# Trial Statistical Analysis Plan

**c23337948**

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| **BI Trial No.:** | 1200.222 |
| **Title:** | A phase II study of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy |
| **Investigational Product(s):** | **Giotrif®/ Gilotrif™ (**afatinib) |
| **Responsible trial statistician(s):** | Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 16 APR 2018 SIGNED |
| **Version:** | Final |

# 1. TABLE OF CONTENTS

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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 |
| OR | Objective response |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| PP | Per-protocol |
| PT | Preferred term |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SD | Stable disease |
| SOC | System organ class |

| Term | Definition / description |
|---|---|
| TKI | Tyrosine kinase inhibitor |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| TTP | Time to 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

There has been no change in the planned analyses from the statistical methods described in the CTP.

# 5. ENDPOINT(S)

## 5.1 PRIMARY ENDPOINT

**Objective response in Part A,** defined as patients with tumor size reduction of a predefined amount using RECIST 1.1 in part A. Objective responses include both confirmed partial responses (PR) plus complete responses (CR).

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoint

There are no key secondary endpoints.

### 5.2.2 Secondary endpoints

**Disease control in Part A**, defined as patients who have achieved confirmed complete response, partial response and stable disease per RECIST 1.1 in part A.

**Progression Free Survival (PFS) in Part A**, defined as the time from the date of starting treatment of afatinib to the date of disease progression per RECIST 1.1, or to the date of death no matter which happens first in part A.

**Overall survival (OS) in Part A,** defined as the time from start of treatment of afatinib until death from any cause.

**Time to progression (TTP) in Part A**, defined as the time from the date of starting treatment of afatinib to the date of disease progression per RECIST 1.1 in part A.

**Duration of response (DoR) in part A,** defined as the time from the first documented response PR or CR to the date of tumor progression evaluated according to RECIST 1.1 or death in part A.

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENT

This is a single arm study, which consists two treatment parts, Afatinib monotherapy (Part A) and Afatinib combined with weekly paclitaxel (Part B). Part A and part B are conducted sequentially.

There is only one treatment group in this study in Part A, which is Afatinib monotherapy. The following study periods for Part A based on actual start and stop dates of study treatment administration are defined:

- Part A Screening Visit 1:

  Patients with positive HER2 Mutation Status= from day of informed consent to day that patient has the texted positive HER2 mutation status or day prior to the first assessment scheduled in screening visit 2 whichever comes late

  Patients with negative HER2 Mutation Status= from day of informed consent to the day that patient has the texted negative HER2 mutation status

- Part A Screening Visit 2: from the first assessment scheduled in screening visit 2 to day prior to starting study treatment of Afatinib.

  The last day of Part A screening visit 1 can be prior to or at the same day as the first day of the screening visit 2.

- Part A on-treatment: from day of first administration of afatinib to the day of last administration of afatinib monotherapy.
- Part A residual effect period (REP): from last day of part A on-treatment period + 1 day through the 30$^{th}$ day after last administration of afatinib monotherapy for patients not entered to Part B
- Part A off-treatment: from 31$^{st}$ day after last administration of afatinib monotherapy for patients not entered to Part B

Part A REP and off-treatment periods are not defined for patients who are entered to Part B. Safety data recorded up to the 30$^{th}$ day after last administration of afatinib monotherapy 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).

There is also only one treatment in Part B, which is afatinib combined with weekly paclitaxel. The following study periods will be defined for Part B:

- Part B screening: from last day of Part A on treatment period +1 day through the day prior to starting study treatment of paclitaxel plus afatinib.
- Part B on-treatment: from day of first administration of combination treatment to the day of last administration of study medication. If the patient entered to Part B but did not receive paclitaxel, the date of administration of afatinib will be used as the start date of Part B on-treatment period.

- Part B residual effect period (REP): from last day of part B on-treatment period + 1 day through the 30th day after last administration of study medication, for patients entered to Part B
- Part B off-treatment: from 31st day after last administration of study medication to the last follow up visit or death, which occurs first, for patients entered to Part B

Safety data recorded up to the 30th day after last administration of study medication 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).

Adverse event with onset date prior to first administration of paclitaxel and afatinib combined therapy will be considered as Part A adverse event. Adverse events with onset date on or after first administration of paclitaxel and afatinib combined therapy will be considered as Part B adverse events.

## 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 | Excluded from |
|---|---|---|---|---|
| A | | Inclusion Criteria Not Met | | |
| | A1 | Inclusion Criteria Not Met for Part A | | |
| | A1.1 | Diagnosis of NSCLC questionable (or incorrect disease stage ) | Inclusion criteria IN1 for part A not met | None |
| | A1.2 | No presence of HER2 mutation in tumor tissue as confirmed by AmoyDx® HER2 Mutation Detection Kit | Inclusion criteria IN2 for part A not met<br>or<br>HER2 mutation negative | None |
| | A1.3 | No measurable tumor lesion that can accurately be measured<br>by CT scan or MRI according to RECIST 1.1 | Inclusion criteria IN3 for part A not met | None |
| | A1.4 | Age <=18 years | Inclusion criteria IN4 for part A not met | None |
| | A1.5 | ECOG performance score > 1 | Inclusion criteria IN5 for part A not met | None |
| | A1.6 | Inadequate organ function | Inclusion criteria IN6 for part A not met | None |
| | A1.7 | Not recovered from any previous therapy related toxicity to ⩽Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia) | Inclusion criteria IN7 for part A not met | None |
| | A2 | Inclusion Criteria Not Met for Part B | | |
| | A2.1 | Inadequate organ function before entering to Part B | Inclusion criteria IN1 for part B not met | None |
| | A2.2 | ECOG performance score > 1before entering to Part B | Inclusion criteria IN2 for part B not met | None |
| | A2.3 | Not enough clinical benefit in part A (that is, tumor response at week 8 and<br>week 12 is CR, PR or SD) | Inclusion criteria IN3 for part B not met | None |
| B | | Exclusion Criteria Met | | |
| | B1 | Exclusion Criteria Met for Part A | | |
| | B1.1 | Prior treatment with EGFR or HER2 targeting small molecules or antibodies. | Exclusion criteria EX1 for part A met | None |
| | B1.2 | Any chemo-, or immune anticancer therapy within 4 weeks prior to start of study treatment, Hormonal treatment within 2 weeks prior to start of study treatment,<br>Radiotherapy within 4 weeks prior to start of study treatment, except as follows:<br>i.) Palliative radiation to target organs other than chest may be allowed up to 2<br>weeks prior to enter, and<br>ii.) Single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling. | Exclusion criteria EX2 for part A met | None |
| | B1.3 | Major surgery within 4 weeks before starting study treatment or scheduled for<br>surgery during the projected course of the study | Exclusion criteria EX3 for part A met | None |
| | B1.4 | Known hypersensitivity to afatinib or the excipients of any of the trial drugs | Exclusion criteria EX4 for part A met | None |

| Category / Code | | Description | Comment/Example | Excluded from |
|---|---|---|---|---|
| | B1.5 | History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥ 3, unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to first Afatinib dose. | Exclusion criteria EX5 for part A met | None |
| | B1.6 | Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug. | Exclusion criteria EX6 for part A met | None |
| | B1.7 | Previous or concomitant malignancies at other sites, except effectively treated non−melanoma 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 EX7 for part A met | None |
| | B1.8 | Requiring treatment with any of the prohibited concomitant medications listed in protocol Section 4.2.2.1 that cannot be stopped for the duration of trial participation | Exclusion criteria EX8 for part A met | None |
| | B1.9 | Known pre-existing interstitial lung disease | Exclusion criteria EX9 for part A met | None |
| | B1.10 | Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption). | Exclusion criteria EX10 for part A met | None |
| | B1.11 | Active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier. | Exclusion criteria EX11 for part A met | None |
| | B1.12 | Known Leptomeningeal carcinomatosis. | Exclusion criteria EX12 for part A met | None |
| | B1.13 | Symptomatic brain metastases; To be eligible patients must be asymptomatic from brain metastases at least 4 weeks without requirement for steroids or anti-epileptic therapy | Exclusion criteria EX13 for part A met | None |
| | B1.14 | Women of child-bearing potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly prior to study entry, for the duration of study participation and for at least 2 weeks after treatment has ended. | Exclusion criteria EX14 for part A met | None |
| | B1.15 | Women who are pregnant, nursing, or who plan to become pregnant while in the trial | Exclusion criteria EX15 for part A met | None |
| | B2 | Exclusion Criteria Met for Part B | | |

| Category / Code | | Description | Comment/Example | Excluded from |
|---|---|---|---|---|
| | B2.1 | Any known contraindication for paclitaxel treatment | Exclusion criteria EX1 for part B met | None |
| | B2.2 | Not able to tolerate lowest dose of 20 mg afatinib. | Exclusion criteria EX2 for part B met | None |
| | B2.3 | Peripheral polyneuropathy >Grade 2. | Exclusion criteria EX3 for part B met | None |
| C | | Informed Consent | | |
| | C1 | Informed consent not given | Inclusion criteria IN8 not met<br>or<br>consent date is missing | None |
| | C2 | Informed consent given too late | Inclusion criteria IN8 not met | None |
| D | | Trial medication and Concomitant medication | | |
| | D1 | Prohibited medication use | Review concomitant medications for prohibited medication use. Refer to Section 4.2.2 of the CTP. | None |
| | D2 | Non-compliance of trial medication | e.g., compliance rate<80% | |
| E | | Others | | |
| | E1 | Subjects who met discontinuation criteria but still continue in the study | | None |

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

## 6.3 PATIENT SETS ANALYSED

### Enrolled set 1 (ES1)

The enrolled set consists of all patients who signed informed consent and entered Screening Visit 1.

### Enrolled set 2 (ES2)

The enrolled set consists of all patients who entered Screening Visit 2. .

### Treated set (TS)

This patient set includes all patients who were dispensed with and documented to have taken at least one dose of study medication. This set of patients will be used for the evaluation of efficacy and safety.

Part A and Part B will be analysed separately.

## 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:

For PFS, duration of tumour response and duration of disease control, if a patient is known to have progressed, but the date of progression (progymd) is not attainable, the following sequence for imputation of progression date will be followed:

- Use the date of cancer related symptoms assessment or visit date in which the progression was recorded (whichever is earliest)
- If this is missing, use the last known visit date or cancer related symptom assessment date prior to the recorded progression (regardless of the disease assessment result at that visit).
- If any such patient has no visit date or cancer related symptoms assessment date recorded at all, the date of first administration of study medication will be used as the date of disease progression

For overall survival, if a patient is known to have died (due to any cause), but date of death is not attainable, the last date when the patient is known to be alive will be used as date of death.

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 for Part A and prior to first administration of afatinib or paclitaxel for Part B.

Except for Cycle 1 (see CTP Flowchart: Part A), the time windows for subsequent clinic visits is 28 -2/+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 first follow-up visit should be between 27 and 33 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 appendix tables, the set of summary statistics is: N/Mean/SD/Min/Q1(lower quartile)/Median /Q3(Upper quartile) /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, all patients in the respective patients set whether they have non-missing values or not). 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
- 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*(height0.725)*(weight0.425))
- Smoking status (Never-smoked, Ex-smoker, Current smoker)
- Alcohol status
- Baseline ECOG score
- Oncology history
- Previous therapies

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics using standard summary tables for the Treated Set (TS) are planned for this section of the report.

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

The primary endpoint of the study is Objective Response (OR) to study treatment in Part A, which is defined as patients with tumour size reduction of a predefined amount, includes CR (Complete Response) or PR (Partial Response), judging by the investigator per RECIST 1.1 in part A. The Objective response rate (ORR) is defined as the proportion of patients with objective response of confirmed CR or PR in part A.

The maximum percentage decrease from baseline in the sum of target lesion diameters will be summarized descriptively, the mean, sd, median, and range will be reported. And a waterfall plot of it will be provided. Besides, the patient percentage change from baseline of the sum of target lesion diameter over time will be plotted.

Number of patients in each of below categories of maximum percentage change from baseline in the sum of target lesion diameters will be provided in the table:
1. Missing;
2. >=20% increase;
3. >=0 - <20% increase;
4. >0 - < 30% decrease;
5. >=30% decrease

The primary analysis of response will be done when all treated patients are evaluable for response, the two-sided 95% confidence intervals will be given for the calculated objective response rate using the exact 95% Clopper-Pearson confidence interval.

In addition, at each tumor assessment visit, patient will be assigned to one of the following RECIST categories based on Investigator assessment, irrespective of protocol violations or missing data：
1. CR
2. PR
3. SD
4. Progressive disease (PD)
5. Unknown

Then n(%) of patients tumour response category will be tabulated by tumour assessment visit (objective response without confirmation, CR without confirmation, PR without confirmation, SD, PD, unknown). The total number of patients assessed at the visit will be used as denominator.

## 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

**Disease Control Rate in Part A**

Patients whose best assessment is confirmed CR, PR or SD according to the treating investigator's assessment per RECISIT 1.1 criteria will be considered to have achieved disease control.
The Disease Control Rate (DCR) is defined as the proportion of patients who have achieved disease control. Its estimation and the exact 95% Clopper-Pearson confidence interval will be calculated.

**Progression-free survival (PFS) in Part A**
Disease progression will be evaluated according to the RECIST 1.1 criteria.
PFS with regard to Part A is defined as the time (number of days) from the date of the first administration of afatinib to the date of progression or to the date of death (due to any cause), whichever occurs first.

PFS in Part A will be derived as:

PFS [days] = (the earliest of: date of progression or death due to any cause under Afatinib monotherapy) – (date of first administration of Afatinib in Part A) + 1

For patients known to be alive and without progression by the end of study or follow-up visit, they will be censored at the date of last imaging without progression. For patients that are known to have progressed, but with unknown date of progression, refer to Section 6.6 for more detail.

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

*Censoring rules for PFS*:

- For patients who have definitely not progressed or died whilst on study treatment, these patients will be censored at the last known visit date or cancer related symptoms assessment date (up to and including the EOT visit).
- For patients with unknown progression status (no tumour assessment reported or 'not evaluable' assessment) at the final on treatment or EOT visit, these patients will be censored at the last known visit or cancer related symptoms assessment date, where the tumour assessment was SD, PR or CR.
- For patients with no on treatment tumour assessments (either missing or 'not evaluable'), these patients will be censored at the date of first administration of afatinib.

**Overall survival (OS) in Part A**
OS (months), defined as the time from the date of first administration of Afatinib to the date of death due to any cause.

OS will be derived as:

Overall Survival [days]=date of death-(date of first administration of Afatinib in Part A) +1;

For patients known to have died (due to any cause), with the date of death missing, refer to Section 6.6 for more detail.

Kaplan-Meier estimates and corresponding 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for overall survival, using Greenwood's standard error estimate. Kaplan-Meier curves will also be produced.
*Censoring rules for OS:*
Patients know to be alive by the end of the trial or follow-up visit (ignoring secondary treatment) will be censored at the last date the patient is known to be alive.

**Time to progression (TTP) in Part A**
TTP in part A is defined as the time (number of days) from the date of starting treatment of afatinib to the date of disease progression in part A.
TTP will be derived as:
TTP [days]=date of progression-date of start first administration of Afatinib in Part A +1

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

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

**Duration of response (DoR) in part A**

Defined as the number of months from first documented objective response (latest of: cancer related symptoms assessment date or visit date where first documented OR recorded) to the time of tumor progression or death (due to any cause) in Part A.

For patients with confirmed objective response only, Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for duration of objective tumour response. Greenwood's standard error estimate will be used. Kaplan-Meier curves will also be produced.

*Censoring rules for duration of objective tumour response (progression date):*

- For patients who have definitely not progressed or died whilst on study treatment, these patients will be censored at the last known visit date or cancer related symptoms assessment date (up to and including the EOT visit).
- For patients with unknown progression status (no tumour assessment reported or 'not evaluable' assessment) at the final on treatment or EOT visit, these patients will be censored at the last known visit or cancer related symptoms assessment date, where the tumour assessment was CR, PR or SD.

## 7.7 EXTENT OF EXPOSURE

Treatment exposure for Treatment A and B will be calculated separately.

Afatinib

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.

Paclitaxel

Total treatment period 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 paclitaxel treatment, date of death) + 1 day

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

## 7.8 SAFETY ANALYSIS

All patients who receive at least one dose of trial medication will be included in the safety analysis. All safety analysis described below will be performed for patients in part A and part B separately. (see CTP Section 7.3.4).

### 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 4.0 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.

Adverse events will be coded using the Medical Dictionary for Regulators Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after the last dose if trial medication, will be assigned to the treatment period for evaluation.

Standard tabulations arranged by MedDRA SOC and PT will include (see CTP Section 7.3.4):

- the overall incidence and intensity of adverse events,
- AE judged to have been related to afatinib
- AE leading to dosage reduction
- AE leading to permanent treatment discontinuation
- SAE
- Fatal outcome

These standard tables will be supplemented with tables in which MedDRA SMQ and HLT (with some modifications) will be used to group MedDRA PT for the following:

- rash/acne
- stomatitis
- paronychia
- fatigue

Listings will be prepared of patients who are identified as having experienced any of the following AE. For AE other than dehydration, identification will be based upon modified MedDRA SMQ and HLT groupings.

- dehydration
- renal insufficiency
- hepatic impairment
- ILD-like events
- heart failure
- Keratitis
- Pancreatitis

- Severe skin reaction
- Gastrointestinal perforation
- Hypersensitivity reaction

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.
- AE of special interest

As per protocol AESI (CTP Sect 5.3.5) hepatic injury is considered as AESI. Some other pre-defined AEs are considered of special interest for the safety analysis too including diarrhea, rash/acne, renal insufficiency, stomatitis, interstitial lung disease, keratitis, severe skin

reactions, pancreatitis, heart failure, gastrointestinal perforation, and hypersensitivity reactions.

For Part B, drug related AE will be displayed separately for afatinib plus paclitaxel.

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/acne, stomatitis, paronychia, fatigue, acute renal failure with severe diarrhea, severe cutaneous AEs, ILD, keratitis, hepatic impairment, pancreatitis, heart failure, gastrointestinal perforation, and hypersensitivity reactions).

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 the AEs of special interest, 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

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). CTCAE version 4.0 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’ (9).

Primary laboratory tests are defined as:

• Low values (-): haemoglobin, total WBC, platelets, neutrophils(only at baseline), potassium, magnesium, sodium, and GFR

• High values (+): AST, ALT, alkaline phosphatase, aPTT, INR, creatinine, and total bilirubin

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 and last values during treatment, and

• frequency of patients with possible clinically significant abnormalities.

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

Frequency and time of onset of liver enzyme elevations will be tabulated. Additional, more in-depth analyses will be performed as needed. These analyses will examine the influence of extent of exposure and time to event onset.

### 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

A 12-lead resting ECG will be performed at the time points specified in the Flow Charts. 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.

# 10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| Final | **16-Apr-18** | | None | This is the final TSAP. |