TRIAL STATISTICAL ANALYSIS PLAN

C03655893-01

BI Trial No.:	1200.209
Title:	A Single Arm Phase IV Study of Afatinib in Elderly Patients with recurrent or Stage IV Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have Common Epidermal Growth Factor Receptor (EGFR) mutations (Exon 19 Deletions or Exon 21 L858R Substitution Mutations) (Including Protocol Amendment 1[U#: c02364424-02] and Protocol Amendment 2[U#: c02364424-03])
Investigational Product(s):	Giotrif®/ Gilotrif® (Afatinib)
Responsible trial statistician(s):	Email:
Date of statistical analysis plan:	25-Mar-2019
Version:	Final

1. TABLE OF CONTENTS

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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
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptors
EOT	End of Treatment
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NSCLC	Non-small cell lung cancer

Term	Definition / description
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
REP	Residual effect period
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
StD	Standard deviation
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9 (1), 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 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following changes have been made in the planned analyses prior to database lock:

- The trial protocol was amended on 15Feb2018 (global amendment 2) to document early study termination due to slow enrollment. The number of patients randomized in this trial is expected to be approximately 25 patients instead of 50.

- Per current standard operating procedures, important protocol violations will be summarized as important protocol deviations.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of this study is the occurrence of adverse events (AEs) leading to dose reduction of Afatinib.

This endpoint is a safety endpoint; therefore, analyses are described in Section 7.8.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 (Other) Secondary endpoints

The secondary endpoints of the study are

- Occurrences of CTCAE grade ≥3 diarrhea,
- Occurrences of CTCAE grade ≥3 rash/acne+,
- Occurrences of CTCAE grade ≥3 stomatitis+,
- Occurrences of CTCAE grade ≥3 paronychia+,
- Time to first dose reduction of Afatinib caused by AEs.

Refer to CTP Section 5.2.1 and Section 7.8 of this TSAP for more details. The terms flagged by a "+" represent MedDRA preferred terms reported together as one grouped term for analysis.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments administered, assignment of dose group and selection of doses, see CTP Section 4. All eligible patients will be assigned to receive Afatinib 30 mg QD in this study. The dose may be reduced to 20 mg QD during the study as described in Section 4.4 of the CTP. Unless otherwise stated, treated patients will be presented under the starting dose, i.e. 30 mg Afatinib.

Table 6.1:1 displays the study periods defined for 1200.209. In this study, treatment is administered in courses of 28 days. The follow-up period extends from the date of last administration of study treatment to the follow-up visit, which should occur 28 to 35 days after the last administration of study treatment. After completion of the follow-up period, vital status will be monitored every 3 months until the end of the trial, which is defined as approximately 12 months after the last patient enters the study.

Table 6.1: 1 Study periods

Study Period	Start time	Stop time
Screening	Date of informed consent	Date of 1st administration of study treatment – 1 day
On-treatment	Date of 1st administration of study treatment	Date of last administration of study treatment
Residual effect period	Date of last administration of study treatment + 1 day	Date of last administration of study treatment + 28 days
Follow-up period (includes residual effect period)	Date of last administration of study treatment + 1 day	Date of follow-up visit (28-35 days after date of last administration of study treatment).
Post-study vital status	Date of follow-up visit +1	End of trial

6.2 IMPORTANT PROTOCOL DEVIATIONS

The following table (Table 6.2: 1) defines the different categories of important protocol deviations (iPD) to be documented during the study. No per-protocol analyses will be performed for this study; however, patients identified with some iPDs may be excluded from certain analyses as specified in the table. Protocol deviations will be reviewed periodically at MQRMs and BRPMs prior to database lock.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Example/Comment	Excluded from	Automatic /Manual
A		Entrance criteria not met			
	A1	Inclusion criteria not met			
	A1.1	Disease criteria not met	Inclusion criteria 1 or 2 not met as specified in the protocol per IE CRF.	None	Automatic
	A1.2	ECOG not 0 or 1.	Inclusion criteria 4 not met or ECOG recorded on screening physical exam CRF not 0 or 1.	None	Automatic
	A1.3	Age at enrollment not ≥ 70 years	Inclusion criterion 3 not met or AGE<70 years on demographics CRF.	None	Automatic
	A1.4	Failure to recover from previous therapy-related toxicity	Inclusion criterion 6 not met.	None	Automatic
	A1.5	Laboratory values do not meet inclusion criteria	Inclusion criterion 5 not met.	None	Automatic
	A1.6	Other inclusion criteria not met	Inclusion criteria 7 or 8 not met.	IN7 =None; IN8 = see B1 below	Automatic
	A2	Exclusion criteria not met			
	A2.1	Prior therapy not consistent with exclusion criteria	Exclusion criteria 1, 2, 3, 4, or 5 not met.	None	Automatic
	A2.2	Patient has excluded medical condition	Exclusion criteria 7, 8, 9, 10, 11, 12, 13, 14, or 15 not met.	None	Automatic
	A2.3	Other exclusion criteria not met	Exclusion criteria 6, 16 or 17.	None	Automatic
B		Informed consent			
	B1	Informed consent not available/not	Informed consent date missing; no signature on ICF	All	Automatic /Manual

Category / Code		Description	Example/Comment	Excluded from	Automatic /Manual
		done			
	B2	Informed consent given late	Informed consent date <actual consent date> after Visit 1 date <Visit 1 date>	None	Automatic /Manual
C		Trial medication			
	C1	Incorrect trial medication taken	Review of dose(s) recorded on the drug administration and dose change CRFs against IWRS reports at MQRM/RPM.	None	Manual
	C2	Dose reduction or treatment discontinuation not according to protocol.	Review of reported dose changes and AEs at MQRM/RPM for compliance with Sections 3.3.4 and 4.4.1 of the CTP.	None	Automatic /Manual
	C3	Non-compliance with trial medication.	Afatinib doses missed for reasons other than drug-related AEs is >25% of the dispensed doses as indicated on compliance CRF.	None	Automatic /Manual
D		Concomitant medication			
	D1	Use of prohibited concomitant medication.	Review of concomitant medication listings at MQRM/RPM for prohibited medications as defined in Section 4.2.2 of the CTP.	None	Manual

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

6.3 PATIENT SETS ANALYSED

The following sets of patient data will be used for analyses:

- Enrolled set:
  This patient set includes all enrolled (screened) patients who signed informed consent, whether treated or not.

- Treated set (TS):
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of study treatment. All planned efficacy and safety analyses will be based on the TS.

6.5 POOLING OF CENTRES

Descriptive summaries will present data from all centers combined. Center/country will not be included in any statistical models.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates will be imputed according to BI standards (see 'Handling of missing and incomplete AE dates'). (4) A separate category for missing values will be displayed in frequency tables only if there are missing values for the variable being summarized.

Time since diagnosis of NSCLC will be calculated from the date of diagnosis and the date of screening. If a partial date of diagnosis is provided, the following imputation rules will be used:

- If the day is missing but month and year are present, impute day as the first day of the month.
- If only the year of diagnosis is present, impute month and day of diagnosis to January 1.

For partial treatment discontinuation dates, the following logic will apply:

- If the patient died within the same month and year as treatment discontinuation, use the date of death as the treatment discontinuation date.

- Otherwise, if day is missing, but month and year are present, use the last day of the month.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, baseline values are the last non-missing measurements collected prior to the first administration of study treatment. Typically, this is the value collected at the screening visit.

Nominal visit numbers as recorded in the eCRF will be used; there will be no windowing of visits. Study day will be calculated relative to the date of first administration of study treatment. The day prior to date of first administration will be 'Day -1', and the date of first administration of study treatment will be 'Day 1'. There will be no 'Day 0'.

7. PLANNED ANALYSIS

Unless otherwise specified, summary statistics for continuous data will include: N, mean, StD, minimum, median and maximum

Tabulations of categorical data will include all possible categories and will display the number of observations in each category with the percentage (%) of the respective treatment group, unless otherwise specified. Percentages will be rounded to one decimal place. A category for missing values will be displayed only if there are actual missing values for a variable.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristics to be summarized include:

- Age [years]
- Sex (male/female)
- Race and ethnicity (as defined in the eCRF)
- Smoking and alcohol use status (as defined in the eCRF)
- Height [cm], weight [kg] and body mass index [kg/m^2]
- ECOG performance status
- EGFR mutation status (negative, L858R, Del19, both, other)
- Oncology history
- Medical conditions,
- Concomitant medications.
- Treatment exposure and compliance
- Vital signs

7.2 CONCOMITANT DISEASES AND MEDICATION

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

7.3 TREATMENT COMPLIANCE

Treatment compliance during each visit interval will be calculated as:

$$\text{Treatment compliance (\%)} = \frac{Number\ of\ doses\ taken\ x\ 100}{Number\ of\ doses\ that\ should\ have\ been\ taken}$$

Overall treatment compliance is the weighted average of available treatment compliance for each visit interval weighted by number of days within the interval. For example: patient whose compliance score=80% at Visit 3, 100% at Visit 4, 100% at Visit 5, the overall compliance for this patient is [(compliance score date at V3 – treatment start date at V2)*0.8 + (compliance score date at V4 - treatment start date at V3)*1 + (compliance score date at V5 - treatment start date at V4)*1]/(compliance score date at V5 - treatment start date).

Overall compliance will be summarized descriptively, and the number and percentage of treated patients reported as compliant with study treatment, defined as overall compliance > 75%, and non-compliance, defined as overall compliance ≤75%, will be summarized.

7.4 PRIMARY ENDPOINT(S)

Primary endpoint analysis is described in Section 7.8 (Safety Analysis).

7.5 SECONDARY AND FURTHER ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoints

Secondary endpoints are described in Section 7.8 (Safety Analysis).

7.7 EXTENT OF EXPOSURE

Total time on treatment (days and number of courses) will be calculated for each patient as follows:

> Exposure time = (date of last administration of study treatment) – (date of first administration of study treatment) + 1

Periods of time reported as off study treatment due to non-compliance or toxicity prior to permanent discontinuation of study treatment will be included in the calculation of treatment time. Descriptive summaries of time on treatment and number of courses of treatment will be presented for all treated patients. Summary of exposure by dose level (30 mg and 20 mg) will also be provided.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

Adverse events will be coded using the most current MedDRA version at the time of database lock. The intensity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

All the analyses of adverse events will be descriptive and will be based on the numbers of patients reported AEs, not on the number of events reported. For further details on summarization of AE data, please refer to the guideline ‘Analysis and presentation of adverse event data from clinical trials‘(5).

Analyses of adverse events will be based on the concept of treatment emergent events. As such, all adverse events with an onset date between the dates of first dose of study treatment until 28 days after the last dose of study treatment will be analyzed as on-treatment AEs. All

adverse events occurring before first dose of study treatment will be assigned to 'screening' and all adverse events occurring after last dose of study treatment + 28 days will be assigned to 'post-treatment'.

An overall summary of adverse events will be presented. This summary will include the following event categories:

- All AEs
- Drug-related AEs
- AEs leading to dose reduction
- AEs leading to treatment discontinuation
- Serious AEs (SAE)
- Highest CTC grade

The frequency and percentage of patients with adverse events will be summarized by highest CTC grade, treatment, primary system organ class (SOC) and preferred term (PT) in each of the following tables:

- All AEs
- Drug-related AEs
- AEs leading to dose reduction
- AEs leading to treatment discontinuation
- Drug-related AEs leading to treatment discontinuation
- SAEs
- Drug-related SAEs
- AEs leading to death

Events in 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.

Primary endpoint: AEs leading to dose reduction

The frequency and percentage of treated patients reporting the primary endpoint of an AE leading to dose reduction will be reported with an exact 95% Clopper-Pearson confidence interval for this proportion. No formal hypothesis testing will be performed.

Secondary endpoint: Time to first dose reduction of study treatment caused by an AE

The following definitions will be used to analyze the secondary endpoint of time to first dose reduction of study treatment caused by an AE.

For patients with AEs leading to dose reduction:

> Time to first dose reduction [days] = (date of first dose reduction) – (date of first administration of study treatment) + 1

For patients without AEs leading to dose reduction:

> Time to first dose reduction (censored) [days] = (date of last administration of study treatment) – (date of first administration of study treatment) + 1

The Kaplan-Meier estimate of median time to first dose reduction of study treatment due to AE will be presented, if calculable. In addition, the cumulative percentage of patients with dose reductions due to each AE by time interval will be summarized..

Secondary endpoint: Occurrence of CTCAE grade 3 or higher diarrhea, rash/acne+, stomatitis+ and paronychia+

The frequency and percentage of treated patients reporting project-defined grouped terms, including diarrhea, rash/acne+, stomatitis+ or paronychia+, will be summarized. The frequency of events will be summarized by highest CTC grade, i.e. grade 3, 4 or 5, treatment, SOC and PT.

Events designated with a '+' are project-defined grouped terms. Definitions of the project-defined groupings are included in the technical TSAP. In the summary table, the grouped AEs will replace the MedDRA PTs for all AEs included in the grouped term. A reference table presenting the grouped terms and the MedDRA PTs within each grouping will also be produced.

Listings for events within the grouped terms of diarrhea, rash/acne+, stomatitis+ or paronychia+ will display intensity, time to onset and clinical consequences of these events.

7.8.2 Laboratory data

Analyses of laboratory data will be descriptive and will be based on BI standards (6).

Primary laboratory tests defined in the protocol include:

- Low values (-): haemoglobin, total WBC, platelets, neutrophils, lymphocytes, potassium, magnesium, sodium, and GFR
- High values (+): AST, ALT, alkaline phosphatase, aPTT, INR, creatinine, total bilirubin, and CPK

The following analyses will be presented for the primary laboratory tests:

- Descriptive statistics at each planned assessment
- Frequency of patients with transitions in CTCAE grade from baseline to worst value and from baseline to last values collected during treatment
- Frequency of patients with possible clinically significant abnormalities

Possible clinically significant abnormalities are defined as CTCAE grade 2 or higher with an increase of at least one grade from baseline.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. Summaries of absolute values and changes from baseline will be presented for systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

7.8.4 ECG

Abnormalities observed on ECGs will be recorded as baseline conditions or adverse events, as appropriate. No additional analyses of ECG findings are necessary.

7.8.5 Others

Not applicable.

8. REFERENCES

1. CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

2.

3. Common terminology criteria for adverse events v4.0 (CTCAE) (publish date: May 28, 2009; v4.03: June 14, 2010). Website: www.oncology.tv/.../NationalCancerInstituteUpdatesCTCAEtov403.aspx; Common Terminology Criteria for Adverse Events, Version 4.03. , NCI, NIH,DHHS, Publish date: May 28, 2009; 4.0, Publish Date: June 14,2010 4.03 [R12-2532].

10. HISTORY TABLE

Table 10.1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	25-Mar 19		None	This is the final TSAP without any modification.