# Clinical Trial Protocol

**Doc. No.: c14890504-01**

| | |
|---|---|
| **BI Trial No.:** | 1200.66 |
| **BI Investigational Product:** | Giotrif®/ Gilotrif™ (afatinib) |
| **Title:** | An open label, multicentre, single-arm trial to assess the safety of afatinib for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) |
| **Clinical Phase:** | IIIb |
| **Trial Clinical Monitor:** | |
| **Co-ordinating Investigator:** | |
| **Status:** | Final Protocol (Revised Protocol based on global amendment 4) |
| **Version and Date:** | Version: 5.0 Date: 3 Feb 2017 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br>Giotrif®/ Gilotrif™ | | | |
| **Name of active ingredient:**<br>afatinib (BIBW 2992) | | | |
| **Protocol date:**<br>29 Mar 2013 | **Trial number:**<br>1200.66 | | **Revision date:**<br>3 Feb 2017 |

| | |
|---|---|
| **Title of trial:** | An open label, multicentre, single-arm trial to assess safety of afatinib for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) |
| **Co-ordinating Investigator :** | |
| **Trial sites:** | Multi-center trial conducted at approximately 40 sites within Asia countries (China Hong Kong, India, Singapore, Taiwan) |
| **Clinical phase:** | IIIb |
| **Objective:** | To evaluate the safety, tolerability and efficacy of afatinib 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-Tyrosine Kinase Inhibitor (TKI) |
| **Methodology:** | Open-label, multi-center, single-arm trial |
| **No. of patients:** | |
| **total entered:** | Approximately **500** patients |
| **each treatment:** | All entered patients will receive afatinib |
| **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 products:** | Afatinib as 40, 30, and 20 mg film-coated tablets<br>Patients will receive starting dose of 40 mg afatinib once daily with an option to reduce the dose based on individual tolerability. |
| **dose:** | 40 mg/day or 30 mg/day or 20 mg/day |
| **mode of admin.:** | Oral, once daily, continuous |

| | | | |
|---|---|---|---|
| **Name of company:**<br><br>Boehringer Ingelheim | | **Tabulated Trial Protocol** | |
| **Name of finished product:**<br><br>Giotrif®/ Gilotrif™ | | | |
| **Name of active ingredient:**<br><br>afatinib (BIBW 2992) | | | |
| **Protocol date:**<br>29 Mar 2013 | **Trial number:**<br>1200.66 | | **Revision date:**<br>3 Feb 2017 |
| **Comparator products:** | None. | | |
| **dose:** | NA | | |
| **mode of admin.:** | NA | | |
| **Duration of treatment:** | Continuous treatment in the absence of progressive disease and trial withdrawal criteria specified in Section 3.3.4.<br><br>In this trial, progression is determined by investigator. Afatinib must be permanently discontinued when investigator judges that patient is no longer benefiting from treatment with afatinib.<br><br>. | | |
| **Criteria for efficacy:** | Time to symptomatic progression (TTSP) as determined by investigator | | |
| **Criteria for safety:** | Adverse events according to Common Terminology Criteria (CTCAE Version 3) | | |
| **Statistical methods:** | Exploratory descriptive statistics of demographic, efficacy and safety data will be presented as appropriate. | | |

# FLOW CHART

| **Procedure** | **Screening** | **Baseline** | | **Treatment and Safety evaluation** | | **End of Treatment** | **Follow-up** |
|---|---|---|---|---|---|---|---|
| **Visits (V)** | **V1*** | | | **V2, V3, V4, V5, V6. Onwards** | **V4, V7, V10, V13, V16... Onwards** | **EOT**** | **FU#** |
| **Days** | **Day -1 (-28 to -1)** | **Day 1** | **Day 15 (±3) (phone call)** | **Day 28 (-7/+2 days) of every treatment cycle** | **Day 28 (-7/+2) of every 3rd treatment cycle** | **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 | |
| Tumour clinical assessment[3] | X | | | | X | X | |
| | | | | | | | |
| ECOG | X | | | X | | X | |
| Safety laboratory testing[5] | X | | | | X | X | |
| Urine examination[6] | X | | | | | X | |
| Pregnancy test[7] | X | | | | | X | |
| Adverse events | X | X | X[8] | X | | X | X[9] |
| Dispense trial medication | | X | | X | | | |
| Compliance | | | | X | | X | |
| Termination of trial medication | | | | | | X | |
| Patient Status | | | | | | | X |
| Diarrhoea diary completion[10] | | X | | X[11] | | | |

* Afatinib 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. All screening procedures conducted as per site standard of care prior to ICF and within the screening period of 28 days prior to first dose can be used for the study.

2 Includes vital signs (pulse, blood pressure), temperature, weight (kg) and an ECOG performance score. Height is only captured at screening visit only.

3. Tumour assessment should be performed by investigator according to local standard at the time of screening. During treatment period, tumour assessment should be conducted according to local standard of care or recorded every 3 cycles. Diagnosis of progression is at the discretion of the investigator. Investigator should confirm there is clinical benefit before patient continues on next cycle of afatinib. See definition of PD in Section 5.1

**4**

**5** Safety laboratory testing: haematology and biochemistry examinations (see Section 5.2.3). All laboratory tests mentioned in Table 5.2.3: 1 are required to be performed at screening, every 12 weeks following first dose. Also recommended to be performed at the discretion of the investigator and in accordance to the current standard of care.

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

**7** 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.

**8** A phone call is required 15 (±3) days after the patient's first dose to assess AEs and dose reductions.

**9** 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. In addition, only SAE that are considered related to the trial medication or trial design must be reported after the FU visit (end of residual effect phase).

**10** Provide a diarrhoea diary with drug supply see sample on in Appendix 10.4. Data on diaries should be checked by the study staff against AEs and Appendix 10.1.1.

**11** Diarrhoea diary will only be dispensed for the first 2 cycles of Afatinib treatment.

** EOT (V): end of treatment (visit) with trial medication. Patients without clinical progression at EOT will be followed as per site standard practice until appearance of clinical progression or start of other anti-cancer treatment whichever occurs earlier.

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

# 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 |
| ASCO | The American Society of Clinical Oncology |
| AST (SGOT) | Aspartate Amino Transferase (Serum Glutamic Oxaloacetic Transaminase) |
| ß-HCG | Beta-Human Chorionic Gonadotropin |
| BI | Boehringer Ingelheim |
| BSC | Best Supportive Care |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| CML | Clinical Monitor Local |
| CRA | Clinical Research Associate |
| CR | Complete Response |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMF | Clinical Trial Master File |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DCR | Disease Control Rate |
| DNA | Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| ECOG | Eastern Cooperative Oncology Group |
| EC | Ethics Committee |
| eCRFs | Electronic Case Report Forms |
| 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) |
| FDA | Food and Drug Administration |
| FU | Follow-up Visit |
| GCP | Good Clinical Practice |
| GGT | y-glutamyltransferase |
| HDPE | High-Density Polyethylene |
| HEPB | Hepatitis B |
| HEP C | Hepatitis C |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonisation |
| ILD | Interstitial Lung Disease |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |

| | |
|---|---|
| ISF | Investigator Site File |
| IUD | Intrauterine Device |
| LDH | Lactic Dehydrogenase |
| LVEF | Left Ventricular Ejection Fraction |
| mL | Milliliter |
| MTD | Maximum Tolerated Dose |
| MUGA | Multiple Gated Acquisition scan |
| NYHA | New York Heart Association |
| NSCLC | Non-Small Cell Lung Cancer |
| OPU | Operating Unit |
| ORR | Overall Response Rate |
| PC | Pemetrexed/Cisplatin |
| PCR | Polymerase Chain Reaction |
| P-gp | P-glycoprotein (P-gp) |
| PK | Pharmacokinetics |
| SAE(s) | Serious Adverse Event |
| SOPs | Standard Operating Procedures |
| SUSARs | Suspected Unexpected Serious Adverse Reactions |
| TCM | Trial Clinical Monitor |
| TDM | Trial Data Manager |
| TKI | Tyrosine Kinase Inhibitor |
| tmax | Time of Occurrence for Maximum Peak Drug Concentration |
| TS | Treated Set |
| 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 deaths in many countries. 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 targeted therapies most extensively studied are the inhibitors of 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 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.

## 1.2 DRUG PROFILE

Afatinib is a potent, selective, and 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, and ErbB4 resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors. [U02-1083, U03-1086, U11-2645-01].

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (c01617169-04) and/or local product label information. All references in this protocol concerning afatinib refer to the free base compound of afatinib.

Afatinib is moderately rapidly absorbed after oral administration, with maximum plasma concentrations of afatinib achieved mainly at 2 to 5 hours after drug oral administration. Afatinib maximum plasma concentrations and area under the curve increased slightly overproportional with increasing doses in the therapeutic range of 20-50mg.. However, moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via 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 is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-glycoprotein (P-gp) transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for 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 s afatinib is not irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two phase I open label dose-escalation trials (U07-3128-02, U08-1023-03) each determined a Maximum Tolerated Dose (MTD) with continuous dosing of afatinib as 40 mg and 50 mg daily, respectively. Both daily doses (40mg and 50mg) have been used in

Phase II and Phase III trials depending on the patient population evaluated. 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 common AEs in Afatinib monotherapy trials were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash/acne, dry skin, pruritus), nail effects, fatigue and decreased appetite.-Early and proactive management of diarrhoea, skin rash, mucositis 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).

At the time of this amendment, afatinib is an approved medicine in most countries for use in patients with EGFR mutation positive NSCLC and is approved in the EU for the treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy and by the FDA for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial will assess the safety of afatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring EGFR mutation(s) and have never been treated with an EGFR-TKI. The trial will also obtain additional data on clinical benefit of afatinib in this patient population.

## 2.2 TRIAL OBJECTIVES

Primary objective of the trial is to evaluate the safety of afatinib 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.

Secondary objective is to assess the efficacy of afatinib in patients with locally advanced or metastatic NSCLC harbouring EGFR mutation(s) and treated with afatinib.

See Section 5 for trial endpoints.

## 2.3 BENEFIT - RISK ASSESSMENT

The benefits of providing afatinib to patients in this trial are based on the results obtained in two prior trials in patients with pathologic confirmation of stage IIIB or stage IV NSCLC. These trials were afatinib 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 and 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

In study 1200.32 (LUX-Lung 3) treatment with afatinib resulted in a significantly prolonged PFS as compared to treatment with chemotherapy by independent review (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 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 (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 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 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 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 arm, with 4 of them (sepsis, dyspnoea, acute respiratory distress syndrome, and death) considered related to afatinib 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]

In study 1200.22 (LUX-Lung 2) confirmed objective responses in the first line setting were noted in 66% of 61 patients with a median PFS of 12.0 months (and of 13.7 months in patients with common EGFR mutation(s) by independent review. Median OS was not reached in the first line population.

1200.34 (LUX-Lung 6)

More recent evidence of the benefits of afatinib 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 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 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, overall survival (OS), patient-

reported outcomes (PRO), and safety and pharmacokinetics of afatinib. 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 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 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 arm and 26.5% in the chemotherapy arm. In the afatinib 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 suppression. There were 14 deaths (5.9%) reported due to on-treatment AEs in the afatinib 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 arm compared to chemotherapy ( P13-06250). Taken together, these results support the efficacy data and conclusions of LUX-Lung 3.

Risks

Adverse events observed in the 359 patients treated with afatinib in the clinical studies described above plus 1544 patients treated in two other studies which were clinically enriched for EGFR mutations (1200.23 [U10-3048-01] and 1200.42 [U12-1167-01]) have been of a nature and severity expected for EGFR inhibitors. Diarrhoea, rash/acne, stomatitis, and lip, nail, and ocular effects represent the mechanistic effect of the inhibition of EGFR by afatinib. As such, diarrhoea and rash/acne were the most frequently reported AEs. Nearly all patients developed diarrhoea with an onset within 2 weeks of treatment exposure. Rash/acne occurred at a high incidence, beginning within 4 weeks of afatinib exposure for about half of cases. These events were mainly of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 with an incidence of CTCAE Grade 3 diarrhoea in the studies

described above of 14-20% and that for rash/acne 9-23%. The occurrence of CTCAE Grade 4 diarrhoea or rash/acne was infrequent, <0.5% overall in these studies.

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. Treatment related AEs that led to discontinuation occurred in 8% of afatinib treated patients in study 1200.32, and 9% in study 1200.22. The frequency of discontinuation due to diarrhoea was <5% for afatinib 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 for as long as there was clinical benefit. In study 1200.32 in which patients were randomised between treatment with afatinib and chemotherapy, overall treatment-related AEs led to discontinuation of therapy in 8% of patients receiving afatinib as compared to 12% of patients receiving pemetrexed/cisplatin in spite of the fact that the afatinib 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 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. [c01617169-04] 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.

Overall these findings demonstrate that for patients with EGFR mutation positive NSCLC the benefits of treatment with afatinib 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 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.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open-label, multicentre, single arm trial, designed to evaluate the safety and efficacy of the investigational drug afatinib 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 in the absence of disease progression or meeting any other trial withdrawal criteria (see Section 3.3.4). In this trial, disease progression is determined by the investigator. Afatinib must be permanently discontinued when investigator judges that patient is no longer benefiting from treatment with afatinib. 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. The investigator will assess the patient at each visit and record adverse events. Investigator can perform radiological assessment according to local standard of care at his discretion. Clinical benefit will be assessed at each visit (i.e., every 28 days) based on change in cancer-related symptoms.

Patients meeting withdrawal criteria will stop treatment with afatinib and undergo End of Treatment (EOT) visit. After end of treatment, all AEs, including those persisting are followed-up for up to 28 days and it should be confirmed if they have resolved or sufficiently characterised. The end of the trial is defined as “last patient out”, ie. Follow-up (refer to Section 3.3.4.1) completed by last patient.

Investigators in this trial will be physicians experienced in treating patients with NSCLC and who can complete the site qualification and initiation process.

### 3.1.1 Administrative structure of the trial

This trial is sponsored by Boehringer Ingelheim (BI).

Boehringer Ingelheim (BI) will appoint a Trial Clinical Monitor (TCM), 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 Monitor Local (CML), 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: Trial Data Manager (TDM), Trial Statistician (TSTAT) and Trial 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 CML 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 an 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).

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.

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

The primary objective of this trial is to assess the safety of afatinib in patients with NSCLC. This trial is a single-arm, open-labeled study.

## 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 recruit approximately 500 patients at approximately 40 sites within China, Hong Kong, India, Singapore and Taiwan.

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) presence of Epidermal Growth Factor Receptor (EGFR) mutation in tumour biopsy. Results of EGFR mutation must be available before enrolment in this trial. No rebiopsy is required for purpose of this trial.

3) male or female patients age ≥18 years (For India only, male or female patients age ≥18 years and ≤75 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) and 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) use of 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 4 weeks 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 from day 1 of first dose of afatinib. At least 7 days should have elapsed since minor surgical procedure including placement of an access device or fine needle aspiration and at least 14 days for diagnostic or palliative video-assisted thoracoscopic surgery (VATS).

5) known hypersensitivity to afatinib 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) Women of Child-Bearing Potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use medically acceptable method of contraception during the trial entry and for at least 4 weeks after treatment has ended. Adequate methods of contraception and Women of Child-Bearing Potential described in Section 4.2.3. Perimenopausal women must be amenorrhoeic for at least 24 months to be considered for non-childbearing potential.

8) childbearing potential (see Section 4.2.3) who:

    a. are nursing or

    b. are pregnant or

    c. are not using an acceptable method of birth control, or do not plan to continue using this method throughout the trial and/or do not agree to submit to pregnancy testing required by this protocol

9) history of or co-existing 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 cannot 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) Known 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 brain metastases, who were previously treated, are eligible provided they have asymptomatic brain metastasis 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
- 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 cannot 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 interstitial lung disease (ILD)
- change in patient's status creating an unfavourable risk/benefit in favour to stop trial treatment.
- termination of the trial
- Start of any other anti-cancer treatment

When discontinuation is due to a AE/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.

The sponsor may remove patients from the study after completion of the primary analysis if the patient has access to afatinib through marketed product, an expanded-access program, named patient use program, or compassionate use protocol or other means based on local regulation. The cost of any ongoing supply of afatinib will be incurred by the sponsor. If a patient is removed from the study treatment, an end of treatment and follow-up visit will be performed to ensure all adverse events are reported and followed up.

#### 3.3.4.1.1 Patient discontinuation of trial participation

Patients who discontinues from the treatmentl, will complete an End of Treatment (EOT) visit (see Section 6.2.3) and then a Follow Up (FU) visit 28 days later (see Section 6.2.4).

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

### 3.3.4.2 Discontinuation of the trial by the sponsor

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

1. 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 for any reason.

4. At the discretion of the sponsor (BI).

# 4. TREATMENTS

## 4.1 TREATMENTS TO BE ADMINISTERED

Boehringer Ingelheim will provide the investigational product afatinib.

### 4.1.1 Identity of BI investigational product and comparator product

| | |
|---|---|
| Substance (INN): | afatinib (BIBW 2992) |
| 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 symptomatic 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

An enrolment form should be faxed to the sponsor, or designee, as soon as written informed consent has been obtained. The form and instructions will be provided in the ISF. Patients who meet all eligibility criteria will be entered into the trial. Enrolment of new patients into the trial will end once enrollment goal, (500 patients) 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. All eligible patients will receive afatinib.

### 4.1.3 Selection of doses in the trial

The starting dose for patients is 40 mg once 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, (c01617169-04) as well as the results of the LUX-Lung 3 (1200.32) study.

### 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 each day. Treatment will stop when the patient meets withdrawal criteria listed in Section 3.3.4.1. Trial drug will be prescribed by the investigator and may be dispensed either by the investigator or designee.

The dose of afatinib for this trial is 40 mg. All dose reductions will be based on individual tolerability (see Section 4.1.4.1). Each dose reduction will be by 10 mg and no reduction is allowed less than 20 mg dose. Patients who are unable to tolerate 20 mg dose must be permanently discontinued from trial.

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

If dosing of whole tablets is not possible, afatinib tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 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 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.

#### 4.1.4.1 Dose reduction scheme

Treatment related adverse events will be managed by treatment pauses and subsequent dose reductions of afatinib 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:<br><br>• Diarrhoea<br>Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration<br><br>• Reduced renal function<br>to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline<br><br>• Any drug related AE Grade ≥3 | Pause treatment until patient has recovered to Grade ≤1 or baseline[1].<br><br>Resume treatment at a reduced dose according to the Dose Reduction Column.<br><br>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.<br>If patient cannot tolerate 20mg/day, permanent discontinuation of afatinib 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 at current dose. If AEs are drug related, follow directions in row above.<br><br>If ILD is confirmed, discontinue afatinib. |

* 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 will be decided by the investigator.

After treatment pause due to drug related adverse events, treatment with afatinib can be resumed after patient recovers to ≤ Grade 1 or baseline. Dose reduction should always follow a treatment pause for drug related AE more than grade 1. In the event of any unrelated adverse events, the investigator may choose to pause the medication to allow the patient to recover, but no dose reduction is required.

Patients will discontinue treatment if they experience deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction is required and is at the discretion of the investigator. If the medication is continuously interrupted for more than 14 days, the decision to continue with afatinib will be made by the investigator following discussion with the sponsor. Investigator can consider permanently discontinue the patient from the trial if they have been off trial medication for more than 6 weeks.

### 4.1.5 Blinding and procedures for unblinding

Not applicable since this is an open-label trial.

### 4.1.6 Packaging, labelling, and re-supply

Afatinib will be supplied by BI (or a designated 3rd party drug distribution vendor) as film-coated tablets in High-Density Polyethylene (HDPE) or Polypropylene (PP), 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. 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 bottles will be dispensed at each visit to last until the next scheduled visit. Afatinib 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 bottles must be kept in a secure, limited access storage area (to authorized people) under storage conditions defined on bottle label until supplied/administered to patient. Temperature logs must be maintained to make certain that the afatinib supplies are stored at the correct temperature. Facilities that have a central temperature alarm do not have to maintain a log; however, a note to file should be kept in the ISF describing the system and the procedure in the event of an alarm. If a site does not have an acceptable central temperature alarm system then the Min/Max temperatures will be documented using a calibrated thermometer with a valid calibration certificate to ensure storage conditions per label. In the event that the temperature would be out of range, this has to be documented in the ISF and reported to the sponsor according the Storage conditions for Trial Medications (STORM) in the ISF.

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

### 4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

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
- proof of a medical license for the principal investigator,

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

Rescue medication

Rescue medications to reverse the action of afatinib are not available. There is no specific antidote for overdosage with afatinib. In cases of suspected overdose, afatinib should be withheld and supportive care initiated. If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage. Potential adverse events should be treated symptomatically. The current version of the Investigator Brochure (IB) lists the AEs expected

with afatinib ( c01617169-04 ). Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhoea, stomatitis/mucositis, 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.

### 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 or total VATS is allowed. 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 continuously interrupted for more than 14 days, the decision to continue will be made by the investigator following discussion with the sponsor.

All concomitant therapy 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 around one week prior to the surgery, and to restart treatment after complete wound healing, provided that complete wound healing occurs ≤ 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. 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 inducers (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).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.

#### 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 unwilling to be abstinent or to use 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 abstinence, 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.<br><br>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).<br><br>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. |
| End of Treatment (EOT) though Follow-up visit | The pregnancy should be reported to the sponsor immediately using the pregnancy monitoring form (Part A).<br><br>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).<br><br>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 investigator. The appropriate number of afatinib tablets will be provided to the patient to be self-administered at home. Patients will be asked to return all unused trial medication at each visit. It is the investigator's or his delegate's responsibility to conduct compliance check at each of these returns. At the end of each visit, remaining medication will be collected. Discrepancies between the number of tablets remaining and the calculated number of tablets that patients should have taken will be documented and explained. If the patient is eligible for a further course of treatment, ~~of~~ a new bottle will be dispensed.

Patients experiencing emesis should not take a replacement dose. Afatinib must not be taken more than once a day under any circumstances.

A maximum of 20% of the dispensed afatinib doses may be missed for other reasons aside from drug-related AEs or instructions from investigator. Patients who miss afatinib treatment more frequently are considered non-compliant. All overdoses are considered as non-compliance.

# 5. VARIABLES AND THEIR ASSESSMENT

The primary endpoint of this study is the safety assessment; refer to Section 5.2.1 for a description of safety endpoints.

## 5.1 EFFICACY

Efficacy assessments are secondary endpoints.

### 5.1.1 Endpoints of efficacy

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

### 5.1.2 Assessment of efficacy

Progression will be assessed by investigator. Lung cancer-related symptoms will be assessed by investigator at each visit. The date in which patient experiences progression requiring change in anti-cancer medication or stopping trial treatment will be defined as date of clinically significant symptomatic progression.

Although radiological assessments are not part of this study, the investigators will be allowed to perform imaging assessments at their discretion. Radiological progression may not occur at same time point as symptomatic progression. .

## 5.2 SAFETY

### 5.2.1 Endpoints of safety

The primary endpoint for safety assessment is number of patients with serious adverse events (SAEs).

Number of patients with adverse events assessed by the treating physician as related to afatinib will be evaluated as a secondary endpoint.

Safety will also 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

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. In addition, any SAE that the investigator becomes aware of after the FU visit (End of Residual effect Phase) which is considered related to trial medication or trial design must also be reported. Residual Effect Phase is defined as >28 days after last trial drug administration.

#### 5.2.2.1 Definitions of adverse events

Adverse event

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

Serious adverse event

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

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

- Hospitalizations for respite care
- 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 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, physical examination, and laboratory test results

Changes in vital signs, 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.

If the investigator determines any protocol-specific significant event is related to trial drug, the administration of the trial drug must be managed according to Section 4.1.4.1 of the protocol.

Expected Adverse Events

For expected (listed) AEs of afatinib, see the current version of the IB ( **c01617169-04**).

#### 5.2.2.2 Adverse event and serious adverse event reporting

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. |
| Post-treatment. (Residual Effect Phase) (>28 days after last trial drug administration) | Report any SAE that the treating physician becomes aware of after the FU visit (End of Residual Phase) which is considered related to trial medication or trial design. This includes all deaths. |

A diagram of the Adverse Event/Serious Adverse Event reporting requirements is provided in Appendix 10.3.

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, 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 and biochemistry examinations. All laboratory tests mentioned in Table 5.2.3: 1 should be performed at screening (Visit 1) and every 12 weeks thereafter. All other 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), ANC |
| Chemistry | Electrolytes:<br>Sodium, and potassium<br><br>Liver function tests:<br>Alkaline phosphatase, aspartate amino transferase (AST/SGOT), alanine amino transferase (ALT/SGPT), γ-glutamyltransferase (GGT), total bilirubin<br><br>Renal function parameters:<br>Blood urea/Blood Urea Nitrogen (BUN), creatinine<br><br>Other:<br>Glucose, albumin, phosphorus, lactate dehydrogenase (LDH), total protein, |
| Urinalysis | pH, protein, glucose, blood/erythrocytes, leucocytes, nitrite; in case of clinically significant finding further evaluation should be performed and results documented. Dipstick testing is sufficient. |
| 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 be only performed at the discretion of the investigator in accordance to local current standard of care for patients.

### 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.

#### 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 considered in patients that develop relevant cardiac sign/symptoms during treatment. In patients with an ejection fraction below the institution's lower limits of normal, cardiac consultation as well as afatinib treatment interruption or discontinuation should be considered. Patients with cardiac risk factors and those with conditions that can affect patients that develop cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

## 5.3 OTHER

### 5.3.1 Documentation of diarrhoea

Patients will receive a diarrhoea diary for the first 2 cycles of Afatinib 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 the 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 quantitative daily diarrhea data (number of bowel movements and consistency of diarrhoea. 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-diarrhoeal medication at first signs of diarrhea, appropriate anti-diarrhoeal medication dose modifications based on the daily diarrhoea symptoms and non-pharmacologic interventions

will facilitate early and appropriate interventions to minimize the duration and severity of dose limiting afatinib-induced diarrhoea. A sample of the diary can be found in Appendix 10.4.

## 5.4 APPROPRIATENESS OF MEASUREMENTS

Safety assessment is the primary objective of the trial. 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.

For patients with EGFR mutation and responding to treatment with an EGFR TKI, continuation of same treatment has shown to improve survival compared to switching patients to chemotherapy (R12-5456). In this protocol, patients can continue to receive afatinib until investigator considers patient to have developed clinically significant increase in lung-cancer symptoms that requires change in treatment. This date will be defined as date of symptomatic progression. Time to symptomatic progression is a well-accepted endpoint to measure clinical benefit.

## 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 Endpoint based on biomarker

Not applicable

### 5.6.2 Methods of sample collection

Not applicable

### 5.6.3 Analytical determinations

Not applicable

## 5.7 PHARMACODYNAMICS

Not applicable since no 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 visit (Visit 1)

Patients considered for this trial will sign an informed consent before screening for eligibility (see Flow chart).

### 6.1.2 Baseline visit (Visit 1)

If patients meet all eligibility requirements they will be dispensed drug for the first 28 day treatment cycle.

### 6.1.3 Treatment and safety evaluation visits

Safety evaluation visits are to be conducted after afatinib 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. A phone call is recommended 15 days (+/- 3 days) after first dose to assess any AEs.

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.

### 6.1.4 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.

### 6.1.5 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. A window period of 7 days is allowed.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The trial procedures are summarized in the Flow chart.

### 6.2.1 Screening and baseline periods

Visit 1/Day -1 – Screening/baseline visit

Informed consent and authorization to release protected health information 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 starting study medication 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 / – Screening visit and baseline visit

| | The following must be performed and information recorded in the patient's chart | What to include in eCRF |
|---|---|---|
| Informed Consent | Written informed consent and authorization to release protected health information 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 |
| Medical history | Oncological and relevant non-oncological history including details of previous treatment for NSCLC (including pathology) | • History of NSCLC:<br>• Oncological and relevant non-oncological history including details of any previous treatment for NSCLC<br>• The date of first histological diagnosis, the primary tumour site, the number and location of metastatic sites (bone, brain, liver, pleural effusion, other)<br>• Tumour assessment/stage at the time of diagnosis according to the TNM-classification<br>• Previous surgeries for NSCLC<br>• 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.<br>• Previous radiotherapy - the total radiation dose and radiation field will be recorded |

| | The following must be performed and information recorded in the patient's chart | What to include in eCRF |
|---|---|---|
| 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). |
| Safety Laboratory Testing | Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations.<br>Blood samples may be collected to perform the following:<br>- Retest for missing laboratory test results required to establish eligibility<br>- 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.<br>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.<br>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. |

| | 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. |
| 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 except for those for rash and diarrhoea. |
| Dispense Trial Medication | Dispense 1 bottle of afatinib for the 28 day treatment cycle (see Section 4.1.4.) | Record: dose dispensed, all medication numbers and date of first dose administration |
| Tumour Assessment | Tumour assessment will be based on the assessment prior to study entry | Radiological assessment to be included on CRF |

### 6.2.2 Treatment periods

Safety evaluation visits are to be conducted after the initiation of afatinib, 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.

Investigator must make a phone call to patient on day 15 to enquire about tolerability. If lack of tolerance is suspected, patient must visit site for dose reduction.

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). | Verify that this physical examination was performed and record results (see Flow Chart). |
| Tumour assessment | Tumour Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site. There is no specific schedule for tumour assessment and can be according to standard of care or every 3 cycles. | Tumour assessment where available will be captured in the CRF |
| Safety Laboratory Testing | Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations and Flow Chart for schedule. | 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<br>No lab values are to be recorded on the eCRF. |
| Urine Examination – Optional | Urine examination. See Section 5.2.3 for recommended urine examinations.<br>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.<br>No values from the urine examination are to be recorded on the 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. |
| Compliance | Check number of tablets remaining and that trial medication was taken correctly, collect any used bottles of afatinib. | Record if the patient is taking the medication according to the protocol. |

| | The following must be performed and information recorded in the patient's chart | What to include in 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 except for those for rash and diarrhoea. |
| Dispense Trial Medication | Dispense sufficient medication for the next cycle of treatment (see Section 4.1.4). | Record: dose dispensed, medication bottle numbers, and only the start date of any dose changes (if applicable). |
| Phone Call | A phone call is required 15 (±3) days after the patient's first dose to assess AEs and dose reductions. | Record when this phone call took place. |

### 6.2.3 End of Treatment and follow-up period

The End of Treatment (EOT) visit marks the end of the patient's treatment, 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). | Verify that this physical examination was performed and record results (see Flow Chart). |
| ECOG Score | The evaluation of the ECOG performance score will be performed | Verify ECOG performance Status |
| Tumour assessment | Tumour Assessment will be based on the assessment of cancer related symptoms and, if available, radiologic assessments as per standard of care at the site. | Tumour assessment where available will be captured in the CRF |
| Safety Laboratory Testing | Hematology, and Biochemistry examination. See Section 5.2.3 for recommended safety laboratory evaluations. | 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<br>No lab values are to be recorded on the CRF. |

| | The following must be performed and information recorded in the patient's chart | What to include in eCRF |
|---|---|---|
| Urine Examination | Urine testing. See Section 5.2.3 for recommended safety laboratory evaluations. | 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. |
| Compliance | Collect all unused or partially used and empty bottles of afatinib from the patient.<br>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 except for those for rash and diarrhoea. |
| 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)<br>When applicable, every effort should be taken to collect and document information on date of death. | Date when the last dose of trial medication was ingested.<br>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.

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.

Patients without clinical progression at EOT will be followed as per site standard practice until appearance of clinical progression or start of other anti-cancer treatment whichever occurs earlier.

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. |
| 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).<br>When applicable, every effort should be taken to collect and document information on date of death.<br>Note: any AE which results in death is considered an SAE. | Any new anti-cancer medication (including date when the new anti-cancer medication is taken) that the patient has taken since EOT visit.<br>Date when the patient completed the planned observation time.<br>Date of death<br>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 and efficacy of the investigational drug afatinib in a particular patient population. After the initial screening visit, patients will enter the open-label treatment period with scheduled 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 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 documented to take 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

**TTSP**

TTSP is the time from the date of the first administration of afatinib to the date of first documented clinically significant symptomatic progression that requires stopping afatinib according to investigator's assessment.

TTSP [days] = date of last administration of trial drug– (date of start of treatment) + 1

Kaplan-Meier estimates and 95% confidence intervals for the 25th, median, and 75th percentiles of the survival distribution will be calculated for TTSP, using Greenwood's standard error estimate. Kaplan-Meier curves will be produced without confidence intervals.

### 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 intakes 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 analyses may be done after over 80% percent of patients have entered the study. The analyses will include the assessment of safety and efficacy if conducted. The result from the interim analyses 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 Time to Symptomatic Progression, 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 is known to have died, but date of death is not attainable, the last contact date will be used as date of death.

## 7.5 RANDOMISATION

No randomisation is required since all patients will be treated with afatinib.

## 7.6 DETERMINATION OF SAMPLE SIZE

The number of patients included into this trial is not based on formal sample size calculations. The sample size consideration in this trial is to expand the access of afatinib treatment to additional patients in the region. The number of patient is determined by the pre-trial feasibility including budget and recruitment.

# 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 Harmonized 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 investigator of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol/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 finalization of the Clinical Trial Report.

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

## 8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

The patient must be informed that his/her personal trial-related data will be used by BI 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 authorized monitors Clinical Monitor Local (CML), Clinical Research Associate (CRA) or Clinical Quality Assurance auditors appointed by BI, 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 (c01617169-04). 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.

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

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

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 2011; 47, 1287 - 1298 .

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). http://ctep.cancer.gov/forms/CTCAEv3.pdf ; Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, 31 March 2003, Publish Date: 12 December 2003 (2003).

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

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 2007; 12 (5), 610 - 621 .

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 2011; 22 (3), 524 - 535 .

R12-5456 Tu L, Sun L. Rechallenge treatment of small molecule inhibitors in NSCLC patients beyond progression. J Thoracic Dis 2012; 4 (6): 647 – 64

## 9.2 UNPUBLISHED REFERENCES

c01617169-04 Investigator's brochure. Afatinib (BIBW 2992). Version17, 1200.P1 - 1200.P13. 05 Jul 2016

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

U02-1391 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 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 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 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 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.

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

U07-1338 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 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 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.

U10-3048-01 Phase IIb/III randomized, double-blind trial of BIBW 2992 plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients failing erlotinib or gefitinib (LUX-Lung 1) 15 December 2011

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

U11-3644-01 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.

U12-1167-01 Phase III randomized trial of BIBW 2992 plus weekly paclitaxel versus investigators choice of chemotherapy following BIBW 2992 monotherapy in non-small cell lung cancer patients failing previous erlotinib or gefitinib treatment. 17 April 2012

U12-1170-01 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 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 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. 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

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. 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 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 related diarrhea

| Severity (CTCAE Grading) | Description | Intervention concerning afatinib treatment | Specific intervention |
|---|---|---|---|
| Mild (Grade 1) | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline | Continue same dose | Stop laxatives and advise patient to drink at least 8-10 glasses of water or clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool (up to 16 mg/day) until bowel movements cease for 12 hours |
| Moderate (Grade 2) | Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with 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 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

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 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

| | |
|---|---|
| Personal hygiene | Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water.<br>Use of very mild shampoos for hair wash.<br>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.<br>Fine cotton clothes should be worn instead of synthetic material.<br>Shaving has to be done very carefully.<br>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.<br>Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended.<br>Patients should be encouraged to consequently stay out of the sun.<br>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.<br>Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness.<br>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.<br>They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail.<br>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

| **Severity (CTCAE Grading)** | **Description** | **Specific intervention** |
|---|---|---|
| **ACNEIFORM RASH** | | |
| Mild (Grade 1) | Macular or papular eruptions or erythema without associated symptoms | Consider topical antibiotics (b.i.d) e.g.: clindamycin 1-2%, or topical erythromycin 1-2% cream of metronidazole 1% or topical nadifloxacin 1%;<br>Isolated scattered lesion: cream preferred<br>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 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus oral antibiotic (for at least 2weeks) e.g., Doxycycline 100 mg b.i.d, Minocycline hydrochloride 100mg b.i.d. |
| Severe (Grade 3) | Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation | Topical and systemic treatment as for Grade 2.<br>Consider referral to dermatologist<br>Consider systemic steroids |
| Life threatening (Grade 4) | Generalized exfoliative, ulcerative, or bullous dermatitis | See Grade 3<br>Systemic steroids are recommended |

| **Severity (CTCAE Grading)** | **Description** | **Specific intervention** |
|---|---|---|
| **EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS** | | |
| Mild (Grade 1) | Mild or localized | Topical polidocanol cream.<br>Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine) |
| Moderate (Grade 2) | Intense or widespread | See Grade 1 plus oral antihistamines (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). Consider topical steroids, e.g. topical hydrocortisone |
| Severe (Grade 3) | Intense or widespread and interfering with ADL | See Grade 2 |
| **XEROSIS (DRY SKIN)** | | |
| Mild (Grade 1) | Asymptomatic | Soap-free shower gel and/or bath oil.<br>Avoid alcoholic solutions and soaps.<br>Urea- or glycerin-based moisturizer.<br>In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream) |
| Moderate (Grade 2) | Symptomatic, not interfering with ADL | See Grade 1.<br>In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream) |
| Severe (Grade 3) | Symptomatic,<br>interfering with ADL | See Grade 2.<br>Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate)<br>Consider oral antibiotics |
| **FISSURES** | | |
| Mild (Grade 1) | Asymptomatic | Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths)<br>Topical applications of aqueous silver nitrate solutions to fissures |
| Moderate (Grade 2) | Symptomatic, not interfering with ADL | See Grade 1.<br>Consider oral antibiotics. |
| Severe (Grade 3) | Symptomatic,<br>Interfering with ADL | See Grade 2. |
| If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.1.4.1: 1 | | |

### 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 related mucositis/stomatitis

| Severity (CTCAE Grading) | Description | Treatment recommendations | Intervention concerning afatinib treatment/dose modification |
|---|---|---|---|
| Mild (Grade 1) | Minimal symptoms; normal diet | Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution. | No change. |
| Moderate (Grade 2) | Symptomatic, but can eat and swallow modified diet | Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis. | Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose. |
| Severe (Grade 3) | Symptomatic and unable to adequately aliment or hydrate orally | Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated. | Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.1. |
| 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. |

### 10.1.4 Management of interstitial lung disease (ILD) and keratitis

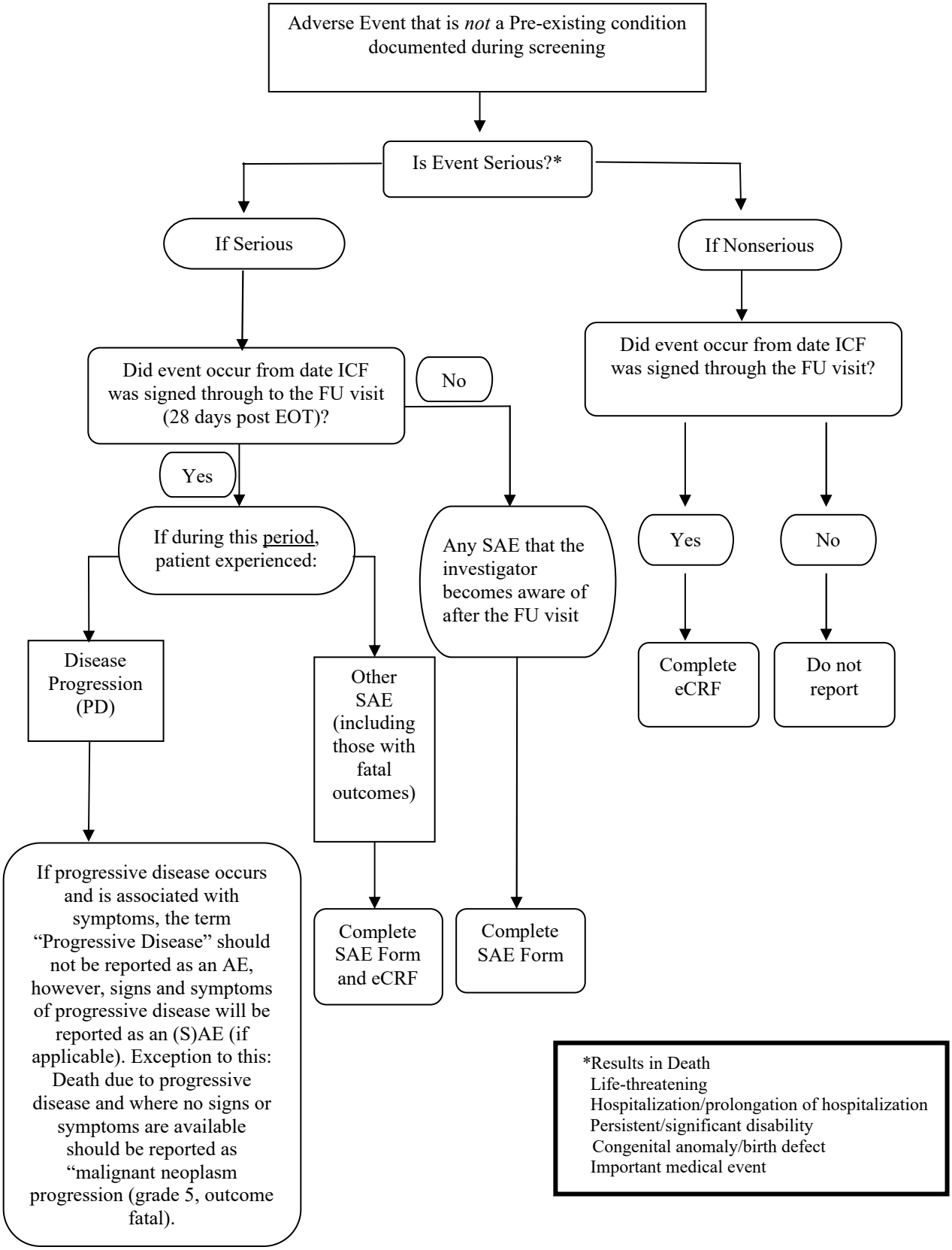
Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

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.

## 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 ADVERSE EVENT/SERIOUS ADVERSE EVENT REPORTING



## 10.4 SAMPLE DIARRHOEA DIARY

**Trial 1200.66 - PATIENT Diarrhoea DIARY**

Site Number _____ Patient Number _____ Cycle Number _____

| | | date | date | date | date | date | date | date |
|---|---|---|---|---|---|---|---|---|
| Study medication taken today? | | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ |
| Did you have diarrhea today? | | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ |
| How many bowel movements did you have today? | | | | | | | | |
| Was your bowel movement: | Hard | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | Regular | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | Soft | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | Loose | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| | Watery | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Did you take any medication for the diarrhea? | | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ |
| Please, list all medications for diarrhea, specifying dose (mg) and time | | | | | | | | |
| How many glasses of water did you drink today? | | | | | | | | |
| Did any of this affect your normal daily activities? | | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ |
| Were you hospitalized due to diarrhea? | | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ | yes☐ no☐ |
| | | | | | | | | |

Reviewer signature and date _____

Trial 1200.66 - Patient Diarrhoea Diary - Version 2 dated 31 May 2013

## 11. DESCRIPTION OF GLOBAL AMENDMENTS

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 25 Jun 2013 |
| **EudraCT number** | | NA |
| **BI Trial number** | | 1200.66 |
| **BI Investigational Product(s)** | | afatinib (BIBW 2992) |
| **Title of protocol** | | An open label, multicentre, single-arm trial to assess the safety of afatinib for 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** | | ☒ |
| **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** | | ☐ |
| | | |
| **Sections to be changed** | | Flow Chart |
| **Description to be changed** | | Deletion of ECG assessment. Addition of following notation under legend No 3. "assessment should be considered only in patients with cardiac risk factors and those with condition that can affect LVEF" |
| **Rationale** | | Global Drug Safety and Therapeutical Area Head agreement that monitoring of cardiac function on regular basis is not required. The protocol should follow CCDs (label) recommendation. |
| | | |
| **Sections to be changed** | | Flow Chart |
| **Description of change** | | Delete LVEF assessment for all assessments visits. Addition of following notation under legend No 3 Assessment should be consider only in patients with cardiac risk factors, those with condition that can affect LVEF and in accordance to the current standard of care. Patients with ejection fraction below the institution's lower limits of normal, cardiac consultation as well as afatinib treatment interruption |

| | | |
|---|---|---|
| | | or discontinuation should be considered. |
| **Rationale for change** | | Global Drug Safety and Therapeutical Area Head agreement that monitoring of and cardiac function on regular basis is not required. The protocol should follow CCDs (label) recommendation. |
| | | |
| **Sections to be changed** | | Flow Chart |
| **Description of change** | | Deletion of D to Dispense Trial Medication |
| **Rationale for change** | | Typographical Error |
| | | |
| **Sections to be changed** | | Section 2.3 and Table 2.3.1 |
| **Description of change** | | Addition of supporting data on afabinib |
| **Rationale for change** | | Update of information |
| | | |
| **Sections to be changed** | | Section 3.3.2 |
| **Description of change** | | Deletion of exclusion criterion of LVEF>50% |
| **Rationale for change** | | Consistent with protocol requirement |
| | | |
| **Sections to be changed** | | Section 3.3.3 |
| **Description of change** | | Amend NYHA classification of >3 to ≥3 |
| **Rationale for change** | | Typographical error |
| | | |
| **Sections to be changed** | | Section 4.1.6 |
| **Description of change** | | Addition of Polypropylene (PP bottles) in additional to the HDPE as it is currently written |
| **Rationale for change** | | Update of information |
| | | |
| **Sections to be changed** | | Section 5.1.2 |
| **Description of change** | | Amend from :<br>However, radiological progression may not occur at same time point as symptomatic progression and study treatment can be continued at the discretion of the investigator until protocol-defined progression is met.<br>Amend to:<br>However, radiological progression may not occur at same time point as symptomatic progression and study treatment can be either discontinued based on radiological progression or continued at the discretion of the investigator until protocol-defined progression is met |
| **Rationale for change** | | Provide clarity to the situation for continuation / discontinuation of treatment |
| | | |
| **Sections to be changed** | | Section 5.2.2 and Table 5.2.2.2:1 |
| **Description of change** | | Amend the sentence from:<br>Report any SAE that the investigator becomes aware of after the FU visit (End of Residual Phase). This includes all deaths. |

| | | |
|---|---|---|
| | | Amended to:<br>Report any SAE that the investigator becomes aware of after the FU visit (End of Residual Phase) considered related to trial medication or trial design must be reported. This includes all deaths. |
| **Rational for Change** | | In accordance to recent SOP variation for Oncology Trials where SAEs reporting after FU period means that reporting is limited the Drug related or trial related SAEs events only. |
| | | |
| **Sections to be changed** | | Section 5.2.2.1 |
| **Description of Change** | | Deletion of mandatory ECG assessment |
| **Rational for Change** | | Compliant with protocol requirement |
| | | |
| **Sections to be changed** | | Section 5.2.4, Tables 6.2.1:1; 6.2.2:1 and 6.2.3:1 |
| **Description of Change** | | ECG assessment is recommended/optional test or procedure according to patient's course as required by clinical condition |
| **Rationale for Change** | | Consistent with protocol requirement. |
| | | |
| **Sections to be changed** | | Section 5.2.5.3; Table 6.2.2.1; Table 6.2.3.1 |
| **Description of change** | | Deletion of LVEF assessment for all assessment except for patients with cardiac risk factors, those with condition that can affect LVEF and in accordance to the current standard of care. Patients with ejection fraction below the institution's lower limits of normal, cardiac consultation as well as afatinib treatment interruption or discontinuation should be considered. |
| **Rationale for change** | | Global Drug Safety and Therapeutical Area Head agreement that monitoring of LVEF and cardiac function on regular basis is not required. The protocol should follow CCDs (label) recommendation. |
| | | |
| **Sections to be changed** | | Table 6.2.1; 6.2.2.1; 6.2.3.1 |
| **Description of change** | | Corrected information of data that is to be collected for the eCRF |
| **Rationale for change** | | Administrative change in order to provide clarity on what data is collected by the eCRF |
| | | |
| **Sections to be changed** | | Section 9.1 |
| **Description of change** | | Addition of literature reference to support afatinib |
| **Rationale for change** | | Additional reference |
| | | |
| **Sections to be changed** | | Section 10.4 |
| **Description of change** | | Correction of name of Diary |
| **Rationale for change** | | Typographical error |
| | | |

| | | |
|---|---|---|
| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | 27 May 2014 |
| **EudraCT number** | | NA |
| **BI Trial number** | | 1200.66 |
| **BI Investigational Product(s)** | | Giotrif®/ Gilotrif™ (afatinib) |
| **Title of protocol** | | An open label, multicentre, single-arm trial to assess the safety of afatinib for 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** | | ☒ |
| **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** | | ☐ |
| | | |
| **Sections to be changed** | | Title page. |
| **Description of change** | | Addition of brand name of Afatinib and change in TCM. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Clinical Trial Protocol Synopsis. |
| **Description of change** | | Addition of brand name to name of finished product. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Flow Chart. |
| **Description of change** | | Addition of columns to indicate visits V4, V7, V10, V13 and V16 onwards. |
| **Rationale for change** | | For clarity on schedule for tumour clinical assessment, and safety laboratory testing. |
| | | |
| **Sections to be changed** | | Flow Chart. |
| **Description of change** | | Deletion of ECG and LVEF. |
| **Rationale for change** | | Update that these are not required per study (can be done as per site standard of care). |

| | | |
|---|---|---|
| | | |
| **Sections to be changed** | | Flow chart Footnote 1. |
| **Description of change** | | Indicate that procedures done as standard of care for patient prior to consent can be used for screening for study. |
| **Rationale for change** | | Clarification to avoid unnecessary repeat of tests for patients. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 3 (from 11). |
| **Description of change** | | Amend of footnote A from:<br>Patient progress assessed by investigator according to local standard and will be recorded at screening and after treatment at each visit until EOT (whenever available). See definition of PD in Section 5.2.<br><br>Amend to:<br>Footnote 3: Tumour assessment should be performed by investigator according to local standard at the time of screening. During treatment period, tumour assessment should be conducted according to local standard of care or recorded every 3 cycles. Diagnosis of progression is at the discretion of the investigator. See definition of PD in Section 5.1. |
| **Rationale for change** | | For clarity on schedule for tumour clinical assessment. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 4 (from 11). |
| **Description of change** | | Indicate the visits at which will be done. |
| **Rationale for change** | | Clarification for sites. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 5 (from 4). |
| **Description of change** | | Indicate that safety laboratory testing consists of haematology and biochemistry (not urine) to be done every 12 weeks. |
| **Rationale for change** | | Update to allow more flexibility for sites where standard of care does not require as frequent safety lab assessments. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 6 (from 7). |
| **Description of change** | | Indicate that urine examination to be done at EOT. |
| **Rationale for change** | | Update for safety assessment required. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 7 (from 6); 8 (from P); 9 (from 14) and 10 (from 7). |
| **Description of change** | | Numbering update. |
| **Rationale for change** | | Admin update. |
| | | |
| **Sections to be changed** | | Flow chart Footnote 11 (from 10) |
| **Description of change** | | Deletion of word “card” from diarrhoea diary card. |

| | | |
|---|---|---|
| **Rationale for change** | | Update for clarity, to consistently use diarrhoea diary term. |
| | | |
| **Sections to be changed** | | Flow chart Footnote ** |
| **Description of change** | | Clarification that follow-up after EOT and prior to clinical progression will be at frequency per site standard practice. |
| **Rationale for change** | | Update to allow more flexibility for sites where standard of care does not require as frequent follow-up. |
| | | |
| **Sections to be changed** | | Flow chart Footnote O and 8. |
| **Description of change** | | Deletion of recommended test and LVEF. |
| **Rationale for change** | | Update as these are not needed for study, to be done per site standard of care. |
| | | |
| **Sections to be changed** | | Table of contents section 6.1.2. |
| **Description of change** | | Change to indicate that Baseline visit is visit 1. |
| **Rationale for change** | | Correction of typographical error. |
| | | |
| **Sections to be changed** | | Abbreviations. |
| **Description of change** | | Deletion of abbreviations not used in protocol. |
| **Rationale for change** | | Correction of typographical errors. |
| | | |
| **Sections to be changed** | | Section 1.1 |
| **Description of change** | | Deletion that trial will only enrol first line EGFR TKI naïve patients with EGFR mutation positive tumours. |
| **Rationale for change** | | Corrections of admin / typographic error for clarity. |
| | | |
| **Sections to be changed** | | Section 3.3. |
| **Description of change** | | Correction that trial will recruit 350 patients. |
| **Rationale for change** | | Correction of typographic error. |
| | | |
| **Sections to be changed** | | Section 3.3.2 Inclusion criteria 4e |
| **Description of change** | | Amend from:<br>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).<br><br>Amend to:<br>Aspartate Amino Transferase (AST) and Alanine Amino Transferase (ALT) < three times the upper limit of (institutional) normal (ULN) (if related to liver metastases < five times ULN). |
| **Rationale for change** | | Clarification of the adequate liver function required. |
| | | |

| | | |
|---|---|---|
| **Sections to be changed** | | Section 3.3.3 Exclusion criteria 2 |
| **Description of change** | | Amend from:<br>hormonal 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)<br><br>Amend to:<br>use of 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) |
| **Rationale for change** | | Clarification on wash-out period needed for previous anti-cancer therapy. |
| | | |
| **Sections to be changed** | | Section 3.3.3 Exclusion criteria 3 |
| **Description of change** | | Amend from:<br>radiotherapy within 14 days prior to drug administration<br><br>Amend to:<br>radiotherapy within 4 weeks prior to drug administration |
| **Rationale for change** | | Correction of typographic error. |
| | | |
| **Sections to be changed** | | Section 3.3.3 Exclusion criteria 7 |
| **Description of change** | | Change that contraception needs to be used for at least 4 weeks after treatment with Afatinib ended. |
| **Rationale for change** | | Clarification in line with residual effect period of afatinib and label for afatinib. |
| | | |
| **Sections to be changed** | | Section 3.3.3 Exclusion criteria 16 |
| **Description of change** | | Amend from:<br>symptomatic brain metastases (patients with asymptomatic brain metastases, who were previously treated, are eligible provided they have asymptomatic brain metastasis had Stable Disease (SD) for at least 4 weeks on stable doses of medication)<br><br>Amend to:<br>symptomatic brain metastases (patients with brain metastases, who were previously treated, are eligible provided they have asymptomatic brain metastasis for at least 4 weeks on stable doses of medication) |
| **Rationale for change** | | Clarification on type of brain metastasis excluded. |
| | | |
| **Sections to be changed** | | Section 4.1.1 |

| | | |
|---|---|---|
| **Description of change** | | Revised the statement that FD&C Blue No. 2 11-14% is not included in the 20 mg tablet to "may not be included in 20mg tablet". |
| **Rationale for change** | | Clarification of excipient for afatinib 20mg tablet |
| | | |
| **Section to be changed** | | Section 4.1.4.1 |
| **Description of change** | | Amend from:<br>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).<br><br>Amend to:<br>After treatment pause due to drug related adverse events, treatment with afatinib can be resumed after patient recovers to $\leq$ Grade 1. Dose reduction should always follow a treatment pause for drug related AE more than grade 1. In the event of any unrelated adverse events, the investigator may choose to pause the medication to allow the patient to recover, but no dose reduction is required. |
| **Rationale for Change** | | Clarification on re-starting afatinib after pause due to drug related AE or non-drug related AE. |
| | | |
| **Sections to be changed** | | Section 4.2.3 |
| **Description of change** | | Change that contraception needs to be used for at least 28 days (instead of 14 days) after treatment with Afatinib ended. |
| **Rationale for change** | | Clarification in line with residual effect period of afatinib and label for afatinib. |
| | | |
| **Sections to be changed** | | Section 4.3 |
| **Description of change** | | Added treatment compliance expected, outside which will be considered as non-compliance. |
| **Rationale for Change** | | Clarification on expectations |
| | | |
| **Sections to be changed** | | Section 5 & 5.1. |
| **Description of change** | | Added that primary endpoint for study is safety assessment and efficacy assessments are secondary endpoints. |
| **Rationale for Change** | | Stating this at start of section for clarity. |
| | | |
| **Sections to be changed** | | Section 5.1.3 |
| **Description of change** | | Update that to be completed health care professional is not optional but mandatory. |
| **Rationale for Change** | | Correction of typographical error |
| | | |

| | | |
|---|---|---|
| **Sections to be changed** | | Section 5.2.1 |
| **Description of change** | | Added specific definition of the primary endpoint and secondary endpoint for safety assessments. |
| **Rationale for Change** | | Clarification of primary and secondary endpoints for safety to fulfil the requirements in the recent updated SOP for CTP on endpoint specification. |
| | | |
| **Sections to be Changed** | | Section 5.2.3 |
| **Description of Change** | | Indicate that safety laboratory testing consists of haematology and biochemistry (not urine) to be done every 12 weeks. |
| **Rationale for Change** | | Update. |
| | | |
| **Sections to be changed** | | Section 5.2.4 |
| **Description of change** | | Indicate that ECG is not required for the study, to be done according to local standard of care. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be Changed** | | Section 5.3.2.1 |
| **Description of Change** | | Correction of typographical error of dehydration when it should have been hydration |
| **Rationale for Change** | | Correction of typographical error |
| | | |
| **Sections to be Changed** | | Section 6.1.2 |
| **Description of Change** | | Change to indicate that Baseline visit is visit 1 |
| **Rationale for Change** | | Correction of typographical error |
| | | |
| **Sections to be Changed** | | Section 6.2.1 |
| **Description of Change** | | Change to indicate that visit 1 is screening and baseline visit. |
| **Rationale for Change** | | Correction of typographical error |
| | | |
| **Sections to be Changed** | | Table 6.2.1:1, Table 6.2.2:1 and Table 6.2.3:1 |
| **Description of Change** | | Update on the study procedures and schedule. |
| **Rationale for Change** | | Updates |
| | | |
| **Sections to be Changed** | | Section 10.5 |
| **Description of Change** | | Update that to be completed health care professional is not optional but mandatory. |
| **Rationale for Change** | | Correction of typographical error |

| | | |
|---|---|---|
| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | 18 Dec 2015 |
| **EudraCT number** | | NA |
| **BI Trial number** | | 1200.66 |
| **BI Investigational Product(s)** | | Giotrif®/ Gilotrif™ (afatinib) |
| **Title of protocol** | | An open label, multicentre, single-arm trial to assess the safety of afatinib for 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** | | ☒ |
| **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** | | ☐ |
| | | |
| **Sections to be changed** | | Clinical Trial Protocol Synopsis. |
| **Description of change** | | Change in total patients entered from 350 to 500. |
| **Rationale for change** | | Update for extension of recruitment numbers for China. |
| | | |
| **Sections to be changed** | | Flow Chart. |
| **Description of change** | | Format of column of Day 15. |
| **Rationale for change** | | For clarity that phone call is only needed on day 15 post first dose. |
| | | |
| **Sections to be changed** | | Flow Chart. |
| **Description of change** | | Visit window for FU visit is changed to +7 instead of -7 days. |
| **Rationale for change** | | REP for Afatinib is 28 days so FU visit should not be less than 28 days post last dose. |
| | | |
| **Sections to be changed** | | Flow Chart Footnote 3. |
| **Description of change** | | Added that cancer related symptoms and clinical benefit for continuing Afatinib need to be assessed at each visit. |

| | | |
|---|---|---|
| **Rationale for change** | | For clarity the assessments needed before patient continues on with next treatment cycle. |
| | | |
| **Sections to be changed** | | Table of contents. |
| **Description of change** | | Added section 10.1.4 |
| **Rationale for change** | | To indicate added section 10.1.4 |
| | | |
| **Sections to be changed** | | Section 1.2 |
| **Description of change** | | Added information about Afatinib profile and update of IB version. |
| **Rationale for change** | | Update per information in current IB. |
| | | |
| **Sections to be changed** | | Section 3.3 |
| **Description of change** | | Change in total patients entered from 350 to 500; number of sites from 35 to 40. |
| **Rationale for change** | | Update for extension of recruitment numbers for China. |
| | | |
| **Sections to be changed** | | Section 3.3.4.1 |
| **Description of change** | | Deleted deterioration in LVEF as one of the reasons for discontinuing patients. |
| **Rationale for change** | | Patients with clinically relevant cardiovascular abnormalities are excluded from the study and elevated LVEF is not an AE of special interest related to afatinib, therefore, it is not necessary to stress LVEF Grade ≥ 3 here. |
| | | |
| **Sections to be changed** | | Section 3.3.4.1 |
| **Description of change** | | Update wording for discontinuation due to cancer related symptoms deterioration and unequivocal disease progression. |
| **Rationale for change** | | To clarify discontinuation due to unequivocal disease progression. Patients with stable symptoms do not need to be discontinued. |
| | | |
| **Sections to be changed** | | Section 3.3.4.1 |
| **Description of change** | | Added that sponsor may move patients from study post primary analysis if patients have access to Afatinib via other alternatives such as marketed source, expanded access program, named patient use program. |
| **Rationale for change** | | Update possible supply of Afatinib for patients post completion of primary analysis and procedures needed. |
| | | |
| **Sections to be changed** | | Section 4.1.2 |
| **Description of change** | | Change in total patients entered from 350 to 500. Added that all eligible patients will receive Afatinib. |

| | | |
|---|---|---|
| **Rationale for change** | | Update for extension of recruitment numbers for China. |
| | | |
| **Sections to be changed** | | Section 4.2.1 |
| **Description of change** | | Added procedures in case of overdose of Afatinib. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Section 5.2.2.1 |
| **Description of change** | | Updated version number of IB. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Section 6.1.5 |
| **Description of change** | | Add that FU visit should be done 28 (+7) days post EOT visit. |
| **Rationale for change** | | Correct visit window to +7 and not -7 days. REP for Afatinib is 28 days so FU visit should not be less than 28 days post last dose. |
| | | |
| **Sections to be changed** | | Section 6.2.4 |
| **Description of change** | | Visit window for FU visit is changed to +7 instead of -7 days. |
| **Rationale for change** | | REP for Afatinib is 28 days so FU visit should not be less than 28 days post last dose. |
| | | |
| **Sections to be changed** | | Section 6.2.4 |
| **Description of change** | | Added that patients without clinical progression at EOT will be followed per site standard practice. |
| **Rationale for change** | | Add to be consistent with flow chart. |
| | | |
| **Sections to be changed** | | Table 6.2.4:1 |
| **Description of change** | | Visit window for FU visit is changed to +7 instead of -7 days. |
| **Rationale for change** | | REP for Afatinib is 28 days so FU visit should not be less than 28 days post last dose. |
| | | |
| **Sections to be changed** | | Table 6.2.4:1 |
| **Description of change** | | Add that date when new anti-cancer medication is taken is collected. |
| **Rationale for change** | | To be consistent with information being collected in RDC. |
| | | |
| **Sections to be changed** | | Section 8.4.1 |
| **Description of change** | | Updated version number of IB. |
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Section 9.2 |
| **Description of change** | | Updated version number of IB. |

| | | |
|---|---|---|
| **Rationale for change** | | Update. |
| | | |
| **Sections to be changed** | | Table 10.1.2:1 |
| **Description of change** | | Correct for typing error of PABA-free. |
| **Rationale for change** | | Correction of typing error. |
| | | |
| **Sections to be changed** | | Table 10.1.2:2 |
| **Description of change** | | Update on treatment recommendation of skin reactions. |
| **Rationale for change** | | Update per latest core protocol for all Afatinib trials. |
| | | |
| **Sections to be changed** | | Section 10.1.4 |
| **Description of change** | | Added wording for management of ILD and keratitis. |
| **Rationale for change** | | Update per information in current IB. |

| | | |
|---|---|---|
| **Number of global amendment** | | 4 |
| **Date of CTP revision** | | 1 Feb 2017 |
| **EudraCT number** | | c14890504-01 |
| **BI Trial number** | | 1200.66 |
| **BI Investigational Product(s)** | | Giotrif®/ Gilotrif™ (afatinib) |
| **Title of protocol** | | An open label, multicentre, single-arm trial to assess the safety of afatinib for 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** | | ☐ |
| **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** | | ☒ |
| | | |
| **Sections to be changed** | | 1.2 drug profile |
| **Description of change** | | Update the maximum plasma concentrations of Afatinib and Afatinib approval information. |
| **Rationale for change** | | Update it according to the current version of IB. |

| | | |
|---|---|---|
| | | |
| **Sections to be changed** | | 3.1 overall trial design and plan |
| **Description of change** | | Clarify that In this trial disease progression is determined by the investigator. Afatinib must be permanently discontinued when investigator judges that patient is no longer benefiting from treatment with afatinib. |
| **Rationale for change** | | Clarify the trial design. |
| | | |
| **Sections to be changed** | | 3.3.2 inclusion criteria |
| **Description of change** | | Add the age range of India patient. |
| **Rationale for change** | | Add India local protocol amendment information to main protocol. |
| | | |
| **Sections to be changed** | | 3.3.4.1 Removal of individual patients |
| **Description of change** | | Clarify that patient may be discontinued if patient receives any other anti-cancer treatment.<br><br>Delete “cancer related symptomatic disease progression, or documented unequivocal disease progression except patients with stable symptoms.” |
| **Rationale for change** | | Clarify the rules of removal of individual patients. |
| | | |
| **Sections to be changed** | | 3.3.4.2 Discontinuation of the trial by the sponsor |
| **Description of change** | | Delete “The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).” |
| **Rationale for change** | | This information is in the contract between site and Sponsor. |
| | | |
| **Section to be changed** | | 4.1.4 drug assignment and administration of doses of each patient |
| **Description of change** | | Clarify that treatment will stop when patient meets withdrawal criteria listed in section 3.3.4.1. |
| **Rationale for change** | | Clarify the criteria of stop treatment. |
| | | |
| **Sections to be changed** | | 4.1.7 storage conditions |
| **Description of change** | | Clarify “in the event that the temperature would be out of range, this has to be documented in the ISF and reported to the sponsor according to Storage conditions for Trial Medications (STORM) in the ISF. |
| **Rationale for change** | | Update according to the current process of reporting temperature excursion. |
| | | |
| **Sections to be changed** | | 5.1.1 Endpoint of efficacy |
| **Description of change** | | Move the definition of to section 5.1.3 other |

| | | |
|---|---|---|
| | | efficacy assessment. |
| **Rationale for change** | | is the other efficacy assessment. |
| | | |
| **Sections to be changed** | | 5.1.2 Assessment of efficacy |
| **Description of change** | | Re-wording the assessment of efficacy. |
| **Rationale for change** | | Clarify the assessment of efficacy. |
| | | |
| **Sections to be changed** | | 5.1.3 Other efficacy assessment |
| **Description of change** | | Move the definition of from section 5.1.1 to 5.1.3. Move the wording regarding from section 5.3.1.1 to 5.1.3 |
| **Rationale for change** | | is the other efficacy assessment. |
| | | |
| **Sections to be changed** | | Section 5.3 Other |
| **Description of change** | | Move the wording regarding from section 5.3.1.1 to 5.1.3. Renumber 5.3.2.1 Documentation of diarrhoea as 5.3.1. |
| **Rationale for change** | | Correct error. |
| | | |
| **Sections to be changed** | | Section 6.2.3 End of treatment and Follow up |
| **Description of change** | | Change “End of trial” to “End of treatment”. |
| **Rationale for change** | | Correct typo. |
| | | |
| **Sections to be changed** | | Section 7.3.2 |
| **Description of change** | | Add TTSP in the secondary analysis and clarify the definition of and delete analysis. |
| **Rationale for change** | | Clarify secondary analysis to be consistent with section 5 efficacy endpoint. |
| | | |
| **Sections to be changed** | | Section 7.3.4 interim analyses |
| **Description of change** | | Add information regarding interim analyses. |
| **Rationale for change** | | Include interim analysis in protocol. |
| | | |
| **Sections to be changed** | | Section 7.4 handling of missing data |
| **Description of change** | | Delete the word |
| **Rationale for change** | | Correct typo. |
| | | |
| **Sections to be changed** | | Section 9.2 unpublished references |
| **Description of change** | | Update the document number, version and date of current IB. |
| **Rationale for change** | | New IB is issued on 03 Jul 2016. |