Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c03517862-03
BI Study Number:	1200.247
BI Investigational Product(s):	Afatinib (GIOTRIF®)
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
Protocol version identifier:	2.0 (incorporating protocol amendment 1)
Date of last version of protocol:	31 July 2018
PASS:	No
EU PAS register number:	Study not registered
Active substance:	Afatinib
Medicinal product:	GIOTRIF 20mg, 30mg, 40mg and 50mg film-coated tablets
Product reference:	Not applicable
Procedure number:	Not applicable
Joint PASS:	No
Research question and objectives:	The study primarily aims at assessing the impact of afatinib therapy on the patient-reported lung cancer-specific symptom burden, after 6 months of therapy. The main secondary objectives include the evaluation of the impact of afatinib on total symptomatic distress, functional activity, HRQoL, as well as the assessment of adherence with treatment and the description of patterns of use of afatinib in routine clinical practice in terms of treatment modifications, and reasons for these modifications, in a representative sample of Greek subjects with advanced NSCLC in real-life clinical settings.
Country(-ies) of study:	Greece
Author:	[redacted]
Marketing authorisation holder(s):	
Date:	31 July 2018

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4. LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALK	Anaplastic Lymphoma Kinase
AESI	Adverse Event of Special Interest
ASBI	Average Symptom Burden Index
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CD-ROM	Compact Disc, read-only-memory
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
DMP	Data Management Plan
EAIR	Exposure Adjusted Incidence Rates
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment
EORTC QLQ-C	EORTC Quality of Life Questionnaire – Cancer

[redacted]

LIST OF ABBREVIATIONS (Continued)

FACT-L	Functional Assessment of Cancer Therapy – Lung
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
ISF	Investigator Site File
[redacted]	
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCI	National Cancer Institute
NIS	Non Interventional Study
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
pDCF	paper Data Clarification Forms
[redacted]	
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PT	Preferred Term
QoL	Quality of Life
RCT	Randomized Clinical Trial
RSE	Relative Standard Error
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDV	Source Data Verification

LIST OF ABBREVIATIONS (Continued)

SFEE	Hellenic Association of Pharmaceutical Companies
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TKI	Tyrosine Kinase Inhibitor
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
WBDC	Web Based Data Capture
WHO	World Health Organisation
WHOCC	WHO Collaborating Centre

5. RESPONSIBLE PARTIES

Study Sponsor

[redacted]

Address: [redacted]

Contract Research Organisation

Name: [redacted]

Address:

Participating Investigators

The list and contact details of all investigators will be kept in a stand-alone document and will be available upon request.

6. ABSTRACT

Name of company: Boehringer Ingelheim		**Tabulated** **Clinical Study Protocol**	
Name of finished medicinal product: GIOTRIF film-coated tablets			
Name of active ingredient: *Pharmacotherapeutic group*: Antineoplastic agents, protein kinase inhibitors, *ATC code*: L01XE13 *Active substance*: Afatinib			
Protocol date: 02 April 2015	**Study number:** 1200.247	**Version/Revision:** 2.0	**Version/Revision date:** 31 July 2018
Title of study:	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 *Original protocol version and date:* V.1.0 - 02 April 2015 *Name and affiliation of main author:* [redacted]		
Rationale and background:	The incidence of lung cancer in developed countries is growing. Moreover, 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. NSCLC bears not only significant mortality but also morbidity as patients suffer from debilitating symptoms, such as cough, chest pain, dyspnea, anorexia, fatigue and hemoptysis. 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 quality of life (QoL) and symptom burden in both clinical research and routine patient care settings. There is a broad array of questionnaires used in the field of NSCLC for the assessment of health-related QoL (HRQoL). Among them, the most commonly used generic instruments assessing global health		

	status are the Euro QoL EQ-5D and the cancer-generic European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire – Cancer (EORTC QLQ-C30). Moreover, disease-specific instruments assessing HRQoL have been developed for patients with NSCLC including the Functional Assessment of Cancer Therapy – Lung (FACT-L), the EORTC QLQ – Lung Cancer (EORTC QLQ-LC13) and the Lung Cancer Symptom Scale (LCSS). For patients with NSCLC tumors 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 survival and increased response rates and improvement of HRQoL. However, resistance to therapy commonly develops, which has led to the development of the irreversible EGFR TKI, afatinib, which targets and blocks signalling from dimers of all ErbB family members, EGFR (ErbB1), HER 2 (ErbB2), ErbB3 and ErbB4. Afatinib (GILOTRIF™ / GIOTRIF®) was approved in 2013 by the FDA and 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 non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. While in Europe, afatinib as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKInaïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s). In the LUX-Lung 3 randomized controlled trial (RCT) patients were randomised (2:1) to receive afatinib 40 mg once daily or up to 6 cycles of premetrexed/cisplatin. According to the results of the study, for the subgroup of patients with common mutations (Del 19, L858R) (204 on afatinib and 104 on chemotherapy) the median PFS was 13.6 vs. 6.9 months [Hazard Ratio (HR) 0.47; 95% CI 0.34-0.65; p<0.0001] and the median OS was 30.3 vs. 26.2 months, demonstrating a clear benefit of afatinib treatment. In addition to the Del19, L858R mutations, certain less common mutations have also been shown to be sensitive to afatinib treatment. Moreover, compared to chemotherapy first-line afatinib was associated with better control of cough (HR, 0.60; 95% CI, 0.41 to 0.87; P=0.007) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.015), as well as improved global health status/QoL (P=0.015), and functional scale scores as assessed with the use of EORTC QLQ-C30 and the EORTC-QLQ-L13. The results of the pivotal LUX-Lung 3 RCT have been supported by the LUX-Lung 6 phase 3 RCT. The LUX-Lung 6 phase 3 trial was the largest conducted in Asian patients with EGFR mutation-positive advanced lung cancer (n=364). The study compared first line afatinib with gemcitabine/cisplatin chemotherapy. In the afatinib arm mean PFS was 11.0 months vs. 5.6 months for those in the chemotherapy arm (HR 0.28; P<0.0001). Side-effects seen with afatinib were manageable through dose reductions and supportive care; treatment-discontinuation rate due to adverse events was 5.9% in the afatinib compared to 39.8% in the

	gemcitabine/cisplatin arm. Regarding symptom improvement and HRQoL, patients treated with afatinib in the LUX-Lung 6 study, demonstrated improvement of cough (P<0.0001), dyspnea (P<0.0001) and pain (P=0.03), as well as decreased time to deterioration of these symptoms compared to those treated with chemotherapy. Global health improvement was also demonstrated by a higher proportion of patients in the afatinib group than in the gemcitabine/cisplatin group (62.7% versus 32.7%; P<0.0001). Notably, prolongation of PFS was associated with improved HRQoL and significantly longer control of disease-related symptoms. Mature survival data from the LUX-Lung 3 and LUX-Lung 6 studies have indicated that with a median follow-up of 41 months in the LUX-Lung 3, and 33 months in the LUX-Lung 6, afatinib offered a significant improvement in OS among patients with Del 19-positive tumors (median 33.3 vs. 21.1 months with chemotherapy, P=0.0015 in LUX-Lung 3; and 31.4 vs. 18.4 months, P=0.023 in LUX-Lung 6). 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 aims primarily at assessing the impact of the therapy on patients' disease-related symptom burden and HRQoL. In addition, it 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 RCTs and assist in the decision-making process of the medical professionals that provide care to this heavily burdened population.
Research question and objectives:	*Primary Objective* • To evaluate the impact of afatinib therapy on the patient-reported lung cancer-specific symptom burden, using the Average Symptom Burden Index (ASBI) of the LCSS in eligible patients, over 6 months of therapy, in a real world clinical setting in Greece. *Secondary Objectives* • 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 *(i.e., at 2-month intervals during the first 12 months of therapy and at 6-month intervals thereafter until the end of the patient's participation in the study);* • To assess the impact of afatinib treatment on the HRQoL of the study population using the EQ-5D-3L questionnaire at the post baseline predefined timepoints; • To assess the impact of afatinib therapy on patient's ECOG performance status (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.
Study design:	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. Since this is purely non-interventional study, primary data 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. The overall study duration period is expected to be 60 months, including a 48-month enrollment 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. The end of study participation is defined as a maximum of 48 months after afatinib treatment intiation or 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.
Population:	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. Physicians will originate from a random pool of specialists in lung cancer and will be recruited from various geographic regions in Greece in order for variations in clinical practice to be reflected. Investigators' selection will be performed by the means of a documented and constructed feasibility assessment process that will account, among others, for physicians' qualifications, previous participation and experience in similar clinical studies and recruitment potential and retention capability. Patients who will be considered as eligible for participation in this study must meet **ALL** the following inclusion criteria and **NONE** of the exclusion criteria presented below: *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 summary of product characteristics (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. <u>*Exclusion Criteria*</u> • 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.
Variables:	<u>*Primary Variable:*</u> • 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, dyspnea, pain, and hemoptysis*- at enrollment and at 2-month intervals over the initial 6-month observation period. <u>*Secondary Variables:*</u> Patient-rated ASBI score of LCSS at the post-baseline predefined timepoints; Patient-rated total LCSS score -*defined as the* average *of the aggregate* score *of all* 9 items *that comprise the LCSS*- at enrollment 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 change(s) and reasons for treatment modifications. *Confounding/Effect Modification Variables* The following variables will be considered as potential confounders or effect modifiers of the main association between treatment with afatinib and change in disease-specific symptom burden: Age; Gender; Body Mass Index (BMI); 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; Adherence to afatinib treatment.
Data sources:	The study will mainly involve new data collection, by means of a web based data capture (WBDC) system. Data will be collected by the study physicians as generated according to the standard clinical practice and by the patients as captured with the use of PROs. No further laboratory tests and examinations are required apart from those recommended by the study medication SmPC. Patient source data pertaining to medical- and lung cancer-related history will be abstracted from patient medical charts/records by the investigators and will be recorded in the relevant section of the WBDC. All afatinib treatment modifications, concomitant medications, study-related routine clinical assessments, vital signs and adverse events (AEs) will also be collected. Concomitant or prior disease-related medications entered into the database will be coded using the Anatomical Therapeutic Chemical (ATC) WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) Drug Reference List. Medical history/comorbidities and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. PROs (LCSS patient scale and EQ-5D-3L) will be collected via self-administered paper questionnaires completed by the patients themselves at study enrolment and periodically throughout study participation, according to the study visit frequency. For the measurement of the adherence to therapy, a patient diary will be used which the patient will be requested to fill in only with the date and reasons for missed pills. In addition, physicians will be requested to assess the patients' performance status using the ECOG PS instrument.
Study 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 LCSS ASBI score after 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 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. 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.
Data analysis:	This study is not aimed to confirm or reject any pre-defined hypotheses; therefore statistical analyses will be of explorative and descriptive nature. Continuous variables will be summarized with the use of descriptive statistical measures (mean value, standard deviation, median and extreme values) and categorical/distinct variables will be displayed as frequency tables (N, %). The normality of distribution of continuous variables will be examined using Shapiro-Wilk test in order to determine whether or not to use parametric methods for the analysis of the sample data. Pertaining to the primary endpoint the proportion of patients experiencing a minimum clinically important symptom improvement (i.e., decrease in the ASBI from enrolment ≥10 in two subsequent measurements) over 6 months of treatment will be calculated along with the respective 95% confidence interval. The symptom improvement rate throughout the study observation period will also be calculated in patient-years. With regard to the secondary endpoints pertaining to the LCSS outcome measures: the mean change of the total LCSS, the LCSS domain subscores and the ASBI subscore, will be calculated from enrolment to all available subsequent study visits and will be examined for statistical significance with the use of the paired t-test or its non-parametric analogue. Pertaining to the change of the mean LCSS as well as the mean ASBI through the observation period, linear mixed models will be applied. The distribution of patients by level (‘level 1: no problems’, ‘level 2: some problems’ and ‘level 3: extreme problems’) for each dimension as well as the distribution of patients in the dichotomized EQ-5D levels [‘no problems’ (level 1) and ‘problems’ (levels 2 and 3)] will be presented in frequency tables (N, %) for all patients with available data. Descriptive statistical measures will be calculated for the EQ-VAS score at each predefined study timepoint along with the observed changes in the EQ-VAS from enrolment, while the paired t-test or the Wilcoxon signed rank test will be used to assess the statistical significance of the change.

	The McNemar's test will be used in order to evaluate the change in the levels ('with problems'/'no problems') of each dimension between enrolment and the post-baseline visits. The distribution of patients in the different ECOG performance status levels at every study time-point will be presented in frequency tables (N, %). Additionally, changes in the status of patients from baseline to post-baseline evaluations will be depicted in shift tables. Adherence to study treatment along with proportion of patients who discontinued permanently or temporarily treatment, dose modifications and reasons for treatment discontinuations will be analysed in descriptive manner. In order to examine the impact of baseline and other characteristics including among others, gender, age, BMI, educational/marital/employment status, disease stage, histological subtype, sites of metastases, EGFR mutation subtype, smoking status, ECOG PS, type of concomitant medications and comorbidity count, as well as adherence to therapy at 6 months on the study primary endpoint, generalized linear models will be applied. In addition, the number and proportion of patients experiencing any serious AE (SAE) and the number and proportion of patients experiencing any non-serious AE (NSAE) will be calculated and presented in frequency tables by MedDRA system organ class (SOC) and preferred (PT) while frequency tables will be presented pertaining to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) toxicity grade classification of AEs. All the aforementioned statistical tests will be two-sided and will be performed at a 0.05 significance level. Statistical analysis will be conducted using a validated statistical software package (e.g., SAS). 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 enrolled 40 patients have completed the 6-month study observation period. 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.
Milestones:	Start of data collection*: 01 March 2016 End of data collection**: 01 March 2021 Interim report of study results: 4 months after the data cut-off date for the purposes of interim analysis (i.e., when the first enrolled 40 patients complete the 6-month study observation period) Final report of study results**: 30 September 2021

	* This date corresponds to the actual date of the start of data collection. ** These milestones are subject to change depending on the actual date of the "Last Patient Out".

7. AMENDMENTS AND UPDATES

The main scope of Amendment #1 is: (a) to decrease the required sample size from 160 to 128; (b) to increase the length of the recruitment period by 12 months, i.e., from 36 to 48 months; (c) to increase the allowable time window of the study visits from ±1 week for Visits 2-7, and ±2weeks for Visits 8-13 to ±3weeks for all; and (d) to include an interim analysis.
The sections of the protocol that are affected, the description of the amendment and the reason for change are displayed in the following table, where deleted text is indicated by strikethrough and added text in bold characters:

Number	Date	Section of study protocol	Amendment or update	Reason
1	19 June 2018	Section 11.1 (Study Design), 4th paragraph	Text changed from: "Follow-up visit frequency will be determined by the treating physician, however study-related data will be collected at 2-month (±1 week) intervals during the first 12 months of study participation and every 6 months (±2 weeks) thereafter until the end of the study observation period." to: "Follow-up visit frequency will be determined by the treating physician, however study-related data will be collected at 2-month (~~±1~~**3 weeks**) intervals during the first 12 months of study participation and every 6 months (~~±2~~**3 weeks**) thereafter until the end of the study observation period."	To widen the time window for the scheduled study visits in order to allow for a data collection schedule that better mirrors the patterns of routine clinical care.
		Section 11.1.2 (Baseline and post-baseline timepoint definitions), 2nd bullet	Text changed from: "Post-baseline predefined timepoints for study-specific assessments are defined as: every 2 months (±1 week) during the first 12 months of therapy and every 6 months (±2 weeks) thereafter until the end of patient's participation in the study." to: "Post-baseline predefined timepoints for study-specific assessments are defined as: every 2 months (~~±1~~**3 weeks**) during the first 12 months of therapy and every 6 months (~~±2~~**3 weeks**) thereafter until the end of	To widen the time window for the scheduled study visits in order to allow for a data collection schedule that better mirrors the patterns of routine clinical care.

Number	Date	Section of study protocol	Amendment or update	Reason
			patient's participation in the study."	
		Section 11.2.1 (Site selection), 1st paragraph	Text changed from: "A total of 160 patients are planned to be enrolled by ten (10) Oncology and Pulmonology hospital centres/clinics in Greece specialized in lung cancer." to: "A total of ~~160~~ **128** patients are planned to be enrolled by ~~ten (10)~~ **seven (7)** Oncology and Pulmonology hospital centres/clinics in Greece specialized in lung cancer."	To decrease the originally planned required sample size from 160 to 128 due to the lower than expected recruitment rate at the time of drafting this amendment, and the participation of fewer than projected study sites.
		Section 11.2.2 (Study time period), 1st paragraph	Text changed from: "The overall study duration period is expected to be 48 months, including a 36-month enrollment period and a minimum 12-month follow-up period." to: "The overall study duration period is expected to be ~~48~~ **60** months, including a ~~36~~ **48**-month enrollment period and a minimum 12-month follow-up period."	To extend the originally planned recruitment period by 12 months in order to facilitate the recruitment of the required sample size.
		Section 11.2.3 (Projected duration of patient participation in the study), 1st paragraph	Text changed from: "In the context of this study, each participant will be treated with afatinib until disease progression, death, withdrawal of consent, unacceptable toxicity, study completion or physician's decision whichever occurs earlier. Thus the maximum	To reflect the change in the overall study duration from 48 to 60 months due to the 12-month recruitment period

Number	Date	Section of study protocol	Amendment or update	Reason
			length of participation in the study pertaining to the first enrolled patient is 48 months while the maximum observation period for the last patient enrolled is 12 months." to: 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. ~~Thus the~~ **The** maximum **48-month** length of participation in the study ~~pertaining to~~ **pertains to the patients enrolled during** the first ~~enrolled patient is 48~~ **12** months **of recruitment,** while the maximum observation period for the last patient enrolled is 12 months."	extension, and to clarify that the maximum observation period remains 48 months and has become applicable to patients enrolled over the first 12 months of recruitment.

Number	Date	Section of study protocol	Amendment or update	Reason
		Table 2 (Study Flow Chart and Assessments), "Visit Window" row	For Follow-up Visits V2 to V7, the visit window was changed from ± 1 week to ± 3 weeks; and for Follow-up Visits V8 to V13, the visit window was changed from ± 2 weeks to ± 3 weeks.	To widen the time window for the scheduled study visits in order to allow for a data collection schedule that better mirrors the patterns of routine clinical care.
		Section 11.6 (Study Size), 2nd and 3rd paragraphs	Text changed <u>from</u>: "…Consequently, the assessment of 120 patients is required to estimate the aforementioned proportion with accuracy (confidence interval) of ± 0.09 at the study population [95% CI: 0.41-0.59; α: 0.05; Relative Standard Error (RSE): 9.1%]. In order to control for an estimated 25% drop out/non-evaluable rate, 160 patients are finally required in order to ensure the aforementioned sample size for the final statistical analysis." <u>to:</u> "…Consequently, the assessment of ~~120~~ **96** patients is required to estimate the aforementioned proportion ~~with accuracy (confidence interval) of ± 0.09 at the study population [95% CI: 0.41-0.59; α: 0.05; Relative Standard Error (RSE): 9.1%].~~ **with a margin of error not exceeding 0.10**	To reduce the originally planned evaluable study size from 120 to 96 patients which represents the minimum required size for estimating the primary outcome measure with the highest scientifically acceptable margin of error.

Number	Date	Section of study protocol	Amendment or update	Reason
			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, ~~160~~ **128** patients are finally required in order to ensure the aforementioned sample size for the final statistical analysis."	

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 11.7 (Data Management), last paragraph	Text changed from: "Prior to the onset of data management activities, a detailed data management plan (DMP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for statistical analysis. In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied." to: "Prior to the onset of data management activities, a detailed data management plan (DMP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for **the interim and final** statistical analysis. In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied **twice during the conduct of the study for the purposes of the interim and final analysis, respectively**."	To add text indicating that an interim analysis is planned to be conducted in the context of the study, and to update the relevant text pertaining to the data cleaning process to be applied.
		Section 11.8 (Data Analysis), 5th paragraph	Text changed from: "A SAP comprising a comprehensive and detailed description of the statistical methodology applied for the purposes of the main analyses along with imputation methods for missing data will be prepared prior to database	To add a clarification that the SAP will also include details on the interim analysis to be carried out.

Number	Date	Section of study protocol	Amendment or update	Reason
			lock." to: "A SAP comprising a comprehensive and detailed description of the statistical methodology applied for the purposes of the ~~main analyses~~ **interim and final analysis** along with imputation methods for missing data will be prepared prior to database lock."	
		Section 11.8 (Data Analysis),	Addition of new subsection #11.8.7 titled "Interim Analysis" The text added under the new section follows: **"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 enrolled 40 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**	To add a section indicating that an interim analysis is planned to be carried out in the context of this study, and to provide the rationale, the purpose and the process for handling the results of this analysis.

Number	Date	Section of study protocol	Amendment or update	Reason
			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. **The confidentiality of the interim analysis data will be controlled by assignment of the analysis to a statistical group that is independent of the Sponsor and investigators, i.e. is not otherwise involved in the study design or conduct. After completion of the analysis the results will be summarized in a synoptic interim CSR and distributed to the study Sponsor. The detailed interim analysis results will not be disclosed to the participating investigators until the overall study completion in order to account for the avoidance of any bias that may result from the premature disclosure and subjective interpretation of the preliminary findings. However, the preliminary results may be announced in the form of an abstract or poster/presentation in a descriptive manner, as per the Sponsor's decision; in such case, the minimum required information will be disclosed aiming at safeguarding the scientific integrity of the final study**	

Number	Date	Section of study protocol	Amendment or update	Reason
			results."	
		Section 8 (Milestones), Table 1	Update of the study milestones taking into consideration the actual date of first patient enrolled, the 12-month recruitment period extension and the incorporation of the interim analysis.	To update the study milestones in order to reflect the extension in the recruitment period, considering also the actual date of the first patient enrolled.
		Section 6 (Abstract)	Amendment of the relevant text that is affected by the aforementioned amendments in the main body of the protocol.	To harmonise the abstract section with all changes performed in the main body of the protocol as a result of this amendment.

8. MILESTONES

Table 1: Study Milestones

Milestone	Planned Date
Start of data collection	01 March 2016*
End of recruitment	01 March 2020 or until the planned sample size of 128 patients has been enrolled, whichever occurs earlier
End of data collection**	01 March 2021
Data cut-off date for the purposes of interim analysis	When the first enrolled 40 patients complete the 6-month study observation period
Interim report (with results of the interim analysis)	4 months after the data cut-off date for the purposes of interim analysis
Final database lock**	01 June 2021
Final report of study results**	30 September 2021

* This date corresponds to the actual date of the start of data collection.

** These milestones are subject to change depending on the actual date of the "Last Patient Out".

9. RATIONALE AND BACKGROUND

9.1 MEDICAL BACKGROUND

The incidence of lung cancer in developed countries is growing. According to 2012 estimates, the age standardized rate of lung cancer (including the trachea and bronchus) was 41.9 per 100,000 cases in Europe, while the respective rate for Greece was 41.6 [1]. Worldwide, lung cancer is the leading cause of cancer-related deaths among males and the second leading cause of cancer-related deaths among women. In Greece, the age-adjusted mortality rates for 2012 were estimated to be 67.7 and 11.8 per 100,000 cases among males and females, respectively [2]. Moreover, 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 [3, 4]. NSCLC is the most common type of lung cancer, and in most cases is diagnosed at an unresectable, locally advanced (stage IIIB) or metastatic stage (IV) [5].

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 [4, 6]. Symptoms are at the cornerstone of patients' well-being, as evidenced in a recent survey in which 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. In regards to the specific symptoms, patients ranked fatigue as the most important risk, followed by diarrhoea, nausea and vomiting [7]. In another study, the majority of the subjects (82%) reported that they would prefer supportive therapy alleviating disease-symptoms to chemotherapy, while 68% of those preferring chemotherapy reported that their choice was based on symptom improvement rather than on prolongation of survival [8]. Symptoms affect the patient's physical and emotional well-being and lead to distress not only to the patients but also to their families [9]. Importantly, depression has been considered as an independent prognostic factor in lung cancer cases, regardless of disease severity [10]. A recent study confirmed a positive association between patient-perceived health-related quality of life (HRQoL) after NSCLC treatment initiation and survival [11]. Moreover in another study, baseline HRQoL measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30-item [QLQ-C30] emerged as the strongest predictor of OS among advanced NSCLC patients, while the EORTC QLQ-Lung Cancer 13 [EORTC QLQ-LC-13] dyspnoea score was also an independent predictor of OS prolongation [12]. 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 HRQoL and symptom burden in both clinical research and routine patient care settings [9, 13, 14, 15].

There is a broad array of questionnaires used in the field of NSCLC for the assessment of HRQoL [16]. Among them, the most commonly used generic instruments assessing global health status are the Euro QoL EQ-5D [17] and the cancer-generic EORTC QLQ-C30 [18]. Moreover, disease-specific instruments assessing HRQoL have been developed for patients with NSCLC including the Functional Assessment of Cancer Therapy – Lung (FACT-L) [19], the EORTC QLQ-LC13 [18] and the Lung Cancer Symptom Scale (LCSS) [20]. Euro QoL

EQ-5D is one of the two most frequently used generic questionnaire in lung cancer clinical trials [16].

Apart from the generic and disease-specific tools used for the assessment of HRQoL, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) developed in 1982 [21], has been used in numerous trials as a tool to evaluate how the disease affects the patients' daily living abilities, while its association with effectiveness outcomes is commonly evaluated. In the elderly with advanced NSCLC, ECOG PS was found to be a significant independent factor for OS [22]. Furthermore, in a study of patients with metastatic NSCLC receiving chemotherapy, EGOG PS 2 versus 0 or 1 was found to be associated with a high number of adverse events and poor survival [23].

It is also worthwhile to mention that the World Health Organisation (WHO) cites non-adherence to therapy as a very important, yet modifiable factor of anti-cancer therapy outcomes. Notably among the many factors linked to adherence to oral therapies, are the severity of disease-related symptoms, and the patients' physical and psychological well-being [24] adding further support to the importance of examining symptom and HRQoL outcomes in clinical studies of heavily burdened populations, but also of capturing treatment adherence.

9.2 TARGETED THERAPIES FOR NSCLC

Over the last decade, several targeted therapies have been added in the treatment armamentarium of NSCLC in an attempt to increase efficiency and reduce side effects of other agents. In the treatment of NSCLC, targeted agents have been developed against the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR), and more recently against anaplastic lymphoma kinase (ALK) [25, 26].

For patients with NSCLC tumors harbouring activating mutations of the epidermal growth factor receptor (EGFR), targeted treatments, including the first generation tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib, have shown benefits in terms of prolongation of PFS and increased response rates and improvement of HRQoL [27].

9.2.1 Afatinib drug profile

Resistance to the first-generation EGFR agents therapy commonly develops, which has led to the development of the irreversible EGFR TKI, afatinib, which targets and blocks signalling from dimers of all ErbB family members, EGFR (ErbB1), HER 2 (ErbB2), ErbB3 and ErbB4. Afatinib (GILOTRIF®/GIOTRIF®) was approved in 2013 by the FDA and EMA based on results of the pivotal phase 3 studies LUX-Lung 3 and LUX-Lung 6. Specifically, in the US afatinib is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test, 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) [3, 4]. Afatinib is available in orally administered film-coated tablets.

The severity of symptoms and HRQoL when treated with afatinib were examined in the LUX-Lung 1 phase IIb/III randomized controlled clinical trial (RCT), where outcomes of patients treated with afatinib were compared to patients receiving placebo with the use of the EORTC QLQ-C30, the EORTC QLQ-LC13 and the EQ-5D at baseline and every 21 days. Global health as assessed by the EQ-5D as well as global health status, physical functioning

and fatigue assessed by the EORTC QLQ-C30 significantly improved with afatinib treatment. In addition, a significantly higher proportion of patients in the afatinib arm compared to placebo demonstrated improvement in disease-related symptoms, such as cough (P<0.0001), dyspnea (P=0.006), and pain (P<0.0001). In addition, afatinib delayed the time to deterioration of cough (P<0.001) [28].

The positive effect of afatinib on symptoms and QoL compared to chemotherapy has been evaluated in the LUX-Lung 3 and LUX-Lung 6 RCTs, where outcomes were assessed using the EORTC QLQ-C30 and LC13 at baseline and every 21 days.

In the LUX-Lung 3 RCT, patients were randomised (2:1) to receive afatinib 40 mg once daily or up to 6 cycles of pemetrexed/cisplatin. According to the results of the study, for the subgroup of patients with common mutations (Del 19, L858R) (204 on afatinib and 104 on chemotherapy) the median PFS was 13.6 versus 6.9 months [Hazard Ratio (HR) 0.47; 95% CI 0.34-0.65; P<0.0001] and the median OS was 30.3 versus 26.2 months, demonstrating a clear benefit of afatinib treatment. In addition to the Del 19, L858R mutations, certain less common mutations have also been shown to be sensitive to afatinib treatment [29]. Moreover, ccompared to chemotherapy first-line afatinib was associated with better control of cough (HR, 0.60; 95% CI, 0.41 to 0.87; P=0.007) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.015), as well as improved global health status/QoL (P=0.015), and functional scale scores as assessed with the use of EORTC QLQ-C30 and the EORTC-QLQ-L13 [30]. Among the functional scale scores, physical (P<0.001), role (P=0.004), and cognitive (P=0.007) functioning were improved compared to chemotherapy.

The results of the pivotal LUX-Lung 3 RCT have been supported by the LUX-Lung 6 RCT conducted in 36 sites in China, Thailand and South Korea among 364 patients. The study compared first line afatinib with gemcitabine/cisplatin chemotherapy. In the afatinib arm, mean PFS was 11.0 months vs. 5.6 months for those in the chemotherapy arm (HR 0.28; P<0.0001). In addition, a significant higher proportion of patients demonstrated improvement of cough (P<0.0001), dyspnea (P<0.0001) and pain (P=0.03), while afatinib also delayed the time to deterioration of these symptoms. Global health improvement was also demonstrated by a higher proportion of patients in the afatinib group than in the gemcitabine and cisplatin group (62·7% versus 32·7%; P<0.0001). Notably, prolongation of PFS was associated with improved HRQoL and significantly longer control of disease-related symptoms [3].

Mature survival data from the LUX-Lung 3 and LUX-Lung 6 studies have recently been published. With a median follow-up of 41 months in the LUX-Lung 3, 62% (213/345) patients had died; in the LUX-Lung 6, with a median follow-up of 33 months in the OS rate was 68% (246/364). Among patients treated with afatinib, the median OS was 28.2 months (95% CI, 24.6 to 33.6) in the LUX-Lung 3 and 23.1 months (95% CI, 20.4 to 27.3) in the LUX-Lung 6, which did not significantly differ from the OS in the respective chemotherapy arms. However, OS was significantly longer in the afatinib group (33.3 and 31.4 months in the LUX-Lung 3 and LUX-Lung 6 trials, respectively) than in the chemotherapy group in both trials (21.1 and 18.4 months, in the chemotherapy group of LUX-Lung 3 and LUX-Lung 6, respectively) among patients with Del 19-positive tumors [31].

9.3 RATIONALE FOR PERFORMING THE STUDY

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 [9]. 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 RCTs and assist in the decision-making process of the medical professionals that provide care to this heavily burdened population.

10. RESEARCH QUESTION AND OBJECTIVES

10.1 PRIMARY OBJECTIVE

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

10.2 SECONDARY OBJECTIVES

- 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 (*please refer to Section 11.1.2, for the definition of the post baseline timepoints*);
- To assess the impact of afatinib treatment on the HRQoL of the study population using the EQ-5D-3L questionnaire at the post baseline predefined timepoints;
- To assess the impact of afatinib therapy on patient's 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.

11. RESEARCH METHODS

11.1 STUDY DESIGN

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.

The main foreseen limitations for this study are attributed to its observational design and are discussed in the relevant Section 11.10. Notably, these limitations are outweighed by the essential role that studies of such design play in evaluating treatment outcomes for marketed products, particularly in heterogeneous patient populations with diseases of complex and heterogeneous biology, such as cancer. The study will provide clinically-relevant real-world data for a broad patient population that will serve as complementary evidence to that of RCTs. In addition, the study outcomes will reflect patient perceptions on symptom burden accounting for variations in local standards of care, treatment patterns and individuals' characteristics.

11.1.1 Synoptic study assessment schedule

A synoptic study diagram reflecting the assessments of interest and the suggested time schedule is presented in the following figure.

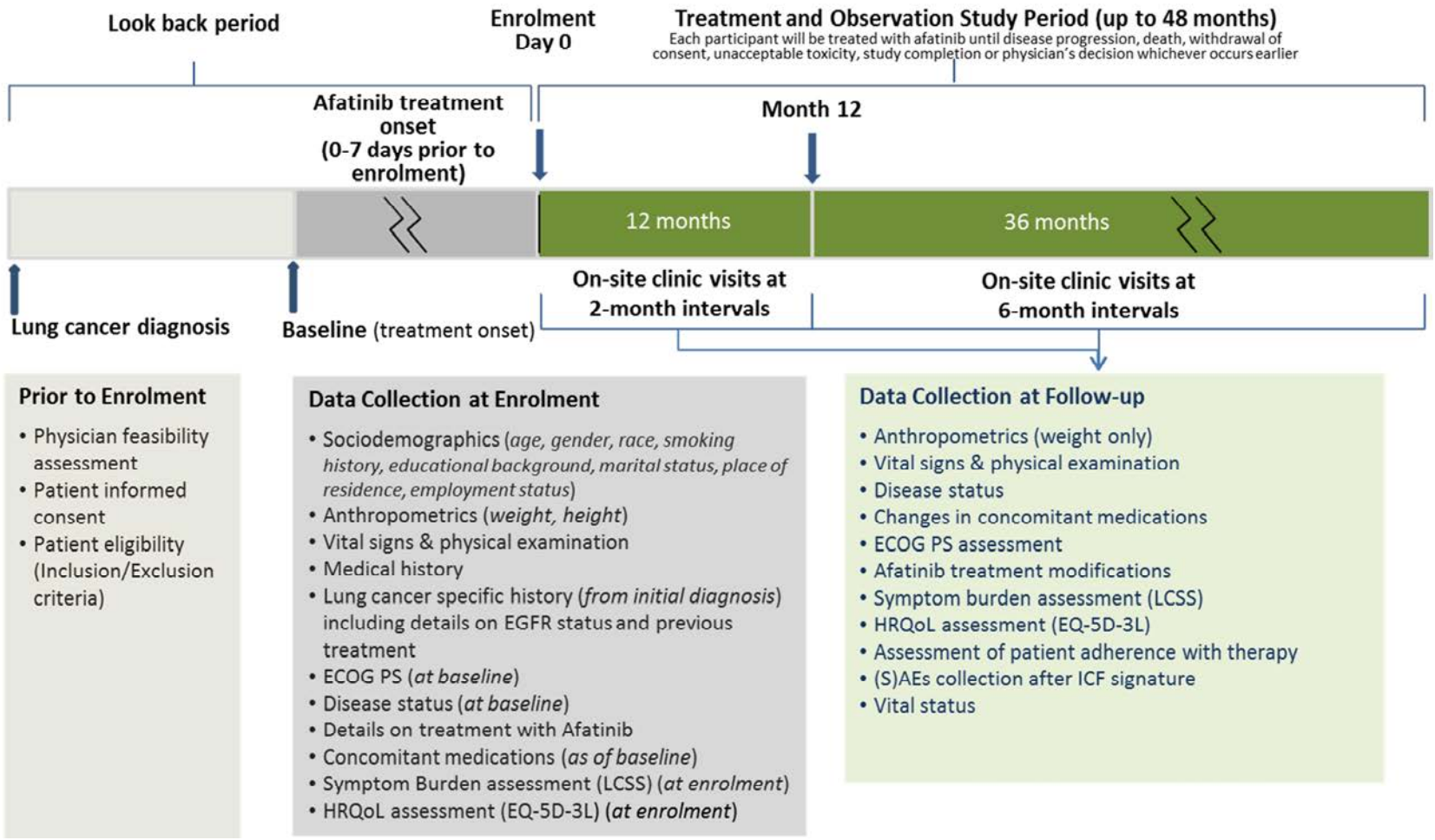


Figure 1: Synoptic Study Diagram

11.1.2 Baseline and post-baseline timepoint definitions

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 (patient-reported LCSS and EQ-5D-3L), the scores that will be collected at the enrolment visit will serve as the baseline data.

- ***Post-baseline predefined timepoints*** for study-specific assessments are defined as: every 2 months (± 3 weeks) during the first 12 months of therapy and every 6 months (±3 weeks) thereafter until the end of patient's participation in the study.

11.1.3 Study primary and secondary endpoints

11.1.3.1 Primary endpoint/outcome measure

- 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 [32, 33, 34]; this magnitude is about the same as the 0.5 standard deviation that has also reported as a universally acceptable minimum clinically important difference [35].

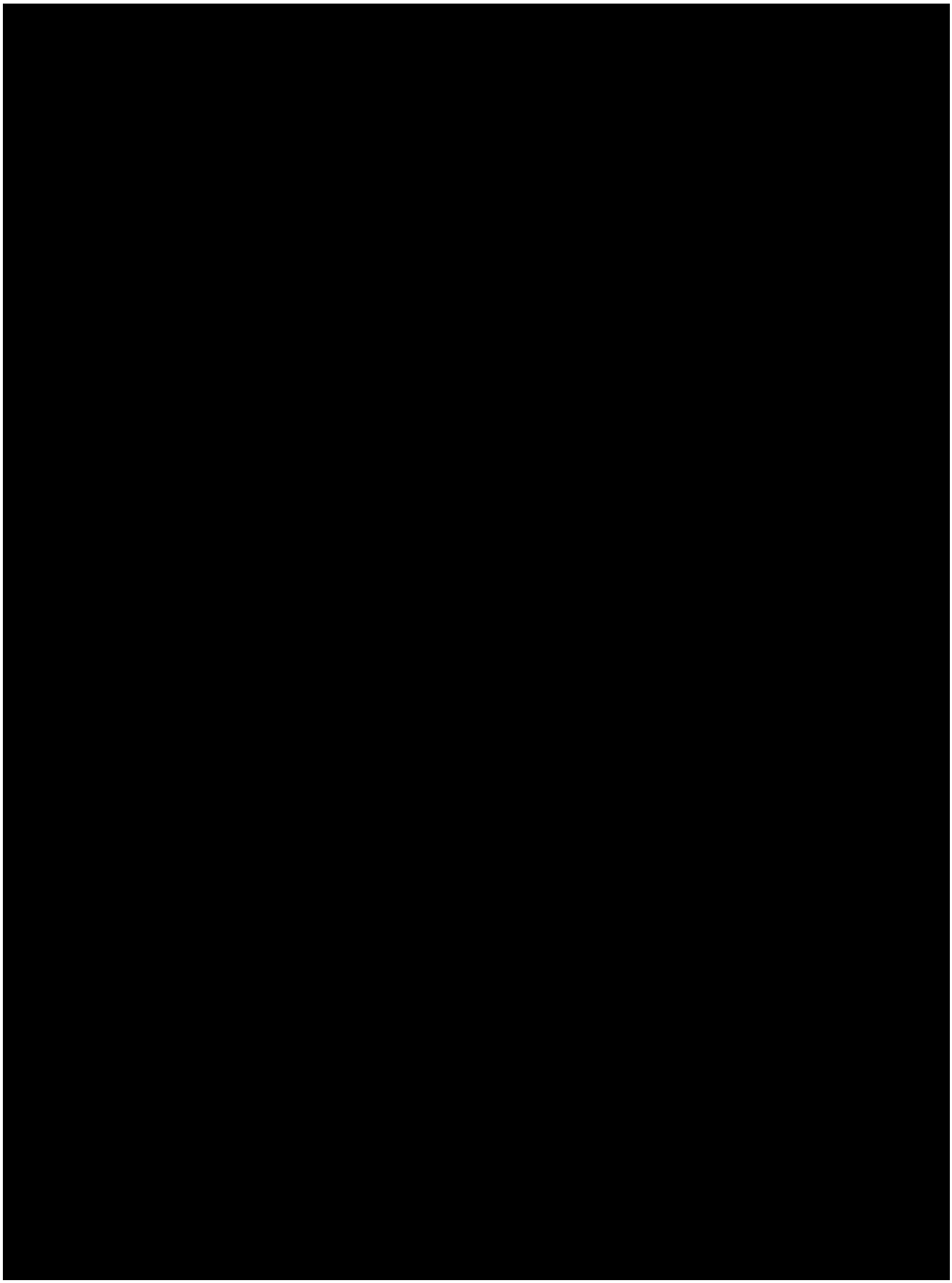
11.1.3.2 Secondary endpoints/outcome measures

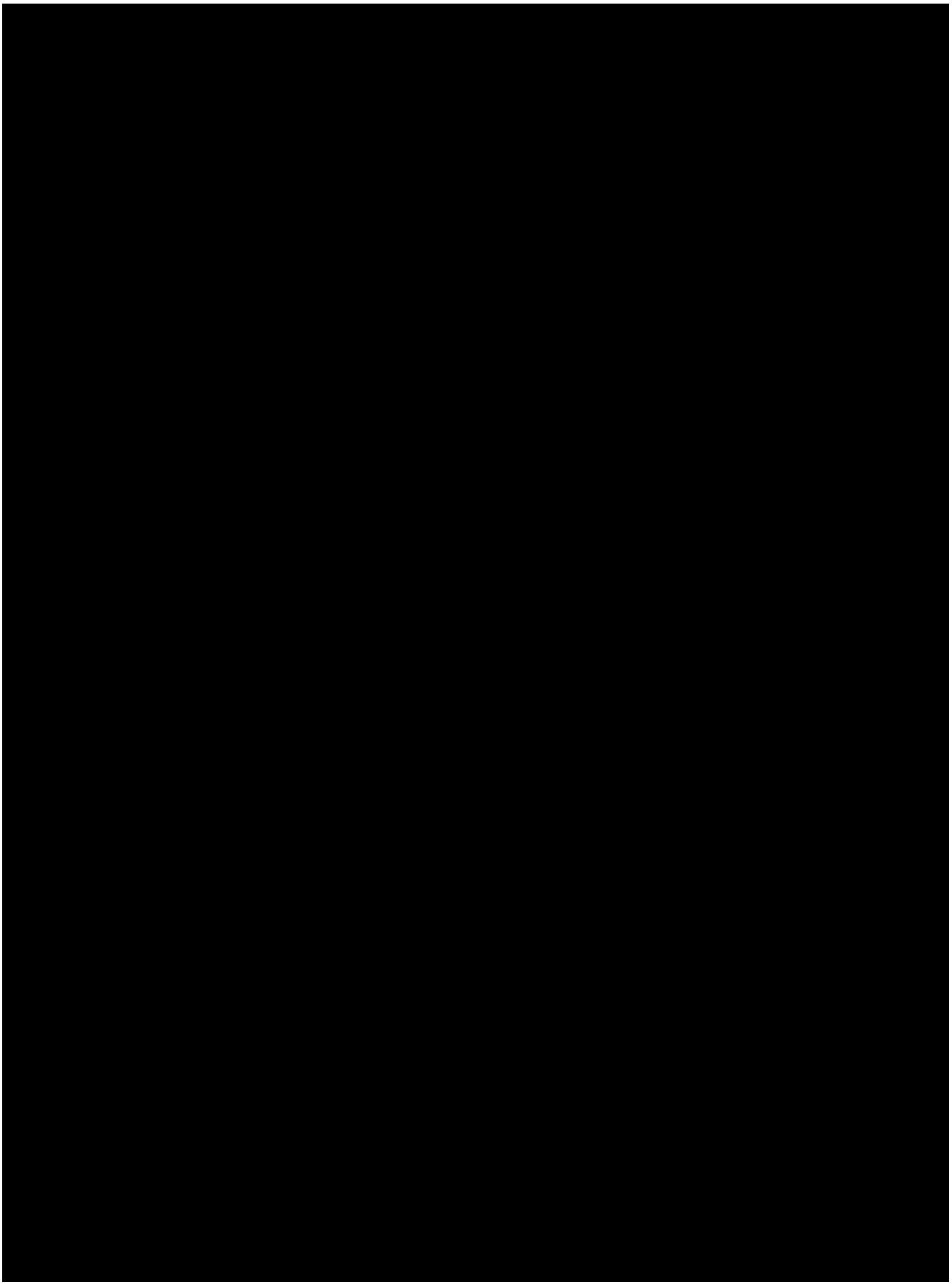
- Change in the total LCSS score, ASBI score and individual domain scores from enrolment to each post-baseline predefined timepoints; in addition change throughout the study observation period will be examined using longitudinal analysis;

- 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.





11.3 STUDY TREATMENT

11.3.1 Dosing/method of administration

Each afatinib film-coated tablet contains 50, 40, 30 or 20 mg active substance (as afatinib dimaleate) and lactose (as monohydrate) as known active ingredient. For the full list of excipients please read the Summary of Product Characteristics.

When assessing a patient's EGFR mutation status, it is important that a well-validated and robust methodology is used to avoid false negative or false positive results.

According to the Summary of Product Characteristics, the recommended afatinib dose in first-line therapy is 40 mg once daily taken orally. Afatinib should be taken without food. Afatinib should be taken 3 hours after and at least 1 hour a meal. Afatinib is taken orally. The tablets are swallowed in one piece with a glass of water. For patients who are unable to swallow the afatinib tablets in one piece, they can be dissolved in about 100 mL of non-carbonated drinking water. Do not use any other liquids for this. The tablets are placed in one piece into the water without breaking them up beforehand. After that the contents of the glass is stirred occasionally for up to 15 minutes until the tablet has dissolved into very small particles. Drink the dispersed solution immediately, then rinse the glass with about 100 mL of water and also drink this water. The dispersed solution can also be administered via a gastric tube. A forgotten afatinib dose should be taken on the same day as soon as the patient remembers it. However, if the time until the next planned dose is less than 8 hours, the patient should not take the forgotten dose.

The treatment with afatinib should be continued until disease progression or until the patient no longer tolerates the medicinal product. A dose escalation to a maximum of 50 mg/day may be considered in patients tolerating the dose of 40 mg/day well in the first 3 weeks (i. e. absence of diarrhoea, rash, stomatitis and other drug-induced events of CTCAE grade >1). The dose should not be escalated in any patients with a prior dose reduction. The maximum daily dose is 50 mg.

11.3.2 Dose adjustment due to adverse events

Symptomatic adverse reactions (e. g. severe/persistent diarrhea or skin-related adverse reactions) can usually be managed successfully by interrupting the treatment and reducing the dose or by discontinuing afatinib:

Adverse reactions according to CTC[1]	**Recommended afatinib dose:**	
Grade 1 or Grade 2	No interruption[2]	No dose adjustment
Grade 2 (prolonged[3] or intolerable) or Grade >3	Interrupt until grade 0/1[2]	Resume with dose reduction in 10 mg decrements[4]

1. *NCI Common Terminology Criteria for Adverse Events*
2. *In case of diarrhoea, patients should take anti-diarrhoeal drugs immediately (e. g. loperamide) and continue to take these drugs in case of persistent diarrhoea until loose bowel movements abate.*
3. *>48 hours of diarrhoea and/or > 7 days of rash*
4. *If the patient cannot tolerate 20 mg/day, permanent discontinuation of the treatment with afatinib should be considered.*

11.3.3 Special warnings and precautions for use

Diarrhoea, including severe diarrhoea, has been reported in patients treated with afatinib. Diarrhoea may result in dehydration (with or without renal impairment), which in rare cases has resulted in fatal outcomes. Diarrhoea usually occurred within the first two weeks of treatment; grade 3 diarrhoea most frequently occurred within the first six weeks of treatment. Proactive treatment of diarrhoea including adequate hydration combined with anti-diarrhoeal drugs especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Anti-diarrhoeal drugs (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Anti-diarrhoeal drugs should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption of the treatment with afatinib, dose reduction or discontinuation of therapy. Dehydrated patients may require administration of intravenous electrolytes and fluids. Patients are therefore instructed to initiate treatment of diarrhoea with anti-diarrhoeal therapy independently and to inform the attending doctor of this immediately.

Rash/acne has been reported in patients treated with afatinib. In general, rash manifests as a mild or moderate erythematous and acneiformous rash, which may occur or worsen in areas exposed to sunlight. Early treatment (such as emollients, antibiotics) of dermatic reactions increases the probability of treatment continuation. Patients with severe skin reactions may also require temporary interruption of therapy, dose reduction, additional therapeutic intervention, or referral to a specialist with expertise in managing these adverse dermatic reactions.

In the event of acute or aggravating respiratory symptoms, interstitial lung disease (ILD) must be considered and afatinib treatment should be interrupted until the cause of these symptoms has been clarified. If interstitial lung disease is confirmed, afatinib must be permanently discontinued and appropriate treatment initiated.

Afatinib is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) and hepatic impairment (Child-Pugh score C).

Higher plasma levels of afatinib have been observed in female patients, patients with lower body weight and those with underlying renal impairment. This could result in a higher risk of developing adverse reactions including diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors. For more information please read the respective Summary of Product Characteristics, in particular the sections on "Contraindications", "Warnings and precautions for use", "Interaction with other medicinal products and other forms of interaction" as well as "Fertility, pregnancy and breast-feeding".

Further information about afatinib can be found in the enclosed Summaries of Product Characteristics.

11.4 VARIABLES

11.4.1 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, dyspnea, pain, and hemoptysis*- at enrollment and at the 2-month intervals until the study visit at 6 months.

11.4.2 Secondary outcome variables

- Patient-rated ASBI score of LCSS at the post-baseline predefined timepoints (these timepoints are defined in Section 11.1.2);

- Patient-rated total LCSS score -defined as the average of the aggregate score of all 9 items that comprise the LCSS- at enrollment 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 change(s) and reasons for treatment modifications.

11.4.3 Other variables

- ***Sociodemographic and anthropometric patient characteristics:***

  - Age (years)
  - Gender: *males, females (n,%); male-to-female ratio*
  - Race: *Caucasian, Asian, African, other;*
  - Place of residence: *urban areas, semi-urban areas, rural areas;*
  - Educational level: *no education, primary education, secondary education, tertiary education;*
  - Marital status: *single, married, divorced, widowed;*
  - Employment status: *unemployed, employed, retired, household duties, other;*
  - Smoking status: *never smoker, former smoker, occasional smoker, current smoker; if former or current smoker: smoking pack-years,* and *if former smoker: years since quitting smoking;*
  - Weight (kg);
  - Height (cm);
  - Body mass index (BMI in kg/m^2);
  - Systolic and diastolic arterial pressure (mmHg);
  - Respiratory rate (bpm [breaths/minute]).

- ***Disease & clinical characteristics***

  - Age at disease diagnosis;
  - Disease stage (IIIB, IV) at baseline;
  - Histologic classification *(adenocarcinoma squamous-cell-carcinoma, other);*
  - EGFR mutation subtype *(exon 19 deletions, Leu858Arg, other);*
  - Sites of metastases at baseline;
  - Previous disease-related treatment patterns;
  - Baseline comorbid conditions;
  - Change in disease status throughout the study period.

- ***Treatment characteristics***

- Time from diagnosis to afatinib treatment onset;
- Length of exposure to afatinib treatment throughout study duration;
- Starting dosage regimen;
- Type of dose modifications over the study observation period;
- Concomitant medications both at baseline and throughout the conduct of the study.

11.4.4 Confounding/effect modification variables

The following variables will be considered as potential confounders or effect modifiers of the main association between treatment with afatinib and change 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.

11.5 DATA SOURCES

The study will mainly involve new data collection, by means of a web based data capture (WBDC) system. Data will be collected by the study physicians as generated according to the standard clinical practice and by the patients as captured with the use of PROs. No further laboratory tests and examinations are required apart from those recommended by the study medication SmPC.

Patient source data pertaining to medical- and lung cancer-related history will be abstracted from patient medical charts/records by the investigators and will be recorded in the relevant section of the WBDC.
All afatinib treatment modifications, concomitant medications, study-related routine clinical assessments, adverse events (AEs) and vital status will also be collected. Regarding vital status, if a patient is prematurely withdrawn from the study, he/she will be contacted by telephone or other methods to assess vital status at the end of study unless the patient has actively withdrawn consent for all forms of contact (refer to section 11.2.4.3).

Concomitant or prior disease-related medications entered into the database will be coded using the Anatomical Therapeutic Chemical (ATC) WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) Drug Reference List.

Medical history/comorbidities and adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

In addition, physicians will be requested to assess:

- **Patients' performance status** using the ECOG PS instrument. *(For a sample of the English version please refer to ANNEX 3: ECOG PERFORMANCE STATUS SCALE).*

Furthermore, the **following PROs** will be collected via self-administered paper questionnaires completed by the patients themselves at study enrolment and periodically throughout study participation, according to the study visit frequency.

- **Disease-specific symptoms** will be measured using the self-administered patient-rated LCSS, a reliable and valid lung cancer-specific instrument that is comprised of two components, the patient-rated scale employed in the present study and the observer-rated [20, 36, 37].
  The patient-rated LCSS questionnaire consists of nine items, each scored with a 100-mm VAS used to evaluate six symptoms associated with lung cancer (loss of appetite, fatigue, cough, dyspnea, pain, and hemoptysis) as well as three global items used to evaluate the interference with normal activities, distress from lung cancer symptoms, and overall QoL. The mean of the 6 major lung cancer symptoms comprises the ASBI that reflects the primary outcome variable in this study. In addition, the LCSS total score defined as the mean of the 9 items of the scale will be determined.
  The time for LCSS patient scale completion is 8 minutes initially for demonstration of the VAS and 3-5 minutes for subsequent administrations.

  Rationale for selecting LCSS: The LCSS has been selected as the main PRO in this study since it is focused on symptom burden which is the main objective of the study as well as is more patient-friendly, less time-consuming and provides less patient and staff burden (it comprises 9 items in total compared to the 43 items of EORTC_LC13) and thus is considered more suitable for use in the common clinical setting in the context of a NIS. In addition, it has demonstrated a good reliability and validity compared to the other PROs [10]. *(For a sample of the English version please refer to ANNEX 3: LCSS PATIENT SCALE).*

- **HRQoL**: The Greek version of Euroqol EQ-5D-3L [38] will be used in order to measure patients' HRQoL at the specific timepoints of the study.
  The EQ-5D-3L is a standardized disease-generic instrument for the measurement QoL that has been widely used in both general and specific disease populations. It is cognitively not demanding, taking only a few minutes to complete. It consists of the EQ-5D descriptive system and the EQ VAS. EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics, and in face-to-face interviews. The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems.
  The EQ VAS records the respondent's self-rated health on a vertical, visual analogue graduated (0–100) scale [17, 39]. *(For a sample of the English version please refer to ANNEX 3: EQ-5D-3L).*

- **Adherence to therapy with afatinib**: A patient diary will be used which the patient will be requested to fill in only with the date and reasons for missed pills. The diary will contain both predefined reasons and free text fields.
  Patient diary is among the accepted methods for estimating treatment adherence. This method has been selected as the less burdensome for the patient (compared with any compliance-specific PRO) and the most accurate in terms of avoiding recall biases [40].

11.5.1 Administration of patient-reported outcome questionnaires

For the purposes of the current study, the validated Greek versions of the LCSS and EQ-5D-3L instruments will be administered to the patients via a paper-and-pencil self-administered format.

The questionnaires shall be provided to the patients before completing any other procedures or clinical exam at the study visit. This ensures that the interaction between the respondent and other health care professionals does not influence the patient's responses. The patient will be provided with instructions and a quiet and comfortable place to complete the questionnaires. The respondent should be alone when completing the PROs. Spouses or other accompanying individuals should wait in a separate area during the PROs administration. This minimizes any influence on the respondent's answer and ensures the PROs responses reflect the patient's perspective, and not someone else's.

When the respondent has completed the questionnaires, the study physician shall review them to ensure all questions have been answered. If there are any missing questions, he/she shall point them out to the respondent so they may be completed. However, respondents may omit any question they do not feel comfortable answering.

In order to protect subject confidentiality the name of the patient will not be mentioned on the questionnaires.

11.5.2 Data collection schedule and study flow chart

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

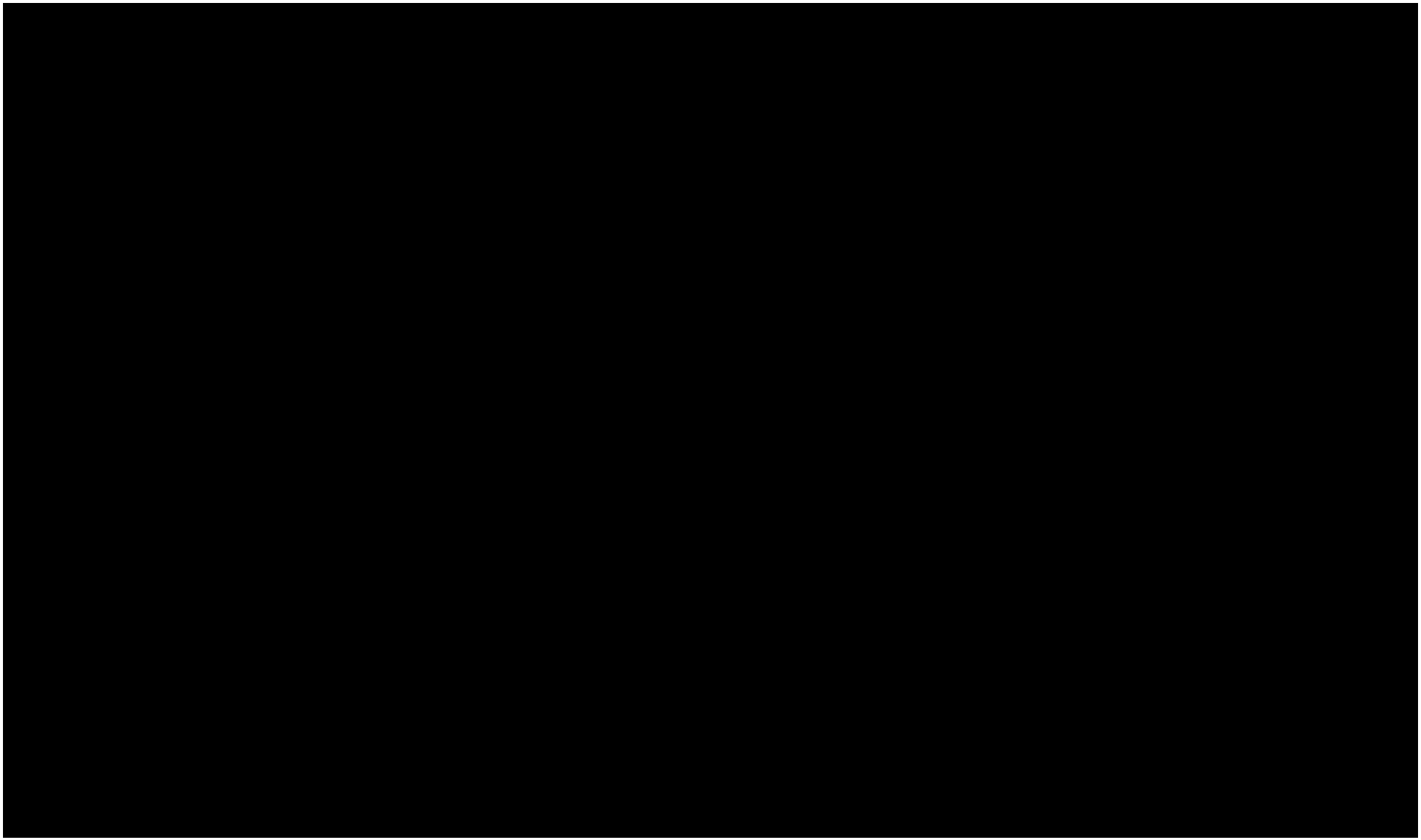
routine medical practice in terms of visit frequency, types of assessments performed and with adherence to the local prescribing requirements for afatinib.

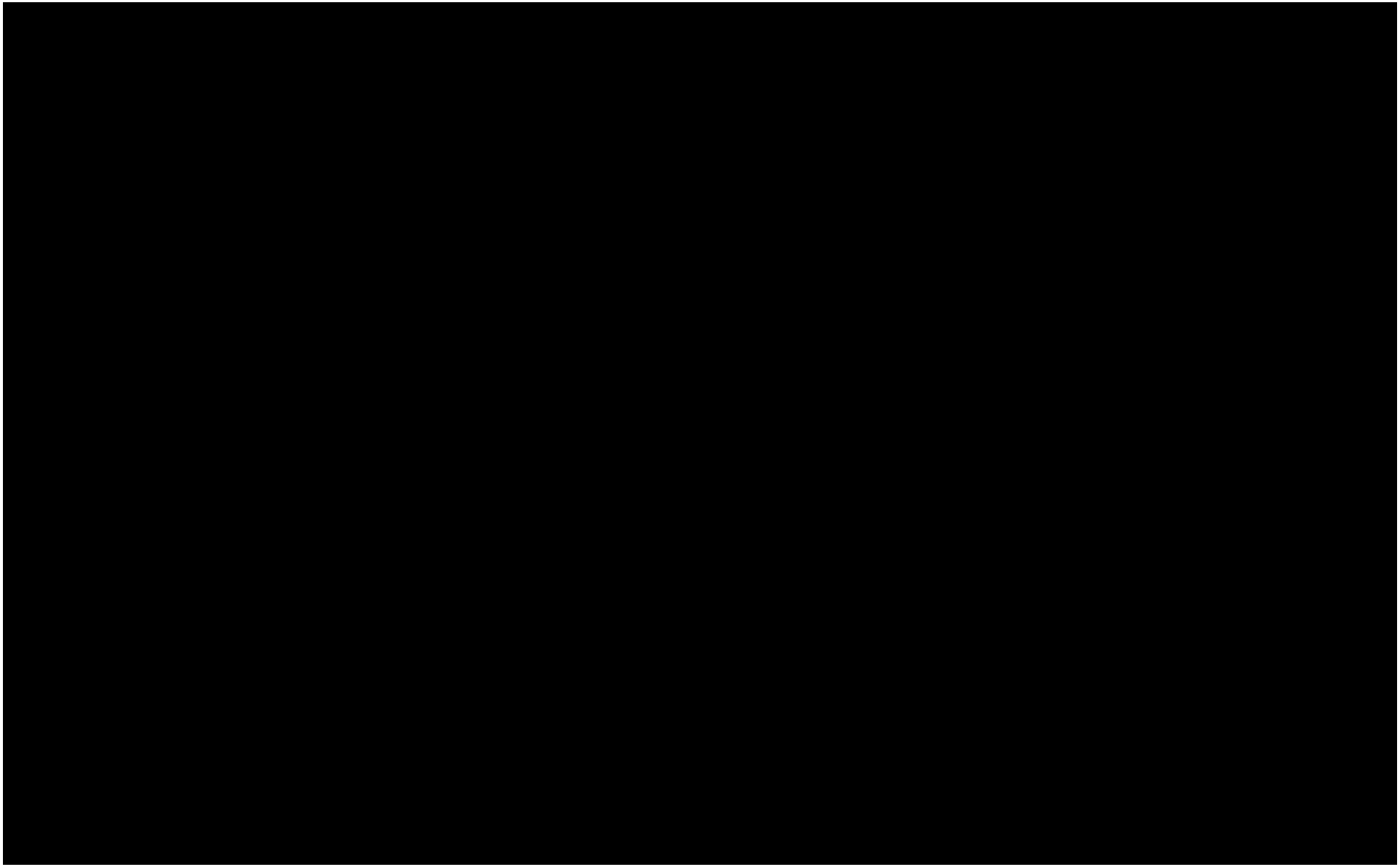
Upon the enrollment of each patient into the study, the investigator shall follow the below-mentioned procedures:

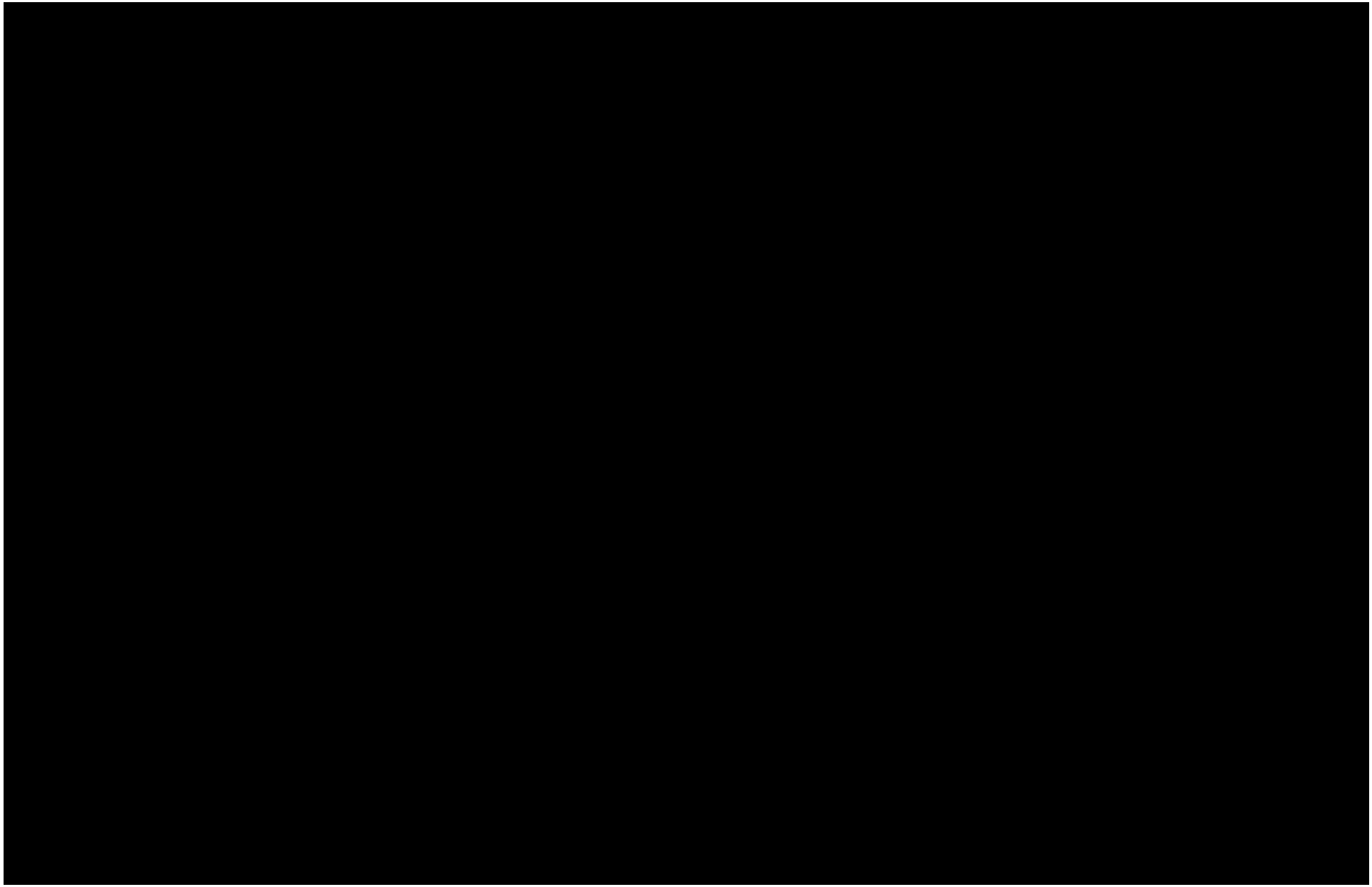
1. Review of patient's personal medical history, in order to confirm if inclusion/exclusion criteria are met.
2. Explanation of study purpose to the patient and obtainment of signed and dated written ICF, after having provided the required time to the patient to carefully read and understand the information leaflet.
3. Collection of the data from the medical records of the eligible patients, as required by the eCRF as well as completion of the eCRF.

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 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 2.







11.6 STUDY 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 11.1.3.1*) 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.

11.7 DATA MANAGEMENT

The study data collection will be carried out through WBDC and paper-and-pencil self-administered PROs.

The WBDC application will be specifically designed for the needs of the study by the designated Clinical Research Organisation (CRO) and will adhere to all applicable data protection regulations and requirements with regard to electronic records. The patients will be identified by subject identification number, site number, and study identification number.

Data (including those recorded in the paper PROs) will be entered in the WBDC system by the study personnel at the Investigator's site, according to the Investigator Instructions Manual. Data entered in the WBDC system will be automatically saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator shall sign the e-CRF electronically as per the agreed project process and data will be locked to prevent further editing.

Query management will be performed through built-in query management functionality that will be incorporated into the WBDC.

Prior to the onset of data management activities, a detailed data management plan (DMP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for the interim and final statistical analysis. In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied twice during the conduct of the study for the purposes of the interim and final analysis, respectively. When all data have been properly validated and the quality control procedure has been completed, a declaration of database lock will take place so that it can be confirmed that all important actions have

been properly performed. In addition, prior to database lock and prior to the initiation of any statistical analysis activities a comprehensive statistical analysis plan (SAP) will be drafted. The SAP will also include information regarding the statistical software(s) to be used for the analysis of the study data and any data imputation methods that may be applied.

11.8 DATA ANALYSIS

The study is not aimed to confirm or reject any pre-defined hypotheses; therefore statistical analyses will be of explorative and descriptive nature.

Continuous variables will be summarized with the use of descriptive statistical measures (mean value, standard deviation, median and extreme values) and categorical/distinct variables will be displayed as frequency tables (N, %). The normality of distribution of continuous variables will be examined using the Shapiro-Wilk test in order to determine whether or not to use parametric methods for the analysis of the sample data.

Differences between the mean values of continuous variables will be evaluated using the paired t-test or the non-parametric analogue (i.e., Wilcoxon signed rank test).

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 three (3) decimals unless the p-value is less than 0.001 (in such case $P<0.001$ will be reported). No adjustment for multiplicity of testing will be performed.

A SAP comprising a comprehensive and detailed description of the statistical methodology applied for the purposes of the interim and final analysis along with imputation methods for missing data will be prepared prior to database lock.

Statistical analysis will be conducted using a validated statistical software package [e.g., Statistical Analysis System (SAS)].

11.8.1 Study populations

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 into 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 LCSS ASBI score.

Subsets of patients with available data will also be created and analysed for the purposes of secondary endpoint analyses.

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).

11.8.2 Analysis for the primary endpoint

Pertaining to the primary endpoint the proportion of patients experiencing a minimum clinically important symptom improvement (*as defined in Section 11.1.3.1*) over a 6-month period of treatment will be calculated along with the respective 95% confidence interval; in addition the relevant proportions of patients whose symptom burden has remained stable and deteriorated will be calculated. The 95% confidence interval will be derived from Wald confidence limits for a binomial proportion.

In order to examine the impact of baseline characteristics including among others, gender, age, BMI, educational/marital/employment status, disease stage, histological subtype, sites of metastases, EGFR mutation subtype, smoking status and smoking history, ECOG PS, type of concomitant medications and comorbidities, as well as adherence to therapy at 6 months on the study primary endpoint, a binary logistic regression model will be applied.

11.8.3 Analysis for the secondary endpoints

With regard to the secondary endpoints pertaining to the LCSS outcome measures, the mean change of the total LCSS, defined as the average value of all individual item scores, will be calculated from enrolment to all available subsequent study visits and will be examined for statistical significance with the use of the paired t-test or its non-parametric analogue. Similar analysis will be performed for the ASBI subscore and each individual domain of LCSS.

If applicable, pertaining to the change of the mean LCSS as well as the mean ASBI through the observation period, linear mixed models will be applied, in order to estimate the monthly predicted change in the aforementioned scores.

Additionally, the symptom improvement rate throughout the study observation period will also be calculated in patient-years.

The distribution of patients by level (‘level 1: no problems’, ‘level 2: some problems’ and ‘level 3: extreme problems’) for each dimension (mobility, self-care, usual activities, pain/discomfort, anxiety/ depression) as well as the distribution of patients in the dichotomized EQ-5D levels [‘no problems’ (level 1) and ‘problems’ (levels 2 and 3)] will be presented in frequency tables (N, %) for all patients with available data. Descriptive statistical measures will be calculated for the EQ-VAS score at each predefined study time-point.

The McNemar’s test will be used in order to evaluate the change in the levels (‘with problems’/ ‘no problems’) of each dimension between enrolment and the post-baseline visits.

Descriptive statistics of the EQ-VAS will be presented for each study visit as well as for the observed changes in the EQ-VAS from the enrolment visit to each post-baseline study time-point; while the paired t-test or the Wilcoxon signed rank test will be used to assess the statistical significance of the change.

The distribution of patients in the different ECOG performance status levels at every study time-point will be presented in frequency tables (N, %). Additionally, changes in the status of patients from baseline to post-baseline evaluations will be depicted in shift tables.

Adherence to treatment with afatinib as well as the proportions of patients who discontinued or interrupted treatment, and those who underwent any dose modifications along with the type of dosage modifications and reasons for these, will be analysed in a descriptive manner.

11.8.4 Analyses for the safety data

All recorded AEs will be mapped by system organ class (SOC) and preferred term (PT) according to MedDRA (*most updated version at the point of coding*).

The number and proportion of patients experiencing any serious or non-serious adverse event will be calculated by SOC and PT.

Specifically, the following data will be tabulated:

- Number and proportion of patients experiencing a serious AE (SAE) by SOC and PT.
- Number and proportion of patients experiencing a non-serious AE (NSAE) by SOC and PT.
- Distribution of AEs by National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) toxicity grade classification and causal relationship to study treatment.

Additionally, the exposure adjusted incidence rates (EAIRs) along with the respective 95% CIs will be calculated for the following patient subpopulations: those experiencing at least one SAE, at least one NSAE.

Available data from other safety-related evaluations (systolic and diastolic arterial blood pressure, respiratory rate and pulse rate) will be summarized descriptively per visit or when they occurred, along with the respective change from baseline to all post-baseline visits.

11.8.5 Drug exposure

The exposure (D_{Exp}) to afatinib treatment will be calculated using the number of days on afatinib, i.e. duration since treatment onset ($date_{First}$) until the date of last treatment administration or until the last date with available data ($date_{Last}$) according to the following formula.

$$D_{Exp} = (date_{Last} - date_{First}) + 1$$

Descriptive statistics (n, mean, standard deviation, median, range) will be calculated for the duration of afatinib treatment for all patients of FAS.

11.8.6 Additional analyses

Descriptive statistics regarding sociodemographic data such as gender, race, smoking history and educational background will be displayed in frequency tables (N, %).

Continuous variables concerning demographics and anthropometric characteristics such as age, body weight, and height as recorded at the enrolment visit will be presented with

mean, SD, median, minimum and maximum values. Quantitative variables will be presented with absolute and relative frequencies.

The number and percentage of patients with at least one medical condition as recorded at the enrollment visit will be calculated. Additionally, the depicting reported terms will be coded by MedDRA (*the most updated version available at the point of coding*) while SOC and PT will be tabulated in a frequency table (N,%).

The number and percentages of patients receiving at least one concomitant medication will be calculated. Concomitant medications coded with the use of ATC Drug Classification dictionary by WHOCC in terms of therapeutic subgroup and chemical substance will be presented in frequency tables (N,%). Similar analyses methods will be performed for all therapies related to NSCLC prior to afatinib onset.

11.8.7 Interim analysis

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 enrolled 40 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.

The confidentiality of the interim analysis data will be controlled by assignment of the analysis to a statistical group that is independent of the Sponsor and investigators, i.e. is not otherwise involved in the study design or conduct. After completion of the analysis the results will be summarized in a synoptic interim CSR and distributed to the study Sponsor. The detailed interim analysis results will not be disclosed to the participating investigators until the overall study completion in order to account for the avoidance of any bias that may result from the premature disclosure and subjective interpretation of the preliminary findings. However, the preliminary results may be announced in the form of an abstract or poster/presentation in a descriptive manner, as per the Sponsor's decision; in such case, the minimum required information will be disclosed aiming at safeguarding the scientific integrity of the final study results.

11.9 QUALITY CONTROL

Proper quality control mechanisms and processes will be implemented in order to ensure data quality and integrity through the conduct of the study. All these procedures will be detailed in the study specific DMP and SAP.

The query management process for the eCRF-collected data will be handled on a real-time-basis through built-in edit and logic checks (validation rules) in the eCRF application. If any discrepancies (other than those predicted by the built-in validation

rules) arise before eCRF lock during source data verification (SDV) process (performed by the project monitor) or data review by the Data Manager, queries will be handled electronically through specific application's query functionality, whereas for discrepancies that may emerge after eCRF application lock, paper Data Clarification Forms (pDCF) will be issued manually, using Microsoft Word. For PRO-collected data no queries will be issued. After all data have been properly validated, the quality control procedure has been completed and database lock has been declared, the extracted file will be transferred to sponsor. Statistical analysis performance & CSR development will be performed by a designated CRO.

Statistical programming performed to generate the results as well as all-related documents and forms will be archived electronically.

e-CRF archivals for each participating site will be prepared in CD-ROMs by the designated CRO, upon study completion and will be distributed to the participating sites.

The study authorized representative will provide the investigators with a folder/file in which the study-related documents should be archived and maintained. All study documents should be stored in this file by the Investigator. The monitor of the study will regularly check the file to ensure that all relevant documents are maintained. The contents of the folder/file may be subjected to audit/inspection by a designated auditor, regulatory authorities or Hospital Institutional Review Boards (IRBs).

The designated CRO will assure database quality by reviewing the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan. The [redacted] may perform quality control visits at study sites to ensure implementation of the study protocol and all relevant regulatory and BI procedures.

11.10 LIMITATIONS OF THE RESEARCH METHODS

The main foreseen limitations for this study are attributed to its observational design and mainly involve patient selection bias, information bias and missing data as well as lack of internal validity (no control group).

In order to control for and minimize patient selection bias, physicians will be requested to consecutively, thus non-selectively, enroll the first patients (based on the site-specific target) attending their clinic that meet the study specific eligibility criteria. In addition the investigators' decision-making to administer afatinib to a patient will be based on current medical practice and precede the consideration of the patient's eligibility for enrolment into the study. A screening log of all potentially eligible patients will be kept at site.

With regard to patient information/recall bias that may be introduced by the collection of data pertaining to patient-reported outcomes, this will be mitigated through the use of widely used PROs that employ no recall period as all questions refer to the symptoms and state of health at the day of completion. In addition, the self-administered PROs shall be completed by the patients themselves before the performance of any study-specific procedure(s) or clinical assessment(s) in order to avoid introducing any response bias.

In regards to the patient-reported symptom and HRQoL outcome measures, a potential confounding factor may arise from the fact that for patients for whom the onset of treatment with afatinib precedes their enrolment in the study, the completion of the PROs will not accurately reflect their baseline symptom burden and health state; nevertheless since the permitted time window between these two time points has been set at a maximum of 7 days, this time lag is not expected to significantly impact the robustness of the outcomes.

Another confounding factor to the patient-reported symptom and HRQoL outcomes is the potential effects of comorbidities and concomitant medications. To account for this, all baseline comorbid conditions as well as of concomitant medications both at baseline and throughout the conduct of the study (*with particular emphasis among others on analgesics, antitussives, antidepressants, antiemetics, and antidiarrheals)* will be collected in order to differentiate anticancer treatment effect from the effects of comorbidities and concomitant medication.

The possible influence of confounding factors on the outcomes of this study will be accounted for in the statistical analyses by use of robust multivariable analyses, if deemed necessary.

With regard to the external validity i.e., the ability to generalize the study results to a more universal population, every effort will be made for the study population to be representative of the overall population of patients with NSCLC treated with afatinib in Greece by enrolling patients from geographically diverse locations throughout Greece with a non-limiting set of clinical characteristics, apart from those indicated by the locally approved product's SmPC, accounting for variations in medical practice paradigms.
Internal validity of the outcomes will be safeguarded to the extent feasible with the implementation of appropriate source data verification and quality assurance measures, as described in the relevant Section 11.9.

11.11 OTHER ASPECTS

11.11.1 Informed consent, data protection, study records

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for GCP and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the CSR.

11.11.1.1 Study approval, patient information, and informed consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and competent authority (CA), where applicable, according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

In particular, as per the national regulatory requirements, the protocol and the informed consent form (ICF) must be submitted to the IRBs (Scientific Council/Board of Directors) of the participating hospitals as part of the approval process. The Scientific Council/Board of Directors of the participating hospitals must also approve any amendment to the protocol or Patient ICF, prior to the implementation of the amendment or the use of the ICF, according to local regulations. The conduct of this non interventional study will adhere to the applicable national regulatory requirements governing the conduct of such type of clinical studies.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the national regulatory and legal requirements. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.11.1.2 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

11.11.1.3 Records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via an Electronic Data Capture (EDC) system.

11.11.1.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records; also current medical records must be available.

All data entered in the eCRFs must be derived from source documents.

11.11.1.3.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA)/on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 11.11.1.3.1.

11.11.1.3.3 Storage and retention of records

Patient files and other source documents must be kept for the maximum period of time permitted by the hospital/institution, or as specified below. The Clinical Research Associate (CRA)/on site monitor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or if he/she is unable to retain them for the specified period.

The investigator must retain study records (*e.g., source documents such as medical records, contracts, e-archivals and signed consent forms*) for the amount of time specified by applicable laws and regulations. At a minimum, study records must be retained for the amount of time specified by the standing legislation, i.e., study records must be retained for at least 5 years after study completion. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the study sponsor.

11.11.1.4 Statement of confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities, i.e. the CA.

11.11.1.5 Completion of study

The IRB (Scientific Council/Board of Directors) of the participating hospital sites will be notified about the end of the study (last patient out) or early termination of the study,

unless otherwise mandated by the national regulations governing the conduct of such type of studies which may have been altered by the time of study completion.

12. PROTECTION OF HUMAN SUBJECTS

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

The confidentiality of patient data will be maintained at all times and no documents containing the patient's name or other identifying information will be collected by the Sponsor. It may be necessary for the sponsor's representatives, the IRBs and regulatory authority representatives to have direct access to the patient's medical records. If study documents need to be photocopied during the process of verifying eCRF data, the patient will be identified by a unique code only; full names/initials and other identifying information will be masked.

By signing this protocol, the investigator also affirms to the sponsor that information provided to the investigator by the sponsor will be maintained in confidence and will be divulged only as necessary to the IRBs and institution employees directly involved in the study. IRB members and employees also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as agreed in the publication policy of this protocol.

By signing the ICF, the patient accepts being informed of the following:

- What kind of personal information (data) will be collected from participants in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- What are the rights of a research participants pertaining to the potential revoke of their authorization for use of their personal data.

In case of patient authorization revoking, the investigator maintains the right to use the information collected prior to the revoke.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

13.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction (ADR)
An adverse reaction 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. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalisation, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Every new occurrence of cancer is to be considered as SAE regardless of the duration between discontinuation of the study medication and the occurrence of the cancer.

Protocol-specified adverse events of special interest (AESIs)
There are no Protocol-specified Adverse Events of Special Interest for this study.

13.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

- all ADRs (serious and non-serious),
- all AEs with fatal outcome,
- all AEs which are relevant for a serious ADR or an AE with fatal outcome.

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced.

- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to the NCI CTCAE version 4.0 [June 2010], in the eCRF.

The NCI CTCAE V4.0 can be viewed on-line at the following NCI weblink:

ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade that specific event:

Table 3: Grading Scale for Toxicities Not Included in the NCI CTCAE

Grade	Definition
1	Mild; Awareness of sign(s) or symptom(s) which is/are easily tolerated
2	Moderate; Enough discomfort to cause interference with usual activity
3	Severe; Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a female subject has been enrolled into the study, after having taken the study drug afatinib, the investigator must report any drug exposure during pregnancy to the Sponsor by means of Part A of the Pregnancy

Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded in addition to the Pregnancy Monitoring Form within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

- All SADRs (serious ADRs) including all AEs which are relevant for a serious ADR immediately (within 24 hours)
- All AEs with fatal outcome including all AEs which are relevant for an AE with fatal outcome immediately (within 24 hours)
- All non-serious ADRs within 7 calendar days
- All Drug Exposure During Pregnancy within 7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form. The NIS AE form is to be forwarded to the defined unique entry point identified for [redacted] Details provided in the Investigator Site File.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the study drug afatinib according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

13.3 TIME WINDOWS

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the study medicinal product (i.e., afatinib) this is the Investigational Brochure (IB). The current version of this reference document is to be provided in the ISF.

13.4 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorisation Holder (MAH) according to local and international regulatory requirements.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Upon completion of the study, a final CSR of the study results will be prepared by the Sponsor in accordance with the schedule.

The results of the study may also be published in a relevant medical journal and may be announced at scientific congresses. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

The publication strategy and the authors' list will be agreed between the [redacted] and the participating investigators.

In addition, the study and its result will be posted on the web-based platform of the Non-Interventional Studies Register [Dilon, weblink: www.dilon.sfee.gr] as per the local requirements. This webpage pertains to the electronic register and is posted on the website of the Hellenic Association of Pharmaceutical Companies (SFEE).

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15.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in the following table of Annex 1 will be maintained separately from the study protocol. They will be clearly identifiable and provided on request.

Table 4: List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	c03664764	24 June 2015	2015-06-24-letter-list-of-participating-investigators (*list and contact details of participating investigators*)

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS (REVISION 2)

Note: Page number(s) refer(s) to the first page number of the relevant Section.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	28
1.1.2 End of data collection	☒	☐	☐	28
1.1.3 Study progress report(s)	☐	☐	☒	-
1.1.4 Interim progress report(s)	☒	☐	☐	28
1.1.5 Registration in the EU PAS register	☐	☐	☒	-
1.1.6 Final report of study results.	☒	☐	☐	28

Comments:

1.1.3 → Not required as per the national requirements for non-interventional studies 1.1.5 → Not required since this study is not considered a PASS

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	31
2.1.2 The objective(s) of the study?	☒	☐	☐	33
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	38
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

2.1.4 & 2.1.5 → This study is not hypothesis-driven and will primarily make use of descriptive statistical methods; any analysis to be performed will be exploratory in nature.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	34
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	36
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	36 & 52

Comments:

N/A

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	38
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	37
4.2.2 Age and sex?	☒	☐	☐	38
4.2.3 Country of origin?	☒	☐	☐	34
4.2.4 Disease/indication?	☒	☐	☐	38
4.2.5 Comorbidity?	☒	☐	☐	38
4.2.6 Seasonality?	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	38

Comments:

4.2.6 → Seasonality variation and pattern fall outside the context of this study and do not directly apply in the study population and disease under observation.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	44 & 54
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

5.2, 5.3, 5.4 & 5.5 → The study medication will be administered as per the routine clinical practice and the locally approved product's label.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	36
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	44 & 53 & 53

Comments:

N/A

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	44 & 53
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	44 & 53

Comments:

N/A

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	44
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	44
8.1.3 Covariates?	☒	☐	☐	44
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	44
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	44
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, comorbidity, co-medications, life style, etc.)	☒	☐	☐	44
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	44
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	-
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	44
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	46

Comments:

8.3.2 → No coding is applicable in the context of the study-specific endpoints.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	51

Comments:

N/A

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	-
10.2 Is the choice of statistical techniques described?	☒	☐	☐	52

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.3 Are descriptive analyses included?	☒	☐	☐	52
10.4 Are stratified analyses included?	☐	☐	☒	-
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	53
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	53

Comments:

10.1 →No excess risks are foreseen due to the non-interventional observational study design that aims at depicting the daily routine clinical practice. 10.4 → No stratification is planned to be implemented per the study design.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	51 & 52
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	51 & 58
11.3 Are methods of quality assurance described?	☒	☐	☐	58
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	58
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

11.5 → The study design does not mandate independent review of the results; however the handling/management and analysis of the data will be performed by an independent CRO assigned by the Sponsor

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	56
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	56
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	37
12.3 Does the protocol address other limitations?	☒	☐	☐	56

Comments:

N/A

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	58
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	61

Comments:

N/A

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	18 & 58

Comments:

N/A

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	67
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	67

Comments:

N/A

Name of the main author of the protocol: _____

Date: / /
Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

ECOG PERFORMANCE STATUS

Table 5: ECOG Performance Status Grading

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

As published in:

R01-0787 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649-655.

EQ-5D-3L (Sample)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

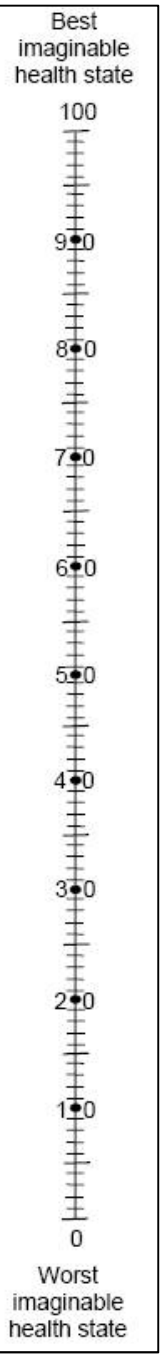
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

EQ-5D-3L (SAMPLE) Continued (Page 2 of 2)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



LCSS PATIENT SCALE (Sample)

Lung Cancer Symptom Scale (LCSS): Patient scale

English Version

Directions: Please place a mark along each line where it would best describe the symptoms of your lung cancer DURING THE PAST DAY (within the last 24 hours).

Example Question:

How good is the weather?

As good as it could be _____ As bad as it could be

1. How good is your appetite?

As good as it could be _____ As bad as it could be

2. How much fatigue do you have?

None _____ As much as it could be

3. How much coughing do you have?

None _____ As much as it could be

4. How much shortness of breath do you have?

None _____ As much as it could be

LCSS (SAMPLE) Continued (Page 2 of 2)

5. How much blood do you see in your sputum?

None |_____| As much as it could be

6. How much pain do you have?

None |_____| As much as it could be

7. How bad are your symptoms from lung cancer?

I have none |_____| As bad as they could be

8. How much has your illness affected your ability to carry out normal activities?

Not at all |_____| So much that I can do nothing for myself

9. How would you rate the quality of your life today?

Very high |_____| Very low

APPROVAL / SIGNATURE PAGE

Document Number: c03517862 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: A multicentre, cohort study to assess the impact on SYMptom burden and patient health-related quality of Life of afatinib treatment in advanced non-small cell lung cancer in a real world setting in Greece. The 'SYM-Less' study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor	[redacted]	31 Aug 2018 14:45 CEST
Approval-Team Member Medical Affairs		31 Aug 2018 14:49 CEST
Approval-Medical [redacted]		31 Aug 2018 14:53 CEST
Approval-Medical [redacted]		31 Aug 2018 15:34 CEST
Approval-Therapeutic Area [redacted]		03 Sep 2018 16:11 CEST
Approval-Biostatistics		10 Sep 2018 17:41 CEST
Approval-[redacted] Safety Evaluation Therapeutic Area		12 Sep 2018 00:21 CEST
Approval [redacted] of Global Epidemiology		18 Sep 2018 10:08 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed