Clinical Trial Protocol

Doc. No.: c02156918-02

EudraCT No.:	2014-001077-14
BI Trial No.:	1200.217
BI Investigational Product(s):	Giotrif® / Gilotrif™ (Afatinib)
Title:	An open label, single-arm phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an EGFR mutation (Del19 or L858R) who have failed first-line treatment with platinum-based chemotherapy
Clinical Phase:	IV
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Co-ordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol
Version and Date:	**Version:** 1 **Date:** 10 April 2014

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif®/ Gilotrif™			
Name of active ingredient: Afatinib			
Protocol date: 10 Apr 2014	**Trial number:** 1200.217		**Revision date:**
Title of trial:	An open label, single-arm phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an EGFR mutation (Del19 or L858R) who have failed first-line treatment with platinum-based chemotherapy.		
Co-ordinating Investigator:	[redacted]		
Trial site(s):	Multi-centre trial		
Clinical phase:	IV		
Objective(s):	To assess the efficacy and safety of afatinib as second line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring a common EGFR mutation who have failed first-line platinum-based chemotherapy and to demonstrate that the efficacy and safety are comparable to the results seen in previous trials (P12-03681, P13-07382).		
Methodology:	Single-arm, open-label		
No. of patients: **total entered:** **each treatment:**	 60 N/A		
Diagnosis :	Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung harbouring an EGFR mutation.		
Main criteria for inclusion:	• Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. • Documented common EGFR mutation (L858R and/or Deletion 19). • Measureable disease according to RECIST 1.1. • Radiologically confirmed progression or recurrence of disease during or following first-line therapy with a platinum-based chemotherapy regimen. • Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Giotrif®/ Gilotrif™			
Name of active ingredient: Afatinib			
Protocol date: 10 Apr 2014	**Trial number:** 1200.217		**Revision date:**

Test product(s):	Afatinib
dose:	Starting dose 40mg/day
mode of admin.:	Oral, once daily continuous
Comparator products:	Not applicable
dose:	Not applicable
mode of admin.:	Not applicable
Duration of treatment:	Continuous treatment in the absence of disease progression or unacceptable treatment-related adverse events.
Criteria for efficacy:	Objective tumour response (complete response (CR), partial response (PR)), progression-free survival (PFS) and disease control (CR, PR and stable disease (SD)) according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1).
Criteria for safety:	Intensity and incidence of adverse events, graded according to US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 3.0).
Statistical methods:	Descriptive statistics will be provided for efficacy and safety evaluation.

FLOW CHART

	Screening		Treatment courses***		End of Treatment****	Follow-up	Follow-up progression *****
Visit abbreviation	**SV1***	**SV2****	**CxV1[a]**	**C1V2**	**EOT**	**FU**	**FUPDx[b]**
Days	**Any time before SV2**	**Up to 28 days before treatment**	**Day 1 (± 2 days)**	**Course 1 Day 15 (± 2 days)**	**0-14 days after permanent discontinuation of afatinib**	**28-35 days after discontinuation of afatinib**	**Every 60 days after follow-up (± 15 days)**
Tissue analysis consent	x[1]						
EGFR mutation analysis	x[1]						
Informed consent (trial participation)		x					
Demographics		x					
Medical history		x					
Physical examination		x	x		x		
Vital signs		x	x	x	x		
Height		x					
Weight		x	x		x		
ECOG performance status		x	x	x	x		
Safety laboratory tests		x	x		x		
Serum pregnancy test		x					
Review of incl/exclusion criteria		x					
Review medication compliance			x		x		
Dispense medication			x				
Administration of afatinib			Continuous				
Adverse events	x[2]	x	x	x	x	x	x[3]
Concomitant therapy		x	x	x	x	x[4]	
Tumour assessment[5]		x	Every 8 weeks (±7 days) from start of treatment until documented progression[5]				
Termination of trial medication					x		
Trial completion timepoint						x[6]	x[6]
Collect patient status information							x[7]

*Screening visit 1 is not required if the patient has already tested positive for a common EGFR mutation.
**Only patients who have tested positive for a common EGFR mutation should proceed to screening visit 2. Procedures which have been performed as part of routine clinical care do not need to be repeated at screening visit 2 if they are within the allowed time window (28 days prior to treatment).
*** All treatment courses are 28 days in duration. Patients may continue on treatment for unlimited courses, until criteria for stopping medication are met (see section 3.3.4)
****If the decision to permanently discontinue afatinib is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.
***** Follow-up progression is only for patients who have no documented disease progression at the follow-up visit.
[a] The visit is performed on the first day of each 28-day course and x is the number of the treatment course
[b] x is the number of the follow-up PD assessment

1 Not required if the patient has already tested positive for a common EGFR mutation and a written copy of the result is available.
2 Between tissue analysis consent and trial informed consent, AEs will only be reported if related to trial procedures.
3 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 or design.
4 After end of treatment, concomitant therapies will only be recorded if indicated for the treatment of an AE (see section 4.2).
5 Tumour assessment should be performed every 8 weeks (every 12 weeks after week 56) calculated from start of treatment until documented progression. If treatment continues after progression, tumour assessment should continue according to the schedule until the decision to stop treatment. In the event of early discontinuation or an interruption/delay to treatment, the tumour assessment schedule should not be changed. See section 5.1.2 for further details.
6 Trial completion occurs at the follow-up visit, unless progression has not been documented, in which case tumour assessment should continue according to the trial schedule until progression or start of further treatment and the trial completion date is the date on which progression was documented or further anti-cancer treatment commenced.
7 Clinical assessments should be performed in accordance with institution practice; trial specific assessments are not required. Status information will include documentation of start of further treatment and/or clinical progression.

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ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase
AUC	Area under the Concentration-time curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
CA	Competent Authority
CI	Confidence Interval
CK	Creatinine Kinase
CML	Local Clinical Monitor
CPK	Creatinine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
EudraCT	European Clinical Trials Database
FU	Follow Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HER	Human Epidermal Growth Factor Receptor
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INR	International Normalised Ratio
IRB	Institutional Review Board
ISF	Investigator Site File

IUD	Intrauterine device
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LD	Longest Diameter
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
OPU	Operative Unit
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PTT	Partial Thromboplastin Time
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
SAE	Serious Adverse Event
SD	Stable Disease
SoD	Sum of Diameters
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Screening Visit
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
WBC	White Blood Cell
WOCBP	Woman of Child Bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

A subset of patients with non-small cell lung cancer (NSCLC) have a mutation in the tumour Epidermal Growth Factor Receptor (EGFR) gene which drives the growth of the tumour.

Standard first-line treatment for patients with locally advanced or metastatic NSCLC harbouring an activating EGFR mutation is with agents targeting EGFR Tyrosine Kinase, such as EGFR Tyrosine Kinase Inhibitors (TKI) (gefitinib/erlotinib) or ErbB receptor family blocker afatinib. Despite this, many patients receive first-line treatment with chemotherapy. The purpose of this trial is to evaluate the efficacy and safety of afatinib as second-line treatment in this latter group of patients.

1.2 DRUG PROFILE

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

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.

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. The pharmacokinetic (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-glycoprotein (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 $AUC_{0-\infty}$ and C_{max} 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 ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators.

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

Two phase I open label dose-escalation studies determined the Maximum Tolerated Dose (MTD) with continuous dosing of afatinib in patients with advanced solid tumours at 40mg and 50mg daily, respectively [U07-3128-02 and 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, P13-03658 and P13-03659].

Afatinib is approved in many countries for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation. Previous studies with afatinib indicate that it is efficacious as a second-line therapy in patients who have received first line chemotherapy. In a phase II study (P12-03681), 68 patients with EGFR mutations received second-line therapy with afatinib (starting dose 40mg or 50mg). Of these, 41 patients (60%) achieved an objective response based on investigator assessment, and 39 (57%) by independent review. Median progression-free survival (PFS) was 8.0 months by independent review and 10.5 months by investigator assessment, with a median overall survival of 23.3 months.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is being conducted at the request of the European Medicines Agency (EMA) as a condition of their favourable approval of afatinib for treatment of EGFR TKI-naïve patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

The European Medicines Agency (EMA) recognised that the main biological predictor of response to afatinib is the presence of an activating EGFR mutation in the tumour, which takes precedence over the line of treatment in which afatinib is being used. As the submission package included limited safety and efficacy data for afatinib at a daily dose of 40mg in the EGFR mutation-positive chemotherapy pre-treated population (P12-03681), this study has been requested to confirm the efficacy and safety of afatinib with a starting dose of 40mg in the second line (post-chemotherapy) setting in a larger cohort of patients.

2.2 TRIAL OBJECTIVES

The objectives of this single-arm, open-label trial are to assess the efficacy and safety of afatinib as second line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring a common EGFR mutation who have failed first-line platinum-based chemotherapy and to demonstrate that the efficacy and safety are comparable to the results seen in previous trials (P12-03681, P13-07382). The primary and secondary endpoints are documented in section 5.

2.3 BENEFIT - RISK ASSESSMENT

According to the evolving global diagnostic and treatment standard, patients with adenocarcinoma of the lung should undergo testing of their tumour to determine the presence of EGFR mutations which in turn determines their treatment strategy. Patients with EGFR mutation positive disease should receive first-line treatment with an agent targeting EGFR (erlotinib, gefitinib or afatinib). Where first-line treatment with an EGFR TKI is not possible, patients become eligible to receive the targeted therapy as their second-line treatment, after initial chemotherapy treatment.

A previous phase II study (P12-03681) has shown that afatinib at a starting dose of 40mg or 50mg is efficacious in this setting, with 57% of patients achieving an objective response (by independent review), median progression-free survival (PFS) of 8.0 months (by independent review) and median overall survival of 23.3 months. The demonstrated activity exceeded the historical performance of chemotherapy agents (docetaxel, pemetrexed) in the second line treatment of unselected NSCLC population (R05-1054) and compared favorably to the limited historical data available for EGFR TKIs in second line treatment of EGFR mutation positive patients (R11-1316, R08-5614).

The side effects of afatinib are well documented (R13-4780) and are manageable with proactive intervention and dose reduction when indicated. The most common side effects are gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects (including paronychia), epistaxis, fatigue and decreased appetite. The standard guidance for management of these side effects is followed in this trial (section 4.1.4.1, section 4.2) and the drug is expected to be well tolerated. Interstitial lung disease (ILD) has been observed during treatment with afatinib but is uncommon (0.7% of treated patients, R13-4780). Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms will be performed to exclude ILD (see section 4.2.1).

Regular and frequent assessment of clinical benefit throughout the trial will ensure that any patient not deriving clinical benefit will be withdrawn from the trial treatment.

Considering the expected efficacy of afatinib in this group of patients, and the expected side effects, it is anticipated that the benefits of second-line therapy with afatinib will outweigh the risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a single-arm open-label phase IV trial for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring a common EGFR mutation.

The diagram below illustrates the trial design.

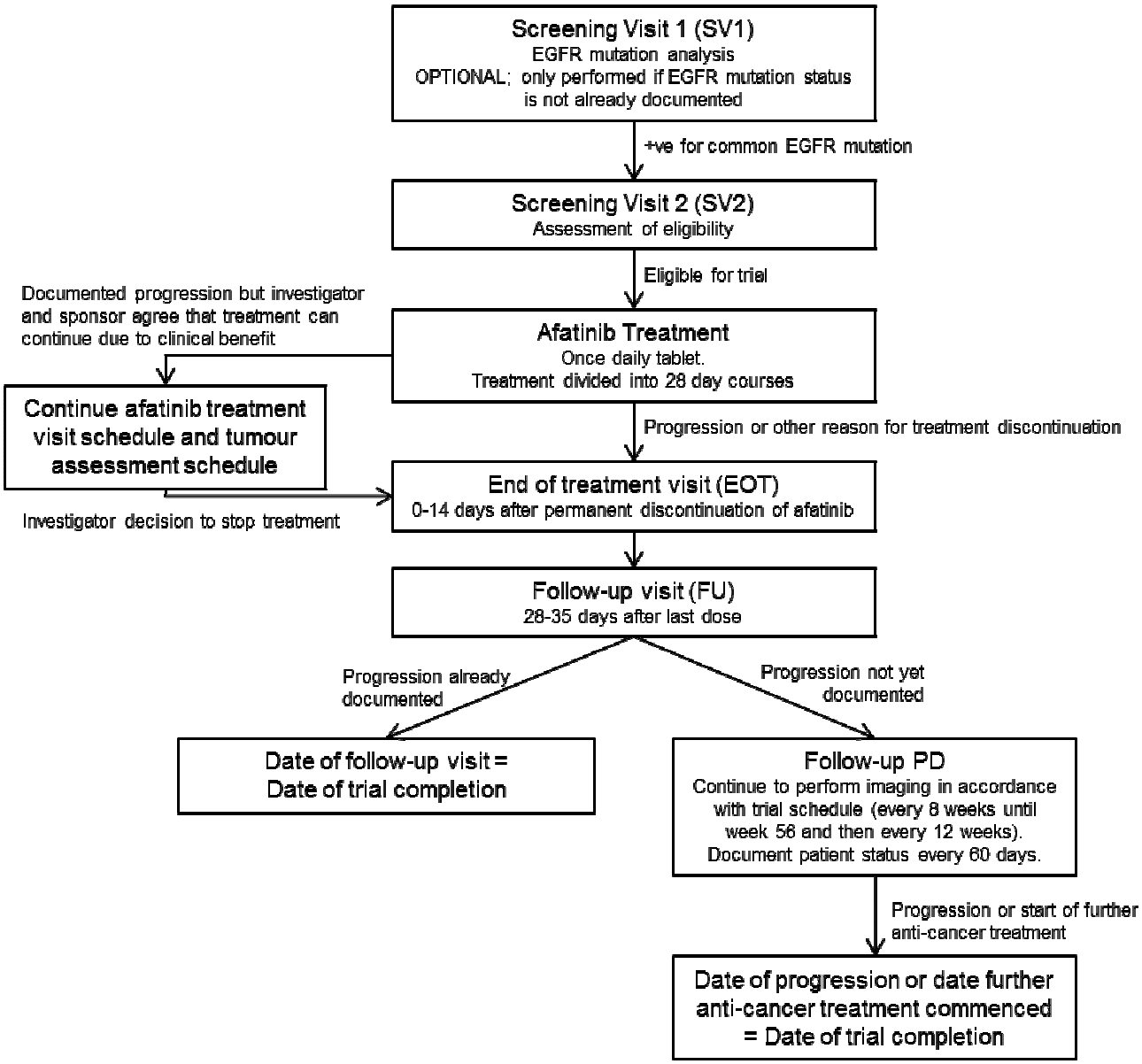

Figure 3.1.1 Trial design

3.1.1 Administrative structure of the trial

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. The trial will be performed by investigators experienced in the treatment of non-small cell lung cancer (NSCLC).

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

Boehringer Ingelheim will appoint CROs for special services such as central laboratory analyses (testing for EGFR mutation), provision of Interactive Voice/Web Response System (IVRS/IWRS) and trial medication logistics.

All trial relevant documentation will be stored in the clinical trial master file (CTMF) 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(S)

This is an exploratory study to assess the efficacy and safety of afatinib given as second-line treatment after chemotherapy and confirm previously reported results using a starting dose of 40mg afatinib. All patients will receive the same treatment and therefore the trial is open-label.

3.3 SELECTION OF TRIAL POPULATION

The trial will be conducted in multiple centres worldwide. 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 investigational drug or not.

The trial explores the use of afatinib as a second-line therapy after first-line chemotherapy and therefore the inclusion/exclusion criteria have been designed to ensure that the trial population reflects this, whilst also accounting for variations in first-line therapy.

Patients who do not have an EGFR test result available will be asked to sign consent to tissue analysis and a sample of their tumour will be sent for EGFR testing. There are no inclusion and exclusion criteria for tissue analysis except that the patient must have tissue available for analysis and must be expected, as far as is possible to determine, to meet all inclusion and exclusion criteria at some point in the future.

The study will include patients who have one (or both) of the most common EGFR mutations; L858R or Deletion 19, with no other documented mutations of EGFR. Patients with less common mutations are excluded because the group of patients with these mutations is expected to be too small for meaningful analysis.

3.3.1 Main diagnosis for study entry

The study will recruit patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring a common EGFR mutation. Patients must have experienced disease progression during or after completion of first-line platinum-based chemotherapy.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria are not eligible for study participation and are not eligible to receive study drug.

3.3.2 Inclusion criteria

1. Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.
2. Documented EGFR mutation (L858R and/or Deletion 19) with no other known EGFR mutation.
3. Measureable disease according to RECIST 1.1 (R09-0262).
4. Radiologically confirmed progression or recurrence of disease during or following first-line therapy with a platinum-based chemotherapy regimen.*
5. Age ≥18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.
7. Adequate organ function, defined as all of the following:
   - Absolute neutrophil count (ANC) > 1500 / mm^3.
   - Platelet count >75,000 / mm^3.
   - Estimated creatinine clearance > 45ml / min. Refer to APPENDIX 10.1.
   - Total Bilirubin < 1.5 times upper limit of institution normal.
   - Aspartate amino transferase (AST) and alanine amino transferase (ALT) < three times the upper limit of institution normal (ULN) (if related to liver metastases < five times ULN).
8. Recovered from any previous therapy-related toxicity to ≤CTCAE Grade 1 at study entry (except for alopecia and stable sensory neuropathy which must be ≤CTCAE Grade 2).
9. Life expectancy of at least three months.
10. Written informed consent that is consistent with ICH-GCP guidelines.

* Additional guidance on prior therapy;

- Patients may have received maintenance chemotherapy (continuous or switch maintenance) following completion of 1st line platinum-based chemotherapy.

- Patients who previously received platinum-based chemoradiotherapy and had a recurrence and evidence of stage IIIB-IV disease within 1 year of completing chemoradiotherapy will be eligible. Those patients who have received 2-3 cycles of further consolidation chemotherapy with the same or different agents will also be eligible if they progressed within 1 year of completion of consolidation treatment.

- Patients who received adjuvant/ neoadjuvant platinum-based chemotherapy and had a recurrence and evidence of stage IIIB-IV disease within 1 year of completing chemotherapy will be eligible.

- Patients who progress more than 1 year after completing chemoradiotherapy, adjuvant or neoadjuvant treatment may be suitable for re-challenge with platinum-based therapy as a first-line treatment for advanced disease and thus are ineligible for this trial. However, if in the opinion of the investigator such patient is eligible to receive second-line treatment, their participation in the study can be discussed on a case-by-case basis with the BI clinical monitor.

3.3.3 Exclusion criteria

1. More than one line of prior therapy for disease.
    - Radiotherapy alone is not counted as a line of therapy.
    - Radiosensitisers and/or intrapleural administration of anti-cancer agents are not counted as a line of therapy.
2. Previously received less than 3 cycles of platinum-based chemotherapy due to toxicity and/or intolerance of treatment.
3. Previous treatment with any EGFR targeting TKI or antibody.
4. Chemotherapy, biological therapy or investigational agents within three weeks prior to the start of study treatment.
5. Hormonal treatment within two weeks prior to start of study treatment.
6. Radiotherapy within 4 weeks prior to study treatment, except as follows:

    i.) Palliative radiation to target organs other than chest is allowed up to 2 weeks prior to study treatment.

    ii.) Single dose palliative treatment for symptomatic metastasis which is outside the above allowance may be allowed but must be discussed with sponsor prior to enrolling.
7. Major surgery within 4 weeks before starting study treatment or surgery scheduled during the projected course of the study.
8. Known hypersensitivity to afatinib or the excipients of afatinib.
9. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3,

unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to study treatment.

10. Women of child-bearing potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use adequate contraception prior to study entry, for the duration of study participation and for at least 28 days after treatment has ended. Adequate methods of contraception and Women of Child-Bearing Potential are described in Section 4.2.2.3.
11. Female patients of childbearing potential (see Section 4.2.2.3) who are nursing or pregnant or do not agree to submit to pregnancy testing required by this protocol.
12. 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 efficacy and safety of the test drug.
13. Previous or concomitant malignancies at other sites, except;
    a) effectively treated non-melanoma skin cancers
    b) effectively treated carcinoma in situ of the cervix
    c) effectively treated ductal carcinoma in situ
    d) other effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.
14. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2 that cannot be stopped for the duration of trial participation.
15. Known pre-existing interstitial lung disease
16. 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 diarrhea, malabsorption).
17. 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.
18. Prior participation in an afatinib clinical study, even if not assigned to afatinib treatment.
19. Meningeal carcinomatosis.
20. Presence or history of brain or subdural metastases, unless patient has completed local therapy and has discontinued the use of corticosteroids or has been on stable dose of corticosteroids 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.

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.

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

A patient is to discontinue study medication if they:

1 Withdraw consent to further study treatment.

2 Have radiologic (or clinical) documentation of progressive disease (section 5.1.2) unless the investigator agrees with the sponsor that the patient may continue treatment beyond progression due to clinical benefit (section 6.1.1).

3 Become pregnant (section 4.2.2.3).

4 Are diagnosed with interstitial lung disease (ILD).

5 Are required to stop treatment due to adverse events as described in section 4.1.4.

6 Have 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.

The EOT visit should be performed 0-14 days after permanent discontinuation of treatment and wherever possible patients should be encouraged to return for a follow-up visit 28-35 days after discontinuation of treatment. Patients who have not progressed prior to the follow-up visit should be encouraged to return for regular follow-up assessments until progression or start of further treatment.

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

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

After completion of the primary efficacy analysis, the sponsor may remove patients from the study treatment if the patient has access to afatinib through marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation. The cost of any ongoing supply of afatinib will be incurred by the sponsor. If a patient is removed from the study treatment, an end of treatment and follow-up visit will be performed to ensure all adverse events are followed up and patients with no documented progression will then enter the Follow-up PD phase. If the sponsor decides that sufficient PFS data has already been collected at the point of transfer, patients will have a follow-up visit but will not enter the Follow-up PD phase (see also 3.3.4.2 and 8.6).

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, the protocol, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.
- The primary efficacy analysis has been completed, sufficient PFS data has been collected, and all patients have either ended study treatment or are eligible to receive afatinib under the conditions listed in section 3.3.4.1.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Eligible patients will receive once daily treatment with afatinib until progression or until other criteria for stopping medication are met (see section 4.1.4).

4.1.1 Identity of BI investigational product and comparator product(s)

Substance (INN)	**Afatinib**
Brand name:	Giotrif®/ Gilotrif™
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	20, 30 and 40mg 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

Patients who have given their written informed consent will be enrolled sequentially on a first come first enrolled basis and will be registered in IVRS/IWRS. Patients who meet all eligibility criteria will be entered into the study and the start of treatment will be registered in IVRS/IWRS. The trial will continue to enrol patients until the goal of approximately 60 entered into the study is reached. Following registration, patients should begin treatment within 2 days.

4.1.3 Selection of doses in the trial

The starting dose and the dose reduction schedule are based on the current summary of product characteristics (SPC) for afatinib (R13-4780). 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 40 mg, continuously, until the development of progressive disease (unless treatment beyond progression has been agreed) or until other criteria for stopping medication are met. The dose of afatinib must be reduced if certain adverse events occur (see sections 4.1.4.1).

The medication should be taken at approximately the same time each day without food (at least one hour before a meal and at least three hours after a meal).

Missed doses of afatinib can be made up during the same day. 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.

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment course. For administrative purposes, a treatment course is defined as 28 days. Treatment will start when the patient takes the first dose of medication and will stop when the patient is diagnosed with disease progression (unless treatment beyond progression has been agreed) or for any reason detailed in section 3.3.4. Study drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

A new bottle of medication will be dispensed on day 1 of each course, regardless of the number of tablets remaining in the bottle from the previous course. The patient will initially receive one bottle of 40mg tablets and in the event that dose reduction is necessary the patient will return to the clinic and new medication will be dispensed.

4.1.4.1 Dose reduction for afatinib

Treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 4.1.4.1: 1 which is based on the SPC for afatinib (R13-4780). Should the guidance in the SPC change during the study, the latest SPC will take precedence. 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, nausea and vomiting or rash should be managed early and proactively as described in Section 4.2.

Table 4.1.4.1: 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 ≥ 3	Interrupt until Grade 0/1[b]	Resume treatment with dose reduction by 10mg decrements[d]

[a] NCI Common Terminology Criteria for Adverse Events v3.0 (R04-0474)

[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.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable

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 ISF.

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 20 mg, 30 mg and 40 mg.

Trial drug bottles will have unique medication numbers which will be used for tracking purposes only.

4.1.7 Storage conditions

Drug supplies, which will be provided by the sponsor and/or a CRO appointed by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. 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 receive the investigational drugs delivered by the sponsor 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 or immediately imminent signing of the clinical trial protocol,
- availability of the proof of a medical licence for the principal investigator (if applicable).

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

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator or delegate will maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or delegate 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 treatment(s)

Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. Potential adverse events should be treated symptomatically. Common adverse events of treatment with afatinib 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 below.

Concomitant 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 to trial participation (SV2), and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after complete wound healing. If 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.

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 interstitial lung disease (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.

4.2.1.1 Management of diarrhoea and hydration status following treatment with afatinib

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and require treatment modification or discontinuation, so early management is essential (Table 4.2.1.1: 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 diarrhoea.

Table 4.2.1.1: 1 Grade specific treatment recommendations for afatinib related diarrhoea

Severity (CTCAE Grading)	**Description**	**Intervention concerning afatinib treatment**	**Specific intervention**
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; 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, diarrhoea 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.

4.2.1.2 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 4.2.1.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.1.2: 2. For dose adjustment of afatinib refer to Table 4.1.4.1:1.

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 4.2.1.2: 1 General recommendations 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 4.2.1.2: 2 Grade specific treatment recommendations 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 body surface area (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

Table 4.2.1.2: 2 Grade specific treatment recommendations of skin reactions to afatinib (continued)

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 4.1.4.1: 1		

4.2.1.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.1.3:1. For dose adjustment refer to Section 4.1.4 and for restrictions on concomitant therapies refer to Sections 4.2.2 and 10.2.

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 4.2.1.3:1 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from P11-09424)

Table 4.2.1.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

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

4.2.2 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.

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 4.2.1.2.

4.2.2.3 Women of Child-Bearing Potential & Pregnancy Prevention

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

All other patients (male or female) are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until end of trial participation or 28 days after last dose of trial medication, whichever is later).

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 using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

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

4.3 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 at the end of each 28 day period to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each 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.

The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient’s safety or render study results for this patient unacceptable.

Patients repeatedly missing scheduled on-treatment study visits, unless due to exceptional circumstances, 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.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoint(s) of efficacy

The efficacy endpoints will be assessed at the time points specified in the flowchart. The time frame will last from start of treatment until the trial completion timepoint.

The primary endpoint will be objective tumour response (Complete response (CR), Partial Response (PR)) according to RECIST 1.1 (R09-0262).

The secondary endpoints are;

- Progression free survival (PFS) according to RECIST 1.1 (R09-0262).
- Disease control (CR, PR, Stable Disease (SD)) according to RECIST 1.1 (R09-0262).

5.1.2 Assessment of efficacy

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) (R09-0262). Tumour response will be assessed by investigator review.

See APPENDIX 10.3, RECIST 1.1 Criteria for details on lesion measurements and response assessment.

Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at every tumour assessment. Assessment will be performed every 8 weeks until week 56 and then every 12 weeks calculated from start of treatment until documented progression. In the event of early discontinuation or an interruption/delay to treatment, the tumour assessment schedule should not be changed. If treatment continues after progression, tumour assessment should continue according to the schedule until the decision to stop treatment.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (R04-0474). Safety is an ‘other’ endpoint.

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 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 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.

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

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

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

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

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

Protocol-specified adverse events of special interest (AESIs)

There are no Protocol-specified Adverse Events of Special Interest for this study.

Expected Adverse Events

For expected (listed) AEs of afatinib, see the current version of the IB (U03-3218).

5.2.2.2 Adverse event and serious adverse event reporting

The Residual Effect Period (REP) for afatinib is 28 days. All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent to trial participation (SV2) onwards through the residual effect period (REP) (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 CRF(s) / 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.

All events reported within 28 days after the last trial medication will be considered on drug. All adverse events will be reported up until 28 days after the last dose of trial medication. If a patient continues on the trial after this point (e.g. for follow-up PD) the investigator should report any SAEs/AEs which are considered related to trial treatment or design. 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.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
From signing of tissue analysis consent (SV1) to signing of informed consent to trial participation (SV2)	Report only AEs and SAEs which are considered related to trial procedures.
For screen failures; From signing of informed consent to trial participation (SV2) to the timepoint where ineligibility is confirmed.	Report all AEs and SAEs. This includes all deaths.
For treated patients; From signing of informed consent to trial participation (SV2) to the end of the REP (28 days after last trial drug administration).	Report all AEs and SAEs regardless of relatedness. This includes all deaths.
After the end of the REP (>28 days after last trial drug administration) until the patient completes the study.	Report only AEs and SAEs which are considered related to trial treatment or trial design. Death should be reported as an SAE only when considered related to trial treatment or trial design.
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.

The investigator must report the following events immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant for the SAEs.

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.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File) or by using the

electronic submission process. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs becomes available.

Pregnancy

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

5.2.3 Assessment of safety laboratory parameters

Safety laboratory samples will be analyzed at the investigator's local laboratory. Safety laboratory examinations will include hematology and biochemistry examinations. Table 5.2.3: 1 presents the laboratory tests to be performed.

Table 5.2.3:1 Clinical Laboratory Tests

Clinical Laboratory Tests

Category	Parameters
Hematology	Haemoglobin, haematocrit, platelet count, white blood cell count (WBC), neutrophils, bands
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	
Electrolytes	Sodium, potassium, calcium, magnesium
Liver function tests	Alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea (preferred) or blood urea nitrogen (BUN), creatinine; Creatinine clearance (see Appendix 10.1).
Other	Glucose, albumin
Pregnancy test	β-HCG testing in urine or serum in women of childbearing potential (WOCBP)

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

5.2.4 Electrocardiogram

Electrocardiogram (ECG) is not required for the purposes of the trial. If an 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 visit 2, 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, temperature and measurement of height (in cm, at screening) and body weight (in kg). Evaluation of the ECOG performance status (see appendix 4) will be performed at the times specified in the flowchart.

5.3 OTHER

5.3.1 EGFR mutation analysis

The presence of a common EGFR mutation (Deletion 19 and/or L858R) is mandatory for study enrolment.

The results of prior local analysis of EGFR mutation status using the institution's local testing methodology will be accepted for study enrolment as long as documentation of the result is available. In this case, patients will not have a Screening Visit 1 (SV1) and will proceed directly to Screening Visit 2 (SV2).

If prior analysis of EGFR mutation status has not been performed, patients will sign informed consent to tissue analysis and EGFR mutation analysis will be performed on tumour biopsy material. The expectation is that this test will use existing material and that a new biopsy will not be required. The EGFR mutation analysis may be performed locally using a validated technique or, if local analysis of EGFR mutation status is not possible, tumour sample may be sent to the central laboratory for analysis as described in the Laboratory Manual and in the Investigator Site File (ISF).

EGFR mutation analysis may be performed at any time prior to Screening Visit 2 as long as the patient is expected to meet the inclusion/exclusion criteria at some point in the future. This allows testing to take place at diagnosis or during first line therapy so that a result is available at the appropriate time. Patients must not proceed to Screening Visit 2 until a positive test result (Deletion 19 and/or L858R) has been documented.

5.4 APPROPRIATENESS OF MEASUREMENTS

All methods used are standard.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Please refer to the flowchart and figure 3.1.1 for the visit schedule. A description of the patient's progress through the trial is given below.

Patients who do not have an EGFR mutation test result available will be asked to sign informed consent to tissue analysis (tissue analysis consent), and analysis of their EGFR mutation status will be performed prior to any further assessments. During this period, adverse events will only be reported if related to trial procedures.

Patients with a documented common EGFR mutation will be asked to sign informed consent to trial participation and will undergo screening. Eligible patients will be administered afatinib once daily until criteria for treatment discontinuation are met (see section 3.3.4). At the time of discontinuing afatinib treatment the End of Treatment visit will be performed.

From the signature of the informed consent to trial participation, during the treatment period, and for 28 days after the last dose of afatinib, all adverse events will be documented. The follow-up visit is performed 28-35 days after the last dose of afatinib and is primarily to collect follow-up safety information. For the majority of patients, progression will already be documented at this point, and this will also be the trial completion timepoint for such patients.

If a patient does not have documented progression prior to the follow-up visit he/she will continue to have regular tumour assessments in accordance with the trial schedule (every 8 weeks until week 56 and every 12 weeks thereafter). Clinical assessments will be performed in accordance with local institution practice, and patient status will be collected every 60 days. Trial completion will occur at the timepoint of disease progression or start of further anti-cancer treatment, whichever occurs first. During this phase, new adverse events will only be documented if they are considered to be related to afatinib or the trial design.

6.1.1 Treatment beyond progression

Patients may continue trial treatment until disease progression as confirmed by imaging or clinical assessment if imaging could not be performed. However, in case of clinical benefit as judged by the investigator and based on careful clinical assessment, patients may be allowed to continue afatinib beyond disease progression as defined by RECIST 1.1 criteria after discussion with the BI clinical monitor. Clinical benefit can include, but will not be restricted to, significant symptom control of originally symptomatic tumours. Patients who continue as described will continue to follow the trial schedule for treatment visits (see flowchart) including the imaging and clinical tumour evaluations. Trial treatment may be continued as long as judged beneficial by the investigator. The date of documented progression will not change if the decision is taken to continue the treatment.

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.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This trial follows a single-arm, open-label design. The aim is to provide more data on efficacy and safety in the second-line (chemotherapy pre-treated) patients with EGFR mutation positive NSCLC. Efficacy and safety will be evaluated in a descriptive manner.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal statistical hypotheses.

7.3 PLANNED ANALYSES

All treated patients will be included in the analysis of efficacy and safety.

The primary analysis of response data will occur when all treated patients are evaluable for response, which is expected to be approximately 16 weeks (the second tumour imaging assessment per flowchart) after the last patient starts treatment.

After all patients reach the point of 'trial completion', the final trial database lock will occur and all endpoints will be analysed based on this final lock.

7.3.1 Primary analyses

The primary analysis will estimate the proportion of patients who achieve confirmed objective response (CR or PR) according to RECIST 1.1. An exact 95% confidence interval will be calculated based on the Clopper-Pearson formula (R06-1080).

7.3.2 Secondary analyses

Similar to the response rate, proportion and 95% confidence interval will be calculated for patients who achieve disease control (i.e. best overall response is CR, PR or SD).

PFS is defined as the time from start of treatment to the earlier date of disease progression or death of any cause. Kaplan-Meier curve will be calculated, from which the median PFS and the PFS probability at specified timepoints will be derived.

7.3.3 Safety analyses

All patients who received at least one dose of afatinib will be included in the analysis of safety. Adverse events within an onset date within the time period from the date first dose of afatinib until 28 days after the last dose of afatinib will be analysed as 'on-treatment' AE. Adverse events are graded according to CTCAE, v3.0 (R04-0474). Safety analysis will be descriptive, in most cases, in the form of frequency tables.

Key safety measures will include: The overall incidence and intensity (CTCAE grade) of AEs, as well as relatedness of AEs to treatment and seriousness

- AEs leading to dose reduction or treatment discontinuation
- Gastrointestinal events (vomiting, nausea, diarrhoea)
- Skin reaction (rash, acne)
- Other serious or significant AEs according to ICH E3
- Potential clinical significance in selected laboratory tests (CTCAE grade >=2 with increase by at least one grade from baseline)
- (low values) haemoglobin, leukocytes (total WBC), neutrophils, lymphocytes, platelets, potassium
- (high values) PTT, creatinine, AST, ALT, bilirubin, alkaline phosphatase, proteinuria
- Descriptive statistics for change from baseline for all laboratory tests

7.3.4 Interim analyses

In the event that primary analysis of response cannot occur in Q2 2016, a preliminary analysis of response and safety data will be provided to EMA in Q2 2016 as agreed.

7.3.5 Pharmacokinetic analyses

Not applicable.

7.3.6 Pharmacodynamic analyses

Not applicable.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

In general, missing values will not be imputed. For efficacy data, every reasonable effort will be undertaken to determine patients' best overall response status and disease progression.

Missing baseline laboratory values (on the date of first dose) will be imputed by the value from the screening visit. For adverse events, every effort will be made to obtain complete information.

7.5 RANDOMISATION

Not applicable.

7.6 DETERMINATION OF SAMPLE SIZE

As explained in previous sections of this protocol, the phase II trial (P12-03681) had total 68 patients treated with afatinib as second-line treatment (7 on 40mg starting dose and 61 on 50mg). The agreement with EMA as post-marketing commitment was to provide more efficacy and safety data on afatinib as second-line treatment with 40mg starting dose. The sample size of 60 is based on how many patients can be recruited within a reasonable time frame, rather than on statistical considerations.

In the phase II trial, the overall confirmed response rate was reported as 60% based on investigator assessment in the total 68 second-line patients (P12-03681).

Given the observed response rate of 60%, with 60 patients, the 95% confidence interval of the response rate would be (46.5%, 72.4%) based on the Clopper-Pearson exact method. In other words, this sample size will provide reasonable precision to the estimation of response rate.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients 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.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance

auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

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

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For afatinib this is the current version of the Investigator's Brochure (U03-3218) The current version of this reference document is 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.

8.6 COMPLETION OF TRIAL

The trial will be completed when all patients have either completed the study (Figure 3.1.1) or withdrawn from the study prior to documented progression (see section 3.3.4.1). The sponsor may decide to complete the trial earlier than this if the primary efficacy analysis has been completed, sufficient PFS data has been collected, and all patients have either ended study treatment or are eligible to receive afatinib under the conditions listed in section 3.3.4.1.

The IEC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out) or early termination of the trial.

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10. APPENDICES

10.1 APPENDIX 1 COCKCROFT-GAULT FORMULA

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

When serum creatinine is measured in mg/dL;

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

When serum creatinine is measured in µmol/L;

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

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

10.2 APPENDIX 2 PGP INHIBITORS AND INDUCERS

List of potent inhibitors and inducers of P-glycoprotein (MDR1)

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

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

10.3 APPENDIX 3 RECIST 1.1

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

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

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

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

For the purposes of this study, patients should be evaluated for response at week 8 and then every 8 weeks until week 56. After week 56, response should be evaluated every 12 weeks. In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

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

Paitents will have their response classified according to the definitions stated below.

Measurability of tumour at baseline

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15mm are also measurable.

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. Measurable lesion if limited to either small (<2cm) solitary visceral lesion or scant (<5cm) lymph nodes only metastasis should be evaluated for additional evidence of malignant nature and discussed with BI trial clinical monitor before enrolling.

Non-measurable disease

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

Lesions in irradiated fields

At baseline, previously irradiated lesions should not be used as indicator lesions unless they have progressed since irradiation. New lesions occurring in previously irradiated fields can be used as indicator lesions

Methods of measurement

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

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

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

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

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

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

Baseline Documentation of Target and Non-target Lesions

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

A sum of diameters (SoD) for all target lesions will be calculated (using ShD for lymph nodes and LD for all other lesions) and reported as the baseline SoD. The baseline SoD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.3:1).

Table 10.3: 1 Evaluation of target lesions

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

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.3:2).

Table 10.3: 2 Evaluations of non-target lesions and new lesions

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

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

Confirmation

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

Evaluation of best response to study treatment

The best response to study treatment (Table 10.3: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.3: 3).

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

Table 10.3: 3 Algorithm for evaluation of overall best response*

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

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

10.4 APPENDIX 4 ECOG PERFORMANCE STATUS

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

R01-0787

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
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		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c02156918 **Version Number**: 2.0

Document Name: clinical-trial-protocol

Title: An open label, single-arm phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an EGFR mutation (Del19 or L858R) who have failed first-line treatment with platinum-based chemotherapy

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	11 Apr 2014 15:27 CEST
Approval-Clinical [redacted]	[redacted]	11 Apr 2014 17:03 CEST
Approval-Therapeutic Area [redacted]	[redacted]	14 Apr 2014 13:29 CEST
Author-Trial Clinical Monitor	[redacted]	22 Apr 2014 22:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed