Clinical Trial Protocol

Doc. No.: c02364424-03

BI Trial No.:	1200.209
BI Investigational Product:	Giotrif®/ Gilotrif® (Afatinib)
Title:	A Single Arm Phase IV Study of Afatinib in Elderly Patients with recurrent or Stage IV Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have Common Epidermal Growth Factor Receptor (EGFR) mutations (Exon 19 Deletions or Exon 21 L858R Substitution Mutations)
Clinical Phase:	IV
Trial Clinical Monitor:	Tel: Mobile: Fax:
Co-ordinating Investigator:	Tel: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	**Version: 3.0** **Date: 15 February 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif®/ Gilotrif® (Afatinib)			
Name of active ingredient: Giotrif®/ Gilotrif® (Afatinib)			
Protocol date: 20 MAR 2015	**Trial number:** 1200.209		**Revision date:** **15FEB2018**
Title of trial:	A Single Arm Phase IV Study of Afatinib in Elderly Patients with recurrent or Stage IV Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have Common Epidermal Growth Factor Receptor (EGFR) mutations (Exon 19 Deletions or Exon 21 L858R Substitution Mutations).		
Co-ordinating Investigator:	Tel: Fax:		
Trial sites:	Multi-center trial in the US		
Clinical phase:	IV		
Objective:	The objective of this study is to describe the occurrence of AEs leading to dose reduction following afatinib treatment in NSCLC patients with common EGFR mutations (Deletion 19 and/or L858R) who are 70 years of age or older.		
Methodology:	Open-label, non-randomized, Phase IV, single arm study		
No. of patients:			
total entered:	Approximately 25		
each treatment:	Approximately 25		
Diagnosis :	Recurrent or Stage IV Non-Small Cell Lung Cancer (includes cytologically proven pleural effusion or pericardial effusion) harbouring EGFR del 19 or L858R mutation.		
Main criteria for inclusion:	• Pathologically confirmed diagnosis of recurrent or stage IV NSCLC (includes cytologically proven pleural effusion or pericardial effusion) not amenable for curative intent local radiotherapy. Staging is based on AJCC Staging for NSCLC 7th Edition • Documented EGFR mutations (deletion 19 and/or L858R substitution) • Age ≥ 70 years • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • No prior systemic therapy for metastatic or recurrent NSCLC		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif®/ Gilotrif® (Afatinib)			
Name of active ingredient: Giotrif®/ Gilotrif® (Afatinib)			
Protocol date: 20 MAR 2015	**Trial number:** 1200.209		**Revision date:** **15FEB2018**

Test product:	Giotrif®/ Gilotrif® (Afatinib)
dose:	Starting dose 30 mg per day
mode of admin.:	Orally, once daily
Comparator products:	Not Applicable
dose:	Not Applicable
mode of admin.:	Not Applicable
Duration of treatment:	Continuous treatment until progression or occurrence of intolerable AE or end of trial
Criteria for efficacy:	Endpoints: Primary and secondary endpoints are safety endpoints
Criteria for safety:	Primary endpoint: Occurrence of AEs leading to dose reduction of afatinib Secondary endpoints: Occurrence of CTCAE grade 3 or higher diarrhoea, rash/acne+, stomatitis+ and paronychia+ (+ represents grouped term) Adverse events; time to first dose reduction of afatinib caused by AEs. Other endpoints (safety): Adverse events will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
Statistical methods:	Descriptive statistics

FLOW CHART

Study Period	**Screening (a)**	**Treatment Courses (b)**						**EOT (c)**	**FU (d)**	**VS (r)**
	SCR	Course 1			Course 2		Course 3 onwards			
Visits (V)		1	2	3	1	2	1	EOT	FU	VS
Days	-28 to -1	1	8	15	1	15	1	≤7 days of last Tx	28 +7 days after last Tx	Q3mths
Maximum Visit window (in days)	0	0	±2	±2	-3, +2	±2	-3, +2			90±14 days
Informed consent (e)	X									X
Demographics	X									
Medical history/ Documentation of EGFR mutation	X									
Inclusion/Exclusion	X									
Height	X									
Weight	X							X		
12 Lead Digital ECG (f)	X									
Physical exam (g)	X	X			X		X	X		
Vital signs (h)	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X		X	X	X	X	X		
Safety lab: CBC, serum chemistries (i,j)	X	X		X	X	X	X	X		
Safety lab: INR, aPTT (j)	X							X		
Safety lab: urinalysis (j,k)	X							X		
Dispense medication		X			X		X			
Interactive Response Technologies call/ notification (m)	X	X			X		X	X		
Administration of afatinib		Continuous								
Compliance check			X	X	X	X	X	X		
Adverse event (n)	X	X	X	X	X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X	X	X (o)	
Termination of trial medication								X		
Conclusion of study participation									X	
Vital Status (r)										X

a Screening: the screening visit should be performed within 28 days of the first dose of afatinib. Safety lab at the screening assessment can serve as the Day 1 pre-treatment assessment of Course 1 if performed within 72 hours before the first treatment and does not need to be repeated

b Treatment courses: all courses are 4 weeks in duration (28 days). During the treatment period, clinical assessments and safety laboratory tests must be performed prior to study drug administration on the visit day. All subsequent visit dates should be calculated based on Course 1 Visit 1 date. One or more visits can be skipped in case of treatment interruption. Patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4).

c EOT: if the decision to permanently discontinue afatinib treatment is taken during a scheduled visit, the End Of Treatment (EOT) visit should be performed instead of the scheduled visit (or within 7 calendar days after last drug administration)

d FU: all patients should have a follow-up (FU) visit 28+7 days after the permanent discontinuation of afatinib

e Written informed consent must be obtained before any protocol specific screening assessment is performed

f A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening and reviewed by the investigator. Refer to Section 5.2.4 for details

g Physical exam: includes a thorough cardiopulmonary, abdominal and regional lymph node exam and an assessment of the mental and neurological status. No need to repeat the physical exam on C1V1D1 if within three calendar days of the screening physical exam and the patient is deemed stable by the investigator

h Vital signs: includes respiratory rate, pulse, temperature and blood pressure

i Safety lab: CBC: include white blood cell count, neutrophil and bands, differential, hemoglobin, hematocrit and platelet count. Serum chemistries: include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, GGT, total bilirubin, alkaline phosphatase, calcium, magnesium. See Section 5.2.3

j Additional laboratory assessments should be performed if clinically indicated

k Urine analysis: include pH, protein, glucose, ketones, blood, leucocytes, nitrite, bilirubin, urobilinogen, and specific gravity. In case of pathological finding, further evaluation should be performed and results documented in the source document

m Interactive Response Technologies (IRT): patient's screening, all drug dispensation visits and EOT will be collected in the IRT system

n Adverse event: from 28 days after last trial drug administration new AEs will only be collected, documented and reported if they are considered related to trial drug

o Concomitant therapy: during FU concomitant therapy only needs to be recorded if indicated for the treatment of an AE

.

r For patients that consent to be followed, vital status will be collected every 3 months until the end of the trial.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptors
EOT	End of Treatment
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HR	Hazard Ratio
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ILD	Interstitial Lung Disease
ISF	Investigator Site File
i.v.	intravenous
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OPU	Operative Unit
QoL	Quality of Life
RDC	Remote Data Capture
REP	Residual Effect Period
SAE	Serious Adverse Event
SCR	Screening
SMQ	Standardised MedDRA Query

SOC	System Organ Class
SRS	Stereotactic Radio Surgery
TCM	Trial Clinical Monitor
TKI	Tyrosine Kinase Inhibitors
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TX	Treatment
ULN	Upper Limit of Normal
VS	Vital Status

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related deaths in many countries, including the US. The prognosis for advanced stage disease has improved modestly in the past 20 years. With an overall 5-year survival rate of only 15% the treatment of this disease clearly remains a major clinical challenge (R05-0867).

While systemic chemotherapy has demonstrated modest activity in advanced NSCLC, novel targeted therapies based on specific molecular and biological characteristics of lung cancer have emerged as a new treatment paradigm. Among the molecules most extensively studied are the Epidermal Growth Factor Receptors (EGFR) or the Subclass I of the superfamily of transmembrane tyrosine kinase receptors (R06-1301, R06-1302).

Aberrant activation of EGFR frequently observed in a variety of malignant tumors can be induced by different molecular mechanisms including receptor overexpression, mutation, ligand-dependent receptor dimerization, and ligand-independent activation. Overexpression of EGFR has been detected in 40% to 80% of NSCLC patients (R06-1301, R06-1393, R06-1394). However, recent clinical experiences with specific EGFR-Tyrosine Kinase Inhibitors (TKI) have demonstrated tumor regression in only 10% to 15% of unselected NSCLC patients (R05-0867, R06-1301, R06-1306). The treatment with EGFR TKIs is associated with higher Response Rate (RR) in patients with tumors which harbor EGFR mutations. In a recent meta-analysis based on 13 randomized trials, the response rate was 70% vs. 33.2% in first-line trials. In three second-line trials, response rates were 47.4% vs. 28.5%, with a benefit similar to first-line trials (Relative Risk, 1.79; p = .04) (R12-4000). Somatic mutations between exons 18 through 21 of the EGFR gene was found to occur in approximately 10% of NSCLC patients from the US, Europe or Australia compared to up to 30% in patients from Japan and Taiwan (R06-1262, R06-1306, R06-1393). The most common EGFR mutations are a short, in-frame deletion in exon 19 (E19del [LREA deletion] found in approximately 46% of patients) and a point mutation (CTG to CGG) that results in a substitution of leucine by arginine at codon 858 of exon 21 ([L858R] found in 37.5% of patients) (R14-2119).

Two large multinational randomized Phase III studies of afatinib in the first line treatment of mutation positive stage IV NSCLC patients have been performed: the LUX-Lung 3 (1200.32) and LUX-Lung 6 (1200.34) studies.

LUX-Lung 3 compared first line afatinib to up to six cycles of cisplatin /pemetrexed (N=345 with 2:1 randomization). Adult patients with performance status (PS) 0-1 were included in the trial without age limitation. Seventy-two percent (72%) of all trial patients were Asian with the remainder classified as non-Asian. In this trial patients treated with afatinib demonstrated significant and clinically meaningful improvements in progression free survival (PFS, median PFS afatinib vs. cisplatin/pemetrexed 11.1 vs. 6.9 months, hazard ratio 0.58; 95% CI, 0.43 to 0.78; P=.001) and Objective Response Rate (ORR, afatinib vs cisplatin /pemetrexed 56% vs. 23%; P= .001). This was accompanied by significant delays in time to deterioration of the cancer-related symptoms of cough (afatinib /cisplatin pemetrexed, Hazard

Ratio, HR, 0.60; 95% CI, 0.41 to 0.87; P = .007) and dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; P =.01). A pre-planned analysis of PFS in patients (n=308) with exon del 19 or L858R mutation was 13.6 months for afatinib and 6.9 months for chemotherapy (HR 0.47; 95% CI: 0.34 to 0.65; P=0.001). Higher response rates were observed in afatinib groups compared with chemotherapy 69% and 44%, respectively (P13-07382).

LUX-Lung 6 compared first line afatinib to up to six cycles of cisplatin/gemcitabine (N=364 with 2:1 randomization afatinib: cisplatin/gemcitabine). All patients were Asian. As in LUX-Lung 3, patients with performance status 0-1 were included in the trial without age limitation. Patients treated with afatinib demonstrated significant improvements in progression free survival (median PFS afatinib vs. cisplatin/gemcitabine 11.0 months vs. 5.6 months, hazard ratio 0.28; 95% CI 0.20 to 0.39; P<0.0001) and ORR (afatinib vs. cisplatin/gemcitabine 66.9% vs. 23.0 %, P <0 .0001). This was accompanied by significant delays in time to deterioration of the cancer-related symptoms of cough (afatinib vs. cisplatin/gemcitabine HR 0.45, 95% CI, 0.30 to 0.68; P = .0001) and dyspnea (HR 0.54; 95% CI, 0.40 to 0.73; P< 0.0001) [P14-00758]

In a separate single arm study (LUX-Lung 2) [P12-03681] in lung adenocarcinoma patients (stage IIIb with pleural effusion or stage IV) with EGFR mutations, 129 patients were treated in first-line or second-line with afatinib, 99 with a starting dose of 50 mg and 30 with a starting dose of 40 mg. 79 (61%) of 129 patients had an objective response (two complete responses, 77 partial responses). 70 (66%) of the 106 patients with the two most common activating EGFR mutations (*deletion 19* or *L858R*) had an objective response, as did nine (39%) of 23 patients with less common mutations.

For patients previously treated with a reversible EGFR TKI and clinically enriched for EGFR mutations, treatment with afatinib plus best supportive care resulted in a significant improvement in median PFS over patients treated with a placebo plus best supportive care (LUX-Lung 1/1200.23) [U10-3048-01].This improvement in PFS was accompanied by significant and meaningful improvements in cough, dyspnoea, and pain, compared to the placebo group. Treatment with afatinib was also found to significantly delay the time to deterioration for Global Health Status/Quality of Life (QoL).

A subsequent and larger study (LUX-Lung 5/1200.42) enrolling a similar population of patients resulted in a very similar median PFS as in LUX-Lung 1. In these studies, the PFS benefit of afatinib was consistent across all pre-planned subgroups with at least 50 patients, including gender, age, race, baseline Eastern Cooperative Oncology Group (ECOG) performance status, type of prior EGFR TKI, baseline tumor size, and lines of prior chemotherapy. In both of these studies (LUX-Lung 1 and 5) treatment with afatinib had the greatest PFS benefit for those patients who belonged to a subgroup highly clinically enriched for EGFR mutations or who were positive for EGFR mutations by testing of tumor tissue.

1.2 DRUG PROFILE

Afatinib (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting

in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

For the latest information on the drug profile of afatinib, please refer to the current afatinib Investigator Brochure (IB) (c01802941-09). All references in this protocol concerning afatinib refer to the free base compound afatinib which is used as the oral formulation.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. 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 in cancer patients. Steady state was reached no later than 8 days after the first administration. 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. Therefore, afatinib should be taken without food (i.e. food should not be consumed for at least 2 hours before and at least 1 hour after taking afatinib). 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.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for AUC0-∞ and Cmax when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib (AUC0-∞) and 22 % (Cmax), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators.
In pre-clinical studies afatinib is not an irritant to intact skin but an ocular irritant.

!"#$%$&'()'$*% *+)+)'$%$, '* -(./%)%' (),,$'&)' "*&.& *+ 0 #/12/ 3)--(*4$#)'.56 789 '$#.& ':. .4-*&;(. ,6 !<= 3)(.) ;%".(':. >;(?.@)' ':. (.>*##.%"." :;#)% "*&. *+A7#/ ")$56@ *(/(.)'.(";($%/ ':. -.($*" *+ *(/)%*/.%.&$& >);&." $%>(.)&." -*&' $#-5)%')'$*% 5*&&)%"B $%)%$#)5&&:*C$%#)'.(%)5 '*4$>$'6B*('$*%)' 5)'. /.&')'$*%)5&')/.&8D%. &)#. &';"6B)' ':. :$/: "*&. 5.?.5 *+E7 #/12/ 3)--(*4$#)'.56 78F'$#.& ':. .4-*&;(. ,6 !<=)' ':. (.>*##.%"." :;#)% "*&. *+A7#/ ")$56@.(. C.(. (.";>." +.')5 C.$/:'&B)%" $%>(.)&.&% ':. $%>$".%*+(;%'&B&C.55)&?$&>.()5%"".(#)5 ?)($)'$*%&D8%).#,(6*+.')5 ".?.5*-#.%' &';"6 $% ()'&B ':.(. C.(. &2.5.')5)5'.()'$*%&>*%&$&'$%$%>*#-5.'. *(".5)6." *&&$+$>)'$*%'&.";>." +.')5 C.$/:')') "*&. *+EG#/12/ 3)--(*4$#)'.56 'C$>. ':. .4-*&;(.)' ':. (.>*##.%"." :;#)% "*&. *+A7#/ ")$56@8

Two phase I open label dose-escalation studies determined the Maximum Tolerated Dose (MTD) with continuous dosing of afatinib in patients with advanced solid tumours at 40mg and 50mg daily, respectively (U07-3128-02, U08-1023-02). Adverse events (AE) observed with afatinib are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent investigator defined drug-related AEs were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects, epistaxis, fatigue, and decreased appetite. Early and proactive management of diarrhoea, mucositis/stomatitis and skin rash 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).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The US registration of the EGFR TKIs afatinib and erlotinib has changed the clinical management of patients with advanced NSCLC (R06-1394, R06-1307, R07-1049, R07-1134). A significant clinical benefit may be achieved by a treatment that controls NSCLC progression with acceptable levels of side effects through a defined and specific targeted molecular mechanism.

Elderly patients (variously defined in the literature as ≥ 65 years of age or ≥70 years of age) tend to be underrepresented in clinical trials (R14-1781, R14-1839, R14-1840). For this trial we will define elderly patients as those patients who are 70 years of age or older.
Half of all NSCLC patients are 70 years of age or older at the time of initial diagnosis (R14-1781).

There are several retrospective subset analyses from large clinical trials of the safety and efficacy of EGFR TKIs in elderly patients (age ≥ 70). These trials were conducted regardless of mutational status and allowed multiple prior lines of therapy (R09-2250, R14-1350). One such study in Canadian patients demonstrated significant improvement in progression free survival in both elderly and younger populations compared to placebo (R09-2250). Elderly patients however, had significantly more overall and severe toxicity (grade 3/4 35% vs. 18.5%; p< .001). The elderly were also more likely to have > grade 3 rash, fatigue, stomatitis, or dehydration.

A subset analysis of a Japanese population based observational study in patients ≥ 75 years of age treated with the same EGFR TKI as in the Canadian study was performed. Patients received treatment without regard to mutational status and had multiple prior lines of therapy. In this study there was a statistical difference between the disease control rate in the elderly and non- elderly (58.2 % vs. 42.5 % P= 0.0228). There was no statistical difference in the time to treatment failure or in overall survival between the two groups. There was also no significant difference in the occurrence of grade > 3 toxicities between the groups. [R15-0770]

Afatinib is approved in the United States for the first line treatment of patients with Exon 19 Deletions or Exon 21(L858R) substitution mutations based on the results of the LUX-Lung 3 clinical trial. In that first line trial, encompassing 345 patients with varying EGFR mutations, the mean age was 60.3 years; 230 patients were randomized to Afatinib, from which 48 patients were 70 years of age. Of these patients, 41 had exon 19 deletions or L858R mutations.

This trial is proposed to obtain additional information about the tolerability of treatment with first line afatinib in the US elderly population by evaluating the proportion of patients with AEs leading to dose reduction of afatinib. It is felt that the use of the 30 mg dose of afatinib in this vulnerable patient population (patients with ECOG PS of 2 or 3) reflects actual clinical practice.

2.2 TRIAL OBJECTIVES

The objective of this study is to describe the occurrence of AEs leading to dose reduction following afatinib treatment in NSCLC patients with common EGFR mutations (Deletion 19 and/or L858R) who are 70 years of age or older.

See Section 5 for a detailed description of the study endpoints.

2.3 BENEFIT - RISK ASSESSMENT

Despite recent advances, NSCLC still has a dismal prognosis with an overall 5 year survival rate of 15%. Afatinib is approved in the United States for the first line treatment of patients with Exon 19 Deletions or Exon 21(L858R) substitution mutations. In the LUX-Lung 3 trial, afatinib showed a statistically significant and clinically meaningful improvement in PFS, response rate and lung cancer symptoms compared to chemotherapy in NSCLC patients with common EGFR mutation (P13-07382). Across all afatinib clinical trials, diarrhoea, including severe diarrhoea, has been reported during treatment. Diarrhoea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Diarrhea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhea is reported in about 15% of patients and most frequently occurred within the first 6 weeks of treatment.

The dermatological AEs in afatinib trials are captured as group terms including rash, acne, paronychia, pruritus, dry skin, eczema, and folliculitis. Across all trials rash/acne occurred at a high frequency and half of the cases begin within 4 weeks of exposure to afatinib. Grade 3 rash was observed in about 17-18% of patients and those at higher risk for Grade 3 rash/acne appear to be the patients of low body weight/body surface area and patients with low baseline renal function.

Interstitial lung disease (ILD) is a rare and serious (potentially fatal) AE reported with other EGFR TKIs. The frequency of ILD-like AEs in all afatinib treated patients was low (approximately 1%) and similar to that observed with other EGFR TKIs. In this study, patients with known pre-existing ILD will be excluded. Afatinib treatment will be interrupted if patients experience acute onset and/or unexplained worsening of pulmonary symptoms (including dyspnea, cough, and fever). If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment should be instituted as necessary.

Although rare, a potential for drug-induced liver injury (DILI) due to afatinib 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 patient safety.

Keratitis was identified using the MedDRA SMQ (Medical Dictionary for Drug Regulatory Activities Standardised MedDRA Queries) (narrow) for corneal disorders and Boehringer Ingelheim's internal database was searched. In all afatinib-treated patients as of 15 January

2013, 32 patients (0.7%) were identified using the SMQ search with the most common preferred term being keratitis (19 patients [0.4%]).

In regard to treatment of older patients, in the LUX-Lung 3 study, the predominant adverse events noted in patients aged 70 and over (N= 48) receiving afatinib treatment were diarrhoea 95.8% (10.4% > grade 3), rash/acne 85.4% (12.5% > grade 3), stomatitis 66.7% (6.3% > grade 3) and nail effects 56.3% (16.7% > grade 3). These adverse events were treated symptomatically, and with treatment interruption and dose reductions. For patients aged 70 and over, therapy was discontinued because of treatment related AEs in 14.6% of the patients receiving afatinib. Of the most common AEs associated with afatinib, only diarrhoea (4.2%) and paronychia (2.1%) were cause for treatment discontinuation. There were no cases of interstitial lung disease-like events potentially related to afatinib in patients 70 years of age or older. Two deaths in this age group were considered to be related to afatinib treatment (one respiratory decompensation and one sepsis). In the first line Lux Lung 6 trial encompassing 364 patients with varying EGFR mutations, one hundred percent of patients were Asian. The mean age was 56 years, 25 (6.9 %) afatinib patients were 70 years of age or older and had exon 19 deletions or L858R mutations. The tolerability of afatinib in this study was consistent with what was reported in the LUX-Lung 3 trial. .

In this study, the guideline for management of expected side effects of afatinib will be followed (refer to Section 4.4). Regular and frequent monitoring of the safety as well as the clinical benefit throughout the trial will be implemented, including scheduled clinical visits when the emergence of afatinib related AEs are expected. Hence, early management and education will take place to mitigate worsening of symptoms. In addition, periodic tumor assessment will be performed by the investigator; patients lacking clinical benefit will be removed from afatinib treatment.

In summary, there is a medical need for improving treatment of elderly patients with EGFR driver mutations.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open label, non-randomized, single arm Phase IV study in patients 70 years of age or older with stage IV or recurrent Non-Small Cell Lung Cancer whose tumors harbor common *EGFR* mutations. A total of approximately 25 patients will be entered into the trial.

After completion of the screening assessments, eligible patients will be treated with a starting dose of 30 mg afatinib daily as monotherapy. The dose may be reduced dependent on the AE profile of the individual patient and concomitant medication. See Section 4.4 on afatinib dose modification.

The patient participation in the trial is considered to be concluded when the follow-up visit is complete. For patients that agree to be followed, vital status will be collected every 3 months until the end of the trial. The end of the trial is defined approximately one year after the last patient has entered the study.

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

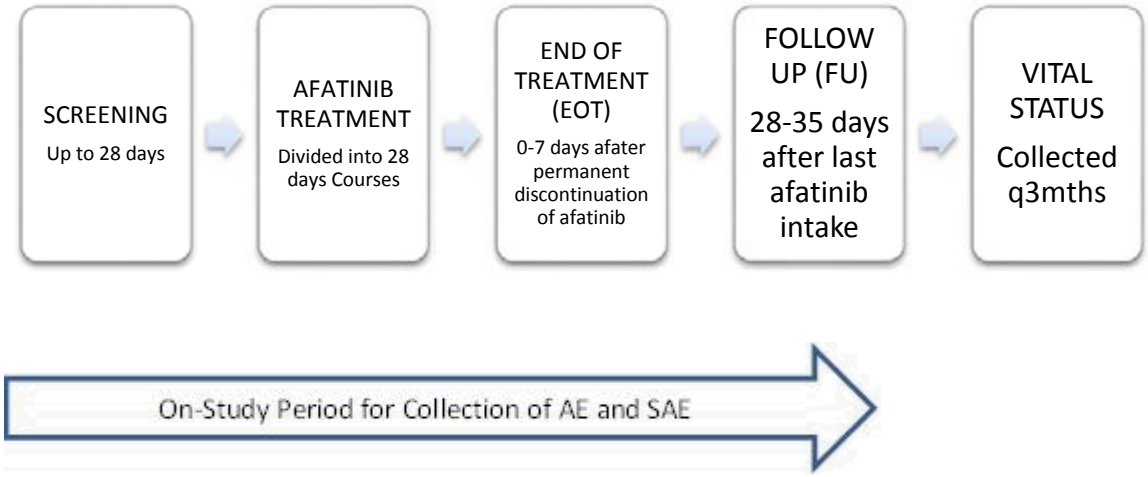

Figure 3.1:1 Study design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim.

The investigators participating in the trial must have experience in diagnosing and treating patients with non-small cell lung cancer. The coordinating investigator is an investigator participating in the trial who is experienced in treatment and investigations of lung cancer. The coordinating investigator has been designated by Boehringer Ingelheim and will sign the clinical trial report. There will be no steering committee or data monitoring committee for this trial.

On-site monitoring will be performed by BI or a Contract Research Organization (CRO) appointed by BI.

All trial relevant documentation will be stored in the Trial Master File (TMF) at BI. 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 GROUP

This trial is a single arm, open-label uncontrolled study. Treatment will be administered in courses of 28 days. The starting dose of afatinib will be 30 mg daily. Dose reductions will be permitted as described in Section 4.4.1.

3.3 SELECTION OF TRIAL POPULATION

Elderly patients determined to have the common *EGFR* mutations *Del 19* and *L858R* as part of standard of care testing will be eligible to be screened for participation in this trial. It is foreseen that approximately 25 patients will be treated at approximately 15 to 20 study sites in the US. The rate of enrolment will vary by study site, but is expected to be approximately 1 to 2 patients per site. Additional sites may be added if necessary. Given changes in the treatment landscape and ability to recruit patients within the study population, study discontinuation prior to meeting expected enrollment goals may be considered as described in Section 3.3.4.2.

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 treated with study drug or not.

3.3.1 Main diagnosis for study entry

The study will be performed in elderly patients with Stage IV or recurrent non-small cell lung cancer harbouring *Deletion 19* and/or *L858R EGFR* mutation.

3.3.2 Inclusion criteria

1. Pathologically or cytologically confirmed Stage IV Cancer NSCLC (includes cytologically proven pleural effusion or pericardial effusion) or recurrent disease not amenable for curative intent local radiotherapy. Staging is based on AJCC Staging for NSCLC 7th edition (R12-4710)

2. Evidence of common *EGFR* mutation (*Del 19* and/or *L858R*)

3. Age ≥ 70 years

4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (R01-0787) (See Appendix 10.1)

5. Adequate organ function, defined as all of the following:
   - Absolute neutrophil count (ANC) > 1500 / mm^3
   - Platelet count >75,000 / mm^3.
   - Baseline creatinine of < or = 1.5 g/dl or, if > 1.5, estimated creatinine clearance > 45ml / min. (Cockcroft-gault formula -refer to Appendix 10.3
   - Total Bilirubin < 1.5 times upper limit of institutional normal (ULN)
   - Aspartate amino transferase (AST) and alanine amino transferase (ALT) < three times ULN (if related to liver metastases < five times ULN)

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

7. Life expectancy of at least three months

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

3.3.3 Exclusion criteria

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

2. Prior systemic therapy for metastatic or recurrent NSCLC including prior treatment with EGFR targeting small molecules or antibodies. . Note: radiotherapy alone and adjuvant/neoadjuvant treatment is not counted as a line of therapy.

3. Concurrent investigational therapy or investigational therapy within 4 weeks of start of afatinib therapy

4. Radiotherapy within 4 weeks prior to start of study treatment, except as follows:
   i.) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to study treatment, or
   ii.) Single dose palliative treatment (e.g SRS or SBRT) for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling.

5. Major surgery within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study

6. Men, capable of fathering a child, who are unwilling to use adequate contraception prior to study entry, for the duration of study participation, and for at least 28 days after treatment has ended. Refer to Section 4.2.2.3 for details

7. Presence of an active infection or with a fever > 38.5 °C within 3 days of the first scheduled day of dosing

8. Known hypersensitivity to afatinib or the excipients of afatinib

9. Known pre-existing interstitial lung disease

10. Meningeal Carcinomatosis - Pathologically documented meningeal carcinomatosis (i.e. cytology (+) lumbar puncture ; radiology reports alone raising this as a possibility, in the absence of true symptomatology, would not constitute an exclusion)

11. Presence of brain or subdural metastases, unless local therapy has been completed and use of corticosteroids has been discontinued or the dose has been stable for at least 4 weeks before starting study treatment. Any symptoms attributed to brain metastases must be stable for at least 4 weeks before starting study treatment Pts post SRS can be enrolled earlier as long as their symptoms are stable or improved and they are off steroids)

12. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 2 years and is considered to be cured

13. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 or 4 unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to start of afatinib treatment

14. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption)

15. Known or suspected active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier

16. Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the safety and efficacy of the test drug

17. Treatment with any of the prohibited concomitant medications (refer to Section 4.2.2.1) that cannot be stopped for the duration of trial participation

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The investigator or patient may stop study treatment at any time for safety or personal reasons.

A patient has to be withdrawn from study treatment in case any of the following applies:

- The patient withdraws consent from study treatment
- Has radiologic (or clinical) documentation of progressive disease (Section 5.1.2). (except for patients who develop symptomatic brain metastasis requiring single dose palliative treatment (e.g SRS) .These patients may remain on study after receiving this radiation treatment if stable post RT and there is no evidence of progression aside from the brain lesions.)
- Is diagnosed with interstitial lung disease (ILD)
- The patient is no longer able to receive study treatments (e.g. adverse events, concomitant diagnoses, surgery, concomitant medications or administrative reasons)
- Has a significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made by the sponsor in agreement with the investigator

Patients who withdraw from the trial after commencing treatment will not be replaced. Procedures that need to be completed are found in Section 6.2.3 and 6.2.4.

After the end of the trial, the sponsor will assist patients still on treatment with access to afatinib through marketed product.

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:

- Failure to meet expected enrolment goals overall or at a particular trial site,
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial.
- Violation of GCP (Good Clinical Practice), the protocol, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

Eligible patients will receive continuous afatinib treatment until progression or intolerable adverse events or other reasons necessitating withdrawal (see Section 3.3.4.1). The manufacturer for afatinib is listed in Section 4.1.1.

4.1.1 Identity of BI investigational product and comparator product

Substance (INN) **(Brand name):**	**Afatinib** Giotrif®/ Gilotrif™
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 and 30 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent to afatinib)
Route of administration:	Oral
Posology	Once daily

4.1.2 Method of assigning patients to treatment groups

This is a single-arm non randomized study. Patients who have given their written informed consent will be enrolled sequentially on a first come first enrolled basis and will be registered in the trial. Patients who meet all eligibility criteria will be entered into the study and the start of treatment will be documented by the investigator. The trial will continue to enroll patients until the goal of approximately 25 patients entered into the study is reached.

4.1.3 Selection of doses in the trial

Per approved label, ':. (.>*##.%"." "*&. *+)+)'$%$$&A7#/ *()556*%>.")$56;%'$5'$&.)&. -(*/(.&&$*%(%*5*%/.('*5.()'." ,6 ':. -)'$.%'8 It is felt that the use of the 30 mg dose of afatinib in this vulnerable patient population (elderly) reflects actual clinical practice.

The daily dose will be modified following careful monitoring of a patient's drug-related adverse events. Refer to Section 4.4 for dose reductions to be made in response to the occurrence of adverse events. Dose escalation will not be allowed during this study.

4.1.4 Drug assignment and administration of doses for each patient

Patients will take a single oral dose of afatinib each day starting at a dose of 30 mg continuously. The dose of afatinib must be reduced if certain adverse events occur (see Section 4.4).

Afatinib should be taken at approximately the same time each day without food (at least one hour before a meal or at least two hours after a meal).

Missed doses of afatinib can be made up within 12 hours of the scheduled time. Otherwise, the dose must be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis must not take a replacement dose.

If dosing of whole tablets is not possible, afatinib tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 min until the tablet is broken up into very small particles. The dispersion should be drunk immediately. The glass should be rinsed with approximately 100 ml of water which should also be drunk. The dispersion can also be administered through a naso-gastric tube.

Afatinib will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy via Interactive Response Technologies (IRT) at the beginning of each treatment course. For administrative purposes, a treatment course is defined as 28 days. Treatment will start when the patient takes the first dose of afatinib (Course 1 Day 1) and continue until the criteria for stopping trial medication in Section 3.3.4.1 are met.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This open-label, single-arm study will be handled in an open fashion throughout, i.e., also for the purpose of data cleaning and preparation of the analysis. No blinding is necessary in this trial, because all patients receive the same treatment.

4.1.5.2 Procedures for emergency unblinding

Not applicable

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the product package insert provided in the ISF.

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 20 mg and 30 mg.

Medication numbers which will be recorded by the site in the eCRF (Electronic Case Report Form) are used for tracking purposes only.

As study medications will be commutable between studies 1200.208 and 1200.209, both study numbers will be pre-printed on the study medication labels. Upon enrolment at Visit 1,

IRT will issue a report showing the study number and patient number for each patient. The report should be filed in the ISF.

4.1.7 Storage conditions

Drug supplies, should be maintained according to the current drug label, must be kept in a secure, limited access storage area under the storage conditions defined on the label instructions. Where necessary, temperature logs must be maintained to make certain that the drug supplies are stored at the correct temperature. If storage temperature is out of range at any time, this has to be reported in the ISF and the sponsor must be notified.

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.

4.1.8 Drug accountability

The investigator or delegate (e.g. pharmacist or investigational drug storage manager) will utilize sponsor provided afatinib when the following requirements are fulfilled:

- Approval of the study protocol by the institutional review board (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 (CTP) or immediately imminent signing of the clinical trial protocol,
- Availability of the proof of a medical licence for the principal investigator (if applicable).
- Availability of the Form 1572 (if applicable)

The Investigator or delegate 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 disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product 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 products received from the Sponsor. At the time of return to the Sponsor, 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

4.2.1.1 Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for over dosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhoea, and rash/acne. 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 in Section 4.4.2.

4.2.1.2 Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Afatinib 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.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

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.

4.2.1.3 Additional treatments

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

After study enrollment, palliative radiotherapy may be given 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 cannot be used for tumor response assessment. During palliative radiotherapy, study treatment should be delayed and may be resumed once the patient has recovered from any radiation-associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by the BI clinical monitor in agreement with the investigator. Patients who are dose interrupted for

>28 days due to palliative radiotherapy must be permanently discontinued from study medication.

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 from the date of signature of informed consent, and ending at the EOT (end of treatment) 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 afatinib is interrupted for more than 14 days, the decision to continue will be made by the BI Clinical Monitor in agreement with the investigator.

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 4.2.1.3.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of 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 afatinib.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.2.

4.2.2.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea.

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.4.2.

4.2.2.3 Men capable of fathering a child and pregnancy prevention

Men who are capable of fathering a child and whose partners have child bearing potential must use adequate contraception throughout the trial (from screening until 28 days after last dose of trial medication).

Acceptable methods of contraception include surgical sterilisation and 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. Accepted 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 with partners using hormonal contraceptives must also be using an additional approved method of contraception (as described above). Natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

Pregnancies that result from a male participating in this trial must be reported following BI internal SOP using the pregnancy monitoring form (refer to ISF).

4.3 TREATMENT COMPLIANCE

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

The appropriate number of afatinib tablets for 28 days of treatment will be provided to patients to be self-administered at home.

Patients will be asked to bring the remaining trial medication to the investigator site for a compliance check according to the Flowchart. 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 28 day period, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.

Patient's repeatedly missing scheduled on-treatment study visits, unless due to exceptional circumstances, should be discussed with the BI trial monitor and be evaluated for compliance. A maximum of 25% of the dispensed afatinib doses may be missed for other reasons than drug-related AEs. Patients who miss afatinib treatment more frequently are considered non-compliant.

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.

4.4 MANAGEMENT OF DOSE REDUCTION AND EXPECTED ADVERSE EVENTS

4.4.1 Management of dose reduction for afatinib

Afatinib treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions according to the schedule described in Table 4.4.1: 1. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhoea, dermatologic adverse events or mucositis/stomatitis should be managed early and proactively as described in Section 4.4.2.

Table 4.4.1: 1 Dose reduction scheme for afatinib

CTCAE[a] Adverse Events related to afatinib	**Action**	**Dose reduction scheme**
Grade 1 or Grade 2	No interruption[b]	No dose adjustment
Grade 2 (prolonged[c] or intolerable) or Grade 2 renal dysfunction or Grade ≥ 3	Interrupt until Grade ≤1[b]	Resume treatment with dose reduction by 10mg decrements[d]

[a] NCI Common Terminology Criteria for Adverse Events V 4.0 (R12-2532)
[b] In case of diarrhoea, anti-diarrhoeal medicinal products (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements ease.
[c] ≥48 hours of diarrhoea and/or ≥7 days of rash
[d] If patient cannot tolerate 20mg/ day, afatinib should be permanently discontinued

Interstitial Lung Disease (ILD) should be considered if a patient develops acute or worsening of respiratory symptoms in which case treatment should be interrupted pending evaluation. If ILD is diagnosed, afatinib should be discontinued and appropriate treatment initiated as necessary.

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 for any reason, the decision to continue with afatinib will be made by the BI clinical monitor in agreement with the investigator.

4.4.2 Management of expected adverse events

4.4.2.1 Management of diarrhoea and hydration status following treatment with afatinib

Diarrhea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhea may lead to dehydration and require treatment modification or discontinuation, so early management is essential (Table 4.4.1:1). At the time of initiation of treatment with afatinib, patients should be given a supply of loperamide to keep with them at all times or access to loperamide should be confirmed; and patients should be counselled on the appropriate use.

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

Table 4.4.2.1: 1 Grade specific treatment recommendations for afatinib related diarrhea

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 water or 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; i.v. 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*	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*	See Grade 3

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

4.4.2.2 Management recommendations for dermatological AEs following treatment with afatinib

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 4.4.2.2: 1 and grade-specific treatment recommendations are summarized in Table 4.4.2.2: 2. For dose adjustment of afatinib refer to Table 4.4.1: 1.

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 4.4.2.2: 1 General recommendation for prophylaxis while receiving afatinib

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 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. Cuticles are not allowed to 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, PAPA 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 anti-EGFR 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 4.4.2.2: 2 Grade specific treatment recommendation of skin reactions to afatinib

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

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
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.
*If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.4.1: 1		

4.4.2.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.4.2.3:1. For dose adjustment refer to Section 4.4.1 and for restrictions on concomitant therapies refer to Section 4.2.2.

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 manoeuvres 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 4.4.2.3:1 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 4.4.2.3: 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 4.4.1.
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 4.4.1

5. VARIABLES AND THEIR ASSESSMENT

There are three categories of endpoints in this trial: 1) the primary endpoint, 2) secondary endpoints and 3) other endpoints. The primary endpoint of this study is a safety endpoint, the occurrence of AEs leading to the dose reduction of afatinib. The secondary endpoints are also safety endpoints. The category of "other endpoints" includes specific safety and efficacy endpoints.

5.1 EFFICACY

5.2 SAFETY

5.2.1 Endpoints of safety

The primary endpoint of the study is the occurrence of AEs leading to dose reduction of afatinib. Patients without AEs leading to dose reduction of afatinib will be considered as "no" for the primary endpoint. No confirmatory analysis is planned (i.e. no formal hypothesis testing will be performed.)

The secondary endpoints of the study are:

- Occurrence of CTCAE grade≥3 diarrhea
- Occurrence of CTCAE grade≥ 3 rash/acne+
- Occurrence of CTCAE grade ≥3 stomatitis+
- Occurrence of CTCAE grade ≥ 3 -)(*%6>:$)H
- Time to first dose reduction of afatinib caused by AEs, defined as time from the date of the first administration of afatinib to the first dose reduction of afatinib caused by AEs.

In the study, MedDRA preferred terms that describe AEs of similar nature will be grouped together as "grouped term" to ensure that important events will not be underestimated. These grouped terms are flagged by a '+'.

Endpoints for safety belonging to the category of 'other endpoints' are:

- Adverse events evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (R12-2532).

5.2.2 Assessment of adverse events

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.

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 4.0 and recorded 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 (CRF).

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 the underlying disease or other pre-existing conditions

Disease Progression in oncology trials is a study endpoint for analysis of efficacy. Disease progression is exempted from reporting as a (S)AE. Progression of the patient's underlying malignancy will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection. Death due to disease progression is to be recorded on the appropriate (e)CRF page and not on a SAE form.

Examples of exempted events of PD are: Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.

• Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)

• Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

When there is evidence suggesting a causal relationship between the drug and the progression of the underlying disease, the event must be reported as (S)AE on the eCRF and SAE form.

Worsening of other pre-existing conditions will be recorded as an (S)AE in the eCRF and SAE form (if applicable).

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

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

Adverse Event of Special Interests (AESIs)

No AESIs have been defined for this trial.

Expected Adverse Events

For expected (listed) AEs of afatinib, see the current version of the IB (Investigator's Brochure) (U03-3218-13).

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 onwards through the follow-up period of 28 days after the last drug administration, Table 5.2.2.2:1) will be collected, documented and reported to the sponsor by the investigator on the appropriate eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

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 Residual Effect Period (REP), defined as the period of time after the last dose of medication when measureable drug levels or pharmacodynamic effects are still likely to be present, is 28 days for Afatinib. All events reported within 28 days of the last study medication will be considered on-treatment.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE that occurred after the patient has completed the clinical trial, it should be reported by the investigator to the sponsor if considered relevant by the investigator.

All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterized or the principal investigator decides to not further pursue them.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
For screen failures; From signing of informed consent to the timepoint where ineligibility is	Report all AEs and SAEs. This includes all

confirmed	deaths.
For treated patients; From signing of informed consent to the end of the follow-up visit (28 days after last trial drug administration)	Report all AEs and SAEs regardless of relatedness or whether the trial drug is administered. This includes all deaths.
After the 28 day followup visit until vital status followup (VS) is completed	Report all related SAEs.
After the patient has completed the study	Active monitoring for adverse events is not required. If the investigator becomes aware of an SAE that occurred after the patient has completed the clinical trial it should be reported to the sponsor if considered relevant by the investigator.

If not stipulated differently in the ISF, the investigator must report the following events using the SAE form via fax immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant to an SAE. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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 Remote Data Capture (RDC) system.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (operative unit) (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 this study, pregnancy is not expected to occur in female participants with the age of 70 years or older. In rare cases, pregnancy might occur in a female partner of a male participant with drug exposure to afatinib; in which case, pregnancy must be reported following BI internal SOP using the pregnancy monitoring form (refer to ISF).

5.2.3 Assessment of safety laboratory parameters

Safety laboratory samples will be analysed at the investigator's local laboratory. Safety laboratory examinations will include hematology, biochemistry and urine examinations.

Table 5.2.3: 1 Laboratory tests to be performed

Category	Parameters
Hematology	Hemoglobin, hematocrit, platelet count, white blood cell count (WBC), with differential (neutrophils and bands)
Coagulation*	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	
Electrolytes	Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO_3)
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin

Table 5.2.3: 1 Laboratory tests to be performed (continued)

Category	Parameters
Renal function parameters	Blood urea nitrogen (BUN), creatinine; Creatinine clearance (see Appendix 10.3)
Other	Glucose, albumin
Urinalysis*	The following will be tested at baseline and at the EOT visit: pH, protein, glucose, ketones, blood, leucocytes, nitrite, bilirubin, urobilinogen, and specific gravity. In case of pathological finding further evaluation should be performed and results documented

* tested at Screening and EOT only

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

Electrocardiogram (ECG) is only required at screening. If any additional ECG is performed as part of routine clinical care and clinically significant results are found, this will be documented in accordance with the adverse event process.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination, vital signs, height and weight

A full physical exam must include cardiopulmonary examination, examination of the regional lymph nodes, and 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 at Screening, on Day 1 of each treatment course and at the End of Treatment visit. A symptom-directed examination is to be performed at all other visits.

5.2.5.2 Vital Signs

Vital sign measurements should include blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiratory rate, temperature and measurement of height (in cm, at screening) and body weight (in kg at screening and end of trial). Evaluation of the ECOG PS (see Appendix 10.1) will be performed at the times specified in the Flowchart.

questionnaire that each contains several short measurement tools. In the final GAM,

5.4 APPROPRIATENESS OF MEASUREMENTS

Both CTCAE and criteria used in the study are standard methods. The present trial will use CTCAE version 4.0.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Please refer to the Flowchart and Figure 3.1:1 for the visit schedule. All patients are to adhere to the visit schedule as specified in the Flow Chart.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Please refer to the Flowchart and section 5 for details of the procedures performed at each visit.

6.2.1 Screening period

All patients must have documented *Deletion 19* and/or *L858R EGFR* mutation prior to the signing of the informed consent. All Screening procedures must be performed within 28 days of the first dose of afatinib. Assessments required for study participation which were completed as part of Standard of Care before the patient signed the informed consent may be used for the screening assessments if they were completed within the allowed timeframe. However, presence of *Deletion 19* and/or *L858R* mutation may have been determined prior to the 28-day screening window.

Patients who meet the inclusion criteria and not violate the exclusion criteria at enrolment are allowed to take part in this study.

6.2.2 Treatment periods

All patients will receive continuous daily treatment with afatinib until the criteria for stopping medication are met (Section 3.3.4.1). For administrative purposes, treatment is divided into courses, which are each 4 weeks (28 days) in duration.

During the treatment phase, visits should be performed as scheduled whenever possible, but within the visit window. Deviation in scheduling for administrative purpose would be acceptable upon agreement between the investigator and the sponsor.

6.2.3 End of treatment visit

End of treatment visit should be performed within 7 calendar days after permanent discontinuation of treatment, regardless of the reason. If the decision to discontinue study treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

6.2.4 Follow-up visit

The follow-up (FU) visit is performed 28-35 days after the last dose of afatinib and is primarily to collect follow-up safety information.

6.2.5 Vital Status

For patients that agree to be followed, vital status will be collected every three months until the end of the trial.

6.3 END OF TRIAL

The end of the trial is defined as approximately 12 months after the last patient is entered (starts trial therapy).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This study is an open-label, single arm study in elderly NSCLC patients with common EGFR mutations treated with afatinib.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing will be performed since this is a single arm, uncontrolled study. This is an exploratory trial and all the statistical analyses will be descriptive.

7.3 PLANNED ANALYSES

All patients who receive at least one dose of afatinib will be included in the treated set. The analyses of safety and efficacy will be performed on the treated set.

Corresponding to the three categories of endpoints, there are three categories of analyses in this trial: 1) the primary analysis, 2) secondary analysis, and 3) other analyses. The primary and secondary analyses are safety analyses. The category “Other analyses” includes both safety and efficacy analyses.

7.3.1 Primary analyses

As the primary endpoint is a safety endpoint, these analyses are described in Section 7.3.3.

7.3.2 Secondary and other analyses

7.3.2.1 Secondary analyses

The secondary safety analyses are described in Section 7.3.3.

7.3.3 Safety analyses

Adverse events will be graded according to CTCAE, Version 4.0 (R12-2532).

Adverse events with an onset date from the date of first dose of afatinib until 28 days after the last dose of afatinib will be analyzed as 'on-treatment' AE.

7.3.3.1 Primary analysis

The proportion of patients with AEs leading to dose reduction of afatinib and an exact 95% Clopper-Pearson confidence interval for this proportion will be calculated. Standard

tabulations (arranged by MedDRA SOC and PT) for patients with AEs leading to dose reduction will also be produced.

7.3.3.2 Secondary analyses

Tables that describe the frequency, time to onset, and clinical consequences will be produced for:

- CTCAE grade ≥ 3 diarrhoea
- CTCAE grade ≥3 rash/acne+
- CTCAE grade ≥3 stomatitis+
- CTCAE grade≥ 3 paronychia+

Time to first dose reduction of afatinib caused by AEs is defined as follows:

For patients with AEs leading to dose reduction:
• Time _1st_dose_reduction [days] = date of 1st dose reduction – (date of start treatment)+1
For patients without AEs leading to dose reduction:
• Time _1st_dose _reduction (censored)[days]=date of last intake of afatinib – (date of start treatment) +1

The time to first dose reduction of afatinib caused by AE's will be described by Kaplan-Meier estimates and curve.

7.3.3.3 Other analyses

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 permanent treatment discontinuation
- Drug related 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+
- conjunctivitis+
- paronychia+
- fatigue+

Tables that describe the frequency, intensity, time to onset, and clinical consequences will be produced for the following AEs:

- diarrhea
- rash/acne+
- stomatitis+
- -)(*%6>:$)H

7.3.3.4 Primary laboratory tests

Primary laboratory tests are defined as:

- Low values (-): haemoglobin, total WBC, platelets, neutrophils, lymphocytes, potassium, magnesium, sodium, and GFR
- High values (+): AST, ALT, Alkaline Phosphatase, aPTT, INR, Creatinine, Total Bilirubin, and CPK

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
- 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.

7.3.4 Interim analyses

No interim analyses are planned for this study.

7.4 HANDLING OF MISSING DATA

Handling of missing data will be defined in the TSAP. The category missing will be displayed in the frequency tables only if there are actually missing values.

7.5 RANDOMISATION

No randomization is necessary since this is a single arm study.

7.6 DETERMINATION OF SAMPLE SIZE

In the general population of the LUX-Lung 3 study, approximately 60% of the patients experienced AEs leading to dose reduction of afatinib. For 25 patients and a 60% dose reduction rate (caused by AEs), the 95% CI half-width for the dose reduction rate would be 19.2% based on a normal approximation, resulting in a two-sided, 95% confidence interval of (40.8%, 79.2%). If a lower dose reduction rate of 50% is observed, the resulting 2-sided, 95% confidence interval would be (30.4%, 69.6%). Similarly, if a higher dose reduction rate of 70% is observed the 2-sided, 95% confidence interval would be (52.0%, 88.0%).

Sample size estimates were derived using nQuery Advisor® 7.0 statistical package by Statistical Solutions Ltd.

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 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) (Local Clinical Monitor / Clinical Research Associate) 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 for individual patients will be provided by the sponsor via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. 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. 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 CRA / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 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 currently approved drug label.* 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 Investigator Site File.

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P07-11507 Moy B, Goss PE. Lapatinib-associated toxicity and practical management recommendations. Oncologist 2007;12(7):756-765.

P10-12524 Yang CH, Shih JX, Su WC, Hsia TC, Tsai CM, Ou SHI, et al. A phase II study of afatinib (BIBW 2992) in patients with adenocarcinoma of the lung and activating EGFR/HER1 mutations (LUX-Lung 2). 35th Ann Cong of the European Society for Medical Oncology (ESMO), Milan, 8-12 Oct 2010 (Poster) 2010.

P10-12525 Seiwert TY, Fayette J, Campo JM del, Clement PM, Hitt R, Cupissol D, et al. Updated results of a randomized, open-label phase II study exploring BIBW 2992 versus cetuximab in patients with platinum-refractory metastatic/recurrent head and neck cancer (SCCHN). 35th Ann Cong of the European Society for Medical Oncology (ESMO), Milan, 8-12 Oct 2010 Ann Oncol 2010;21(Suppl 8):VIII316 Abstr 1010PD.

P10-12529 Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, et al. Phase IIb/III trial of afatinib (BIBW 2992) + best supportive care (BSC) vs. placebo + BSC in patients failing 1-2 lines of chemotherapy and erlotinib/gefitinib (LUX-Lung 1). 35th Ann Cong of the European Society for Medical Oncology (ESMO), Milan 8-12 Oct 2010 (Oral Presentation).

P11-09424 Porta C, Osanto S, Ravaud A, Climen MA, Vaishampayan U, White DA et al. Management of adverse events associated with use of everolimus in patients with advance renal cell carcinoma. Eur J Cancer 2011; 47:1287-1298.

P12-03681 Yang JC, Shih JY, Su WC, Hsia TC, Tsai CM, Ou SH, Yu CJ, Chang GC, Ho CL, Sequist LV, Dudek AZ, Shahidi M, Cong XJ, Lorence RM, Yang PC, Miller VA. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol. 2012 May;13(5):539-48. doi: 10.1016/S1470-2045(12)70086-4. Epub 2012 Mar 26.

P13-07382 Sequist LV, Yang JCH, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31 (27), 3327-3334.

P14-00758 Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-

small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014 Feb;15(2):213-22.

R01-0787 Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

R04-0474 Common terminology criteria for adverse events Version 3.0 (CTCAE) (Publish Date: 12 December 2003). http://ctep.cancer.gov/forms/CTCAEv3.pdf; Cancer therapy evaluation program, common terminology criteria for adverse events, Version 3.0, DCTD, NCI, NIH, DHHS, 31 March 2003, Publish Date:12 December 2003.

R05-0867 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, Kooten M van, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L, National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):123-132.

R06-1262 Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. J Clin Oncol 2005;23(11):2556-2568.

R06-1301 Lynch TJ, Adjei AA, Bunn PA, Eisen TG, Engelman J, Goss GD, Haber DA, Heymach JV, Janne PA, Johnson BE, Johnson DH, Lilenbaum RC, Meyerson M, Sandler AB, Sequist LV, Settleman J, Wong KK, Hart CS. Summary statement: novel agents in the treatment of lung cancer: advances in epidermal growth factor receptor-targeted agents. Clin Cancer Res 2006; 12(14)(Suppl): 4365S-4371S.

R06-1302 Engelman JA, Cantley LC. The role of the ErbB family members in non - small cell lung cancers sensitive to epidermal growth factor receptor kinase inhibitors. 3rd Cambridge Conf on Novel Agents in the Treatment of Lung Cancer: Advances in EGFR-Targeted Agents, Cambridge, 23 - 24 Sep 2005 Clin Cancer Res 2006;12(14)(Suppl):4372S-4376S.

R06-1306 Janne PA, Johnson BE. Effect of epidermal growth factor receptor tyrosine kinase domain mutations on the outcome of patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors. 3rd Cambridge Conf on Novel Agents in the Treatment of Lung Cancer: Advances in EGFR-Targeted Agents, Cambridge, 23 - 24 Sep 2005 Clin Cancer Res 2006;12(14)(Suppl):4416S-4420S.

R06-1307 Heymach JV, Nilsson M, Blumenschein G, Papadimitrakopoulou V, Herbst R Epidermal growth factor receptor inhibitors in development for the treatment of non-small cell lung cancer. 3rd Cambridge Conf on Novel Agents in the

Treatment of Lung Cancer: Advances in EGFR-Targeted Agents, Cambridge, 23 - 24 Sep 2005 Clin Cancer Res 2006;12 (14) (Suppl), 4441S - 4445S.

R06-1393 Johnson BE, Janne PA. Epidermal growth factor receptor mutations in patients with non-small cell lung cancer. Cancer Res 2005;65(17):7525-7529.

R06-1394 Doroshow JH. Targeting EGFR in non-small-cell lung cancer. N Engl J Med 2005;353(2):200-202.

R07-1049 Sequist LV, Bell DW, Lynch TJ, Haber DA. Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. J Clin Oncol 2007;25(5), 587-595.

R07-1134 Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res 2006;12 (24), 7232–7241.

R07-4077 Giaccone G, Melosky B, Reck M. Epidermal growth factor receptor inhibitor (EGFRI)-associated rash: a suggested novel management paradigm. A consensus position from the EGFRI dermatologic toxicity forum. ECCO 14, 14th Eur Cancer Conf, Barcelona, 23 - 27 Sep 2007 (Poster) 2007.

R07-4078 Lynch TJ, Kim ES, Eaby B, Garey J, West DP, Lacoutoure ME. Epidermal growth factor inhibitor-associated toxicities: an evolving paradigm in clinical management. Oncologist 2007; 12(5): 610-621.

R08-2899 Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA, McCallum R, Mitchell EP, O'Dorisio TM, Vokes EE, Wadler S. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004;22 (14), 2918–2926.

R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45, 228 – 247.

R09-2250 Wheatley-Price P, Ding K, Seymour L, Clark GM and Shepherd FA. Erlotinib for advanced non-small cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group BR.21. J Clin Oncol 2008;26(14), 2350-2357.

R11-0826 Potthoff K, Hoffheinz R, Hassel JC, Volkenandt M, Lordick F, Hartman JT, et al. Interdisciplinary management of EGFR-inhibitor-induced skin reactions: a German expert opinion. Ann Oncol 2011;22(3):524-535.

R12-2532 Common terminology criteria for adverse events v4.0 (CTCAE) (publish date: May 28, 2009; v4.03: June 14, 2010). Website:

www.oncology.tv/.../NationalCancerInstituteUpdatesCTCAEtov403.aspx ; Common Terminology Criteria for Adverse Events, Version 4.03. , NCI, NIH, DHHS, Publish date: May 28, 2009; 4.0, Publish Date: June 14,2010 4.03.

R12-4000 Petrelli F, Borgonovo K, Cabiddu M, Barni S. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer 2012;13 (2), 107 – 114.

R12-4710 American Joint Committee on Cancer (AJCC). Lung cancer staging. http://www.cancerstaging.org/staging/posters/lung12x15.pdf (access date: 23 October 2012) ; (Cancer Staging Poster Series) American Joint Committee on Cancer (AJCC) 2009

R14-1350 Merimsky O, Cheng CK, Au JSK, Pawel J von, Reck M
Efficacy and safety of first-line erlotinib in elderly patients with advanced non-small cell lung cancer. Oncol Rep 2012; 28, 721–727.

R14-1781 Meoni G, Cecere FL, Lucherini E, Di Costanzo F. Medical treatment of advanced non-small cell lung cancer in elderly patients: a review of the role of chemotherapy and targeted agents. J Geriatr Oncol 2013;4(3), 282-290.

R14-1839 Lewis JH, Kilgore ML et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21(7), 1383-1389.

R14-1840 Hutchins LF, Unger JM, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. NEJM 1999;341:20161-7.

R14-2119 Siegelin MD, Borczuk AC. Epidermal growth factor receptor mutations in lung adenocarcinoma. Lab Invest. 2014 Feb; 94(2):129-37.

R15-0770 Kurishima K. Erlotinib for elderly patients with non-small-cell lung cancer: Subset analysis from a population-based observational study by the Ibaraki Thoracic Integrative (POSITIVE) Research Group. Molecular and Clinical Oncology 2013; 1:8928-832.

R15-0802 Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29(25):3457-65.

9.2 UNPUBLISHED REFERENCES

c01802941-09 Investigator’s brochure. Afatinib (BIBW 2992). Version 15. 03 Jul 2014.

U03-3218-13 . Investigator's Brochure BIBW 2992; Indication: Oral Treatment of Cancer. Revised 04 July 2013

U07-3128-02 A Phase I open-label dose escalation study of continuous once-daily oral treatment with BIBW 2992 in patients with advanced solid tumours. Trial 1200.4. 30March 2007. Revised 23 April 2010.

U08-1023-02 . A Phase I open-label dose escalation study of continuous once-daily oral treatment with BIBW 2992 in patients with advanced solid tumors. Trial 1200.3. 30 January 2008. Revised 25 February 2010.

<E7IJ7AK7E P:)&. DD,1DD)%'*#$R."B "*;,5. I,5$%"($)5*+TDTU 9VV9-5;&,.&' &;--*('$?. >)(. 3TO=@.(&;& -5)>.,* -5;&TO= $%%*%&#)55 >.55 5;%/ >)%>.(-)'$.%'& +)$5$%/ .(5*'$%$, *(/.+$'$%$3W<XW;%/E@E0 Y.>.#,.(97EE8

<EEIJGAA7E W<XW;%/9^! -:)&. DD&$%/5.)(# '($)5*+TDTU 9VV9$%%*%&#)55>.555;%/>)%>.(-)'$.%'&C$': Z_`S)>'$?)'$%/#;')'$*%&87GY.>.#,.(97EE8

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1.0
Date of CTP revision		21DEC215
EudraCT number		
BI Trial number		1200.209
BI Investigational Product(s)		afatinib
Title of protocol		
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		Protocol Synopsis – Test Product Dose
Description of change		Starting dose 30mg daily
Rationale for change		Consistent with clinical practice in vulnerable population
Section to be changed		Protocol Synopsis – Efficacy Endpoints
Description of change		
Rationale for change		
Section to be changed		Flow Chart
Description of change		Vital Status added to assessments
Rationale for change		
Section to be changed	3.1	Overall Trial Design and Plan
Description of change		Starting dose 30mg daily for eligible patients
Rationale for change		All patients will start at 30 mg daily
Section to be changed	3.2	Discussion of Trial Design, Including the Choice of Treatment

Number of global amendment		1.0
Description of change		Starting dose 30mg daily for eligible patients
Rationale for change		All patients will start at 30 mg daily
Section to be changed	3.3.3	Exclusion Criteria #10
Description of change		Added additional language “Pathologically documented meningeal carcinomatosis (i.e. cytology (+) lumbar puncture ; radiology reports alone raising this as a possibility, in the absence of true symptomatology, would not constitute an exclusion)”
Rationale for change		Clarification on definition of Meningeal Carcinomatosis
Section to be changed	3.3.3	Exclusion #12
Description of change		Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 2 years and is considered to be cured
Rationale for change		Changed number of years in remission from 3 to 2 years
Section to be changed	3.3.4	Removal of patients from therapy or assessments
Description of change		Patients that develop brain metastasis during the study may continue on trial treatment if there is lack of progression in other areas.
Rationale for change		Changed to be consistent with current NCCN guidelines
Section to be changed	4.1	Treatments to be Administered
Description of change		Dose strengths 20mg and 30mg tablets
Rationale for change		Starting dose changed to 30mg daily
Section to be changed	4.1.3	Selection of doses in the trial
Description of change		Starting dose 30mg daily for eligible patients. The 30 mg dose of afatinib in this vulnerable patient population (elderly) reflects actual clinical practice.
Rationale for change		All patients will start at 30 mg daily
Section to be changed	4.1.4	Drug assignment and administration of doses for each patient
Description of change		Starting dose 30mg daily for eligible patients

Number of global amendment		1.0
Rationale for change		All patients will start at 30 mg daily
Section to be changed	4.1.6	Packaging, Labeling and Re-supply
Description of change		Available dosage strengths will be 20 and 30mg
Rationale for change		All patients will start at 30 mg daily

Section to be changed	5.2.2	Assessments of safety
Description of change		The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded in the eCRF.
Rationale for change		Change in CTCAE version from 3.0 to 4.0
Section to be changed	5.2.2.1	Worsening of the underlying disease or other pre-existing conditions
Description of change		If progressive disease occurs and is associated with symptoms, the term "Progressive Disease" should not be reported as (S)AE. , however, signs Signs and symptoms of progressive disease will NOT be reported as an (S)AE (if applicable).
Rationale for change		Clarification on how PD is captured in the data set
Section to be changed	6.2.5	Vital Status Assessments
Description of change		Vital Status to be collected q3 months until the end of the trial.
Rationale for change		

Section to be changed	7.3.3	Safety Analysis
Description of change		CTC AE Version 4.0

Number of global amendment		1.0
Rationale for change		Change in CTC AE version from 3.0 to 4.0

Number of global amendment		2.0
Date of CTP revision		15 FEB 2018
EudraCT number		N/A
BI Trial number		1200.209
BI Investigational Product(s)		Afatinib
Title of protocol		A Single Arm Phase IV Study of Afatinib in Elderly Patients with recurrent or Stage IV Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have Common Epidermal Growth Factor Receptor (EGFR) mutations (Exon 19 Deletions or Exon 21 L858R Substitution Mutations)
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 and Protocol Synopsis
Description of change		Trial Clinical Monitor
Rationale for change		Change in personnel
Section to be changed		Protocol Synopsis
Description of change		Number of patients
Rationale for change		Number of anticipated patients changed from approximately 50 to approximately 25 given slow recruitment and identification of new potential patients.
Section to be changed		Flow Chart
Description of change		AE collection
Rationale for change		Clarification that AE collection should

Number of global amendment		2.0
		occur during screening visit and during followup for vital status to be consistent with CTP section 5.2.2.2 and Flowchart footnote n.
Section to be changed		Flowchart
Description of change		Footnote n
Rationale for change		Clarification that AEs are to be collected until 28 days after last trial drug administration and that it no longer required to collect AEs related to trial design.
Section to be changed	3.1	Overall Trial Design and Plan
Description of change		Number of patients
Rationale for change		Number of anticipated patients changed from approximately 50 to approximately 25 given slow recruitment and identification of new potential patients.
Section to be changed	3.3	Selection of Trial Population
Description of change		Number of patients
Rationale for change		Number of anticipated patients changed from approximately 50 to approximately 25 given slow recruitment and identification of new potential patients. Reference to section 3.3.4.2 added.
Section to be changed	3.3	Selection of Trial Population
Description of change		Number of patients enrolled per site
Rationale for change		Number of anticipated patients changed from approximately 3-4 patients per site to approximately 1-2 patients per site.
Section to be changed	4.1.2	Method of assigning patients to treatment groups
Description of change		Number of patients
Rationale for change		Number of anticipated patients changed from approximately 50 to approximately 25 given slow recruitment and identification of new potential patients.
Section to be changed	3.3.2	Inclusion Criteria
Description of change		Inclusion Criteria #2 updated
Rationale for change		Text clarified due to typographical error in previous amendment
Section to be changed	3.3.2	Inclusion Criteria
Description of change		Inclusion Criteria #5 updated
Rationale for change		Text clarified due to typographical error to denote that AST and ALT are to meet defined criteria.

Number of global amendment		2.0
Section to be changed	5.2.2.1	Definitions of adverse events
Description of change		Clarification that worsening will be recorded as an (S)AE in the eCRF and SAE form (if applicable).
Rationale for change		Addition of SAE form for SAE reporting (if applicable).
Section to be changed	5.2.2.2	AE and SAE Reporting
Description of change		Miscellaneous clarifications: 1) Removal of AESI 2) Clarification of reporting period 3) Removal of electronic submission process for SAE
Rationale for change		Reference to AESI removed as no AESIs are defined for the trial. Clarification that events are to be collected until 28 days after last administration of trial drug. Clarification of requirements for reporting during followup for vital status.Electronic submission process for SAE collection is no longer in effect.

Section to be changed	7.6	Determination of Sample Size
Description of change		Number of patients
Rationale for change		Number of anticipated patients changed from approximately 50 to approximately 25, and sample size has been clarified.

APPROVAL / SIGNATURE PAGE

Document Number: c02364424 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: A Single Arm Phase IV Study of Afatinib in Elderly Patients with recurrent or Stage IV Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have Common Epidermal Growth Factor Receptor (EGFR) mutations (Exon 19 Deletions or Exon 21 L858R Substitution Mutations)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor		22 Feb 2018 17:03 CET
Author-Trial Statistician		22 Feb 2018 18:36 CET
Approval–Clinical Monitor		27 Feb 2018 21:50 CET
Approval-Team Member Medical Affairs		27 Feb 2018 22:30 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**