Clinical Trial Protocol

Doc. No.: U11-3487-03

EudraCT No.:	2011-002380-24	
BI Trial No.:	1200.125	
BI Investigational Product:	Giotrif® / Gilotrif®, afatinib	
Title:	**LUX-Lung 8**: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy	
Clinical Phase:	III	
Sponsor Contacts:	*Trial Clinical Monitor:* Phone: Fax : Email:	*Team Member Medicine:* Phone: Fax : Email:
Co-ordinating Investigators:	Phone:	Phone:
Status:	Revised Protocol based on Global Amendment 2	
Version and Date:	**Version:** 3 **Date:** 24 June 2016	

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif® / Gilotrif®, Afatinib			
Name of active ingredient: BIBW 2992			
Protocol date: 15 Nov 2011	**Trial number:** 1200.125		**Revision date:** **24 June 2016**

Title of trial:	**LUX-Lung 8**: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy
Co-ordinating Investigators:	
Trial sites:	Multi-center trial
Clinical phase:	III
Objectives:	Primary: Compare efficacy of afatinib with erlotinib as second-line treatment for patients with squamous cell carcinoma of the lung, as measured by progression-free survival (PFS). Key secondary: Compare overall survival (OS) in both treatment groups Secondary: Objective response rate (ORR), disease control rate (DCR), tumour shrinkage and the assessment of Health-related Quality of Life (HRQoL) and safety in both treatment groups
Methodology:	Randomised, open-label, active control study comparing afatinib vs. erlotinib. Eligible patients will be randomized to receive either afatinib or erlotinib in a 1:1 ratio. Independent assessment of the primary endpoint will be completed in a treatment-blinded manner. Randomization will be stratified based on race (Eastern Asian vs. non-Eastern Asian).
No. of patients:	
total entered:	795
each treatment:	Afatinib: 398 Erlotinib: 397
Diagnosis :	Patients with diagnosis of advanced NSCLC squamous or mixed histology, who have completed at least 4 cycles of platinum-based doublet chemotherapy and who are eligible to receive 2nd line therapy.

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Main criteria for inclusion:	• Diagnosis of advanced stage NSCLC considered to be squamous histology, including mixed histology, in the opinion of the investigator. • Eligible for EGFR-directed therapy in 2nd line setting. • Measurable disease according to RECIST 1.1. • Eastern Cooperative Oncology Group (ECOG) score: 0 or 1. • Availability of tumour tissue material for correlative studies. Archived tumour tissue is acceptable. • Adequate organ function. • No prior treatment with EGFR directed small molecules or antibodies.		
Test products:	Afatinib (BIBW 2992)		
dose:	Starting dose 40 mg once daily. Escalation to 50 mg/day at beginning of Course 2 in patients meeting specified safety and compliance criteria. Dose reduction to 40 (if applicable), 30, and 20 mg/day in the presence of drug-related adverse events.		
mode of admin.:	Oral		
Comparator products:	Erlotinib		
dose:	Starting dose of 150 mg once daily. Dose reduction to 100 and 50 mg/day in the presence of known drug-related adverse events.		
mode of admin.:	Oral		
Duration of treatment:	Until patient experiences disease progression, according to RECIST 1.1.		

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Criteria for efficacy:	The primary endpoint of this study is progression-free survival, as determined by RECIST 1.1. Key Secondary endpoint: • Overall survival Secondary endpoints of this trial are: • Objective response (CR, PR) according to RECIST 1.1 • Disease control (CR, PR, SD) according to RECIST 1.1 • Tumour shrinkage • Health-related Quality of Life (HRQoL)		
Criteria for safety:	Safety of afatinib and erlotinib will be evaluated by intensity and incidence of adverse events, graded according to NCI CTCAE version 3.0, including: • The overall incidence and intensity of adverse events • Gastrointestinal events (vomiting, nausea, diarrhoea) • Skin reactions (rash, acne) Tolerability of afatinib and erlotinib will be assessed based on dosage reductions and discontinuation due to adverse events.		

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Statistical methods:

The primary analysis will compare afatinib vs erlotinib in terms of progression-free survival (PFS). The randomised treatment regimens will be compared using a log-rank test stratified by race (Eastern Asian vs non-Eastern Asian). A stratified Cox proportional-hazards model will be used to derive the hazard ratio and 95% confidence interval (CI) between the two regimens. Kaplan-Meier estimates and 95% CI will be calculated at landmark time points. Three hundred seventy-two PFS events would be expected to provide 90% power for the log-rank test, assuming a hazard ratio of 0.714 for afatinib relative to erlotinib (corresponding to median times of 14 vs 10 weeks, respectively) with two-sided $\alpha = 0.05$.

An interim analysis will be performed after at least 300 patients have been randomized and when 130 patients have experienced PD, as determined by assessment at the study sites, among the first 176 patients randomized into the trial. The analysis will be reviewed by the DMC and will result in one of the following decisions: 1.) No change in planned accrual, 2.) partial curtailment of accrual, or 3.) stop of accrual.

Overall survival (OS) is a key secondary endpoint. The analysis of OS will estimate the hazard ratio and the corresponding 95% confidence interval based on a Cox-PH model. Additionally, a stratified log-rank test will be performed. Kaplan-Meier estimates of OS will be tabulated. 632 deaths would be expected to provide 80% power for log-rank test, presuming a hazard ratio of 0.800 for afatinib relative to erlotinib (corresponding to median survival times of 8.75 vs. 7.00 months, respectively) with two-sided $\alpha = 0.05$.

OS will be analysed twice. The first analysis will be performed at the time of the primary PFS analysis using a Haybittle-Peto stopping boundary for efficacy (p-value <0.0001). The primary analysis of survival is planned at 632 deaths. However, if the futility analysis curtails accrual at 500 patients, the primary analysis of OS will be performed after 80% of the randomized patients have died.

FLOW CHART

Visit	Screening	Course 1		Course 2 and subsequent courses*	End of treatment **	Follow-up	Observation Period
Visit Abbreviation	SCR	C1V1	C1V2	CxV1[a]	EOT	FUP	OPy[b]
Day	Up to 28 days before treatment	Day 1***	Day 8 (± 2 days)	Day 1 of each course (- 3 to +2 days)****	0-7 days after permanent discontinuation of study drug	28 Days after discontinuation of study drug (+ 7 days)	Every 28 Days (± 7 days) after FUP
Informed consent	X						
Tumour sample shipment [1]		X					
Demographics	X						
Medical history	X						
Complete Physical exam [2]	X				X		
Clinical Assessment [3]		X	X	X		X	
Vital signs	X	X	X	X	X	X	
Performance status	X	X		X	X	X	
ECG (as indicated)[4]	X		X	X[4]	X		
Safety laboratory tests [5]	X	X		X	X	X	
Pregnancy Test	X	X			X		
ECHO or MUGA[6]	X			X[6]	X[6]		
Review of in-/exclusion criteria	X	X					
Randomization		X					
Collection of blood for Biomarker analysis[8]		X		X	X		
Patient-reported outcomes[9]		X		X[9]	X	X	
Adverse event evaluation[10]		X----------				----------X	
Concomitant therapy	X	X----------				----------X	
Tumour assessments[12]	X	Tumour assessments are completed at weeks 8, 12, 16, and every 8 weeks thereafter. After approval of protocol version 3, assessments to be performed every 18 weeks unless clinically indicated.					
Treatment Adherence Check[13]			X	X	X		
Dispense Trial Drug		X		X			
Termination of trial medication					X		
IXRS	X	X		X	X		
Collection of Vital Status[14]							X

* All courses are 4 weeks in duration (28 days). Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met (see Section 3.3.4.1).
** If the decision to permanently discontinue study drug is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.
*** Randomization into the study via the IXRS is permitted up to 2 days prior to the C1V1 if site procedures require advance randomization to accommodate the logistics of dispensing study medication to patients. Sites that use this option must include a copy of this policy in the ISF and submit a copy to the sponsor.
**** Except as noted for ECHO or MUGA and tumour assessments
[a] x is the course number in CxV1
[b] y is the visit number in Op[y]

1. Randomization into study does not need to be delayed for shipment of tumour sample; however, availability of tumour sample for shipment to central laboratory must be confirmed prior to randomization and shipped within 28 days of randomization.
2. Includes height (at screening only) and weight.
3. Limited physical examination to capture clinical assessment of ongoing or new adverse events and monitor for signs and symptoms of clinical response.
4. A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening to establish a baseline assessment, at C1V2 (Day 8 of treatment), at the start of every third course thereafter (C4, C7, etc.) and EOT. After approval of Protocol Version 3.0, ECG will only be performed if clinically indicated.
5. Includes hematology, serum biochemistry, and urinalysis. Refer to the Investigator Site File (ISF).
6. ECHO or MUGA (At German sites, only ECHO is allowed) will be performed during screening, at Course 4 and then at every third course (Course 7, 10, 13 etc.), and at EOT (if not performed in the previous 8 weeks). Requirement for EOT ECHO or MUGA may be waived for patients meeting all of the following criteria: 1) too sick from their disease or disease related symptoms to travel in the opinion of the investigator, 2) have had evidence of stable LVEF on the previous scheduled post treatment assessment and 3) have no evidence of cardiovascular disease. For LVEF evaluations, the assessment can occur ±7days of the scheduled Day 1 of the corresponding course.
   After approval of Protocol Version 3.0, ECHO or MUGA will only be performed if clinically indicated.

8. Blood sample will be collected and plasma will be sent to logistics laboratory at baseline (C1V1), C2, and at EOT or determination of disease progression. After approval of Protocol Version 3.0, the collection of blood sample at EOT will no longer be required.
9. EQ-5D, EORTC QLQ-C30 and EORTC QLQ LC-13 questionnaires will be completed at baseline and then (before seen by the investigator) at the start of course 2, 3, 4, and every 2nd course thereafter, EOT and FUP. After approval of Protocol Version 3.0, the collection of EQ-5D, EORTC QLQ-C30 and EORTC QLQ LC-13 questionnaires will no longer be required.
10. See Appendix 10.7: Adverse Event Reporting Process

12. Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). See Appendix 10.1 for lesion measurement specifications. Assessment will be performed at the following timepoints until progression or start of further treatment for disease. In the event of early discontinuation due to Adverse Events or an interruption/delay to treatment the tumour assessment schedule will not be changed.
    Screening Period (up to 21 days before randomization)
    During week 8 (56-64 days after randomization)

During week 12 (84-91 days after randomization). German sites only will have an X-ray completed instead of a CT or MRI for the week 12 assessment. If disease progression is suspected, a follow-up CT or MRI will then be completed
During week 16 (112-119 days after randomization)
Every 8 weeks thereafter until progression/ start of further treatment.
After approval of protocol version 3, tumour assessments to be performed every 18 weeks unless clinically indicated until progression or start of further treatment.

13. Confirm adherence to study medication and supportive care for adverse events noted in Section 4.1.4
14. Collection of information on progression, further anti-cancer treatment and death. Information should be collected from the patient notes or by telephone contact with the patient. In countries where regulations allow, public records may be utilized to assess the mortality status for patients lost to follow up or where mortality information is not readily available through 3 attempted contacts. A formal study visit is not required. Once Protocol Version 3.0 is final (and where required locally, approvals are obtained by the site as per Section 8.1), the collection of Observation Period data will no longer be required.

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ABBREVIATIONS

AE	Adverse Event
ADL	Activities of Daily Living
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Concentration-time curve
B-HCG	Beta-Human Chorionic Gonadotrophin
BI	Boehringer Ingelheim
BSA	Body Surface Area
BUN	Blood Urea/ Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence Interval
CK	Creatinine Kinase
CML	Clinical Monitor Local
CR	Complete Response
CRA	Clinical Research Assistant/Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CTC	Common Terminology Criteria
CTC AE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
DCR	Disease Control Rate
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC/IEC	(Independent) Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
erbB	Epidermal Growth Factor family of receptors
EudraCT	European Clinical Trials Database
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridisation
FU/FUP	Follow Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate

GGT	Gamma-glutamyltansferase
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
Iv	Intravenous
IUD	Intrauterine Device
IXRS	Combined Interactive Voice Response System and Interactive Web-based Response System
LD	Longest Diameter
LDH	Lactate dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Drug Regulatory Activities
Mg	Milligram
MOS	Median Overall Survival
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NE	Not Evaluated
NSCLC	Non Small Cell Lung Cancer
NYHA	New York Heart Association
OP	Observation Period
OPU	Operative Unit (of BI)
ORR	Objective Response Rate
OS	Overall Survival
PABA	Para-Aminobenzoic Acid
PD	Progressive Disease
PFS	Progression Free Survival
PI	Package Insert
PK	Pharmacokinetic
PR	Partial Response
PS	Performance status
PT	Prothrombin Time/ Preferred Term
PVC	Polyvinyl Chloride

RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SCCHN	Squamous Cell Cancer of Head and Neck
SD	Stable Disease
SMQ	Standard MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPF	Sun Protection Factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time to maximum plasma concentration
TK	Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential
Wt	Wild-type

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-small cell lung cancer (NSCLC) is a leading cause of cancer death globally. It has been the most commonly diagnosed cancer each year since 1985 with an estimated 1.35 million new cases diagnosed and approximately 1.2 million deaths each year worldwide (R05-0876, R06-0221). The disease is associated with high mortality and morbidity with 5-year-survival rates estimated in the United States at 16% for patients with metastatic disease (R11-0764). Surgical resection is reserved as initial treatment option for eligible patients with early stage disease while systemic therapy is the mainstay for those with advanced stage or metastatic disease. Many patients carry comorbidities from smoking history and advanced age such as limited cardio-pulmonary reserve that restricts treatment options.

Patients with locally advanced and/or metastatic NSCLC in good performance status and those able to tolerate are generally treated with platinum based combination chemotherapy as a first-line treatment. The goal is prolongation of survival and palliation of symptoms but cure is rarely seen. Despite responses and transient regressions, most patients eventually relapse and succumb to their illness. Many patients such as elderly and those with poor performance status or significant co-morbidity may also not be able to tolerate the side effects associated with chemotherapy and thus choices may be limited further for these patients. Novel therapies that improve survival with a better tolerability profile are thus needed.

Patients relapsing after first-line chemotherapy may be eligible for additional chemotherapy with alternate single agents such as docetaxel and pemetrexed. While systemic chemotherapy has been the mainstay of treatment options in advanced NSCLC, its activity is at best modest with significant morbidity. Several agents have shown activity in this setting however only a few have been approved. In most instances, it has been difficult to identify and select populations where individual chemotherapeutic agents have a higher likelihood of benefit. While docetaxel has been studied and approved as second-line therapy across NSCLC histology, benefit from pemetrexed is limited only to patients with adenocarcinoma histology. However, in the recent years novel targeted therapies based on specific molecular and biological characteristics have emerged as a new treatment paradigm in select populations, offering an alternative to chemotherapy with an improved safety and efficacy profile. The targets most extensively studied include the epidermal growth factor receptor (EGFR) or the Subclass I of the superfamily of transmembrane kinase inhibitors (R06-1302, R07-1049, R07-1135).

Aberrant activation of EGFR is frequently observed in a variety of malignant tumours and may be caused by a variety of molecular processes including mutations, receptor overexpression, ligand-dependent receptor dimerization, and ligand-independent activation. Overexpression of EGFR has been detected in 40-80% of NSCLC, validated as a therapeutic target and has led to the development of specific small molecule EGFR antagonists to treat this disease (R06-1301, R06-1393, R06-1394). First-generation EGFR small molecule tyrosine-kinase inhibitors (TKI) act as ATP analogues, compete reversibly for the tyrosine kinase (TK) catalytic site, and include gefitinib (Iressa®) and erlotinib (Tarceva®). Recent

clinical experience with these agents has demonstrated tumour regression in about 10-15% of unselected NSCLC patients (R05-0867, R06-1301, and R06-1306). This benefit has been demonstrated across NSCLC histology in patients progressing after initial chemotherapy as well as in a maintenance setting following initial platinum based chemotherapy. While the most impressive responses are noted in the molecularly defined select population of adenocarcinoma with activation mutations of EGFR (R08-5155, R09-4437, R11-1274), patients with wild type (wt) EGFR including those with squamous histology seem to benefit as well.

Erlotinib, a first-generation EGFR TKI, is approved as monotherapy in second- and third-line setting in patients with locally advanced and/or metastatic NSCLC. Its approval was based on the BR21 trial conducted in patients with Stage IIIB/IV NSCLC that had failed one or two prior chemotherapy regimens. Patients randomized to erlotinib achieved improved response rates (8.9% vs. 0.9%) and prolongation of median overall survival (MOS) (6.7 vs. 4.7 months) and progression free survival (PFS) (9.9 vs. 7.9 weeks) versus placebo (R05-0867). Of the 488 patients randomized in a 2:1 fashion to erlotinib vs. 243 to placebo, 29.5% had squamous histology in the erlotinib arm vs. 32.1% in placebo arm. In addition erlotinib has demonstrated activity as a single agent in the maintenance setting in non-progressive patients following first-line chemotherapy with a platinum doublet combination. In the Sequential Tarceva® (erlotinib) in Unresectable NSCLC (SATURN) study 889 patients who did not have progressive disease following four cycles of platinum based chemotherapy were randomized into the maintenance part of the study to receive either erlotinib (437 patients eligible for PFS analysis) or placebo (447 patients eligible for PFS analysis). Of these, 166 patients receiving erlotinib had squamous cell carcinoma compared to 194 receiving placebo. PFS was reported to be prolonged in patients independent of all histology and irrespective of EGFR status: 12.3 weeks for patients in the erlotinib group vs. 11.1 weeks for those in the placebo group (HR 0.71, 95%CI= 0.62-0.82; p<0.0001). The objective response rate was 11.9% (52 patients) with erlotinib vs 5.4% (24 patients) with placebo (P=0.0006) (R11-1185).

In contrast docetaxel and pemetrexed, two of the most commonly used agents in the second-line treatment of advanced NSCLC (R05-1054) have shown response rates of 8.8% and 9.1% respectively with median PFS and OS in similar ranges to erlotinib (median PFS of 2.9 months in each arm, and median survival time of 8.3 months for pemetrexed versus 7.9 months for docetaxel, p=not significant). Docetaxel is associated with significant risk of febrile neutropenia and the benefit of pemetrexed is restricted to non-squamous histology (R04-2230).

Thus, despite the availability of these options to treat locally advanced and/or metastatic NSCLC, further alternatives are needed. Even patients eligible for these second-line therapies may have limited tolerability to these agents. Similarly, given the selective efficacy of pemetrexed in patients with adenocarcinoma and improved efficacy of EGFR TKIs in patients with EGFR mutations (most frequently seen in patients with adenocarcinoma, non-smokers) these patients may also have a wider selection of treatment options as compared to those with squamous histology and prior smoking history highlighting a high unmet medical need.

Afatinib is a member of the second generation TKIs which binds irreversibly to the erbB family of receptors. It is hypothesised that the prolonged and irreversible inhibition of the receptor has the potential for further improvement in response to treatment over the first generation TKIs such as erlotinib and gefitinib (U03-3218).

Afatinib has demonstrated activity in the treatment of NSCLC in several clinical studies. The results from LUX-Lung 1, a placebo-controlled, Phase III trial in patients who progressed after receiving chemotherapy and a first-line-EGFR TKI demonstrated clinical activity of afatinib in this NSCLC population with adenocarcinoma histology. A tripling in the median PFS of afatinib compared to placebo (3.3 months vs. 1.1 month) was observed (P10-12529). Similarly significant responses have been noted in patients with mutated EGFR in the LUX-Lung 2 trial, reporting a confirmed ORR of 60% (78 of 129 patients), that support the hypothesis of improved efficacy with the irreversible inhibition of the target(P10-09976, P10-12524). At the time of publication for this protocol, two Phase III trials comparing afatinib to platinum based chemotherapy in patients harboring EGFR mutation as first-line treatment are ongoing.

Albeit there is a preponderance of data of efficacy in adenocarcinoma histology of NSCLC, there is growing evidence that patients with squamous histology also derive benefit from EGFR TKIs. In addition to the data outlined above for erlotinib, additional proof of activity in this subset has been noted with another irreversible inhibitor of EGFR family of TKI – PF299804. In a randomized Phase II study PF299804, a second-generation TKI, was compared to erlotinib in patients with advanced NSCLC who had failed at least one line of chemotherapy. Of the 188 patients enrolled in this 1:1 randomized study that included nearly a third of patients with non-adenocarcinoma histology and approximately 60% with wild type EGFR, PF299804 demonstrated a significant improvement in median PFS compared to erlotinib (12.4 weeks vs. 8.3 weeks) (R10-6208). The potential activity of PF299804 in squamous histology was also reported in a Phase II study in recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) where ORR of 10.5% was noted. A median PFS of 3.4 months was reported along with 63.2% of patients achieving SD as their best response (R11-1184).

In the current ongoing trials of afatinib additional proof of activity in cancers of squamous histology and beyond NSCLC with mutated EGFR has been observed. In a Phase II trial (1200.40) of EGFR FISH positive NSCLC patients, 12 of 59 (20%) evaluable patients on afatinib achieved an objective response with 8 confirmed responses (1 CR, 7 PR) so far and 21 (36%) of all patients had disease control for at least 16 weeks. Of the 28 evaluable patients that tested negative for EGFR mutation so far the ORR was still 21% (6/28) and of the 4 patients treated with afatinib with squamous histology 1 achieved PR and 2 SD as their best evaluable response. In addition, LUX-Lung 5 (1200.42) is a large ongoing randomized Phase III trial of afatinib plus weekly paclitaxel versus investigator's choice of chemotherapy following afatinib monotherapy in NSCLC patients failing previous erlotinib or gefitinib treatment. At the time of publication of this protocol, preliminary RECIST tumour assessment was available for 54 patients with squamous cell histology receiving the initial afatinib monotherapy. Two patients (3.7%) and 35 (65%) patients achieved an overall best assessment of PR and SD respectively regardless of confirmation (Data on File).

In LUX-Lung 1 (1200.23) a randomized Phase IIb/III trial comparing afatinib to placebo in a clinically enriched population for EGFR mutations and prior EGFR TKI therapy; 5 patients with squamous histology were treated on afatinib (protocol violations). Four of these had SD and 1 an unconfirmed PR (Data on File).

Additional proof of concept of afatinib in squamous histology is derived from trial 1200.28 in patients with recurrent/metastatic SCCHN who had failed prior platinum-containing chemotherapy. Sixty-one patients were randomized to receive afatinib vs. 60 to receive cetuximab (a monoclonal antibody against the EGFR) and upon progression cross over were allowed. In a preliminary analysis reported in 2010, of the 34/74 patients randomized to afatinib in Stage 1 of the trial 6/34 patients achieved PR and 18/34 had SD (P10-12525, P10-12526). An expansion into two Phase III trials was in preparation at the time of initial publication of this protocol.

The 1200.125 trial (LUX-Lung 8) will build on the positive data to date observed with second-generation TKIs in squamous histology cancers by further evaluating afatinib's activity in this NSCLC population. The patients with squamous histology represent a significant population of patients with advanced NSCLC who have a large unmet medical need. With the inbuilt futility analysis into this trial and the large unmet medical need in this population, it is conceived that the current design is a valid approach to test the hypothesis in a reasonable time frame.

1.2 DRUG PROFILE

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning afatinib (BIBW 2992) refer to the free base compound which is used as the oral formulation.

Afatinib is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits phosphorylation of erbB receptors resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express erbB receptors.

Afatinib is moderately fast absorbed after oral administration, with median t_{max} values approximately 3 hours after drug administration. In general, afatinib gMean maximum plasma concentration and exposure increased with increasing doses after a single dose and at steady state. However, moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant

inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

In pre-clinical studies afatinib is not an irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two Phase I open label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumours at 40mg and 50mg daily (U07-3128, U08-1023). Adverse events (AEs) observed with afatinib are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent drug-related toxicities were associated with gastrointestinal disorders (including diarrhoea, nausea, vomiting, and mucositis/stomatitis), skin and subcutaneous tissue disorders (including rash, pruritus, acneiform rash, acne), general disorders (including fatigue and mucosal inflammation), respiratory disorders (including epistaxis), and metabolism and nutritional disorders (including anorexia, dehydration). Early and proactive management of diarrhoea, skin rash, and stomatitis together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies (R07-4077, P07-11507, R07-4078, R11-0826).

Afatinib has been approved as monotherapy to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

Giotrif® (Afatinib) has been approved in EU to treat patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. In the US, Gilotrif® (Afatinib) has also been approved to treat patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Patients with NSCLC squamous cell histology represent a population with a large unmet medical need. Chemotherapy choices for these patients is not only restricted from an efficacy standpoint but also limited by the ability of these patients to tolerate these agents. These patients tend to be older, have prevalent smoking history and are associated with higher comorbidities. In the second-line setting their choices are mostly restricted to single agents. Although several treatments may have shown limited activity, only docetaxel and erlotinib are approved. Afatinib is an ideal candidate that needs further evaluation in this setting. From a mechanistic standpoint it offers the chance to irreversibly inhibit the erbB family of receptors compared to the first generation EGFR TKI erlotinib and its adverse event profile appears comparable to erlotinib as well. Afatinib has established proof of concept in SCCHN and has shown evidence of activity in NSCLC squamous-cell histology. Similar agents have already established randomized Phase II data in NSCLC that supports further exploration of this concept in a direct comparison to erlotinib.

Given the large unmet medical need and a desire to provide patients with treatment alternatives that are time and cost efficient the current trial is proposed. The trial is designed with an inbuilt futility analysis to be completed in the first 176 patients enrolled to provide adequate confidence of futility of this direct comparison with erlotinib. Details of the analysis are further provided in Section 7.3.4.

2.2 TRIAL OBJECTIVES

This randomized, open label Phase III trial will be performed in patients with squamous cell carcinoma of the lung.

2.2.1 Primary Objective

The primary objective of the trial is to compare the efficacy of afatinib with erlotinib as second-line treatment for this group of patients, as measured by PFS.

2.2.2 Secondary Objectives

The key secondary trial objective is to compare the OS in both treatment groups.

Other secondary objectives are to compare the ORR, DCR and tumour shrinkage of afatinib with erlotinib, and the assessment of HRQoL and safety in both treatment groups.

Study endpoints are provided in Sections 5.1, 5.2, and 5.3.

2.3 BENEFIT - RISK ASSESSMENT

Treatment options for patients with advanced squamous cell carcinoma of the lung are limited following first-line chemotherapy, with most patients recurring and eventually succumbing to their disease. For patients eligible to tolerate, chemotherapy has been an option and docetaxel is indicated in the second-line setting for patients with advanced NSCLC with associated chemotherapy related morbidity. Afatinib is an irreversible EGFR inhibitor with a favourable risk benefit ratio that is currently in Phase III clinical trials in lung cancer, breast cancer and squamous cancer of head and neck (SCCHN). The clinical experience of afatinib includes over 2000 patients. Afatinib is relatively well tolerated, with most common adverse events being diarrhoea, rash and stomatitis as expected for this class of agents.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

Afatinib has shown evidence of clinical activity in patients with squamous cancer of the head and neck in a randomized clinical Phase II trial and early evidence of clinical activity in patients with squamous carcinoma of the lung in ongoing clinical trials (P10-12525, P10-12526). This study will have an interim futility analysis planned for the first 176 patients and is outlined in Section 7.3.4. In addition a Steering Committee providing study oversight and a Data Monitoring Committee (DMC) is planned. See Section 3.1.1 for a detailed description of the procedures of these committees.

The large unmet medical need of this patient population combined with the above and the planned interim futility analysis supports the validity of this study.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomized, open-label Phase III trial is designed to compare the efficacy of afatinib with erlotinib for the second-line treatment of patients with advanced NSCLC of squamous or predominantly squamous histology. The primary endpoint of the trial will be progression-free survival.

Eligible patients will be randomized in a 1:1 fashion to receive either afatinib or erlotinib. Patients will receive continuous daily dosing of study drug assigned until disease progression, unacceptable adverse events or other reason necessitating withdrawal (see Appendix 10.1 and Sections 4.1.4 and 3.3.4). Study drug dose will be modified as in Section 4.1.4 for the management of adverse treatment effects. The starting dose of afatinib will be 40 mg daily oral and erlotinib will be 150 mg daily oral. For patients adequately tolerating therapy the dose of afatinib will be further titrated to 50 mg daily oral at the end of 4 weeks.

Patients will have tumour assessments at the intervals specified in the flow chart for assessment of response. Tumour assessment must continue for patients who discontinue study drug due adverse events until the patient experiences disease progression or starts other anti-cancer treatment. Tumour response and progression will be assessed according to RECIST 1.1 (R09-0262) and assessment at the investigator site will be sufficient for decisions on continuation of treatment (Appendix 10.1). An independent analysis of response will also be performed by a Central Imaging Unit (see Section 5.1.2.1.1); however this will not be used to make treatment decisions. After approval of Protocol Version 3.0, the central imaging review of tumour response will be discontinued.

All patients will also have regular evaluations for assessment of safety parameters as detailed in the flow chart.

An End of Treatment (EOT) evaluation is to be completed when a patient permanently discontinues study drug, either for disease progression or any reason listed in Section 3.3.4. The assessments required are listed in the flow chart. Patients who discontinue study drug due to toxicity will continue to have tumour assessments according to the Flow Chart until disease progression.

A Follow-up evaluation will be completed 28 (+7) days after permanent discontinuation of study drug. Refer to the flow chart and diagram below for details. This visit will be defined as the last visit for this trial.

Patients will subsequently be monitored for vital status in the Observation Period of this protocol. Once Protocol Version 3.0 is final (and where required locally, approvals are obtained by the site as per Section 8.1), the collection of vital status data will no longer be required.

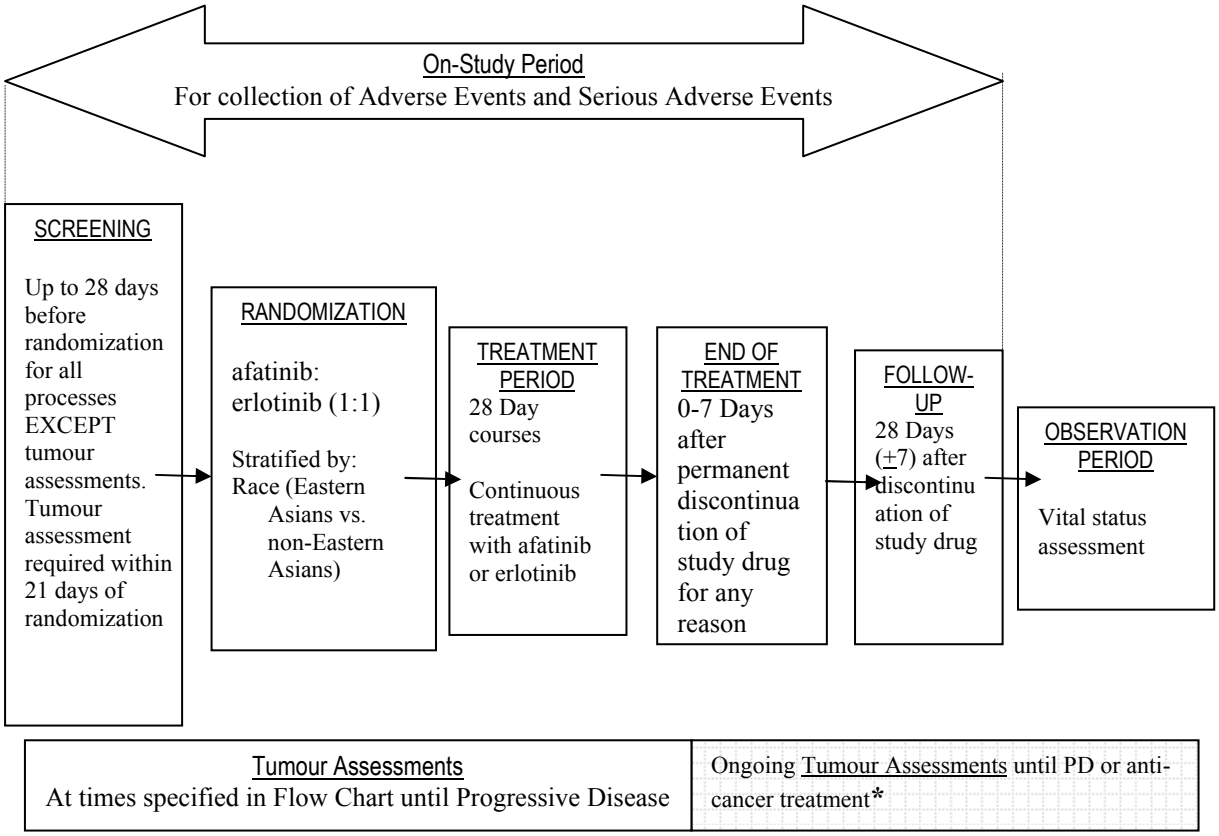
The trial is considered completed when:

1.) The PFS and OS events required for analysis in Section 7.3 have occurred.

AND

2.) All patients have discontinued trial medication, as explained in Section 3.3.4.

The diagram below depicts the stages of a patient's participation in this protocol.



*For patients who discontinue study drug due to Adverse Event

3.1.1 Administrative structure of the trial

The coordinating investigators are oncologists with experience with this type of trial and investigations. The coordinating investigators have been designated by BI and will sign the clinical trial report.

The trial will be performed by investigators specialised in oncology.

A steering committee including the coordinating investigators, experienced investigators and BI representatives will monitor the trial on a regular basis (all operational aspects, recruitment issues, data quality, etc.). A steering committee charter will be prepared specifying the objectives of the committee.

A data monitoring committee (DMC) will be formed consisting of three experienced and independent members, including two clinicians and one biostatistician who, collectively, have expertise in the management of patients with lung cancer and in the conduct and monitoring of randomised clinical trials.

The DMC will meet regularly and their responsibility is to continuously assess the trial data to ensure overall safety in the treated patients, monitor the quality and provide BI and the trial steering committee with advice about the conduct of the trial and the integrity of the data. The DMC will oversee the interim analysis planned in the study. Details of the DMC responsibilities will be described in the DMC charter.

Inclusion of patients in the trial will continue during the scheduled meetings of the DMC. Decisions on trial termination, amendment or cessation of patient recruitment, based on safety or outcome findings will be made after recommendations from the DMC have been assessed by the sponsor.

, a Contract Research Organization (CRO), will be responsible for DMC management and oversight. will also coordinate and provide medical writing support for the DMC charter. Clinical Trial Master File (CTMF) contents relating to DMC conduct will be maintained at through the course of the study, and will be transferred to the BI CTMF at the end of the trial.

On-site monitoring will be performed by BI or a CRO appointed by BI.

BI will appoint CROs and independent service providers for special services such as central independent review of CT scans and MR images, central laboratory services, electronic collection of QoL questionnaires, and Interactive Voice/Web Response System (IXRS) for randomisation and trial medication logistics.

All trial relevant documentation will be stored in the clinical trial master file (CTMF) at BI, with the exception of DMC correspondence as explained above. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This study will be a head-to-head comparison of a reversible first-generation TKI (erlotinib) to an irreversible second-generation TKI (afatinib) as second-line treatment in patients with advanced squamous NSCLC. These patients have a limited life expectancy after disease progression following first-line therapy. This study will evaluate PFS as a primary endpoint; however, the study has adequate statistical power to meet the key secondary endpoint of increased OS in the patients receiving afatinib.

The unique management of adverse events for afatinib and the comparator, which includes temporary and permanent discontinuation of study drug, presents significant challenges to effectively managing this trial while monitoring patient safety if the patient treatment assignment were blinded to the trial team. Additionally, a double-blinded trial would require either over-encapsulation and subsequent equivalency testing be completed for two distinct packaging schema of the comparator (i.e. bottles in the US and PVC blister-packaging in the rest of world). Therefore, this study will be conducted in an open-label fashion with ICH E9 recommendations to minimize potential bias incorporated (R08-2251).

Steps to minimize potential bias, especially in the assessment of the primary objective, are in place for this study. These include the use of a central randomization method, to eliminate the potential that an investigator's decision to enroll the next study patient be influenced by knowing the next treatment assignment. The PFS primary endpoint will have an independent radiology review in which the assessors will be blinded. Potential bias of the sponsor management of the trial will be minimized by not allowing the trial team access to aggregate data analysis by assigned treatment groups during the conduct of the study up to formal disclosure of PFS and/or OS results to the trial team (see Section 4.1.5.1). Any data reviews will present patients in Dummy treatment groups, and all options to complete reviews by aggregate treatment group (i.e. by use of JReview data review tool) will be disabled to all trial team members. The treatment group assignment will be known on a per-patient basis in the eCRF.

Several studies enrolling all NSCLC histologies have been completed with first-generation TKIs. Details of these have been discussed in Sections 1 and 2.

Initial activity of afatinib in squamous cell carcinoma including NSCLC has been assessed in several trials as described in Sections 1 & 2.

It is considered that a difference of four weeks improvement in PFS for afatinib compared to the approved treatment (erlotinib) is clinically meaningful in this tough to treat patient population that has limited alternatives for treatment.

3.3 SELECTION OF TRIAL POPULATION

Approximately 800 patients will be randomized at approximately 200 study sites globally. The study will be conducted in approximately 24 countries. The rate of randomization will vary by study site, but is expected to be approximately 2-15 patients per site.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been randomized into the trial or not.

3.3.1 Main diagnosis for study entry

This study will enroll patients with a diagnosis of advanced NSCLC squamous cell histology; who have disease progression after completion of at least 4 cycles of platinum-based doublet

chemotherapy treatment in the 1st line setting of advanced disease; and who are eligible to receive 2nd-line therapy.

NOTE: All staging criteria listed below are based on AJCC Staging for NSCLC 7th Edition (R11-1417).

3.3.2 Inclusion criteria

1. Diagnosis of advanced stage NSCLC considered to be squamous histology, including mixed histology, in the opinion of the investigator.

2. Completion of at least 4 cycles of platinum-based doublet chemotherapy, with or without additional [non-EGFR] targeted agents, as 1st line treatment of Stage IIIB/IV NSCLC. *Note* the below scenarios are also considered to meet this requirement:

    a. Patients relapsing within 6 months of completing adjuvant/neo-adjuvant/curative -intent chemotherapy/chemoradiotherapy (*Note:* these patients are still required to have had the equivalent of 4 cycles of platinum-based doublet chemotherapy except in setting noted below).

    OR

    b. Patients intending to receive four cycles of platinum-based doublet chemotherapy but due to toxicity, and not PD, discontinue just the platinum agent after at least two cycles of platinum doublet had been administered.

3. Eligible to receive 2nd line therapy in the opinion of the investigator. Patients who received non-EGFR based therapy for maintenance are eligible.

4. Measurable disease according to RECIST 1.1 (R09-0262). Refer to Appendix 10.1.

5. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 (R01-0787). Refer to Appendix 10.2.

6. Availability of tumour tissue material for correlative studies (refer to Section 5.6). Archived tumour tissue is acceptable.

7. Adequate organ function, defined as all of the following:

    a. LVEF >50% or within institution normal values.

    b. Absolute neutrophil count (ANC) > 1500 / mm^3. (ANC >1000/mm^3 may be considered in special circumstances such as benign cyclical neutropenia as judged by the investigator and in discussion with the sponsor).

    c. Platelet count >75,000 / mm^3.

    d. Estimated creatinine clearance > 45ml / min. Refer to Appendix 10.3.

e. Total bilirubin < 1.5 times institutional ULN (Patients with Gilbert's Syndrome total bilirubin must be <4 times institutional ULN).

f. Aspartate amino transferase (AST) or alanine amino transferase (ALT) < three times the institutional upper limit of normal (ULN) (if related to liver metastases < five times institutional ULN).

8. Recovered from any previous therapy related toxicity to ≤CTCAE Grade 1 at study entry (except for stable sensory neuropathy ≤CTCAE Grade 2 and alopecia).

9. Ability to take oral medication in the opinion of the investigator.

10. Age ≥ 18 years.

11. Written informed consent that is consistent with ICH-GCP guidelines.

3.3.3 Exclusion criteria

1. Prior treatment with EGFR directed small molecules or antibodies.

2. Curative intent chemoradiotherapy as the only treatment for stage IIIB NSCLC unless relapse occurs within 6 months of completion of treatment, and in the opinion of the investigator the patient has received an equivalent of 4 cycles of platinum-based doublet therapy.

3. Radiotherapy within 4 weeks prior to randomization, except as follows:

   a. Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to randomization, and

   b. Single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling.

4. Active brain metastases (stable for <4 weeks, symptomatic, or leptomeningeal disease). Dexamethasone therapy will be allowed if administered as a stable dose for at least 4 weeks before randomization.

5. Any other current malignancy or malignancy diagnosed within the past three (3) years (other than basal-cell carcinoma of the skin, in situ cervical cancer, in situ prostate cancer).

6. Known pre-existing interstitial lung disease.

7. Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom e.g. Crohn's disease, malabsorption or CTC grade ≥2 diarrhoea of any aetiology, based on investigator assessment.

8. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (Refer to Appendix 10.4), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to randomisation.

9. Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test drug.

10. Women of child-bearing potential and men who are able to father a child, unwilling to be abstinent or use adequate contraception prior to study entry, for the duration of study participation and for at least 2 months after treatment has ended. Adequate methods of contraception and Women of Child-Bearing Potential are discussed in Section 4.2.2.3.

11. Female patients of childbearing potential (see Section 4.2.2.3) who are nursing or are pregnant.

12. Patients unable to comply with the protocol in the opinion of the investigator.

13. Active hepatitis B infection (defined as presence of Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier.

14. Known or suspected active drug or alcohol abuse in the opinion of the investigator.

15. Requirement for treatment with any of the prohibited concomitant medications listed in Section 4.2.2.

16. Any contraindications for therapy with afatinib or erlotinib.

17. Known hypersensitivity to erlotinib, afatinib or the excipients of any of the trial drugs.

18. Major surgery within 4 weeks of starting study treatment.

19. Prior participation in an afatinib clinical study, even if not assigned to afatinib.

20. Use of any investigational drug within 4 weeks of randomisation (unless a longer time period is required by local regulations or by the guidelines for the investigational product).

21. Patients without Progressive disease.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The Investigator or subject themselves may stop study treatment at any time for safety or due to patient personal reasons.

If a patient is entered in violation of inclusion/exclusion criteria, the sponsor will determine the medical risk/benefit on a case-by-case basis and can require such a patient be discontinued from the study treatment.

A patient is to discontinue study medication if the patient:

1. Withdraws consent to further study medication.
2. Has radiologically documented progressive disease (Section 5.1.2).
3. Becomes pregnant (Section 5.2.2.2).
4. Is diagnosed with ILD.
5. Has the need for study drug discontinuation due to AEs or for further dose reductions considered necessary but not allowed according to the protocol (Section 4.1.4).

The sponsor may remove patients from the study after completion of the primary efficacy analysis if the patient has access to study treatment via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation. This may mean a change in packaging and labelling. The cost of any ongoing supply of study medication (afatinib or erlotinib) will be incurred by the sponsor until disease progression occurs. If a patient is removed from the study treatment, an end of treatment and a follow up visit 28 days later will be performed to ensure all adverse events are followed up and then the patient will be considered to have completed the trial.

Patients who withdraw from the trial after randomisation will not be replaced.

3.3.4.1.1 Patient discontinuation of study participation

A patient who has discontinued study drug for any of the reasons listed above except reason 5 (i.e. study drug toxicity), will complete a FUP visit and then continue in the Observation Period of the study for vital status and anti-cancer treatment monitoring. Patients who discontinue study drug due to any reasons other than 2 or 3 above will continue to have tumour assessments until disease progression or start of new anti-cancer therapy, following the same schedule Observation Period assessments will be completed as indicated in the Flow Chart. Once Protocol Version 3.0 is final (and where required locally, approvals are obtained by the site as per Section 8.1), the collection of vital status data will be ceased.

If a patient withdraws consent for any further trial procedures and follow-up activities, no additional study assessments will be completed. This will be documented in the eCRF.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial.
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.
4. The recommendation of the DMC that would require discontinuation of the trial, or the planned futility analysis response is not met.
5. Discontinuation of the clinical development programme with afatinib due to emerging data on afatinib.
6. The primary analysis has been completed and all patients have either ended study treatment or are eligible to receive afatinib under the conditions indicated in 3.3.4.1.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be randomized to receive either afatinib or erlotinib.

4.1.1 Identity of BI investigational product and comparator products

Substance (INN):	**Afatinib**
Pharmaceutical form:	Film-coated Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 mg, 40mg, 30mg and 20mg film-coated Tablets (the dose of afatinib in the film-coated Tablets is related to the free base equivalent of afatinib)
Posology:	Once daily
Route of administration:	Oral (swallowed)

Substance (INN):	**Erlotinib (Tarceva®)**
Pharmaceutical formulation:	Film-coated Tablets
Source:	OSI Pharmaceuticals Inc. and Roche Ltd.
Unit Strength:	150 mg, 100mg, 25mg film-coated Tablets (the dose of strength of erlotinib hydrochloride of 163.9 mg, 109.3 mg and 27.3 mg is equivalent to erlotinib strengths 150 mg, 100 mg, and 25 mg, respectively)
Posology:	Once daily
Route of administration:	Oral (swallowed)

4.1.2 Method of assigning patients to treatment groups

Patients will be randomised 1:1 to either afatinib or erlotinib. The randomisation will be stratified based on race (Eastern Asian vs. non-Eastern Asian), as specified in the flow chart.

Randomisation will be carried out centrally using an Interactive Voice/Web Response System (IXRS). The company that provides the IXRS system will receive the randomisation list from Boehringer Ingelheim Clinical Trial Support Group or a CRO appointed by the Sponsor. The BI standard validated random number generating system will be used to generate the

randomisation schedules which will be verified by an independent statistician who is not involved in the study. The access to the randomisation code will be supervised by Clinical Trial Support Group. Persons directly involved in the conduct and analysis of the trial have no access to the randomisation schedule prior to database lock.

Investigators and site staff delegated IXRS responsibilities will receive unique user IDs and passwords; and a manual describing how to access and use the IXRS.

4.1.3 Selection of doses in the trial

Based on early phase clinical trials, a daily dose of 50 mg in the monotherapy setting was identified as the dose for further development. This was used initially in EGFR TKI refractory population and several other Phase II/III and proof of concept trials. Given a higher propensity of grade 3/4 AEs (especially diarrhoea) and no loss of efficacy especially in the EGFR mutation positive population, the dose was reduced to 40 mg in the pivotal Phase III trials in EGFR mutated population (P10-12524, P10-12525, P10-12529). The 1200.22 (LUX-Lung 2) study enrolled 99 patients who started afatinib at 50mg, and 30 patients starting at 40mg. While there was no substantial change in the occurrence of all AE grades for the two most frequent AEs, diarrhoea (96.7% in the 40 mg group compared to 93.9% in the 50 mg group) and rash/acne (90.0% in the 40 mg group compared to 92.9% in the 50 mg group); there was a substantial difference in the occurrence of grade 3 AEs for diarrhea (6.7% in the 40 mg group vs 24.2% in the 50mg group) and rash/acne (6.7% in the 40 mg group and 25.3% in the 50 mg group). Neither group had grade 4 or 5 AEs reported for these terms (P10-12524). Refer to the current IB for additional details (U03-3218). In NSCLC and other indications, durable responses (>20 months) have been observed with daily dosing of afatinib of 40 mg and less (P10-09678). The dose selection for this trial follows the above principle especially noting that the population in the trial will be naive to EGFR TKI, and with associated comorbidities from smoking history may be at risk for higher rate of discontinuation if a starting dose of 50 mg daily were chosen. Additionally, squamous cell NSCLC patients represent EGFR wt population that may benefit from intensifying maximal doses. Thus, in this trial development of afatinib will continue at a starting dose of 40 mg to optimize the tolerability and efficacy balance. The daily dose will be modified following careful monitoring of patient's drug-related adverse events and medication compliance; with option to dose-escalate to 50 mg for patients meeting the criteria specified in Section 4.1.4.1.

The starting dose for erlotinib is 150 mg daily continuously in accordance with the Tarceva® package insert. In case of drug-related adverse events, the dose will be reduced to 100 mg and 50 mg daily, as described in Section 4.1.4.2.1.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Afatinib assignment and administration

Patients randomised to the afatinib arm will take a single oral dose of afatinib each day starting at a dose of 40 mg, continuously, until the development of progressive disease or

unacceptable adverse events. Dose escalation and reductions can occur. See Sections 4.1.4.1.1 and 4.1.4.1.2.

The medication should be taken at the same time each day at least one hour before food intake and at least three hours after food intake. The tablet should be swallowed with a glass of water (250 mL).

Missed doses of afatinib can be made up during the same day, following the administration guidelines in the above paragraph. Otherwise, the dose must be skipped and patients should take the next scheduled dose at the usual time. Patient with emesis must not take a replacement dose.

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment course. For administrative purposes, a treatment course is defined as 28 days. Treatment will start when the patient is randomized and stop when the patient is determined to have disease progression or for any reasons detailed in Section 3.3.4.1. Study drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

4.1.4.1.1 Dose escalation for afatinib

The dose of afatinib administered may be escalated to 50 mg at the start of Course 2 if all of the following criteria are met during Course 1:

- Drug-related CTCAE grade ≤1 skin rash
- Absence of diarrhoea, mucositis, and/or any drug-related event (any grade) other than skin rash CTCAE ≤1
- Afatinib dose was not previously reduced due to any of the AEs depicted in the Dose reduction scheme Table 4.1.4.1.2: 1
- Compliant dosing of afatinib, as described in Section 4.3

Dose escalation is prohibited in any situation other than that prescribed above. The patient should remain on 50 mg unless dose reduction becomes necessary (see Table 4.1.4.1.2: 1).

4.1.4.1.2 Dose reduction for afatinib

In the event of treatment-related toxicities, the treatment with afatinib should be handled according to the schedule in Table 4.1.4.1.2: 1.

Table 4.1.4.1.2: 1 Dose reduction scheme for afatinib

AE type and CTCAE Grade	Action	Dose reduction scheme
Events related to study drug: • Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration • Nausea and/or Vomiting Grade 2 persisting for 7 or more consecutive days despite anti-emetic treatment/hydration • Reduced renal function to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥3	Pause treatment until patient has recovered to Grade ≤1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤1 or baseline[1] within 14 days study treatment must be permanently discontinued[2].	If patient was receiving 50 mg, resume treatment at a dose of 40 mg. If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib.
Acute onset and/or unexplained worsening of pulmonary systems (dyspnea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue afatinib

[1] Baseline is defined as the CTCAE Grade at the start of treatment
[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with afatinib will be made by the

investigator in agreement with the BI Clinical Monitor. Continuous dose interruption of >28 days is not allowed.

4.1.4.2 Erlotinib

Patients randomised to the erlotinib arm will take a single oral dose of erlotinib each day starting at a dose of 150 mg, continuously, until the development of progressive disease or unacceptable adverse events. Dose reductions can occur. See Section 4.1.4.2.1. Erlotinib should be taken the same time each day, always one hour before food intake and two hours after food intake. Missed dose can be taken the same day at least one hour before or two hours after the ingestion of food. If daily dose is missed entirely, the regularly prescribed dose should be taken the next day. Do not double the dose of erlotinib.

For administrative reasons, treatment courses are 28 days (4 weeks). At the beginning of each treatment course, patients will be provided either a bottle containing 30 tablets of 150 mg or 100 mg erlotinib if the patients are receiving 150 mg or 100 mg of erlotinib, respectively, or 2 bottles containing 30 tablets in each bottle of 25 mg of erlotinib if the patients are receiving erlotinib 50 mg; or blister packs containing 30 tablets of either 150 mg or 100 mg erlotinib if the patients are receiving 150 mg or 100 mg of erlotinib, respectively, or a blister pack containing 60 tablets of 25 mg erlotinib if the patient is receiving 50 mg of erlotinib daily. Study treatment will be started at Course 1, visit 1 and will end when patient discontinues study drug due progressive disease progression or for any reasons detailed in Section 3.3.4.1. Study drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

4.1.4.2.1 Dose reduction and discontinuation of erlotinib

In the event of treatment toxicities, the treatment with erlotinib should be handled according to the schedule in Table 4.1.4.2.1: 1.

Table 4.1.4.2.1: 1 Dose reduction and discontinuation scheme for erlotinib

AE type and CTCAE Grade	Action	Dose reduction scheme
• Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration • Ocular disorders Onset of ocular disorders requiring treatment intervention or ≥CTCAE Grade 3 OR worsening ocular disorders >1 CTCAE Grade • Dermatology/skin Any dermatology/skin CTCAE ≥Grade 3 • Total bilirubin >3 x ULN and/or transaminases are >5 x ULN in pts with normal baseline • Total bilirubin >3 x ULN in pts with hepatic impairment (total bilirubin > ULN or Child Pugh A,B and C) • Dehydration in patients at risk for renal failure • Any drug related AE Grade ≥3	Pause treatment until patient has recovered to Grade ≤1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤1 or baseline[1] within 14 days study treatment must be permanently discontinued[2].	If patient was receiving 150 mg, resume treatment at a dose of 100 mg. If patient was receiving 100 mg, resume treatment at a dose of 50 mg. If patient was receiving 50 mg, discontinue erlotinib.
• Hepatic failure or gastrointestinal perforation • Acute/ worsening ocular disorders more severe than allowed above for dose reduction		Discontinue erlotinib

Table 4.1.4.2.1: 1(continued) Dose reduction and discontinuation scheme for erlotinib

AE type and CTCAE Grade	Action	Dose reduction scheme
Acute onset and/or unexplained worsening of pulmonary systems (dyspnea, cough, fever)	Pause erlotinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume erlotinib at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue erlotinib.

* Patients taking erlotinib with an inhibitor of both CYP3A4 and CYP1A2 and experiencing a severe adverse reaction should be evaluated for a dose reduction of erlotinib.
[1] Baseline is defined as the CTCAE Grade at the start of treatment
[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with erlotinib will be decided in agreement between the sponsor and the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This open-label trial will be treated as blinded by the sponsor until primary analysis database lock.

The Data Monitoring Committee (DMC) will be provided with unblinded data in order to ensure the ongoing safety and efficacy of the trial. Data unblinding as required for the DMC review will be conducted on an ongoing basis by a data manager or CRO not involved in the trial in order to keep the trial team blinded.

For the primary analysis of PFS, the trial team will complete the aggregate analysis.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

Details of packaging and sample labels will be found in the Investigator Study File (ISF).

Trial drug packages will have unique medication numbers which will be used for tracking purposes only. The medication numbers will not be linked to randomisation numbers.

Afatinib will be supplied as film-coated Tablets. Available dosage strength will be 20 mg, 30 mg, 40 mg, and 50 mg. Tablets will be supplied in , child-resistant, tamper-evident bottles.

Erlotinib will be supplied as film-coated Tablets. Available dosage strength will be 25 mg, 100 mg, and 150 mg. Tablets will be supplied in child-resistant bottles in the US and Canada. For all other countries, erlotinib will be supplied in polyvinyl chloride (PVC) blister sealed with aluminium foil.

Resupply of all study medication will be managed by the IXRS system. Details are provided in the ISF and IXRS User Guides.

4.1.7 Storage conditions

Trial medication, which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined below until supplied/administered to patient. Temperature logs must be maintained to make certain that the drug supplies are stored at the correct temperature. In case temperature would be out of range, this has to be reported in the ISF and the sponsor be notified.

4.1.7.1 Storage conditions for afatinib

Afatinib must be stored in the original package in order to protect from light. Film-coated Tablets are humidity-sensitive; therefore, bottles must be kept tightly closed to protect from moisture. Tablets must be stored according to the instructions on the label.

Patients should be instructed to keep the bottles tightly closed to protect from moisture.

4.1.7.2 Storage conditions for erlotinib

Erlotinib must be stored in the original packaging according to the instructions on the label.

If the erlotinib storage conditions are found to be outside the specified range, contact the local clinical monitor as provided in the list of contacts.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor or CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. A temperature log (documenting at least a weekly min/max temperature reading) at

the study site must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator /pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor or CRO when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol, if permitted by local regulations.
- All other local requirements are met (i.e. submission of completed, signed Form 1572 in the US)

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib include diarrhoea, nausea, vomiting, rash/acne and stomatitis. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

Concomitant treatments

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After randomization, palliative radiotherapy may be initiated for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area can not be used for tumour response assessment. During palliative radiotherapy, study treatment should be held and may be resumed once the patient has recovered from any radiation associated toxicity. If the medication is interrupted for more than 14 days, the decision to continue will be made by the investigator in agreement with the BI Clinical Monitor. Continuous dose interruption of >28 days due to palliative radiotherapy is not allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the eCRF during the screening and treatment period, starting with any medications taken within 4 weeks of the screening visit, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after complete wound healing. If the medication is interrupted for more than 14 days, the decision to continue medication will be made by the investigator in agreement with the BI Clinical Monitor.

Refer to the Tarceva® SPC/PI included in the site ISF for management of AEs due to treatment with erlotinib.

Emergency procedures

For patients receiving either afatinib or erlotinib, careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary. Refer to Tables 4.1.4.1.2: 1 and 4.1.4.2.1:1 for details.

Emergency contact information is provided in the ISF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.

Palliative radiotherapy may be given as described in Section 4.2.1.

Patients receiving erlotinib and taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in PT and INR.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment; with the exception of bisphosphonates (denosumab is excluded), megestrol acetate and use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer; or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Erlotinib

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP1A2 would be expected to increase exposure to the drug. Caution should be used during co-treatment with erlotinib and CYP3A4 inhibitors, and in some situations a decreased dose of erlotinib may be required. CYP3A4 inducers may increase clearance of erlotinib. See Appendix 10.6 for a list of common CYP3A4 inhibitors and inducers. Alternate treatments should be considered. If an alternate treatment is not possible, erlotinib dose modifications should considered.

Grapefruit and grapefruit juice can reduce the availability of CYP3A4 enough to significantly increases the bioavailability of drugs metabolized by CYP3A4 (P04-06229).

St. John's Wort increases the activity of CYP3A4, effectively decreasing the bioavailability of drugs metabolized by the same system.

Erlotinib is metabolized to a lesser extent by CYP1A2. Caution should be used during co-treatment with erlotinib and CYP1A2 inhibitors, and in some situations a decreased dose of erlotinib may be required (R11-1186).

Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib AUC. The concomitant use of proton pump inhibitors should be avoided if possible.

Co-administration of erlotinib with ranitidine, an H2 receptor antagonist, decreased the erlotinib AUC. Erlotinib and any H2 receptor antagonist should be taken in a staggered manner. Erlotinib must be taken once a day 10 hours after the H_2 receptor antagonist dosing and at least 2 hours before the next dose of H_2 receptor antagonist.

Refer to Appendix 10.6 and the Tarceva® SPC or PI included in the ISF for more information.

4.2.2.2 Restrictions on diet and life style

Patients receiving either afatinib or erlotinib should be advised to avoid intense irradiation with UV light and harsh detergents to prevent skin related adverse events.

Patients receiving afatinib or erlotinib should be advised to avoid any foods known to aggravate diarrhoea.

Suggest patients receiving afatinib or erlotinib use a thick, alcohol-free cream on dry areas of the body.

4.2.2.3 Women of child-bearing potential and pregnancy prevention

Patients who are not of child-bearing potential due to being postmenopausal (1 year without menstruations and at least 2 years without menstruation following chemotherapy) (R11-1406) or surgical sterilization (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for participation in this trial.

All other patients are considered to have child-bearing potential and must use adequate contraception while participating in this trial (from screening until end of trial participation or 2 months after last dose of trial medication, whichever is later).

Acceptable methods of birth control include surgical sterilization or double barrier method, and must be in accordance with local regulations where applicable. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Acceptable barrier methods include diaphragm, female condom, cervical cap, male condom, and intrauterine device (IUD) (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). Those using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural “rhythm”, and spermicidal jelly/cream are not acceptable methods of contraception.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in Section 5.2.2.2.

4.2.3 Management of expected adverse events

Dermatologic adverse events and diarrhoea are the most common side-effects associated with treatment with afatinib. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

The most common adverse events in NSCLC patients receiving erlotinib are rash and diarrhoea, anorexia, fatigue, dyspnea, cough, nausea, infection and vomiting (R11-1186). Refer to the Tarceva package insert for management of these events.

4.2.3.1 Management of diarrhoea and hydration status

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.3.1: 1). At the time of initiation of treatment with afatinib, site staff should ensure patients are counseled on prompt reporting of any diarrhoea and instituting corrective measures such as hydration and treatment with antidiarrhoeals. Sites should confirm that a patient has ready access to antidiarrhoeal medication.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea.

Table 4.2.3.1: 1 Grade specific treatment of study-drug related diarrhoea

Severity (CTCAE Grading)	Description	Intervention concerning afatinib treatment	Specific intervention
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of clear fluids per day; 4 mg (2 Tablets) of loperamide to be taken immediately, followed by 2 mg (1 Tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; iv. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose *unless Grade 2 diarrhoea continues for ≥ 2 days (48 hours)* in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide; assess for dehydration and electrolyte imbalance; consider iv fluids and electrolyte replacement
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; iv fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction[1]	See Grade 2; plus: an infectious process should be ruled out with stool cultures; aggressive iv fluid replacement ≥ 24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic;
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction[1]	See Grade 3

[1]If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTC AE Grade ≤1 within 14 days, treatment with afatinib must be permanently discontinued.

4.2.3.2 Management of dermatological AEs

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 4.2.3.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.3.2: 2. For dose adjustment of afatinib and erlotinib refer to Section 4.1.4.

Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered. (Adapted from R11-0826).

Table 4.2.3.2: 1 General recommendation for prophylaxis while receiving study drug

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. It is recommended that cuticles not be trimmed because this procedure increases the risk of nail bed infections.
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended. Patients should be encouraged to consequently stay out of the sun. Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	It is important to moisturize the skin as soon as therapy is started. Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications.
Prevention of paronychia	Patients should keep their hands dry and out of water if ever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions

Severity (CTCAE Grading)	Description	Specific intervention
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred. Multiple scattered areas: lotion preferred.
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical treatment as for Grade 1 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d.

Table 4.2.3.2: 2(continued) Grade specific treatment recommendations of skin reactions

Severity (CTCAE Grading)	Description	Specific intervention
ACNEIFORM RASH		
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist. Consider systemic steroids.
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3. Systemic steroids are recommended.
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines (e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine).
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone.
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream).
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream).
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics.

Table 4.2.3.2: 2(continued) Grade specific treatment recommendations of skin reactions

FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths). Topical application of aqueous silver nitrate solutions to fissures.
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics.
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.

4.2.3.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.3.3: 1. For dose adjustment refer to Section 4.1.4 and for restrictions on concomitant therapies refer to Sections 4.2.3, 10.5 and 10.6.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manuovers such as promotion of soft, non irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.3.3: 1 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from P11-09424)

Table 4.2.3.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations	Intervention concerning afatinib treatment/ dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution.	No change.
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4

4.3 TREATMENT COMPLIANCE

The study medication will be given in accordance with the protocol and the instructions of the site investigator.

The appropriate number of study medication for one cycle, or 4 weeks, of treatment will be provided to patients to be self-administered at home.

Patients will be asked to bring the remaining trial medication at the end of each cycle to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each cycle any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. Patients repeatedly missing scheduled on-treatment study visits, unless due to exceptional circumstances, are considered non-compliant. A maximum of 20% of doses of study drug may be missed for other reasons than drug-related AEs. Patients who miss taking study drug more frequently are considered non-compliant. The BI clinical monitor must be contacted and these patients will be discussed.

Non-compliant patients will be included in the efficacy analysis (as part of all patients randomized) and the safety analysis (as part of all patients treated).

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

The primary endpoint of this study is progression-free survival, as determined by RECIST 1.1(R09-0262).

The key secondary endpoint of this trial is:

- Overall survival

Other secondary endpoints of this trial are:

- Objective response (CR, PR) according to RECIST 1.1 (R09-0262)
- Disease control (CR, PR, SD) according to RECIST 1.1 (R09-0262)
- Tumour shrinkage
- Health-related Quality of Life (HRQoL)

5.1.2 Assessment of efficacy

5.1.2.1 Tumour Assessment

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumours (RECIST) guideline version 1.1(R09-0262). Tumour response will be assessed by investigator for clinical management of the patient and by a retrospective central review. Progression free survival will be defined as time from the date of randomization to the date of progression or to the date of death, whichever occurs first.

Full details of imaging procedures and RECIST 1.1 assessment can be found in Appendix 10.1

5.1.2.1.1 Central imaging

All image data will be sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment based on a uniform interpretation of radiographic image data for all patients enrolled in the trial. Upon receipt, the central imaging unit will log all image data into a tracking system and perform quality control of digitised radiographic images. An independent review of radiographic images including (i) sequential lesion selection and measurement and (ii) incremental radiological response assessment followed by (iii) global review of tumour response or progression will be performed by two blinded (with regard to patient, treatment, and visit) radiologists. In the case of disagreement on the radiological assessment at any timepoint between the two primary reviewers, a third

adjudicating radiologist will select one of the primary reviewer's interpretations for all timepoints. The data will also be reviewed by an oncologist who will provide a final assessment for each patient.

The review of the image data will be performed by independent radiologists, who are not affiliated with the study. All procedures will be done according to the specifications provided in the investigator site file. The purpose of the blinded reading is to independently assess patient response to therapy and disease progression.

Modifications of the conventional RECIST 1.1 lesion measurement criteria will be introduced into the measurement process in an attempt to reduce variability in the measurements for the independent central imaging review.

Eligibility and treatment decisions will be based on the assessment of disease by the investigator. Central imaging will not be used for this purpose and the results of the central imaging review will not be communicated to the investigator.

After approval of Protocol Version 3.0, the independent imaging review will be discontinued and sites will no longer require to send images to the central imaging unit.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety of afatinib and erlotinib will be evaluated by intensity and incidence of adverse events, graded according to NCI CTCAE version 3.0 (R04-0474). Safety endpoints include:

- The overall incidence and intensity of adverse events
- Gastrointestinal events (vomiting, nausea, diarrhoea)
- Skin reactions (rash, acne)

Tolerability of afatinib and erlotinib will be assessed based on dosage reduction and discontinuation due to adverse events.

5.2.2 Assessment of adverse events

A diagram of the Adverse event/Serious Adverse events reporting requirements is presented in Appendix 10.7.

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

The following hospitalizations are not considered to be serious adverse events (SAEs) because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 in the eCRF.

Causal relationship of adverse event

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. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE in the eCRF.

If progressive disease occurs and is associated with symptoms , the term "Progressive Disease" should not be reported as AE, however, signs and symptoms of progressive disease will be reported as an (S)AE (if applicable). Exception to this: Death due to progressive disease and where no signs or symptoms are available should be reported as "neoplasm progression (grade 5, outcome fatal)."

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory tests will be recorded as an AE in the eCRF, if they are judged clinically relevant by the investigator.

Adverse Events of Special Interest (AESIs)

Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered as AESI. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes are important for patient safety.

The following are considered as AESIs:

Hepatic injury defined by the following alterations of liver parameters: Hepatic injury defined by the following alterations of liver parameters:

- For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT >3 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.9 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

- For patients with abnormal liver function at baseline an elevation of AST and/or ALT >5 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to Appendix 10.9 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

AESIs are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria - for details please see Chapter 5.2.2.2.

If the investigator determines any AESI is related to study drug, the administration of the study drug must be managed according to Section 4.1.4 of the protocol.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent through to the Follow-up) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Serious AEs and AESIs occurring later than 28 days after the last administration of study drug will only be reported if deemed to be related to study drug. Following approval of Protocol Version 3.0 and after the individual patient's end of trial, the investigator does not require to actively monitor the patient for AEs but should only report relevant SAEs and AESIs that the investigator may become aware of. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event

Reporting' Section of the Investigator Site File. A diagram of the reporting requirements is provided in Appendix 10.7.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The investigator also has the responsibility to report AEs according to the table below and Appendix 10.7:

Table 5.2.2.2: 1 AE/SAE Reporting

Time period	Reporting requirements
From signing of informed consent through to 28 days after last trial drug administration	Report all AEs, SAEs and AESIs regardless of relatedness or whether the trial drug was administered. This includes all deaths.
Post-treatment (>28 days after last trial drug administration)	Report only SAEs and AESIs which are considered related to trial treatment that the investigator may become aware of. Death should be reported as an SAE only when considered related to trial treatment (because death is an endpoint and will be followed-up separately).

Any AEs reported to the sponsor during this phase must be documented in the safety database.

The investigator must report the events via telephone/fax using the SAE form immediately (within 24 hours) to the sponsor: SAEs, AESIs and non-serious AEs occurring at the same time as an SAE or AESI and/or which are medically related to the SAE or AESI. With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs, AESIs and non-serious AEs must include a causal relationship assessment made by the investigator.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Safety laboratory samples will be analyzed at a central laboratory (Quest Diagnostics). Safety laboratory examinations will include haematology, biochemistry and urine examinations. Table 5.2.3: 1 presents the laboratory tests to be performed.

After approval of Protocol Version 3.0, the safety laboratory samples will be analyzed in a laboratory facility at or nearby the investigational site; provided that the laboratory is appropriately certified and reference ranges are available.

Table 5.2.3: 1 Clinical laboratory tests

Category	Parameters
Hematology	haemoglobin, haematocrit, platelet count, white blood cell count (WBC). At screening only: neutrophils
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	
Electrolytes	sodium, potassium, calcium, magnesium
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	blood urea/blood urea nitrogen (BUN), creatinine; Glomerular Filtration Rate (GFR) will be estimated utilising serum creatinine values (see Appendix 10.3)
Other	glucose, albumin
Urinalysis	pH, protein, glucose, blood, leucocytes, nitrite, in case of pathological finding further evaluation should be performed and results documented
Pregnancy test	β-HCG testing in urine or serum in women of childbearing potential (WOCBP)

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal findings from these investigations need to be reported as an Adverse Event.

5.2.4 Electrocardiogram

12-lead ECGs will be taken at the time points specified in the flow chart if clinically indicated. ECGs will be completed locally at the study sites. The investigator will review the ECG recording at the time of the visit and record any ECG abnormality that meets AE criteria.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical Examination, Performance Status

A full physical exam must include cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen, and an assessment of the mental and neurological

status. Additional symptoms which have not been reported during a previous examination must be clarified. Wherever possible the same investigator should perform this examination.

A complete physical examination will be done as indicated on the flow chart. A symptom-directed examination is to be performed at all other visits as indicated in the flow chart.

5.2.5.2 Vital Signs

Vital sign measurements- blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiratory rate, temperature, measurement of height (in cm, at screening) and body weight (in kg), and the evaluation of the ECOG performance status will be performed at the times specified in the flow chart.

5.2.5.3 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by ECHO or MUGA (ECHO only in Germany) will be assessed at time points specified in the flow chart if clinically indicated. The same method of measurement must be used throughout the trial.

5.3 OTHER

5.3.1 Other endpoints

Patient-reported outcomes will be measured with the following multidimensional questionnaires included in Appendix 10.8.

- EQ-5D health status self-assessment questionnaire (R96-2382)
- EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (R99-1213, R07-2064)
- EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) (R07-2060, R07-2065)

All three questionnaires will be completed at the time points specified in the Flow Chart. After approval of Protocol Version 3.0, the completion of EQ-5D, EORTC QLQ-C30 and EORTC QLQ LC-13 questionnaires will no longer be required.

Questionnaires should be completed by patients prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status so that the responses are not influenced (biased). The questionnaires represent source documents. Validated translations exist for all questionnaires for all countries participating in the study and patients will receive the questionnaires in their native language.

Any unsolicited information provided by the patient on the questionnaire and any safety related data obtained from the patient's responses to the standard questions on the questionnaires will be immediately reported to the investigator. The investigator will review the patient's responses against the clinical assessment which corresponds to the timepoint the

questionnaire was completed for any potential AEs not captured during the clinical assessment. If the investigator determines a new AE has occurred, this will be appropriately reported in the eCRF.

If local regulations require the completed questionnaires to be confidential (i.e. not seen by the site staff) appropriate arrangements will be made to ensure confidentiality.

The patient perspective is considered a supportive contribution to inform physicians on the clinical utility of afatinib compared to erlotinib in the NSCLC population under investigation. In addition, the EQ-5D, HRQoL assessment will inform a later health economic (cost-effectiveness) analysis.

EQ-5D

The EQ-5D is a disease generic instrument that has been widely used and has been found to capture HRQOL changes in NSCLC (R07-2129, R07-2130). The EQ-5D comprises the following two questionnaires:

1. The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems).

2. The EQ VAS records the respondents self-rated health status on a vertical graduated (0- 100) visual analogue scale.

For the EQ-5D the respondent is asked to indicate his/her health state by placing a cross in the box against the most appropriate statement in each of the 5 dimensions. Additional instructions are provided in the ISF.

QLQ-C30 and LC-13

The QLQ-C30 is comprised of 30 questions. The QLQ-C30 incorporates both multi-items scales and single-item measures. These include one global health status/HRQoL scale, five functional scales, three symptoms scales and six single items to assess dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Each of the multi-item scales includes a different set of items – no item occurs in more than one scale (R07-2064). The QLQ-LC13 module comprises 13 questions. The module is designed for use in patients receiving treatment with chemotherapy and / or radiotherapy. The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis (R07-2064).

planned visits specified in the flow chart for homecare use. Resource use collection will

5.3.2 Other assessments

5.3.2.1 Demographics and history

Demographics (sex, birth date, race), alcohol history, and histological subtype will be collected during the screening 1 visit. The smoking history will be documented as follows:

- Smoking status: smoker vs. non-smoker
- Number of pack years = (number of cigarettes smoked per day x number of years smoked)/ 20 (R08-4072)
- Date of last cigarette

History of NSCLC will be obtained during screening and reported in the eCRF:

- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites (bone, brain, liver, pleural effusion, other)
- Tumour Stage according to the TNM-classification at initial diagnosis and study entry (i.e. re-staging of TNM).
- Previous surgery and radiotherapy for NSCLC
- Previously administered chemotherapy including start and end dates and the outcome

5.4 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumours. RECIST version 1.1 is used for assessment of the change in tumour burden. These criteria are well established and well received by the regulatory authorities and scientific community.

CTCAE criteria are used in the assessment of adverse events in cancer patients. Although an updated version is published, in the present trial CTCAE version 3.0 will be used. As several pivotal oncology trials are currently ongoing with the investigational product that utilize CTCAE version 3.0, it is considered more appropriate to continue to collect safety data using the same criteria.

The HRQoL questionnaires used in the present trial are recommended by and/or acceptable to multiple national authorities.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Pharmacokinetic analyses are not planned to be part of this trial.

5.6 BIOMARKERS

There are no approved predictive tumour- or serum-derived biomarkers for patients with advanced squamous cell carcinoma of the lung using erbB directed agents as second-line therapy following first-line platinum-based chemotherapy. Consequently, there is a strong rationale to identify predictive markers which are features at baseline that may predict responsiveness to ErbB TKI in this population. For the purpose of this trial, all patients are required to have archival tissue available and should consent blood samples for biomarker analyses.

If archival tumour tissue is available from more than one occasion the latest obtained sample should be used wherever possible. The site of biopsy (primary tumour or metastatic site) should be recorded in the eCRF.

Tumour tissue derived biomarker

An optimal of 10 slides (minimum 5) from archival tumour tissue will be required for each patient randomized into the study. Based on volume of tumour tissue in the submitted sample, testing will be conducted by a laboratory(s) designated by BI to evaluate diagnostics related to EGFR signalling pathways and/or cancer related genes (non-germline) which could impact the anti-tumor activity of afatinib. These may consist of tests to detect gene amplification (e.g. FISH), genomic sequencing (e.g. EGFR mutation analysis) and/or

immunohistochemical expression (e.g. H-score). Further details will be provided in the laboratory manual. These tests are considered investigational and the results will not be available to the PI or patient while a patient is receiving study drug. Results will be available upon request of the PI for patients who have discontinued study drug. Details of the request process will be provided in the ISF.

Serum derived biomarkers

The analyses will include determination of biomarkers similar to those previously described (R11-1316). Serum samples will be collected at baseline, at 4 weeks from the start of treatment and upon progression (EOT). All the analyses will be done by a central laboratory. Further details are provided in the laboratory manual.

5.6.1 Endpoints based on biomarkers

No endpoints in this trial are based on biomarkers.

5.6.2 Methods of sample collection

Detailed instructions for the collection and shipping of all tissue samples will be provided in the laboratory manual in the ISF.

5.6.3 Analytical determinations

See section **5.6 BIOMARKERS**.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients must provide written informed consent (ICF) before any study related screening procedures can be used. A diagram of the stages of a patient's participation in this trial is included in Section 3.1, and allowable time windows for visits are included in the flow chart.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

Refer to the Flow Chart for procedure details.

Tumour assessments at screening must be completed within 21 days of randomization. All other screening assessment must be completed within 28 days of randomization. Assessments required for study participation which were completed as part of Standard of Care before the patient signed the ICF can be used for the screening assessments if they were completed within the allowed timeframe.

6.2.2 Treatment period

Course 1, Visit 1 (Day 1 of 1st treatment course)

All procedures must be completed on Day 1 of Course 1. Refer to the flow chart for details.

Study medication must be administered as soon as possible after randomization, but within 2 days at the latest. Sites are strongly encouraged to have the patient take the first dose of study medication while he/she is still at the investigative site, and to document this in the site source documentation.

Course 1, Visit 2 (8 ±2 days after start of study drug)

Refer to the flow chart for details.

Course 2 (Day 1, -3 to +2 days) and all subsequent visits

Refer to the flow chart for details.

In case a patient misses the scheduled study visit but reports to the investigative site before the next scheduled study visit, the missed visit should be performed. The current date and reason for the delayed visit should be noted in the source documentation. All subsequent study visits should take place at the start of the next treatment cycle per the flow chart. In the event of any study drug interruption or delay of treatment, the tumour assessment schedule will not be changed.

6.2.3 End of trial and follow-up period

End of Treatment

Refer to the flow chart for details.

Follow-up (28 +7 days after discontinuation of study drug)

Refer to the flow chart for details.

Observation Period (Every 28 ±7 days after FUP)

Collect vital status of patient. Refer to flow chart for details.

Once Protocol Version 3.0 is final (and where required locally, approvals are obtained by the site as per Section 8.1), the collection of vital status data will be ceased.

End of Trial

The end of trial will be defined as when both of the following are met:

1. All events, for both PFS and OS analysis, have occurred

   AND

2. All randomized patients have completed the Follow Up visit 28 days after discontinuation study drug

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, open-label Phase III trial to evaluate the efficacy and safety of afatinib versus erlotinib in patients with squamous cell NSCLC eligible to receive therapy in the second-line setting. Patients will be randomized to afatinib or erlotinib in a 1:1 ratio. Randomization will be stratified with respect to race (Eastern Asian vs. non-Eastern Asian).

An interim analysis will be performed as described in Section 7.3.4.

Overall survival is the key secondary endpoint. OS will be tested only if the primary endpoint of PFS shows statistical significance ($p<0.05$, two-sided).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The alternative hypothesis of the primary analysis is that the progression-free survival time for patients treated with afatinib is different from that of patients who receive erlotinib. That is

$$H_A: S_{afatinib}(t) \neq S_{erlotinib}(t), \text{ for } t>0$$

The null hypothesis tested by this trial is:

$$H_0: S_{afatinib}(t) = S_{erlotinib}(t), \text{ for } t>0$$

where S(t) is the probability that a patient passes time t without dying or experiencing disease progression. The subscripts represent the two treatment groups of either afatinib or erlotinib. The null hypothesis will be tested at the two-sided 0.05 level with any adjustment necessary for the interim analysis.

7.3 PLANNED ANALYSES

Two analysis datasets will be used:

Randomized Set (RS): this dataset includes all patients who are randomised, regardless of taking investigational treatment.

Treated Set (TS): the dataset includes all randomised patients who take at least one dose of investigational treatment.

7.3.1 Primary analyses

The primary efficacy analysis will include all randomised patients regardless of taking investigational treatment (RS) and patients will be analysed as randomised.

7.3.1.1 Primary endpoint PFS

The primary analysis of PFS will be conducted after 372 patients have progressed or died.

Disease progression will be evaluated according to the RECIST 1.1 criteria (R09-0262). The analysis will be based upon the evaluation of tumour imaging as determined by central imaging. Clinical deterioration without image-based progression will be excluded from the primary analysis, but will be examined as part of a sensitivity analysis.

For patients with known date of progression (or death):

- PFS [days] = date of progression or death – date of randomisation + 1.

Patients with unknown disease progression status or date, or who are treated with new anti-cancer therapy will be handled as described in Section 7.4.

A stratified log-rank test will be used to compare afatinib to erlotinib. The test will be stratified by race (Eastern Asian vs. non-Eastern Asian).

A stratified Cox proportional-hazards model will be used to derive the hazard ratio and 95% confidence interval (CI) between the two randomised regimens. Kaplan-Meier estimates and 95% CI will be calculated at landmark time points.

7.3.2 Secondary analyses

OS will be tested only if the primary endpoint of PFS shows statistical significance. The treatment regimens will be compared in terms of time to death as the key secondary endpoint, but treatment after progression is expected to obscure any effect of afatinib relative to erlotinib.

The analysis of OS will estimate the hazard ratio and the corresponding 95% confidence interval based on a Cox-PH model. Additionally, a stratified log-rank test will be performed. Kaplan-Meier estimates of OS will be tabulated and K M estimates will be presented graphically.

OS will be analysed twice. The first analysis will be performed at the time of the primary PFS analysis using a Haybittle-Peto stopping boundary (p-value <0.0001). The primary analysis of survival is planned at 632 deaths. However, if the futility analysis curtails accrual at 500 patients, the primary analysis of OS will be performed after 80% of the randomized patients have died.

7.3.2.1 Other secondary analyses

A descriptive analysis of PFS will be performed at the time of the final analysis.

7.3.2.1.2 Best RECIST assessment

Each patient will be assigned to one of the following RECIST categories, irrespective of protocol violations or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)
- PD (progressive disease)
- unknown (not assessable, insufficient data)

Objective response is defined as CR or PR. Time to objective response is the time from randomization to the date of first documented CR or PR. The duration of objective response is the time from first documented CR or PR to the time of progression or death. Disease control is defined as CR, PR, or SD.

Logistic regression will be used to test for a difference between regimens for objective response and for disease control. The statistical model will include the same stratification factors that will be used for the analysis of PFS. Nominal significance levels will be reported.

Descriptive statistics will be calculated for the duration of objective response and duration of disease control.

7.3.2.1.3 Tumour shrinkage

The two treatment groups will be compared in terms of the minimum sum of target lesion diameters recorded for each patient after randomisation.

The analysis will compare the treatments using analysis of covariance (ANCOVA) for minimum sum of diameters, using baseline sum of diameters as a covariate. The randomization strata will be included as classification factors.

Waterfall plots will display the maximum percentage reduction from baseline sum of target lesion diameters.

7.3.2.1.4 Patient-reported Outcomes

The analyses will focus on cough, dyspnea, and pain measured on the EQ-5D, EORTC QLQ-C30 and QLQ-LC13 questionnaires.

For each of the summary scales and items measuring cough, dyspnea, and pain, the randomized treatments will be compared in terms of:

- The proportion of patients that are improved

  Improvement is defined as scores that improve by at least 10 points at any time during the study. All randomized patients will be included in the denominator.

- Time to deterioration

Time to deterioration will be defined as the time to a 10-point worsening from the baseline score.

Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQoL assessments will be censored at day of randomisation.

Time to deterioration will be analysed similarly to PFS i.e. log-rank test stratified by the stratification factors used at randomisation will be used to test for the effect of afatinib.

- Change in cough, dyspnea and pain scores over time

The change in cough, dyspnea and pain will be assessed using a mixed-effects growth curve model with the average profile over time for each endpoint described by a piecewise linear.

The results of the time to deterioration analyses and the longitudinal analysis will be displayed using Forest plots.

In addition, similar analyses will be summarized for all QLQ-C30 and QLQ-LC13 subscales/items (where a single item is scored).

Finally, the usage of cough, dyspnea and pain medication will be described.

7.3.3 Safety analyses

All patients who receive afatinib or erlotinib will be included in the analysis of safety.

The analysis of adverse events will include events that start within the period defined by the first treatment administration until 28 days after the last administration.

Adverse events and laboratory parameters will be graded according to CTCA , Version 3.0 (R04-0474).

Standard tabulations arranged by MedDRA SOC and PT will include:

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

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

- rash/acne
- stomatitis
- ocular effects
- lip effects
- nail effects
- fatigue

Tables that describe the frequency, intensity, time to onset, and clinical consequences will be produced for the following AE of special interest:

- diarrhea
- rash/acne

Listings will be prepared of patients who are identified as having experienced any of the following AE. For AE other than the single PT dehydration, identification will be based upon modified MedDRA SMQ and HLT groupings. If sufficient events occur within the trial, analyses similar to those for diarrhea and rash may be performed.

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

Primary laboratory tests are defined as:

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

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

- descriptive statistics at each planned assessment,
- frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment, and
- frequency of patients with possible clinically significant abnormalities.

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

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

7.3.4 Interim analyses

An interim analysis will be performed after at least 300 but not more than 500 patients have been randomized and when 130 patients have experienced PD or death, as determined by assessment at the study sites, among the first 176 patients randomized into the trial. (In the event that the 130 PD events occur before 300 patients are randomized, a decision on when to complete the analysis will be made in discussion with the DMC.) A Heybittle-Peto boundary (p-value <0.0001) will be used for stopping for superiority. Screening will be stopped when recruitment is expected to reach 500 patients if any required actions from the DMC Data Review Meeting have not been implemented. This analysis will lead to one of the three following decisions:

(1) No change- Accrual will continue until 800 patients have been randomized.

(2) Partial curtailment- Accrual will be stopped after the 500 patients needed for the analysis of PFS have been randomized.

(3) No further accrual- The trial will be stopped for superiority or futility.

While waiting for 130 PFS failures to occur, accrual of patients will continue, as described above, but only the first 176 patients will be included in the interim analysis. Additional details of the interim analysis are contained in the data monitoring committee charter.

7.4 HANDLING OF MISSING DATA

Table 7.4: 1 describes how patients will be classified for the analysis of PFS.

Table 7.4: 1 Rules to determine events and censoring for PFS

Rule #	Situation	Outcome (event or censored)	Date of PFS event or censoring
1	No baseline tumour assessment (no death before second scheduled assessment)	censored	Date of randomisation
2	Progressed from central imaging (no missed radiologic assessments)	event	Date of PD
3a	Non-PD from central imaging[1], death before next scheduled assessment	event	Date of death
3b	Non-PD from central imaging[1], one missed assessment, death or progression after date of missed assessment, but before a second scheduled assessment	event	Date of PD or death
3c	Non-PD from central imaging[1], more than one consecutive missed assessment, death or progression after date of second missed assessment	censored	Date of last imaging before missed assessment
3d	Non-PD from central imaging[1], more than one consecutive missed assessment, non-PD according to imaging after missed assessments	censored	Date of last non-PD imaging
4	New anti-cancer medication before progression or death	censored	Date of last imaging before new anti-cancer medication
5	Death before the scheduled date of first imaging	event	Date of death
6a	No imaging performed post-baseline, patient dies between first and second scheduled assessments	event	Date of death
6b	No imaging performed post-baseline, patient dies after second scheduled assessment	censored	Date of randomisation
6c	No imaging performed post-baseline, vital status is unknown or patient known to be alive	censored	Date of randomisation
7	Alive and not progressed from central imaging (no missed assessments)	censored	Date of last imaging

[1] - From the last assessment at which CR, PR or SD was assessed.

7.5 RANDOMISATION

Equal proportions of patients will be randomised to afatinib and to erlotinib. Randomization will be performed in blocks and stratified by race (Eastern Asian vs. non-Eastern Asian). The process of randomisation will be performed as described in Section 4.1.2.

7.6 DETERMINATION OF SAMPLE SIZE

Table 7.6: 1 shows the number of PFS events required for the primary analysis. The Table indicates that 372 PFS events would be expected to provide 90% power for the log-rank test,

presuming a hazard ratio of 0.714 for afatinib relative to erlotinib (corresponding to median PFS times of 14 vs. 10 weeks, respectively). Data on file (R10-6208).

Table 7.6: 1 Number of PFS events required for 80% and 90% power[1]

	80% Power	90% Power
Median PFS for afatinib	14 weeks	14 weeks
Median PFS for erlotinib	10 weeks	10 weeks
Hazard ratio of afatinib vs erlotinib	0.714	0.714
Number of events required for both groups[2]	278	372
Total Number of randomised patients	350	500

[1] log-rank test, alpha = 0.05, two-sided
[2] The number of required events was calculated using EAST-5 software excluding interim analysis, with patients randomised in a 1:1 ratio at a rate of 6 patients per week.

Table 7.6: 2 indicates that 632 deaths would be expected to provide 80% power for the log-rank test, presuming a hazard ratio of 0.800 for afatinib relative to erlotinib (corresponding to median survival times of 8.75 vs. 7.00 months, respectively).

Table 7.6: 2 Number of deaths required for 80% and 90% power[1]

	80% Power	90% Power
Median OS for afatinib	8.75 months	8.75 months
Median OS for erlotinib	7.00 months	7.00 months
Hazard ratio of afatinib vs erlotinib	0.80	0.80
Number of events required for both groups[2]	632	845
Total Number of randomised patients	800	1040

[1] log-rank test, alpha = 0.05, two-sided
[2] The number of required events was calculated using EAST-5 software excluding interim analysis, with patients randomised in a 1:1 ratio at a rate of 36 patients per month.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial 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 Good Clinical Practice (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 trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial 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) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. 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 trial 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 trial-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.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial 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 trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 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, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/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 trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

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 afatinib, this is the current version of the Investigator's Brochure (U03-3218). For erlotinib this is the EU SPC. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for study design or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial 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 trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1 (R09-0262).

The preferred method of assessment is a spiral CT scan with IV and oral contrast, unless IV and/or oral contrast are medically contraindicated. CT scans of the chest, abdomen and other areas of known or newly suspected disease must be performed. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

Skin lesions followed as target lesions must be documented by colour digital photography and must include in the image a ruler with millimetre subdivisions and a label that includes the patients ID and date.

Bone scans (using ^{99}m-technetium polyphosphonate scintigraphy) are recommended at baseline if the patient has any signs and symptoms consistent with bone metastasis or a history of bone metastasis. Bone metastasis identified at baseline must be documented and assessed according to RECIST 1.1 at the times of the other tumour measurements indicated in the flow chart. During the study bone scans should be repeated as clinically indicated in patients without bone metastasis at Baseline.

For the purposes of this study, patients should be re-evaluated for response at weeks 8, 12, 16, and every 8 weeks thereafter. In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

After approval of protocol version 3, tumour assessment will be performed every 18 weeks unless clinically indicated until progression or start of further treatment.

Follow-up tumour assessments must utilize the same CT/MRI/photographic method and acquisition technique (including use or non-use of IV contrast) as were used for screening assessments to ensure comparability. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of CT/MRI/bone scan.

Only those patients who have measurable disease present at baseline, have received at least 3 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurability of tumour at baseline

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray).

Pathological lymph nodes, defined as lymph nodes with a short axis >15mm are also measurable.

Measurable disease

Measurable disease requires the presence of at least one measurable lesion.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

New lesions in irradiated fields

Previously irradiated lesions should not be used as indicator lesions. However, new lesions occurring in previously irradiated fields can be used to assess the antitumour response.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5mm should be applied. If the lesion is not visible, a default measurement of 0mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is obligatory.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured (longest diameter = LD) and numbered at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Lymph nodes must be ≥15mm in order to be considered as target lesions.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.1: 1).

Table 10.1: 1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression (PD)	At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started, together with an absolute increase in the sum of LD of at least 5mm. OR The appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, taking as reference the baseline SoD, nor sufficient increase to qualify for PD taking as reference the smallest SoD since the treatment started.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.1: 2).

Table 10.1: 2 Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level.
Non-CR/ Non-PD	Persistence of one or more non-target lesions or/and maintenance of tumour marker level above normal limits.
Progression (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

In the case of SD, follow-up measurements must have met SD criteria at least once after study entry at a minimum interval of six weeks.

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.1: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.1: 3).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.1: 3 Algorithm for evaluation of overall best response*

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of six (6) weeks.

10.2 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
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 selfcare 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 Am. J. Clin.
R01-0787

10.3 FORMULA FOR ESTIMATED CREATININE CLEARANCE RATE

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. On-line calculators or formulas which are institution standards for the calculation of estimated creatine clearance may also be used. The calculation and result must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \; if \; Female]}{72 \cdot \text{Serum Creatinine}(\text{in mg/dL})}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot \text{Constant}}{\text{Serum Creatinine}(\text{in µmol/L})}$$

Where *Constant* is *1.23* for men and *1.04* for women.

10.4 NYHA CLASSIFICATION OF HEART FAILURE

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.5 LIST OF POTENT INHIBITORS AND INDUCERS OF P-GLYCOPROTEIN (MDR1)

Inhibitors	Inducers
Cyclosporine A	Rifampicin
Ketoconazole	St John's Wort
Itraconazole	Carbamazepine
Erythromycin	Phenytoin
Verapamil	Phenobarbital Salt
Quinidine	Tipranavir
Tacrolimus	Ritonavir
Nelfinavir	
Ritonavir	
Saquinavir	
Amiodarone	
Azithromycin	
Captopril	
Carvedilol	
Clarithromycin	
Conivaptan	
Diltiazem	
Dronedarone	
Felodipine	
Lopinavir	
Ranolazine	
Ticagrelor	

As the information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess such status on concomitant therapies and in case of questions contact BI clinical monitor.

10.6 LIST OF STRONG CYP3A4 INHIBITORS INDUCERS

The following lists the more frequently used CYP3A4 inhibitors, but is not intended to be all-inclusive:

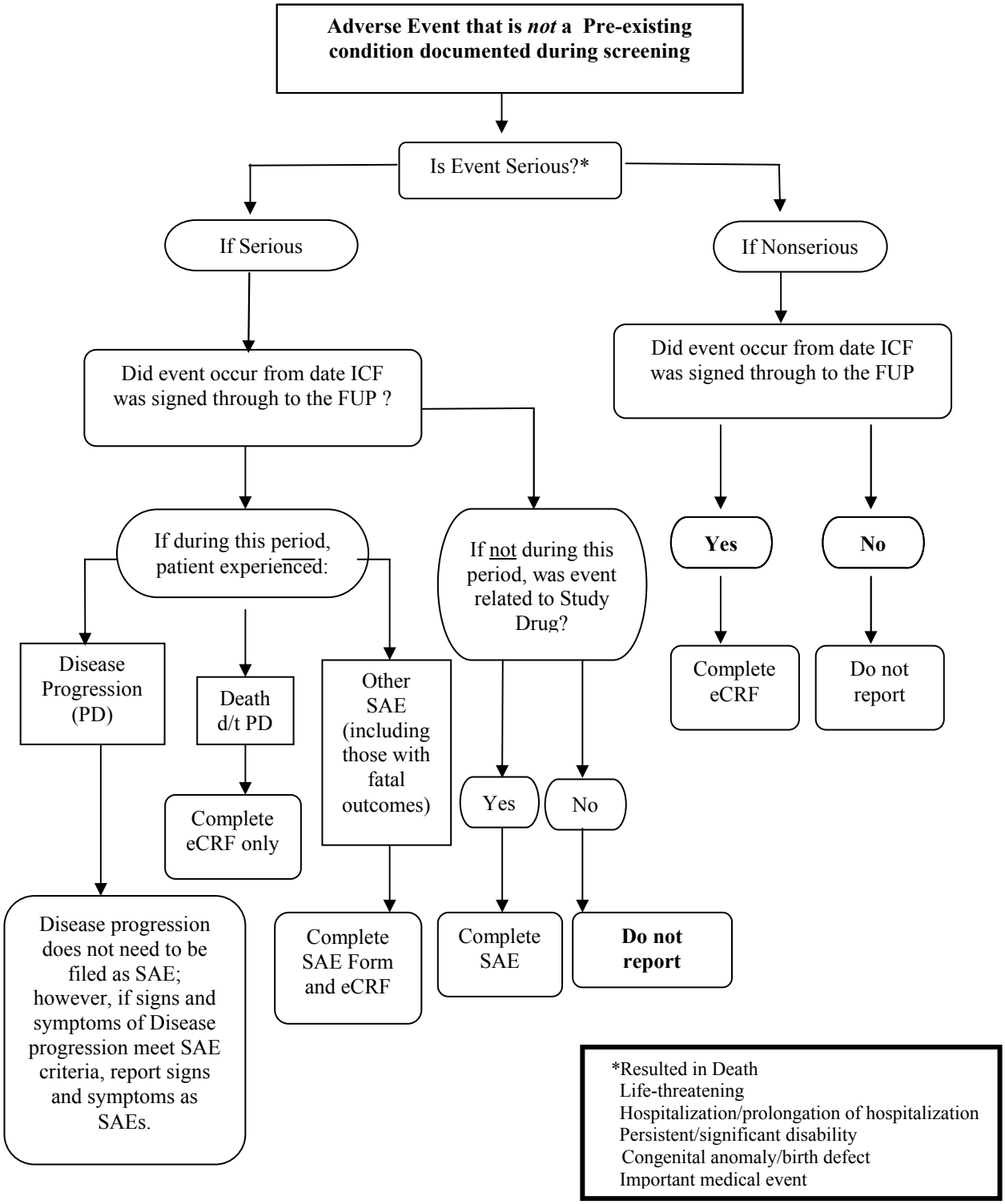
atazanavir	troleandomycin (TAO)
indinavir	itraconazole
nelfinavir	ketoconazole
ritonavir	voriconazole
saquinavir	nefazodone
clarithromycin	grapefruit
telithromycin	grapefruit juice

The following lists the more frequently used CYP3A4 inducers, but is not intended to be all-inclusive:

rifabutin	phenobarbitol
rifampicin	phenytoin
rifapentine	St. John's Wort
carbamazepine	

(R11-1186)

10.7 ADVERSE EVENT/SERIOUS ADVERSE EVENT REPORTING



10.8 QOL QUESTIONNAIRES

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

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

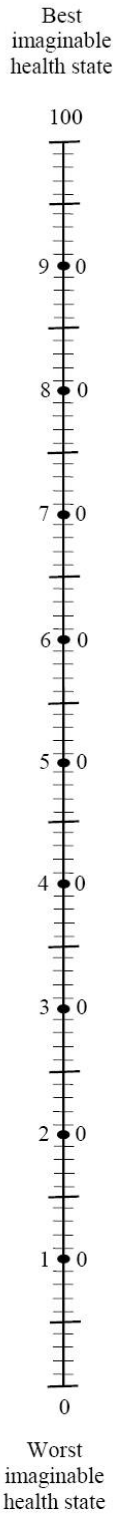
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

The following page was added in protocol version 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



10.9 CLINICAL EVALUATION OF LIVER INJURY

10.9.1 Introduction

Alterations of liver parameters, as described in Section 5.2.2.1 (AESIs), are to be further evaluated using the following procedures:

10.9.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert would be confirmed by local laboratory on initial sample if possible. If, due to technical error, the laboratory is not able to complete the confirmatory testing, an alert will be generated.

If a site receives a potential DILI alert notice from the local laboratory, the following must be completed:

1.) Evaluate patient within 48 hours and
2.) Perform following laboratory tests locally for confirmation
    1. Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
    2. Haptoglobin
    3. Complete blood count and cell morphology
    4. Reticulocyte count
    5. Creatinine kinase (CK)
    6. Lactate dehydrogenase (LDH)
    7. Alkaline Phosphatase

If the initial alert values (i.e. AST,ALT, and bilirubin) are confirmed on the second sample described as above, then an abdominal ultrasound or clinically appropriate alternate imaging (to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm) must be completed within 48 hours

The findings from the hepatic imaging (including comparison to prior imaging if available) must be made available as soon as possible as part of the adverse event reporting process. In the event the etiology of the abnormal liver tests results is not identified based on the imaging (e.g. biliary tract, pancreatic or intrahepatic pathology), then the "DILI checklist" must be completed. Details of the "DILI checklist" are provided in the ISF. The following assessments need to be performed in order to complete the "DILI checklist" and results will be reported via the eCRF:

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF;

- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;

- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;

- complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:

  - *Clinical chemistry*
    alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin*, amylase, lipase, fasting glucose, cholesterol,triglycerides

  - *Serology*
    Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*

  - *Hormones, tumormarker*
    Thyroid-stimulating hormone(TSH)*

  - *Haematology*
    Thrombocytes, eosinophils

    **If clinically indicated (e.g. immunocompromised patients)*

- **Long term follow-up**

  - Initiate close observation of subjects by repeat testing of ALT, AST, and bilirubin (with fractionation to total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

and report these via the eCRF.

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		*24 Oct 2012*
EudraCT number		*2011-002380-24*
BI Trial number		*1200.125*
BI Investigational Product		*Afatinib, BIBW 2992*
Title of protocol		**LUX-Lung 8**: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		FLOW CHART
Description of change		Change in footnote *** from afatinib to study drug
Rationale for change		The discontinuation visits apply to either study drug.
Section to be changed		1.1 MEDICAL BACKGROUND
Description of change		Added hyperlink
Rationale for change		Omitted in error in previous version.
Section to be changed		1.2 Drug Profile
Description of change		
Rationale for change		
Section to be changed		3.3.2 Inclusion criteria
Description of change		Modified inclusion criterion 2.
Rationale for change		Clarify this criterion.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Added exclusion criterion 21.

Number of global amendment		1
Rationale for change		Align the criterion with the language in 3.3.1, specifying patients need to have disease progression after completion of 1st line treatment.
Section to be changed		3.3.4.1.1 Patient discontinuation of study participation
Description of change		Clarification of assessments to be completed for patients who discontinue therapy without disease progression.
Rationale for change		Clarification of language.
Section to be changed		4.1.5.1 Blinding
Description of change		Changed language clarifying the timing of trial team unblinding will be at the time of the snapshot used for the primary analysis.
Rationale for change		The previous protocol stated the trial team will remain unblinded for as long as feasible. This threshold will be at the time of the aggregate data reviews of the database snapshot used for primary analysis.
Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatments/
Description of change		Added: There is no specific antidote for overdosage with afatinib.
Rationale for change		Provide clarification.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		
Rationale for change		
Section to be changed		4.2.3.3 Management of mucositis/stomatitis
Description of change		Added hyperlink.
Rationale for change		Required due to new break in page.
Section to be changed		5.2.3.1 Assessment of safety laboratory parameters
Description of change		Added hyperlink.
Rationale for change		Required due to new break in page.
Section to be changed		
Description of change		
Rationale for change		Align protocol language with ongoing data collection.
Section to be changed		5.6.3 Analytical determinations
Description of change		Added section.
Rationale for change		Omitted in error in previous version and required for sponsor SOPs.
Section to be changed		7.2 NULL AND ALTERNATIVE HYPOTHESES
Description of change		Changed title.
Rationale for change		Error in previous version and to align with sponsor SOPs.
Section to be changed		
Description of change		Added and deleted medications; and added statement.
Rationale for change		Align the protocol with IB v13 and to provide updated information and disclosure on assessing medications not listed.

Number of global amendment		1
Section to be changed		10.8 QOL QUESTIONNAIRES
Description of change		Added last page of the EQ-5D
Rationale for change		Omitted in error in previous version.

Number of global amendment		2
Date of CTP revision		25 May 2016
EudraCT number		2011-002380-24
BI Trial number		1200.125
BI Investigational Product		Afatinib, BIBW 2992
Title of protocol		**LUX-Lung 8**: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**Title page**
Description of change		Change in BI product name and Sponsor contacts.
Rationale for change		To provide current and up-to-date information.
Section to be changed		**Protocol Synopsis**
Description of change		Change in BI Product name and number of patients entered.
Rationale for change		To provide current and up-to-date information.
Section to be changed		**Flow chart**
Description of change		Follow-up visit: update visit allowed window to +7days. Footnote numbers: - 4: change to frequency and review of ECG - 6: change to frequency and review of ECHO/MUGA - 9: no longer required to complete QOL questionnaires - - 12: change to imaging assessment frequency - 14: no longer required to collect Observation Period data
Rationale for change		Follow-up visit: to be in lined with the current BI guideline. Footnote: following the database lock for the primary analysis of OS data, patients would have been on treatment for more than 2 years and as such: sufficient vital status and health related QOL, data have been collected and

Number of global amendment		2
		therefore no longer required; and a more frequent ECG, ECHO/MUGA and imaging assessment is no longer considered necessary.
Section to be changed		**1.2 Drug profile**
Description of change		Afatinib is now approved by both EMA & FDA.
Rationale for change		To provide current and up-to-date information.
Section to be changed		**3.1 Overall Trial Design and Plan**
Description of change		Discontinue central imaging review and cease the collection of vital status data. Update the visit window for the Follow-up visit to +7days.
Rationale for change		Following the database lock for the primary analysis of OS data: - There is no longer the requirement for central analysis of imaging as the primary endpoint of PFS has been assessed and reported; - Sufficient vital status data have been collected and therefore no longer required. Update the Follow-up visit window to be in lined with the current BI current guideline for reporting SAE/AESI.
Section to be changed		**3.3.4. Removal of patients from therapy or assessments**
Description of change		Further clarify the option in allowing patients to access study treatment via an alternative source and that collection of vital status will no longer be required for these patients.
Rationale for change		To ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial.
Section to be changed		**5.1.2.1.1 Central imaging**
Description of change		Discontinue central imaging review and sending images to Central Imaging Unit will no longer be required.
Rationale for change		Following the database lock for the primary analysis of OS data, there is no longer the requirement for central analysis of imaging as the primary endpoint of PFS has been assessed and reported.
Section to be changed		**5.2.2 Assessment of Adverse Events**
Description of change		Update the terminology for protocol-specified significant events to AESIs. Update the reporting timeline and requirements for SAE and AESIs.
Rationale for change		To be in lined with BI current guideline for reporting SAE/AESI.
Section to be changed		**5.2.3 Assessment of safety laboratory parameters**
Description of change		Safety lab samples will no longer be sent to central lab for analysis but will be done at local lab instead.
Rationale for change		Following the database lock for the primary analysis, there is no longer the requirement for sending blood samples to central lab for analysis.
Section to be changed		**5.2.4 Electrocardiogram**
Description of change		ECG will be performed at the time points specified in the flow chart only if clinically indicated.
Rationale for change		Following the data base lock for the primary analysis, sufficient ECG data has been collected for analysis.

Number of global amendment		2
Section to be changed		**5.2.5.3 Left ventricular function**
Description of change		LVEF will be performed at the time points specified in the flow chart only if clinically indicated.
Rationale for change		No safety signals in terms of the effect on cardiac contractility have been identified for afatinib in the context of this trial and using a larger safety database. Therefore routine monitoring of left ventricular (LVEF) is not warranted.
Section to be changed		**5.3.1 Other endpoints**
Description of change		Discontinue the collection of QOL questionnaires and the
Rationale for change		Following the database lock for the primary analysis of OS data, sufficient health related QOL and have been collected and therefore no longer required.
Section to be changed		**6.2.3 End of trial and follow-up period**
Description of change		Cease the collection of Observation Period data.
Rationale for change		Following the database lock for the primary analysis of OS data, sufficient vital status data have been collected and therefore no longer required.
Section to be changed		**Appendix 10.1 RECIST 1.1 criteria**
Description of change		Reduce imaging assessment frequency.
Rationale for change		Since patients have been on treatment for more than 2 years, therefore such frequent imaging assessment is no longer considered necessary.
Section to be changed		**Appendix 10.9 Clinical Evaluation of Liver Injury**
Description of change		Further evaluations of liver parameters will be performed at local lab.
Rationale for change		It is no longer required to send blood samples to central lab for analysis and this will instead be performed at local lab.