- For patients who have 'other AE', 'non-compliance with protocol', 'lost to follow-up', 'patient refusal to continue taking trial medication' or 'other' recorded on the termination of trial medication eCRF page, these patients will be censored at the date of last administration of the trial drug recorded on the termination of trial drug page;
- For patients who are still on treatment, these patients will be censored at cut-off date for interim analysis and at the date of EOT visit for final analysis.

7.7   EXTENT OF EXPOSURE

Total treatment time (days) will be calculated for each patient; total treatment time will include any dose interruptions or off-drug periods.

The definition of exposure is:

Treatment stop date – treatment start date + 1

In case of death due to any cause, the treatment stop date will be imputed as the earlier of (date of last administration of afatinib treatment, date of death) + 1 day

Standard descriptive summaries of these data will be provided for the treated set of patients.

Total treatment time (days) will be summarized by afatinib dose level (40 mg, 30 mg, 20 mg and total), and by number of therapy lines. The number of therapy lines for afatinib will be

derived as: the number of all previous therapy lines + 1. The number of all previous therapy lines that the patient received prior to the start of the treatment includes number of lines of all of the following:

- Systemic chemotherapies: count the number of previous chemotherapies obtained from the field "Line of therapy" on the previous chemotherapies eCRF page .
- Other anti-cancer therapies: count the number of anti-cancer therapies obtained from the field "Line of therapy" on the other anti-cancer therapies eCRF page. If there is a therapy with the same name and same start and end dates as a therapy present in Systemic chemotherapies eCRF page, then ignore this as it has already been counted earlier.

7.8   SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1   Adverse events

The intensity of adverse events were classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 in the eCRF.

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.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following apply:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

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' (2) [001-MCG-156]

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 study drug intake until 28 days after last study 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 exclude the rows 'Severe AEs', 'Significant AEs' and 'Other significant AEs' but will include additional

rows for 'AEs leading to dose reduction' 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), treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- All AEs collected
- Drug related AEs.
- AEs leading to dose reduction.
- AEs leading to treatment discontinuation.
- Drug related AEs leading to treatment discontinuation
- Serious AEs.
- Drug related serious AEs.
- 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).

The above tables except for AEs leading to death will be repeated with the project defined grouping of AE terms (rash, stomatitis, ocular effects, lip effects, nail effects and fatigue). Details of the project defined groupings 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 of the project defined groupings and MedDRA PTs within each grouping will also be produced.

Additional AE tables will be produced for AEs of special interest (diarrhoea, and the project defined groupings of rash and renal insufficiency), providing further details on highest CTC grade, action taken with study drug and time to first onset of AE.

Number of patients with adverse events with incidence greater than 5% will be summarised by treatment, primary system organ class (SOC) and preferred term (PT).

7.8.2 Laboratory data

Only the date of samples are collected; laboratory data are not collected. Laboratory values that are considered clinically relevant will be recorded with Baseline Conditions or Adverse Events as appropriate.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. A summary of the actual value and the change from baseline will be presented in 4-week periods for the following parameters: Systolic blood pressure, Diastolic blood pressure, Pulse rate, Temperature, Weight.

Other than at baseline, repeat, ad-hoc or unscheduled data will not be included in the summary tables.

A listing for pregnancy test results of patients with child bearing potential will be provided.

7.8.4   ECG

Only the date of the tracing is collected if this is done per site standard of care. Abnormalities will be recorded with Baseline Conditions or Adverse Events as appropriate.
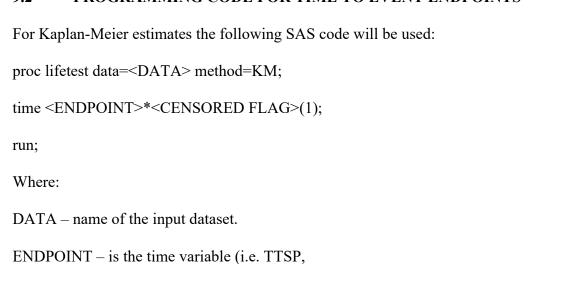
7.8.5   Others

Not applicable.

8.   REFERENCES

1   *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current
     version; IDEA for CON.
2   *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial
     reports and integrated summaries", current version; IDEA for CON.

9.   ADDITIONAL SECTIONS

9.2   PROGRAMMING CODE FOR TIME TO EVENT ENDPOINTS

For Kaplan-Meier estimates the following SAS code will be used:

proc lifetest data=<DATA> method=KM;

time <ENDPOINT>*<CENSORED FLAG>(1);

run;

Where:

DATA – name of the input dataset.

ENDPOINT – is the time variable (i.e. TTSP,

CENSORED FLAG – is the binary variable with value 1 denoting a censored observation and value 0 (zero) indicating the observation that was not censored (so the event had occurred)

10. HISTORY TABLE

Table 10: 1   History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**26-NOV-15**		None	This is the final TSAP without any modification.
Revised	**28-MAR-17**		5.3, 6.1, 6.7, 7.5.2, 7.6, 9.1	and Revised the definition of study period in section 6.1; Changed the follow-up visit window (section 6.7) to be consistent with the flow chart in CTP; Revised the censoring rules for TTSP in section 7.5.2; and