CLINICAL TRIAL PROTOCOL

	Document Number:	**c03510257-02**
EudraCT No.:	2015-005427-10	
BI Trial No.:	1200.261	
BI Investigational Product(s):	Afatinib (Giotrif, Gilotrif)	
Title:	LUX-Bladder 1: Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with genetic alterations in ERBB receptors.	
Brief Title:	Afatinib monotherapy in patients with ERBB-deregulated metastatic urothelial tract carcinoma after failure of platinum based chemotherapy.	
Clinical Phase:	II	
Trial Clinical Monitor:	Phone: Fax:	
Coordinating Investigator:	Phone: Fax:	
Status:	Final protocol (Revised Protocol (based on Global amendment 1))	
Version and Date:	**Version: 2.0**	**Date: 13 Mar 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Giotrif, Gilotrif	
Name of active ingredient:		Afatinib (BIBW 2992)	
Protocol date: 17 FEB 2016	**Trial number:** 1200.261		**Revision date:** 13 MAR 2017

Title of trial:	LUX-Bladder 1: Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with genetic alterations in ERBB receptors.
Coordinating Investigator:	Phone: - Fax:
Trial site(s):	Multicentre trial conducted in Europe with participation of SOGUG and CNIO
Clinical phase:	Phase II
Objective(s):	To investigate the efficacy in terms of 6 month progression free survival (PFS6) and objective response rate (ORR) of afatinib, in patients with advanced/metastatic urothelial tract carcinoma who have progressed despite prior platinum based chemotherapy. Two cohorts will be analysed separately: Cohort A will investigate patients with ERBB2 amplification and ERBB2 or ERBB3 mutations; Cohort B will investigate patients with EGFR amplification. Other measures of efficacy include progression free survival (PFS), overall survival (OS), disease control rate (DCR), duration of objective response (DOR), and tumour shrinkage. Safety will be assessed throughout the trial by AEs according to NCI CTCAE v. 4.03.
Methodology:	Un-controlled, open–label phase II trial using a two stage design for Cohort A. Cohort B will be hypothesis generating. Patients will be assigned to Cohort A (ERBB2/3 genetic alterations) or Cohort B (EGFR amplification) based on screening biomarkers. In case of competing recruitment, Cohort A will be accrued first.

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Name of finished product:		Giotrif, Gilotrif	
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No. of patients:	Approximately 350 patients will need to be screened to allow for 80 patients who are entered and treated in Cohort A (up to 70 patients) and Cohort B (up to 10 patients) and evaluable for PFS6
total entered:	Approximately 350 patients to be screened Up to 80 patients to be treated
each treatment:	Approximately 350 patients to be screened Cohort A: up to 70 patients treated • Stage 1: 25 patients • Stage 2: 45 patients Cohort B: up to 10 patients treated
Diagnosis :	Patients with histologically confirmed advanced/metastatic urothelial tract carcinoma who progressed despite platinum based therapy, and show mutations in ERBB2 or ERBB3 or amplification in ERBB2 (Cohort A), or EGFR amplification (Cohort B).
Main criteria for inclusion:	• Histologically confirmed urothelial tract carcinoma of the bladder, upper tract or urethra • Locally advanced or metastatic urothelial tract carcinoma not amenable to surgical treatment • Progressed on or after platinum based therapy prior to enrolment and not candidate for another platinum therapy. • Measurable disease per RECIST 1.1 • Archival tissue sample available for biomarker testing and tissue banking o Cohort A: ERBB2 or ERBB3-mutation(s) or ERBB2-amplification o Cohort B: EGFR amplification • ECOG performance status 0-1 • Adequate bone marrow, hepatic and renal function
Test product(s):	Afatinib (Giotrif, Gilotrif) 20 mg, 30 mg, 40 mg afatinib film coated tablets
dose:	40 mg once daily given continuously; the dose can be reduced in 10 mg decrements down to 20 mg daily in case of intolerable AEs.

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mode of administration:	Oral, p.o
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment:	Therapy with afatinib will continue until progression of disease as confirmed by imaging according to RECIST 1.1, or patient´s withdrawal of consent for continuation of treatment, or other reasons requiring treatment discontinuation (see Section 3.3.4.1). It is anticipated that the average time on treatment will be ≥ 6 months.
Endpoints	Primary endpoint: Progression free survival rate at 6 months (PFS6) for Cohort A patients. Key secondary endpoint: ORR for Cohort A patients Other secondary endpoints: PFS, OS, DCR, DOR, tumour shrinkage for Cohort A patients. Cohort A and Cohort B will be analyzed separately.
Safety criteria:	Evaluation of safety and tolerability of afatinib by incidence and severity of adverse events according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
Statistical methods:	Cohort A: Will be evaluated with a two stage design based on PFS6. PFS6 will be calculated as the proportion of patients who are alive and without disease progression at the 24-week tumour assessment. Objective response rate will be calculated as the proportion of patients with confirmed complete response or confirmed partial response. Further, PFS and OS will be evaluated using the Kaplan-Meier estimate. Duration of objective response will be summarized descriptively. All analyses will be descriptive in nature. Cohort B: The analyses will be exploratory and descriptive in nature.

FLOW CHART

Trial periods	**Pre-screening**	**Screening**	**Treatment courses**							**EOT[1]**	**EoR[2]**	**Follow-up for progression[3]**	**Follow-ip for OS[4]**
Course[5]			**1**			**2**		**3**	**4 and onwards**				
Visit			**1**	**2**	**3**	**1**	**2**	**1**	**1**				
Day of period	**Any time prior to day -29[6]**	**-28 to -1**	**1**	**8 ±2**	**15 ±2[7]**	**1 ±2**	**8 ±2[7]**	**1 ±2**	**1 ±2**				
Pre-screening consent	X[8]												
Tumour sample tissue availability	X[9]												
Informed consent		X[10]											
Demographics		X											
Medical history		X											
Physical examination		X	X	X		X		X	X	X			
Performance score[11]		X	X			X		X	X	X		X	
Vital signs		X	X	X		X		X	X	X			
Height		X											
Weight		X	X	X		X		X	X	X			
Safety laboratory tests[12]		X	X	X		X		X	X	X			
Pregnancy test (if appl.)[13]		X								X			
12 lead-ECG[14]		X		X					X	X			
Disease assessment imaging[15]		X								X		X	
Review in-/ex- criteria		X											
Blood and urine for biomarker testing[16]		X							X	X		X	
Blood for PGx			X[17]										
Dose assessment			X			X		X	X				
Dispense trial drug[18]			X			X		X	X				
Afatinib administration							X						
Adverse events[19]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies		X	X	X	X	X	X	X	X	X	X	X	
Compliance check						X		X	X	X			
Eligibility for treatment continuation						X		X	X				
Conclusion of treatment										X			
Conclusion of patient participation[20]											X	X	X
Survival status													X[1]
Subsequent anti-cancer therapy												X	X

1. EOT = End of treatment – When the decision is taken to permanently discontinue the study medication, the EOT visit must be performed within 7 days after last administration of afatinib. If the decision is taken at a scheduled visit, the EOT visit will be performed instead of the scheduled visit. Examinations performed at this time may need to be renamed for the actual visit conducted
2. EoR = End of residual effect period. Safety follow-up visit not earlier than 30 days (+7 days) after last afatinib administration.
3. Follow-up for progression = Additional follow-up visit. Patients who have not progressed at EOR should have additional limited follow-up visits at scheduled tumour assessment timepoints until progression, consent withdrawal, lost to follow-up or death.
4. Follow-up for OS= Follow-up for overall survival: collection of information on vital status every 90 days. Information could be collected from the patient's notes or by telephone contact. A formal visit is not required
5. All courses are of 4 weeks duration (28 days). Day 1 of a new course should take place on day 29. Patients may continue on treatment for unlimited courses until the criteria for stopping medication are met (see Section 3.3.4). Two additional visits are performed during course 1 to assess tolerability. From course 3 onwards, only one visit per course is required

6. Pre-screening period can start at any time after signature of pre-screening consent, but please allow at least 4 weeks for assessment of biomarkers and delivery of results.
7. Patient contact to be done 15 days after starting study medication, and one week after starting treatment Course 2, to check for Adverse Events and Concomitant medication. Information could be collected by telephone contact. A formal visit is not required if not needed.
8. Before tumour tissue sample collection for assessment of eligibility into the trial the patient has to give informed consent according to the local regulatory requirements. This consent includes consent to maintain 5x1 mm cores for TMAs of tissue sample when the patient is not eligible, or the tissue block if the patient is eligible.
9. Patient must consent for collection of tumour sample, to (i) perform pre-screening for inclusion into the trial and (ii) archiving of tissue for bridging of companion diagnostics assay if needed.
10. Once the patient was eligible for the trial by pre-screening, before to commence any additional trial procedure the patient has to give informed consent/assent for trial participation according to the local regulatory requirements. At each moment along the trial, the site staff must disclose and discuss any new information that might affect willingness to continue trial participation with the patient and/or legal guardian.
11. Performance score will be assessed according to ECOG
12. Safety lab tests to be performed as described in Section 5.3.3, but should not be repeated if previous tests are older than 48 hours
13. Mandatory for female patients of child bearing potential (post menarchal) within 7 days prior to first treatment and at EOT. To ensure early detection of pregnancy, test might be repeated as necessary during the treatment period depending on the local law
14. ECG is required at screening, at C1V2, and V1 of every third course thereafter (i.e. C4V1, C7V1…) and EOT
15. Tumour assessment by Imaging (CT or MRI) should be performed every 8 weeks (+/- 1 week) calculated from the first treatment day to the end of study treatment. If treatment discontinuation is for other reason than disease progression, further tumour assessments should be obtained as follows: every 8 weeks (+/-1 week) until month 6, and every 12 weeks (+/-2 weeks) from 6 months onwards, until documented progression of disease. Baseline CT/MRI must be performed within 28 days before start of study treatment (if an assessment was performed within this timeframe, patient would not need to repeat this test).
16. Blood and urine for biomarker testing will be collected at screening, then every 4th cycle during treatment, and also at End of Treatment. If a patient has not progressed at End of Treatment then samples should continue to be collected at every 4th follow-up visit and also at the last follow-up visit (as described in Section 5.5).
17. Pharmacogenetics: one optional blood sample, to be obtained only after signing of PGx consent at any treatment visit.
18. New kit(s) of trial drug must be dispensed at visit1 of each course. If needed (e.g. in case a dose adaptation has to be applied during treatment course), new kit(s) of trial drug might be dispensed outside of the planned visit schedule
19. AE/SAE should be reviewed at every treatment visit,at EOT, EOR and thereafter as described in section 5.3.6.
20. Conclusion of patient participation: should be recorded at the last follow-up visit, when PD/Death occurs, consent withdrawal or death
21. All patients will be followed-up for overall survival at 90 days intervals. For patients who progressed on treatment, the observation period for overall survival starts after the EoR. For patients who have not progressed on treatment, this period starts after the last follow-up for progression visit. The End of the Trial will be achieved as described in Section 8.6.

TABLE OF CONTENTS

ABBREVIATIONS

ADL	Activity of Daily Life
AEs	Adverse Events
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Proteins
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BSA	Body Surface Area
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDx	Companion Diagnostics
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CMV	Cisplatin, methotrexate, and vinblastine
CYP	cytochrome P450
CNIO	National Center for Oncology investigations
CPK	Creatine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DDMVAC	Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin
DILI	Drug Induced Liver Injury
DNA	Desoxyribonucleic Acid
DOR	Duration of Objective Response
eCCR	Estimated Creatinine Clearance Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EoFU	End of Follow Up
EoR	End of residual effect period
EOT	End of Treatment
ERBB	Erythroblastic leukaemia viral oncogene homolog of the human EGFepidermal growth factor family of receptors

EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridation
FOXA1	Forkhead box protein A1
FU	Follow-up
GATA	GATA Binding protein
GCP	Good Clinical Practice
GFR	Glomerular Filtration
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HCO	Bicarbonate
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HIV	Human immunodeficiency virus
HLT	High Level Term
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
i.v.	Intravenous
KG	Kilogram
KRT	Keratin
LD	Longest Diameter
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
MIBC	Muscle-invasive bladder cancer
MQRMs	Medical and Quality Review Meetings
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NMIBC	Non Muscle-invasive bladder cancer
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OR	Objective Response
ORR	Objective Response Rate

OS	Overall Survival
PABA	Para-aminobenzoic Acid
PC	Patient Completion
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
p.o.	per os (oral)
PR	Partial response
q.d.	Quaque die (once a day)
PT	Preferred Term
RBC	Red Blood Cell Count
RDC	Remote Data Capture
RECIST	Response evaluation criteria in solid tumours
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
sAG	Surface Antigen
SOC	System Organ Class
SD	Stable Disease
SEER	Surveillance, Epidemiology and End Results program
SOGUG	Spanish Oncology Genito-Urinary Group
SOP	Standard Operation Procedure
SmPC	Summary of Product Characteristics
SMQ	Standarised MedDRA Queries
SPF	Sunscreen Protection Factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCCU	Urothelial Carcinomas
TCM	Trial Clinical Monitor
TKIs	Tyrosine Kinase Inhibitor
TMAs	Tissue Microarrays
TSAP	Trial Statistical Analysis Plan
UC	Urothelial Cancer
ULN	Upper Limit of Normal
US	United States
WBC	White blood cells
WOCBP	Woman of childbearing potential

1. INTRODUCTION

Afatinib (Giotrif®, Gilotrif®) is an irreversible ERBB-family blocker. It binds to and efficaciously blocks signalling from all homo- and heterodimers formed by the ERBB family members ERBB1 (EGFR), ERBB2 (HER2), ERBB3 and ERBB4. Afatinib demonstrated a significant therapeutic effect in patients with non-small cell lung cancer (NSCLC) harbouring EGFR activating mutations and is currently an approved treatment for TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s) (R14-5311) and by US FDA as first-line treatment of patients with metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (R15-4558).

Lately various molecular profiling programmes have been integrated into adult oncology clinics aiming to enrich trials with patients whose tumours carry certain molecular pathway defects (R14-4189; R14-4191; R14-4174; R14-4175; P15-08257). Molecular profiling of tumours has increased the knowledge regarding genomic and proteomic aberrations and offers more options to target actionable mutations and to provide new treatment options (R15-3968; R15-3974).

As part of "The Cancer Genome Atlas Project", several very recent publications have highlighted the importance of the ERBB pathway for patients with various subtypes of urothelial cancer and render ERBB pathway genetic alterations, i.e. ERBB2 or ERBB3 gene copy number variations, ERBB2 and ERBB3 mutations, as well as EGFR amplifications suitable targets for ERBB family blockers (R15-3968; R15-3974). EGFR amplifications are also frequently observed in patients with basal like histology of urothelial cancer, a form of high-grade muscle-invasive tumour that harbors distinct gene expression patterns and shares common biological features as well as the poor prognosis of basal like breast cancer (R15-5167, R15-5166). These dismal tumours pose a therapeutic challenge but due to EGFR amplification may be targetable by ERBB family inhibitors.

1.1 MEDICAL BACKGROUND

Bladder cancer is the most common cancer of the urinary tract with ~380,000 new cases and ~150,000 deaths per year worldwide (R13-1113). It is the fifth most prevalent among cancers in men in Western countries and >90% of bladder cancers are transitional cell carcinomas of the urothelium (TCCU), or, to simplify, urothelial carcinomas(R15-3970). In 2012, there were an estimated 577,403 people living with bladder cancer in the US and the number of new cases of bladder cancer was 20.3 per 100,000 men and women per year with 4.4 deaths per 100,000 men and women per year. These rates are age-adjusted and based on 2008-2012 cases and deaths (R15-5922). Muscle-invasive bladder cancers (MIBC) account for 33% of all bladder cancers, i.e about 125,400 patients per year are diagnosed with this subtype, and an additional 15-30% (37,620 to 75,240) of patients'with non muscle-invasive bladder cancers (NMIBC) progress into MIBC. As described by Knolwes et al and Rebouissou et al (R15-3968; R15-3974) about 20% of patients with urothelial cancer carry ERBB genetic alterations.

Adjuvant treatment consists of neoadjuvantly or adjuvantly applied chemotherapy with DDMVAC, gemcitabine and cisplatin or CMV with or without radiotherapy and surgical cystectomy. Treatment in 1st line metastatic setting is largely confined to chemotherapy utilizing the regimes given in adjuvant setting (R15-3966). Treatment for patients with platinum refractory locally advanced or metastatic TCCU has not advanced for several decades, and at present no established standard of care nor an approved therapy by FDA or EMA exists and patients are generally entered into clinical trials (R15-3966, R15-5942). Median PFS published from various trial settings ranges between 2.9 and 4.0 months, median OS between 5.0 to 9.6 months (R15-3967; R15-3969; R15-3971; R15-3972; R15-3973). Until recently chemotherapeutic agents of randomized trials have not been able to show OS benefit when compared to best supportive care (BSC), and have had the added burden of toxicity. New therapies for this disease, which has a very dismal prognosis, are needed.

A recently published trial by Choudhury et al showed that five patients who carried ERBB2/ERBB3 mutations or ERBB2 gene amplifications had a prolonged time to progression/treatment discontinuation of 6.6 months on average compared to the remaining 18 patients in the cohort without ERBB alterations whose disease progressed after only 1.4 months (P16-03913).
Recently, treatments with checkpoint inhibitors (antiPD1, antiPD-L1) such as Atezolizumab, Pembrolizumab and Nivolumab, have demonstrated benefit in this patient population mainly for those who were PD-L1 positive (R16-1588, R17-0679, R17-0602).

1.2 DRUG PROFILE

For the latest information on the drug profile of afatinib, please refer to the current Investigators´ Brochure (IB) (c01617169-04) and/or local product label information. All references in this protocol concerning afatinib refer to the free base compound which is used as the oral formulation.

Afatinib (Giotrif®, Gilotrif®) is a small molecule, selective and irreversible ERBB family blocker. In preclinical models it effectively inhibits signaling from all homo- and heterodimers formed by the ERBB family members EGFR (ERBB1), ERBB2 (HER2), 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.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

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

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

Two phase I open label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumours at 40mg and 50mg daily, respectively (U07-3128 and U08-1023). Both daily doses (40mg and 50mg) have been used in phase II and phase III trials depending on the patient population evaluated. Adverse events (AE) observed with afatinib are consistent with those reported for EGFR and dual EGFR/ERBB2 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, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/ERBB2 TKIs and monoclonal antibodies (R07-4077; P07-11507; R07-4078; P13-03658 and P13-03659).

Afatinib was approved as monotherapy to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.
Giotrif® (Afatinib) has been approved in EU to treat patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. In the US, Gilotrif® (Afatinib) has also been approved to treat patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As described in Chapter 1.1 the prognosis of second line metastatic or recurrent urothelial cancer after platinum therapy is dismal and in light of no standard therapy, new treatment options are urgently needed. So far, no molecularly targeted agents have been approved for treatment of urothelial cancer. As part of "The Cancer Genome Atlas Project", however, an integrated analysis of 131 urothelial carcinomas provided a comprehensive landscape of molecular alterations, showing ERBB2 and ERBB3 gene copy number variations, ERBB2 and ERBB3 mutations and EGFR amplifications in various subtypes (R15-5165; R15-3968; R15-3974). Thus irreversible blockade of ERBB signalling with afatinib, is therefore an attractive therapeutic strategy for such patients.
Further support comes from a recently published trial by Choudhury et al, who demonstrated that in the first part of this trial 5 of 23 patients treated with afatinib, who carried ERBB3 mutations or showed ERBB2 gene amplifications achieved PFS3. These patients had a prolonged time to progression/treatment discontinuation of 6.6 months on average, compared to the cohort of patients without any ERBB alterations who did not achieve PFS3 and whose disease progressed after a median of 1.4 months (P16-03913).

Considering advances in tumour genotyping indicating the ERBB pathway as an actionable target and early clinical signal with afatinib in a biomarker-selected population with bladder cancer, this trial aims to provide further evidence of afatinib activity in patients with urothelial cancer harbouring ERBB2/3 mutations or ERBB2 amplification (Cohort A). Furthermore due to EGFR amplifications being frequently observed in patients with high-grade muscle-invasive urothelial cancer of basal like histology (R15-5166), ERBB family inhibitors may provide a suitable new option for targeted treatment of these poor prognostic tumours.

2.2 TRIAL OBJECTIVES

The purpose of this trial is to assess the anti-tumour activity and safety of afatinib monotherapy in patients with urothelial tract carcinoma carrying ERBB2 or ERBB3 mutations or ERBB2 amplifications (Cohort A), and EGFR amplification positive tumours (Cohort B), progressing despite previous platinum based chemotherapy, and thereby to improve their prognosis.
The antitumour activity of afatinib monotherapy in these patients will be assessed by progression free survival rate at 6 months (PFS6) (R17-0395). This will be the primary endpoint of the trial. A key secondary endpoint will also be defined, the objective response rate (ORR).
Further evaluation criteria for efficacy include progression free survival (PFS), Overall Survival (OS), disease control rate (DCR), duration of objective response (DOR) and tumour shrinkage. Safety will be assessed throughout the trial by the monitoring of AEs.
Trial objectives will be analysed separately for Cohorts A and B.

2.3 BENEFIT - RISK ASSESSMENT

Safety and efficacy of afatinib are well described in adults. A positive benefit/risk assessment for afatinb in adult patients with EGFR M+ NSCLC has been demonstrated in a comprehensive development program which led to registration of this compound. Additional efficacy was shown in metastatic squamous cell lung cancer patients (P15-06906; P15-05707; P14-14349) recurrent and metastatic head and neck squamous cell carcinoma (P15-03867) and clinical activity was observed in ERBB2 positive metastatic breast cancer patients (P15-00660; P14-14350; P14-09513).
In clinical studies, the pattern of AEs observed for afatinib was as expected for EGFR inhibitors, including predominantly gastrointestinal and dermatological AEs which were dose-dependent. Early and effective management of these AEs is mandated in ongoing and forthcoming clinical trials with the opportunity to reduce the dose where appropriate. Typical AEs associated with afatinib treatment are diarrhoea (which in severe cases may lead to dehydration with or without renal insufficiency) and effects on skin and its appendages: rash/acne, paronychia, pruritus, dryness and eczema. Besides diarrhoea, other gastrointestinal AEs observed were stomatitis, mouth ulceration, dry mouth, and oral pain. Additional AEs seen in Afatinib clinical trials were mucosal inflammation; respiratory disorders such as epistaxis and rhinorrhoea; eye disorders such as conjunctivitis .
The most common effect on the liver is a transient, reversible transaminase elevation, although hepatic failure, including fatalities, has been reported during treatment with afatinib in less than 1% of patients. Afatinib does not appear to have adverse effects on cardiac contractility or QTcF. The frequency of interstitial lung disease (ILD) -like AEs in all afatinib treated patients was low (approximately 1.5%) and similar to that observed with other EGFR TKIs (c01617169-04). However, several cases of ILD have been reported with administration of EGFR TKIs in NSCLC patients that had been previously treated with immunotherapy. It is unclear whether the extended use of EGFR TKIs after administration of immunotherapy increases the risk of ILD (R16-4467, P16-11904).
For an early detection of rare but potential AEs, patients in this trial will be monitored for:

- Interstitial lung disease (ILD), a rare and serious (potentially fatal) AE that has been reported with administration of EGFR TKIs in NSCLC patients that had been previously treated with immunotherapy (R16-4467, P16-11904). It is unclear whether the extended use of EGFR TKIs after administration of Nivolumab increases the risk of ILD. In case of suspected ILD on treatment please refer to Section 4.2.3.4.
- Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.5.

Exposure of afatinib was similar in patients with mild and moderate liver impairment and in healthy controls. Subjects with moderate renal impairment had approximately 20% higher total exposure and similar peak exposure to afatinib when compared with matched healthy control subjects. In subjects with severe renal impairment, total afatinib exposure was approximately 50% higher and peak exposure approximately 20% higher than that for healthy matched controls. Drug drug interactions of afatinib with Pgp- modulators, CYP-inhibitors

and BCRP were thoroughly investigated and information is summarized in the IB, SmPC and Patient Information (c01617169-04; R14-5311).
The trial medication is available as oral formulation, i.e. film coated tablets of 40 mg, 30 mg and 20 mg strength which allows for dose reduction in case of adverse events. Afatinib 40 mg is the preferred dose. In human PK studies Cmax at a daily dose of 40 mg afatinib was determined to be 78 nM (P13-07487). As the compound demonstrates efficacy at 4-12 nM in ERBB2AMP driven cell lines (c01617169-04) an EC50 between 10-20 nM in the ERBB2 mutated lung cancer cell line H1787 (P09-00886), and due to its irreversible and covalent binding (P12-09544) plasma levels reached in patients treated with 40 mg afatinib daily should be sufficient to treat ERBB2 driven tumours.
Considering the (i) well established side effect profile of afatinib in adult patients which is consistent with the observed side effect profile in a previous trial conducted in the target population of urothelial cancer patients (P15-03441), (ii) the established concomitant treatment algorithms for afatinib related side effects, (iii) close safety monitoring as performed during the conduct of this trial and (iv) early signs of clinical anti-tumour activity observed in the target population, the lack of treatment options and dismal prognosis of the disease, pre-selection of patients by ERBB genetic alterations is expected to maximize patients' benefit from afatinib in both treatment cohorts. Overall the expected benefits from afatinib treatment for the patients included in this trial will outweigh anticipated risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This will be an exploratory open label phase II trial to assess the anti-tumour activity of afatinib monotherapy in patients with urothelial tract carcinoma and genetic alterations in ERBB receptors 1-3 who have previously progressed despite platinum based therapy.

As described in Sections 2.1 and Section 2.2, patients will be recruited into two cohorts (A and B) which will be analysed separately. Assignment into the respective cohorts will be according to biomarkers assessed in tumour biopsies.

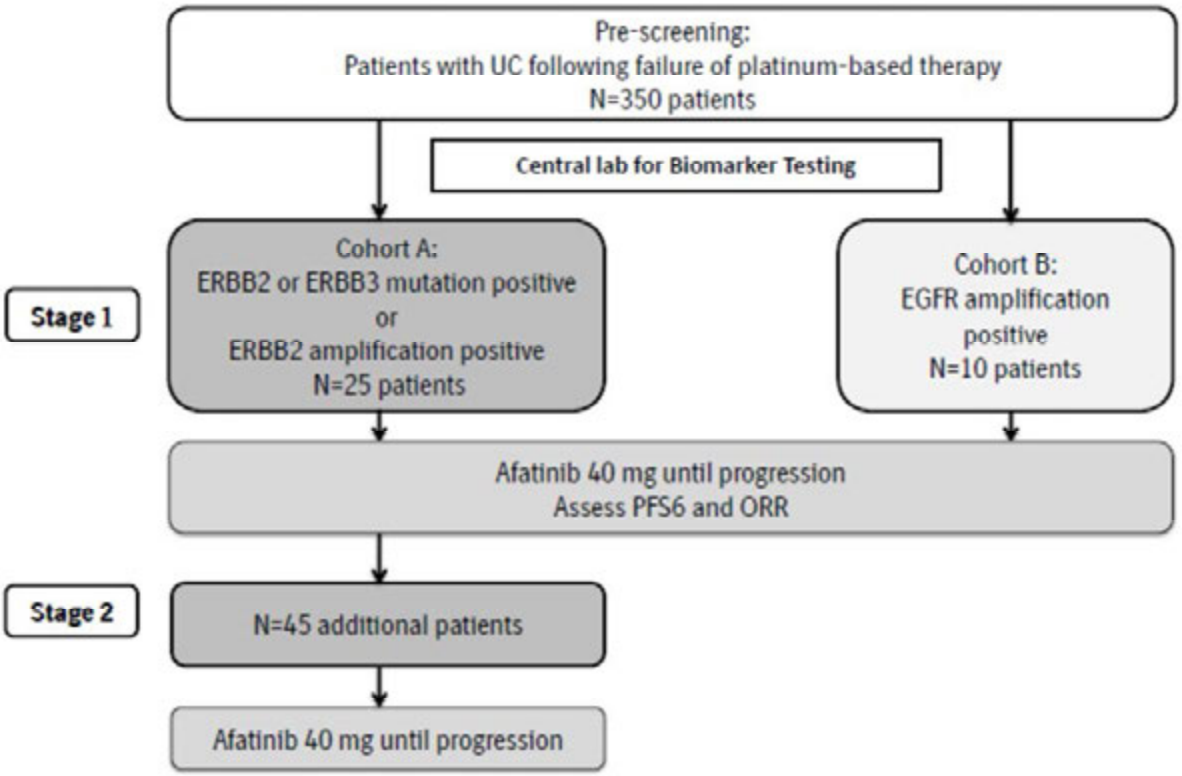
Prior to biomarker testing, all patients will need to sign a pre-screening informed consent form (see Section 3.3.1). An archival tissue sample will be required from all patients at pre-screening. All patients must have genetic alterations in ERBB receptors 1-3 present in their respective tumours and patients with ERBB2 and ERBB3 mutation and ERBB2 amplification will be included into Cohort A, while patients with EGFR amplifications into Cohort B. For details on biomarker assessment refer to section 5.5. The remaining tumour sample of eligible patients will be stored for exploratory and potential future biomarker analyses (see section 5.5.2). For patients not eligible to participate in the trial, 3 x 1mm cores from the tissue sample will be archived as TMAs and the remaining tumour sample will be repatriated to the site.
Approximately 350 patients are expected to be pre-screened to identify up to 80 eligible patients.

Pre-screening will be performed by a GCP validated lab authorized by BI. A summary report of all pre-screening biomarkers will determine if the patient was “a screening failure” , will be eligible for recruitment into “Cohort A “ or “Cohort B”. The report will be sent to the investigator by the central lab.

Cohort A will be recruited using a two-stage design. Differentiation per prognostic factors such as visceral metastases, ECOG and Hemoglobin will be done during the final analysis (R15-6019). These factors will be defined in the TSAP.
Recruitment of 45 patients into stage 2 will depend on the anti-tumour activity demonstrated in the first 25 patients included into stage 1.

Cohort B will include 10 patients in an exploratory design.

Figure 3.1:1 Trial design



All patients recruited will continue trial treatment until disease progression as confirmed by imaging according to RECIST 1.1, or patient´s withdrawal of consent for continuation of treatment, or other reasons requiring treatment discontinuation (see section 3.3.4.1).

The active treatment phase will be followed by a Residual effect Period, a follow up for progression (when needed), and a follow up for overall survival (see Section 6.2 and flowchart).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating investigators and other important participants, including their curricula vitae, will be filed in ISF.

The trial will be conducted in collaboration with SOGUG a Spanish Cooperative group specialized in the treatment of genitourinary cancers and CNIO the National Center for Oncology investigations in Spain. About 30-35 trial sites in Europe are expected to screen and recruit patients into in this trial. The actual recruitment period is anticipated to be 21 months, i.e. 9 months for stage 1 and 12 months for stage 2. There will not be interruption in

enrolment after completing Cohort A. Therefore by the time of PFS6 and ORR evaluation on the first 25 patients is available, there may be additional patients enrolled into the study.

Biomarker analyses for pre-screening purposes will be performed by a CRO or central lab authorised by BI.

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.
Safety and efficacy will be continuously monitored by the investigator, and sponsor.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

This trial will be a single arm open label trial of afatinib monotherapy. No control group will be included as there are no standard treatments available for the patient population investigated.
Patients with metastatic urothelial cancer after failure of, or progression on platinum-containing regimens were selected because they lack treatment options. However, these patients are deemed to benefit from ERBB inhibition if their tumours express ERBB genetic alterations (for details refer to Sections 2.1 and 2.2).
The assignment of patients into 2 separate cohorts is based on observations of anti-tumour activity and biomarker profiles described by Choudhury et al (P15-03441) for Cohort A and on biomarker profiles demonstrated by Jaegil Kim et al (R15-6019).
Up to 70 patients will be included into Cohort A using a two stage design which will test the working hypothesis that the true PFS6 rate is >40% at the end of stage 2. The trial will be stopped if ≤11/25 patients at stage 1 show PFS 6 and ≤1 patient has a confirmed response.
Cohort B will be exploratory in nature and only include 10 patients.

3.3 SELECTION OF TRIAL POPULATION

Two logs, one for all patients who signed pre-screening consent and one for all patients enrolled into the trial (i.e. who have signed the screening informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

Patients to be recruited into this trial must have advanced or metastatic urothelial tract carcinoma that is not amenable to surgical treatment and must have progressed despite previous platinum based chemotherapy. Elegibility for trial participation is also based on positive pre-screening biomarkers – for details refer to Section 3.1. Patients who consent for pre-screening must be willing to provide tumor tissue (including tumour banking) for biomarker analyses (for details refer to Section 5.5) and storage of 3 x 1mm cores for TMAs. Patients who are eligible to receive treatment on the trial must fulfill the below inclusion criteria (See Section 3.3.2) and must not meet any exclusion criteria (Section 3.3.3).

3.3.2 Inclusion criteria

1. Adult patients ≥ 18 years old
2. Patients must have histologically confirmed urothelial tract carcinoma. Patients with urothelial carcinoma of the bladder, upper tract or urethra are eligible.
3. Locally advanced or metastatic urothelial tract carcinoma that is not amenable to surgical treatment.
4. Progressive disease on or after platinum-containing regimen and is not a candidate for another platinum therapy. Following cases will be considered as one line of chemo:
    - Patients receiving platinum-based regimen in the peri-operative setting and subsequently in the metastatic setting
    - Patients who are not refractory to platinum based chemotherapy after one line in metastatic setting (defined as more than 6 months without clinical or radiological PD after the end of first line platinum based chemotherapy) and subsequently receive another line of platinum based chemotherapy in metastatic setting
5. Received no more than one line of prior systemic chemotherapy for recurrent/metastatic disease, and this previous chemotherapy should be platinum based (immunotherapy is not considered as a systemic chemotherapy). If platinum based chemotherapy was administered in the peri-operative setting, patient should have progressed during or within 12 months after treatment .
6. Measurable disease according to RECIST 1.1.
7. ECOG performance status 0 or 1
8. Life expectancy of at least 3 months (12 weeks)
9. Archival tissue biopsies (blocks) available for biomarker testing at pre-screening and for tissue banking for a potential bridging study for CDx (for details refer to Section 5.5).
10. Patients should complete a pre-screening biomarker analysis and should fulfill the following:
    - Cohort A: Tumour with a ERBB2 or ERBB3 mutation, or ERBB2 gene amplification (for definitions please refer to section 5.5.1)
    - Cohort B: Tumour with EGFR amplification (for definitions please refer to section 5.5.1)
11. Adequate organ function, defined as all of the following:
    a. Absolute neutrophil count (ANC) ≥1500 / mm^3.
    b. Platelet count ≥75,000 / mm^3.

c. Estimated creatinine clearance > 45ml / min. Refer to Appendix 10.2.
d. Total Bilirubin ≤ 1.5 times upper limit of (institutional/central) normal (Patients with Gilbert's syndrome total bilirubin must be ≤4 times institutional upper limit of normal).
e. Aspartate amino transferase (AST) or alanine amino transferase (ALT) ≤ three times the upper limit of (institutional/central) normal (ULN) (if related to liver metastases ≤ five times ULN).

12. Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia)
13. Written informed consent for pre-screening that is consistent with ICH-GCP guidelines for tissue, blood, urine collecting and biomarker assessment to confirm eligibility for enrollment into pre-screening phase.
14. Written informed consent that is consistent with ICH-GCP guidelines to confirm eligibility for enrollment into the trial once pre-screening was successfully completed.

3.3.3 Exclusion criteria

1. Chemotherapy within 4 weeks prior to the start of study treatment. Biological therapy or investigational agents within 4 weeks prior to the start of study treatment or prior to passing 5 half-lives(i.e. systemic clearance), whatever comes first.
2. Prior use of EGFR, ERBB2 or ERBB3 targeted treatment
3. Major Surgery within 4 weeks before starting study treatment or planned surgery during the projected course of the study which compromises patient's trial participation by investigator judgement.
4. Radiotherapy within 4 weeks prior to start of study treatment , except palliative radiation to non-target lesions, which may be allowed up to 2 weeks prior to start of study treatment. Tumour lesions situated in a previously irradiated area are usually not considered target lesions unless there has been demonstrated progression in the lesion.
5. Known hypersensitivity to afatinib or its excipients
6. History or presence of clinically relevant cardiovascular abnormalities such as but not limited to uncontrolled hypertension, congestive heart failure NYHA classification of ≥ 3 (Refer to Appendix 10.6), unstable angina or poorly controlled arrhythmia as by the investigator judgement. Myocardial infarction within 6 months prior to start of study treatment.
7. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug
8. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ, non-invasive urothelial cancer at a different site than the primary tumour or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured, or incidental localized prostate cancer not requiring treatment

according to investigator´s judgement.

9. Requiring treatment with any of the prohibited concomitant medications as described in Section 4.2.2.1 that cannot be stopped for the duration of trial participation
10. Known pre-existing interstitial lung disease or signs and symptoms indicative of the latter as per investigator judgement
11. Any history or presence of poorly controlled gastrointestinal disorders that could affect the intake/absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) as per investigator judgement
12. Active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier.
13. Known brain metastases or signs hereof, uncontrolled spinal cord compression or leptomeningeal carcinomatosis
14. Female patients who are nursing or are pregnant or are planning to become pregnant on this trial
15. Women of child-bearing potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly prior to study entry*, for the duration of study participation and for at least 2 weeks after treatment has ended. Patients will be considered to be of childbearing potential unless surgically permanently sterilized (e.g. hysterectomy, bilateral oophorectomy, bilateral salpingectomy), or post-menopausal for at least 12 months without an alternative medical cause.

*A list of contraception methods meeting these criteria is provided in the patient information sheet, and Section 4.2.2.3.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from trial treatment if the patient:

1. Withdraws consent for study participation, without the need to justify the decision.
2. Has radiologic documentation by CTscan or MRI of progressive disease (Section 5.1.2) and is no longer receiving clinical benefit, in the opinion of the investigator.
3. Can no longer be treated with trial medication for other reasons (e.g. AE, pregnancy, surgery, concomitant diagnoses, or concomitant therapies) or administrative reasons.
4. Is diagnosed with ILD
5. Has the need for further dose reductions considered necessary but not allowed according to the protocol (Section 4.1.4)

Given the patient's agreement, the patient will undergo the procedures for treatment discontinuation and/or EoR as well as follow up such as vital status collection as outlined in the flow chart and Section 6.2.3. For all patients the reason for withdrawal (e.g. adverse

events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

The sponsor may remove patients from the study after completion of the primary efficacy analysis if the patient has access to afatinib study treatment via options included but not limited to an alternative clinical trial, marketed product, an expanded-access program, named patient use program, or compassionate use protocol or other means based on local regulation. This may mean a change in packaging and labelling. The cost of any ongoing supply of study medication will be incurred by the sponsor until disease progression occurs. If a patient is removed from the study treatment, an end of treatment and a follow up visit 30 days later will be performed to ensure all adverse events are followed up and then the patient will be considered to have completed the trial.

3.3.4.2 Discontinuation of the trial by the sponsor

The sponsor may suspend recruitment after completing enrolment of the predefined 25 patients into stage 1 in the event of low likelihood to meet the criteria to move from Stage 1 to Stage 2.

Further to this, BI reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial
- The primary analysis has been completed and all patients have either ended study treatment or are eligible to receive afatinib under the conditions indicated in section 3.3.4.1.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be treated with once daily oral dosing of afatinib. Patients will initially receive 40 mg tablets q.d.

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

Table 4.1.1: 1 Test product: afatinib

Substance (Brand Name):	Afatinib (Giotrif® / Gilotrif®)
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg, 30 mg, 40 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent to afatinib)
Posology	Once daily
Route of administration:	Oral

4.1.2 Method of assigning patients to treatment groups

After assessment of all in- and exclusion criteria, the medication number for each eligible patient will be assigned via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is assigned at trial entry). To facilitate the use of the IRT, the investigator will receive all necessary instructions.

4.1.3 Selection of doses in the trial

Based on early phase clinical trials, a daily dose of 50mg in the monotherapy setting was identified as the dose for further development. This was used initially in EGFR TKI refractory population and several other phase II/III and proof of concept trials. Given a higher propensity of grade 3/4 AEs (especially diarrhoea), and no loss of efficacy especially in the EGFR mutation positive population dose was reduced to 40 mg in the pivotal phase III trials in EGFR mutated population (P10-12524, P10-12525, P10-12529). The 1200.22 (LUX- Lung 2) study enrolled 99 patients who started afatinib at 50 mg, and 30 patients starting at 40mg. While there was no substantial change in the occurrence of all AE grades for the two most frequent AEs, diarrhoea (96.7% in the 40 mg group compared to 93.9% in the 50 mg group) and rash/acne (90.0% in the 40 mg group compared to 94.9% in the 50mg group); there was a substantial difference in the occurrence of grade 3 AEs for diarrhoea (6.7% in the 40 mg group vs. 24.2% in the 50mg group) and rash/acne (6.7% in the 40 mg group and 28.3% in the 50 mg group). Neither group had grade 4 or 5 AEs reported for these terms (P10-12524).

In NSCLC and other indications, durable responses (>20 months) have been observed with daily dosing of afatinib of 40 mg and less (P10-09678) in a sensitive biomarker-positive population. The compound demonstrates efficacy at 4-12 nM in ERBB2AMP driven cell lines (c01617169-04), an EC50 between 10-20 nM in the ERBB2 mutated lung cancer cell line H1787, (P09-00886) irreversibly and covalently binds to its targets (P12-09544). Plasma levels reached in patients treated with 40 mg afatinib daily should be sufficient to treat ERBB2 driven tumours. The population in the trial will be naive to EGFR, ERBB2, ERBB3 targeted treatment. Patients with urothelial cancer will suffer from disease-associated co-morbidities such as proteinuria, renal insufficiency, and side effects from previous anti-cancer treatment such as polyneuropathy or long-term effects from prior abdominal irradiations. Therefore afatinib will be used at a dose of 40 mg to optimize the tolerability and efficacy balance. The daily dose will be modified following careful monitoring of patient's drug-related adverse events and medication compliance.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Administration of afatinib

Patients will take a single oral dose of afatinib each day starting at a dose of 40 mg, continuously, until progression of disease as confirmed by imaging according to RECIST 1.1 or patient´s withdrawal of consent for continuation of treatment or other reasons requiring treatment discontinuation (see section 3.3.4.1).. Dose reductions of afatinib can occur. See Section 4.1.4.1.1.

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

Missed doses of afatinib can be made up during the same day as soon as the patient remembers. However, if the next schedule dose is due within eight hours then the missed dose must be skipped. Patients with emesis must not take a replacement dose.

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment course. For administrative purposes, a treatment course is defined as 28 days. Treatment will start when the patient is taking the first dose of medication and stop when the patient is diagnosed with disease progression or for any reason detailed in Section 3.3.4, unless clinical benefit is obtained beyond PD (see Section 3.2). Study drug will be prescribed by the investigator through IRT system, and may be dispensed either by the investigator, site staff or affiliated pharmacy.

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

4.1.4.1.1 Dose reduction for afatinib

Treatment related AEs will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 4.1.4.1.1: 1. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhoea, nausea and vomiting or rash should be managed early and proactive as described in Section 4.2.

Table 4.1.4.1.1: 1 Dose reduction scheme for afatinib

AE Type and CTCAE Grade	Action	Dose reduction scheme
Events related to study drug: • Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration • Reduced renal function caused by dehydration secondary to diarrhea to Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline • Any drug related AE Grade ≥3	Pause treatment until patient has recovered to Grade ≤1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤1 or baseline[1] within 14 days study treatment must be permanently discontinued[2].	If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue afatinib.
Acute onset and/or unexplained worsening of pulmonary systems (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. If ILD is confirmed, discontinue afatinib

[1] Baseline is defined as the CTCAE Grade at the start of treatment

[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between BI Clinical Monitor and the investigator.

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

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Afatinib tablets will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation to be certain that the drug supplies are stored at proper temperature.

4.1.8 Drug accountability

The Investigator or Pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB/ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- 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

The Investigator or 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 disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator/Pharmacist/investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor, the Investigator/Pharmacist/investigational drug storage manager must verify that

all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

Rescue medication

Rescue medications to reverse the actions 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.

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 below.

Concomitant treatments

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

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

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Palliative radiotherapy may be given as described in Section 4.2.1.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with P-gp modulators. For a list of potent P-gp inhibitors and inducers and further recommendations see Appendix 10.1. More details and explanations on afatinb´s interactions can be found in the IB (c01617169-04).

4.2.2.2 Restrictions on diet and life style

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

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.2.3.2.

4.2.2.3 Restrictions regarding women of child-bearing potential

Patients who are not of childbearing potential due to being postmenopausal (i.e. 12 months with no menses without alternative medical cause, predefined hormonal level according to local regulation or etc.) or being permanently sterilized (bilateral oophorectomy, bilateral salphingectomy, or hysterectomy) do not need to use contraception to be eligible for the trial.

All other patients are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until end of trial participation or 2 weeks after last dose of trial medication, whichever is later).

Highly effective methods of birth control should be applied to women of childbearing potential as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, and must be in accordance with local regulations where applicable.
Highly effective method of birth control include:
- hormonal methods of contraception associated with inhibition of ovulation (oral, intravaginal or transdermal combined – estrogen and progestogen containing - hormonal contraception; or, oral, injectable or implantable progestogen-only hormonal contraception),
- placement of intrauterine device or intrauterine hormone releasing system,
- bilateral tubal occlusion, vasectomized sexual partner or complete sexual abstinence (when this is in line with the preferred and usual lifestyle of the study participant).

This list of contraception methods meeting the ICH M3 criteria is provided in the patient information.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy .must be reported following procedures detailed in Section 5.3.5.1.

4.2.3 Management of expected adverse events

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

4.2.3.1 Management of diarrhoea and hydration status following treatment with afatinib

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.3.1:1). At the time of initiation of treatment with afatinib patients should be given a supply of loperamide to keep with them at all times or access to loperamide should be confirmed; and patients should be counselled on the appropriate use.
Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea.

Table 4.2.3.1: 1 Grade specific treatment recommendations for afatinib related diarrhoea

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

Table 4.2.3.1: 1 Grade specific treatment recommendations for afatinib related diarrhea (continued)

Severity (CTCAE Grading)	**Description**	**Intervention concerning afatinib treatment**	**Specific intervention**
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose unless Grade 2 diarrhoea continues for ≥ 2 days (48 hours) in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 2; plus: an infectious process should be ruled out with stool cultures; aggressive iv fluid replacement ≥ 24 hours; hospitalization to monitor progress; Consider prophylactic antibiotics if patient is also neutropenic
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTCAE Grade ≤ 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between BI Clinical Monitor and the investigator.

4.2.3.2 Management recommendations for dermatological AEs following treatment with afatinib

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 4.2.3.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.3.2: 2. For dose adjustment of afatinib refer to Table 4.1.4.1.2: 1.

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

Table 4.2.3.2: 1 General recommendations for dermatological AE prophylaxis while receiving afatinib

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended Patients should be encouraged to consequently stay out of the sun. Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	It is important to moisturize the skin as soon as anti-EGFR therapy is started. Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications.

Table 4.2.3.2: 1 General recommendations for dermatological AE prophylaxis while receiving afatinib (continued)

Prevention of paronychia	Patients should keep their hands dry and out of water if ever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions to afatinib

Severity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical treatment as for Grade 1 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist Consider systemic steroids
Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3 Systemic steroids are recommended

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

Severity (CTCAE Grading)	**Description**	**Specific intervention**
EARLY AND LATE XEROTIC SKIN REACTIONS – PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; consider topical steroids, e.g. topical hydrocortisone.
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics

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

Severity (CTCAE Grading)	**Description**	**Specific intervention**
FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths). Topical application of aqueous sliver nitrate solutions to fissures.
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics.
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2.
If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.1.4.1.2:1.		

4.2.3.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.3.3: 1. For dose adjustment refer to Section 4.1.4.1.1 and for restrictions on concomitant therapies refer to Sections 4.2.2 and 10.1.

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

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

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

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

4.2.3.4 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.

4.3 TREATMENT COMPLIANCE

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

Patients will be asked to bring the remaining trial medication at the end of each treatment cycle to the investigator site for a compliance check. The remaining film- coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken must be documented and explained. At the end of each treatment course, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication must be dispensed.
The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. Patients who do not attend a minimum of 75% of scheduled study visits, unless due to exceptional circumstances (e.g. vacation), should be discussed with the BI trial monitor and be evaluated for compliance. For afatinib, a maximum of 25% of the dispensed afatinib doses may be missed for other reasons than recovery from drug-related AEs. Patients who miss afatinib treatment more frequently are considered non-compliant.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

Progression Free Survival rate at 6 months (PFS6) in Cohort A defined as the proportion of patients who does not show disease progression by the 24-week tumour assessment. Disease progression will be determined according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. for Cohort A and Cohort B.

5.1.2 Secondary Endpoints

A Key Secondary Endpoint will be assessed for Cohort A patients, the Objective response rate (ORR), defined as number of complete response (CR) or partial response (PR) according to RECIST 1.1.

Further secondary endpoints of efficacy will be assessed for Cohort A patients, and include:

- Progression free survival (PFS), defined as the time from first drug administration to the date of disease progression, or date of death whichever is earlier. Disease progression will be determined according to RECIST 1.1.
- Overall Survival (OS), defined as the time from first drug administration to the date of death.
- Disease Control Rate (DCR), defined as CR, PR, stable disease (SD) or Non-CR/Non-PD (NN) according to RECIST 1.1
- Duration of objective response (DOR), according to RECIST 1.1
- Tumour shrinkage for each patient, measured as the maximum percentage decrease from baseline sum of target lesion diameters after treatment until disease progression.

None of the primary or secondary endpoints are related to safety issues.

5.2 ASSESSMENT OF EFFICACY

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) (R09-0262). Tumour response will be assessed by investigator review. Images will be stored in case independent radiology review may need to be introduced at stage 2.

It is critical to continue response evaluation until progression if patients withdrew consent from continuation of treatment but agreed to participate in follow-up tumour assessment.

See Appendix 10.5, RECIST 1.1 Criteria for details on lesion measurements and response assessment.

Tumour assessment by Imaging (CT or MRI) should be performed at screening, and then every 8 weeks (+/- 1 week) calculated from the first treatment day to the end of study treatment . If treatment discontinuation is for other reason than disease progression, further tumour assessments should be obtained as follows: every 8 weeks (+/-1week) until month 6, and every 12 weeks (+/-2 week) from 6 months onwards, until documented progression of disease.

5.3 ASSESSMENT OF SAFETY

Safety will be assessed throughout the trial by AEs determined according to NCI CTCAE (Version 4.03).

5.3.1 Physical examination

A full physical exam must include: vital sign measurements, cardiopulmonary examination, examination of the regional lymph nodes, an examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination must be clarified. Wherever possible the same investigator should perform this examination.
Measurement of height (in cm), body weight (in kg) and the evaluation of the performance score ECOG will be conducted at the times specified in the Flow Chart.

5.3.2 Vital Signs

Vital sign measurements include blood pressure (systolic blood pressure, diastolic blood pressure), pulse rate, temperature.

5.3.3 Safety laboratory parameters

Safety lab will be performed locally at each participating site. Following parameters should be evaluated at each timepoint:

Table 5.3.3: 1 Safety laboratory parameters

Category	**Parameters**
Hematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, white blood cell count (WBC), with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT), Fibrinogen.
Chemistry	
Electrolytes	Sodium, potassium, calcium, magnesium, chloride, bicarbonate (HCO_3)
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine; Creatinine clearance (see Appendix 10.2).
Other	glucose, albumin, cholesterol, triglycerides, phosphorus, lactate dehydrogenase (LDH), total protein, uric acid, creatine phosphokinase (CPK); in case of pathological CPK further evaluation (e.g by determination of isoenzymes, troponin assays, ECG exam) should be performed as clinically indicated
Urinalysis	pH, protein, glucose, ketones, blood, leucocytes, nitrite; in case of pathological finding further evaluation should be performed and results documented. Proteinuria per se will only result in treatment interruptions if associated to other renal pathology which would qualify for treatment interruption i.e. CTCAE >/= 3 AE, or decrease in renal clearance to < 45 ml/min GFR
Pregnancy test	β -HCG testing in urine or serum in women of childbearing potential (WOCBP)

The investigator should complete additional evaluations of laboratory tests as clinically indicated.

5.3.4 Electrocardiogram

12-lead ECG will be taken at the time points specified in the Flow Chart. The investigator will review the ECG recording, comment on any clinical significance and if applicable record any ECG abnormality that meets AE criteria.

5.3.5 Assessment of adverse events

5.3.5.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include offlabel use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- 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 judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

If cancer is the indication for treatment, only cancers of new histology qualify as a serious event. Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the RDC. These events should always be reported as SAEs as described in Section 5.3.6.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see Section 5.3.6.
The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits at baseline):
  - an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
  - Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

- For patients with abnormal liver function at baseline (AST and/or ALT>ULN)
  - an elevation of AST and/or ALT ≥ 5 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, with the exclusion of the causes due to underlying diseases.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided via the RDC system. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the (e)CRF.

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:
• The event is consistent with the known pharmacology of the drug
• The event is known to be caused by or attributed to the drug class.
• A plausible time to onset of the event relative to the time of drug exposure.
• Evidence that the event is reproducible when the drug is re-introduced
• No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
• The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
• An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

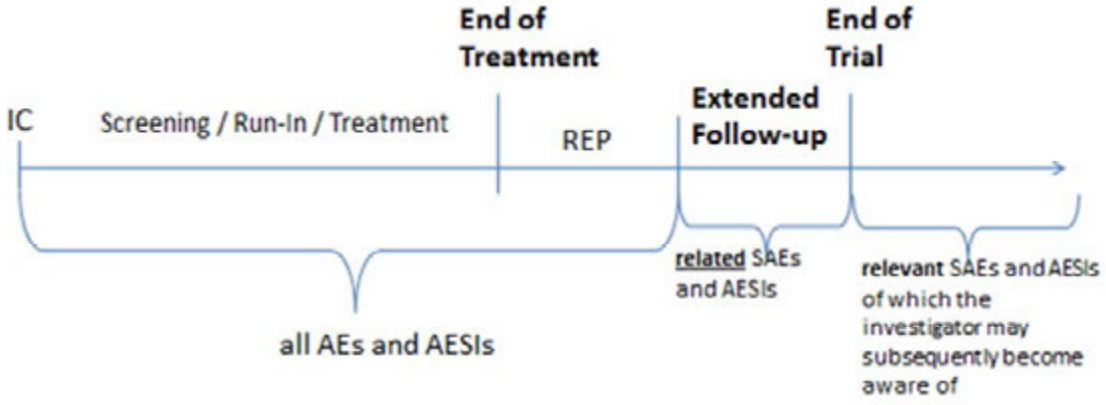
Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:
• No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
• Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
• Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
• Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.3.6 Adverse event collection and reporting

AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patient files.
The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the screening informed consent onwards until the end of treatment (including the Residual Effect period, REP):
  - all AEs (non-serious and serious) and all AESIs.
- After the end of treatment (including the REP) until the individual patient's end of trial: all related SAEs and related AESIs.
- After the individual patient's end of the trial:

the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of. The rules for Adverse Event Reporting exemptions still apply.



The REP is defined as 30 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the (e)CRF and SAE form (if applicable):
- Worsening of pre-existing conditions other than underlying disease will be recorded as an (S)AE in the eCRF.
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

Exemptions to SAE Reporting
Disease Progression in oncology trials is a study endpoint for analysis of efficacy, and as such is exempted from reporting as a (S)AE. Progression of the patient's underlying malignancy will be recorded in the appropriate pages of the (e)CRF as part of efficacy data collection and will not be reported on the (S)AE form. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on a SAE form. It will therefore not be entered in the safety database and hence not get expeditiously reported.
However, when there is evidence suggesting a causal relationship between the study drug and the progression of the underlying malignancy, the event must be reported as (S)AE on the eCRF and on the SAE form.

Examples of exempted events of PD are:

- Progression of underlying malignancy (Progressive disease PD): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (with or without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are monitored at appropriate intervals by Medical and Quality Review Meetings (MQRMs).

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

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

5.4.2 Methods of sample collection

Not applicable.

5.4.3 Analytical determinations

Not applicable.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.5 BIOMARKER ASSESSMENTS

Three mandatory biomarker activities will be performed in the course of the trial.

1. **Screening biomarkers:** As described in Section 3.3, all patients must provide a tumour sample which will be screened in a central laboratory for biomarkers of ERBB deregulation. Local testing will not be permitted. Patients whose tumour is positive for one or more of the screening biomarkers will be eligible for inclusion. The biomarker screening assessments are described in more detail in Section 5.5.1.
2. **Exploratory biomarkers:** Exploratory, retrospective, evaluation of several biomarkers will be performed in a descriptive way. The exploratory biomarker assessments are described in more detail in Section 5.5.2..
3. **Sample Storage:** Storage of tumour tissue and of plasma and serum prepared from a venous blood sample and urine for confirmatory testing of biomarkers will be performed and is described in Section 5.5.4. In addition a sample of whole venous blood will be optionally collected and banked in order to enable unspecified pharmacogenetic analyses as indicated in the flow chart. The provision of the banking sample for pharmacogenetics is described in Section 5.5.3.

No formal endpoints based on these biomarkers have been defined.

5.5.1 Screening biomarkers

Tumour tissue is required from each patient at screening in order to pre-screen for the presence of the following molecular markers.

1. Non-synonymous somatic mutation of either the ERBB2 or ERBB3 gene.
2. Amplification of the ERBB2 gene.

Amplification of the ERBB2 gene will be defined according to the ASCO-CAP guidelines for ERBB2 FISH analysis (R15-6055): after counting at least 20 cells.

- Dual-probe ERBB2/CEP17 ratio ≥2.0 with an average ERBB2 copy number ≥4.0 signals/cell
- Dual-probe ERBB2/CEP17 ratio ≥2.0 with an average ERBB2 copy number <4.0 signals/cell
- Dual-probe ERBB2/CEP17 ratio < 2.0 with an average ERBB2 Copy number ≥6.0 signals/cell

If the patient's tumour is positive for either marker 1 or 2 then the patient is eligible for inclusion in cohort A.

3. Amplification of the EGFR gene.

Amplification of the EGFR gene will be defined using an exploratory threshold: after counting 50 cells a case will be considered to be amplified when there are > 6 EGFR copies in >20% of evaluated cells.

If the patient's tumour is positive for marker 3 then the patient is eligible for inclusion in cohort B.

5.5.1.1 Method of Sample Collection

The provision of tumour tissue for biomarker screening is mandatory. Each patient should provide a formalin-preserved, paraffin embedded tumour block of sufficient size to allow for sections to be cut in order for all screening assessments to be performed.

If it is not possible to provide a tumour block then it is acceptable to provide 1 H/E slide plus 14 x 3-4 microns thickness tissue sections for FISH studies, and 5 x10 microns tissue sections on untreated glass slides for DNA extractions and repetitions. 4 of these sections of 3-4 micron thickness for use in biomarker screening. Please note that in addition to the tissue required for screening, additional tissue sections are required for exploratory analyses and for assay validation purposes (n=10; this is more fully described in sections 5.5.2 and 5.5.4.).

Detailed instructions for sampling, handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF. All material such as test tubes and labels will be provided. Date of sampling will be recorded in the eCRF.

Biomarker screening will be performed in a single central laboratory and the result of the screening will be made available to the investigator within a maximum of 26 days.

5.5.1.2 Analytical Determinations

DNA will be extracted from the tumour tissue and will be used to sequence the coding regions of the ERBB2 and ERBB3 genes. Patients whose tumour contains a non-synonomous mutation in either ERBB2 or ERBB3 will be eligible for inclusion in Cohort A.

The number of copies of the EGFR and ERBB2 genes contained in the tumour cells will be counted using FISH (Fluorescence in-situ Hybridisation). Patients whose tumour contains cells with an elevated number of copies of ERBB2 will be eligible for inclusion in cohort A.

Patients whose tumour contains cells with an elevated number of copies of EGFR will be eligible for inclusion in Cohort B.

5.5.2 Exploratory Biomarkers

5.5.2.1 Exploratory Tumour Tissue Analyses

The provision of tumour tissue for exploratory biomarker assessments is mandatory. It is preferred that each patient provides a formalin-preserved, paraffin embedded tumour block of sufficient size to allow for sections to be cut in order for all exploratory assessments to be performed. In addition 3 cores of 1mm^2 cross section will be taken from the block in order to prepare a tissue microarray (TMA).

If it is not possible to provide a tumour block then it is acceptable to provide 10 sections of 3-4 micron thickness for use in exploratory biomarker assessments. This tissue is in addition to the tissue provided for use in biomarker screening (section 5.5.1.1).

The exploratory evaluation of the following biomarkers will be performed in a descriptive way:

DNA will be extracted from the tumour tissue and will be used to sequence the coding regions of the EGFR and ERBB4 genes in order to identify the frequency of non-synonomous somatic mutation in these genes in the trial population and to clarify the frequency of the co-occurrence of these mutations with the other biomarkers which will be measured in these patients.

5.5.2.2 Exploratory Biomarker assessments in Plasma and Urine

As described in Section 5.5.4, tissue and serum and plasma and urine from patients included in the trial will be stored and will be available for additional exploratory testing of biomarkers which may be prognostic or predictive of response to drug treatments such as afatinib or other therapies. This is necessary due to the emerging scientific understanding of

the biology of urothelial cancers and the emergence of new treatment strategies in this setting.

Blood samples for circulating tumour DNA (ctDNA) analysis and urine samples should be taken as specified in the flowchart. 20 mL of blood should be taken for ctDNA analyses. Up to 50 mL of urine should be obtained. Full instructions for the processing of the blood and urine samples will be provided in the laboratory manual included in the ISF.

A Screening Visit sample of blood and of urine is to be taken. Subsequent samples should then be obtained every 4th cycle during treatment and also at End of Treatment. If a patient has not progressed at End of Treatment then samples should continue to be collected at every 4th follow-up visit and also at the last follow-up visit.

These blood and urine samples will be primarily used for the extraction and analysis of circulating DNA. The use of the samples will be at the discretion of the trial sponsor but could include the sequencing of genes relevant to cancer by NGS in order to research the mutations occurring in urothelial cancer and how urothelial tumours evolve upon drug treatment. In addition the samples may be used in the development of a diagnostic test for patients eligible for treatment with afatinib. They may also be utilized for the measurement of proteins whose levels may be of prognostic relevance to the patients' response to the study medications.

Plasma,serum, urine or the derived DNA collected from all subjects, irrespective of their tumour's ERBB biomarker status and their subsequent participation in the trial, will be stored for up to 15 years following the completion of the trial.

5.5.3 Pharmacogenetics

Pharmacogenetics (PGx) investigates genetic variations in patients to explain and to predict their individual response to drugs.

Collection of the unspecified blood sample for DNA banking for PGx is optional. All patients will be asked to provide a blood sample for DNA banking at C1V1, after a separate informed consent has been obtained in accordance with local ethical and regulatory requirements.

The DNA Banking sample, derived from the original blood sample, will be stored by Boehringer Ingelheim for up to 15 years after the end of the clinical trial.

The stored DNA may be retrospectively analysed, e.g., to identify whether there are genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.5.4 Sample Storage

Samples will be stored at a central location in complicance with best clinical practice and will be used for CDx test development and for exploratory biomarker analyses as described elsewhere in section 5.5. Full instructions for the collection of samples for storage are provided in the laboratory manual.

Samples may be stored for up to 15 years upon completion of the trial.

The samples to be stored comprise:

1. Tissue blocks or tissue slides provided for the development of a CDx assay and to perform exploratory biomarker analyses. See 5.5.1.1 and 5.5.2.
2. Blood samples or the derived plasma or serum for circulating tumour DNA (ctDNA) analysis.
3. Urine samples or the derived sediments for biomarker assessments.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All clinical assessments are standard measurements commonly used in studies of advanced solid tumours. Response evaluation criteria in solid tumours (RECIST) version 1.1 are used for assessment of the change in tumour burden. These criteria are well established and well received by the regulatory authorities and scientific community. Frequency of assessment is accordingly to standard clinical routine in advanced cancer patients.

The CTCAE criteria are used in the assessment of adverse events in cancer patients. In the present trial CTCAE version 4.03 will be used although an updated version is published. Since several pivotal oncology trials are currently ongoing with the investigational product it is considered more appropriate to continue to collect safety data using the same criteria.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

As described in Section 3, patients will attend a screening period divided in two visits: the pre-screening visit where a mutation analysis will be completed in order to determine the eligibility of the patient, and when all subjects should sign a pre-screening informed consent to allow the analysis of their tumour samples; and a screening visit once the eligibility of the patient for either Cohort A or Cohort B has been determined, and subject will undergo the rest of screening tests. After the screening visit, patients will have to come to the investigational site on the days provided in the Flow Chart. More visits can be performed if deemed necessary by patient or investigator.

A diagram of the stages of a patient´s participation in this trial is included in Section 3.1, and permitted time windows for visits are included in the Flow Chart.

Afatinib will be dispensed at the first visit of each treatment course according to the flow chart, and patients will receive continuous daily treatment with afatinib until the criteria for stopping medication are met (Section 3.3.4). As soon as the treatment with afatinib will be permanently discontinued, the patient has to undergo the end of treatment visit (i.e within 7 days of last afatinib administration). A new visit will be performed at the end of the residual effect period (i.e. no earlier than 30 days after the last afatinib administration) for safety follow-up (EoR). After this visit, patients who have not progressed on treatment will have additional follow-up visits at scheduled tumour assessment timepoints until progression, withdrawal of consent for participating in the study, lost to follow-up or death.
After progression, all patients will enter an observational period where they will be followed-up for overall survival at 90 days intervals.

Concomitant medication must be collected starting from Screening Visit until the EoR visit. For adverse events refer to Section 5.3.6.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Pre-screening visit

During this visit, patient will be asked to review and sign a pre-screening consent, and his/her archived tumor material wll be taken and sent to a central laboratory for biomarker analysis. Further to this, 3 x1 mm cores of all pre-screened patients, and the remaining tissue block/slides for patients eligible to continue on trial will be banked. For details refer to Section 5.5. Only patients who test positive for either Cohort A or Cohort B will proceed to Screening Visit.

Screening visit

Before starting the screening visit, a new informed consent should be delivered to patients who were eligible for recruitment into Cohorts A or B based on biomarker results (see Section 5.5). After signature of this new consent, all screening assessments including tumor imaging scan and ECG must be completed in the 28 days prior to the first administration of study medication. However, if a tumour assessment (CT scan or MRI) was performed within this timeframe, patient would not need to repeat it.
Patients who failed screening may repeat the screening after discussion between investigator and BI Clinical Monitor providing that reasons for screening failure were reversible and have resolved.
Patients who meet the eligibility criteria (See section 3.3) will be allowed to start study treatment.

6.2.2 Treatment period(s)

Every treatment course is defined as 28 days. All subsequent visit dates should be calculated based on Course 1 Visit 1 date. If a visit is missed there will be no re-scheduling; if a patient should attend the study site between the "missed" and the next scheduled visit, then the missed visit assessments should be performed.

The investigations are outlined in the Flow Chart and will be performed at the respective visit, but are described in detail in the following sections.

During the first visit of each treatment course, the following procedures will be performed:
- Physical examination: complete medical examination including body weight
- ECOG performance status
- Vital signs
- Safety lab: haematology, biochemistry, coagulation parameters and urine analysis as described in Section 5.3.3.
- Dispense study medication, and dose assessment
- Review of adverse events and concomitant medication

During Course 1, an additional visit will be performed 8 days after the start of treatment (C1V2). The main objective of this visit is to assess the safety profile of trial drug. The exact procedures to be done are described in the study flowchart.
Additionally, a patient contact is to be done 15 days after starting study medication, and one week after starting treatment Course 2, to check for adverse events and concomitant medication. Information for these contacts could be collected by phone. A formal visit is not required if not needed.

Additionally, the following procedures will be done at specific timeponts:
- 12-lead ECG, to be performed at screening, C1V2, C4V1, and every third course thereafter (C7V1, C10V1,…)
- At the end of second treatment cycle, i.e. 8 weeks after the start of study medication and every 8 weeks thereafter, tumour imaging to assess response to treatment must be

performed. In case of objective response, the latter has to be confirmed 4 to 6 weeks after initial OR observation.
- A plasma and an urine sample will be stored for exploratory analyses – for details see Section 5.5.

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment visit (EOT)

The EOT visit will be performed after permanent discontinuation of trial medication for any reason as soon as possible, but no later than 7 days after permanent discontinuation of the trial medication or when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.
Refer to the Flow Chart for details. The patient must return all study drugs, and the site must document the reason for permanent discontinuation of study medication. If permanent discontinuation of study drug occurs during a scheduled visit, examinations as defined for EOT visit should be performed instead of the examinations for the scheduled visit.

6.2.3.2 End of Residual effect period (EoR)

The EoR is defined in Section 5.3.6. The EoR visit should not be performed earlier than 30 days (+7 days) after permanent discontinuation of the trial medication. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT.

6.2.3.3 Extended follow-up period

6.2.3.3.1 Follow-up for progression

Additional follow-up visits after the EoR visit will be performed for patients who did not progress on treatment, every 8 weeks (+/- 1week) until month 6, and every 12 weeks (+/-2 weeks) from 6 months onwards.
The follow-up for progression period will end at the earliest if one of the following events is met:
- Completion of the predefined FU for progression period
- Lost to follow-up
- Disease progression
- Death
- End of whole trial as specified in Section 8.6

At the end of the follow-up period, the EoFU (End of Follow-Up) visit has to be performed.
The following will be obtained and / or performed during the follow-up visits and the EoFU visit:
- Record AESI or SAEs, if assessed as related by the investigator, and a follow-up of adverse events ongoing since EoR to EoFU as entered in source data

- Concomitant medications for treatment of an adverse event reported in the (e)CRF including trade name, indication and dates of administration
- Record performance score (e.g. ECOG)
- Perform tumour assessment and imaging if applicable
- Treatment and date with any other anti-cancer drug including the name and type of the anti-cancer drug and/or best supportive care (if applicable)
- PD (the actual date of PD shall be recorded)

6.2.3.3.2 Follow-up for Overall Survival

All patients will be followed-up for overall survival at 90 days intervals after the EoR visit or last follow-up for progression visit (as specified in Section 6.2.3.3.1) until death, lost to follow-up or completion of the whole trial (as specified in Section 8.6) whatever occurs earlier. For patients who progressed on treatment, the observation period for overall survival starts after the EoR visit. For patients who have not progressed on treatment, this period starts after the last FU for progression visit.

These visits may also be performed by e.g. telephone interview or via written correspondence in case the patient is unable to visit the investigator.

The following information will be collected during the follow-up for survival period:
- Date of contact
- Further anti-cancer treatment: regimen and drug name, start and stop dates, reason for stopping this treatment and/or best supportive care (if applicable)
- Outcome event (e.g. death: Record date of and reason for outcome event)
- Follow-up of adverse events in case they were not yet recovered at EoR, and AESI or SAEs if assessed as related by the investigator.

6.2.3.4 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:
- Completion of planned follow-up period (or follow-up for overall survival if applicable)
- Lost to follow-up
- Refusal to be followed-up
- Death

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an open label, uncontrolled, exploratory phase II trial with two patient cohorts. Cohort A of the study follows a two stage design where an analysis for futility will be performed at the end of stage 1 to determine if the stage 2 of cohort A will be carried out. Cohort B of the study will include up to 10 patients with EGFR amplification. Analysis will be conducted in parallel to, and independent of cohort A.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The exploratory null and alternative hypotheses were set up for the primary endpoint PFS6 based on a two-stage design with H_0: PFS6 ≤ 40% and H_a: PFS6 >40%. PFS6 is defined as patient being alive and without disease progression at the 24-week tumour assessment.

The null hypothesis for key secondary endpoint ORR is H_0: ORR ≤ 5% and H_a: ORR >5%.
A Hochberg multiple adjustement procedure will be used to control the family-wise error rate at 0.05 (one-sided) for testing PFS6 and ORR.

7.3 PLANNED ANALYSES

All eligible patients, who take at least one dose of afatinib will be included in the analysis dataset.

7.3.1 Primary endpoint analyses

The primary endpoint of the study is PFS rate at 6 months (PFS6). This will be calculated as the proportion of patients who are alive and without disease progression at the 24-week tumour assessment, out of all analysed patients. Patient prematurely discontinued without the 24-week assessment will be considered as not achieving PFS6 regardless of the reason for discontinuation.
For Cohort A, the first stage will include 25 patients treated with Afatinib, as described in Section 7.4. When the criteria for transition into the second stage are met, the study will move on to the full accrual and there will be up to 70 patients treated in Cohort A.
At the end of the second stage, the significance level for testing the null hypothesis H_0: PFS6 ≤ 40% will be calculated as the exact binomial probability i.e. Prob($X \geq s$| n, p=0.40), where 's' is the observed number of patients achieving PFS6 and 'n' is the total number of patients. A Wilson 90% confidence interval will be provided also.

PFS6 for Cohort B patients will be analysed descriptively when all patients in Cohort B have completed the 24-week tumour assessment.

7.3.2 Secondary endpoint analyses

Key Secondary Endpoint

Objective response rate (ORR) defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) is the key-secondary endpoint.
At the end of the second stage, the significance level for testing the null hypothesis H_0: ORR $\leq$ 5% will be calculated as the exact binomial probability i.e. Prob($X \geq s|$ n, p=0.05), where 's' is the observed number of patients achieving a confirmed objective response and 'n' is the total number of patients. A Wilson 90% confidence interval will be provided also.

Other Secondary Endpoints

Progression-free survival will be analysed by Kaplan-Meier method. Clinical deterioration without image-based progression will not be counted towards progression. Detailed censoring rule for PFS and sensitivity analysis will be specified in the Trial Statistical Analysis Plan (TSAP).

Disease control rate (DCR) defined as the proportion of patients with confirmed CR, PR or stable disease (SD) will be analysed similarly to ORR.

Duration of objective response is defined as the time from first documented CR or PR to the time of progression or death. Duration of objective response will be summarized descriptively.

Kaplan-Meier estimates of overall survival will be provided.

Tumor shrinkage from baseline will be summarized descriptively and by waterfall plot of the maximum percentage decrease from baseline of the sum of the longest diameters of target lesions will be presented.

7.3.4 Safety analyses

All patients who receive at least one dose of trial medication will be included in the safety analysis. Adverse events will be graded according to CTCAE, Version 4.03.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.

Standard tabulations arranged by MedDRA SOC and PT will include:
- The overall incidence and intensity of adverse events,
- AE judged to have been related to afatinib
- AE leading to dosage reduction
- AE leading to permanent treatment discontinuation
- SAE
- Fatal outcome

These standard tables will be supplemented with tables in which MedDRA SMQ and HLT (with some modifications) will be used to group MedDRA PT for the following:
- rash/acne
- stomatitis
- paronychia

Tables that describe the frequency, intensity, time to onset, and clinical consequences will be produced for the following AEs of special interest:
- diarrhea
- rash/acne
- stomatitis

Listings will be prepared of patients who are identified as having experienced any of the following AE. For AE other than dehydration, identification will be based upon modified MedDRA SMQ and HLT groupings.
- Dehydration
- Renal insufficiency
- hepatic impairment
- ILD-like events
- heart failure
- Keratitis
- Pancreatitis
- Severe skin reaction
- Gastrointestinal perforation
- Hypersensitivity reaction
- Developmental toxicity

Primary laboratory tests are defined as:
- Low values (-): haemoglobin, total WBC, platelets, neutrophils, lymphocytes, potassium, magnesium, sodium, creatinine clearance and GFR
- High values (+): AST, ALT, alkaline phosphatase, aPTT, INR, and total bilirubin

The following analyses will be presented for the primary laboratory tests:
- descriptive statistics at each planned assessment,
- frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment, and
- frequency of patients with possible clinically significant abnormalities.

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

7.3.5 Pharmacokinetic analyses

No pharmacokinetic analyses are planned.

7.4 INTERIM ANALYSES

PFS6 and confirmed ORR will be evaluated for the first 25 treated patients when the last patient among them completes the 24-week tumor assessment. If 12 or more patients achieve PFS6, or at least 2 have a confirmed response, the study will move on to the full targeted accrual in Stage 2. The primary analysis will be conducted when 70 patients in Cohort A complete the 24-week tumor assessment.

If fewer than 12 patients achieve PFS6 and fewer than 2 patients have a confirmed response, the trial will be stopped for futility. All patients enrolled will be followed until disease progression and a full analysis will be carried out after all patients discontinue the study.

Stages 1 and 2 of the study will be conducted in a seamless fashion with no interruption in enrolment after treating 25 patients. Therefore by the time of the futility assessment, more than 25 patients might have been treated. The sponsor may however suspend recruitment after enrolling the pre-defined 25 patients in Stage 1 in the event of low likelihood to meet the criteria to move from Stage 1 to Stage 2.

7.5 HANDLING OF MISSING DATA

In general, missing data will not be imputed. Missing or incomplete AE onset and end dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”). Missing of imaging data will be handled with the censoring rules for PFS.

7.6 RANDOMISATION

Not applicable.

7.7 DETERMINATION OF SAMPLE SIZE

Table 7.7: 1 shows that 70 patients would be expected to provide appoximately 90% power for PFS6, with PFS6=60% under the alternative hypothesis and PFS6=40% under the null. Although the Stage 1 futility criterion will reduce the power, the power after adjustment for the futility analysis would likely be between the unadjusted and adjusted power estimates in Table 7.7:1, because the futility criterion allows the trial to proceed to Stage 2 with fewer than 12 patients with successful PFS6, provided at least two patients have confirmed response.

Table 7.7: 1 Power[1] for PFS6 in Cohort A, with PFS6=60% under the alternative hypothesis.

	N=65	N=70	N=75
Without adjustment for Stage 1			
alpha=0.025	87.2%	90.9%	93.6%
alpha=0.050	91.7%	94.3%	96.0%
With adjustment for Stage 1 (N=25, PFS6≥12)			
alpha=0.025	83.5%	86.3%	88.2%
alpha=0.050	87.1%	88.8%	89.9%

[1]Based upon simulating one million samples under the alternative hypothesis of PFS6=60%. For each sample a significance level was calculated as the binomial probability (X≥s| n, p=0.40), where 's' is the observed number of patients achieving PFS6 and 'n' is the total number of patients.

Table 7.7: 2 shows that 70 patients would be expected to provide approximately 80% power for ORR, with ORR=15% under the alternative hypothesis and ORR=5% under the null.

Tables 7.7:1 and 7.7:2 present power for both alpha=0.025 and 0.05 because the Hochberg multiplicity procedure would compare the higher of the observed significance levels for PFS6 and ORR to 0.05. If the larger significance level is smaller than 0.05, then we can reject null hypothese for both PFS6 and ORR. If the larger significance level is greater than 0.05, then the smaller significance level would be compared to a more stringent threshold 0.025, in order to refrain the family-wise error rate at 0.05.

If the underlying PFS6 rate is 40%, the probability of observing fewer than 12 patients out of 25 in Stage 1 would be 73%. Under the alternative that PFS6=60%, the chance of observing at least 12 patients would be 92%.

For ORR under the null ORR=5%, the probability of observing fewer than 2 confirmed responses in Stage 1 would be 64%. Under the alternative that ORR=15%, the chance of observing at least 2 responses would be 91%.

For Cohort B the analyses will be exploratory and descriptive in nature and the sample size is determined based on feasibility and practical considerations.

Table 7.7: 2 Power[1] for ORR in Cohort A, with ORR=15% under the alternative hypothesis.

	N=65	N=70	N=75
Without adjustment for Stage 1			
alpha=0.025	77.8%	84.2%	81.1%
alpha=0.050	87.4%	84.2%	89.2%
With adjustment for Stage 1 (N=25, ORR≥2)			
alpha=0.025	74.3%	79.6%	76.9%
alpha=0.050	82.4%	79.6%	83.5%

[1]Based upon simulating one million samples under the alternative hypothesis of ORR=15%. For each sample a significance level was calculated as the binomial probability ($X \geq s|\ n, p=0.05$), where 's' is the observed number of patients achieving a confirmed objective response and 'n' is the total number of patients.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

The Investigator will 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 or of ICH GCP.

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

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

8.1 TRIAL 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 Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by IRB/IEC 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

(e)CRF for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.
All data in eCRFs must be derived from source documents:

- Patient identification (gender, year of birth)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Completion of Patient's Participation in the trial"
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

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. CRF/eCRF 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 BI's clinical trial monitor,

auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA)/on site monitor and auditor may review all CRF/eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For afatinib it is the current version of the Investigator's Brochure (c01617169-04).
The current version of this reference document is provided in the ISF. No AEs are classified as listed for trial design, or invasive procedures.

8.4.2 Expedited reporting of Adeverse Events

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this protocol.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.
Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.
The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out", LPO). And LPO is when the last patient has 24 months FU or evaluable for PFS6.
The **"Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10. APPENDICES

10.1 APPENDIX 1: PGP INHIBITORS AND INDUCERS

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

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

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

10.2 APPENDIX 2: COCKCROFT-GAULT FORMULA

The following formula may be used for estimated creatinine clearance rate (eCCR) using Cockcroft-Gault formula. Other on-line calculators or formulas which are institution standards for eCCR and differ slightly may also be used.

When serum creatinine is measured in mg/dL:

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

Or when serum creatinine is measured in µmol/L

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

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

10.3 APPENDIX 3: ECOG PERFORMANCE STATUS

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

R01-0787

10.4 APPENDIX 4: CLINICAL EVALUATION OF LIVER INJURY

10.4.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.5.1 (Adverse Events of Special Interest), are to be further evaluated using the following procedures:

10.4.2 Procedures

Any elevation of ALT/AST and bilirubin qualifying as laboratory alert should be confirmed using the initial sample if possible.

If the alert is confirmed on initial sample, or it is not possible to repeat testing using initial sample, the following must be completed;

1) Evaluate the patient within 48 hours and,
2) Perform the following laboratory tests:
    1. Repeat of AST, ALT, bilirubin (with fractionation to total and direct)
    2. Complete blood count and cell morphology
    3. Reticulocyte count
    4. CK
    5. LDH
    6. Alkaline Phosphatase

The results of these laboratory tests must be reported to BI as soon as possible.

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

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

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF;
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;

- complete the following laboratory tests as detailed in the DILI checklist provided in the ISF:
    - *Clinical chemistry*
      alkaline phosphatase, cholinesterase (serum)*, albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin*, amylase, lipase, fasting glucose, cholesterol, triglycerides
    - *Serology*
      Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs,DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Antinuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM)*, varicella (IgG, IgM)*, parvovirus (IgG, IgM)*
    - *Hormones, tumormarker*
      Thyroid-stimulating hormone(TSH)*
    - *Haematology*
      Thrombocytes, eosinophils
      *If clinically indicated (e.g immunocompromised patients)

Long term follow-up

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

Report any resulting diagnoses via the eCRF.

10.5 APPENDIX 5: RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1 (R09-0262).
The preferred method of assessment is a spiral CT scan with IV and oral contrast, unless IV and/or oral contrast are medically contraindicated. CT scans of the chest, abdomen and other areas of known or newly suspected disease must be performed. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

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

Bone scans (using ^{99}m-technetium polyphosphonate scintigraphy) are recommended at baseline if the patient has any signs and symptoms consistent with bone metastasis or a

history of bone metastasis. Bone metastasis identified at baseline must be documented and assessed according to RECIST 1.1 at the times of the other tumour measurements indicated in the flow chart. During the study bone scans should be repeated as clinically indicated in patients without bone metastasis at Baseline.

For the purposes of this study, patients should be re-evaluated for response at weeks 8, 16, 24 and every 8 weeks thereafter. In the event of a treatment delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule.

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

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

Measurability of the disease
Measurable lesions
Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15mm are also measurable.
Measurable disease
Measurable disease requires the presence of at least one measurable lesion. Measurable lesion if limited to either small (<2cm) solitary visceral lesion or scant (<5cm) lymph nodes only metastasis should be evaluated for additional evidence of malignant nature and discussed with BI trial clinical monitor before enrolling.
Non-measurable disease
Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Lesions with prior local treatment
Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion

Methods of measurement
All measurements must be recorded in metric notation, using a ruler or calipers. All baseline evaluations must be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure,

a default measurement of 5mm should be applied. If the lesion is not visible, a default measurement of 0 mm should be applied.
The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.
Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is obligatory.
CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.
Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.
Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions
All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured (longest diameter = LD) and numbered at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Lymph nodes must be ≥15mm in order to be considered as target lesions.
A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see table below):

Table 10.5: 1 Evaluation of target lesions

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

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent" (see Table 10.5: 2).

Table 10.5: 2 Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesions or/and maintenance of tumour marker level above normal limits.
Progression (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

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

Confirmation
In case of tumour response (CR or PR), confirmation will be performed with a repeat assessment no less than 4 weeks after the RECIST criteria for response have been met. In the case of SD, measurement must have met the SD criteria at least once after study entry at an interval of not less than 6 weeks.

Evaluation of best response to study treatment
The best response to study treatment (Table 10.5: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.5: 3).
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.5: 3 Algorithm for evaluation of overall response

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

10.6 APPENDIX 6: NYHA CLASSIFICATION OF HEART FAILURE

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		13 MAR 2017
EudraCT number		2015-005427-10
BI Trial number		1200.261
BI Investigational Product(s)		Afatinib (Giotrif, Gilotrif)
Title of protocol		Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with ERBB receptor deregulation.
To be implemented only after approval of the IRB / IEC / Competent Authorities		Y
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		N
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		N
Section to be changed		Study title
Description of change		Addition of an acronym to the trial (LUX-Bladder 1), and revision of the wording (change “deregulation” by “genetic alterations”)
Rationale for change		The addition of the name to the trial was implemented for an easier reference to this trial, while the revision of the wording was included to have amore accurate definition of the genetic characteristics.
Section to be changed		Clinical trial protocol synopsis – Methodology
Description of change		Revision of the wording referring to genetic charachteristics (change “deregulation” by “genetic alterations”)
Rationale for change		To have a more accurate definition of the ERBB alterations
Section to be changed		Clinical trial protocol synopsis – Duration of

		treatment
Description of change		Addition of the need to confirm disease progression by RECIST 1.1, and inclusion of the adverse events under a global cathegory of "other reasons requiring treatment discontinuation"
Rationale for change		To refine the criteria about treatment discontinuation and align with project guidelines.
Section to be changed		Clinical trial protocol synopsis – Objectives and Safety criteria
Description of change		Revision of the CTCAE version used to 4.03
Rationale for change		To keep consistency throughout the protocol
Section to be changed		Clinical trial protocol synopsis – No. of patients each treatment
Description of change		Increase of the number of patients to be included in Stage 2
Rationale for change		To keep consistency with Section 7 and new statistical assumptions.
Section to be changed		Flow chart
Description of change		Addition of one visit one week after starting second course of treatment.
Rationale for change		To add a better follow up and management of potential adverse events
Section to be changed		Flow chart
Description of change		Addition of a column on description of visits after Course 3
Rationale for change		To have a better and clearer description of trial procedures
Section to be changed		Flow chart footnote #2
Description of change		Addition of the window for EoR visit
Rationale for change		To add flexibility to the conduct of this visit, and keep consistency with section 6.2.3.2
Section to be changed		Flow chart footnote #4
Description of change		Change the units of timeframe for vital status collection (from months to days)
Rationale for change		To keep consistency throughout the protocol and have all timeframes in days
Section to be changed		Flow chart footnote #5
Description of change		To clarify that after course 3 of treatment only one

		visit per cycle is required.
Rationale for change		To keep consistency throughout the protocol as a consequence of the addition of the new visit after C21V1.
Section to be changed		Flow chart footnote #7
Description of change		Addition of a comment about the need to have one more vistit one week after starting course 2
Rationale for change		To add a better follow up and management of potential adverse events
Section to be changed		Flow chart footnote #15
Description of change		Clarification regarding previous image assessments obtained within 28 days of starting study treatment
Rationale for change		To add clarity on trial procedures
Section to be changed		1. Introduction
Description of change		Change ErbB1 by ERBB1, and rewording of specific parts of the text
Rationale for change		To have a more accurate definition on genetic alterations and better English wording.
Section to be changed		1.1 Medical Background
Description of change		Expansion of what TCCU stands for, better definition of genetic alterations, and updates on previous trials.
Rationale for change		To have a more accurate definition of the ERBB alterations, better English wording, and updated results on previous investigations.
Section to be changed		1.2 Drug Profile
Description of change		Update on Investigators´ Brochure reference number and Giotrif approvals
Rationale for change		To update protocol on latest afatinib´s documents and labelling.
Section to be changed		2.1 Rationale for performing the trial
Description of change		Update on the results of previous trials
Rationale for change		To keep protocol updated according to recent publications
Section to be changed		2.2 Trial Objectives
Description of change		Addition of a reference and rewording of parts of the section.
Rationale for change		To add clarity to this section.

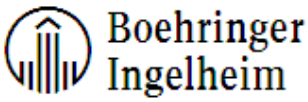
Section to be changed		2.3 Benefit-risk assessment
Description of change		Revision of the AEs related to afatinib
Rationale for change		To align the protocol with latest updates on Afatinib and project requirements.
Section to be changed		3.1 Overall trial design and plan
Description of change		Revision of the wording referring to genetic charachteristics and conditions for treatment discontinuation
Rationale for change		To keep consistency throughout the trial protocol
Section to be changed		3.1.1 Administrative structure of the trial
Description of change		Increase the number of participating sites
Rationale for change		This is consequence of the expansion of the trial to two additional countries in Europe
Section to be changed		3.2 Discussion of trial design, including the choice of control groups
Description of change		Revision of the text referring to the statistical analysis
Rationale for change		To keep consistency with Section 7.
Section to be changed		3.3.2 Inclusion criteria #4
Description of change		Rewording of the criteria, specifying what could be considered as one line of chemotherapy
Rationale for change		To add clarity to the criteria.
Section to be changed		3.3.2 Inclusion criteria #5
Description of change		Revision of the criteria about previous treatments
Rationale for change		To add clarity to the criteria, especially regarding the use of previous immunotherapy, which was not detailed before.
Section to be changed		3.3.3 Exclusion criteria #4
Description of change		Revision of the wording regarding previous radiotherapy
Rationale for change		To add clarity to the criteria and align to RECIST 1.1
Section to be changed		3.3.3 Exclusion criteria #8
Description of change		Addition of the incidental localized prostate cancer to previous or concomitant allowed malignancies
Rationale for change		To allow for this patients to be entered, since patients with incidental localized prostate cancer

		have good prognostic and would not need further treatment, which would interfere with treatment of urothelial cancer.
Section to be changed		3.3.3 Exclusion criteria #14 and #15
Description of change		Revision of the text referring to women of child-bearing potential
Rationale for change		To align with project standards and current international guidelines (ICH)
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Rewording of the removal criteria and addition of a text referring to potential treatment with Afatinib beyond study
Rationale for change		To add clarity to the removal criteria and align with project standards.
Section to be changed		3.3.4.2 Discontinuation of the trial by the sponsor
Description of change		Addition of one reason for trial discontinuation, and the possibility to suspend the trial after completing recruitment in stage 1.
Rationale for change		To align with project standards, and to include the possibility of suspending recruitment (after stage 1 is completed and before its analysis) when there are possibilities that the the drug is not working.
Section to be changed		4.1.4.1 Administration of Afatinib
Description of change		Revision of the duration of treatment with afatinib
Rationale for change		To keep the consistency throughout the protocol regarding the treatment duration.
Section to be changed		4.1.4.1.2:1 Dose reduction scheme for Afatinib
Description of change		Revision of the wording of the AE related to renal function to specify that only if caused by dehydration secondary to diarrhea.
Rationale for change		To update te protocol according to Afatinib safety profile and to clarify that afatinib does not cause renal failure per se (only diarrhea, that can lead to pre-renal failure). Consequently, only renal impairment related to dehydration caused by diarrhea should lead to dose reduction of Afatinib.
Section to be changed		4.2.2.3 Restrictions regarding women of child-bearing potential
Description of change		Revision of the text describing women of child-

		bearing potential and methods of birth control
Rationale for change		To align with project standards and current international guidelines (ICH)
Section to be changed		Table 4.2.3.2:1 General recommendations for prophylaxis while receiving afatinib
Description of change		Change in the table title to specify that the table refers to "dermatological AEs"
Rationale for change		In the previous version of the protocol this mention was missing.
Section to be changed		5.1.2 Secondary endpoints
Description of change		Rewording of part of the section and correction of typos.
Rationale for change		To add clarity and facilitate reading of the section.
Section to be changed		5.3 Assessment of Safety 5.3.5.1 Definitions of AEs – Intensity of AEs 5.7 Appropiateness of measurements
Description of change		
Rationale for change		
Section to be changed		5.5 Biomarker assessments
Description of change		Change of the word "biobanking" to "sample storage"
Rationale for change		Technically, BI is not intended to build a biobank because the samples will only be used for trial purposes. Therefore, wording has been adapted accordingly.
Section to be changed		5.5.1.1 Method of sample collection
Description of change		Revision of the number of required slides from tumour samples
Rationale for change		To align the protocol with the lab manual.
Section to be changed		5.5.2.1 Exploratory tumour tissue analyses
Description of change		Removal of the "mRNA expression of the ERBB receptors, their ligands and genes of relevance by technologies such as nanostring or RT PCR" and addition of the "expression of mRNAs by Next generation sequencing"
Rationale for change		To update the trial tests according to latest investigations on biomarkers in urothelial cancer.

Section to be changed		5.5.4 Biobanking
Description of change		Addition of the whole section and change of title
Rationale for change		The whole section was missing in the previous version of the protocol.
Section to be changed		6.2.1 Screening period – pre-screening visit
Description of change		Clarification regarding previous image assessments obtained within 28 days of starting study treatment
Rationale for change		To add clarity on trial procedures
Section to be changed		6.2.2 Treatment period
Description of change		Addition of a patient contact one week after starting second course of treatment
Rationale for change		To add a better follow up and management of potential adverse events
Section to be changed		6.2.3.2 End of residual effect period (EoR)
Description of change		Addition of a window for this visit
Rationale for change		To add flexibility to the conduct of this visit.
Section to be changed		6.2.3.3.1 Follow-up for progression
Description of change		Increasing of the window to perform imaging tests in this visit, from 2 days to 1 week.
Rationale for change		To add flexibility to the conduct of this visit.
Section to be changed		6.2.3.3.2 Follow-up for Overall survival
Description of change		Change the units on timeframe for vital status collection (from months to days), and rewording of the follow up visit
Rationale for change		To keep consistency throughout the protocol (to and have all timeframes in days, and to correctly name the visits according to flowchart).
Section to be changed		7 Statistical Methods and determination of the sample size
Description of change		Revision of the whole section
Rationale for change		To refine the statistical model and better describe trial hypotheses and analysis.
Section to be changed		7.3.4 Safety analysis
Description of change		Updates on the tables and listing that will be provided with these analyses
Rationale for change		To align the protocol with project standards and latest updates on Afatinib safety profile.

Section to be changed		9 References
Description of change		Addition of few publications and removal of outdated ones
Rationale for change		To update the protocol on latest published data
Section to be changed		10.1 Appendix 1
Description of change		Addition of the whole section and title
Rationale for change		The whole section was missing in the previous version of the protocol.
Section to be changed		10.2 Appendix 2: Cockcroft-Gault formula
Description of change		Remove the need to add calculation in patient´s chart and rewording.
Rationale for change		All variables used for eCcr are already present in patient´s chart and do not see the need to detail the calculations.
Section to be changed		10.4 Appendix 4: Clinical Evaluation of liver injury
Description of change		Removal of Haptoglobin from the required parameters to be obtained in case of confirmed DILI case
Rationale for change		To update the protocol according to BI standard: DILI Checklist was revised and this parameter is not longer required.
Section to be changed		10.5 Appendix 5: RECIST 1.1 criteria
Description of change		Revision of the text about new lesions in irradiated fields
Rationale for change		To adapt the trial protocol to the latest version of RECIST 1.1 criteria.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Ingelheim

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed