Clinical Trial Protocol

	Document Number:	**c08988429-02**
BI Trial No.:	1200.222	
BI Investigational Product(s):	BIBW2992 (afatinib)/ Giotrif®/ Giotrif™	
Title:	A phase II study of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy	
Brief Title:	Afatinib in NSCLC with HER2 mutation	
Clinical Phase:	II	
Trial Clinical Monitor:		
	Phone: Fax:	
Principal Investigator:		
	Phone: Fax:	
Status:	Final Protocol (Revised protocol (based on global amendment 02)	
Version and Date:	**Version:**	**Date:**
	3.0	16 Aug 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Giotrif®/ Giotrif™	
Name of active ingredient:		BIBW2992 (afatinib)	
Protocol date: 17 Jun 2015	**Trial number:** 1200.222		**Revision date:** 16 Aug 2017

Title of trial:	A phase II study of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy
Principal Investigator:	
Trial site(s):	Multi-centre trial
Clinical phase:	II
Objective(s):	To investigate efficacy and safety of afatinib in the advanced NSCLC patients with HER2 mutations, previously treated with chemotherapy
Methodology:	Open label, single arm study
No. of patients:	Approximately 1400 screened patients, 40 entered patients
Diagnosis :	HER2 mutant metastatic NSCLC
Main criteria for inclusion:	Inclusion criteria for part A: 1. Patients with *Histologically or cytologically* confirmed diagnosis of stage IIIb/ IV NSCLC (AJCC 7.0), who had failed one or two systemic chemotherapy regimens, one of which must be platinum-based. 2. Presence of HER2 mutation in tumor tissue as confirmed by AmoyDx® HER2 Mutation Detection Kit 3. Patients with at least one measurable tumor lesion that can accurately be measured by CT scan or MRI according to RECIST 1.1 (R09-0262) 4. Age ≥18 years 5. ECOG performance score 0 or 1 6. Adequate organ function 7. Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia) 8. Written informed consent that is consistent with ICH-GCP and local GCP guidelines Inclusion criteria for part B: 1. Adequate organ function, as per inclusion criteria No.6 in part A

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	2. ECOG performance score ≤ 2 3. More than 12 weeks clinical benefit in part A
Test product(s):	
Dose and mode of administration:	Part A of study: Afatinib, starting 40 mg per day Oral, once daily continuous Part B of study: Afatinib plus Paclitaxel 80 mg/m2 intravenously, weekly. Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator. Dose of afatinib in part B will be last dose received in part A of study
Duration of treatment:	Part A: continuous treatment with afatinib until disease progression or intolerable toxicity or consent withdrawal for any reason. Part B: patient with more than 12 weeks clinical benefit in part A before disease progression would enter into Part B, and be treated with afatinib combined with weekly paclitaxel, continuous treatment until disease progression or intolerable toxicity or consent withdrawal for any reason.
Endpoints	Primary endpoint: Objective response in part A according to RECIST 1.1, Secondary endpoints: Disease control in part A Progression free survival (PFS) in part A,, Overall survival (OS), Time to progression(TTP) in part A, Duration of response(DOR) in part A,
Safety criteria:	Safety assessed by intensity and incidence of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)
Statistical methods:	Efficacy analysis: The objective response rate and its exact 95% Clopper-Pearson confidence interval will be calculated. The disease control rate will also be calculated similarly. All of the time-to-event data (PFS, TTP, DOR and OS) will be estimated using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed(use the Greenwood's formula for estimation of standard errors). Safety analysis: Incidence and severity of adverse events according to the NCI-CTCAE (V 4.0) will

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	be summarized and displayed in number/percentage. The exposure extent to the study drug will be displayed		

FLOW CHART: PART A (AFATINIB MONOTHERAPY)

	Screening		Afatinib Treatment Cycles			End of Treatment in Part A	Follow-up for patient not entering Part B [9]	
			Cycle-1		Cycle-2 onwards[7]			
Visit (V)	**SV1**	**SV2**	**A-C1V1**	**A-C1V2**	**A-CxV1**	**A-EOT[8]**	**A-FU1**	**A-FU-x**
Days	**SV1 is prior to or at the same day as SV2,**	**total duration of SV2 is up to 28**	**Day 1**	**Day 8±3**	**Day 28±2**	**0-14 days after last administration**	**EOT + 30 (+3) days**	**Every 60(±7) days (telephone call)**
Informed Consent [1]	X							
Medical History and Demography		X						
Documentation of HER2 Mutation Status[2]	X							
12 Lead Digital ECG**		X				X		
Review of in-/exclusion Criteria		X						
Physical examination[3*]		X	X		X	X		
Vital Signs *		X	X	X	X	X	X	
ECOG Performance Status *		X	X	X	X	X	X	
Safety Lab[4**]		X	X		X	X		
Pregnancy Test[5]		X						
Tumour Assessment[6]		X	At weeks 8, 12, then every 8 weeks till week 52, then 12 weeks interval after week 52			X		
Concomitant Medications ***	X	X	X	X	X	X	X	
Study Medication Compliance Check				X	X	X		
Adverse Events ***	X	X	X	X	X	X	X	X
Dispense Trial drug (afatinib)			X		X			
Afatinib treatment			X	X	X			
Termination of Trial Medication						X		
Screening visit part B of study						X		
Collection of Vital Status and further anti-cancer treatment Information								X

1. Written informed consent must be obtained from patient before any protocol specific screening assessments are performed, procedure performed as part of routine clinical care do not need to be repeated at screening visit if they are within the allowed time window.
2. For patient who has already tested positive for HER2 mutation as confirmed by AmoyDx® HER2 Mutation Detection Kit before enrollment to this trial, the repeated HER2 mutation testing is not required again.
   For patients who have HER2 mutation tested negative in screening visit 1, no need proceed to screening visit 2.
3. Physical examination must include recording of height only at screening visit,
4. Safety lab would be performed at local lab. The normal reference ranges must be available. Results of previous testing are acceptable and need not be repeated if performed within one week of scheduled test.
5. Pregnancy test can be performed either by urine or blood, should be done within 28 days prior to the start of treatment in Part A.
6. Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis brain) using an appropriate method. The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment. Assessment will be performed at Screening Visit, weeks 8 and 12 (for week 12 tumor assessment, time window is +1week), then every 8 weeks thereafter, after week 52, assessments will be performed every 12 weeks until progression or start of further treatment. Tumour assessment does not need to be performed at the Screening Visit if there are valid results available from assessments which were performed as part of a routine clinical practice within 28 days prior to start of treatment. In the event of early discontinuation or an interruption/delay to treatment, tumour assessment schedule should not be changed, that means, if patient discontinue trial treatment prematurely without objective progression, then tumor assessment would be continued in follow up visit until progression or death or start of new anti-cancer treatment
7. A window period of 2 days is acceptable for each cycle.
8. If the decision to permanently discontinue afatinib is taken during a scheduled visit, the End of Treatment (EOT) Visit should be performed instead of the scheduled visit. Otherwise, 0-14 days after the last administration. For patients who continue to part B, EOT visit can be merged with screening visit of part B.
9. Patients not willing or not eligible to continue in part B of the study can withdraw from main study. These patients will only be followed through telephone for gathering information on vital status. In the event tumor assessment continue in follow up visit, the visit interval would be modified to every 8 or 12 weeks to match the tumor assessment interval.

*: If Physical examination, Vital Signs and ECOG Performance Status in screening period is done within 3 days prior to start of treatment , no need to be repeated on day 1 in cycle 1.
**: the 12 Lead Digital ECG in SV2 should be done within one week prior to the start of treatment.

***: In SV1, only those SAE related with study procedure need to be reported； the AE and Concomitant Medication do not need to be collected in EDC.

FLOW CHART: PART B (AFATINIB PLUS PACLITAXEL THERAPY)

	Screening[5] (EOT of part A)	**Treatment Cycles[6]**				**End of Treatment**	**Follow-up**	**Observation period**
Visit (V)	**SV**	**B-CxV1**	**B-CxV2**	**B-CxV3**	**B-CxV4**	**B-EOT[8]**	**B-FUx[10]**	**B-OPx [12]**
Days	**n.a**	**Day 1**	**Day 8±3**	**Day 15±3**	**Day 22±3**	**0-14 days after last administration**	**EOT + 30 (+3) days[11]**	**FU + 60 (±7) days**
Review in-/exclusion Criteria of part B[1]	X							
Physical examination	X	X				X		
Vital Signs	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	
Safety Lab [2]	X	X[7]	X[7]	X[7]	X[7]	X		
12 Lead Digital ECG	X		X			X		
Tumour Assessment [3]	X	At weeks 8, 12, then every 8 weeks till week 52, then 12 weeks interval after week 52				X	X[11]	
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X
Dispense Afatinib		X						
Afatinib treatment		X	X	X	X			
Premedication and Paclitaxel Administration[4]		X	X	X	X			
Study Medication Compliance Check		X				X		
Termination of Trial Medication						X[9]		
Collection of Vital Status and further anti-cancer treatment Information								X

1. Inclusion/exclusion criteria, particularly Part B-specific criteria, will be reviewed. Patients who fail screening and are not eligible to enter Part B will have their FU Visit as described in Part A.
2. Safety lab would be performed at local lab. The normal reference ranges must be available. Results of previous testing are acceptable and need not be repeated if performed within one week of scheduled test.
3. Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis brain) using an appropriate method. The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment. Assessment will be performed at Screening Visit and every 8 weeks thereafter until progression or start of further treatment, after week 52, assessments will be performed every 12 weeks. Tumour assessment does not need to be performed at the Screening Visit if there are valid results available within 28 days prior to start of part B treatment. In the event of early discontinuation or an interruption/delay to treatment tumour assessment schedule should not be changed, that means, if patient discontinue trial treatment prematurely without objective progression, then tumor assessment would be continued in follow up visit until progression or death or start of new anti-cancer treatment.
4. For pretreatment medication, package label/summary of product characteristics should be followed. Standard pretreatment medications include dexamethasone 20 mg intravenous (IV), diphenhydramine 50 mg, and ranitidine 50 mg IV or cimetidine 300 mg IV 30 minutes prior to weekly paclitaxel; however, a reduction in the dose of dexamethasone is allowed if patients exhibit no signs of hypersensitivity. Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator.
5. Screening Visit should occur during the scheduled visit at which progression is determined (Part A) or as soon as possible **(within 14 days of last afatinib dosage)**. Patient should continue with treatment at the same dose last taken in Part A. Screening visit for part B can be combined with EOT visit of part A and seamlessly with Day 1 of Cycle 1 in part B.
6. Cycles are 28 days ($\pm$2 days). Each new cycle should occur within 28 $\pm$ 2 days from Day 1 of the preceding cycle. X: cycle number, V: Visit, B: Part B.
7. Hematology only before each administration of chemotherapy. This can be done up to one day before the visit.
8. 0-14 days after last administration.
9. In case patient can't tolerate the combination therapy, if there is clinical benefit to continue the monotherapy of Afatinib as the discretion of investigator, investigator could report this case to sponsor and obtain the permission from TCM.
10. All patients should have a first Follow-Up Visit 30 (+3) days after the EOT visit. Patients who have not progressed and have not started further treatment should have tumour assessments until progression or start of further treatment.
11. In the event of tumor assessment continue in follow up visit, the visit interval would be modified to every 8 or 12 weeks to match the tumor assessment interval after FU1.
12. X is the number of Observation Period Visits. Every 60 days ($\pm$7 days) after last FU Visit until death or lost to follow-up. 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.

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ABBREVIATIONS

ADL	Activity of daily living
AE	Adverse Event
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
AESI	Adverse Event of Special Interest
ASE	American Society of Echocardiography
AST	Aspartate Amino Transferase
ATP	Adenosine Triphosphate
AUC	Area under the Curve
β-HCG	Beta-Human Chorionic Gonadotropin
BSA	Body surface area
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
CA	Competent (Regulatory) Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
Cmax	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CPK	Creatine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
erbB	Epidermal Growth Factor family of receptors (erB1/EGFR/HER1, erB2/HER2, erB3/HER3, erB4/HER4)
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart

FU	Follow-up Visit
GI	Gastrointestinal
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
gMean	Geometric Mean
HER	Human Epidermal Growth Factor Receptor
HERG	Human à ether go-go Gene
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HPC	Human Pharmacology Center
IB	Investigator's Brochure
ICC	Investigator's choice chemotherapy
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
K-RAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LD	Longest Diameter
LVEF	Left Ventricular Ejection Fraction
MASCC	Multinational Association of Supportive Care in cancer
MDR1	MultiDrug-Resistance protein 1
mg	Milligram
min	Minute
ml	Millilitre
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Sub team
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OPU	Operative Unit
OP	Observation Period
ORR	Objective response rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
p.o.	per os (oral)
PT	Prothrombin Time

PTT	Partial Thromboplastin Time
PCC	Protocol Challenge Committee
q.d.	quaque die (once a day)
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TKI	Tyrosine Kinase Inhibitor
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TMW	Trial Medical Writer
TNM	Tumour, (lymph) Node, Metastasis
TSAP	Trial Statistical Analysis Plan
WBC	White Blood Cell

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death globally with an estimated one million new cases diagnosed and 880,000 deaths each year. The therapeutic landscape of NSCLC has dramatically changed in the last few years with the introduction of molecularly targeted agents, leading to unprecedented results in lung tumors with a paradigmatic shift from a "one size fits all" approach to a histologic and molecular-based approach. Among them, epidermal growth factor receptor (EGFR) –activating mutations or rearrangement of the anaplastic lymphomakinase (ALK) gene are associated with better outcomes when targeted by selective tyrosine kinase inhibitors. Based on these results, the identification of other activating mutations has been pursued in hopes of improving survival in NSCLC by specifically treating the genomic alterations.

Human epidermal growth factor 2 (HER2 erbB-2/neu) is a member of the erbB receptor tyrosine kinase family. The ERBB2 gene, which encodes for HER2, is a major proliferative driver that activates downstream signaling through PI3K-AKT and MEK-ERK pathways (R13-1023). No ligand has been described for this receptor, which is activated by homodimerization or heterodimerization with other members of the erbB family.

Recently, a renewed interest has been emerging on the human epidermal growth factor-2 (HER2) pathway. Genetic aberrations of this signaling pathway have been reported over time to be associated in NSCLC with different sensitivity to the EGFR TKIs, to have a possible prognostic role and more recently have been emerged as a possible mechanism in EGFR-mutated tumors of acquired resistance to the EGFR TKIs. In addition, dysregulation of the HER2 pathway, in particular HER2 mutations, may represent a possible novel therapeutic target in NSCLC, paving the way for a new generation of targeted agents in NSCLC. Since anecdotal case reports of clinical activity of anti-HER2 agents in NSCLC patients with HER2 mutations, several targeted agents have been evaluated in HER2-mutated patients, generating a growing interest in this oncogenic driver, leading to the design of molecularly selected trials with anti-HER2 compounds, such as Afatinib (P09-10062, P13-05288).

In this trial, patients with adenocarcinoma of the lung with mutant HER2 will receive the irreversible ErbB family blocker afatinib to explore the efficacy and safety of afatinib in those patients population.

1.2 DRUG PROFILE

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) (c01802941-09) 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 (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models, it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting

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

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were observed. 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 $AUC_{0-\infty}$ and Cmax when given 1 hour before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib ($AUC_{0-\infty}$) and 22 % (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 phases 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 [U08-1023-02]. 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/HER2 inhibitors. The most common AEs in Afatinib monotherapy trials were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash/acne, dry skin, pruritus), nail effects, fatigue and decreased appetite. Early and proactive management of diarrhoea, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies [R07-4077, P07-11507, R07-4078, P13-03658 and P13-03659].

Afatinib 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 worldwide, including US, Europe, Japan and many other countries.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

HER2 overexpression and gene amplification has been observed in breast, gastric and ovarian malignancies, inducing sensitivity to HER2 targeting drugs. Both amplification and high copy number gains have also been identified in NSCLC. Considering that HER2-mutant or HER2–amplified NSCLC may benefit from HER2 inhibition or duel EGFR/HER2 inhibition, but not from single blockage of EGFR, novel TKIs simultaneously targeting EGFR/HER2 is investigated.

ErbB family blocker including afatinib have been shown to be effective in lung cancer with HER2 mutations in pre-clinical setting and with HER2 mutations or amplification in limited clinical studies (P09-10062, P13-05288). Afatinib as monotherapy or in combination with sirolimus displays antitumor activity in transgenic animals expressing HER2 mutations (P09-00886). Furthermore, afatinib combination with taxanes have also shown additive anti-tumour effects (P07-03251). Therefore, a clinical study assessing the effect of afatinib in lung adenocarcinoma with genetic aberrations (mutations) of HER2 should be warranted.

The efficacy and safety of afatinib monotherapy in the subset of EGFR mutation positive NSCLC have been demonstrated through robust clinical data (P14-00758). Moreover, in later lines of treatment afatinib may be more effective in combination with cytotoxic drugs (U12-1167). Phase I clinical data have shown clinical activity with combination therapy at doses that were well tolerated (P09-10062, P09-10056). 1200.42 trial is a randomized, phase III study to compare the efficacy and safety of Afatinib combine weekly paclitaxel with investigator's choice chemotherapy (ICC) in the treatment of NSCLC patients with previous EGFR TKIs and at least one chemotherapy treatment failure. The results demonstrated Afatinib combining weekly paclitaxel treatment with afatinib plus paclitaxel led to a statistically significant and clinically meaningful prolongation of PFS compared with treatment with ICC (hazard ratio 0.60; 95% CI 0.43, 0.85; p=0.0031). Median PFS was 5.59 months in the afatinib plus paclitaxel arm and 2.79 months in the ICC arm.and safety is manageable (U12-1167). Clinical benefit of continuing EGFR TKI beyond radiological progression has the potential to improve survival in patients with NSCLC with mutation in EGFR gene. Furthermore, both Afatinib monotherapy and Afatinib combining with weekly paclitaxel showed benefit to patients with HER2 mutation even after failure of other EGFR and/or HER2 targeting treatment (P12-01885).

This study will include only NSCLC patients with documented evidence of HER2 mutation. The study is divided into two parts. In part A, metastatic NSCLC patients with Her 2 mutation who has progressed after 1 or 2 chemotherapy treatment including one platinum-based chemotherapy will receive afatinib 40mg/day monotherapy until disease progression, intolerable toxicity or withdrawal consent for any reason.

Patients who experience more than 12 weeks clinical benefit before disease progression in part A of the study will continue treatment in part B of the trial and will receive afatinib in combination with weekly paclitaxel. Continuation of treatment with EGFR TKI beyond radiological progression is emerging as an acceptable option (P07-03251).

2.2 TRIAL OBJECTIVES

To investigate efficacy and safety of afatinib in NSCLC patients with HER2 mutation, previously treated with 1 or 2 of chemotherapy regimen which include one platinum-based regimen.

The primary objective of this study is to assess afatinib monotherapy's efficacy in the treatment of advanced NSCLC patients with HER2 mutation, who previously received and failed 1 or 2 chemotherapy including one platinum-based regimen.

The secondary objectives of this study are to assess whether afatinib when given as monotherapy or in combination with paclitaxel is able to demonstrate favorable progression-free survival, disease control rate (DCR), overall survival, time to progression and duration of response in NSCLC patients with HER2 mutation, and also drug safety.

2.3 BENEFIT - RISK ASSESSMENT

NCCN guidelines of NSCLC version 3 recommend trastuzumab and Afatinib for NSCLC patients with HER 2 mutation. In a retrospective study of patients with NSCLC with HER2 mutation and previously treated with chemotherapy, a DCR of 100% was observed with afatinib (n=3) treatment (P09-10062). This encouraging signal showing potential benefit of afatinib warrants further exploration in a prospectively designed phase II trial.

The most frequent AE reported with afatinib treatment are GI-related side effects and skin rashes. Both are manageable and can be reversed with proactive management.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.3.

The recommended dose for combination therapy with paclitaxel is 40 mg afatinib daily and 80 mg/m2 paclitaxel weekly. Toxicities with this dose were generally mild to moderate and manageable (P09-05119). This dose, together with proactive management of common side effects and the proposed dose reduction scheme, should be well tolerated. The most common side effects are expected to be primarily gastrointestinal (including diarrhoea, nausea,vomiting and anorexia), as well as fatigue and rash. Although skin and gastrointestinal adverse events are common with afatinib, they are rarely serious and almost always reversible; chemotherapy, however, is associated with potentially life threatening side effects as a result of bone marrow suppression, in some instances, as well as potentially irreversible side effects.

As this is a known class effect of other EGFR/HER2 inhibitors, patients with known interstitial lung disease (ILD) will be excluded from clinical trials with afatinib and careful monitoring of pulmonary symptoms with sudden onset is warranted in all clinical trial protocols. The risk benefit ratio remains unchanged. The clinical benefit of therapy with afatinib with paclitaxel is anticipated to outweigh the risks through 1200.42 study results (U12-1167).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This prospective, open-label, single-arm, multicentre, phase II study will be performed in patients with advanced NSCLC who have previously received and failed 1 or 2 cytotoxic chemotherapy regimens for metastatic disease and harbor HER2 mutation. It is planned that approximately 40 HER2 mutation patients will enter into the trial.

This trial will be performed by investigators with experience in treating patients with NSCLC. The study is divided into two parts.

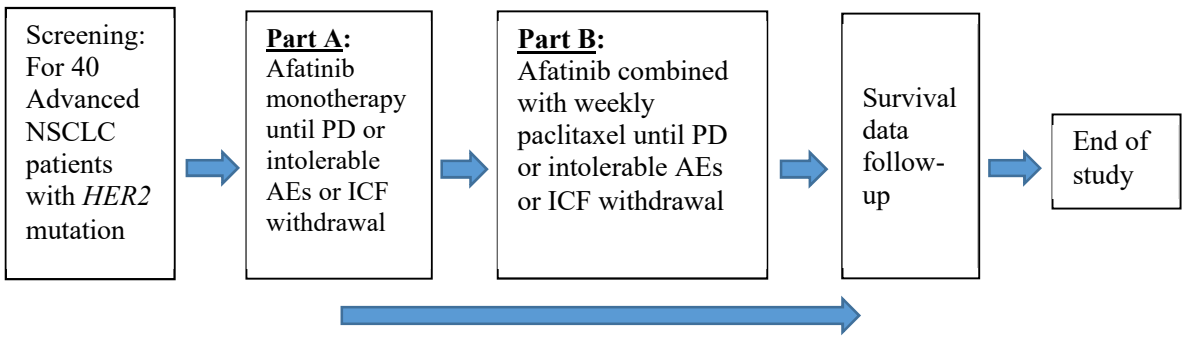
Part A: All eligible patients will first enter part A of the trial. Patients will initially receive a starting dose of 40 mg afatinib and thereafter investigator will be allowed to adjust dose of afatinib based on tolerability. Patients must receive afatinib as continuous daily dosing but for administrative reason, each 28 day treatment will be defined as one treatment cycle. Patients who tolerate afatinib well can be allowed to escalate dose of afatinib to 50 mg once daily from second cycle onwards. In the event of a drug-related adverse event, dose reduction will be allowed. Each dose reduction will decrease dose of afatinib by 10 mg with minimum acceptable dose of 20 mg afatinib. If the patient is not able to tolerate afatinib even after temporary interruptions and reducing dose to 20 mg then the patient must be permanently withdrawn from the trial due to reason of intolerable toxicity. Patients will continue to receive treatment with afatinib monotherapy until progression by RECIST 1.1 or intolerable toxicity or withdrawal of consent.

Part B: All patients who experience more than 12 weeks clinical benefit before disease progression in part A and are able to tolerate afatinib at least 20 mg will be allowed to enter part B of the study and continue treatment with afatinib combined with weekly paclitaxel (80 mg/m2) until disease progression by RECIST 1.1 again or intolerable toxicity.

All patients will visit the investigator at intervals described in the Flow Charts for determination of safety laboratory parameters, assessment of adverse events and additional investigations. An assessment of tumour response will be performed at Screening Visit, at weeks 8 and 12, then at 8 weeks intervals, till week 52 and then at 12 weeks interval thereafter in parts A of the study until documentation of disease progression by RECIST 1.1 (R09-0262). For tumor assessment in Part B, 8 weeks interval would be followed (12 week intervals after 52 weeks) until documentation of disease progression by RECIST 1.1.

The trial drug afatinib will be provided by Boehringer Ingelheim or an authorized Contract Research Organization (CRO) to the study sites, where it will be stored according to the specified storage conditions. Paclitaxel can be purchased from local hospital pharmacy by patient themselves and administered according to the manufacturer's recommendations as described in the package insert, the costs of paclitaxel would be reimbursed by sponsor.

This trial will be entered into a publicly accessible trial registry.
Total patients =40 with *HER2* mutation



3.1.1 Administrative structure of the trial

This study is sponsored by Boehringer Ingelheim. The Coordinating Investigator as specified on the cover page of this protocol, coordinates the investigators at different sites participating in this multicenter, international trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in BIRDS. The Principal Investigator (PI) at each site will be responsible for assuring the proper conduct of the trial, patient care, and safety at the site. The investigator or in some cases one or more sub-investigators will be responsible for the daily conduct of the trial, patient visits, eCRF completion, and for assisting the CRAs in site monitoring.

A complete list of investigators and other persons whose participation materially will affect the conduct of the trial will be filed in the Clinical Trial Master File (TMF) and provided in the Clinical Trial Report (CTR).

The safety laboratory investigations (haematological, biochemical, coagulation, and urine) will be performed at the investigator site and no central laboratory will be used for this. The certification and/or accreditation for each laboratory or evidence that it participates in an established “quality” program must be provided by the investigator and filed at the Sponsor and the local ISF of the site, as well as the normal ranges of each test performed.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

All trial relevant documentation will be stored in BI’s clinical trial master file (TMF). Trial relevant documentation which has to be at the trial site will be filed in the investigator site file (ISF) at the investigator site. The Investigator Site File (ISF) document will be kept in print-out version at the sites as far as required by local regulation and BI-SOP.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The primary objective of this Phase II trial is to assess the efficacy of afatinib in patients with NSCLC harboring HER2 mutation who have progressed after previous chemotherapy treatment. The study is divided into two parts.

Part A: Starting dose of 40 mg afatinib once daily oral dosing
Part B: Afatinib (last received dose in part A) combined with paclitaxel weekly (for example, patients dose reduced to 30 mg afatinib in Part A due to a related adverse event will receive 30 mg afatinib once daily plus paclitaxel)

Patients will be treated until disease progression according to RECIST 1.1 (R09-0262), or intolerable toxicity, or consent withdrawal for any reason, or study termination.

3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not. It is estimated that there are approximately 1400 patients would be screened for 40 entered patients because of the low HER2 mutation rate in NSCLC patients.

3.3.1 Main diagnosis for trial entry

The trial will be performed in metastatic NSCLC patients harbouring HER2 mutation who progressed from previous 1or 2 chemotherapy regimens, one of which is platinum-based chemotherapy.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria in part A

1. Patients with *Histologically or cytologically* confirmed diagnosis of stage IIIb/ IV NSCLC (AJCC 7.0), who had failed one or two systemic chemotherapy regimens, one of which is platinum-based.
2. Presence of HER2 mutation in tumor tissue as confirmed by AmoyDx® HER2 Mutation Detection Kit
3. Patients with at least one measurable tumor lesion that can accurately be measured by CT scan or MRI according to RECIST 1.1 (R09-0262)
4. Age ≥18 years
5. ECOG performance score 0 or 1
6. Adequate organ function, defined as all of the following:

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

b) Platelet count ≥75,000 / mm^3.

c) Estimated creatinine clearance > 45ml / min. Refer to APPENDIX 10.3.

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

e) Aspartate amino transferase (AST) or alanine amino transferase (ALT) ≤ three times the upper limit of (institutional) normal (ULN) (if related to liver metastases ≤ five times ULN).

7. Recovered from any previous therapy related toxicity to ≤Grade 1 at study entry (except for stable sensory neuropathy ≤Grade 2 and alopecia)
8. Written informed consents that is consistent with ICH-GCP and local GCP guidelines

3.3.2.1 Inclusion criterion for Part B

1. Adequate organ function, as inclusion criteria No.6 in Part A
2. ECOG performance score =< 2
3. More than 12 weeks clinical benefit in part A (that is, tumor response at week 8 and week 12 is CR, PR or SD)

3.3.3 Exclusion criteria in part A

1. Prior treatment with EGFR or HER2 targeting small molecules or antibodies.
2. Any chemo-, or immune anticancer therapy within 4 weeks prior to start of study treatment, Hormonal treatment within 2 weeks prior to start of study treatment, Radiotherapy within 4 weeks prior to start of study treatment, except as follows:
   i.) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to enter, and
   ii.) Single dose palliative treatment for symptomatic metastasis outside above allowance to be discussed with sponsor prior to enrolling.
3. Major surgery within 4 weeks before starting study treatment or scheduled for surgery during the projected course of the study
4. Known hypersensitivity to afatinib or the excipients of any of the trial drugs
5. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥ 3 (Refer to APPENDIX 10.4), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to first Afatinib dose.
6. 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.
7. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ or

effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.

8. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2.1 that cannot be stopped for the duration of trial participation
9. Known pre-existing interstitial lung disease.
10. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption).
11. 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.
12. Known Leptomeningeal carcinomatosis.
13. Symptomatic brain metastases; To be eligible patients must be asymptomatic from brain metastases at least 4 weeks without requirement for steroids or anti-epileptic therapy
14. 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.
15. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

*Women of childbearing potential are defined as:
Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

Women not of childbearing potential are defined as:
Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

3.3.3.1 Exclusion criterion for Part B

1. Any known contraindication for paclitaxel treatment.
2. Not able to tolerate lowest dose of 20 mg afatinib.
3. Peripheral polyneuropathy >Grade 2.

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 withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient has radiologic documentation of progressive disease (APPENDIX 10.1). For patient eligible for part B treatment after end of part A, who would be treated with afatinib plus weekly paclitaxel until further progression or other treatment termination criteria is met.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient is diagnosed with ILD.
- Has the need for further dose reductions considered necessary but not allowed according to the protocol (Section 4.1.4)
- The patient is allergy to afatinib or paclitaxel.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the flowchart and Section 6.2.3.
For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. 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 and the patient has access to afatinib through an expanded-access program, named patient use program, or compassionate use protocol, or other means based on local regulation.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial
4. At the discretion of the sponsor (BI) for other reason.

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

4.1.1 Identity of BI investigational product(s)

Table 4.1.1: 1 afatinib:

Substance:	Afatinib
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit strength:	20, 30, 40 and 50 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
Duration of use	Continuous daily dosing until progression, unacceptable adverse events or other reason necessitating withdrawal. For administrative purposes each treatment cycle is 4 weeks (28 days).

Table 4.1.1: 2 Paclitaxel:

Substance:	Paclitaxel
Pharmaceutical formulation:	Concentrate for intravenous infusion
Source:	Locally available commercial supply
Unit strength:	80 mg/m^2 weekly infusion
Posology	weekly
Route of administration:	Intravenous infusion according to package insert or summary of product characteristics (SPC)
Duration of use	Continuous weekly dosing until progression, unacceptable adverse events or other reason necessitating withdrawal. Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator.

4.1.2 Method of assigning patients to treatment groups

Eligible patients will be screened and entered. Only one treatment regimen will be employed.

4.1.3 Selection of doses in the trial

Part A: The starting dose for afatinib continuous oral dosing is 40 mg.

In this trial development of afatinib will continue at a starting 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; with option to dose-escalate to 50 mg for patients meeting the criteria specified in Section 4.1.4.1.1.

Part B: The starting dose of afatinib is last tolerated dose in part A, paclitaxel would be iv weekly at the dose of 80 mg/m2. Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator.

For example, patients will start with 30 mg afatinib daily if dose was reduced to 30 mg in Part A. Paclitaxel will be administered every 7 days of each cycle and according to the package insert or SPC.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Administration of afatinib

Eligible patients will take a single oral dose of afatinib each day starting at a dose of 40 mg, continuously, until the development of progressive disease or unacceptable adverse events. Dose escalation and reductions of afatinib can occur. See Section 4.1.4.

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 8 hours then the missed dose must be skipped. Patients with emesis must not take a replacement dose.

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

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment cycle. For administrative purposes, a treatment cycle is defined as 28 days. Treatment will start when patient is eligible and entered C1V1 and stop when the patient is diagnosed with disease progression or for any reason detailed in Section 3.3.4. Study drug

will be prescribed by the investigator and may be dispensed either by the investigator, site staff or affiliated pharmacy.

4.1.4.1.1 Dose escalation for afatinib

The dose of afatinib administered may be escalated to 50 mg at the start of Cycle 2 if all of the following criteria during Cycle 1 are met:

- Absence of diarrhoea, skin rash, stomatitis, and other drug-related events of CTCAE > 1 in the first 4 weeks
- Afatinib dose was not previously reduced due to any of the AEs depicted in the Dose reduction scheme (Table 4.1.4.1.2: 1)
- Compliant dosing of afatinib, as described in Section 4.3

Dose escalation is prohibited in any situation other than that prescribed above. The patient should remain on 50 mg unless dose reduction becomes necessary (see Table 4.1.4.1.2: 1)

4.1.4.1.2 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 4.1.4.1.2: 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 4.1.4.1.2: 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 to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration	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	If patient was receiving 50 mg, resume treatment at a dose of 40 mg. 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

rate of more than 50% from baseline • Any drug related AE Grade ≥3	permanently discontinued[2].	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 the sponsor 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.

4.1.4.1.2.1 Dose reduction for Afatinib plus paclitaxel weekly

All patients receiving IV paclitaxel should be premedicated with oral corticosteroids (dexamethasone, 20 mg PO at 12 hours and 6 hours prior to treatment or dexamethasone 20 mg IV as a single dose 30 minutes prior to the infusion). Additionally, patients should be premedicated with diphenhydramine 25-50 mg IV or PO and a H_2-receptor antagonist (cimetidine 300 mg IV or PO, famotidine 20 mg IV or PO, or ranitidine 50 mg IV or PO) 30 minutes prior to infusion. In case of good tolerability to paclitaxel the dosage of these premedications may be reduced for future paclitaxel administration. Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator. For antiemetic recommendations, please refer to the SmPC or package insert of paclitaxel.

In case of skin toxicity or diarrhoea, afatinib will be dose reduced according to Table 4.1.4.1.2:1. If the patient has not recovered from skin toxicity or diarrhea after the two reductions with afatinib, the investigator will be allowed to reduce the dose of paclitaxel once (refer to the SmPC or package insert of paclitaxel). If the patient still has not recovered after dose reduction with paclitaxel, the patient should be discontinued from the treatment.

In case of hematoxicity requiring dose reduction, paclitaxel will be dose reduced. In cases of other side effects both compounds will be reduced in parallel. In case paclitaxel is dose reduced, the dose will be reduced to 70 mg/m2 in the event of the first drug-related adverse event. In the event of a second drug-related adverse event, the dose will be further reduced to 60 mg/m2. No further reduction will be allowed.

Dose reduction should always follow a treatment pause (Table 4.1.4.1.2: 1). In the event of a treatment pause, subsequent visits/cycles should not be delayed.

Any patient who experiences deterioration in left ventricular cardiac function (LVEF) with resting ejection fraction to less than 50% or ILD will discontinue treatment (Section 3.3.2). In the event of a prolonged (≥7 consecutive days) >Grade 2 drug-related event not listed in Table 4.1.4.1.2: 1, which is poorly tolerated by the patient, the Investigator may choose to pause the medication for up to 14 days to allow the patient to recover, followed by a dose reduction according to Section 4.1.4.1.2.

Any patient in Part B who does not recover to CTCAE <Grade 1 or baseline within 14 days of treatment pause should be permanently discontinued.

In the event of any unrelated adverse event or unrelated serious adverse event, the Investigator may choose to pause treatment for up to 14 days to allow the patient to recover, but no dose reduction should occur. If the Investigator chooses to pause treatment for more than 14 days and believes that the patient would derive clinical benefit from continuing medication, the decision to continue medication will be made by the BI clinical monitor in agreement with the Investigator.

4.1.5 Blinding and procedures for unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 20mg, 30mg, 40mg and 50mg. Tablets will be supplied in polypropylene (PP), child-resistant, tamper-evident bottles.

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

A new bottle of medication will be dispensed on day 1 of each cycle, regardless of the number of tablets remaining in the bottle from the previous cycle. The patient will initially receive one bottle of 40mg tablets and in the event that dose increase or reduction is necessary the patient will return to the clinic and new medication will be dispensed. Medication numbers will be unique to each bottle and will be used for tracking purposes only.

4.1.7 Storage conditions

Afatinib will be kept in their original packaging and 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.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

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 or appointed CRO, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

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.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Palliative radiotherapy may be given as described in Section 4.2.1.
Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate and use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer), or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of 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 see Appendix 10.5.

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 childbearing 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, hysterectomy and/or tubal ligation) 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 – placement of intrauterine device or intrauterine system, “double barrier” methods of contraception, male sterilisation or etc.) when used consistently and correctly, and must be in accordance with local regulations where applicable. The list of contraception methods meeting these 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 5.3.6.

4.2.3 Management of expected adverse events

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

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

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTC AE Grade ≤ 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is

deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

4.2.3.2 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 prophylaxis while receiving afatinib

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

Table 4.2.3.2: 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
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)

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

Severity (CTCAE Grading)	Description	Specific intervention
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics
FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths) Topical application of aqueous silver nitrate solutions to fissures

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

Severity (CTCAE Grading)	Description	Specific intervention
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics.
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
1 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 4.1.4.1.2 and for restrictions on concomitant therapies refer to Sections 4.2.2, and 10.5.

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

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.

Management of expected adverse events due to paclitaxel

The major toxicities expected with paclitaxel are myelosuppression, nausea/vomiting and peripheral neuropathies. Appropriate measures should be instituted according to institutional procedures or the paclitaxel label before the first injection of paclitaxel and should be continued for as long as the product is being administered. In the case that paclitaxel is well tolerated the dosage of premedications may be reduced for subsequent paclitaxel administrations.

As a general rule, for warnings, precautions, contraindications and other information, see the package insert or the SPC. Investigators should also follow institutional procedures for the administration of chemotherapies.

4.3 TREATMENT COMPLIANCE

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

The appropriate number of afatinib tablets for 4-week of treatment will be provided to patients to be self-administered at home.

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the Sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actually taken} \times 100}{\text{Number of which should have been taken}}$$

If the number of doses taken is not between 80-120%, site staff will explain the patient the importance of treatment compliance.

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, 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 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

The primary endpoint is Objective Response in part A, defined as patients with tumor size reduction of a predefined amount using RECIST 1.1 in part A. Objective responses include both confirmed partial responses (PR) plus complete responses (CR).

5.1.2 Secondary Endpoints

The secondary endpoints are:

- Disease control in part A, defined as patients who have achieved confirmed complete response, partial response and stable disease per RECIST 1.1 in part A.
- Progression free survival (PFS) in part A , defined as the time from the date of starting treatment of afatinib to the date of disease progression per RECIST 1.1, or to the date of death no matter which happens first in part A.
- Overall survival (OS), defined as the time from start of treatment of afatinib until death from any cause.
- Time to progression (TTP) in Part A, defined as the time from the date of starting treatment of afatinib to the date of disease progression per RECIST 1.1 in part A.
- Duration of response (DoR) in part A, defined as the time from the first documented response PR or CR to the date of tumor progression evaluated according to RECIST 1.1 or death in part A.

5.2 ASSESSMENT OF EFFICACY

5.2.1 Tumor assessment

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 assessment.

For the purposes of this study, patients should be evaluated for response as specified in flowchart. The tumor assessments must occur seamlessly during Part A, Part B and until end of study at intervals of 8 weeks + 3 days (or 12 weeks + 3 days after week 52) regardless of treatment interruptions. In the event of a treatment delay, interruption or discontinuation of treatment, tumor assessment should continue to follow the original schedule of 8 weeks intervals (or 12 weeks interval after week 52) calculated from date of starting afatinib monotherapy in part A. Investigator will evaluate for each patient whether Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) occurred.

See APPENDIX 10.1, RECIST 1.1 Criteria for details on lesion measurements, response assessment and response confirmation.

Every effort should be made to objectively evaluate tumor response and confirm tumor progression with radiological tumor imaging for all patients who enter into the trial, including those who discontinue prematurely.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at screening and at the time points specified in the Flow Chart.

A full physical exam serves as a clinical tumour assessment and should include a cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. Wherever possible the same investigator should perform this examination.

Measurement of height (in cm), body weight (in kg) and body temperature and the evaluation of the ECOG performance score will be performed at the time points specified in the Flow Chart.

5.3.2 Vital Signs

Vital signs (blood pressure and pulse after 2 minutes supine rest or 5 minutes seating) and temperature will be recorded at the screening visit and at the time points specified in the Flow Chart

5.3.3 Safety laboratory parameters

Blood samples will be collected at the time points specified in the Flow Chart and analysed in a laboratory facility at the investigational site. Safety laboratory examinations include haematology and biochemistry. In case of neutropenia, blood will be examined as clinically indicated at the discretion of the investigator until recovery.

In part A, approximately 6~10 blood samples will be drawn to test blood for safety. Each sample will require approximately 5ml blood from a vein. On average, approximately 30~50ml blood will be drawn totally per patient.

In part B, approximately 10~18 blood samples will be drawn to test blood for safety, each sample will require approximately 5ml or 2 ml (if only hematology testing is needed) of blood from a vein. On average, approximately 30~40ml blood will be drawn totally per patient.

Safety laboratory assessment may be performed according to local practice but must include at least the following parameters:

Category	Parameters
Hematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, reticulocytes, white blood cell count (WBC) and absolute differential
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Chemistry	
Electrolytes	sodium, potassium, calcium
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 will be calculated using the Cockroft-Gault Formula (see Appendix 10.3).
Other	glucose, albumin, 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
Pregnancy test	β-HCG testing in urine or serum in women of childbearing potential (WOCBP)

At screening, creatinine clearance for study eligibility may be measured or may be calculated using the Cockroft-Gault Formula (Appendix 10.3).

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

Results from previous laboratory testing may be used at screening if testing was done within one week prior to inclusion into the trial, i.e., no repeat investigation is requested for the purpose of the trial.

If haematology results [particularly red blood cell (RBC) count, haemoglobin (HB), haematocrit, white blood cell (WBC) count, absolute neutrophil count (ANC) or platelets] indicate Grade 3 or 4 toxicity the test should be repeated at least once per week and as clinically indicated to characterize the event. If haematologic toxicity resolves to Grade 2 toxicity or upon discussion with the BI clinical monitor, the normal testing routine, as outlined in the Flow Charts and Section 6.2, may be followed.

5.3.4 Electrocardiogram

A 12-lead resting ECG will be performed at the time points specified in the Flow Charts. ECGs will be performed using the routine facility at investigators' sites. No central evaluation of ECG data will be performed.

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.

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 and cases where there is clear evidence of exacerbation of an existing cancer 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" 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 the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities"

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 in the (e)CRF.

Causal relationship of AEs
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.
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.
The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. paclitaxel) and for trial procedure.

5.3.6 Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate eCRF by the Investigator:

From signing the informed consent onwards through the Residual Effect period (REP), until the end of the REP all AEs (non-serious and serious), and AESIs,

In SV1, only those SAE related with study procedure need to be reported; the E and Concomitant Medication do not need to be collected in EDC.

After the end of the REP until individual patient's end of trial, all related SAEs and all related AESIs.

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 please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

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.

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 trial procedures outlined under Section 6.2, and any possible interactions between the investigational drug(s) and a non-investigational medicinal product (NIMP).

The following should also be recorded as an (S)AE in the (e)CRF and SAE form:

- Worsening of the underlying disease or of other pre-existing conditions
- 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.

Screening failures:

SAEs occurring in patients after having discontinued in the trial due to screening failures, i.e. after the screening period and who did not receive any trial medication, are to be reported if the Investigator considered the SAE related to the screening procedure. SAEs which occurred during the screening period are to be reported according to standard procedures.

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the 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).

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

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

Examples of exempted events of PD are:

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER

Not applicable.

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.

The CTCAE criteria are used in the assessment of adverse events in cancer patients. In the present trial CTCAE version 4.0 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

This trial is an open-label trial for patients with NSCLC harbouring HER2 mutation Patients meeting all the inclusion and none of the exclusion criteria and who have given their written informed consent are eligible for participation.

6.1 VISIT SCHEDULE

The Screening Visit must be performed prior to the first administration of afatinib monotherapy for Part A of the trial, Each treatment cycle is defined as 28 days.

Patients who progress after afatinib monotherapy in Part A but are ineligible to continue into Part B or patients who no longer wish to participate in the trial for other reasons (Section 6.2.3) should have their EOT evaluation within 14 days after their last afatinib administration. The first Follow-Up Visit would be undergo 30 + 3 days after the EOT Visit. Further Follow-Up Visits will only be performed to obtain vital status and can be done through telephone every 60 $\pm$ 7 days until death.

In case patient is eligible for participation in the Part B of the trial. EOT Visit of Part A will be same as Screening Visit of Part B.

Before the treatment of Part B, tumor will be assessed to establish a new 'baseline' according to RECIST 1.1. In case there are valid assessments within 4 weeks before first medication administration of part B, tumor assessment does not need to be performed at the Screening Visit of Part B.

Treatment in part B must commence as soon as patient is found eligible. Treatment with afatinib must be continued at the dose taken in Part A and combined with weekly 80 mg/m^2 paclitaxel. These patients will be treated until progression, withdrawal, study termination, death or are lost to follow-up. In the event that patients progress further (compare to the new baseline in part B and according to RECIST 1.1) or no longer wish to participate in the trial, they will undergo an EOT evaluation within 14 days of their last treatment administration, followed by a first Follow-Up Visit 30 + 3 days after the EOT Visit. If patients experience no PD before EOT visit (for those who withdraw or are removed from treatment), patients will have further tumor assessment in future FU Visits until disease progression, death, start of a new anti-cancer therapy, study termination, or are lost to follow-up. After the final Follow-Up Visit, the patients will be observed (Observation Period through Telephone) every 60 $\pm$ 7 days until death, study termination or are lost to follow-up.

If a visit is missed and the patient reports to the Investigator between the missed visit and the next scheduled visit, the missed visit should be performed. The current date and the reason for the delayed visit should be noted in the patient's chart. The next visit, however, should take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Please refer to flowchart for detailed trial procedures information at each visit.

6.2.1 Screening for Part A

Informed consent would be signed (including consent form for archival tumour biopsy sampling for HER2 mutation) before demographics (sex, birth date, race, smoking, alcohol status and histological subtype) would be collected.

In screening visit 1,if HER2 mutation had been confirmed by AmoyDx® HER2 Mutation Detection Kit before enrollment to this trial (the specification of AmoyDx® HER2 Mutation Detection Kit could be found in the investigator study folder), and solid documentation of test results are available, the repeated HER2 Mutation testing is not required again, other trial screening activities in screening visit 2 could be initiated after HER2 mutation positive result is available

For patients who have HER2 mutation tested negative in screening visit 1, no need proceed to screening visit 2.

6.2.2 Treatment periods in Part A

The daily treatment with Afatinib monotherapy would continue until disease progression or other criteria for stopping medication (refer to Section 6.2.3).

Treatment is divided into 28-day cycles for administrative purposes.

6.2.3 End of study treatment and follow-up period in Part A

EOT Visit will only be performed in patients who will not continue into Part B of the trial. For patients entering part B, EOT visit will be merged with screening visit of Part B.

In case the patient did not progress on treatment in part A, but discontinue the Afatinib monotherapy treatment because of intolerant toxicity or other reason, the tumor assessment would be repeated as scheduled time slot (every 8 weeks firstly, then 12 weeks after 52 weeks) until:

- Lost to follow-up
- Disease progression
- Start of a new anti–cancer therapy
- Death

All patients not entering Part B will have the FU Visit to obtain vital status information from patient or caregivers until death of patient or lost to follow-up after the first follow-up visit. The information can be obtained through telephone and recorded in eCRF every 60+/-7 days.

6.2.4 Screening for Part B

Screening Visit should occur during the scheduled visit at which progression is determined in Part A or as soon as possible, but no more than 14 days after last dosage in part A. For patients who are eligible to Part B, No separated informed consent would be signed for Part B since all the Part B related procedure and requirement had been mentioned in inform consent before enrolled into Part A.

6.2.5 Treatment periods in Part B

In part B, patient would be treated with Afatinib combined with weekly paclitaxel (80 mg/m2, iv) until further disease progression or other criteria for stopping medication (refer to Section 6.2.3). Patients will be allowed to rest from treatment every 8th week (7 weeks on/1 week off) at the discretion of investigator

In case patient can't tolerate the combination therapy, if there is clinical benefit to continue the monotherapy of Afatinib as the discretion of investigator, investigator could report this case to sponsor and obtain the permission from TCM.

The tumor assessments must occur seamlessly during Part A, Part B and until end of study at intervals of 8 weeks regardless of treatment interruptions (refer to Section 5.2.1).

6.2.6 Follow-up period and Trial Completion in Part B

6.2.6.1 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 14 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.

6.2.6.2 Residual effect period (REP)

The REP is defined in Section 5.3.6. The End of REP (EoR) visit should not be performed earlier than 30 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. In this trial, the REP visit would be the same visit of first follow-up visit after EOT as specified in flowchart.

6.2.6.3 Extended follow-up period

6.2.6.3.1 Follow-up for progression

Additional follow-up visits after the first follow-up visit will be performed for patients who did not progress on treatment.
The follow-up for progression period will end at the earliest if one of the following events is met:

- Lost to follow-up
- Disease progression
- Start of a new anti–cancer therapy
- Death
- End of whole trial as specified in Section 8.6

The following will be obtained and / or performed during the follow-up visits.
- Record AESI or SAEs 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 every 8 weeks (+/- 3 days), and 12 weeks (+/- 3 days) interval after 52 weeks until progression or death.
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD shall be recorded)

6.2.6.3.2 Observation period for Overall Survival

All patients will be followed-up for overall survival at 2 monthly intervals after the last follow-up for progression visit (as specified in Section 6.2.6.3.1) 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 patient complete the first FU 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 survival observation period:
- Date and type of contact
- Further anti-cancer treatment: regimen and drug name, start and stop dates, reason for stopping this treatment
- Outcome event (Record date of and reason for death)
- Follow-up of adverse events in case they were not yet recovered at previous visit.

6.2.6.4 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 and observation period
- Lost to follow-up
- Withdrawal to be followed-up
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the CRF.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an open-label, single-arm, multi-center Phase II trial that is designed to explore the efficacy of afatinib in treating patients with NSCLC harbouring HER2 mutation. The primary endpoint of this trial is the objective response in part A, as determined according to RECIST 1.1.

7.2 NULL AND ALTERNATIVE HYPOTHESES

In this exploratory trial, inferences about the effects of afatinib in the patients with advanced NSCLC harbouring HER2 mutations will be based upon the magnitude and consistency of the results over time, and across endpoints and prognostic factors, rather than on formal hypothesis tests.

7.3 PLANNED ANALYSES

All patients that receive at least one dose of afatinib will be included in the analyses of efficacy and safety.

Two separate analyses will be performed for objective response rates. One based on all patients treated with afatinib monotherapy (Part A) and the second for all patients treated with afatinib and paclitaxel (Part B). The first analysis will consider all assessment from start of monotherapy until progression under afatinib monotherapy. The second analysis will consider all assessments from start of treatment in part B until progression under treatment with afatinib + paclitaxel.

7.3.1 Primary endpoint analyses

The primary endpoint is Objective Response in part A by investigator assessment per RECIST 1.1 criteria. The Objective Response Rate (ORR) is defined as the proportion of patients with objective response of confirmed CR or PR in part A.

The primary analysis of response will be done when all treated patients are evaluable for response, which is expected to be approximately 20 weeks after the last patient starts treatment.

An exact 95% Clopper-Pearson confidence interval will be calculated for ORR.

Each patient will be assigned to one of the following RECIST categories based on Investigator assessment, irrespective of protocol violations or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)

- PD (progressive disease)
- unknown (not assessable, insufficient data)

Patients' objective responses during treatment, determined without requiring confirmation, will be tabulated separately.

7.3.2 Secondary endpoint analyses

• Disease Control Rate in Part A

One of the secondary endpoint is Disease control in part A by investigator assessment per RECIST 1.1 criteria. The Disease Control Rate (DCR) is defined as the proportion of patients with objective response of confirmed CR, PR and SD. It will be estimated and the exact 95% Clopper-Pearson confidence interval will be calculated.

• PFS in Part A

Disease progression will be evaluated according to the RECIST 1.1 criteria (R09-0262).
PFS with regard to Part A is given as:

- PFSday] = date of progression (under afatinib monotherapy) or death – date of first administration of afatinib in part A+1.

For patients known to be alive and without progression by the end of study or follow-up visit, they will be censored at the date of last imaging without progression. Patients with unknown disease progression status or date, or who are treated with new anticancer therapy will be handled as described in Section 7.6.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence interval, using Greenwood's standard error estimate, will be presented.

• Overall Survival (OS)

OS is defined as time from the date of first administration of afatinib until death due to any cause.

OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact. Rules for missing dates of death are described in Section 7.6.
OS will be estimated using the Kaplan-Meier method. The median OS along with 95% CI will be presented.

• Time to Progression (TTP) in part A

TTP in part A is defined as the time from the date of starting treatment of afatinib to the date of disease progression in part A. It will be estimated using the Kaplan-Meier method, and the median TTP along with 95% CI will be presented.

• Duration of Response (DoR) in part A

Among all the patients with confirmed PR or CR in part A, DoR is defined as the time from the first documented response PR or CR to the date of tumor progression according to

RECIST 1.1 or death in part A. It will be estimated using the Kaplan-Meier method, and the median DoR along with 95% CI will be presented.

Duration of response (DoR) in part A, defined as the time from the first documented response PR or CR to the date of tumor progression evaluated according to RECIST 1.1 or death in part A.

7.3.4 Safety analyses

All patients who receive at least one dose of trial medication will be included in the safety analysis. All safety analysis described below will be performed for patients in part A and part B separately.

Adverse events will be graded according to CTCAE, Version 4.0.

Adverse events will be coded using the Medical Dictionary for Regulators 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 if 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
- fatigue

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

Not applicable

7.4 INTERIM ANALYSES

No interim analysis will be done, but the primary analysis will take place after the last enrolled patient complete the 20- week treatment and tumor evaluation in part A .. All efficacy and safety analysis for patients treated in part A will be performed.

Moreover , a secondly analysis will be done after the last enrolled patient complete the Afatinib treatment in Part A.

Additional exploratory efficacy and safety analyses for part B will be performed in the final analysis when study ends.

7.5 HANDLING OF MISSING DATA

Patients will continue to be followed for both progression and death after discontinuation of study treatment. All reasonable efforts will be undertaken to determine date and cause of death for each patient.

Table 7.5:1 describes how patients will be classified for the analysis of PFS. Sensitivity analyses will examine the effect of using alternative rules.

7.5.1 Table 7.5:1 Endpoint determination for PFS in part A

Situation	Outcome (event or censored)	Date of PFS or censoring
No baseline tumour assessment for part A	censored	Date of first treatment (Part A)
Progressed according to imaging (no missed radiological assessments)	event	Date of PD in part A
Non-PD from imaging assessment[1], death before next scheduled assessment	event	Date of death
Non-PD from imaging assessment[1], one missed assessment, death or progression after date of missed assessment, but before a second scheduled assessment	event	Date of PD in part A or death
Non-PD from imaging assessment[1], more than one consecutive missed assessment, death or progression after date of second missed assessment	censored	Date of last imaging in part A before missed assessment
New anti-cancer medication before progression or death	censored	Date of last imaging in part A before new anti-cancer medication
Death before the scheduled date of first imaging	event	Date of death
No imaging performed post-baseline, patient dies between first and second scheduled assessments	event	Date of death
No imaging performed post-baseline, Patient dies after second scheduled assessment	censored	Date of first treatment (Part A)
No imaging performed post-baseline, vital status is unknown or patient is known	censored	Date of first treatment (Part A)

Situation	Outcome (event or censored)	Date of PFS or censoring
to be alive		

Table 7.5:1 (continued) Endpoint determination for PFS in part A

Situation	Outcome (event or censored)	Date of PFS or censoring
Alive and not progressed according to imaging assessment (no missed radiological assessments)	censored	Date of last imaging in part A

[1] This is from the last assessment at which non-PD (SD or better) was assessed.

Table 7.5:2 describes how patients will be classified for the analysis of death. Patients will be censored at the date of last contact if the Investigator is no longer able to contact a patient or caregiver, and vital status cannot otherwise be determined, provided that no other information indicates that the patient was near death at that point.

7.5.2 Table 7.5:2 Endpoint determination for overall survival

Situation	Outcome (event or censored)	Date of death or censoring
Patients died and the date of death is known	event	Date of death
Patients died and date of death is unknown	censored	Date of last contact when the patient is known to be alive
Patient alive	censored	Date of last contact
Unknown	censored	Date of last contact when the patient is known to be alive

7.6 RANDOMISATION

No randomization is necessary since this is an uncontrolled, non-randomized trial. Eligible patients will be entered into the trial sequentially.

7.7 DETERMINATION OF SAMPLE SIZE

Assuming the underlying objective response rate for the selected patient population is 40%. A sample size of 40 patients are expected in order to obtain an exact binomial 95% CI for ORR with a lower bound greater than 24%, which is considered clinically meaningful (R14-4573). Table 7.7.1 provides the exact binomial 95% CI for various observed ORRs for the 40 patients. The calculations above were performed in R version 3.0.3.

Table 7.7:1 Exact Binomial 95% Confidence Intervals for Various Observed ORRs (n=40)

Observed ORR	Number of Patients with Confirmed PR or CR	Exact 95% CI
35%	14	(20.6%, 51.7%)
40%	16	(24.9%, 56.7%)
45%	18	(29.3%, 61.5%)
50%	20	(33.8%, 66.2%)

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) and 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 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.

For the eCRF, all data need to be derived from source documents, eg:

- Patient identification (gender, date 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 Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all 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 this is the current version of the Investigator's Brochure (c01802941-09). for the non-investigational medicinal product paclitaxel, the reference document is the current version of SmPC. The current versions of these reference documents are to be provided in the ISF.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

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 END OF TRIAL

The trial will end when:

- All patients have stopped the treatment because of disease progression or death or intolerant toxicity.

And 90% events for overall survival had been achieved.

The sponsor may decide to discontinue the trial earlier than this if the primary efficacy

analysis has been completed, sufficient PFS data has been collected, and all patients have either ended study treatment or are eligible to receive afatinib under the conditions listed in Section 3.3.4.1.

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10. APPENDICES

10.1 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.

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.

Only those patients who have measurable disease present at baseline, have received at least 3 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. 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.

New lesions in irradiated fields

Previously irradiated lesions should not be used as indicator lesions. However, new lesions occurring in previously irradiated fields can be used to assess the antitumour response.

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 0mm should be applied.

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

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

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

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

Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.

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 characterize the objective tumour response of the measurable dimension of the disease (see Table 10.1:1).

10.1.1 Table 10.1:1 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 sum LD, nor sufficient increase to qualify for PD taking as reference the smallest sum LD 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 10.1:2).

10.1.2 Table 10.1:2 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. A confirmation of PR or CR should be conducted 4 weeks after the initial assessment, then continue the scheduled tumor assessments until PD occurs.

In the case of SD, measurement must have met the SD criteria at least once after 1st dose at an interval of not less than 6 weeks.

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.1:3) 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 10.1:3).

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.

10.1.3 Table 10.1:3 Algorithm for evaluation of overall best response

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

10.2 CLINICAL EVALUATION OF LIVER INJURY

10.2.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.5 (Protocol-specified Significant Events), are to be further evaluated using the following procedures:

10.2.2 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. Haptoglobin
    3. Complete blood count and cell morphology
    4. Reticulocyte count
    5. CK
    6. LDH
    7. 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.

10.3 COCKCROFT-GAULT FORMULA

Estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula

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

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

10.4 NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

10.5 LIST OF POTENT INHIBITORS AND INDUCERS OF PGP

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

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

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.

10.6 ECOG PERFORMANCE STATUS

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		05 Feb 2016
EudraCT number		NA
BI Trial number		1200.222
BI Investigational Product(s)		BIBW2992 (afatinib)/ Giotrif®/ Giotrif™
Title of protocol		A phase II study of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Trial Clinical Monitor information in Title Page
Description of change		TCM was changed from to
Rationale for change		TCM was changed
Section to be changed		Flow Chart (Part A) Screening Visit
Description of change		Screening Visit is split into SV1 and SV2 The previous footnote: 2. Documented test results from each investigator's accredited labs are acceptable for eligibility. Other trial screening activities could be initiated after HER2 mutation positive result is available.

		Was changed to: 2. For patient who has already tested positive for HER2 mutation as confirmed by AmoyDx® HER2 Mutation Detection Kit before enrollment to this trial, the repeated HER2 Mutation testing is not required again. For patients who have HER2 mutation tested negative in screening visit 1, no need proceed to screening visit 2.
Rationale for change		To lessen the unnecessary procedure in screening visit for negative HER2 mutation and previous tested positive patients.
Section to be changed		FLOW CHART: PartA (A-FU-x) and PartB (Observation period)
Description of change		ECOG Performance Status was removed from A-FU-x in Part A and Observation period in Part B
Rationale for change		Not necessary and feasible to record the ECOG Performance status in this visit
Section to be changed		3.3.3
Description of change		Previous text: i.) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to randomization, Was changed to: i.) Palliative radiation to target organs other than chest may be allowed up to 2 weeks prior to enter
Rationale for change		No randomization is applicable.
Section to be changed		6.2.1
Description of change		Previous text: Documentation of HER2 Mutation Status, if HER2 mutation had been confirmed by the site with the same method, that means HER2 mutations as confirmed by AmoyDx® HER2 Mutation Detection Kit before enrollment to this trial (the specification of AmoyDx® HER2 Mutation

		Detection Kit could be found in the investigator study folder), and solid documentation of test results are available, the repeating HER2 Mutation testing is not required again. One copy of archival tumor biopsy sample would be collected for future double confirmation of HER2 mutation at coordinator investigator's site, the method of HER2 mutation double confirmation could be AmoyDx® kit testing or DNA sequencing. Was changed to: In screening visit 1, if HER2 mutation had been confirmed by AmoyDx® HER2 Mutation Detection Kit before enrollment to this trial (the specification of AmoyDx® HER2 Mutation Detection Kit could be found in the investigator study folder), and solid documentation of test results are available, the repeated HER2 Mutation testing is not required again, other trial screening activities in screening visit 2 could be initiated after HER2 mutation positive result is available For patients who have HER2 mutation tested negative in screening visit 1, no need proceed to screening visit 2.
Rationale for change		The double testing in central lab (Shanghai pulmonary hospital) for HER2 mutation confirmation is waived. To lessen the unnecessary procedure in screening visit for negative HER2 mutation and previous tested positive patients.

Number of global amendment		2.0
Date of CTP revision		16 Aug 2017
EudraCT number		NA
BI Trial number		1200.222
BI Investigational Product(s)		BIBW2992 (afatinib)/ Giotrif®/ Giotrif™
Title of protocol		A phase II study of afatinib in patients with advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Main criteriafor inclusion 1 in the title page and 3.3.2
Description of change		"IIIb" is added in the stage, and "systemic" is added in the chemotherapy.
Rationale for change		1) The advanced NSCLC including IIIb and IV in common practice,cause IIIb patient may benefit from afatinib treatment. 2) The "systemic" is to clarify the general chemotherapy, and exclude other local therapy.
Section to be changed		3.3.4.2
Description of change		Added: 4. At the discretion of the sponsor (BI) for other reason.
Rationale for change		To list other unexpected cause

Section to be changed		Flowchart in part A
Description of change		1) SV1 is separated from SV2; 2) the X for study medication compliance check in A-FU1 was removed to concomitant medication in A-FU1; 3) should be done within 28 days prior to the start of treatment in Part A" is added in note 3; 4) * note is attached with physical examination, vital signs and ECOG Performance status ; 5)** note is attached with 12 Lead Digital ECG and safety lab; 6)*** note is attached with AE and concomitant medication.
Rationale for change		1) SV1 duration is not limited, to allow potential eligible patient in chemotherapy to join the trial 2) This is an edit error in previous version. 3) The time limit for pregnancy test prior to study treatment is requested. 4) The time limit is requested to avoid the unnecessary repeated procedure but ensure the validity prior to study treatment. 5) The time limit is requested to avoid the unnecessary repeated procedure but ensure the validity prior to study treatment. 6) To decrease the undesired data collection for SV1 in EDC, waive the reporting of SAE not related with study procedure in SV1 prior to study treatment.
Section to be changed		5.3.3
Description of change		The volum of blood drawing for safety lab testing is added.
Rationale for change		To specify the blood volum to keep consistent with ICF
Section to be changed		5.3.6
Description of change		Added: In SV1, only those SAE related with study procedure need to be reported; the AE and Concomitant Medication do not need to be collected in EDC.
Rationale for change		To be consistent with the note of flowchart in part A, decrease the undesired data collection for SV1

		in EDC, waive the reporting of SAE not related with study procedure in SV1 prior to study treatment.
Section to be changed		6.1
Description of change		"Within 28 days" is removed
Rationale for change		To be consistent with flowchart in Part A
Section to be changed		7.3.1
Description of change		Added: The primary analysis of response will be done when all treated patients are evaluable for response, which is expected to be approximately 20 weeks after the last patient starts treatment.
Rationale for change		To specify the evaluation timepoint of primary endpoint
Section to be changed		7.3.2
Description of change		PFS2 is updated as PFS
Rationale for change		Edit error
Section to be changed		7.3.4
Description of change		Removed :Tables that describe the frequency, intensity, time to onset, and clinical consequences will be produced for the following AE of special interest: • diarrhea • rash/acne • stomatitis
Rationale for change		To consistent with the AESI in 5.3.5.1
Section to be changed		7.4
Description of change		A Primary analysis and secondary analysis is planned.
Rationale for change		No interim analysis but the primary and secondary analysis is planned to show the analysis result before study end.
Section to be changed		8.6
Description of change		Added: The sponsor may decide to discontinue the study earlier than this if the primary efficacy analysis has been completed, sufficient PFS data

		has been collected, and all patients have either ended study treatment or are eligible to receive afatinib under the conditions listed in section 3.3.4.1.
Rationale for change		Clarify the other cause that sponsor discontinue the study.
Section to be changed		10.1 confirmation
Description of change		Added: A confirmation of PR or CR should be conducted 4 weeks after the initial assessment, then continue the scheduled tumor assessments until PD occurs. "study entry" is updated as "1st dose"
Rationale for change		The confirmation of PR or CR is clarified. The "study entry" is replaced by "1st dose" to make more accurate.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program		17 Aug 2017 16:57 CEST
Approval–Clinical Monitor		18 Aug 2017 03:22 CEST
Author-Trial Statistician		18 Aug 2017 03:28 CEST
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Meaning of Signature	Signed by	Date Signed