Clinical Trial Protocol

Doc. No.: c02215411

EudraCT No.:	2009-017661-34
BI Trial No.:	1200.55
BI Investigational Product(s):	Afatinib (Giotrif®) (BIBW 2992)
Title:	An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)
Clinical Phase:	IIIb
Clinical Trial Leader:	[redacted] Tel: [redacted] Fax: [redacted]
Co-ordinating Investigator:	[redacted] Phone: [redacted] Fax : [redacted]
Status:	Final protocol (Revised Protocol (based on global amendment 3))
Version and Date:	**Version: 4** **Date: 08 Feb 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: afatinib (BIBW 2992)			
Protocol date: 13 Mar 2013	**Trial number:** **1200.55**		**Revision date:** 08 Feb 2021

Title of trial:	An open label trial of afatinib (Giotrif®) in treatment-naive (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)
Co-ordinating Investigator:	[redacted]
Trial site(s):	Multi-center trial conducted at up to 200 sites within approximately 11 countries
Clinical phase:	IIIb
Objective(s):	To evaluate the safety, tolerability and efficacy of afatinib **(Giotrif®)** in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI
Methodology:	Open-label, multi-center, single-arm trial
No. of patients:	
total entered:	481 patients
each treatment:	All entered patients will receive afatinib (Giotrif®)
Diagnosis:	Patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI
Main criteria for inclusion:	All patients should have locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI
Test product(s):	Afatinib (Giotrif®) as 40, 30 and 20 mg film-coated tablets
dose:	40 mg/day or 30 mg/day or 20 mg/day
mode of admin.:	Oral, once daily, continuous
Comparator products:	None.
dose:	
mode of admin.:	

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: afatinib (BIBW 2992)			
Protocol date: 13 Mar 2013	**Trial number:** **1200.55**		**Revision date:** 08 Feb 2021
Duration of treatment:	Continuous treatment in the absence of disease progression or other trial withdrawal criteria. The trial is considered concluded when all patients have discontinued trial medication and/or have access to Afatinib via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation, and completed the follow up or are lost to follow up.		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: afatinib (BIBW 2992)			
Protocol date: 13 Mar 2013	**Trial number:** **1200.55**		**Revision date:** 08 Feb 2021
Criteria for efficacy:	Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiological assessments as per standard of care at the site.		
Criteria for safety:	Adverse events according to Common Terminology Criteria (CTCAE) Version 3.0 (R04 0474).		
Statistical methods:	Exploratory descriptive statistics of demographic, efficacy and safety data will be presented as appropriate		

FLOW CHART

Procedure	**Screening & Dispensing***	**Treatment and Safety evaluation**	**End of Treatment**	**Follow-up**
Visits (V)	**V1**	**V2 onwards*** **	**EOT**/*** **	**FU#**
Days	**Day -1 (-28 to -1)**	**Day 28 (-7/+2 days) and every 28th day (-7/+2) onwards**	**0-14 Days after last trial drug intake**	**EOT**+ 28 (-7)**
Informed consent[1]	X			
Demographics	X			
Medical history	X			
In/Exclusion criteria	X			
Physical examination[2]	X	X	X	
Disease Assessment		X	X	
ECG[3]	X°	X°	X°	
LVEF assessments[3]	X°	X°	X°	
Safety Laboratory Testing[4]	X	X°	X°	
Urine Examination[5]	X	X°	X°	
Pregnancy test[6]	X		X	
Adverse events	X[P(Day15)]	X	X	X[7]
Dispense Trial Medication[8]	X[*D]	X[D]		
Compliance		X	X	
Termination of Trial Medication			X	
Patient Status				X

* Afatinib (Giotrif®) will be dispensed only after verification that all trial requirements are met.

1 Written informed consent must be obtained before any screening/baseline assessments are performed.

2 Includes vital signs (pulse, blood pressure), temperature, height (cm), weight (kg) and an ECOG performance score.

3 ECG/LVEF to be conducted for patients with cardiac risk factors at the discretion of the investigator and in accordance to the current standard of care. In patients with ejection fraction below the institution's lower limits of normal, cardiac consultation as well as afatinib (Giotrif®) treatment interruption or discontinuation should be considered.

4 Safety laboratory testing: haematology, biochemistry and urine examinations (see Section 5.2.3). All laboratory tests mentioned in Table 5.2.3: 1 are required to be performed at screening and are recommended to be performed at the discretion of the investigator and in accordance to the current standard of care.

5 Urine examinations (see Table 5.2.3: 1) are required to be performed at screening and are recommended to be performed at the discretion of the investigator and in accordance to the current standard of care.

6 Beta-Human Chorionic Gonadotropin (β-HCG) testing in urine or serum in women of childbearing potential. A negative result is required for inclusion in the trial.

D Provide a diarrhoea diary with drug supply at cycle 1 and 2. Data on diaries should be checked by the study staff against AEs and Appendix 10.1.1.

P A contact is required 15 (±3) days after the patient's first dose to assess AEs and dose reductions.

O Indicates a recommended/optional test or procedure according to patient's course as required by clinical condition

** EOT(V): end of treatment (visit) with trial medication.

FU (V): Follow-up visit (end of observational phase) which should occur 28 days after the end of treatment (EOT) visit – This visit can be conducted by a phone call.

7 Within 28 days after last trial drug administration all AEs will be collected and documented. SAEs must always be collected, documented, and reported within this 28 day time period. 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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

8 In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), shipment of trial medication to patient's home may be arranged or dispensation of two kits may be done.

*** In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), patient visits may be performed remotely.

TABLE OF CONTENTS

ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ALT (SGPT)	Alanine Amino Transferase (Serum Glutamate Pyruvate Transaminase)
ANC	Absolute Neutrophil Count
AST (SGOT)	Aspartate Amino Transferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area under the Curve
β-HCG	Beta-Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
BSA	Body Surface Area
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence Interval
CML	Clinical Monitor Local
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CR	Complete Response
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
e.g.	Exempli gratia
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
erbB	Epidermal Growth Factor family of receptors (erB1/EGFR/HER1, erB2/HER2, erB3/HER3, erB4/HER4)
EU	European
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FU	Follow-up Visit
GABA	Gamma-Aminobutryic Acid
GCP	Good Clinical Practice
GGT	y-glutamyltransferase

G-Tube	Gastronomy-tube
HDPE	High-Density Polyethylene
HEPB	Hepatitis B
HEPC	Hepatitis C
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine Device
i.v.	intravenous
IWRS	Interactive Web-based Response System
LDH	Lactic Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	miligrams
min	Minute
mL	Milliliter
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition scan
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
OPU	Operative Unit
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PC	Pemetrexed/Cisplatin
PCR	Polymerase Chain Reaction
P-gp	P-glycoprotein (P-gp)
PD	Progression Disease
PDM	Project Data Manager
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PSTAT	Project Statistician
RDC	Remote Data Capture
REP	Residual Effect Period
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard Of Care

SOPs	Standard Operating Procedures
SPF	Sun Protection Factor
SUSARs	Suspected Unexpected Serious Adverse Reactions
TKI	Tyrosine Kinase Inhibitor
tmax	Time of Occurrence for Maximum Peak Drug Concentration
TS	Treated Set
ULN	Upper Limit of Normal
USA	United States of America
UVA	Ultraviolet A
UVB	Ultraviolet B
WBC	White Blood Cell Count
WOCBP	Women of Child-Bearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related death globally. It has been the most commonly diagnosed cancer each year since 1985 with an estimated 1.36 million new cases diagnosed and approximately 1.2 million deaths each year worldwide (R05-0876, R06-0221). The prognosis for advanced stage disease has improved modestly in the past 20 years. With an overall 5-year survival rate of only 15% the treatment of this disease clearly remains a major clinical challenge (R05-0876).

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

Aberrant activation of EGFR frequently observed in a variety of malignant tumours can be induced by different molecular mechanisms including receptor overexpression, mutation, ligand-dependent receptor dimerization, and ligand-independent activation. Overexpression of EGFR has been detected in 40% to 80% of NSCLC patients (R06-1301, R06-1393, R06-1394). However, recent clinical experiences with specific EGFR-Tyrosine Kinase Inhibitors (TKI) have demonstrated tumour regression in only 10% to 15% of unselected NSCLC patients (R05-0867, R06-1301, R06-1306). The frequency of EGFR somatic mutations was found to be approximately 10% in NSCLC patients from the US, Europe or Australia compared to a mutation rate of up to 30% in patients from Japan and Taiwan (R06-1262, R06-1306, R06-1393).

This is in general agreement with composite data from three retrospective analyses, in which the response rates for NSCLC patients harboring EGFR mutations ranged from 65% to 94% (R06-1306).

The pre-clinical and clinical data support the clinical testing of irreversible inhibitors of EGFR in NSCLC patients who are naïve to previous EGFR-TKI treatment as well as in patients who have progressed after treatment with a reversible EGFR-TKIs such as gefitinib and erlotinib (R06-1307, R07-1162), for which the only remaining standard treatment option is currently Best Supportive Care (BSC).

In preclinical disease models with Epidermal Growth Factor Family of Receptors (ErbB) pathway deregulation, afatinib (an irreversible TKI) effectively inhibits ErbB receptor signaling resulting in tumour growth inhibition or tumour regression.[U02-1391, U02-1702, U02-1703, U02-1660, U02-1614, U07-1338, P08-06904] As a single agent it retains significant anti- tumour activity in NSCLC cell lines (*in vitro)* and tumour models (*in vivo*, xenografts or transgenic models) driven by mutant EGFR isoforms known to be resistant to the reversible EGFR TKIs erlotinib and gefitinib.[P08-06904]

A number of clinical trials with afatinib (Giotrif®) have evaluated treatment of NSCLC patients, both those who are EGFR TKI naïve as well as those previously treated with a reversible EGFR TKI (see Section 2.3).

First line EGFR TKI naïve patients with EGFR mutation positive tumours showed significant and clinically meaningful improvements in Progression Free Survival (PFS) and Overall Response Rate (ORR) accompanied by significant delays in time to deterioration of the cancer-related symptoms of cough and dyspnoea as compared to patients receiving up to six cycles of pemetrexed/cisplatin (LUX-Lung 3/1200.32). In a separate single arm trial, (LUX-Lung 2/1200.22) [U11-3644-01] enrolling both first and second line TKI naïve patients, high ORRs and disease control rates (DCRs) were seen in both groups (61%, and 82%, respectively) and were confirmed by independent review.

Lastly, in trial 1200.34 (LUX-Lung 6), afatinib treatment compared to gemcitabine/cisplatin as first-line treatment for patients with Stage IIIB or IV adenocarcinoma resulted in a prolonged PFS and higher ORR observed in patients treated with afatinib (P13-06250).

1.2 DRUG PROFILE

Afatinib (Giotrif®) is a potent and selective, irreversible ErbB Family Blocker in preclinical models. It covalently binds to and irreversibly blocks signaling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER 2(ErbB2), ErbB3, ErbB4. [U02-1083, U03-1086, U11-2645-01].

For the latest information on the drug profile of afatinib (Giotrif®), please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning afatinib (Giotrif®) refer to the free base compound of afatinib (Giotrif®).

Afatinib (Giotrif®) is moderately rapidly absorbed after oral administration, with median Time of Occurrence for Maximum Peak Drug Concentration (tmax values) approximately 3 hours after drug administration. In general, afatinib gMean maximum plasma concentration and exposure increased with increasing doses after a single dose and at steady state. However, moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib (Giotrif®) 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. The major route of elimination of afatinib (Giotrif®) was via feces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The Pharmacokinetics (PK) characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib (Giotrif®) is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib (Giotrif®) 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 (Giotrif®) 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 (Giotrif®) when taken simultaneously with or 6 h after afatinib (Giotrif®) but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for AUC0-∞ and Cmax when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib (AUC0-∞) and 22 % (Cmax), respectively. If P-gp inhibitors need to be taken, they should be administered simultaneously with afatinib (see Section 4.2.2.1) [U12-1170-01].

In pre-clinical trials afatinib is not irritant to intact skin but an ocular irritant. Afatinib (Giotrif®) 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 trials (U07-3128-02, U08-1023-03) each determined a Maximum Tolerated Dose (MTD) with continuous dosing of afatinib (Giotrif®) as 40 mg and 50 mg daily, respectively. Adverse Events (AEs) observed with afatinib are consistent with those reported for EGFR and dual EGFR/ Human Epidermal Growth Factor Receptor 2 (HER2) inhibitors. The most frequent drug-related toxicities were associated with gastrointestinal disorders (including diarrhoea, nausea, vomiting, and mucositis/stomatitis), skin and subcutaneous tissue disorders (including rash, pruritus, acneiform rash, acne, paronychia), general disorders (including fatigue and mucosal inflammation), respiratory disorders (including epistaxis), and metabolism and nutritional disorders (including anorexia, dehydration). Early and proactive management of diarrhoea, skin rash, and stomatitis together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies (R07-4077, P07-11507, R07-4078, R11-0826).

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

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial will evaluate the safety, tolerability and efficacy of afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI.

2.2 TRIAL OBJECTIVES

To evaluate the safety, tolerability and efficacy of afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI.

See Section 5 for trial endpoints.

2.3 BENEFIT - RISK ASSESSMENT

The benefits of providing afatinib (Giotrif®) to patients via enrollment in this trial are based on the results obtained in two prior studies in patients with pathologic confirmation of stage IIIB or stage IV NSCLC. These trials were afatinib (Giotrif®) monotherapy trials and were either Phase III or large (>100 patients) Phase II trials with particular relevance for the proposed population for this trial in that they included NSCLC patients with confirmed EGFR mutations. Both trials enrolled EGFR TKI-naïve patients (1200.32 and 1200.22).

In addition, data from a third study, a Phase III open label, randomized trial in Asian patients with EGFR mutation-positive advanced adenocarcinoma of the lung, confirmed these results.

An overview of the characteristics of these trials is provided in Table 2.3: 1.

Table 2.3: 1 Study characteristics of LUX-Lung 2, 3 and 6

Trial	Regions	EGFR mutation status	Line of treatment	Prior EGFR TKI	Afatinib starting dose	Comparator	Patients per treatment group
1200.32 LUX-Lung 3	Asia, Europe, North America, South America	Positive	First	No	40 mg	Chemo [1]	Afatinib: 230 Chemo: 115
1200.22 LUX-Lung 2	Taiwan, USA	Positive	First or second	No	40 mg or 50 mg	None	129 (40 mg: 30; 50 mg: 99)
1200.34 LUX-Lung 6	China, South Korea, Thailand	Positive	First	No	40 mg	Chemo[2]	Afatinib: 242 Chemo: 122

[1] Chemotherapy with pemetrexed/cisplatin
[2] Chemotherapy with gemcitabine/cisplatin

EGFR TKI Naïve Patients

1200.32 (LUX-Lung 3)

The study was a randomised, open-label, phase III study of afatinib (Giotrif®) versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harboring an EGFR activating mutation who were not eligible for standard curative-intent treatment with surgery or chemo-radiotherapy and who had received no prior systemic treatment for locally advanced, recurrent or metastatic NSCLC. The primary objective of the study was to assess the efficacy of afatinib (Giotrif®) as defined by progression-free survival (PFS) by central independent review. Secondary endpoints included ORR and Health Related Quality of Life (HRQoL) including NSCLC specific symptom control. A central test for EGFR mutations was carried out using the companion diagnostic TheraScreen® EGFR RGQ PCR kit. Three hundred forty five (345) patients were randomised in a 2:1 ratio to receive either afatinib (n=230) 40 mg daily continuous treatment in the absence of disease progression or adverse events or Pemetrexed/Cisplatin (PC) (n=115) 500 mg/m^2 + 75 mg/m^2 q21 days up to 6 cycles. Baseline characteristics were well balanced between arms: overall the median age was 61 years, 65% of patients were female, 72% were Asian, 68% were never-smokers and 89% had Stage IV disease. Regarding EGFR mutation status, 49% had deletions in exon 19 (Del19), 40% had the L858R mutation and 11% had a variety of other less common mutations.

As assessed by central independent review, treatment with afatinib (Giotrif®) resulted in a significantly prolonged PFS as compared to treatment with PC (median 11.1 vs 6.9 months, HR 0.58; 0.43–0.78; p=0.0004). In patients with common EGFR mutations (Del19/L858R), the median PFS for afatinib (Giotrif®) treated patients was 13.6 months as compared to 6.9 months for patients receiving PC (HR=0.47; 0.34-0.65; p<0.0001). The ORR for patients treated with afatinib (Giotrif®) (56%) was significantly higher than that for patients treated with PC (23%) (p<0.0001). The prolonged PFS and higher ORR observed in patients treated with afatinib (Giotrif®) were accompanied by significant delays (as compared to patients treated with PC) in time to deterioration of the cancer-related symptoms of cough (HR=0.60, p=0.0072) and dyspnoea (HR=0.68, p=0.0145). The pre-specified number of events necessary to evaluate Overall Survival (OS) has not yet been reached.

In the afatinib (Giotrif®) arm, the highest CTCAE Grade of AEs was Grade 3 in 51.1%, Grade 4 in 3.9%, and Grade 5 in 5.7% of patients. In the chemotherapy arm, the highest CTCAE Grade of AEs was Grade 3 in 44.1%, Grade 4 in 9.9%, and Grade 5 in 2.7% of patients. The incidence of patients with AEs leading to dose reduction was 57.2% (afatinib) and 16.2% (chemotherapy). The incidence of AEs leading to treatment discontinuation was 14.0% (afatinib) and 15.3% (chemotherapy). Drug-related AEs leading to treatment discontinuation were experienced by 7.9% (afatinib) and 11.7% of patients (chemotherapy). SAEs were reported in 28.8% (afatinib) and 22.5% (chemotherapy) of patients, 14.4% of patients in each treatment arm experienced drug-related SAEs. The most frequent SAEs related to treatment with afatinib (Giotrif®) were diarrhoea (6.6%) and vomiting (3.5%). The most frequent SAEs related to chemotherapy were vomiting (2.7%) and fatigue (2.7%). There were 13 deaths (5.7%) reported due to on-treatment AEs in the afatinib (Giotrif®) arm, with 4 of them (sepsis, dyspnoea, acute respiratory distress syndrome, and death) considered related to afatinib (Giotrif®) by the investigator. Three deaths (2.7%) were reported due to

on-treatment AEs in the chemotherapy group; none of them were considered related to chemotherapy by the investigator.[U12-1199-01]

1200.22 (LUX-Lung 2)

Further evidence of the benefits of afatinib (Giotrif®) in EGFR TKI-naïve patients with NSCLC was obtained in trial 1200.22, an exploratory open-label single arm Phase II trial of afatinib (Giotrif®) as first- or second-line treatment. The primary objective of the study was to assess the efficacy of afatinib (Giotrif®) as defined by the objective response rate (ORR). Patients were screened for EGFR mutations determined centrally by sequencing and/or using a Genzyme assay consisting of PCR amplification followed by direct sequencing performed bidirectionally. Secondary endpoints included PFS by both independent and investigator assessments, clinical benefit (CR, PR, SD) and OS.

The study enrolled and treated a total of 129 patients including 61 first-line patients (23 who received a starting dose of 40 mg and 38 who received a starting dose of 50 mg) and 68 second-line patients (7 who received a starting dose of 40 mg and 61 who received a starting dose of 50 mg). Of the patients, 41.9% were male, 58.1% were female, the median age was 61 years, 96.9% had a baseline ECOG performance status of 0 or 1, 12.4% were Caucasian and 86.8% were Asian.

In the first-line setting, confirmed objective responses were noted in 66% of 61 patients with a median PFS of 12.0 months by independent review and 15.6 months by investigator assessment. DCR was 87%. Efficacy was similarly high in the group of patients who had received prior first-line chemotherapy (N=68; ORR 57%; PFS by independent review 8 months and by investigator assessment 10.5 months; DCR 78%). Median OS was not reached in the first line population. Median OS in second line patients was 23.3 months (95 % CI 18.5-38).

Similar high rates of response of between 57% and 69% by independent review were seen across subgroups divided by lines of treatment (first and second line), by starting dose (50 and 40 mg), by gender (men and women), by country (Taiwan and USA), by race (Asians and Caucasians), and by the type of the two most common EGFR mutations (Del19 and L858R).

The most common AEs were diarrhoea (94.6%), rash/acne (93.8%), nail effect (85.3%), stomatitis (81.4%) and pruritus (57.4%). Diarrhoea was reported by 96.7% of patients in the 40 mg starting dose group and 93.9% in the 50 mg starting dose group. For 20.2% of patients that started on either the 40mg or 50 mg dose, diarrhoea was reported as Grade 3 at the highest during the course of the event, with no Grade 4 or 5 diarrhoea reported. Diarrhoea was reported as an SAE for 1.6% of patients (2/129); both of whom received a starting dose of 50 mg. While 24.8% of patients had their dose reduced due to diarrhoea, no patients discontinued from the study due to diarrhoea. Rash/acne was reported in 90.0% of patients in the 40 mg starting dose group and 94.9% in the 50 mg starting dose group. Overall, 23.3% of patients developed Grade 3 rash/acne, with 28/30 of these patients in the 50 mg starting dose group. No Grade 4 or 5 rash/acne was reported. Rash/acne was reported as an SAE for 3.9% of patients, all of whom received a starting dose of 50 mg. Overall, 26.4% of patients had

their dose reduced due to rash/acne but only 2 (1.6%) discontinued treatment due to rash/acne.[U11-3644-01]

1200.34 (LUX-Lung 6)

More recent evidence of the benefits of afatinib (Giotrif®) versus chemotherapy in EGFR TKI-naïve asian patients with NSCLC was obtained in trial 1200.34, an open-label, randomized, Phase III trial of afatinib (Giotrif®) versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harboring an EGFR activating mutation who had received no prior chemotherapy or EGFR-targeting drugs for advanced NSCLC. The primary objective of the study was to assess the efficacy of afatinib (Giotrif®) as defined by progression-free survival (PFS) by central independent review and determined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included ORR, disease control rate (DCR), duration of response, tumor shrinkage, overal survival (OS), patient-reported outcomes (PRO), and safety and pharmicokinetics of afatinib (Giotrif®). A central test for EGFR mutations was carried out using the companion diagnostic TheraScreen® EGFR RGQ PCR kit. Three hundred and sixty four (364) patients were randomised in a 2:1 ratio to receive either afatinib (n=242) 40 mg daily continuous treatment in the absence of disease progression or adverse events, or Gemcitabine/Cisplatin (GC) (n=122), with Gemcitabine 1000 mg/m^2 on Day 1 and Day 8, with cycplatin 75 mg/m^2 every 21 days up to 6 cycles. Baseline characteristics were well balanced between arms: overall the median age was 58 years, 65% of patients were female, 77% were never-smokers and 94% had Stage IV disease. Regarding EGFR mutation status, 51% had deletions in exon 19 (Del19), 38% had the L858R mutation and 11% had a variety of other less common mutations.

As assessed by central independent review, treatment with afatinib(Giotrif®) resulted in a significantly prolonged PFS as compared to treatment with GC (median 11.0 vs. 5.6 months, HR 0.28, p<0.0001). The ORR for patients treated with afatinib (66.9%) was significantly higher than that for patients treated with GC (23%) (p<0.0001). The prolonged PFS and higher ORR observed in patients treated with afatinib (Giotrif®) were accompanied by significant delays (as compared to patients treated with GC) in time to deterioration of the cancer-related symptoms of cough (HR=0.45, p=0.0001) and dyspnoea (HR=0.54, p<0.0001). The pre-specified number of events necessary to Overall Survival (OS) has not yet been reached.

The incidence of patients with AEs leading to dose reduction was 32.2% in the afatinib (Giotrif®) arm and 26.5% in the chemotherapy arm. In the afatinib (Giotrif®) arm, drug-related AEs leading to treatment discontinuation were experienced by 5.9% of the patients as compared to 39.8% of the patients in the chemotherapy arm. The most frequent reported afatinib-related AEs were diarrhoea, rash/acne and stomatitis. The most frequent reported chemotherapy-related AEs were nausea/vomiting , fatigue, and bone-marrow suppresion. There were 14 deaths (5.9%) reported due to on-treatment AEs in the afatinib (Giotrif®) arm, and three deaths (2.7%) were reported due to on-treatment AEs in the chemotherapy group.

Significant differences between the proportion of patients with improvements in lung cancer symptoms of cough, dyspnoea, and pain were observed with patient in afatinib (Giotrif®)

arm compared to chemotherapy (P13-06250). Taken together, these results support the efficacy data and conclusions of LUX-Lung 3.

Risks

Most diarrhoea and rash/acne was adequately managed by a combination of pausing treatment, reducing the dose, and supportive treatment with loperamide for diarrhoea and topical antibiotics for rash. Dose reduction was required to manage common AEs in approximately half of patients treated with afatinib (Giotrif®). Treatment related AEs that led to discontinuation occurred in 8% of afatinib (Giotrif®) treated patients in study 1200.32, and 9% in study 1200.22. The frequency of discontinuation due to diarrhoea was <5% for afatinib (Giotrif®) treated patients in each of the aforementioned studies.

The low rates of discontinuation due to diarrhoea and rash/acne compared with the incidence of these events suggested that the protocol-defined dose reduction scheme and recommended medical management were effective and allowed patients to continue treatment with afatinib (Giotrif®) for as long as there was clinical benefit. In study 1200.32 in which patients were randomised between treatment with afatinib (Giotrif®) and chemotherapy, overall treatment-related AEs led to discontinuation of therapy in 8% of patients receiving afatinib (Giotrif®) as compared to 12% of patients receiving pemetrexed/cisplatin in spite of the fact that the afatinib (Giotrif®) treatment patients remained on treatment for a significantly longer period.

In a pooled analysis of patients taking the 40 mg dose in monotherapy trials, the frequency of patients with serious adverse events were: diarrhoea (3.2%), vomiting (2.6%), dyspnoea (1.6%), metastases to central nervous system (1.4%), fatigue (1.0), pneumonia (1.0), and respiratory failure; all others occurred at a rate less than 1% (U12-1482-01).

Interstitial Lung Disease (ILD) or ILD-like events are a known and infrequent risk associated with EGFR inhibitor therapy and encompass a variety of clinical entities. Diagnosis is often made on clinical and/or radiographic findings and at times is difficult to distinguish from pulmonary processes, such as infection or malignancy. In afatinib (Giotrif®) monotherapy and combination therapy trials, adverse events identified as potential ILD or ILD-like, were reported infrequently (unadjudicated frequency 1.5%; investigator assigned drug related frequency 0.7%). The frequency of these events is similar to that observed with other EGFR inhibitors. [U03-3218] As this is a known class effect of other EGFR/HER2 inhibitors, patients with known ILD will be excluded from this trial and careful monitoring of pulmonary symptoms with sudden onset is warranted in patients treated with afatinib (Giotrif®).

Overall these findings demonstrate that for patients with EGFR mutation positive NSCLC the benefits of treatment with afatinib (Giotrif®) outweigh the associated risks. These patients experienced significant improvements in time to disease progression that were accompanied by significant and clinically meaningful improvements in disease related symptoms. Adverse events observed following treatment with afatinib (Giotrif®) have been of a nature and severity expected for EGFR inhibitors. Dose reduction was frequently required to manage common AEs, but the dose reduction scheme and the proposed supportive care described for

common AEs allowed the vast majority of patients to remain on treatment for as long as there was clinical benefit.

Gastrointestinal perforation, including fatalities, has been reported during treatment with afatinib in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking afatinib, treatment should be permanently discontinued.

2.4 BENEFIT - RISK ASSESSMENT IN CONTEXT OF COVID-19 INFECTION

2.4.1 Relevant information on the product in relationship to COVID-19

Relevant mechanism of action, clinical pharmacology aspects, relevant non-clinical and clinical data are described in the current afatinib Investigator's Brochure [c01617169-11] and the current afatinib drug label. There is no non-clinical nor clinical data on how afatinib may affect COVID-19 viral infections. Gastrointestinal effects of afatinib like stomatitis or diarrhea or skin toxicities may enhance susceptibility for viral infections thus effective management of these side effects is important. There is no non-clinical nor clinical data to suggest that afatinib may directly alleviate nor exacerbate viral infections like COVID-19, and based on the mechanism of action (specific inhibition of the tyrosine kinases of the ErbB family), there would be no expectation of such direct interaction to affect COVID-19 disease.

Recent afatinib trials have implemented mitigations in order to reduce the patient risk of contracting COVID-19 due to the local COVID situation. Depending on the local COVID situation, protocol-defined trial procedures requiring travel to the study site may impose a potential COVID risk and therefore should be appropriately mitigated with measures, if these are deemed necessary by investigator.

2.4.2 Benefits and Risks Conclusions and Recommendations

Patients in clinical trials with afatinib have advanced late stage cancer with limited treatment options. Given the life threatening nature of the underlying disease, the approach recommended by professional oncology organizations (e.g. ASCO, ESMO) remains to treat patients with cancer as under normal circumstances. No consensus on recommendations exist regarding holding or delaying treatment in cancer patients with no signs of a COVID-19 infection. Withdrawing treatment in a cancer patient who may have few or any alternative treatment options requires a careful, individual evaluation.

There is no evidence/indication that based on the pharmacological mechanism and existing non-clinical and clinical data that afatinib may increase the risk of progression of COVID-19 infection.

To date, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of ErbB family of tyrosine kinases targeted by afatinib. Available non-clinical and clinical data from completed clinical trials have not shown an increased risk of infections with afatinib.

Considering the limited and sparse data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality from COVID-19 infection [R20-0918; R20-0916] , there may be some factors representing the risk for using ErbB tyrosine kinases that are currently still unknown. The information about the risk factors, the severity and the activity of immune response in patients with COVID-19 infections will be constantly monitored as it evolves.

All up-to-date information about the investigational compounds (preclinical, clinical, clinical pharmacology) is included in the trial documentation, including IB, clinical trial protocol for the guidance of the investigator. The latter also outlines the measures for management of associated AEs, required dose reductions etc. The risk mitigation measures currently in place within the clinical trial protocols are a sufficient safeguard, as patients are frequently monitored with comprehensive safety evaluations. Based on laboratory data and any adverse event that may occur, clinical trial protocols include guidance for the continuation, interruption, dose reduction, and discontinuation of study drugs.

Therefore, assuming the protocol-defined requirements for continued study drug administration are met, the decision about concomitant use of experimental anti-cancer therapy with afatinib with COVID-19 treatment in case of contracted COVID-19 infection will be left to the investigator's benefit-risk assessment on a case-by-case basis.

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's continued participation in the trial. BI as the sponsor, recommend to adhere to the trial protocol as much as possible and where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the patient. BI has provided guidance to investigators on how to manage these situations if they occur.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

This trial will evaluate the safety, tolerability and efficacy of the investigational drug afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-TKI. EGFR mutation positivity of all patients needs to be established and documented prior to enrolment into the trial. Treated patients will visit the investigator at regular intervals as specified in the Flow chart.

All entered patients (i.e., patients that have been treated with the trial medication) will receive continuous treatment of afatinib (Giotrif®) in the absence of disease progression or meeting any other trial withdrawal criteria (see Section 3.3.4). The trial is considered concluded when all patients have discontinued trial medication and/or have access to Afatinib via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation and completed the follow up or are lost to follow up.

Enrolment of new patients into the trial will end once enrolment goal in the trial has been met and/or if any of the criteria in Section 3.3.4.2 are met.

All patients will visit the investigator at regular intervals for assessment of safety as outlined in the Flow chart. Disease Assessment will be performed at each visit (i.e., every 28 days) until disease progression or withdrawal for another reason. Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care (SOC) at the site. The investigator is not obligated to perform any radiologic scans as part of this trial. However, if such scans were performed as part of standard of care this information should be recorded on the Disease Assessment case report form.

Participation will be open to physicians experienced in treating patients with NSCLC and who can complete the site qualification and initiation process.

3.1 OVERALL TRIAL DESIGN AND PLAN

3.1.1 Administrative structure of the trial

This trial is sponsored by Boehringer Ingelheim (BI).

Boehringer Ingelheim (BI) will appoint a Clinical Trial Leader (CTL), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, ordering the materials as needed for the trial, ensuring appropriate training and information of a local Clinical Trial Manager (CTM), Clinical Research Associates (CRAs), and investigator.

Data Management and Statistical evaluation will be performed by BI and/or a Contract Research Organization (CRO) according to BI SOPs. A BI: Project Data Manager (PDM), Project Statistician (PSTAT) and Project Programmer will provide oversight for these activities.

Tasks and functions assigned in order to organize, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons will be provided in the Clinical Trial Master File (CTMF) document.

The organization of the trial will be done by the respective local BI-organization Operating Unit (OPU) or by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. A CTM will be appointed and will be responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs.

The coordinating investigator is a investigator participating in the trial that has experience of this type of trial and investigations. The coordinating investigator has been designated by BI and will sign the Clinical Trial Report (CTR). Since this trial will not require any blinding or randomisation there will be no steering committee or data monitoring committee needed for this trial.

The trial will be performed by investigators specialized in the treatment of lung cancer.

Documents on the coordinating investigator and other important participants, especially their curricula vitae, will be filed in the CTMF.

Details on handling of the trial supplies including responsible institutions are given in Section 4 of this protocol.

Boehringer Ingelheim will appoint CROs to be responsible for special services, such as: trial medication logistics and data management activities (eCRF and discrepancy management).

All relevant trial documentation will be stored in the CTMF at BI. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site, as required by local regulation and BI SOP.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Because of the exploratory nature of this trial there will be no control group.

3.3 SELECTION OF TRIAL POPULATION

A log of all patients screened/enrolled into the trial (i.e., patients who provided consent) will be maintained in the ISF at the investigator's site regardless of whether they have been treated with the investigational drug or not. This trial will accommodate up to 500 patients at up to 200 sites within Europe, in Australia and in Israel.

Participation in this trial will be available to patients with advanced NSCLC who meet all the eligibility requirements specified in Sections 3.3.2 and 3.3.3 (i.e., inclusion and exclusion criteria).

3.3.1 Main diagnosis for study entry

All patients should have locally advanced or metastatic NSCLC harboring EGFR mutation(s) and have never been treated with an EGFR-TKI.

3.3.2 Inclusion criteria

Patients with:

1) locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC)

2) Epidermal Growth Factor Receptor (EGFR) mutation-positive result per the institution's testing methodology.

3) male or female patients age ≥18 years

4) Adequate organ function, defined as all of the following:

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

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

    c. Serum creatinine < 1.5 times of the upper limit of normal

    d. Total Bilirubin < 1.5 times upper limit of (institutional) normal (Patients with Gilbert's syndrome total bilirubin must be <4 times institutional upper limit of normal).

    e. Aspartate Amino Transferase (AST) or Alanine Amino Transferase (ALT) < three times the upper limit of (institutional) normal (ULN) (if related to liver metastases < five times ULN).

5) ECOG score between 0 - 2

6) written informed consent by patient or guardian prior to admission into the trial that is consistent with International Conference on Harmonisation (ICH)- Good Clinical Practice (GCP) guidelines and local law.

3.3.3 Exclusion criteria

Patients who or with:

1) prior treatment with an EGFR tyrosine kinase inhibitor (TKI)

2) anti-cancer treatment within 2 weeks prior to start of trial treatment (continued use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer permitted)

3) radiotherapy within 14 days prior to drug administration, except as follows:

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

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

4) major surgery within 4 weeks before starting trial treatment or scheduled for surgery during the projected course of the trial

5) known hypersensitivity to afatinib (Giotrif®) or any of its excipients (see Section 4.1.1)

6) history or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure New York Heart Association (NYHA) classification of 3 (Refer to Appendix 10.2), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to starting trial treatment.

7) are Women of Child-Bearing Potential (WOCBP) and men who are able to father a child, unwilling to use adequate contraception prior to trial entry, for the duration of trial participation and for at least 28 days after treatment has ended. Adequate methods of contraception and Women of Child-Bearing Potential described in Section 4.2.3.

8) are WOCBP childbearing potential (see Section 4.2.3) who are nursing or are pregnant or do not agree to submit to pregnancy testing required by this protocol

9) any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the trial or interfere with the evaluation of safety for the trial drug

10) previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.

11) requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2 that can not be stopped for the duration of trial participation

12) known pre-existing interstitial lung disease

13) presence of poorly controlled gastrointestinal disorders that could affect the absorption of the trial drug (e.g. Crohn's disease, ulcerative colitis, malabsorption, or CTC grade ≥2 diarrhoea of any aetiology) based on investigator assessment.

14) active hepatitis B infection (defined as presence of Hepatitis B (HepB) sAg and/or HepB DNA), active Hepatitis C (HEP C) infection (defined as presence of Hep C RNA) and/or known Human Immunodeficiency Virus (HIV) carrier.

15) meningeal carcinomatosis

16) symptomatic brain metastases (patients with asymptomatic brain metastases, who were previously treated, are eligible provided they have had Stable Disease (SD) for at least 4 weeks on stable doses of medication)

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The investigator or patient themselves may stop trial 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 trial treatment.

The investigator or the sponsor may permanently discontinue a patient's participation at any time for any of the following reasons:

- patient withdraws consent, without the need to justify the decision
- unequivocal disease progression. Study treatment can be continued beyond radiological progression only (without symptomatic progression) until clinical progression if it is deemed in the patient's benefit following a careful risk benefit assessment and confirmation of clinical benefit by the investigator. Each case must be discussed in details and agreed between the investigator and the Sponsor, and only after sponsor approval, the trial treatment can continue.
- patient fails to follow protocol requirements/directions and represent a safety issue for the patient
- eligibility criteria are violated and represent a safety issue for the patient
- patient requires concomitant medication which may interfere with the trial medication (see Section 4.2.2)
- patient is no longer able to participate for other medical reasons (e.g., surgery, adverse events or other diseases)
- adverse events that can not be managed by dose reduction
- further dose reductions considered necessary but not allowed according to the protocol (see Section 4.1.4.1)
- patient is found to be pregnant during trial participation (please refer to Table 4.2.3: 1)
- is diagnosed with ILD
- is diagnosed with gastrointestinal perforations
- change in the patient's status creating an unfavourable risk/benefit in favour to stop trial treatment
- termination of the trial

The sponsor may remove patients from the study if the patient has access to afatinib via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation. This may mean a change in packaging and labelling. The cost of any ongoing supply of study medication will be incurred by the sponsor until progression occurs. If a patient is removed from the study treatment, an end of treatment 0-14 days later and a follow up visit 28 days later will be performed to ensure all adverse events are followed up and then the patient will be considered to have completed the trial.

When discontinuation is due to a SAE the investigator must follow the event until it is resolved, becomes chronic, or remains stable with no resolution expected. Data on these events must be collected in the electronic case report form (eCRF). For guidelines in the management of class expected adverse events, refer to Appendix 10.1.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Emergence of any efficacy/safety information that could significantly affect continuation of the trial
2. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract by a trial site staff or investigator, disturbing the appropriate conduct of the trial.
3. Discontinuation or modification of the clinical development program with afatinib (Giotrif®) for any reason
4. At the discretion of the sponsor. Drug supply will be arranged for ongoing patients if Sponsor decides to terminate the trial.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Boehringer Ingelheim will provide the investigational product afatinib (Giotrif®).

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

Substance (INN):	afatinib (Giotrif®)
Pharmaceutical form:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	40, 30, and 20 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent of afatinib)
Daily dose:	40 mg with an option to reduce the dose based on individual tolerability (see Section 4.1.4.1).
Duration of use:	Continuous daily dosing, one cycle consists of 28 days. Patients are eligible for repeated treatment cycles in the absence of disease progression or other trial withdrawal criteria.
Route of administration:	Oral (swallowed)
Posology:	Once daily
Excipients	Core Tablet: Lactose monohydrate, Microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone, and Magnesium stearate. Film-coat: Hypromellose 2910, Polyethylene glycol 400, Titanium dioxide, Talc, FD&C Blue No. 2 11-14% (may not be included in 20 mg tablet), and Polysorbate 80.

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the treatment period, treatment assignment will be by means of a third-party web-based system. This will involve the use of an Interactive Web Response System (IWRS). The instructions will be provided in the ISF. Investigators and site staff will receive unique user IDs and passwords; and a manual describing how to access and use the IWRS.

Patients who meet all eligibility criteria will be entered into the trial. Enrolment of new patients into the trial will end once enrollment goal in the trial has been met and/or if any of the criteria in Section 3.3.4.2 are met.

There is no comparator group in this trial.

4.1.3 Selection of doses in the trial

The dose for patients is 40 mg daily, continuously. This dose was selected based on the results from the LUX-Lung 2/1200.22 (P12-03681) [U11-3644-01] study (see Section 1.1 and the current version of the Investigator's Brochure, U03-3218) as well as the results of the LUX-Lung 3 (1200.32) study. At the discretion of the treating physician patients can have their dose decreased based on the on the criteria mentioned in Section 4.1.4.1.

4.1.4 Drug assignment and administration of doses for each patient

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment cycle. For administrative purposes treatment will be divided into treatment cycles, which are each 4 weeks (28 days) in duration. Patients will take a single oral dose of afatinib (Giotrif®) each day. Treatment will stop when the patient is diagnosed with disease progression or any other reason listed in Section 3.3.4.1. Trial drug will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

The dose of afatinib (Giotrif®) for this trial is 40 mg. All dose reductions will be based on individual tolerability (see Section 4.1.4.1).

The medication should be taken at approximately the same time each day. Food should not be ingested for at least three hours before and at least one hour after taking afatinib (Giotrif®) film-coated tablets.

If the patient does not meet any of the criteria on Table 4.1.4.1: 1 then the dose of afatinib (Giotrif®) should remain on the 40 mg dose (unless dose reduction is necessary - see Section 4.1.4.1). Dose escalation is prohibited.

Patients will take a single oral dose of afatinib (Giotrif®) daily. The tablet should be swallowed with a glass of water (~250 Milliliter (mL)). Afatinib (Giotrif®) tablets are film-coated and therefore should not be chewed or crushed, but may be administered after dispersing the afatinib (Giotrif®) tablets according to the following procedure:

If dosing of whole tablets is not possible, afatinib (Giotrif®) 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 Minutes (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 gastronomy tube (G-tube).

If a dose of afatinib (Giotrif®) is missed, it should be taken during the same day as soon as the patient remembers. However, if the next scheduled dose is due within eight hours then the missed dose must be skipped.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still

decide to continue trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the patients' home or two bottles of trial medication may be dispensed at the beginning of a treatment cycle, so that the next visit can be performed remotely.

4.1.4.1 Dose reduction scheme

Treatment related adverse events will be managed by treatment pauses and subsequent dose reductions of afatinib (Giotrif®) according to the schedule described in Table 4.1.4.1: 1. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

The investigator is responsible for determining the necessity and frequency of any additional/unscheduled visits as well as the extent of the evaluation (e.g., physical examination, laboratory testing, adverse events, etc.) performed at these visits. At a minimum the investigator should note in the patient's chart when an additional/unscheduled visit occurs and make relevant entries on the AE and medication dispensing eCRFs.

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 Appendix 10.1.

Table 4.1.4.1: 1 Dose reduction scheme

AE type and CTC-AE*Grade	Action	Dose Reduction Scheme
Events related to trial drug: • Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration • Reduced renal function to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥3	Pause treatment until patient has recovered to Grade ≤1 or baseline[1]. Resume treatment at a reduced dose according to the Dose Reduction Column. If patient has not recovered to Grade ≤1 or baseline[1] within 6 weeks trial treatment must be permanently discontinued[2].	Resume with dose reduction by 10mg decrements. If patient cannot tolerate 20mg/day, permanent discontinuation of afatinib (Giotrif®) should be considered.
Acute onset and/or unexplained worsening of pulmonary systems (dyspnoea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib (Giotrif®) at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue afatinib (Giotrif®).
Gastrointestinal perforations	Permanently discontinue afatinib (Giotrif®).	NA

* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v 3.0 (CTC-AE)
1 Baseline is defined as the CTCAE Grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with afatinib (Giotrif®) will be decided by the investigator.

After treatment pause due to adverse events, treatment at a reduced dose (i.e., with a new bottle of medication) will restart at the predefined schedule/cycle (i.e., 28 days (-7/+2 days) on the new dose).

In the event of any unrelated adverse events, the investigator may choose to pause the medication for up to 14 days, but no dose reduction should occur. If the medication is paused for more than 14 days, the decision to continue with afatinib (Giotrif®) will be made by the investigator. Patients should be discontinued from the trial if they have been off trial medication for more than 6 weeks.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable since this is an open-label trial.

4.1.6 Packaging, labelling, and re-supply

Afatinib (Giotrif®) will be supplied by BI (or a designated 3rd party drug distribution vendor) as film-coated tablets. Available dosage strengths will be 40 mg, 30 mg and 20 mg. Tablets will be supplied in child-resistant, tamper-evident bottles. Each bottle will contain 30 tablets of identical dosage strength.

Each bottle will be labelled according to dosage strength and will also include the trial number, medication number, expiry ('use by') dates, and instructions for use. Examples of the labelling of the bottles are found in the ISF. Adequate supply of afatinib (Giotrif®) bottles will be dispensed at each visit to last until the next scheduled visit. Afatinib (Giotrif®) must be dispensed in the original bottles. Patients should be instructed to keep the bottles tightly closed to protect from moisture.

4.1.7 Storage conditions

Afatinib (Giotrif®) bottles must be kept in a secure, limited access storage area (to authorized people) under storage conditions defined below until supplied/administered to patient. Temperature logs must be maintained to make certain that the afatinib (Giotrif®) supplies are stored at the correct temperature. In the event that the temperature would be out of range, this has to be documented in the ISF and reported to the sponsor.

Afatinib (Giotrif®) must be stored in the original package in order to protect from light. Film-coated tablets are humidity sensitive, therefore bottles must be kept tightly closed to protect from moisture. Tablets must be stored according to the storage instructions on the bottle label and in the ISF.

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

4.1.8 Drug accountability

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

- approval of the clinical trial protocol by the Institutional Review Board (IRB)/Ethics Committee (EC),
- availability of a signed and dated clinical trial contract between the sponsor and the investigator /institution,
- 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
- all other local requirements are met.

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication

Rescue medications to reverse the action of afatinib (Giotrif®) are not available. Potential adverse events should be treated symptomatically. The current version of the Investigator Brochure (IB) lists the AEs expected with afatinib (Giotrif®) (U03-3218). Common adverse events of treatment with afatinib (Giotrif®) with specified management recommendations and/or requirements include diarrhoea, and rash/acne. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described in Appendix 10.1. Symptomatic treatments of side effects or tumour -associated symptoms are allowed.

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). Trial drug should be paused pending investigation of these symptoms. If interstitial lung disease is diagnosed, trial 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.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In this trial supportive treatments will be defined as the best care available judged by the investigator, according to the institutional standards for each center. Concomitant medications (or therapy) to provide adequate care, may be given as clinically necessary.

For symptom control, palliative radiation therapy is allowed provided that the reason for the radiotherapy does not reflect treatment of progressive disease on afatinib (Giotrif®). After trial enrolment, 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. During palliative radiotherapy, trial treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is paused for more than 14 days, the decision to continue will be made by the investigator. Continuous interruption of > 6 weeks due to palliative radiotherapy will not be allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the patient's chart during the screening and treatment period, starting from the date of signature of informed consent, and ending at the Follow-Up Visit (FU).

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib (Giotrif®) around one week prior to the surgery, and to restart treatment after complete wound healing, provided that complete wound healing occurs ≤ 6 weeks (patients should be discontinued from the trial if they have been off trial medication for more than 6 weeks).

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 trial treatment.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib (Giotrif®) with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.3. As the information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the treating physician to assess such status on concomitant therapies.

4.2.2.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea (see Appendix 10.1.1).

To prevent skin related adverse events it is recommended to avoid long exposure to sunlight and intense exposure to UV light and/or harsh detergents (pH5 neutral), see also Appendix 10.1.2.

4.2.3 Contraception and pregnancy

Female patients must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing trial treatment.

Females will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years. Women of childbearing potential who are sexually active and not using an acceptable method of birth control during the trial and for at least 28 days after the end of active therapy are not allowed to participate in the trial.

Acceptable methods of contraception for females include hormonal contraception and double barrier method. 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). If hormonal contraceptives are used, at least one barrier method should also be used. Partner vasectomy, natural 'rhythm' and spermicidal jelly/cream are not acceptable as methods of contraception.

Female patients who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilization (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception.

Male patients should use adequate contraception (e.g., condom and spermicidal jelly) during the trial and for at least 28 days after the end of active therapy.

If a woman becomes pregnant during the treatment period this must be reported as a drug exposure during pregnancy case, even if no event occurred. For cases of paternal exposure to the BI product during the trial, the pregnancy (mother is not a participant in the trial) has also to be reported to BI, if the father (participant in the trial) voluntarily reports it to the investigator.

In both cases the pregnant woman has to be followed up until birth of the baby; then it has to be reported whether the woman had a normal delivery or not and whether the newborn showed any pathological findings.

If pregnancy is associated with a SAE, both, SAE form and pregnancy monitoring form must be completed.

Table 4.2.3: 1 Pregnancy reporting

Timing of pregnancy	Action
Prior to commencing trial medication	Patient should be withdrawn from the trial immediately, as per exclusion criteria #7. No reporting necessary.
During trial treatment	Treatment must be stopped immediately and the pregnancy should be reported to the sponsor immediately using the pregnancy monitoring form (Part A). If the investigator wishes to give any further treatment with trial medication, this must be discussed and agreed upon with the BI clinical monitor. If trial medication is continued despite pregnancy, a risk/benefit analysis should be documented. The pregnancy should be followed up to final outcome and the outcome, including the health status of the newborn and/or any premature termination should be reported to the sponsor on the pregnancy monitoring form (Part B) (refer to Section 5.2.2.2). If a pregnancy is accompanied by an SAE, an SAE form must also be completed. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death and congenital malformation/anomaly) must be reported as an SAE.
End of Treatment (EOT) though Follow-up visit/end of observational phase	The pregnancy should be reported to the sponsor immediately using the pregnancy monitoring form (Part A). The pregnancy should be followed up to final outcome and the outcome, including the health status of the newborn and/or any premature termination should be reported to the sponsor on the pregnancy monitoring form (Part B). If a pregnancy is accompanied by an SAE, an SAE form must also be completed. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death) must be reported as an SAE.

4.3 TREATMENT COMPLIANCE

The trial medication will be given to the patient in accordance with the protocol and the instructions of the treating physician. The treating physician is responsible for assessing patient compliance. Patients will be asked to return all unused trial medication at each visit. Tablet counts must be reviewed by the treating physician (or designee) in order to assess

compliance with trial medication. Patients will be encouraged to strictly comply with drug administration procedures.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

The primary endpoint of this study is the safety assessment, refer to Section 5.2.1 for a description of safety endpoints. No specific schedule or type of tumour measurements or assessments are required in this trial.

5.1.1 Endpoint(s) of efficacy

Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.

Data regarding tumour assessments that are performed according to local standard of care for NSCLC may contribute to:

- Time to symptomatic progression (TTSP) is defined as the time from first administration of afatinib (Giotrif®) to the date of first documented clinically significant symptomatic progression that required change in or stopping anti-cancer treatment according to investigator's assessment.

Data regarding tumour assessments that are performed according to local standard of care for NSCLC may contribute to Progression-Free Survival (PFS), defined as time from the date of the first administration of afatinib (Giotrif®) to the date of progression or to the date of death, whichever occurs first.

No specific tumour measurements are required per trial protocol.

5.1.2 Assessment of efficacy

See Section 5.1.1.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Safety will primarily be assessed by adverse events according to Common Terminology Criteria (CTCAE Version 3) in a descriptive fashion.

No confirmatory safety analysis is planned.

Please refer to Section 5.2.2.2 for details on the collection and reporting of adverse events and SAEs.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) and includes daily record of diarrhea status as reported by the patient for the first two cycles. In addition, 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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

Adverse event

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

Serious adverse event

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

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

- Hospitalizations for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post trial drug administration)

Intensity of adverse event

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

Causal relationship of adverse event

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

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

Worsening of 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.

Expected Adverse Events

For expected (listed) AEs of afatinib (Giotrif®), 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 this trial is defined as 28 days after last intake of study drug.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
From signing of informed consent to ≤28 days after last trial drug administration	Report all AEs and SAEs regardless of relatedness or whether the trial drug was administered. This includes all deaths.

Table 5.2.2.2:1 (continued) AE/SAE reporting requirements

Post-treatment (>28 days after last trial drug administration)	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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

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

The investigator must report the following events using the SAE form immediately (within 24 hours) to the sponsor: SAEs, non-serious AEs relevant to a reported SAE, adverse events of special interest. Further details regarding AE reporting procedure are provided in the ISF.

Pregnancy

Pregnancy is an exclusion criterion in this trial.

In rare cases, pregnancy might occur in clinical trials and observational trials. In such cases the actions delineated in Table 4.2.3: 1 should be followed.

Once a female subject has been entered into the clinical trial, after having taken trial 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) 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). In the presence of an (S)AE, both the Pregnancy Monitoring Form for Clinical Trials and the SAE form must be completed (see Table 4.2.3: 1).

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 haematology, biochemistry and urine examinations. All laboratory tests mentioned in Table 5.2.3: 1 should be performed at screening (Visit 1). All post screening laboratory testing is optional and should be performed at the discretion of the investigator and in accordance to the current standard of care. The recommended safety laboratory examinations laboratory tests can also be found in Table 5.2.3: 1.

Table 5.2.3: 1 Clinical laboratory tests

Category	Parameters
Haematology	Haemoglobin, platelet count, and White Blood Cell (WBC)
Chemistry	Electrolytes: Sodium, and potassium Liver function tests: Alkaline phosphatase, aspartate amino transferase (AST/SGOT), alanine amino transferase (ALT/SGPT), γ-glutamyltransferase (GGT), total bilirubin Renal function parameters: Blood urea/Blood Urea Nitrogen (BUN), creatinine Other: Glucose, albumin, phosphorus, lactate dehydrogenase (LDH), total protein, and Creatine Phosphokinase (CPK); in case of pathological CPK further evaluation (e.g., by determination of isoenzymes, troponin assays, ~~ECG exam~~) should be performed as clinically indicated.
Urinalysis	pH, protein, glucose, blood/erythrocytes, leucocytes, nitrite; in case of pathological finding further evaluation should be performed and results documented
Pregnancy test	β-HCG testing in urine or serum in Women Of Child-Bearing Potential (WOCBP) (see Section 4.2.3)

5.2.4 Electrocardiogram

Twelve-lead ECGs will only be performed locally at the trial sites at the discretion of the investigator in accordance to local current standard of care for patients (see Flow chart). When performed, the investigator will review the ECG recording at the time of the visit and record any ECG abnormality that meets AE criteria.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination

A general physical examination (which includes measurement of height (in cm) and body weight (in kg)) will be performed at screening and at the time points specified in the Flow chart. The evaluation of the ECOG performance score will be performed only at Visit 1.

5.2.5.2 Vital signs

Vital signs (blood pressure and pulse rate after two minutes rest) and temperature (preferably oral and/or tympanic: if other locations are used the same location should be used at each time point when body temperature is measured) will be recorded at the time points specified in the Flow chart.

5.2.5.3 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by Echocardiography (ECHO) or Multiple Gated Acquisition scan (MUGA) will be assessed if clinically indicated. The testing of this function and cardiac monitoring should be considered in patients that develop relevant cardiac signs/symptoms during treatment. In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as afatinib treatment interruption or discontinuation should be considered.

5.3 OTHER

5.3.1 Other endpoint(s)

Not applicable.

5.3.2 Other assessment(s)

5.3.2.1 Documentation of diarrhoea

Patients will receive a diarrhoea diary for the first 2 cycles of Afatinib (Giotrif®) treatment. Patients will receive instructions on how to record daily diarrhoea events. A copy of the instructions and the diary will be provided in the ISF.

All data on diaries will be reviewed at visit 2 and 3 and will be checked against the reported AEs and adherence to the instructions in Section 10.1.1 (Management of diarrhoea and hydration status following treatment with afatinib).

Use of a daily recording diary will capture quantitatively diarrhea data (number of bowel movements and consistency of diarrhea).

The diary will be used as a tool for investigators in order to get more granular information on the severity and duration of diarrhoea and whether patients followed recommendations in terms of anti-diarrheal concomitant medication and sufficient hydration. The diary is also a tool for the patient which reminds to contact the investigator in case high number of bowel movements are present over some days or in case of any concerns.

Accurate and constant assessment of diarrhoea symptoms, timely initiation of anti-diarrheal medication at first signs of diarrhoea, appropriate anti-diarrheal medication dose modifications based on the daily diarrhea symptoms, and non-pharmacologic interventions will facilitate early and appropriate interventions to minimize the duration and severity of dose limiting afatinib-induced diarrhea.

5.3.3 Pharmacogenomic evaluation

Not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable since no pharmacokinetic data will be collected or analyzed in this trial.

5.6 BIOMARKER

5.6.1 Endpoints based on biomarker(s)

EGFR – Mutation analysis

As per Section 1.1, there is a strong rationale to identify predictive markers which are features at baseline that may predict responsiveness to ErbB TKI in this population.

Enrolment

The presence of an EGFR mutation is mandatory for trial enrolment. Hence, the EGFR mutation analysis must be performed prior to enrolment into the trial (i.e., before a patient is consented). Any EGFR mutation-positive result must be documented and the analysis can be performed using the institution's local testing methodology.

5.6.2 Methods of sample collection

Not applicable since no samples are being collected within the trial.

[redacted]

5.7 PHARMACODYNAMICS

Not applicable since no pharmacodynamic data will be collected or analyzed in this trial.

5.7.1 Pharmacodynamic endpoints

Not applicable since no pharmacokinetic or pharmacodynamic data will be collected or analyzed in this trial.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable since no pharmacokinetic or pharmacodynamic data will be collected or analyzed in this trial.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

6.1.1 Screening and dispensing visit

Patients considered for this trial will undergo an eligibility evaluation (see Flow Chart). If patients meet all eligibility requirements they will be dispensed drug for the first 28 day treatment cycle.

A contact is required 15 (± 3) days after the patient's first dose to assess any AEs.

6.1.2 Treatment and safety evaluation visits

Safety evaluation visits are to be conducted after afatinib **(Giotrif®)** administration, at Day 28 (-7/+2)/Visit 2, and every 28 (-7/+2) days onwards. Please refer to the required and optional procedures to be performed at these visits in the Flow Chart and in Section 6.2.1.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war,) patients visits may be performed remotely to collect/report study data such as adverse events, concomitant therapies, clinical evaluation of tumour by symptoms and study medication compliance check. Where permitted by local law and regulations, trial medication may be shipped directly to the patients' home or two bottles of trial medication may be dispensed at the beginning of a treatment cycle, so that the next visit can be performed remotely.

The investigator is responsible for determining the necessity and frequency of any additional/unscheduled visits as well as the extent of the evaluation (e.g., physical examination, laboratory testing, adverse events, etc.) performed at these visits. At a minimum the investigator should note in the patient's chart when an additional/unscheduled visit occurs and make relevant entries on the AE and medication dispensing eCRFs.

A treatment cycle is defined as 28 days.

6.1.3 End of Treatment (EOT) visit

All patients should be evaluated at the end of their trial treatment. This visit should be completed on the day of the patient's last dose on trial medication or up to 14 days later.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war,) patient visit may be performed remotely to collect/report study data such as adverse events, concomitant therapies, clinical evaluation of tumour by symptoms and study medication compliance check.

6.1.4 Follow-Up (FU) visit

Patients should be contacted 28 (-7) days after the EOT visit to follow-up on their general condition and any adverse events which were not yet recovered at the EOT visit or any AEs

that started since then. In addition, information regarding patients' status will be collected at this visit. This information can be obtained by a phone call.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The trial procedures are summarized in the Flow Chart.

6.2.1 Screening and run-in period(s)

Visit 1/Day -1 – Screening and dispensing visit

Informed consent must be obtained prior to any trial related procedures taking place.

Tests for which results are not already available as part of the patient's standard of care, may be ordered after the patient signs informed consent.

Prior to determining eligibility the investigator should: 1) review all information obtained at this visit, 2) review the inclusion/exclusion criteria and 3) confirm that the patient has discontinued all prohibited therapy or medications (see Sections 4.2.2 and 4.2.2.1) and an adequate washout period has passed.

Table 6.2.1: 1 Visit 1 /Day -1 – Screening and dispensing visit

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Informed Consent	Written informed consent must be obtained prior to any trial related procedures taking place.	Date of informed consent
Demographics	Obtain the following demographic data: sex, birth date, race, smoking and alcohol history	Sex, birth date, race, ethnicity, and smoking history

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Medical history	Oncological and relevant non-oncological history including details of previous treatment for NSCLC (including pathology)	• History of NSCLC: • Oncological and relevant non-oncological history including details of any previous treatment for NSCLC • The date of first histological diagnosis, the primary tumour site, the number and location of metastatic sites (bone, brain, liver, pleural effusion, other) • Tumour assessment/stage at the time of diagnosis according to the TNM-classification • Previous surgeries for NSCLC • Previously administered chemo-, immuno-, hormone therapy will be reported including start and end dates, the treatment regimen with the number of courses (chemo-immunotherapy), the best response obtained (complete response, partial response, stable disease, progressive disease, unknown), and progression date. • Previous radiotherapy - the total radiation dose and radiation field will be recorded
Inclusion and Exclusion criteria	Assessment of eligibility according to inclusion and exclusion criteria should be performed.	Verify that the patient has met all the inclusion and exclusion criteria.
Physical examination	Physical examination results (see Flow Chart). The evaluation of the ECOG performance score will be performed.	Verify that this physical examination was performed and record results (see Flow Chart).

Table 6.2.1: 1 (continued) Visit 1/Day -1 – Screening and dispensing visit (Page 2 of 3)

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
ECG	12-lead resting ECG may be performed at the discretion of the investigator.	Verify if an ECG was performed. Any abnormal results are reported on baseline conditions form.
LVEF (Left Ventricular Ejection Fraction)	Cardiac left ventricular function assessment by either ECHO (or MUGA) only for patients with cardiac risk factors and those with condition that can affect LVEF, at the discretion of the investigator and in accordance to the current standard of care.	Verify if an ECHO (or MUGA) was performed.
Safety Laboratory Testing	Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations. Blood samples may be collected to perform the following: - Retest for missing laboratory test results required to establish eligibility - Safety laboratory testing as deemed necessary by the investigator	Verify that all recommended safety laboratory testing were performed and that values met eligibility criteria according to the protocol. No lab values are to be recorded on the CRF.
Urine Examination	Urine examination. (see Section 5.2.3)	Verify if all recommended urine testing was performed. No lab values are to be recorded on the CRF.
Pregnancy test	β-HCG testing in urine or serum will be performed in females of childbearing potential (see Section 5.2.3). A negative result is required for enrolment in the trial.	Verify that β-HCG testing in urine or serum was performed and that patient is not pregnant.

Table 6.2.1: 1 (continued) Visit 1/Day -1 – Screening and dispensing visit (Page 3 of 3)

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Adverse events	Patients should be asked to report any hospitalizations, emergency treatments, or new medications as well as any general health issues that may have surfaced since signing the informed consent form. All the information collected should be recorded in the patient's chart. Refer to Sections: 5.2.2 and 5.2.2.2 for protocol specific requirements regarding the collection and reporting of adverse event information.	All relevant AEs and all SAEs.
Concomitant Medications	Patients should be asked to report any concomitant drug use (including, but not limited to,: non-prescription medications, anaesthetic agents, homeopathic/herbal remedies and dietary supplement preparations).	No concomitant medications will be recorded on eCRFs.
Dispense Trial Medication	Dispense 1 bottle of afatinib (Giotrif®) for the 28 day treatment cycle (see Section 4.1.4.)	Record: dose dispensed, amount of bottles dispensed, all medication numbers and date of first dose administration

6.2.2 Treatment period

Safety evaluation visits are to be conducted after the initiation of afatinib (Giotrif®), at Day 28 (-7/+2)/Visit 2 and every 28 (-7/+2) days onwards. Additional safety evaluation visits may be conducted as necessary, at the investigator's discretion. The investigator is responsible for determining the necessity and frequency of the additional safety visits as well as the extent of the evaluation (physical examination, laboratory testing, etc.) at each visit.

Table 6.2.2: 1 Visit 2/Day 28 (-7/+2) and every 28 (-7/+2) days onwards - treatment and safety evaluation

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Physical examination	Physical examination results (see Flow Chart). The evaluation of the ECOG performance score will be performed.	Verify that this physical examination was performed and record results (see Flow Chart).
Disease Assessment	Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.	Disease Assessment to be included on CRF.
ECG	ECGs may be performed at the discretion of the investigator.	Verify if an ECG was performed prior to or during any safety evaluation.
LVEF (Left Ventricular Ejection Fraction)	Cardiac left ventricular function assessment by either ECHO or MUGA only for patients with cardiac risk factors and those with condition that can affect LVEF, at the discretion of the investigator and in accordance to the current standard of care.	Verify if an ECHO (or MUGA) was performed prior to or during this visit. Verify that LVEF has not deteriorated to CTCAE Grade ≥3. If CTCAE Grade ≥3, see Section 4.1.4.1
Safety Laboratory Testing – Optional	Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations. Laboratory testing is optional at this visit and may be performed at the discretion of the investigator and in accordance to the current standard of care. Refer to Section 5.2.3 for a list of recommended safety laboratory tests. If performed as part of a safety evaluation visit, the test results must be filed or recorded in the patient's chart.	Verify if all recommended safety laboratory testing was performed and that values were acceptable according to the protocol. If not, see Sections: 4.1.4.1 and 5.2.2.1 No lab values are to be recorded on the CRF.
Urine Examination – Optional	Urine examination. See Section 5.2.3 for recommended urine examinations. Urine Examination is optional at this visit and may be performed at the discretion of the investigator and in accordance to the current standard of care.	Verify if all recommended urine testing was performed. No values from the urine examination are to be recorded on the CRF.

Table 6.2.2: 1 (continued) Visit 2/Day 28 and every 28 (-7/+2) days onwards - treatment and safety evaluation (Page 2 of 2)

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Adverse events	Patients should be asked to report any hospitalizations, emergency treatments, or new medications as well as any general health issues that may have surfaced since their last visit. All the information collected should be recorded in the patient's chart. Refer to Sections: 5.2.2 and 5.2.2.2 for protocol specific requirements regarding the collection and reporting of adverse event information.	All relevant AEs and all SAEs.
Compliance	Check number of tablets remaining and that trial medication was taken correctly, collect any used bottles of afatinib (Giotrif®).	Record if the patient is taking the medication according to the protocol.
Concomitant Medications	Patients should be asked to report any concomitant drug use (including, but not limited to,: non-prescription medications, anaesthetic agents, homeopathic/herbal remedies and dietary supplement preparations)	No concomitant medications will be recorded on eCRFs.
Dispense Trial Medication	Dispense sufficient medication for the next cycle of treatment (see Section 4.1.4).	Record: dose dispensed, medication numbers of bottles dispensed, and only the start date of any dose changes (if applicable).
Contact	A contact is required 15 (±3) days after the patient's first dose to assess AEs and dose reductions.	Record when this contact took place.

6.2.3 End of trial and follow-up period

The End of Treatment (EOT) visit marks the end of the patient's treatment in the trial, and should be conducted as soon as the patient discontinues trial medication (afatinib), and may occur at any time during the trial. The investigator may discontinue patients due to any of the reasons presented in Section 3.3.4.1.

Table 6.2.3: 1 End of Treatment (EOT) Visit

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Physical examination	Physical examination results (see Flow Chart). The evaluation of the ECOG performance score will be performed.	Verify that this physical examination was performed and record results (see Flow Chart).
Disease Assessment	Disease Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site.	Disease Assessment to be included on CRF.
ECG	An ECG may be performed at the discretion of the investigator.	Verify if an ECG was performed.
LVEF (Left Ventricular Ejection Fraction)	Cardiac left ventricular function assessment by either ECHO or (MUGA) only for patients with cardiac risk factors and those with condition that can affect LVEF, at the discretion of the investigator and in accordance to the current standard of care.	Verify if an ECHO (or MUGA) was performed.
Safety Laboratory Testing – Optional	Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations. Laboratory testing is optional at this visit and may be performed at the discretion of investigator and in accordance to the current standard of care. Refer to Section 5.2.3 for a list of recommended safety laboratory tests. If performed as part of a safety evaluation visit, the test results must be filed or recorded in the patient's chart.	Verify if all recommended safety laboratory testing was performed and that values were acceptable according to the protocol. If not, see Section 5.2.2.1 No lab values are to be recorded on the CRF.
Urine Examination – Optional	Urine examination. (see Section 5.2.3 for recommended urine examinations). Urine testing is optional at this visit and may be performed at the discretion of the investigator and in accordance to the current standard of care.	Verify if all recommended safety Urine testing was performed. No values from the urine examination are to be recorded on the CRF.
Pregnancy test	β-HCG testing in urine or serum will be performed in females of childbearing potential.	Verify that β-HCG testing in urine or serum was performed and that patient is not pregnant.
Adverse events	Patients should be asked to report any hospitalizations, emergency treatments, or new medications as well as any general health issues that may have surfaced since their last visit. All the information collected should be recorded in the patient's chart. Refer to Sections: 5.2.2 and 5.2.2.2 for protocol specific requirements regarding the collection and reporting of adverse event information.	All relevant AEs and all SAEs.

Table 6.2.3: 1 (continued) End of Treatment (EOT) Visit (Page 2 of 2)

	The following must be performed and information recorded in the patient's chart	What to include in eCRF
Compliance	Collect all unused or partially used and empty bottles of afatinib (Giotrif®) from the patient. Check number of tablets remaining and check that trial medication taken correctly.	Record if the patient took the medication according to the protocol. This information should be captured on the Termination of Trial Medication eCRF.
Concomitant Medications	Patients should be asked to report any concomitant drug use (including, but not limited to,: non-prescription medications, anaesthetic agents, homeopathic/herbal remedies and dietary supplement preparations).	No concomitant medications will be recorded on eCRFs.
Termination of Trial Medication	Document any information regarding the patient's last dose of trial drug and why it was stopped. (e.g., date of withdrawal of consent, lost to follow-up, disease progression) When applicable, every effort should be taken to collect and document information on date of death. Note: any AE which results in death* is considered an SAE.	Date when the last dose of trial medication was ingested. Reason for discontinuation.

* The term "Death" should not be reported as the SAE, it is the outcome of an AE.

6.2.4 Follow-Up

The Follow-up (FU) visit should occur 28 (-7) days after the EOT visit.

Follow-up visits should be scheduled for patients who met the trial withdrawal criteria (see Section 3.3.4). This visit marks the end of the patient's participation in the trial. Patients will not be required to attend the clinic for this visit. The clinic staff will contact the patients or their caregivers by telephone and inquire about any adverse events that might have occurred since the last visit and if applicable follow up on any unforeseen pregnancy during the trial. All concomitant medication should be added to the patient's chart. The Patient Status eCRF will be completed at this time.

Any additional (unscheduled) follow-up visits should be scheduled for patients with unresolved SAEs, AEs, or laboratory abnormalities who have discontinued trial participation. These events must be followed until resolution or until agreement is reached between the local medical monitor and the investigator that further follow-up is no longer required.

Table 6.2.4: 1 Follow-up (FU) Visit/EOT + 28 Days (-7)

	What to Include in the Patient's Chart	What to include in eCRF
Adverse events	Patients should be asked to report any hospitalizations, emergency treatments, or new medications as well as any general health issues that may have surfaced since their last visit. All the information collected should be recorded in the patient's chart. Refer to Sections: 5.2.2 and 5.2.2.2 for protocol specific requirements regarding the collection and reporting of adverse event information.	All relevant AEs and all SAEs.
Concomitant Medications	Patients should be asked to report any concomitant drug use (including, but not limited to,: non-prescription medications, anaesthetic agents, homeopathic/herbal remedies and dietary supplement preparations).	No concomitant medications will be recorded on eCRFs.
Patient Status	Document any information regarding the patient's status during the planned observation time (i.e., 28 days after the patient's last dose of medication). When applicable, every effort should be taken to collect and document information on date of death. Note: any AE which results in death is considered an SAE.	Any new anti-cancer medication that the patient has taken since EOT visit. Date when the patient completed the planned observation time. Date of death Patient's status

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Exploratory descriptive statistics of demographic, efficacy and safety data will be presented.

7.1 STATISTICAL DESIGN - MODEL

This is an open-label, multi-centre, non-randomised, uncontrolled, single arm trial designed to evaluate the safety, tolerability and efficacy of the investigational drug afatinib (Giotrif®) in a particular patient population. After the initial screening visit, patients will enter the open-label treatment period with safety visits at approximately every 28 days until the end of the trial.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses with regard to the endpoints described in Section 7.3.2 confirmatory sense since the objective of this trial is to describe the safety of long term use of afatinib (Giotrif®) in this patient population in an uncontrolled manner.

7.3 PLANNED ANALYSES

All analyses will be based on the Treated Set (TS) which includes all patients who were dispensed trial medication and have taken at least one dose of investigational treatment (afatinib).

7.3.1 Primary analyses

Refer to Section 7.3.3 for a description of the analysis of safety and tolerability, the primary objectives of this trial.

7.3.2 Secondary analyses

Progression-free survival

Progression-free survival is the time from start of treatment to the date of disease progression or death, whichever comes first.

For patients with known date of progression:
Progression-free survival [days] = date of progression (or of death if no earlier progression) – (date of start of treatment) + 1

For patients known not to have progressed, i.e., those remaining on trial drug:
Progression-free survival (censored) [days] = date of last contact showing no disease progression or death - (date of start of treatment) + 1.
Patients with unknown progression status or unknown date of progression will be censored at the last contact date, refer to Section 7.4 for more detail.
Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for progression-free survival,

using Greenwood's standard error estimate. Kaplan-Meier curves will be produced without confidence intervals.

Tumour response according to investigator's assessment

Each patient will be assigned to one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progressive disease
5. Not evaluable for response, reasons to be specified (e.g. early death, tumour assessments incomplete, etc.)

In the case that the tumour assessment was not based on radiological tumour imaging the categories 'complete response' and 'partial response' will be grouped together. Objective Response (OR) is defined as complete and partial responses according to investigator's assessment.

Time to tumour response is defined as the time from the start of treatment to the date of first recorded CR or PR.

The duration of tumour response is the time from first documented CR or PR to the time of progression or death (or date of censoring for PFS).

Patients whose best assessment is stable disease, partial, or complete response will be considered to have achieved disease control. Duration of disease control will be the same as time to progression, but restricted to patients who achieve disease control.

Descriptive statistics will be calculated for the duration of objective tumour response and disease control. Finally, the proportion of patients in each response category will be tabulated, if feasible (confirmation of response not required). Two-sided 95% confidence intervals will be given for the calculated best response rate. Best response is defined as the best individual response from the date of the first administration until the earliest recording of PD, death or end of treatment (as long as no other anti-cancer therapy has been given).

7.3.3 Safety analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between first drug intake until 28 days (inclusive) after last treatment administration will be considered 'treatment-emergent'. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Adverse events will be graded according to CTCAE, Version 3.0 (R04-0474).

CTC grades will be applied to laboratory parameters using the current BI oncology standard as detailed in the document 'Conversion of laboratory parameters to CTCAE grades within BI.'

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.4 Interim analyses

This is a single-arm open label study. The interim analysis may be done after recruitment has been completed. The analyses will include the assessment of safety and efficacy if conducted. The result from the interim analysis may be presented at professional conferences and published in articles after stop of recruitment.

7.4 HANDLING OF MISSING DATA

Missing or incomplete AE dates are imputed according to BI standards.

- For PFS:
  - If a patient is known to have progressed, but the date of progression is not attainable, the last date when the patient was assessed will be used as date of progression.
  - If a patient's vital status or progression status is unknown at the follow-up visit, the patient will be censored at the last contact date.

7.5 RANDOMISATION

No randomisation is required since all patients will be treated with afatinib (Giotrif®).

7.6 DETERMINATION OF SAMPLE SIZE

The number of patients included into this trial is not based on sample size calculations.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

The patient must be informed that his / her medical records may be examined by authorised monitors (CTM/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 via remote data capture. Since this is an open label trial emergency code breaks will not be necessary. 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 reported on Electronic Case Report Forms (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., Food and Drug Administration (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 fulfill the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e., is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI investigational product (afatinib) this is the current version of the Investigator's Brochure (U03-3218). The current version of this reference document is provided in the ISF.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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

P08-06904 Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008; 27(34), 4702 - 4711.

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

P12-03681 Yang JCH, Shih JY, Su WC, Hsia TC, Tsai CM, Ou SHI, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncology, Published Online March 26, 2012, doi:10.1016/S1470-2045(12)70086-4 Lancet Oncol 2012.

P13-06250 Wu YL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Massey D, Shi Y, Chen J, Zazulina V, Geater SL. LUX-Lung 6: a randomized, open-label, phase III study of afatinib (A) vs emcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. 49th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 31 May - 4 Jun 2013 J Clin Oncol 31 (Suppl), (2013)

R04-0474 Common terminology criteria for adverse events v3.0 (CTCAE) (publish date: December 12, 2003). Website: ctep.cancer.gov/forms/CTCAEv3.pdf ; Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, 31 March 2003, Publish Date: 12 December 2003 (2003).P13

R05-0867 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al,National Cancer Institute of Canada Clinical Trials GroupErlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353 (2), 123 - 132 (2005) .

R05-0876 Schrump DS, Altorki NK, Henschke CL, Carter D, Turrisi AT, Gutierrez ME. Non-small cell lung cancer. Cancer: principles and practice of oncology, 7th Edition, DeVita VT, Hellman S, Rosenberg SA (eds.), Lippincott Williams and Wilkins. 2005; 753-809.

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

R06-1301 Lynch TJ, Adjei AA, Bunn PA, Eisen TG, Engelman J, Goss G, et al Summary statement: Novel agents in the treatment of lung cancer: Advances in epidermal growth factor receptor-targeted agents. Clin Cancer Res. 2006; 12(14 Suppl.): 4365-4371.

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

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

R06-1307 Heymach JV, Nilsson M, Blumenschein G, Papadimitrakopoulou V, Herbst R. Epidermal growth factor receptor inhibitors in development for the treatment of non-small cell lung cancer. 3rd Cambridge Con on Novel Agents in the Treatment of Lung Cancer: Advances in EGFR-Targeted Agents, Cambridge, 23-24 Sep 2005. Clin Cancer Res. 2006; 12(14 Suppl.): 4441-4445.

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

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

R07-1162 Sequist LV. Second generation epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. Oncologist. 2007; 12: 325-330.

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

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

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

R06-0221 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA 2005;55(2)74-108.

R20-0916 Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol 2020 ; 38(1) ; 1-9.

R20-0918 Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (CoV-19 or SARS- CoV-2): anti-inflammatory strategies. Journal of Biological Regulators & Homeostatic Agents, epub ahead of print, doi: 10.23812/CONTI-E; 2020.

9.2 UNPUBLISHED REFERENCES

U02-1083 [redacted] Study of BIBW 2992BS, BIBW 3022BS, and BIBW 3049BS in various receptor binding assays. 03-02 8810241. 30January 2002.

U02-1391 [redacted] Effects of BIBW 2992 on endogenous EGFR and HER2 phosphorylation states and on proliferation in various cell lines. 22-02 23. June 2002.

U02-1614 [redacted] Anti-tumour activity of the combined EGFR and HER2 inhibitor BIBW 2992 BS in nude mouse xenografts derived from the human gastric carcinoma cell NCI-N87. 25-02. 16 October 2002.

U02-1660 [redacted] Anti-tumour activity of the combined EGFR and HER2 inhibitor BIBW 2992 BS in nude mouse xenografts derived from the human ovarian carcinoma cell line SKOV-3. 26-02 4 November 2002

U02-1702 [redacted] Minimum effective dose of the epidermal growth factor receptor (EGFR) inhibitor BIBW 2992 BS in nude mouse xenografts derived from the EGFR-overexpressing human epidermoid carcinoma cell line A431. 32-02. 25 November 2002.

U02-1703 [redacted] Anti-tumour activity of the combined EGFR and HER2 inhibitor BIBW 2992 BS in nude mouse xenografts derived from human breast carcinoma cell line MDA-MB-453. 31-02 25 November 2002.

c01617169-11 Investigator's Brochure Afatinib (BIBW 2992)

U03-1086 [redacted]. Inactivation of the EGF signaling pathway by BIBW 2992: A time course analysis.28-02 30November 2002.

U07-1338 [redacted]: BIBW 2992, an irreversible dual EGFR/HER2 kinase inhibitor, shows activity on L858R- and L858R/T790M-EGFR mutants, 07-06. 11 June 2007.

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

U08-1023-03 [redacted] A phase I open- label dose escalation study of continuous once-daily oral treatment with BIBW 2992 in patients with advanced solid tumours. 30-January-2008. Revised 25-October-2011.

U11-2645-01 [redacted] Potency of BIBW 2992 in HER4 kinase assays in vitro. 23 November 2011.

U11-3644-01 [redacted]LUX Lung 2: A phase II single-arm trial of BIBW 2992 in non-small cell lung cancer patients with EGFR activating mutations. 06 December 2011.

U12-1170-01 [redacted] Relative bioavailability of a single oral dose of 40 mg afatinib given alone compared to concomitant and timed administration of multiple oral doses of ritonavir - an open-label, randomised, three-way crossover trial in healthy male volunteers.16-May-2012.

U12-1199-01 [redacted] LUX-Lung 3; A randomised, open-label, phase III study ofBIBW 2992 versus chemotherapy as first-line treatment for patientswith stage IIIB or IV adenocarcinoma of the lung harbouring anEGFR-activating mutation. 04-July-2012.

U12-1482-01 [redacted]Clinical Summary: Afatinib film-coated tablets, 20mg, 30 mg, 40 mg, 50 mg. 25-Jul-2012.

10. APPENDICES

10.1 MANAGEMENT OF EXPECTED ADVERSE EVENTS

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

10.1.1 Management of diarrhoea and hydration status following treatment with afatinib (Giotrif®)

Patients should be advised to avoid foods known to aggravate diarrhoea, such as: spicy, greasy, or fried foods, raw vegetables, fresh fruit or whole grain bread.

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib (Giotrif®). Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 10.1.1: 1). At the time of initiation of treatment with afatinib (Giotrif®) patients should be given a supply of loperamide to keep with them at all times and should be counselled on the appropriate use. Patients should be advised to start taking loperamide with the onset of diarrhoea.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea. A daily fluid intake of approximately ≥2 liters is recommended to avoid dehydration; some fluids should contain sugar or salt to avoid hyponatremia and hypokalemia caused by electrolyte loss.

Table 10.1.1: 1 Grade specific treatment recommendations for afatinib **(Giotrif®)** related diarrhoea

Severity (CTCAE Grading)	Description	Intervention concerning afatinib (Giotrif®) treatment	Specific intervention
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water or clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool (up to 16 mg/day) until bowel movements cease for 12 hours. However it is advised to consult regional prescribing reccomandations.
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 Activities of Daily Living (ADL)	Continue same dose unless Grade 2 diarrhoea continues for ≥ 2 days (48 hours) in which case treatment must be paused until recovered to ≤ Grade 1 followed by dose reduction	See Grade 1; continue loperamide; assess for dehydration and electrolyte imbalance; consider intravenous 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	Pause dose 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)	Pause dose until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment pause, diarrhoea does not resolve to CTCAE Grade ≤1 or baseline (CTCAE Grade at the start of treatment) within 6 weeks, treatment with afatinib (Giotrif®) must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with afatinib will be decided by the investigator.

10.1.2 Management recommendations for dermatological AEs following treatment with afatinib (Giotrif®)

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 10.1.2: 1 and grade-specific treatment recommendations are summarized in Table 10.1.2: 2. For dose adjustment of afatinib (Giotrif®) 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)

Patients with an intolerable NCI-CTCAE grade 2 or who develop a grade 3 or higher dermatological event should be referred to a dermatologist, with prior experience of treating patients who have received EGFR therapy, for a more appropriate dermatologic treatment option.

Table 10.1.2: 1 General recommendations for prophylaxis while receiving afatinib (Giotrif®)

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 10.1.2: 2 Grade specific treatment recommendations of skin reactions to afatinib (Giotrif®)

Severity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Topical steroids (e.g., moderate/low strength: triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, fluticasone propionate 0.05%, hydrocortisone acetate 1%) or tacrolimus ointment alternative. Consider topical antibiotics (b.i.d) e.g.: clindamycin 1-2%, or topical erythromycin 1-2% cream of metronidazole 1% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical steroid treatment as for Grade 1 oral antibiotic (for 6 weeks) e.g., Doxycycline 100 mg b.i.d, Minocycline hydrochloride 100mg b.i.d. or, if available, oxytetracycline 500 mg b.i.d; stop topical antibiotic if being used.
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. If infection suspected (yellow crusts, purulent discharge, painful skin/nares): • Switch to oral antibiotic to broad spectrum/gram negative cover • Consider skin swab for bacterial culture
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3

Table 10.1.2: 2 (continued) Grade specific treatment recommendations of skin reactions to afatinib (Giotrif®) (Page 2 of 3)

Severity (CTCAE Grading)	Description	Specific intervention
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (Grade 1)	Mild or localized	Topical steroid moderate strength OR topical anti-pruritics (pramoxine 1%, doxepin 5% cream) applied b.i.d
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines (e.g: levocetirizine 5 mg qd, desloratadine 5 mg qd, diphenhydramine 25–50 mg t.i.d, hydroxyzine 25 mg t.i.d, fexofenadine 60 mg t.i.d)
Severe (Grade 3)	Intense or widespread and interfering with ADL	Oral antihistamines (e.g: levocetirizine 5 mg qd, desloratadine 5 mg qd, diphenhydramine 25–50 mg t.i.d, hydroxizine 25 mg t.i.d, fexofenadine 60 mg t.i.d) AND GABA agonists (e.g.: (adjust if renal impairment): gabapentin 300 mg every 8 hours, pregabalin 50–75 mg every 8 hours) OR tricyclics: (e.g.: doxepin 25–50 mg every 8 hours)
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Over-the-counter moisturizing cream or ointment to face b.i.d AND ammonium lactate 12% cream to body b.i.d.
Moderate (Grade 2)	Symptomatic, not interfering with ADL	Over-the-counter moisturizing cream or ointment to face b.i.d AND ammonium lactate 12% cream to body b.i.d. OR salicyclic acid 6% cream to body b.i.d.
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics Over-the-counter moisturizing cream or ointment to face b.i.d AND ammonium lactate 12% cream to body b.i.d. OR salicyclic acid 6% cream to body b.i.d. AND topical steroid (moderate/low strength; e.g.: triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, fluticasone propionate 0.05%) to eczematous area b.i.d

Table 10.1.2: 2 (continued) Grade specific treatment recommendations of skin reactions to afatinib (Giotrif®) (Page 3 of 3)

Severity (CTCAE Grading)	Description	Specific intervention
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; or topical applications.
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 (Giotrif®) according to the dose reduction scheme in Table 4.1.4.1: 1		

10.1.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 10.1.3: 1. For dose adjustment refer to Section 4.1.4.1 and for restrictions on concomitant therapies refer to Sections 4.2.2.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary maneuvers 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, chilies, 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 10.1.3: 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 10.1.3: 1 Grade specific treatment recommendations for afatinib (Giotrif®) related mucositis/stomatitis

Severity (CTCAE Grading)	Description	Treatment recommendations	Intervention concerning afatinib (Giotrif®) 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 4.1.4.1.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.1.

10.2 NEW YORK HEART ASSOCIATION CLASSIFICATION OF HEART FAILURE

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

10.3 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.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		*5 November 2013*
EudraCT number		2009-017661-34
BI Trial number		*1200.55*
BI Investigational Product(s)		*Afatinib (BIBW 2992)*
Title of protocol		An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		All
Description of change		Added: Giotrif®
Rationale for change		Approved name of the marketed drug

Section to be changed		Page 1
Description of change		[redacted]

		[redacted] Phone: [redacted] Fax : [redacted] **Was changed to:** [redacted] Phone: [redacted] Fax : [redacted]
Rationale for change		International coordinator moves to another hospital.

Section to be changed		Flowchart, 3.3.2 Inclusion criteria, 3.3.4 Removal of patients from therapy or assessments, 4.1.4.1 Dose reduction scheme, Section 5.2.4 Electrocardiogram, 5.2.5.3 Left ventricular function, Table 6.2.1:1 Visit 1 /Day -1 – Screening and dispensing visit, Table 6.2.2:1 Visit 2/Day 28 (-7/+2) and every 28 (-7/+2) days onwards - treatment and safety evaluation, Table 6.2.3:1 End of Treatment (EOT) Visit
Description of change		Flowchart, Note 3 "To be conducted at screening and at every 12 weeks thereafter by either ECHO or MUGA scans. For LVEF evaluations, the assessment can occur ±7 days of the scheduled Day 1 of the corresponding cycle" **Was changed to:** "ECG/LVEF to be conducted for patients with cardiac risk factors at the discretion of the investigator and in accordance to the current standard of care. In patients with ejection fraction below the institution's lower limits of normal, cardiac consultation as well as afatinib (Giotrif®) treatment interruption or discontinuation should be considered." *Deleted:* note 8 in the Flowchart.

		Section 3.3.2, Deleted: Inclusion criterion 4a "Left Ventricular Ejection Fraction (LVEF) > 50% or within institution normal values." *Section 3.3.4, Deleted:* "deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3." *Section 4.1.4.1, Deleted: "*Patients will discontinue treatment if they experience deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3." In section 5.2.4, "A 12-lead ECGs will be performed at Screening visit (see Flow chart). All post screening ECGs are optional and should be performed at the discretion of the investigator and in accordance to local current standard of care. ECGs will be completed locally at the trial sites. ECG machines used for this trial should be able to indicate QTc interval. The investigator will review the ECG recording at the time of the visit and record any ECG abnormality that meets AE criteria." **Was changed to:** "Twelve-lead ECGs will only be performed locally at the trial sites at the discretion of the investigator in accordance to local current standard of care for patients (see Flow chart). When performed, the investigator will review the ECG recording at the time of the visit and record any ECG abnormality that meets AE criteria." In section 5.2.5.3 "Left Ventricular Ejection Fraction (LVEF) as measured by Echocardiography (ECHO) or Multiple Gated Acquisition scan (MUGA) will be assessed at: Screening visit, every 12 weeks thereafter and at EOT visit (see Flow chart). The same method of measurement must be used throughout the trial. LVEF at EOT does not need to be performed if assessment was already done within previous 8 weeks. Requirement for EOT-LVEF assessment may be waived for patients meeting all the following criteria: 1) too sick from their disease

		or disease related symptoms to travel in the opinion of the investigator, 2) have evidence of stable LVEF on the most recent on-treatment assessment, and 3) have no evidence of cardiovascular disease" **Was changed to** "Left Ventricular Ejection Fraction (LVEF) as measured by Echocardiography (ECHO) or Multiple Gated Acquisition scan (MUGA) will be assessed if clinically indicated. The testing of this function and cardiac monitoring should be considered in patients that develop relevant cardiac signs/symptoms during treatment. In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as afatinib treatment interruption or discontinuation should be considered. " In Table 6.2.1:1, "12-lead resting ECG will be performed at the discretion of the investigator." and "Verify that this ECG was performed". **Were changed to:** "12-lead resting ECG may be performed at the discretion of the investigator." and "Verify if an ECG was performed." In Table 6.2.1:1, 6.2.2:1 and 6.2.3:1, *Added:* "only for patients with cardiac risk factors and those with condition that can affect LVEF, at the discretion of the investigator and in accordance to the current standard of care." In Table 6.2.1:1 and 6.2.3:1, "Verify that an ECHO (or MUGA) was performed." **Was changed to:** "Verify if an ECHO (or MUGA) was performed." *In Table 6.2.1:1, Deleted:* "Verify that LVEF > 50% or within institutional normal values."
Rationale for change		ECG/LFEV assessments to be performed only if clinically indicated. Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available

		clinical trial data, there is no suggestion that afatinib causes an adverse effect on cardiac contractility. However, afatinib has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during afatinib treatment, should be considered. In patients that develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Section to be changed		Flowchart, 5.2.2.1 Definitions of adverse events
Description of change		*Flowchart, Note D, Added*: At cycle 1 and 2 *Section 5.2.2.1, Added:* for the first two cycles
Rationale for change		Clarification on when dispensing the diary

Section to be changed		Flowchart, 6.1.1 Screening & dispensing visit, Table 6.2.2:1
Description of change		Flowchart, Note P "A phone call is required" **Was changed to:** "A contact is required" Section 6.1.1 "A phone call is required 15 (± 3) days after the patient's first dose to assess any AEs." **Was changed to:** "A contact is required 15 (± 3) days after the patient's first dose to assess any AEs." In Table 6.2.2:1, "phone call" **Was changed to:** "contact"
Rationale for change		Clarification on procedures.

Section to be changed		Flowchart, 5.2.2.1 Definitions of adverse events, 5.2.2.2 Adverse event and serious adverse event reporting, Table 5.2.2.2:1 AE/SAE reporting requirements, Appendix 10.3 Adverse

		event/Serious Adverse Event Reporting
Description of change		In the flowchart "In addition, any SAE that the treating physician becomes aware of after this period should also be reported" **Was changed to:** "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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator." In section 5.2.2.1 "In addition, any SAE that the treating physician becomes aware of after this period should also be reported" **Was changed to** "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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator." In table 5.2.2.2:1 "Report any SAE that the treating physician becomes aware of. This includes all deaths." **Was changed to** "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(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator." In section 5.2.2.2, *deleted*: "A diagram of the Adverse Event/Serious Adverse Event reporting requirements is provided in Appendix 10.3."

		Appendix 10.3 has been deleted.
Rationale for change		Variation on SAEs reporting after FU period.

Section to be changed		1.1 Medical background, 2.3 Benefit – Risk Assessment
Description of change		*In section 1.1, Added:* "Lastly, in trial 1200.34 (LUX-Lung 6), afatinib treatment compared to gemcitabine/cisplatin as first-line treatment for patients with Stage IIIB or IV adenocarcinoma resulted in a prolonged PFS and higher ORR observed in patients treated with afatinib (P13-06250)." *In section 2.3, Added:* "In addition, data from a third study, a Phase III open label, randomized trial in Asian patients with EGFR mutation-positive advanced adenocarcinoma of the lung, confirmed these results." *and added:* "1200.34 (LUX-Lung 6) More recent evidence of the benefits of afatinib (Giotrif®) versus chemotherapy in EGFR TKI-naïve asian patients with NSCLC was obtained in trial 1200.34, an open-label, randomized, Phase III trial of afatinib (Giotrif®) versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harboring an EGFR activating mutation who had received no prior chemotherapy or EGFR-targeting drugs for advanced NSCLC. The primary objective of the study was to assess the efficacy of afatinib (Giotrif®) as defined by progression-free survival (PFS) by central independent review and determined by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included ORR, disease control rate (DCR), duration of response, tumor shrinkage, overal survival (OS), patient-reported outcomes (PRO), and safety and pharmicokinetics of afatinib (Giotrif®). A central test for EGFR mutations was carried out using the companion diagnostic TheraScreen® EGFR RGQ PCR kit. Three hundred and sixty four (364) patients were randomised in a 2:1 ratio to receive either afatinib (n=242) 40 mg daily continuous treatment in the absence of disease progression or adverse events,

		or Gemcitabine/Cisplatin (GC) (n=122), with Gemcitabine 1000 mg/m2 on Day 1 and Day 8, with cycplatin 75 mg/m2 every 21 days up to 6 cycles. Baseline characteristics were well balanced between arms: overall the median age was 58 years, 65% of patients were female, 77% were never-smokers and 94% had Stage IV disease. Regarding EGFR mutation status, 51% had deletions in exon 19 (Del19), 38% had the L858R mutation and 11% had a variety of other less common mutations. As assessed by central independent review, treatment with afatinib (Giotrif®) resulted in a significantly prolonged PFS as compared to treatment with GC (median 11.0 vs. 5.6 months, HR 0.28, p<0.0001). The ORR for patients treated with afatinib (66.9%) was significantly higher than that for patients treated with GC (23%) (p<0.0001). The prolonged PFS and higher ORR observed in patients treated with afatinib (Giotrif®) were accompanied by significant delays (as compared to patients treated with GC) in time to deterioration of the cancer-related symptoms of cough (HR=0.45, p=0.0001) and dyspnoea (HR=0.54, p<0.0001). The pre-specified number of events necessary to Overall Survival (OS) has not yet been reached. The incidence of patients with AEs leading to dose reduction was 32.2% in the afatinib (Giotrif®) arm and 26.5% in the chemotherapy arm. In the afatinib (Giotrif®) arm, drug-related AEs leading to treatment discontinuation were experienced by 5.9% of the patients as compared to 39.8% of the patients in the chemotherapy arm. The most frequent reported afatinib-related AEs were diarrhoea, rash/acne and stomatitis. The most frequent reported chemotherapy-related AEs were nausea/vomiting , fatigue, and bone-marrow suppresion. There were 14 deaths (5.9%) reported due to on-treatment AEs in the afatinib (Giotrif®) arm, and three deaths (2.7%) were reported due to on-treatment AEs in the chemotherapy group. Significant differences between the proportion of patients with improvements in lung cancer symptoms of cough, dyspnoea, and pain were

		observed with patient in afatinib (Giotrif®) arm compared to chemotherapy (P13-06250). Taken together, these results support the efficacy data and conclusions of LUX-Lung 3." In Table 2.3:1, added data on 1200.43.
Rationale for change		Data on trial 1200.34 available

Section to be changed		3.3 Selection of trial population
Description of change		The statement "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" was reported twice, and one has been deleted
Rationale for change		Typo

Section to be changed		4.1.1 Identity of BI investigational product and comparator products; 4.1.6 Packaging, labelling, and re-supply
Description of change		In section 4.1.1, "Core Tablet: Lactose monohydrate, Microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone, and Magnesium stearate. Film-coat: Hypromellose 2910, Polyethylene glycol 400, Titanium dioxide, Talc, FD&C Blue No. 2 11-14% (not included in 20 mg tablet), and Polysorbate 80." **Was changed to:** Core Tablet: Lactose monohydrate, Microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone, and Magnesium stearate. Film-coat: Hypromellose 2910, Polyethylene glycol 400, Titanium dioxide, Talc, FD&C Blue No. 2 11-14% (may not be included in 20 mg tablet), and Polysorbate 80. In section 4.1.6 "Afatinib (Giotrif®) will be supplied by BI (or a designated 3rd party drug distribution vendor) as film-coated tablets in High-Density Polyethylene (HDPE), child-resistant, tamper-evident bottles. Available dosage strengths will be 40 mg, 30 mg and 20 mg. Each plastic bottle will contain 30 tablets of

		identical dosage strength." **Was changed to:** "Afatinib (Giotrif®) will be supplied by BI (or a designated 3rd party drug distribution vendor) as film-coated tablets. Available dosage strengths will be 40 mg, 30 mg and 20 mg. Tablets will be supplied in child-resistant, tamper-evident bottles. Each bottle will contain 30 tablets of identical dosage strength."
Rationale for change		Possible change in image tablets and bottles.

Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		*Added:* 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.
Rationale for change		New information.

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment, Appendix 10.3 List of potent inhibitors and inducers of P glycoprotein (MDR1)
Description of change		"Strong inhibitors of P-gp (including: Amiodarone, Azithromycin, Captopril, Carvedilol, Clarithromycin, Conivaptan, Cyclosporine, Diltiazem, Dronedarone, Erythromycin, Felodipine, Itraconazole, Ketoconazole, Lopinavir, Nelfinavir, Ritonavir, Quinidine, Ranolazine, Saquinavir, Tacrolimus, Ticagrelor, Verapamil) if administered prior to afatinib may lead to increased exposure to afatinib and therefore should be used with

		caution. If P-gp inhibitors (including: Carbamazepine, Phenytoin, Rifampicin, St John's Wort, Phenobarbital Salt, Tipranavir, Ritonavir) need to be taken, they should be administered simultaneously with or after afatinib. Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (U12-1482-01)." **Was changed to:** "Caution should be exercised when combining afatinib (Giotrif®) with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.3." *Added:* Appendix 10.3
Rationale for change		Updated information.

Section to be changed		3.3.3 Exclusion criteria, 4.2.3 Contraception and pregnancy
Description of change		Section 3.3.3, exclusion criterion n. 7 "are Women of Child-Bearing Potential (WOCBP) and men who are able to father a child, unwilling to use adequate contraception prior to trial entry, for the duration of trial participation and for at least 2 weeks after treatment has ended." **Was changed to:** "are Women of Child-Bearing Potential (WOCBP) and men who are able to father a child, unwilling to use adequate contraception prior to trial entry, for the duration of trial participation and for at least 28 days after treatment has ended." Section 4.2.3, "Women of childbearing potential who are sexually active and not using an acceptable method of birth control during the trial and for at least 14 days after the end of active therapy are not allowed to participate in the trial." **Was changed to:** "Women of childbearing potential who are sexually active and not using an acceptable method of birth control during the trial and for at

		least 28 days after the end of active therapy are not allowed to participate in the trial." "Male patients should use adequate contraception (e.g., condom and spermicidal jelly) during the trial and for at least 14 days after the end of active therapy." **Was changed to:** "Male patients should use adequate contraception (e.g., condom and spermicidal jelly) during the trial and for at least 28 days after the end of active therapy."
Rationale for change		Acceptable methods of birth control should be used for at least 28 days after the end of active therapy to align to the SPC.

Section to be changed		4.2.3 Contraception and pregnancy
Description of change		*Deleted:* Abstinence is not an acceptable method of birth control for this trial.
Rationale for change		The method is acceptable

Section to be changed		Table 4.2.3: 1 Pregnancy reporting
Description of change		*Added:* "and congenital malformation/anomaly"
Rationale for change		Also congenital malformation/anomaly must be reported as SAE.

Section to be changed		5.3.2.1 Documentation of diarrhoea
Description of change		"dehydration" **Was changed to:** "hydration"
Rationale for change		Typo.

Section to be changed		Table 6.2.1:1, Table 6.2.2:1, Table 6.2.3:1, Table 6.2.4:1
Description of change		Added: "and all SAEs"
Rationale for change		Clarification.

Section to be changed		9.1 Published references

Description of change		*Added:* "P13-06250 Wu YL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Massey D, Shi Y, Chen J, Zazulina V, Geater SL. LUX-Lung 6: a randomized, open-label, phase III study of afatinib (A) vs emcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. 49th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 31 May - 4 Jun 2013 J Clin Oncol 31 (Suppl), (2013)"
Rationale for change		New reference.

Number of global amendment		2
Date of CTP revision		17 Jul 2017
EudraCT number		2009-017661-34
BI Trial number		1200.55
BI Investigational Product(s)		Afatinib (BIBW 2992)
Title of protocol		An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)
To be implemented only after approval of the IRB/IEC/Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Number of entered patients changed from up to 500 to 481
Rationale for change		To reflect the actual number
Section to be changed		Clinical Trial Protocol Synopsis – Duration of treatment and Section 3: Description of design and trial population
Description of change		The following sentence has been added: "…and/or have access to Afatinib via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation,…"
Rationale for change		To ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial
Section to be changed		Section 3.3.4.1:
Description of change		The following statement has been added: Study treatment can be continued beyond radiological progression only (without symptomatic progression) until clinical progression if it is deemed in the patient's benefit following a careful risk benefit assessment and confirmation of clinical benefit by the investigator. Each case must be discussed in details and agreed between the investigator and the Sponsor, and only after sponsor approval, the trial treatment can continue.
Rationale for change		Clarification
Section to be changed		Section 3.3.4.1 Removal of individual patients
Description of change		The sponsor may remove patients from the study if the patient has access to afatinib via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, compassionate use protocol or other means based on local regulation. This may mean a change in packaging and labelling. The cost of any ongoing supply of study medication will be incurred by the sponsor until progression occurs. If a patient is

		removed from the study treatment, an end of treatment 0-14 days later and a follow up visit 28 days later will be performed to ensure all adverse events are followed up and then the patient will be considered to have completed the trial.
Rationale for change		To ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial
Section to be changed		Section 3.3.4.2: Discontinuation of the trial by the Sponsor
Description of change		The following point has been added: 4.At the discretion of the sponsor. Drug supply will be arranged for ongoing patients if Sponsor decides to terminate the trial.
Rationale for change		To ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial
Section to be changed		Section 7.3.4: Interim analyses
Description of change		The following sentence has been added: “This is a single-arm open label study. The interim analysis may be done after recruitment has been completed. The analyses will include the assessment of safety and efficacy if conducted. The result from the interim analysis may be presented at professional conferences and published in articles after stop of recruitment.”
Rationale for change		Include interim analysis in protocol.

Number of global amendment		3
Date of CTP revision		08 Feb 2020
EudraCT number		2009-017661-34
BI Trial number		1200.55
BI Investigational Product(s)		Afatinib (BIBW 2992)
Title of protocol		An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)
To be implemented only after approval of the		X

Number of global amendment		3
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		Flow chart
Description of change		The following footnotes have been added: 8 In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), shipment of trial medication to patient's home may be arranged or dispensation of two kits may be done. *** In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), patient visits may be performed remotely.
Rationale for change		Experiences from the COVID-19 first wave situation; to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment.
Section to be changed		Cover page; Abbreviations; Section 3.1.1 Administrative structure of the trial Section 8.1 Study approval, Patient Information, and Informed Consent
Description of change		The following wording: TCM Trial Clinical Monitor CML Local Clinical Manager

Number of global amendment		3
		was changed to: CTL Clinical Trial Leader CTM Clinical Trial Manager
Rationale for change		Administrative change
Section to be changed		2.3 Benefit – risk assessment
Description of change		The following wording has been added: Gastrointestinal perforation, including fatalities, has been reported during treatment with afatinib in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking afatinib, treatment should be permanently discontinued.
Rationale for change		Update based on the current IB
Section to be changed		Section 2.4 Benefit – risk assessment in context of COVID-19 infection.
Description of change		The section has been added.
Rationale for change		New information on benefit/risk due to COVID-19 pandemic situation.
Section to be changed		3.3.4.1 Removal of individual patients Table 4.1.4.1: 1 Dose reduction scheme
Description of change		If gastrointestinal perforations is diagnosed, afatinib (Giotrif®) must be discontinued and patient must complete trial participation.
Rationale for change		According to current IB
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		The following statement has been added:

Number of global amendment		3
		In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the patients' home or two bottles of trial medication may be dispensed at the beginning of a treatment cycle, so that the next visit can be performed remotely.
Rationale for change		Experiences from the COVID-19 first wave situation; to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment.
Section to be changed		Section 6.1.2: Treatment and safety evaluation visits; Section 6.1.3: End of Treatment (EOT) visit
Description of change		The following statement has been added: In the event of force majeure or other disrupting circumstances (e.g. pandemic, war,) patients visit may be performed remotely to collect/report study data such as adverse events, concomitant therapies, clinical evaluation of tumour by symptoms and study medication compliance check. Where permitted by local law and regulations, trial medication may be shipped directly to the patients' home or two bottles of trial medication may be dispensed at the beginning of a treatment cycle, so that the next visit can be performed remotely.
Rationale for change		Experiences from the COVID-19 first wave situation; to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment.
Section to be changed		9 References
Description of change		Updates of references

Number of global amendment		3
Rationale for change		Updates of references

APPROVAL / SIGNATURE PAGE

Document Number: c02215411 **Technical Version Number:17.0**

Document Name: 1200-0055--protocol-revision-03

Title: An open label trial of afatinib (Giotrif) in treatment-naive (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	08 Feb 2021 15:06 CET
Approval-Therapeutic Area [redacted]		08 Feb 2021 15:13 CET
Approval-Team Member Medicine		10 Feb 2021 09:17 CET
Approval-Team Member Medicine		10 Feb 2021 09:20 CET
Approval-Clinical Trial Leader		10 Feb 2021 09:35 CET
Approval-Therapeutic Area [redacted]		10 Feb 2021 15:38 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

CO-ORDINATING INVESTIGATOR SIGNATURE

Trial Title: An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)

Trial Number: 1200.55

Protocol Version: 4.0

I herewith certify that I agree to adhere to the trial protocol and to all documents referenced in the trial protocol.

Date: 08 FEB 2021

Name: [redacted]

Signature [redacted]

Affiliation:

[redacted]

Signed signature page is located in BIRDS