Trial Statistical Analysis Plan

c01527097-02

BI Trial No.:	1200.55
Title:	An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s).
Investigational Product(s):	Afatinib (Giotrif®) (BIBW 2992)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted] [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	12 Jun 2017 Signed
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse event
BAS	Biomarker analysis set
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
MI	Myocardial infarction
Min	Minimum
mRNA	Messenger Ribonucleic Acid
N	Denotes number of patients
NSCLC	Non-small cell lung cancer
IPV	Important protocol violation
OR	Objective response
OS	Overall survival
PD	Progressive disease

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

3. INTRODUCTION

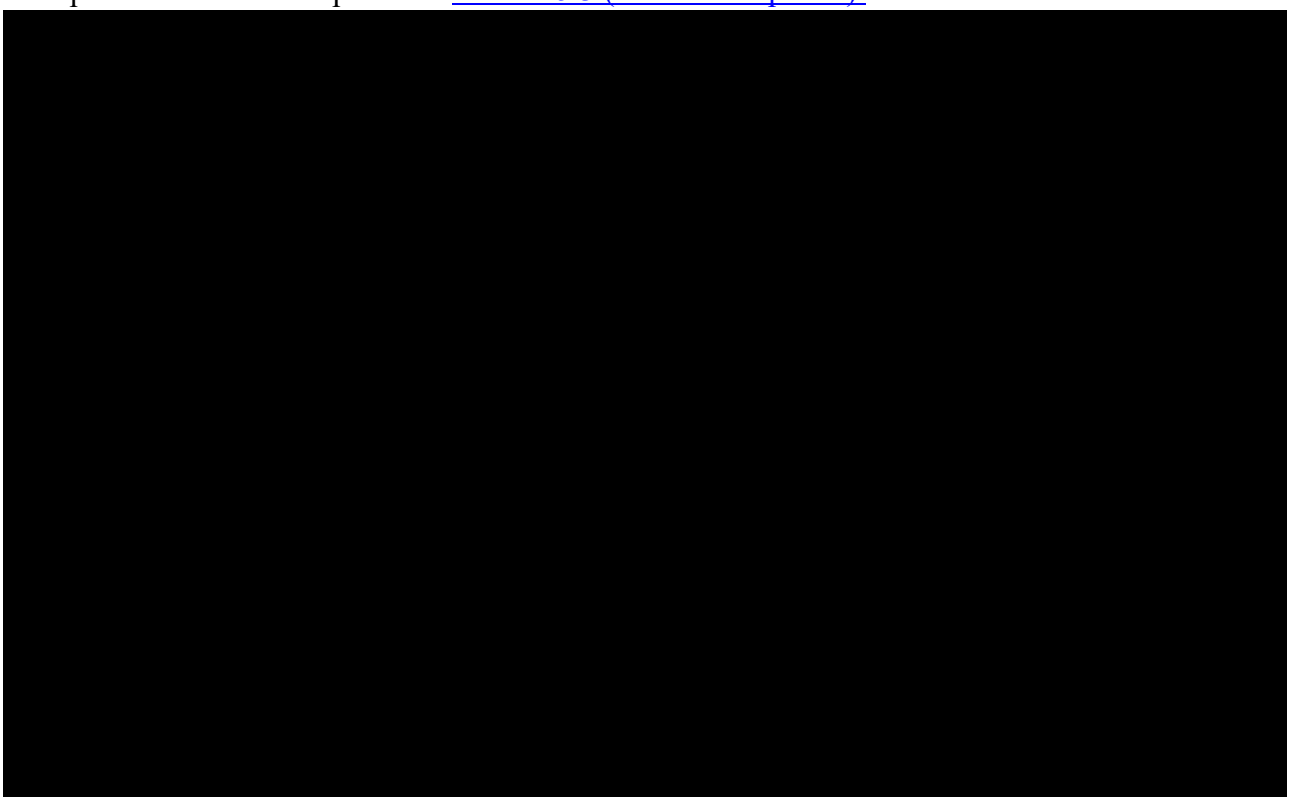
As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This 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 9.2 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Section 7.3.2 of the CTP describes the "Secondary Analysis" of the efficacy endpoints. It was decided to consider the efficacy endpoints as further endpoints rather than secondary endpoints due to disclosure requirements. Hence this TSAP describes these efficacy endpoints as further endpoints in Section 5.3 (Further Endpoints).



5. ENDPOINTS

This is an open-label, multi-centre, non-randomised, uncontrolled, single arm trial designed to evaluate the safety, tolerability and anti-tumour activity 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 tolerability and anti-tumour activity of afatinib (Giotrif®) in this cohort of patients. Of main interest are AEs, collected throughout the study.

No specific tumour measurements are required in this program. Disease assessment will be based on the assessment of cancer related symptoms, tumour assessment (clinical, radiological or other), overall clinical benefit and, if available, radiologic assessments as per standard of care at the site. Data on tumour response, progression-free survival (PFS) and overall survival (OS) will be collected where possible.

5.1 PRIMARY ENDPOINT

The number of patients with adverse events according to CTCAE V 3.0.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

There are no key secondary endpoints.

5.2.2 Secondary endpoints

There are no secondary endpoints.

[redacted]

[redacted]

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 reduce further to 20 mg from 30 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 study treatment, 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: From day after last administration of study treatment to the 28^{th} day after last administration of study treatment

- Follow-up: After the residual effect period and up to the last per protocol contact if last per protocol contact is after residual effect period.

- Post-study: After the last per protocol contact or residual effect period (if last per protocol contact is same as 28^{th} day after last administration of study treatment) 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 residual effect periods defined above will be combined into one 'on-treatment' analysis period).

Safety data recorded after the residual effect period and up to the last per protocol contact will be listed as follow-up events. Those recorded after the last per protocol contact but entered in the database before lock will be listed as post-study events but not tabulated.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol (PP) 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	Locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC)	Inclusion criterion IN1 not met	E
	A1.2	Epidermal Growth Factor Receptor (EGFR) mutation-positive result per the institution's testing methodology.	Inclusion criterion IN2 not met or EGFR mutation positive result is marked as No	E
	A1.3	Male or female patients age ≥18 years	Inclusion criterion IN3 not met or patient's age <18 years	E/S
	A1.4.1	Adequate organ function as defined in protocol version 1	Inclusion criterion IN4 not met	E/S
	A1.4.2	Adequate organ function as defined in protocol version 2	Inclusion criterion IN4 not met	E/S
	A1.5	ECOG score between 0 – 2	Inclusion criterion IN5 not met or Baseline ECOG score not between 0-2	E
	A2	Exclusion Criteria Met		
	A2.1	prior treatment with an EGFR tyrosine kinase inhibitor (TKI)	Exclusion criterion EX1 met	E
	A2.2	Anti-cancer treatment within 2 weeks prior to start of trial treatment	Exclusion criterion EX2 met	E
	A2.3	Radiotherapy within 14 days prior to drug administration	Exclusion criterion EX3 met	E
	A2.4	Major surgery within 4 weeks before starting trial treatment or scheduled for surgery during the projected course of the trial	Exclusion criterion EX4 met	E/S
	A2.5	Known hypersensitivity to afatinib or any of its excipients	Exclusion criterion EX5 met	S
	A2.6	History or presence of clinically relevant cardiovascular abnormalities or MI within 6 months prior to starting trial treatment	Exclusion criterion EX6 met	S
	A2.7.1	Women of child-bearing potential and men who are able to father a child, unwilling to use adequate contraception prior to trial entry, for the duration of trial participation and for at least 2 weeks after treatment has ended (protocol version 1).	Exclusion criterion EX7 met	S
	A2.7.2	Women of child-bearing potential and men who are able to father a child, unwilling to use adequate contraception prior to trial entry, for the duration of trial participation and for at least 28 days after treatment has ended (protocol version 2).	Exclusion criterion EX7 met	S

Table 6.2: 1 Important protocol violations (cont.)

Category / Code		Description	Comment/Example	Efficacy/ Safety
	A2.8	Women of child-bearing potential who are nursing or pregnant or do not agree to submit to pregnancy testing as required by this protocol	Exclusion criterion EX8 met	S
	A2.9	Any history of or concomitant 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 criterion EX9 met	E/S
	A2.10	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 criterion 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 criterion EX11 met	E
	A2.12	Known pre-existing interstitial lung disease	Exclusion criterion EX12 met	S
	A2.13	Presence of poorly controlled gastrointestinal disorders that could affect the absorption of the trial drug	Exclusion criterion EX13 met	E
	A2.14	Active hepatitis B infection, active Hepatitis C (HEP C) and/or known Human Immunodeficiency Virus (HIV) carrier.	Exclusion criterion EX14 met	S
	A2.15	Meningeal carcinomatosis	Exclusion criterion EX15 met	E/S
	A2.16	Symptomatic brain metastases	Exclusion criterion EX16 met	E/S
B		Informed Consent		
	B1	Informed consent not given	Inclusion criterion IN6 not met or Written informed consent by patient or guardian prior to admission into the trial is not given.	S
	B2	Informed consent given too late	Inclusion criterion IN6 not met	S
	B3	Incorrect or not updated Informed consent given		S
	B4	Informed consent conducted by staff not on trial staff list		S
	B5	Incomplete informed consent		S
	B6	Informed consent not completed by patient		S

Table 6.2: 1 Important protocol violations (cont.)

Category / Code		Description	Comment/Example	Efficacy/ Safety
C		On Study		
	C1	Serious GCP non-compliance [e.g. delayed SAE reporting, expired drugs, incorrect trial medication dose, source data not available]		S
	C2	Incorrect timing of measurements at visit days		S
	C3	Other PV affecting efficacy and possibly safety		E/S
	C4	Other PV affecting safety only		S

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol violations. 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 study treatment (afatinib) and are documented to have taken at least one dose of study treatment (afatinib).

[redacted]

[redacted]

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 objective response and duration of disease control, if a patient is **known** to have progressed during the treatment period, but the date of progression 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, the last known visit date or cancer related symptoms assessment date prior to the recorded progression (regardless of the disease assessment result at that visit) will be used.
    - 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.

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.

Missing biomarker values will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is 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 intake of afatinib and the follow-up visit should be between 21 and 28 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 afatinib. The day prior to first administration of afatinib will be 'Day -1' and the day of first administration of afatinib 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 (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 details
    - Previous therapies:
        - Systemic chemotherapies
        - Other anti-cancer therapies
        - Radiotherapies (listed only)
    - Previous surgeries for trial disease

This section will include a summary of all the subgroup variables detailed in Section 6.4(Subgroups). This is presented based on treated set.

It is expected that biomarker values will only be available for a subset of the study population. Therefore, demographics and baseline characteristics will be provided for the BAS as well and compared with the study population.

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 eCRF 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 as no data on compliance is collected.

7.4 PRIMARY ENDPOINT

Refer to Section 7.8 (Safety Analysis).

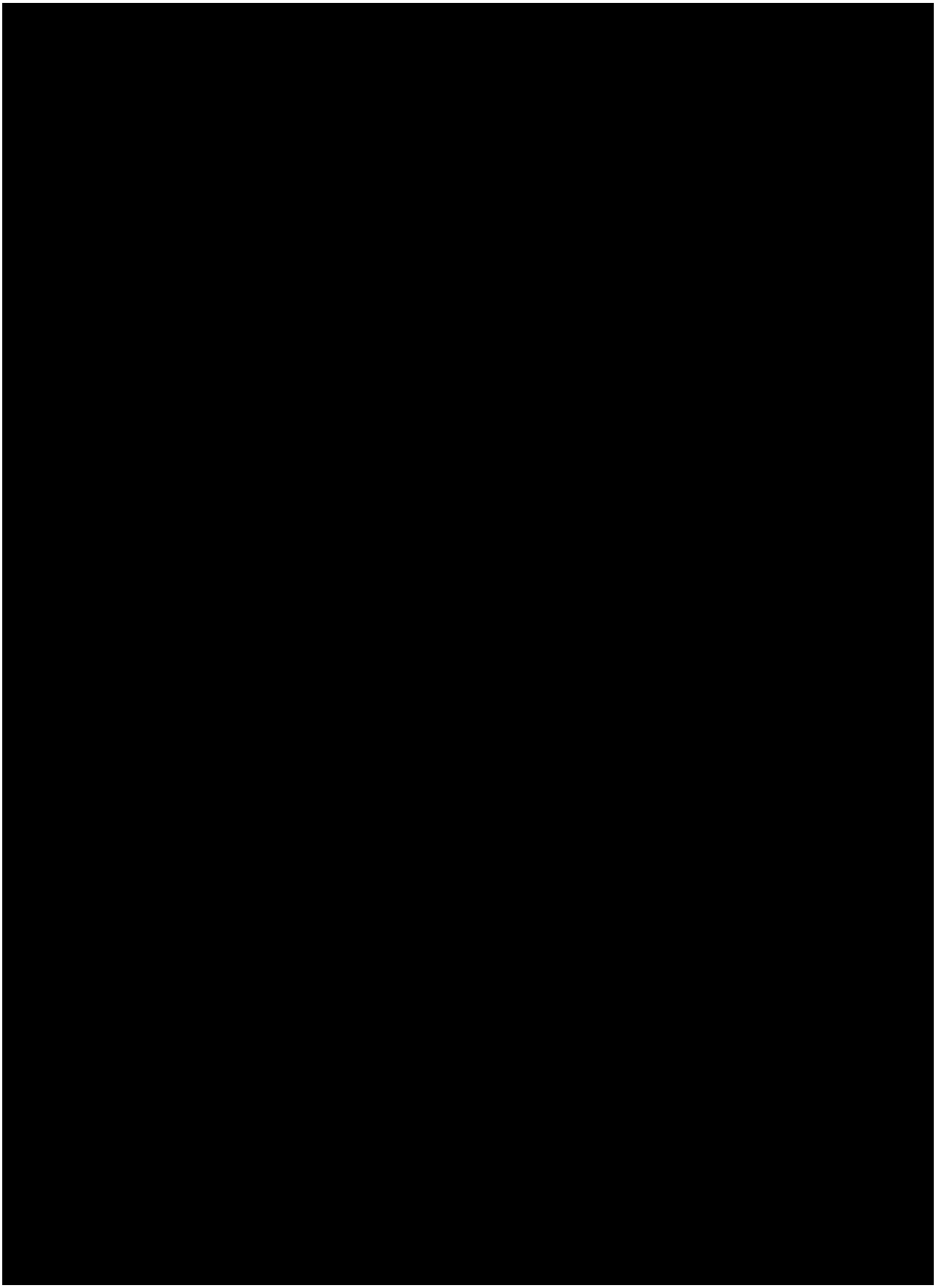
7.5 SECONDARY ENDPOINTS

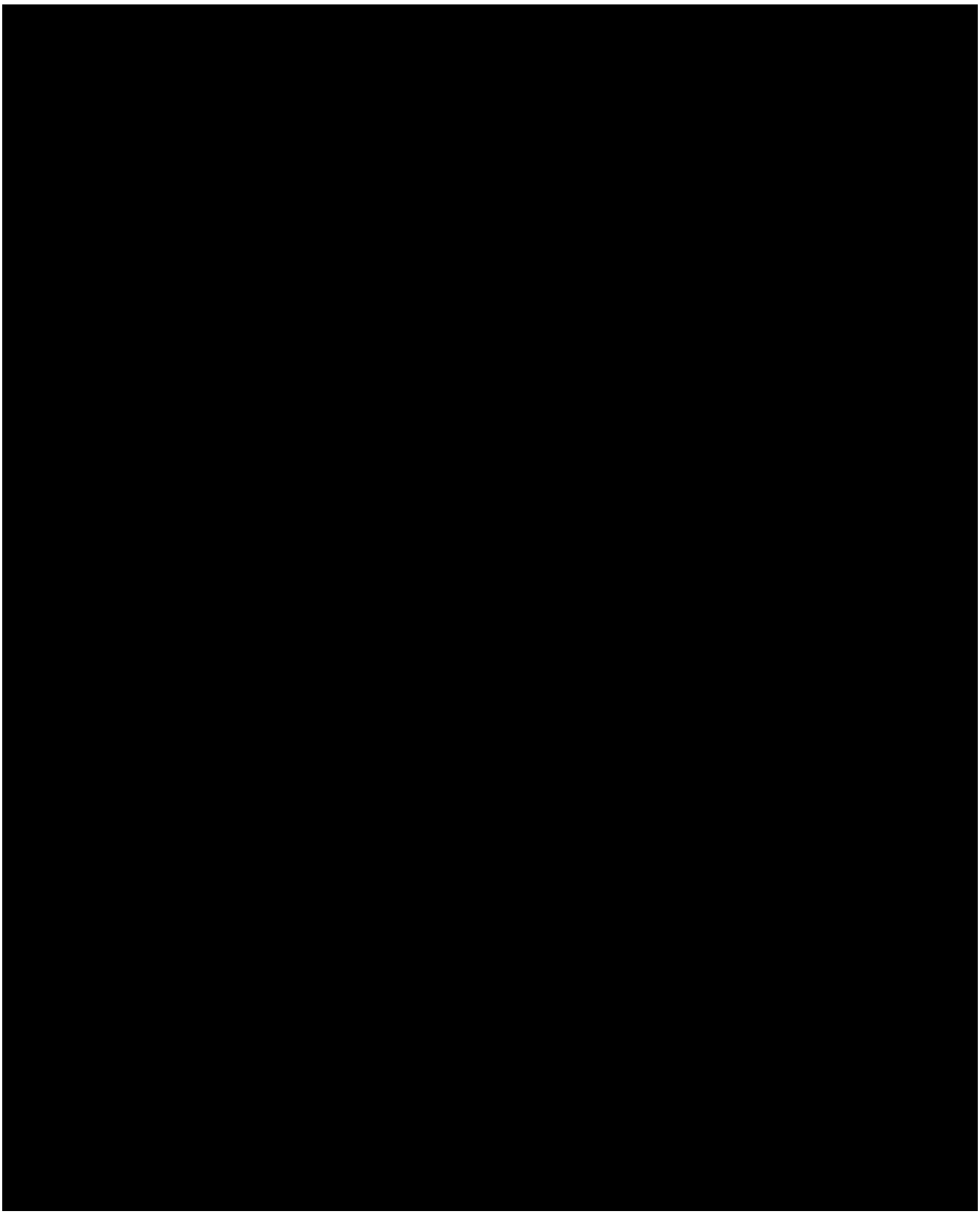
7.5.1 Key secondary endpoints

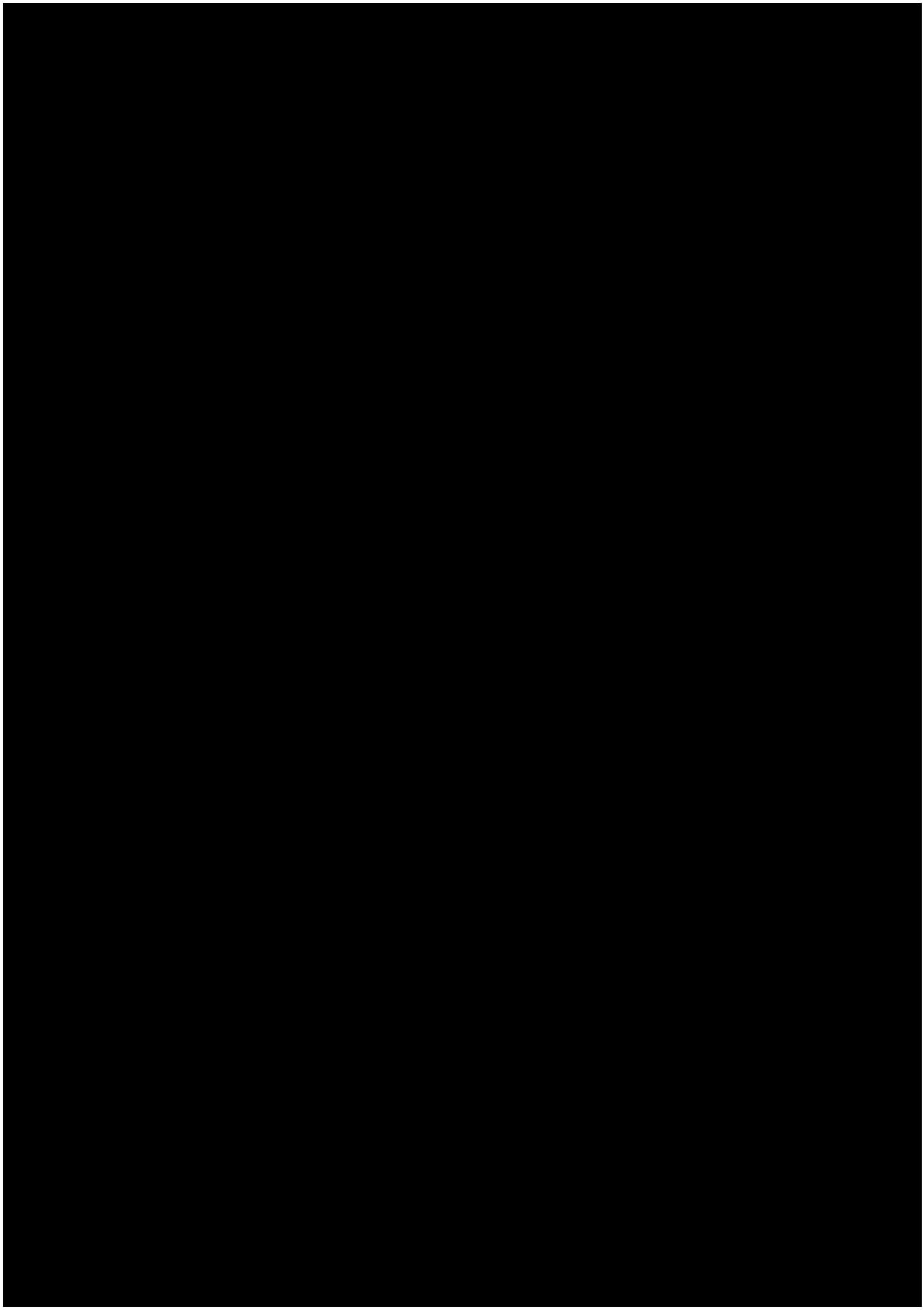
This section is not applicable as no key secondary endpoints have been specified in the protocol.

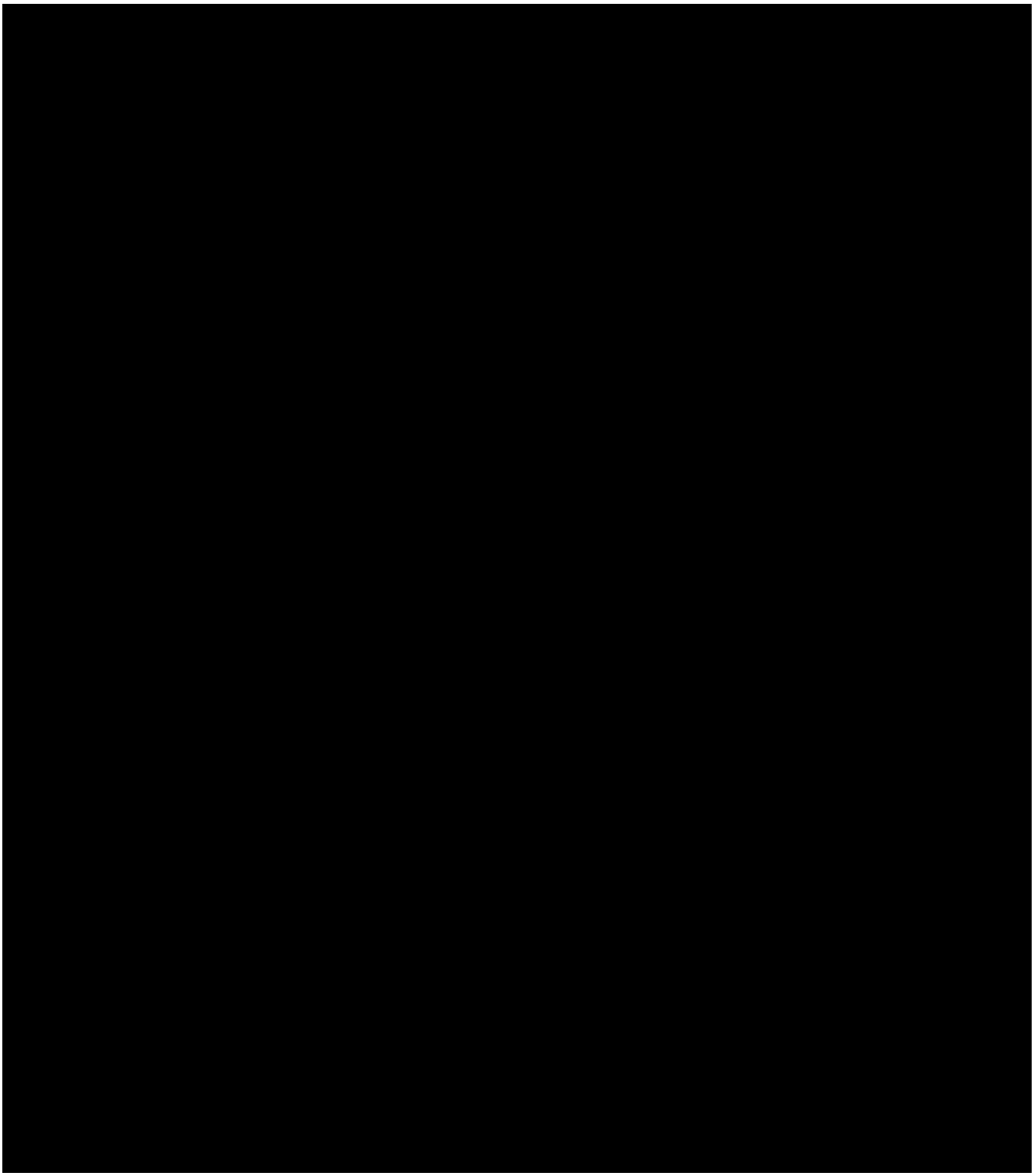
7.5.2 Secondary endpoints

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









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, 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 at the 40 mg dose. 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 treatment includes number of lines of all of the following:

- Systemic chemotherapies: count the number of previous chemotherapies with "therapy mode" as "advanced/palliative" on the previous chemotherapies eCRF page. If "therapy mode" is "neo-adjuvant" or "adjuvant" and taken within 1 year prior to study enrolment, then count them as a separate "line of therapy".
- Other anti-cancer therapies: count the number of anti-cancer therapies with "therapy mode" as "advanced/palliative" on the other anti-cancer therapies eCRF page. If "therapy mode" is "neo-adjuvant" or "adjuvant" and taken within 1 year prior to study enrolment, then count them as a separate "line of therapy". If there is a therapy with the same name and same start and end dates as a therapy present in previous 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 AEs 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 AEs 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 AE data for clinical trial reports and integrated summaries' (2) [001-MCG-156]

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first study treatment intake until 28 days after last study treatment 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(Treatment) and will only be listed unless stated otherwise.

An overall summary of AEs 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 for Adverse Events (CTCAE)' grade.

The frequency of patients with AEs will be summarised by highest CTCAE grade (grades 3, 4, 5 and all grades including 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 for 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 CTCAE grade, action taken with study drug and time to first onset of AE.

Number of patients with AEs with an incidence greater than 5% will be summarised by treatment, primary SOC and PT.

7.8.2 Laboratory data

Only the date of samples is collected; laboratory data are not collected. Laboratory values that are considered clinically relevant will be recorded as baseline conditions or AEs as appropriate.

7.8.3 Vital signs and physical examination

Only descriptive statistics are planned for this section of the report. A summary of the absolute values and the changes from baseline will be presented in 4-week periods and at the EoT visit for the following parameters: systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and body weight.

Other than at baseline, repeat, adhoc 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.

A listing for LVEF results of patients will also be provided. Patients with a significant LVEF event will be flagged in the listing; a significant event is defined as a decrease of ≥20% from baseline that is also below the lower limit of normal for the particular site (50% will be used if the lower limit of normal is missing).

7.8.4 ECG

Only the date of the tracing is collected. Abnormalities will be recorded as baseline conditions or AEs 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	**24-Apr-2017**	[redacted]	None	This is the final TSAP without any modification