Statistical Analysis Plan
for the 'SYM-Less' Study

Study Title:

"A multicentre, cohort study to assess the impact on **SYM**ptom burden and patient health-related quality of **L**ife of afatinib tr**e**atment in advanced non-**s**mall cell lung cancer in a real world **s**etting in Greece.

The '**SYM-Less**' study"

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1.0	18/12/2018	N/A	Initial Release	N/A

LIST OF ABBREVIATIONS

AE	Adverse Event
AIC	Akaike Information Criterion
ASBI	Average Symptom Burden Index
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EAIR	Exposure-Adjusted Incidence Rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRFs	electronic Case Report Forms
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment
[redacted]	
FAS	Full Analysis Set
FDA	Food and Drug Administration
HRQoL	Health-Related Quality of Life
[redacted]	
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCI	National Cancer Institute
NIS	Non-Interventional Study
[redacted]	

NSADR	Non-Serious Adverse Drug Reaction
NSAE	Non-Serious Adverse Event
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PFS	Progression-Free Survival
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire – Cancer
QoL	Quality of Life
RCT	Randomized Clinical Trial
RSE	Relative Standard Error
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TKIs	Tyrosine Kinase Inhibitors
[redacted]	
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centre for Drug Statistics Methodology

1 INTRODUCTION

1.1 Objectives and Scope of the Statistical Analysis Plan

The purpose of this document is to address the basic statistical activities/methods to be applied for the purposes of the statistical analysis of the data of the clinical study titled "A multicentre, cohort study to assess the impact on **SYM**ptom burden and patient health-related quality of **L**ife of afatinib tr**e**atment in advanced non-**s**mall cell lung cancer in a real world **s**etting in Greece. The '**SYM-Less**' study".

The preparation of this Statistical Analysis Plan (SAP) has been based on the '**SYM-Less**' study protocol version 2.0 (incorporating amendment 1) dated 31 July 2018.

The study data collection will be carried out through electronic Case Report Forms (eCRFs). Data will be handled by the Contract Research Organization (CRO) [redacted], which will also undertake the performance of the statistical analysis and the preparation of the clinical study report (CSR).

1.2 Version Control of the Statistical Analysis Plan

The [redacted] Director or delegate and the Sponsor review and approve the SAP drafted by the Biostatistician. The aforementioned core reviewers ([redacted] Team & Sponsor) must agree to any subsequent changes to the SAP. These changes will require a new version date except for minor changes (i.e. spelling, etc.) that can be made without a version change. The new version must be re-signed by the original signatories and distributed to all involved parties. A master copy of the signed final SAP, as well as the earlier versions, shall be archived in both electronic and hard copy form in the project-specific file.

2 PROTOCOL SUMMARY

Despite a wealth of therapies, prognosis of advanced stage non-small cell lung cancer (NSCLC) is poor, with a median overall survival (OS) approaching 10 months with platinum-based chemotherapy and 2 years with targeted therapies[1,2]. NSCLC bears not only significant mortality but also morbidity as patients suffer from debilitating symptoms, such as cough, chest pain, dyspnoea, anorexia, fatigue and haemoptysis [2,3]. Symptoms are at the cornerstone of patients' well-being, as in a recent survey patients reported that prolongation of progression-free survival (PFS) is the most important factor for choosing a treatment only when disease-specific symptoms are mild, while PFS plays a less central role when considering a treatment choice in the presence of severe symptoms. It is thus not surprising that alleviation of symptom burden has been added to the core of disease management, making it imperative to evaluate not only treatment effectiveness but also health-related quality of life (HRQoL) and symptom burden in both clinical research and routine patient care settings [4,5,6,7].

There is a broad array of questionnaires used in the field of NSCLC for the assessment of HRQoL[8]. Among them, the most commonly used generic instruments assessing global health status are the EuroQoL-5 Dimension (EQ-5D)[9] and the cancer-generic European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire – Cancer (EORTC QLQ-C30)[10]. Moreover, disease-specific instruments assessing HRQoL have been developed for patients with NSCLC including the Functional Assessment of Cancer Therapy – Lung (FACT-L)[11], the EORTC QLQ – Lung Cancer (EORTC QLQ-LC13)[10] and the Lung Cancer Symptom Scale (LCSS)[12].

For patients with NSCLC tumours harbouring mutations of the epidermal growth factor receptor (EGFR), targeted treatments, including the first generation tyrosine kinase inhibitors (TKIs), erlotinib and gefinitib, have shown benefits in terms of prolongation of PFS and increased response rates and improvement of HRQoL[13]. However, resistance to therapy commonly develops, which has led to the development of the irreversible EGFR TKI, afatinib. Afatinib (GILOTRI® / GIOTRIF®) was approved in 2013 by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on results of the pivotal phase 3 studies LUX-Lung 3 and LUX-Lung 6. In the US afatinib is indicated for the first-line treatment of patients with metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, while in Europe, afatinib as monotherapy is indicated for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s)[1,2].

On the ground of the aforementioned evidence, afatinib represents a great advance in the therapeutic armamentarium of advanced NSCLC with activating EGFR mutations. Taking into consideration the limited real-world evidence that is attributed to the recent advent of afatinib in the market, this field non-interventional study (NIS with new data collection) aims primarily at assessing the impact of the therapy on patients' disease-related symptom burden and HRQoL. These parameters are considered as very important for the evaluation of medicines, especially those aiming to treat complicated diseases that impose a heavy symptom burden, impaired quality of life and poor prognosis, such as NSCLC[4]. Importantly, patients' adherence to this orally administered medication will also be assessed.

In addition, the study represents an attempt towards gaining experience on the routine use of afatinib in daily clinical practice in a representative sample of Greek subjects with advanced NSCLC in real-life clinical settings. The study will complement the evidence available from the randomized clinical trials (RCTs) and assist in the decision-making process of the medical professionals that provide care to this heavily burdened population.

2.1 Study objectives and endpoints

2.1.1 Primary objective and endpoint

The primary objective of the study is:

- To evaluate the impact of afatinib therapy on the patient-reported lung cancer-specific symptom burden, using the Average Symptom Burden Index (ASBI) of LCSS in eligible patients, over 6 months of therapy, in a real world clinical setting in Greece.

The primary endpoint of the present study is:

- 6-month symptom improvement rate using the LCSS ASBI, i.e., proportion of patients who will experience a minimum clinically important improvement in symptoms (defined as a decrease in the ASBI from enrolment ≥10 in two consecutive assessments) over 6 months of treatment.

Note: A patient will be categorized as having:

- ✓ *an **improved ASBI** if the mean of any two consecutive post-baseline ASBI assessments for that patient is at least 10 points below the patient's ASBI at enrolment;*
- ✓ *a **worsened ASBI** if the mean of any two consecutive post-baseline ASBI assessments for that patient is at least 10 points above the value at enrolment;*
- ✓ *a **stable ASBI** if the mean of any two consecutive post-baseline ASBI assessments for that patient is within 10 points of the value at enrolment.*

A change of 10 points on a 0-100 scale is considered sufficient to indicate a clinically meaningful change[14,15,16] ; this magnitude is about the same as the 0.5 standard deviation that has also reported as a universally acceptable minimum clinically important difference[17].

2.1.2 Secondary objectives and endpoints

The secondary objectives of the study are:

- To evaluate the effect of afatinib therapy on the patient-reported lung cancer-specific symptom burden, total symptomatic distress, functional activity status and global quality of life, using the LCSS total score and domain subscores, at the post-baseline predefined timepoints;
- To assess the impact of afatinib treatment on the HRQoL of the study population using the EuroQoL- 5 Dimensions- 3 Levels (EQ-5D-3L) questionnaire at the post baseline predefined timepoints;
- To assess the impact of afatinib therapy on patient's Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the post baseline predefined timepoints;
- To record patient adherence to treatment with afatinib during the study observation period as well as the reasons for missing doses;

- To assess the patterns of use of afatinib in routine clinical practice in terms of treatment modifications (permanent discontinuations, temporary interruptions, dose changes), and reasons for these modifications.

The secondary endpoints of the study, pertaining to secondary objectives are the following:

- Change in the total LCSS score, ASBI score and individual domain scores from enrolment to each post-baseline predefined timepoints; in addition change throughout the study observation period will be examined using longitudinal analysis;
- Proportion of patients (n, %) with reported problems for each level for each dimension of EQ-5D and proportion of patients with '*no problems*' (i.e., level 1) and '*with problems*' (i.e., level 2 & 3) at enrolment and at the post-baseline predefined timepoints;
- EQ-visual analogue scale (VAS) score (mean ± SD) at enrolment and at the post-baseline predefined timepoints;
- Change in the proportion of patients in each of the EQ-5D dimension levels (no problems, with problems) and change in the EQ-VAS score between enrolment and post-baseline predefined timepoints;
- Change in ECOG PS scores from baseline to post-baseline predefined timepoints;
- Ratio of doses actually taken to doses prescribed over the study participation period and reasons for discrepancies;
- Proportions of patients with treatment discontinuations, temporary interruptions, or dose change(s) and reasons for treatment modifications.

2.2 Study variables

2.2.1 Efficacy outcome (s)

2.2.1.1 Primary outcome variable

- ASBI score of LCSS -*defined as the mean of the score of the 6 major lung cancer symptoms, i.e. loss of appetite, fatigue, cough, dyspnoea, pain, and haemoptysis*- at enrolment and at the 2-month intervals until the study visit at 6 months.

2.2.1.2 Secondary outcome variables

- Patient-rated ASBI score of LCSS at the post-baseline predefined timepoints *(as defined in Section 3.2);*
- Patient-rated total LCSS score -*defined as the average of the aggregate score of all 9 items that comprise the LCSS*- at enrolment and at the post-baseline predefined timepoints;
- Patient-rated individual LCSS domain scores at enrolment and at the post-baseline predefined timepoints;

- Proportion of patients with reported problems for each level for each dimension of EQ-5D and proportion of patients with 'no problems' (i.e., level 1) and 'with problems' (i.e., level 2 & 3) at enrolment and at the post-baseline predefined timepoints;
- EQ-VAS score at enrolment and at the post-baseline predefined timepoints;
- ECOG PS score at baseline and at the post-baseline predefined timepoints;
- Ratio of doses actually taken to doses prescribed over the study participation period and reasons for discrepancies;
- Proportions of patients with treatment discontinuations, temporary interruptions, or dose modifications and reasons for treatment modifications.

[redacted]

[redacted]

2.2.2 Safety outcome(s)

- ✓ Adverse event (AE) description;
- ✓ Onset date;
- ✓ End date;

- ✓ Ongoing *(yes, no);*
- ✓ Causally related with GIOTRIF® *(yes, no);*
- ✓ Intensity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (*Grade 1 or mild, Grade 2 or moderate, Grade 3 or high, Grade 4 or life-threatening, Grade 5 or death*);
- ✓ Actions taken regarding GIOTRIF® for management of AE *(none, dose reduction, permanent discontinuation, dose increase, completion of treatment according to protocol, treatment interruption and re-initiation, not applicable);*
- ✓ Outcome (recovery, has not yet been recovered/ongoing, recovery with sequelae, death, unknown);
- ✓ Seriousness (yes, no).

2.3 Study design and conduct

This is a non-interventional, multicentre, cohort study, based on new data collection, which will include a representative sample of patients with advanced/metastatic NSCLC in Greece.

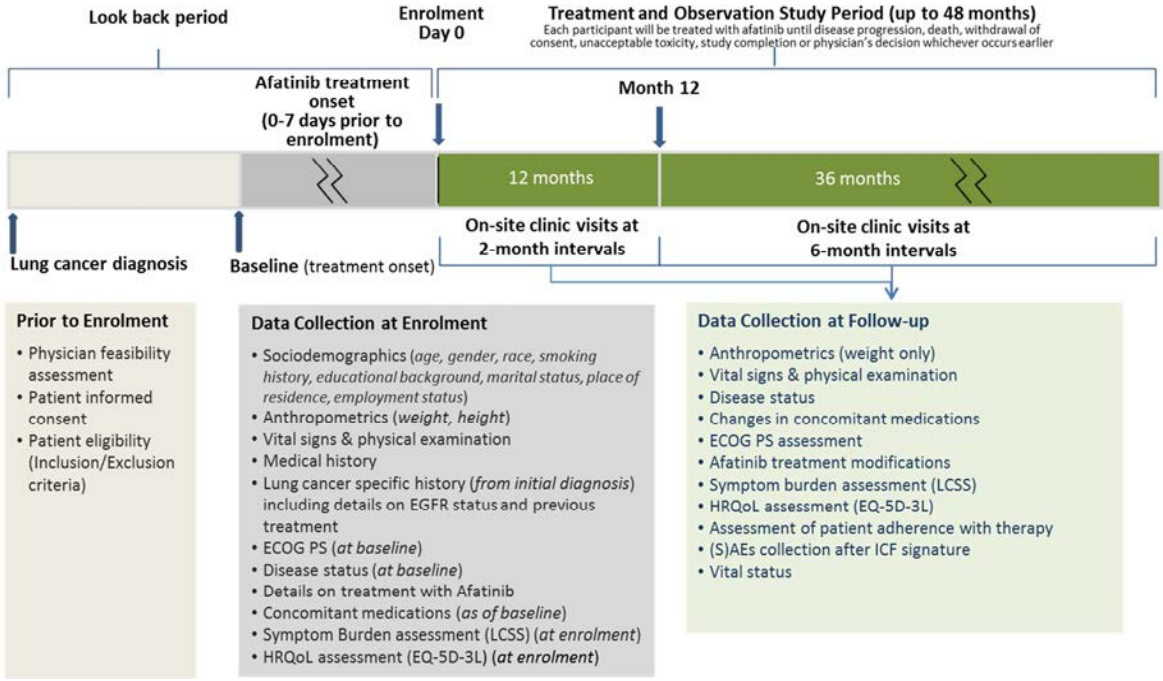
Patients will be treated according to the local prescribing information of the study medication (afatinib, GIOTRIF®) and routine medical practice in terms of visit frequency and types of assessments performed. The assignment of the patient to this therapeutic strategy is not decided in advance by the study protocol but falls within current practice and the prescription of afatinib is clearly separated from the physician's decision to include the patient in the current study.

Since this is purely non-interventional study, primary data -which will be obtained prospectively during the study visits through patients' interview and patient reported outcomes (PROs) or as performed per standard clinical practice- will mainly be employed.

Follow-up visit frequency will be determined by the treating physician, however study-related data will be collected at 2-month (±3 weeks) intervals during the first 12 months of study participation and every 6 months (± 3 weeks) thereafter until the end of the study observation period.

A synoptic study diagram reflecting the assessments of interest and the suggested time schedule is presented in the following Figure 1:

Figure 1: Synoptic Study Diagram



A total of 128 patients are planned to be enrolled by seven (7) Oncology and Pulmonology hospital centres/clinics in Greece specialized in lung cancer.

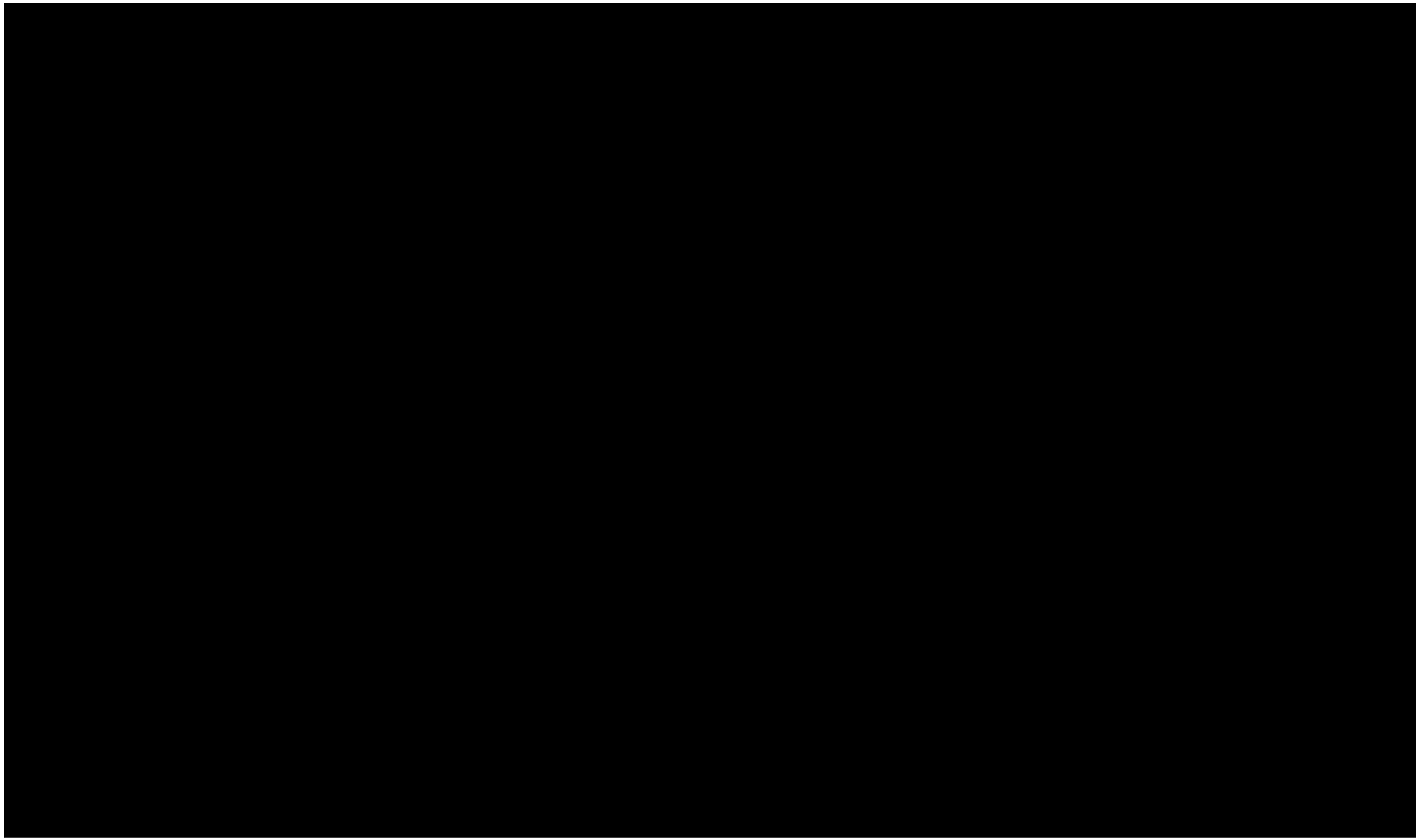
The overall study duration period is expected to be 60 months, including a 48-month enrolment period and a minimum 12-month follow-up period. During the observation period, data will be collected at routine clinical visits at 2-month intervals for the first 12 months and at 6-month intervals thereafter until the end of study participation.

In the context of this study which is planned to have an overall duration of 60 months, each participant will be treated with afatinib and observed in the context of the study until the end of study participation defined as a maximum of 48 months after afatinib treatment initiation or until disease progression, death, withdrawal of consent, unacceptable toxicity, study completion or physician's decision whichever occurs earlier. The maximum 48-month length of participation in the study pertains to the patients enrolled during the first 12 months of recruitment, while the maximum observation period for the last patient enrolled is 12 months.

Being non-interventional and observational in nature, this study does not impose any diagnostic/therapeutic interventions or strict visit schedule. Patients will be treated as per the routine medical practice in terms of visit frequency, types of assessments performed and with

adherence to the local prescribing requirements for afatinib. Investigators shall record all (S)AEs that are observed by them or reported by the patients. As this is an observational study, patients will continue to be followed by their physicians according to current medical practice and the product's summary of product characteristics (SmPC) requirements.

An assessment schedule in tabular format providing information on the recommended data collection schedule that most likely reflects the patterns of routine clinical care of most patients being treated with afatinib is depicted at Table 1.



[redacted]

2.4 Determination of sample size

Sample size calculation has been based on study's primary endpoint, which involves the determination of the proportion of study population with clinically meaningful improvement in the LCSS ASBI score over a 6-month treatment period.

Due to the lack of published data on the effect of afatinib on symptom burden using the LCSS, the worst case scenario has been taken into account, i.e., that the proportion of patients experiencing symptom improvement (*as defined in Section 2.1.1*) after 6 months of therapy will be approximately 0.50. Consequently, the assessment of 96 patients is required to estimate the aforementioned proportion with a margin of error not exceeding 0.10 which represents a scientifically acceptable level of precision of the estimate [95% CI: 0.40-0.60; α: 0.05; Relative Standard Error (RSE): 10.21%]. This means that for any proportion between 0.05 and 0.95, the precision will range from 0.04 to 0.10 at a 95% confidence limit. The sample size determination has been performed using the statistical software package SAS v9.4 (SAS Institute, Cary, NC).

In order to control for an estimated 25% drop out/non-evaluable rate, 128 patients are finally required in order to ensure the aforementioned sample size for the final statistical analysis.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables and patient data listings will be performed using SAS® statistical analysis software (the most updated version at the time of analysis onset). Figures will be created by validated graph programs, such as SAS® and/or Microsoft Excel.

Summary statistics will consist of frequency tables (n_{pt}, %) for categorical variables. For continuous variables, descriptive statistics [number of patients with available observations (n_{pt}), number of missing observations (n_{miss}), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum (min) and maximum (max)] will be tabulated.

The normality of distribution of continuous variables will be examined using the Shapiro-Wilk test. Concerning binomial proportions 95% CIs will be derived from Wald confidence limits for binomial proportions. In order to examine the differences in the values of continuous variables, the paired t-test or the Wilcoxon signed-rank test for two dependent samples will be used. The association between categorical variables will be assessed with the use of the McNemar's test for paired samples.

Potentially, linear mixed-effects models for repeated-measures will be fitted in order to describe the trend of continuous variables over time. The impact of patient characteristics on variables of interest will be evaluated with the use of logistic regression models for dichotomous outcome variables. Pertaining to data presentation, when reporting relative frequencies or other percent values the following rules will apply:

- ✓ For values where all patients fulfil a certain criterion, the percent value will be displayed as 100.0.

- ✓ For values where the absolute frequency is 0, '.' will be presented instead.
- ✓ All other percent values will be displayed using one decimal place.

In terms of decimal places for descriptive statistics:

- ✓ n_{pt}, n_{miss} will be integers.
- ✓ Mean, SD, median, 25th percentile, 75th percentile, min and max will be rounded to one decimal place or to the minimum number of decimal places recorded in the eCRF plus one.

All statistical tests will be two-sided and will be performed at a 0.05 significance level. The exact p-values will be reported, even for non-significant results, rounded to 3 decimals unless the p-value is less than 0.001 or greater than 0.999 (in such cases $p<0.001$ and $p>0.999$ will be reported, respectively).

3.2 Analysis time points and assessment windows

The analysis time points of the study are the following:

- ✓ Enrolment/Baseline
- ✓ Post-baseline timepoints: At 2 months; 4 months; 6 months; 8 months; 10 months; 12 months; 18 months; 24 months; 30 months; 36 months; 42 months; 48 months post-afatinib treatment onset with a ±3-week window allowed;

3.3 Definition baseline and post-baseline values

In the context of this study the following definitions apply for the baseline and post-baseline assessments:

- ✓ **Baseline assessments**: are defined as the assessments performed prior to or at afatinib treatment onset. For PROs (EQ-5D-3L, LCSS) as well as for anthropometric characteristics, vital signs, and physical examination) data collected at the enrolment visit will serve as the baseline data.
- ✓ **Post-baseline predefined time points**: are defined as those performed at the post-baseline time points as defined in Section 3.2.

Note: Data measured/collected at premature study withdrawal will also be considered as post-baseline values provided they have been collected within the predefined post-baseline time points.

3.4 Protocol deviations/violations

Patients who will be considered as eligible for participation in this study must meet **all** the following inclusion criteria:

- ✓ Adult outpatients (18 years and older) of either gender;

- ✓ Histologically or cytologically confirmed locally advanced or metastatic (IIIB/IV) NSCLC of any histological type with activating EGFR mutation(s) according to local laboratory EGFR testing;
- ✓ EGFR-TKI naïve patients;
- ✓ Patients for whom the decision to prescribe therapy with afatinib (GIOTRIF®) according to the locally approved product's SmPC has already been taken prior to their enrolment in the study and is clearly separated from the physician's decision to include the patient in the current study;
- ✓ Patients must be able and willing to provide written informed consent and to comply with the requirements of this study protocol;
- ✓ Patients must have signed an informed consent document;
- ✓ Patients must be able to read, understand and complete the study specific questionnaires.

A patient who meets **any** of the following criteria will be excluded from participation in this study:

- ✓ Patients who have initiated treatment with afatinib more than 7 days prior to their enrolment into the study;
- ✓ Patients that meet any of the contraindications to the administration of the study drug according to the approved SmPC;
- ✓ Patients currently receive treatment with any investigational drug/device/intervention or have received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever is longer) before the commencement of therapy with afatinib.

3.5 Analysis sets

In accordance to the non-interventional design of the study, all statistical analyses will be performed in the Full Analysis Set (FAS) comprised of all eligible subjects who have been enrolled in the study, regardless of whether or not they have finally completed their projected participation in the study.

The analysis of the primary objective of the study will be performed in the Per Protocol Set (PPS) which will include all eligible study patients with available data pertaining to the study primary endpoint, i.e. 6-month symptom improvement rate as per the LCSS ASBI score. In case that the size of the PPS differs substantially (i.e. ≥20%) from the size of the FAS, then descriptive statistics of demographic and baseline disease and clinical characteristics will also be presented in the PPS.

Subsets of FAS with available data will also be created and analysed for the purposes of secondary endpoint analyses. The safety analysis will also be applied in the FAS.

Patients erroneously enrolled in the study (i.e., not fulfilling the eligibility criteria) will be excluded from all analyses of this study and any deviations from the protocol will be reported in detail in the clinical study report (CSR).

3.6 Coding dictionaries

MedDRA dictionary

The Medical Dictionary for Regulatory Activities (MedDRA) (*the last updated version available at the onset of medical coding*) will be used for the coding of the verbatim terms of significant medical history/comorbidities and reported AEs.

Recorded terms will be coded according to Lower Level Term (LLT), Preferred Term (PT) and System Organ Class (SOC) and will be presented by PT and SOC.

WHOCC-ATC classification dictionary

Concomitant and prior treatment for NSCLC will be coded using the Anatomical Therapeutic Chemical (ATC) controlled by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology (WHOCC).

In particular, recorded prior treatment for NSCLC will be presented in the categories pre-specified in the eCRF (i.e. surgical procedures, radiotherapy, systemic chemotherapy), while all other medications recorded in the field 'other' will be coded by the WHOCC ATC in terms of chemical subgroup (4^{th} level) and chemical substance (5^{th} level). Concomitant treatment for NSCLC will be presented as radiotherapy (predefined option in the eCRF), while medications will be coded according to the WHOCC ATC, therapeutic subgroup (2^{nd} level), chemical subgroup (4^{th} level) and chemical substance (5^{th} level), as applicable.

3.7 Definitions of study-specific derived variables

3.7.1 Derived variables

- ✓ Age at enrolment

  Age at enrolment (years) = (Date of enrolment - Date of birth)/365.25.

- ✓ BMI (kg/m^2) = Weight (Kg) / Height^2 (m)

  BMI (kg/m^2) will be calculated at the enrolment visit and at the post-baseline time points.

- ✓ BMI (kg/m^2) classification:

  - *Underweight (BMI < 18.5 Kg/m^2);*
  - *Normal (18.5 $Kg/m^2 \leq$ BMI < 25 Kg/m^2);*
  - *Overweight (25 $Kg/m^2 \leq$ BMI < 30 Kg/m^2);*
  - *Obese (BMI $\geq$ 30 Kg/m^2).*

- ✓ Pack-years of smoking

Pack-years of smoking = $\frac{\text{Average number of cigarettes/day} \times \text{Years of smoking}}{20}$.

- ✓ Age at initial diagnosis of NSCLC

  Age at initial diagnosis of NSCLC (years) = (Date of initial diagnosis of NSCLC – Date of birth)/365.25.

- ✓ Age at diagnosis of locally advanced/metastatic NSCLC

  Age at diagnosis of locally advanced/metastatic NSCLC (years) = (Date of diagnosis of locally advanced/metastatic NSCLC – Date of birth)/365.25.

- ✓ Time elapsed from initial diagnosis of NSCLC to locally advanced /metastatic NSCLC

  Time elapsed from initial diagnosis of NSCLC to locally advanced /metastatic NSCLC (months) = (Date of diagnosis of locally advanced/metastatic NSCLC - Date of initial diagnosis of NSLC)/30.5.

- ✓ Time elapsed from diagnosis of locally advanced/metastatic NSCLC to enrolment

  Time elapsed from diagnosis of locally advanced/metastatic NSCLC to enrolment (months) = (Date of enrolment – Date of diagnosis of locally advanced/metastatic NSCLC)/30.5.

- ✓ Age at afatinib treatment onset

  Age at afatinib treatment onset (years) = (Date of afatinib treatment onset - Date of birth)/365.25.

- ✓ Time elapsed from afatinib treatment onset to enrolment

  Time elapsed from afatinib treatment onset to enrolment (days) = (Date of enrolment – Date of afatinib treatment onset).

- ✓ Time elapsed from the diagnosis of locally advanced/metastatic NSCLC to afatinib treatment onset

  Time elapsed from the diagnosis of locally advanced/metastatic NSCLC to afatinib treatment onset (months) = (Date of afatinib treatment onset - Date of diagnosis of locally advanced/metastatic NSCLC)/30.5.

- ✓ Duration of afatinib treatment

  Duration of afatinib treatment (months) = (Date of afatinib discontinuation – Date of afatinib treatment onset+1)/30.5; *for patients who discontinued afatinib treatment*

  or

  Duration on afatinib treatment (months) = (End date of study participation – Date of afatinib treatment onset+1)/30.5; *for patients who did not discontinue afatinib treatment.*

3.7.2 Patient Reported Outcomes

In regards to PROs the scoring instructions provided from the Sponsor will be followed.

- ✓ *Total LCSS score & ASBI score*

The patient-rated LCSS scale consists of six symptom-specific questions that address loss appetite, fatigue, cough, dyspnoea, pain and haemoptysis, as well as three global items overall symptomatic distress, interference with normal activity, global Quality of Life (QoL). Each item is scored on a 100-mm VAS, with score reported from 0 to 100 with 0 representing the best score.

- *Total LCSS score will be calculated by the mean of the 9 items of the scale. For a given assessment, if any of the nine items have not been completed, the total LCSS score will not be calculated.*
- *ASBI score will be calculated by the mean of the 6 major lung cancer symptoms (loss appetite, fatigue, cough, dyspnoea, pain and haemoptysis). For a given assessment, if any of the six symptom-specific questions have not been completed, the ASBI score will not be calculated.*

- ✓ *EQ-5D utility index score*

The EQ-5D-3L descriptive system consists of the following 5 dimensions: *mobility*, *self-care*, *usual activities*, *pain/discomfort* and *anxiety/depression*. Each dimension has 3 levels: *1*="*no problems*"*; 2*="*some problems*"*; 3*= "*extreme problems*" *(*which have no arithmetic properties and are not used as a cardinal score [EuroQol Group 1990[18]; Rabin and de Charro 2001[9]).

For the calculation of the EQ-5D utility index score based on the patients' responses to the 5 dimensions, each patient's responses will be assigned to a health state. The specific EQ-5D index score assigned to each health state will be based on value sets provided by the Sponsor.

3.8 Changes from planned analyses

No change from the planned analysis has been conducted.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The following variables will be considered as potential confounders or effect modifiers of the impact of treatment with afatinib on the improvement in disease-specific symptom burden.

- ✓ Age at baseline;
- ✓ Gender;
- ✓ BMI at baseline;
- ✓ Educational/marital/employment status;
- ✓ Baseline comorbidity count with particular emphasis on gastrointestinal, psychiatric, and musculoskeletal and connective tissue disorders;

- ✓ Concomitant medications both at baseline and at the time of symptom burden assessment with particular emphasis among others on analgesics, antitussives, antidepressants, antiemetics, and antidiarrheals;
- ✓ Disease stage at baseline;
- ✓ Baseline ECOG PS;
- ✓ Baseline smoking status and lifetime tobacco exposure*;*
- ✓ Lung cancer histologic classification;
- ✓ EGFR mutation subtype;
- ✓ Sites of metastases at baseline;
- ✓ Adherence to afatinib treatment over the 6-month observation period and over the whole study participation duration.

4.2 Handling of dropouts or missing data

With regard to partial start dates with a missing start day, e.g. _ _JUN2016, the day will be set to the first of the month, 01JUN2016. If the month is missing e.g. 17_ _ 2016, the month will be set to January for that year, 17JAN2016. The reverse will apply for a partial end date, with the missing day set to the end of the month and the missing month set to December. If there is only a year and both the day and month are missing, then both are imputed, giving 1st January for a start date or 31st December for a stop date. In case where a partial date after the general imputation rule comes in reasonable opposition with another variable of the eCRF, then the date will be imputed so as to be in reasonable time sequence.

In the context of the final analysis, regarding the primary outcome measure, in case of a high non-evaluable rate (i.e. >20%) the primary endpoint analysis will also be conducted in the subset of patients with at least one post-baseline measurement of the ASBI score. Details about this analysis are presented in Section 8.1.3.

4.3 Interim analyses

Taking into consideration the long-term study duration as well as the current limited evidence on the real-world clinical outcomes of treatment with afatinib in patients with NSCLC, an interim analysis is planned to be performed after the first 40 enrolled patients (i.e., around one-third of the overall sample size) have completed the 6-month study observation period (i.e., have attended the 6-month study visit [V4] or have discontinued study participation, whichever occurs first).

The main purpose of the interim analysis is to gain preliminary information on the impact of afatinib in the study key outcome measures. No resultant decisions and actions will be taken in terms of the study progress as a consequence of the interim analysis. The interim analysis does not involve any stopping boundary for early stop due to efficacy or for sample size adjustment, thus no multiplicity adjustment will be performed.

In the context of the interim analysis, taking into consideration that the sample size of this analysis will be 40 patients (around one-third of the overall sample size) and aiming to ensure the scientific validity of the results, the missing rate of the primary and key secondary outcomes (i.e. symptoms improvement, LCSS score, EQ-5D, and ECOG) will be calculated and each of the respective analyses will be performed only in those cases that the missing data rate does not exceed 20%.

Only descriptive statistical measures and epidemiological methods will be applied for the purposes of the interim analysis. Continuous variables will be summarized with the use of descriptive statistical measures (n_{pt}, n_{miss}, mean, SD, median, 25th and 75th percentiles and range) and categorical variables will be presented with the use of frequency tables (n_{pt}, %). All the analyses will be conducted providing that the number of patients included in each analysis will allow for meaningful inferences.

4.4 Multiple comparisons/multiplicity

No formal multiple comparisons between specific subgroups of patients have been foreseen and therefore statistical adjustment does not fall within the scope of this analysis, while control of type I error is not required.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of patients enrolled, eligible, those that have completed each post-baseline visit as well as those prematurely withdrawn, along with the reasons for study withdrawal will be presented. Also, the eligible and non-eligible patients per participating site will be tabulated.

5.2 Protocol deviations

All protocol deviations resulting in patients' exclusion from the analysis will be reported in the CSR. More specifically, a listing with deviators will be created containing site number, patient number and description of deviation.

6 PATIENT CHARACTERISTICS

6.1 Sociodemographic and anthropometric characteristics

Descriptive statistics (n_{pt}, n_{miss}, mean, SD, median, 25th and 75th percentiles, min and max) will be presented for patients' age at the time of enrolment. Patient distribution by gender, race, place of residence, educational level, marital status, employment status will be presented in frequency tables (n_{pt}, %).

Summary statistics will be presented for body weight (kg), height (cm), BMI (kg/m^2) at baseline. Body weight (kg) and BMI (kg/m^2) will also be summarized for the predefined post-baseline time points along with the changes from enrolment. In addition, patient distribution per BMI categories at enrolment and at post-baseline time points will be displayed using absolute and relative frequencies.

In regards to smoking history, the distribution of patients per smoking status at enrolment will be displayed in a frequency table (n_{pt}, %). Pack-years of smoking will be presented with the use of summary statistics for current and former smokers, while the time since smoking cessation and years of smoking will be summarized for former and occasional smokers, respectively. In addition, the number and proportion of patients that changed their smoking habits from enrolment to the end of observation period or to the time of premature withdrawal as well as the type of change and smoking status at the end of observation period/withdrawal will be presented.

6.2 NSCLC disease characteristics

The age at initial diagnosis of NSCLC, the age at diagnosis of locally advanced or metastatic NSCLC, the time from initial diagnosis of NSCLC to locally advanced or metastatic NSCLC diagnosis as well as the time from diagnosis of locally advanced/metastatic NSCLC to enrolment will be summarized.

In regards to the initial diagnosis of NSCLC, the distribution of patients per type of diagnosis, per stage of diagnosis, per primary tumor localization as well as per histologic classification will be tabulated in frequency tables (n_{pt}, %).

Moreover, the NSCLC stage along with the TNM staging at the time of afatinib initiation and the sites of metastases (*only for patients with $T_{any}N_{any}M1b$ stage*) will be presented by absolute and relative frequencies. The total number of metastatic lesions for patients with *stage IV disease* will be presented by using summary statistics (n_{pt}, n_{miss}, mean, SD, median, 25^{th} and 75^{th} percentiles, min and max). Patients distribution per EGFR mutation location and mutation type as well as per method of identification of the EGFR mutation(s) will be displayed by frequency tables (n_{pt}, %).

Finally, the distribution of patients per disease stage at the end of study observation period or at the time of premature withdrawal will be displayed in frequency table (n_{pt}, %). The change in disease stage from study treatment initiation to end of study observation period/ premature withdrawal will be presented by shift table.

In addition, patient distribution (n_{pt}, %) by change in the disease status (improvement, stable, progression) from baseline and evaluation criteria (imaging, clinical, laboratory) at each of the post-baseline timepoints will be presented. The number and proportion of patients with progression with at least one of the evaluation methods; with improvement with any of the evaluation methods and no progression as well as with stable status with no progression/improvement according to the available evaluation methods at each post-baseline timepoints will be presented in frequency tables (n_{pt}, %). In regards to patients with improvement with at least one evaluation method and no progression, the combinations of the disease statuses with each evaluation (imaging, clinical, laboratory) method will be presented in absolute and relative frequencies. For patients for whom a change in the disease status was identified using an imaging method summary statistics will be presented for the number of metastatic lesions at the time of improvement or deterioration, along with the change from baseline; in addition, for patients with a deterioration the new metastatic sites will be

presented (as applicable), while for those with improvement the changes in the metastatic sites will be presented. Finally, the number and proportion of patients with at least one progression as well as those with at least one improvement as assessed using an imaging method over 6, 12, 18, 24, 30, 36, 42 and 48 months and throughout the study observation period will be displayed.

6.3 Physical examination and significant medical history/comorbidities excluding NSCLC

The number and proportion of patients in which the physical examination was performed, those with at least one pathological finding and those with a normal physical examination in all examined major organs systems, will be calculated and presented at baseline. In addition, patients with pathological findings in each of the examined major organ systems will be presented.

Furthermore, the number and proportion of patients with no clinically significant diseases/medical conditions/surgeries at enrolment, those with at least one medical condition/comorbidity/surgery at enrolment as well as those with at least one ongoing medical condition/comorbidity will be calculated and presented.

Additionally, the depicting reported terms coded by MedDRA SOC and PT will be tabulated. Moreover, clinically relevant medical conditions will be presented separately with the use of frequency tables (n_{pt}, %) according to time of diagnosis '<6 months prior to afatinib initiation', 6-12 months prior afatinib initiation', '>12 months prior to afatinib initiation', 'Unknown' as well as whether they are 'Past' or 'Ongoing' at time of afatinib onset and whether they are 'Treated' or 'Not treated' at the time of afatinib onset.

6.4 Prior and concomitant medications

Number and proportion of patients with prior treatment for NSCLC at enrolment as well as the type of prior treatment (surgical intervention, radiotherapy, systemic chemotherapy, other-therapy) for NSCLC will be displayed in a frequency table (n_{pt}, %). Also, frequency tables (n_{pt}, %) will be presented for the reasons that surgeries were performed, for the type of radiotherapy and of discontinuation of the most recent chemotherapeutic regimen.

Summary statistics will be calculated for the number of surgical procedures and the number of previous chemotherapeutic regimens. In addition, the time elapsed from the most recent surgical procedure, from the most recent radiotherapy completion and from the discontinuation of the most recent chemotherapeutic regimen to afatinib treatment onset will be calculated and summarized.

Regarding concomitant medications with afatinib including radiotherapy, the number and proportion of patients receiving at least one concomitant therapy (pharmacological/non-pharmacological/radiotherapy), at least one pharmacological therapy and at least one non-pharmacological therapy (including radiotherapy) during the observational period will be calculated and presented. Frequency tables (n_{pt}, %) will be presented for the concomitant medications in terms of therapeutic subgroup and chemical substance (as coded by WHOCC ATC) and for radiotherapy, along with the indication/reason of receipt.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Adherence to treatment comprises a secondary objective of the study and the relevant analysis is described in the Section 8.2

[redacted]

[redacted]

[redacted]

[redacted]

9 SAFETY ANALYSES

The analysis set that will be used for the safety analyses is described in Section 3.5.

9.1 Extent of exposure

All afatinib treatment characteristics, including the age at afatinib treatment onset, the time elapsed from afatinib treatment onset to enrolment , the time elapsed from the diagnosis of locally advanced/metastatic NSCLC to afatinib initiation will be presented by the use of summary statistics.

Moreover, the duration on afatinib treatment (*as defined in Section 3.7*) as well as the length of exposure in afatinib during the observation period will be presented by descriptive statistics. The length of exposure in afatinib will be calculated by subtracting the intervals of temporary interruptions from the duration of afatinib treatment.

9.2 Adverse events

The following adverse events are collected from the time the patient has signed the informed consent until the completion of his/her participation in the study: all serious and non-serious adverse drug reactions (ADRs) related to GIOTRIF; all AEs with fatal outcome (regardless of causal relationship with GIOTRIF); and all AEs (serious and non-serious) which are relevant to a serious ADR or to an AE with fatal outcome. An ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

All recorded adverse events will be mapped by LLT, PT and SOC according to MedDRA (the most updated version available at the time of coding onset). If two or more AEs (PTs) are reported as a unit, the individual terms will be reported as separate events.

A descriptive summary table will be created with the number and proportion of patients experiencing at least one adverse drug reaction regardless of seriousness (N)SADR, serious adverse drug reaction (SADR), non-serious adverse drug reaction (NSADR) and SAE. The percentage of patients who discontinued their treatment with afatinib due to AEs will also be tabulated.

Additionally, the following data will be provided in frequency tables:

- ✓ Number and percentage of patients experiencing at least one (N)SADR by SOC and PT.
- ✓ Number and percentage of patients experiencing at least one SADR by SOC and PT.
- ✓ Number and percentage of patients experiencing at least one NSADR by SOC and PT.
- ✓ Number and percentage of patients experiencing at least one SAE by SOC and PT.

The aforementioned analysis will also be performed by outcome and action taken with afatinib.

- ✓ Number and percentage of patients experiencing at least one (N)SADR by SOC, PT and NCI CTCAE grade.
- ✓ Number and percentage of patients experiencing at least one SADR by SOC, PT and NCI CTCAE grade .
- ✓ Number and percentage of patients experiencing at least one NSADR by SOC, PT and NCI CTCAE grade .
- ✓ Number and percentage of patients experiencing at least one SAE by SOC, PT and NCI CTCAE grade .

A patient data listing of all reported AEs will also be created and presented. The listing will include information related to the reported events [i.e. patient ID, center ID, verbatim term of AE, MedDRA terms (LLT, PT, SOC), onset date of AE, end date, outcome, causal relationship with afatinib, NCI CTCAE grade, seriousness, action(s) taken].

Additionally, the exposure-adjusted incidence rates (EAIRs) along with the respective 95% CI will be calculated for those experiencing at least one (N)SADR, at least one SADR, at least one NSADR.

Specifically, the EAIR is defined as the number of patients with a specific event divided by the total exposure-time in subject-year:

$$EAIR = \frac{n}{\sum t_i} 100$$

where n is the number of patients with at least one event and t_i is a patient's follow-up in subject-years.

If a patient has multiple events, then t_i is defined as the time from treatment onset to the occurrence of the first event. For a patient without any event, the t_i will be censored at the last follow-up time for that patient. The respective 95% CIs will also be calculated as follows:

Lower confidence limit: $LCL = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise

Upper confidence limit: $UCL = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$,

where α=0.05, D is the number of subjects with at least one event and $c_{\alpha,k}$ is the α^{th} quantile of the χ^2distribution with k degrees of freedom.

9.3 Vital signs

Summary statistics for heart rate (beats/minute), respiratory rate (breath/minute), systolic and diastolic blood pressure (mmHg) at enrolment as well as at post-baseline predefined time points will be calculated and presented along with the relevant changes from enrolment.

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11 APPENDICES

N/A