Clinical Trial Protocol

Doc. No.: U10-3034-01

BI Trial No.:	1200.34
Investigational Product(s):	BIBW 2992
Title:	LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation
Clinical Phase:	Phase III
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status, Version, and Date of Protocol:	Final, 22 Jan 2010
Planned Dates of Trial:	March 2010 – March 2012

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BIBW 2992			
Protocol date 22 Jan 2010	**Trial number** 1200.34	**Planned trial period** Mar 2010 – Mar 2012	

Title of trial:	LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation
Co-ordinating Investigator:	
Trial site(s) :	Multi-centre trial in Asia (China, India and Korea)
Clinical phase:	Phase III
Objectives:	To investigate the efficacy and safety of BIBW 2992 compared to standard first-line chemotherapy in patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation.
Methodology:	Open-label, randomized study
No. of patients:	
total:	1366 screened 330 randomized
each treatment:	Arm A (BIBW 2992): 220 patients Arm B (Chemotherapy- Gemcitabine /Cisplatin) : 110 patients
Diagnosis and main criteria for inclusion:	Patients with stage IIIB or IV adenocarcinoma of the lung who have an activating mutation of EGFR Not eligible for standard curative-intent treatment with surgery or chemo-radiotherapy. No prior systemic treatment for locally advanced, recurrent or metastatic NSCLC.
Test product(s) :	Arm A: BIBW 2992
dose:	Starting dose 40 mg / day
mode of admin. :	Oral, once daily continuous
Reference therapy:	Arm B: Chemotherapy
dose:	Gemcitabine 1000 mg/m^2 on day 1 and day 8, Cisplatin 75 mg / m^2 on day 1 six courses should be given
mode of admin. :	i.v

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Name of finished product: Not applicable			
Name of active ingredient: BIBW 2992			
Protocol date 22 Jan 2010	**Trial number** 1200.34	**Planned trial period** Mar 2010 – Mar 2012	
Duration of treatment:	Arm A: continuous treatment in the absence of disease progression or adverse events. Arm B: 6 treatment courses (3 weeks per treatment course)		
Criteria for *efficacy:*	• Progression-free survival (PFS) • Complete response (CR), partial response (PR), stable disease (SD), progressive disease(PD) according to RECIST 1.1 • Overall survival (OS)		
Criteria for safety:	Adverse events according to Common Terminology Criteria for Adverse Events (CTC AE Version 3).		
Statistical methods:	The primary objective of the statistical analysis is to determine whether BIBW 2992 prolongs progression-free survival (PFS) in comparison to chemotherapy. A log-rank test will be used to test for the effect of BIBW 2992. Unequal treatment after progression is expected to obscure the effect of BIBW 2992 on survival. Survival will be assessed as a secondary endpoint. The analyses will describe the overall pattern of time to death, together with the extent and influence of post-progression treatment.		

FLOW CHART: ARM A (BIBW 2992)

	Screening*		Treatment Courses 1 - 2***		Treatment Course 3 and subsequent courses	End of Treatment	Follow-up	Observation period
Visit abbreviation	**SV1**	**SV2****	**CxV1[a]**	**CxV2[a]**	**CxV1[a]**	**EOT**	**FUx[b]**	**OP**
Days	**Up to 6 weeks before treatment**	**Up to 28 days before treatment**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 1 (± 2 days)**	**0-14 days after permanent discontinuation of BIBW 2992**	**Every 21 days after EOT visit (± 7 days)*****	**Every 60 days after last follow-up visit (± 15 days)**
Informed Consent 1	X (1)							
Informed Consent 2		X (2)						
Demographics	X	X						
Medical History		X						
Review of In-/Exclusion criteria		X						
Randomization		X (3)						
Complete physical examination (4)		X				X		
Limited physical examination (4)			X		X		X	
Vital Signs		X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	
HRQOL and caregiver support assessment			X		X	X	X	
12 Lead Digital ECG (5)		X		X (5)	X (5)	X (5)		
ECHO or MUGA (6)		X			X (6)	X (6)		
Safety lab (7)		X	X		X	X	X	
Pregnancy test		X						
Tumour biopsy for EGFR mutation analysis (8)	X						X (8)	
Blood sample for EGFR mutation analysis (9)			X (9)				X (9)	
Blood sample for DNA banking (10)			X (10)					
Blood sample for pharmacokinetic analysis (11)			X (11)	X (11)	X (11)			
Tumour assessment (12)		X	See schedule below (12)					
Concomitant medications		X	X	X	X	X	X	
Compliance Check			X	X	X	X		
Adverse events and healthcare usage		X	X	X	X	X	X	
Dispense Trial drugs			X		X			
BIBW 2992 treatment			Continuous					
Termination of trial medication						X		
Trial Completion							X	
Collection of vital status information (13)								X

* The screening visits are identical for all patients but have been included on both flow charts for clarity.

** EGFR mutation analysis will be performed at Screening visit 1. Only patients who test positive for an EGFR activating mutation should proceed to Screening visit 2. Procedures which are performed as part of routine clinical care prior to receiving the EGFR mutation test result do not need to be repeated at Screening visit 2 if they are within the allowed time window (within 28 days prior to treatment).

*** All courses are 3 weeks in duration (21 days). Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met (see Section 6.3.1).

**** If the decision to permanently discontinue BIBW 2992 is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

***** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment.

a x is the number of the treatment course

b x is the number of the follow-up visit

1 Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

2 Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.

3 Treatment must commence as soon as possible after randomization, but within 2 days at the latest.

4 Includes height (at screening only) and weight.

5 A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening, on Day 8 of Course 1, and then on Day 1 of every third course (Day 1 of Course 4, 7, 10 etc.), and at EOT (if not performed in the previous 8 weeks).

6 ECHO or MUGA will be performed at Screening, on Day 1 of Course 4 and then at every third course (Course 7, 10, 13, 16 etc.), and at EOT (if not performed in the previous 8 weeks).

7 Includes haematology, serum biochemistry, and urinalysis. Creatinine clearance must be measured at screening for all patients.

8 Tumour biopsy to be collected at screening visit 1 for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Tumour biopsy at follow-up (at the time of PD) is desirable but optional.

9 A single blood sample for EGFR mutation testing is mandatory at start of treatment and should be taken on Day 1 of Course 1. A single blood sample at follow-up for EGFR mutation testing is desirable but optional.

10 The blood sample for DNA banking is optional. Separate consent must be obtained. The sample may be taken any time after randomization, but preferably on Course1Day1.

11 Pharmacokinetic sampling will take place at C2V1, C2V2 and C3V1. For detailed PK sampling time schedule, refer to Section 5.5.

12 Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment (see Section 5.1.3 for more detail). Assessment will be performed at the following time points until progression or start of further treatment for disease;

Screening visit 2
During week 6 (35-42 days after randomization)
During week 12 (77-84 days after randomization)
During week 18 (119-126 days after randomization)
During week 24 (161-168 days after randomization)
During week 30 (203-210 days after randomization)
Every 6 weeks thereafter until progression/ start of further treatment. After week 48, assessments will be performed every 12 weeks.

In the event of early discontinuation or an interruption/delay to treatment the tumour assessment schedule should not be changed.

13 Collection of information on progression, further treatment and death. Information should be collected from the patient notes or by telephone contact with the patient. A formal study visit is not required.

FLOW CHART: ARM B (GEMCITABINE/ CISPLATIN)

	Screening*		Treatment Courses ***			End of Treatment	Follow-up	Observation period
Visit abbreviation	**SV1**	**SV2****	**$C_{1-2}V1$[a]**	**$C_{3-6}V1$[a]**	**$C_{1-6}V2$[a]**	**EOT**	**FUx[b]**	**OP**
Days	**Up to 6 weeks before treatment**	**Up to 28 days before treatment**	**Day 1 (± 2 days)**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**21 days after Course 6 Day 1 (± 7 days) or If patient does not complete 6 courses, 0-14 days after decision to end treatment**	**Every 21 days after EOT visit (± 7 days) ******	**Every 60 days after last follow-up visit (± 15 days)**
Informed Consent 1	X (1)							
Informed Consent 2		X (2)						
Demographics	X	X						
Medical History		X						
Review of In-/Exclusion criteria		X						
Randomization		X (3)						
Complete physical examination (4)		X				X		
Limited physical examination (4)			X	X			X	
Vital Signs		X	X	X	X	X	X	
ECOG performance status		X	X	X	X	X	X	
HRQOL and caregiver support assessment			X	X		X	X	
12 Lead Digital ECG (5)		X	X (5)					
ECHO or MUGA (6)		X	X (6)					
Safety lab (7)		X	X	X	X	X	X	
Pregnancy test		X						
Tumour biopsy for EGFR mutation analysis (8)	X						X (8)	
Blood sample for EGFR mutation analysis (9)			X (9)				X (9)	
Blood sample for DNA banking (10)			X (10)					
Tumour assessment (11)		X	See schedule below (11)					
Concomitant medications		X	X	X	X	X	X	
Adverse events and healthcare usage		X	X	X	X	X	X	
Dispense Trial drugs			X	X				
Chemotherapy			X(13)	X(13)	X(13)			
Termination of trial medication						X		
Trial Completion							X	
Collection of vital status information (12)								X

* The screening visits are identical for all patients but have been included on both flow charts for clarity.

** EGFR mutation analysis will be performed at Screening visit 1. Only patients who test positive for an EGFR activating mutation should proceed to Screening visit 2. Procedures which are performed as part of routine clinical care prior to receiving the EGFR mutation test result do not need to be repeated at Screening visit 2 if they are within the allowed time window (within 28 days prior to treatment).

*** Courses 1-6 are each 3 weeks (21 days).

**** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment.

a C_{1-2}, Course 1 and course 2, C1-6 Course 1 to course 6

b x is the number of the follow-up visit

1 Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

2 Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.

3 Treatment must commence as soon as possible after randomization, but within 2 days at the latest.

4 Includes height (at screening only) and weight.

5 A 12-lead resting digital electrocardiogram (ECG) will be performed at Screening and then at any other time point if clinically indicated.

6 ECHO or MUGA will be performed at Screening and then at any other time point if clinically indicated.

7 Includes haematology, serum biochemistry, and urinalysis. Creatinine clearance must be measured at screening for all patients.

8 Tumour biopsy to be collected at screening visit 1 for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Tumour biopsy at follow-up (at the time of PD) is desirable but optional.

9 A single blood sample for EGFR mutation testing is mandatory at start of treatment and should be taken on Day 1 of Course 1. A single blood sample at follow-up for EGFR mutation testing is desirable but optional.

10 The blood sample for DNA banking is optional. Separate consent must be obtained. The sample may be taken any time after randomization, but preferably on Course1 Day1.

11 Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must be used throughout the study. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment (see Section 5.1.3 for more detail). Assessment will be performed at the following time points until progression or start of further treatment for disease;

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Every 6 weeks thereafter until progression/ start of further treatment. After week 48, assessments will be performed every 12 weeks.

12 Collection of information on progression, further treatment and death. Information should be collected from the patient notes or by telephone contact with the patient. A formal study visit is not required

13. Day 1, Gemcitabine 1000 mg/m^2 and Cisplatin 75 mg / m^2; Day 8, Gemcitabine 1000 mg/m^2

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ASE	American Society of Echocardiography
AST	Aspartate Amino Transferase
ATP	Adenosine Triphosphate
AUC	Area under the plasma concentration time curve of the analyte in plasma
β-HCG	Beta-Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
CA	Competent (Regulatory) Authority
Cmax	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
CPK	Creatine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CT	Computed Tomography
CTC	Common Terminology Criteria
CTC AE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOC	Documentation of Change
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EC/IEC	(Independent) Ethics Committee
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)
FAS	Full Analysis Set
FU	Follow-up Visit
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
HRQOL	Health-related Quality of Life
HRU	Healthcare Resource Usage
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INR	International Normalised Ratio
IRB	Institutional review board
ISF	Investigator Site File
IVRS	Interactive Voice Response System
IWRS	Interactive Web 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
mg	Milligram
min	Minute
ml	Millilitre
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition Scan
MTS	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl) -2-(4-sulfophenyl) -2H-tetrazolium
No.	Number
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OPU	Operative Unit (of BI)
OP	Observation Period
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QLQ	Quality of Life Questionnaire
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SD	Stable Disease
SFDA	State Food and Drug Administration
SOC	System Organ Class

SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPF	Sun Protection Factor
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Terminal half-life of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TGF	Transforming Growth Factor
TK	Tyrosine Kinase
TKI	Tyrosine Kinase Inhibitor
tmax	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TNM	Tumour, (lymph) Node, Metastasis
ULN	Upper Limit of Normal
US-NCI	United States National Cancer Institute
VEGF	Vascular endothelial growth factor
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 estimated one million new cases diagnosed and 880,000 deaths each year. The prognosis for advanced Stage disease has not changed significantly in the past 20 years. With an overall 5-year survival rate of only 15%, the treatment of this disease remains a major clinical challenge (R05-0876).

In patients with advanced NSCLC (Stage IIIB pleural effusion or Stage IV metastatic disease) systemic chemotherapy is considered the first line treatment of choice, prolonging the median survival and palliating tumour-related symptoms (R05-0876). In an Eastern Cooperative Oncology Group (ECOG) trial, platinum-based doublets achieved an objective response in approximately 20% of advanced NSCLC patients and prolonged median survival to 7.9 months with a one-year survival rate of 33% and a two-year survival rate of 11% (R04-1314). Currently, several different platinum-based doublet combinations are in use worldwide as historically there has been no globally recognised superior regimen.

While systemic chemotherapy has demonstrated modest activity in advanced NSCLC, novel targeted therapies based on specific molecular and biological characteristics of lung cancer have emerged as a new treatment paradigm. The targets most extensively studied include the epidermal growth factor receptors (EGFR) or the Subclass I of the superfamily of transmembrane tyrosine kinase receptors (R06-1302, R07-1049, R07-1135). The Epidermal Growth Factor Receptor was the first member to be cloned and is the most biologically relevant receptor for NSCLC. The erbB signaling system now comprises four closely related tyrosine kinase receptors: human epidermal growth factor receptor 1, HER 1 (erbB1/EGFR), HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4) (R06-1301, R06-1302). Growth factors, such as epidermal growth factor (EGF) and transforming growth factor-α (TGF-α), bind to EGFR and trigger the dimerisation of two EGFR molecules or the heterodimerisation with other closely related receptors, such as HER2. Autophosphorylation and transphosphorylation of the EGFR through its tyrosine kinase domain leads to the recruitment of downstream effector molecules and the activation of multiple intracellular signal transduction pathways. Activation of these signalling cascades is essential for controlling malignant cell growth and metastasis (R06-1262, R06-1301, R06-1302).

Aberrant activation of EGFR is frequently observed in a variety of malignant tumours and can be caused by different molecular mechanisms including mutations, receptor over-expression, ligand-dependent receptor dimerisation, and ligand-independent activation. Over-expression of EGFR is detected in 40% to 80% of NSCLC and this has led to the development of specific small molecule EGFR antagonists (R06-1301, R06-1393, R06-1394). First-generation EGFR small molecule tyrosine kinase inhibitors (TKI) act as ATP analogues, competing reversibly for the tyrosine kinase (TK) catalytic site, and include gefitinib (Iressa®) and erlotinib (Tarceva®).

Despite the high levels of EGFR over-expression in tumours in the majority of patients with NSCLC, recent clinical experiences with specific EGFR-tyrosine kinase inhibitors have

demonstrated tumour regression in only 10% to 15% of unselected NSCLC patients (R05-0867, R06-1301, R06-1306). Further analysis has demonstrated that an objective tumour response to TKI therapy is more likely to occur in Asian females with adenocarcinomas (often with bronchoalveolar differentiation) and with a history of modest or no cigarette smoking (R06-1259, R06-1306, R06-1395, R07-1049).

Further investigations in patients who respond to TKI therapy have indicated that the sensitivity to therapy may correlate with the presence of EGFR activating mutations. Sequence analysis of tissue samples from NSCLC patients responsive to TKI therapy revealed approximately 30 different somatic mutations in the tyrosine kinase domain of EGFR (R06-1262, R06-1393). The frequency of EGFR somatic mutations in the general NSCLC population was found to be approximately 10% in patients from the US, Europe or Australia and up to 30% in patients from Japan and Taiwan (R06-1262, R06-1306, R06-1393).

Specific mutations sensitising EGFR to TKI therapy are either short, in-frame nucleotide deletions, in-frame duplications/insertions or single-nucleotide substitutions clustered around the region of the ATP binding-pocket of the receptor tyrosine kinase domain (R04-4507, R06-1311, R07-1134, R07-1135). The two most common mutations, accounting for more than 90% of known sensitising EGFR mutations in NSCLC specimens result in an in-frame deletion, including the amino acids at codons 746 to 750 (E746 to A750) in Exon 19 and a point mutation resulting in an amino acid substitution at codon 858 (L858R) in Exon 21 (R04-4507, R06-1311, R06-1393, R07-1134, R07-1135). Structural analysis has revealed that these mutations lead to a conformational change within the kinase domain, narrowing of the ATP binding cleft and result in enhanced ligand-dependent receptor activation (R06-1264). In addition, these mutations result in stabilisation of both ATP and competitive small molecule inhibitors within the binding pocket.

Retrospective analyses of studies have indicated that patients with activating Exon 19 and Exon 21 EGFR mutations have a higher response rate and a prolonged survival following treatment with single-agent TKIs compared to patients with wild-type EGFR (R06-1306, R06-1311, R06-1406, R08-4128). Several prospective phase II studies have investigated further the use of TKIs in patients harbouring EGFR mutations (R06-1310, R06-1458, R06-1459, R08-4048, R08-4078, R08-4049). The median PFS observed in these studies ranged from 8.9 months to 12 months, with response rates of between 55% and 90%. Overall survival of up to 24 months has been observed in patients with EGFR mutations receiving customised treatment (R08-4049). The largest cumulative series to date is a combined analysis from seven trials of first-line gefitinib monotherapy in patients with EGFR mutations (R08-4050). This analysis included 148 patients and demonstrated a PFS of 9.7 months and a response rate of 76.4%.

The IPASS trial is a phase III randomized trial of gefitinib versus carboplatin/paclitaxel chemotherapy as first-line treatment for Asian patients selected based on demographic features associated with a higher frequency of mutations (adenocarcinoma, never or light exsmokers) (R08-4132). Recently presented data from this trial indicated that the median progression-free survival (PFS) was equivalent in the two treatment arms (5.7 months with

gefitinib versus 5.8 months with carboplatin/ paclitaxel) (R09-4437). A subgroup of the overall population was tested for EGFR mutation status and an analysis was performed on this subgroup. Amongst the patients tested, the rate of mutation observed was 60%. Patients who tested positive for EGFR mutation had a significantly higher response rate when treated with gefitinib (71.2%) compared to treatment with carboplatin/ paclitaxel (47.3%). Patients who tested negative for EGFR mutation had a significantly higher response rate when treated with carboplatin/ paclitaxel (23.5%) compared to treatment with gefitinib (1.1%). Similarly when compared to chemotherapy, PFS was significantly longer in the presence of EGFR mutations (HR=0.48) and significantly shorter in the absence of EGFR mutations (HR=2.85) in the gefitinib arm. These results strongly suggest that the use of single agent TKIs for first-line therapy may only be of value in patients with EGFR mutations but that in this group of patients, treatment with single-agent TKIs may be more beneficial than chemotherapy.

The efficacy of EGFR TKIs in NSCLC with activating EGFR mutations depends on the type of mutation. Patients with one of the two most common mutations, Exon 19 deletions and L858R, have the highest response rates (84.2%) whereas patients with other, less common, mutations have lower response rates of less than 20% (R08-4109).

In trial 1200.34, patients with adenocarcinoma of the lung harbouring an EGFR mutation will be randomized to receive either Gemcitabine/Cisplatin chemotherapy or the irreversible EGFR small molecule inhibitor BIBW 2992.

BIBW 2992 is a member of the second generation of TKIs which bind irreversibly to EGFR and HER2 and are thought to have potential benefit over first generation TKIs such as erlotinib and gefitinib. One of the reasons for the potential benefit is that BIBW 2992 may have activity against mutations which are resistant to the first generation TKIs (U03-3218). Additionally the irreversible binding may confer more prolonged activity further delaying tumour progression when compared to reversible TKIs.

Despite initially promising responses, most patients treated with currently available EGFRTKI therapies will eventually develop disease progression. Molecular analyses of relapsed NSCLC samples from this group of patients have demonstrated an EGFR mutation rendering the tumour cells resistant to EGFR-TKI therapy (R06-1263, R06-1264, R06-1265, R06-1266, R06-1393). This specific mutation in Exon 20 causes a single base pair change leading to a threonine to methionine amino acid alteration in position 790 (T790M). This specific threonine residue at position 790 serves as the ‘gatekeeper’ deep in the catalytic ATP-binding site of the kinase domain. The bulkier methionine side chain confers drug resistance to the tumour cells by sterically hindering the access of TKIs such as erlotinib or gefitinib to the ATP binding site (R06-1264).

Studies of tumour biopsies taken at diagnosis have shown that the T790M is rarely detected prior to treatment with EGFR TKIs (R06-1405). However, a recent study of EGFR mutations in circulating tumour cells detected the T790M mutation in 38% of patients prior to commencing treatment (R08-4065). The authors also observed that the T790M mutation was present at a relatively low frequency, suggesting that it is present in only a sub-clone of cells and may not be detected by conventional techniques. Following treatment with TKIs, the

T790M mutation is detectable in approximately 50% of NSCLC with acquired resistance to erlotinib and gefitinib (R06-1264).

One of the proposed strategies to prevent or overcome the acquired resistance to TKI therapy in malignant tumours is the use of small molecule inhibitors with higher binding affinity, i.e., irreversible kinase inhibitors (R06-1263, R06-1389, R06-1390, R06-1391, R07-1135, R07-1162). Recently published experimental data strongly support this strategy (R06-1307). Bronchioloalveolar NCI-H1650 NSCLC cells in vitro rapidly developed resistance to gefitinib but not to the irreversible EGFR inhibitors HKI-357, HKI-272, and EKB-569. Moreover, stable over-expression of T790M mutant EGFR conferred high-level biochemical resistance to the EGFR-TKIs gefitinib and erlotinib in Ba/F3 murine hematopoietic progenitor cells that remain sensitive to the irreversible EGFR small molecule inhibitor CL-367,785 (R06-1390). BIBW 2992 also belongs to this class of irreversible kinase inhibitors and has recently shown in vitro activity against NIH-3T3 cell lines expressing the T790M mutation (P08-06904). BIBW 2992 also demonstrated activity in xenograft and transgenic lung cancer models expressing the T790M mutation. In the same experiment these xenografts were resistant to lapatinib and gefitinib (P08-06904).

These preclinical data support the hypothesis that BIBW 2992 may be more efficacious in the treatment of tumours harbouring EGFR mutations than the currently available TKIs.

1.2 DRUG PROFILE

BIBW 2992 is a highly selective and potent low molecular weight, irreversible inhibitor of the erbB-family of tyrosine kinase receptors EGFR (erbB1 / HER1) and HER 2 (erbB2). All references in this protocol concerning BIBW 2992 refer to the oral formulation (U03-3218).

The potency of BIBW 2992 was determined in enzymatic assays using recombinant human wild-type EGFR (IC50 0.5 nM) and HER2 (IC50 14 nm) (U03-3218). A panel of recombinant human kinases tested in parallel was not inhibited, demonstrating the high target specificity of BIBW 2992 (U03-3218). Molecular modeling revealed that BIBW 2992 binds covalently and with high affinity to Cys773 within the catalytic cleft of the ATP-binding pocket of the EGF receptor. It has been reported that this specific molecular interaction results in irreversible inhibition of the EGFR tyrosine kinase domain (R02-2292). Experimental data from in vitro washout studies confirmed the irreversible binding of BIBW 2992 to its molecular target. In constitutively EGFR-overexpressing A431 human epidermoid cancer cells, BIBW 2992 inhibition of EGFR-signaling lasted for up to 7 hours after removal of the compound from the cell cultures (U03-3218). In contrast, A431 cells exposed to reversible EGFR TKIs regained full receptor function almost immediately after inhibitor washout.

The specific activity of BIBW 2992 was determined in two independent *in vitro* assay systems: i) EGF-induced EGFR autophosphorylation using immunoprecipitation and Western blot and ii) clonogenic, anchorage-independent cell growth in a soft-agar assay system (P07-02467). The antiproliferative effects observed with BIBW 2992 compare favourably to activity data published for gefitinib in the same NSCLC cell models (R06-1388). In addition, BIBW 2992 suppressed EGFR phosphorylation and clonogenic growth in the gefitinib-

resistant NCI-H1975 model, suggesting that tumour cells harboring the T790M EGFR TKI resistance mutation remain sensitive to this irreversible EGFR small molecule inhibitor (R06-1391).

The in vivo activity of BIBW 2992 against EGFR was investigated in an A431 subcutaneous xenograft model (U03-3218). Daily oral treatment with BIBW 2992 at doses of 20 mg/kg resulted in an almost complete inhibition of tumour growth over a period of 25 days. Similar anti-tumour activity was observed in NCI-N87 tumour bearing mice treated with BIBW 2992 at similar concentrations. In these in vivo studies, BIBW 2992 plasma concentrations of 80-285 nM corresponding to an AUC_{0-24} of 589-3198 nM*h were required for anti-tumour activity. All BIBW 2992 doses shown to be effective in mouse xenograft models were well tolerated.

Pharmacology and toxicology profile

The absolute bioavailability of BIBW 2992 after oral ingestion is 45% in rats with a median t_{max} reached after 4 hours and a terminal half-life ($t_{1/2}$) of 4.5 hours. In rats the exposure was dose proportional and no gender-related effects or compound accumulation was observed. BIBW 2992 is primarily excreted via the faeces. No relevant inhibition of cytochrome P450 isoenzymes was found. *In vitro* BIBW 2992 is however a CYP3A4 substrate (U05-1723-01). Since this is not considered a dominant metabolic pathway, in vitro drug-drug interactions with CYP3A4 inducers or inhibitors are not expected (U03-3218). In vivo BIBW 2992 was metabolised only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for BIBW 2992 and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of BIBW 2992 in vivo. Only approx. 2 % of the dose were metabolised by FMO3 in vivo. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers (U07-1737, U06-2055- 01, U07-1296-01). Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or CYP3A4 in vivo are expected to be of little, if any, relevance for the pharmacokinetics of BIBW 2992. The human ADME data confirmed the results of the preclinical [^{14}C] ADME studies and all metabolites of the human [^{14}C] ADME study were observed in the rat or the minipig (See U04-1028 and U06-1093, respectively).

In acute toxicology studies, oral administration of single doses in rats and mice indicated a low acute toxic potential of BIBW 2992. Changes in renal and hepatic function occurred only at doses that were 10-30 fold above the levels required for antitumour activity. BIBW 2992 had effects on gastrointestinal function that were dose-dependent and in high doses, leading to profound inhibition. No acute toxic effects on the central nervous system were detected. In oral repeated dose studies for up to 26 weeks in rats and minipigs, the main target organs were the gastrointestinal tract (rats and minipigs), kidneys (rat), and the skin (rats). In the gastrointestinal tract, increasing systemic exposure was associated with dose-dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomach of rats and minipigs. In rat kidneys papillary necrosis and dilated tubules were found. Cutaneous alterations, i.e., epithelial atrophy were observed in rats. However, BIBW 2992 is not irritating to intact skin in albino rabbits and the effects observed in rats are most likely related

to the specific pharmacodynamic mechanism of EGFR-inhibition (U03-3218). A variety of organs including the aerodigestive tract and reproductive organs were affected by epithelial atrophy. These atrophic changes were not severe and fully reversed during a 2-week recovery period. Minor cardiovascular effects (increased blood pressure and heart rate) and a dose-dependent decrease of QT time in the electrocardiogram (ECG) occurred in BIBW 2992-treated minipigs. These data do not indicate a risk for QT-prolongation related arrhythmia. BIBW 2992 had no pro-arrhythmic potential. BIBW 2992 demonstrated mutagenic potential in bacteria but had no genotoxic potential in vivo even at highly toxic/lethal doses in animals. Because of its specific pharmacodynamic mechanism of action, BIBW 2992 is potentially embryo/ foetotoxic and/or teratogenic.

BIBW 2992 Phase I and Phase II trial program

The most up to date trial and safety information can be found in the current version of the Investigator Brochure (U03-3218).

BIBW 2992 showed moderately fast absorption with median t_{max} values between 1 h to 6 h after administration. The gMean terminal half-life ($t_{1/2}$) of BIBW 2992 mainly ranged between 13 h to 57 h. In general, the maximum blood concentration (C_{max}) and the integral of the concentration time curve (AUC) of BIBW 2992 increased in a dose-proportional way (U03-3218).

The maximum tolerated dose (MTD) of BIBW 2992 was identified as 50 mg once daily in phase I continuous dosing monotherapy trials. The 50mg dose is currently used in the phase IIb/III trial 1200.23 in NSCLC patients progressing on erlotinib or gefitinib, as maximum EGFR inhibition is required in this last-line population enriched for the presence of resistance mutations. For a more sensitive population with EGFR activating mutation, a starting dose of 40mg is expected to be sufficient. In phase I clinical trials of BIBW 2992, durable responses (>20 months) were seen at daily doses of 40mg and less.

In this trial, a starting dose of 40 mg will be used in order to optimize the efficacy/toxicity balance in the very sensitive population of first-line patients with EGFR activating mutations. Variability is expected in the incidence and severity of adverse events and to ensure maximum EGFR inhibition, dose escalation to 50mg will be allowed after the first course of treatment (21 days) in patients with minimal treatment-related adverse events. An interim analysis based on response rate is planned to allow an early assessment of the efficacy of the starting dose of 40mg (see Section 7.3.4).

The Adverse Events (AEs) observed to date in Phase I and Phase II trials are consistent with those reported for other EGFR tyrosine kinase inhibitors (dose dependent diarrhoea and skin related adverse events including rash and acne). Other AEs were in the expected range for patients with advanced cancer disease (U03-3218). In the BIBW 2992 Phase I monotherapy trials, the most frequent drug-related adverse events were associated with gastrointestinal disorders (diarrhoea, nausea, vomiting, stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, and acne), general disorders and administration site

conditions (fatigue, mucosal inflammation), respiratory disorders (epistaxis, typically grade 1), and metabolism and nutritional disorders (anorexia, dehydration).

Diarrhoea is the single most often reported gastrointestinal AE. An increased incidence of diarrhoea grade 3 (22.4%) has been observed in phase II monotherapy trials (starting dose of 50 mg qd). Prompt and proactive management of diarrhoea together with timely treatment pause and dose reduction is crucial to reduce the severity of diarrhoea and its potential complications such as dehydration leading to serum electrolyte changes (hyponatraemia, hypokalaemia and hypomagnesaemia) and/or renal impairment.

Nausea and vomiting are the other commonly reported gastrointestinal adverse events and can be generally managed successfully with the use of antiemetics.

Skin related adverse events present in a number of forms, i.e., rash (including erythematous, maculo-papular, papular, etc.), acne, dermatitis acneiform, dry skin, skin reaction and pruritis. Folliculitis as well as nail changes (including paronychia) are other reported manifestations of skin-related adverse events with BIBW 2992. Early and adequate management of skin-related adverse events can reduce the frequency and the severity of them (R07-4077).

Further AEs included oral discomfort (stomatitis, mouth ulceration, oral pain, dry mouth) soft tissue disorder) and mucosal inflammation. Conjunctivitis and rhinorrhoea as a result of inflammation in the mucosal membranes have been reported. Mucosal and skin dryness can lead to epistaxis, which has always been observed at CTCAE Grade 1. Anorexia, fatigue and asthenia are also frequently observed.

Of 22 evaluable patients with NSCLC from Phase I trials, there have been four partial responses (PRs) (3 confirmed and 1 unconfirmed PR) ranging in duration from 5 months to 24 months. All 4 patients were non-smoking Caucasian with adenocarcinoma of the lung. In two of these three patients with confirmed PR, EGFR sequencing has shown Exon 19 inframe deletions. These preliminary clinical efficacy data suggest that BIBW 2992 may be efficacious in patients with recurrent NSCLC harbouring sensitising EGFR mutations.

The efficacy and safety of BIBW 2992 in NSCLC is being evaluated in a phase II trial. In this trial, patients with Stage IIIB/IV lung adenocarcinoma with EGFR mutation in exons 18-21 and failure of one line of systemic chemotherapy are treated with BIBW 2992 at a dose of 50mg once daily until disease progression. Preliminary results of 67 patients treated in the 2nd line setting have shown tumour size reductions in the majority of patients with disease control rate of 97% and overall response rate of 66%. After amending and allowing first line patients into the trial preliminary data show an overall response rate of 63% and a disease control rate of 97% of patients in a total of 38 first line patients Diarrhoea (83.3%) and skin-related adverse events (87.4%) have been the main side effects but have been manageable with appropriate dose interruption/reduction (P08-07355).

A global, randomized, placebo controlled, double blind phase IIB/III trial (LUX-Lung 1) is currently ongoing and is assessing the efficacy of BIBW 2992 plus best supportive care

(BSC) when compared to placebo plus BSC in non-small cell lung cancer patients failing erlotinib or gefitinib. Based on the planned interim analysis of safety and efficacy described in the protocol, the independent DMC has allowed for continuation of recruitment in the trial.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The introduction of the EGFR-TKIs gefitinib and erlotinib has changed the clinical management of patients with advanced NSCLC (R06-1394, R06-1307, R07-1049, R07-1134). For the first time, a significant clinical benefit may be achieved by a treatment that controls NSCLC progression with acceptable levels of side effects through a defined and specific, targeted molecular mechanism (R06-1394).

Patients with adenocarcinoma who have an EGFR mutation have a particularly significant benefit from treatment with TKIs (R08-5155). In these patients the objective response rates achieved with TKI therapy are superior to those obtained with chemotherapy. BIBW 2992 is a second generation irreversible EGFR-TKI (R07-1135, R07-1162) which may have improved potency when compared to erlotinib and gefitinib. BIBW 2992 may also prevent the emergence of the T790M resistance mutation which is commonly seen in patients relapsing after gefinitib or erlotinib. The preliminary results of a second-line study performed in EGFR mutation positive patients show a disease control rate of 87.5% with BIBW 2992 (P08-07355). These promising data support the conduct of a phase III trial with BIBW 2992 in patients with EGFR mutations.

In this trial eligible patients will be randomized (2:1) into two treatment arms to receive either (Arm A) BIBW 2992 or (Arm B) Gemcitabine/Cisplatin chemotherapy.

In the comparator arm of this trial, bevacizumab in addition to chemotherapy will not be included. Two recently reported randomized Phase III studies in the first line treatment of NSCLC, indicated that the addition of bevacizumab to standard paclitaxel and carboplatin (E4599) or gemcitabine and cisplatin chemotherapy (B017704) increased the progression free survival from 4.8 to 6.4 months (R07-1161) and 6.1 to 6.7 months (R08-0542) respectively. But in the AVAIL trial no significant difference in overall survival was observed. Based on this data, and the restrictions on its use, bevacizumab is currently not widely used worldwide as standard first-line treatment for NSCLC and will not be included in the comparator arm of this trial.

Efficacy will be assessed by measuring progression-free survival according to RECIST 1.1 criteria (R09-0262), while safety will be analysed using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 (R04-0474). In addition to evaluating treatment efficacy and safety, the study will also assess health-related quality of life and pharmacokinetics of BIBW 2992.

1.4 BENEFIT - RISK ASSESSMENT

The outcome for patients diagnosed with advanced NSCLC is poor, with an overall 5-year survival rate of only 15%. In recent years tyrosine kinase inhibitors have been developed to target the molecular pathways involved in tumour growth. There is now evidence that these agents are effective in NSCLC patients and particularly in the subgroup of patients whose tumours harbour mutations in the EGFR gene (R08-5155).

The currently available preclinical data indicate that BIBW 2992 is potentially superior to reversible EGFR TKIs (gefitinib, erlotinib) (P08-06904). The preliminary clinical data from trial 1200.22 supports this (P08-07355). The results of first-line treatment with EGFR TKIs compare favourably with historical controls. However, only prospective and controlled clinical trials can establish these treatments as a new standard. The objective of this trial is to assess whether a targeted treatment for a targeted population can be identified, providing maximum benefit to the enriched population, whilst sparing those patients who are not likely to benefit.

Based on the toxicology findings and the experiences from the phase I and II studies, a continuous oral daily dose of 40mg BIBW 2992, together with proactive management of common side effects and the proposed dose reduction scheme, will 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. As an oral drug BIBW 2992 will be a much more convenient treatment for patients when compared to chemotherapy and the side effect profile is expected to be in favour of BIBW 2992. Although skin and gastrointestinal adverse events are common with BIBW 2992, they are rarely serious and almost always reversible, whereas chemotherapy is associated with potentially life-threatening side effects as a result of bone marrow suppression as well as potential irreversible side effects.

Regular and frequent assessment of clinical benefit (including early imaging with first radiological tumour assessment after 6 weeks of treatment) throughout Study 1200.34 will ensure that any patient not deriving clinical benefit will be withdrawn from the trial treatment. Furthermore an independent Data Safety Monitoring Board will oversee the study and will advise on the further conduct of the trial based on the ongoing assessment of efficacy and safety data.

Considering the poor outcome in this group of patients and the need for the development of specific treatments with less side effects, it is expected that the benefits of first-line therapy with BIBW 2992 will outweigh the risks.

2. TRIAL OBJECTIVES

2.1 GENERAL AIM - OBJECTIVES

This randomized, open label phase III trial will be performed in patients with adenocarcinoma of the lung with tumours harbouring an EGFR activating mutation. The objectives of the trial are to compare the efficacy of single agent BIBW 2992 (Arm A) with Gemcitabine/Cisplatin chemotherapy (Arm B) as first line treatment for this group of patients.

2.2 PRIMARY ENDPOINT

The primary endpoint will be progression free survival in all randomized patients, as determined by RECIST 1.1 (R09- 0262).

2.3 SECONDARY ENDPOINTS

The secondary endpoints of this trial are:

- Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) according to RECIST 1.1 (R09-0262)
- Overall survival (OS)
- Deterioration of body weight and ECOG performance status
- Health-related quality of life (HRQOL)
- Pharmacokinetics of BIBW 2992
- Safety of BIBW 2992 as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 (R04-0474)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN - DESCRIPTION

This multi-centre, open-label, randomized phase III trial is designed to compare the efficacy of single agent BIBW 2992 with Gemcitabine/Cisplatin chemotherapy for the first-line treatment of patients with Stage IIIB (with pleural effusion) or IV adenocarcinoma of the lung harbouring an EGFR activating mutation. The primary endpoint of the trial will be progression free survival in all randomized patients.

The trial will be performed by investigators specialised in the treatment of lung cancer in Asia countries (China, India and Korea). It is estimated that approximately 1366 patients will be screened for the trial in order to find 330 eligible patients.

All patients will be required to provide a tumour biopsy sample at screening for EGFR mutation testing, which will be performed by a central laboratory.

Eligible patients will be randomized (2:1) to receive either single agent BIBW 2992 (Arm A) or chemotherapy with Gemcitabine/Cisplatin (Arm B).

In Arm A (BIBW 2992) 220 patients will receive continuous daily treatment with BIBW 2992 until progression, unacceptable adverse events or other reason necessitating withdrawal (see Section 6.3.1). The treatment will be administered as courses of 21 days. The starting dose of BIBW 2992 will be 40 mg once daily. In the event of no or minimal drug-related adverse events after one course of treatment, the dose will be increased to 50 mg (see Section 4.1.4.1 for details). As detailed in Section 4.1.4.1.1, dose reduction will occur in the event of certain drug-related adverse events. Dose reduction will be in increments of 10 mg, with the lowest dose being 20mg. Patients receiving 20 mg will be withdrawn from treatment if a drug-related grade 3 adverse event occurs. Regardless of the dose taken, a patient will be withdrawn from treatment if certain drug related events persist for more than 14 days despite stopping treatment (see Section 4.1.4.1.1), and then followed up as described in Section 6.1.4.

A limited pharmacokinetic sampling approach will be carried out for patients in arm A (BIBW 2992) - only trough PK samples will be taken (refer to Section 5.5).

In arm B (chemotherapy) 110 patients will receive Gemcitabine (1000 mg /m^2) on day 1 and day 8, Cisplatin (75 mg /m^2) on day 1 of each course. Patients will receive 6 courses of 3 weeks of treatment unless unacceptable side effects prevent this. All patients who receive at least one dose of treatment will be followed every 3 weeks after ending treatment until progression or other reason necessitating withdrawal (see Section 6.3.1). Dose reduction will occur in the event of certain adverse events (see Section 4.1.4.2).

Appendix 1 provides an overview of the trial design.

All patients will visit the investigator at regular intervals for assessment of safety parameters and adverse events as outlined in the flow chart. Assessments of response will be made at 6 weeks, 12 weeks and every 6 weeks thereafter until progression or withdrawal for another

reason. After week 48, assessment of response will be performed every 12 weeks until progression of withdrawal for another reason. Tumour response and progression will be assessed using RECIST 1.1 (R09-0262) and assessment at the investigator site will be sufficient for decisions on continuation of treatment. An independent analysis of response will also be performed by a Central Imaging Unit (see Section 5.1.4) but this will not be used to make treatment decisions.

BIBW 2992, Gemcitabine and Cisplatin will be provided to the study sites by Boehringer Ingelheim and will be stored according to the specified conditions (see Section 4.1.7).

All trial relevant documentation will be stored in the clinical trial master file (CTMF) at Boehringer Ingelheim. In addition each site will have an Investigator Site File (ISF) containing all trial documents relevant for the site.

The coordinating investigators are investigators participating in the trial who have experience of this type of trial and investigations. The coordinating investigators have been designated by Boehringer Ingelheim and will sign the clinical trial report.

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

The primary objective of this trial is to compare the efficacy of BIBW 2992 to chemotherapy in patients with adenocarcinoma of the lung harbouring an EGFR activating mutation. Patients will be randomized to receive either BIBW 2992 or chemotherapy with Gemcitabine/Cisplatin. Due to the inherent differences between the two treatment arms, the trial will be open-label.

The primary endpoint of the trial is progression-free survival and therefore the patients will be followed until progression.

3.3 SELECTION OF TRIAL POPULATION

A log of all patients who have signed the informed consent form will be maintained in the ISF at the investigational site. The trial will be conducted in multiple centres in Asia (China, India and Korea). It is estimated that approximately 1366 patients will be screened in order to recruit 330 eligible patients.

Additional centres may be opened in the event of slower than expected recruitment and underperforming centres may be closed. Recruitment rates will vary between centres but it is expected that 36 patients per month will be randomized into the trial over a period of 9-10 months recruitment.

3.3.1 Inclusion criteria

Patients are eligible for inclusion (enrolment) if they fulfill the following criteria:

1. Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology.

2. EGFR mutation detected by central laboratory analysis of tumour biopsy material.
3. Measurable disease according to RECIST 1.1 (R09-0262).

4. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 (R01-0787).

5. Age ≥ 18 years.

6. Life expectancy of at least three (3) months.

7. Written informed consent that is consistent with ICH-GCP guidelines.

3.3.2 Exclusion criteria

Patients with any of the following conditions will be excluded:

1. Prior chemotherapy for relapsed and/or metastatic NSCLC. Neoadjuvant/adjuvant chemotherapy is permitted if at least 12 months has elapsed between the end of chemotherapy and randomization.

2. Prior treatment with EGFR targeting small molecules or antibodies.

3. Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization.

4. Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease).

5. Any other current malignancy or malignancy diagnosed within the past five (5) years (other than non-melanomatous skin cancer and in situ cervical cancer).

6. Known pre-existing interstitial lung disease.

7. Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom e.g. Crohn's disease, malabsorption or CTC grade ≥2 diarrhoea of any aetiology.

8. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomization.

9. Cardiac left ventricular function with resting ejection fraction of less than 50%.

10. Any other concomitant serious illness or organ system dysfunction which in the

opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test drug.

11. Absolute neutrophil count (ANC) < 1500 / mm^3.

12. Platelet count < 100,000 / $mm^{3.}$

13. Creatinine clearance < 60 ml / min or serum creatinine > 1.5 times upper limit of normal.

14. Bilirubin > 1.5 times upper limit of normal.

15. Aspartate amino transferase (AST) or alanine amino transferase (ALT) > 3 times the upper limit of normal (ULN) (if related to liver metastases > 5 times ULN).

16. Women of childbearing potential, or men who are able to father a child, unwilling to use a medically acceptable method of contraception during the trial.

17. Pregnancy or breast-feeding.

18. Patients unable to comply with the protocol.

19. Active hepatitis B infection, active hepatitis C infection or known HIV carrier.

20. Known or suspected active drug or alcohol abuse.

21. Requirement for treatment with any of the prohibited concomitant medications listed in Section 4.2.2.2.

22. Any contraindications for therapy with gemcitabine / cisplatin.

23. Known hypersensitivity to BIBW 2992 or the excipients of any of the trial drugs.

24. Use of any investigational drug within 4 weeks of randomization.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will be randomized to receive either BIBW 2992 or Gemcitabine/Cisplatin chemotherapy.

4.1.1 Identity of investigational product

Substance: BIBW 2992

Pharmaceutical form: Film-coated tablets

Source: Boehringer Ingelheim Pharma GmbH & Co. KG

Unit strength: 50mg, 40mg, 30mg and 20mg film-coated tablets (the dose of BIBW 2992 in the film-coated tablets is related to the free base equivalent of BIBW 2992)

Daily Dose: Starting dose 40mg

Duration of use: Continuous daily dosing until progression, unacceptable adverse events or other reason necessitating withdrawal. For administrative purposes treatment is divided into courses which are each 3 weeks (21 days) in duration.

Route of administration: Oral (swallowed)

Posology: Once daily.

4.1.1.1 Identity of comparator treatment

Chemotherapy: Gemcitabine/Cisplatin

Source: Boehringer Ingelheim will provide commercially available gemcitabine/cisplatin.

Unit strength: Gemcitabine, vial containing 200 mg white, lyophilized powder of gemcitabine for reconstitution

Gemcitabine, vial containing 1000 mg white, lyophilized powder of gemcitabine for reconstitution

Cisplatin, vial containing 50ml solution of cisplatin [1mg/ml]

Daily Dose:	Gemcitabine 1000 mg /m^2 infusion over 30 min followed by Cisplatin 75 mg/ m^2 infusion on day 1 of each course; Gemcitabine 1000 mg /m^2 infusion over 30 min on day 8.
Duration of use:	Each course is 21 days in duration. Patients may receive a maximum of 6 courses.
Route of administration:	Intravenous
Gemcitabine reconstitution:	The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride. Add 5 mL of 0.9% sodium chloride to the 200-mg vial. The total volume upon reconstitution will be 5.26 mL. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% sodium chloride to concentrations as low as 0.1 mg/mL. Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. Reconstituted solution and infusion solution should be used immediately. Do not refrigerate solutions. Discard any unused medicine.
Cisplatin reconstitution:	Cisplatin should be reconstituted with 0.9% sodium chloride. From a microbiological point of view the product should be used immediately. Only use clear reconstituted solutions. Do not refrigerate or freeze. Discard any unused medicine. Administration sets, cannulae and syringes containing aluminium must not be used with the product.
Additional information:	Drugs should be administered according to the summary of product characteristics. The recommendations for supportive care should be followed (see Appendix 2).

4.1.2 Method of assigning patients to treatment groups

Patients will be randomized 2:1 to either BIBW 2992 (Arm A) or chemotherapy with Gemcitabine/Cisplatin (Arm B). The randomization will be stratified according to the type of mutation present. Details of stratification can be found in Section 7.5.

Randomization will be carried out centrally using an Interactive Voice/Web Response System (IVRS/IWRS). The company that provides the IVRS/IWRS system will receive the randomization list from Boehringer Ingelheim Clinical Trial Support Group or a CRO appointed by the sponsor. The BI standard validated random number generating system will be used to generate the randomization schedules which will be verified by an independent statistician who is not involved in the study. The access to the randomization code will be supervised by the Clinical Trial Support Group and persons directly involved in the conduct and analysis of the trial will have no access to the randomization schedule.

4.1.3 Selection of doses in the trial

Arm A: The starting dose for BIBW 2992 continuous dosing is 40 mg.

Arm B: Standard chemotherapy with;
Gemcitabine 1000 mg/m^2 followed by Cisplatin 75 mg/ m^2

These doses have been chosen according to the published information for these drugs.

4.1.4 Selection and timing of doses for each patient

4.1.4.1 BIBW 2992 (Arm A)

For administrative purposes treatment will be divided into treatment courses, which are each 3 weeks (21 days) in duration. Patients will take a single oral dose of 40mg BIBW 2992 each day for the first course (21 days).

If the patient experiences ≥ Grade 1 diarrhoea, skin-related adverse events or mucositis or any drug-related event ≥ Grade 2 during the first course, the dose of BIBW 2992 should be continued at 40mg (unless dose reduction is necessary - see Section 4.1.4.1.1).

If none of the above events are experienced during the first course of treatment, the dose for Course 2 should be increased to 50 mg. The patient should remain on 50 mg for subsequent treatment courses, unless dose reduction is necessary (see Section 4.1.4.1.1). Any exceptions to this will be decided by the Boehringer Ingelheim clinical monitor in agreement with the investigator.

Dose escalation is prohibited in any situation other than that described above.

The medication should be taken at the same time each day (± 2 hours) at least one hour before food intake and at least three hours after food intake. The tablet should be swallowed with a glass of water. BIBW 2992 tablets are film-coated and therefore should not be chewed or crushed, but may be administered via G-tube after dispersing the BIBW 2992 tablets according to the following procedure: Place the tablet into a glass containing 50 mL isotonic sodium chloride solution. Stir until the tablet is broken up into very fine particles (about 15 minutes). Drink the suspension immediately or administer via a gastric tube. Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the gastric-tube again (to pick up any drug remaining in the glass/gastric-tube).

Pharmacokinetic sampling will be performed on Day 1 and Day 8 of Course 2 and on Day 1 of Course 3. On these days patients should not take the trial medication and should not eat for at least three hours prior to their visit to the study site. If a patient needs to eat within 3 hours of a scheduled visit, tablets should be taken as usual and the time of food intake noted on the CRF.

4.1.4.1.1 Dose reduction scheme for BIBW 2992

In the event of treatment-related toxicities, the treatment with BIBW 2992 should be handled according to the schedule in Table 4.1.4.1.1:1

Table 4.1.4.1.1:1 Dose reduction scheme

AE type and grade	Action Dose	Dose reduction scheme
Events related to study drug; • Any **drug related** AE CTCAE Grade ≥3. • CTCAE Grade ≥2 diarrhoea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/ hydration. • CTCAE Grade ≥2 nausea and/or vomiting persisting for 7 or more consecutive days despite antiemetic treatment/ hydration. • CTCAE Grade ≥2 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline.	Pause treatment with BIBW 2992 until patient has recovered to CTCAE Grade ≤ 1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤ 1 or baseline[1] within 14 days study treatment should be permanently discontinued[2]	If patient was receiving 50mg, resume treatment at a dose of 40mg. If patient was receiving 40mg, resume treatment at a dose of 30mg. If patient was receiving 30mg, resume treatment at a dose of 20mg. If patient was receiving 20mg, discontinue BIBW 2992.

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 in the opinion of the investigator, but has not recovered within 14 days, the further treatment of the patient will be decided by the BI clinical monitor in agreement with the investigator

Dose reduction should always follow a treatment pause. In the event of a treatment pause, subsequent visits/courses should not be delayed.

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

In the event of a prolonged (≥7 consecutive days) Grade 2 drug-related event not listed in Table 4.1.4.1.1:1, 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 the schedule in Table 4.1.4.1.1:1.

In the event of any unrelated adverse events or unrelated serious adverse events, the investigator may choose to pause the medication for up to 7 days to allow the patient to recover, but no dose reduction should occur. If the investigator chooses to pause the

medication for more than 7 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.

4.1.4.2 Chemotherapy (Arm B)

Gemcitabine/Cisplatin chemotherapy will be administered at the investigator site and will be prepared and administered in accordance with the current summary of product characteristics (SPC). Up to six 3 week (21 day) courses of chemotherapy will be administered.

Haematology should be checked prior to commencing each course and treatment should be delayed if platelet count is <100,000 cells/ mm^3 or ANC is < 1500 cells/ mm^3.

The patient must be given supportive care (such as anti-emetics, hydration and vitamin supplements) during chemotherapy in accordance with the current summary of product characteristics and institutional guidelines. A summary of the current SPC is provided in Appendix 2.

In the event of treatment related adverse events, the treatment with chemotherapy will be delayed and/or the dose will be reduced in accordance with the guidance in the current summary of product characteristics (SPC). A summary of the current SPC is provided in Appendix 2.

In the event of a delay due to adverse events, subsequent courses and assessments should also be delayed, with the exception of the tumour assessment which should be performed according to the original schedule.

In the event of adverse events or serious adverse events which are not related to treatment, the investigator may choose to delay the medication for up to 7 days to allow the patient to recover, but no dose reduction should occur. If the investigator chooses to delay the medication for more than 7 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

Not applicable.

4.1.6 Packaging, labelling, and re-supply

4.1.6.1 BIBW 2992

BIBW 2992 will be supplied as film-coated tablets. Available dosage strengths will be 20mg, 30mg, 40mg and 50mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles.

Bottles will be labelled according to local regulations and will include the following as a minimum;

- Study number (1200.34)
- Product name (BIBW 2992)
- Contents of the bottle (30 tablets)
- Tablet strength
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical trial use only

Examples of the labels will be filed in the investigator site file (ISF).

Medication numbers will be unique to each bottle and will be used for tracking purposes only. The medication numbers will not be linked to randomization numbers.

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

Gemcitabine will be supplied as vials containing 200 mg or 1000mg of gemcitabine. Cisplatin will be supplied as a 50-ml vial containing 1mg/ml solution of cisplatin.

Vials will be labeled according to local regulations and will include the following as a minimum;

- Study number (1200.34)
- Product name
- Contents of the vial

- Dose strength
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical trial use only
-

Examples of the labels will be filed in the investigator site file (ISF).

Medication numbers will be unique to each vial and will be used for tracking purposes only. The medication numbers will not be linked to randomization numbers.

4.1.7 Storage conditions

BIBW 2992 must be stored in the original packaging in order to protect from light. Film-coated tablets are humidity sensitive and therefore bottles must be kept tightly closed. Tablets will be stored at the study site in a limited access area and must not be stored above 25ºC.

Gemcitabine and Cisplatin will be stored in accordance with the instructions on the label.

4.2 CONCOMITANT THERAPY

Pre-treatment hydration with 1 - 2 litres of fluid infused for 8 - 12 hours prior to Cisplatin will initiate diuresis. Adequate subsequent hydration should maintain diuresis during the 24 hours following administration. Additional pre-medications immediately after randomization are listed in Appendix 2.

During study participation symptomatic treatment of tumour-associated symptoms is allowed. Concomitant medications or therapy to provide adequate care, including bisphosphonates, may be given as clinically necessary. Localised radiation therapy to alleviate symptoms such as bone pain is allowed provided that the total dose delivered is in a palliative range according to institutional standards and does not involve a target lesion(s) utilised for response determination.

Treatment with certain agents which may interfere with trial medication is prohibited (see Section 4.2.2).

All concomitant (non-oncological) medications which are taken between informed consent and the last follow-up visit should be recorded in the electronic case report form (CRF), including anaesthetic agents, vitamins, homeopathic remedies and nutritional supplements. If a patient requires parenteral nutrition it is not necessary to specify the detail on the CRF; it will be sufficient to indicate "parenteral nutrition".

4.2.1 Rescue medication and additional treatments

Rescue medications to reverse the actions of BIBW 2992, Gemcitabine and Cisplatin are not available. Side effects of these treatments should be treated symptomatically.

The current version of the investigator brochure lists the AEs expected with BIBW 2992 (U03-3218). Suggested treatments for diarrhoea, nausea, vomiting, rash/acne and stomatitis are described in Section 4.4 below.

G-CSF use is permitted but not mandated for patients who experience CTCAE Grade 3 or 4 neutropenia or who develop neutropenic fever between cycles of Gemcitabine/Cisplatin chemotherapy. The following doses and schedules are recommended; G-CSF (Filgastrim, 5µg/kg/day) SC beginning 24 hours after the completion of Gemcitabine and continued daily until the neutrophil count is >10,000/µL in two successive analysis or G-CSF (Pentagastrim, 6 mg) SC once per chemotherapy cycle at least 24 hours after completion of Gemcitabine.

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

4.2.2 Restrictions

4.2.2.1 Restrictions for patients randomized to arm A (BIBW 2992)

Patients randomized to treatment with BIBW 2992 should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

4.2.2.2 Restrictions for patients randomized to arm B (Gemcitabine/Cisplatin chemotherapy)

Patients randomized to treatment with Gemcitabine/Cisplatin chemotherapy should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate), maintenance therapy for

NSCLC or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

Patients should not receive any of the prohibited medications as listed in the current summary of product characteristics (SPC) for the Gemcitabine /Cisplatin chemotherapy regimen.

4.3 TREATMENT COMPLIANCE

Study medications will be given in accordance with the protocol and under the instruction of the site investigator.

4.3.1 BIBW 2992 (Arm A)

Patients randomized to BIBW 2992 should take the first dose of treatment at the trial site and subsequent doses will be taken at home. A compliance check should be performed on day 8 of course 1 to ensure that the medication is being taken correctly. Subsequently, at the end of each course of treatment the patient should bring all remaining medication to the site and a compliance check should be performed. Discrepancies between the number of tablets remaining and the calculated number of tablets that the patient should have taken should be documented and explained. At the end of each course any remaining medication should be collected. If the patient is eligible for a further course of treatment a new bottle should be dispensed.

Patients experiencing emesis should not take a replacement dose. BIBW 2992 should not be taken more than once a day under any circumstances.

4.3.2 Gemcitabine/Cisplatin Chemotherapy (Arm B)

Chemotherapy will be administered at the trial site under the supervision of the investigator.

In the event that the patient does not receive the full dose of chemotherapy this should be documented and a reason given.
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4.4 MANAGEMENT OF ADVERSE EVENTS

4.4.1 Management of diarrhoea following treatment with BIBW 2992 (Arm A)

Close monitoring and proactive management of diarrhoea is essential for successful treatment of patients with BIBW 2992. Early and appropriate intervention can prevent the development of more severe diarrhoea. In most cases, loperamide controls diarrhoea caused by BIBW 2992. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating treatment with BIBW 2992.

The recommendations for management are as follows:

- If any diarrhoea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).
- In the event of diarrhoea patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.
- Oral hydration is essential regardless of severity; appropriate rehydration (1.5 l/m2/day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured in the event of CTCAE Grade 2 and Grade 3 adverse events.
- For CTCAE Grade 3 diarrhoea or CTCAE Grade 2 diarrhoea lasting ≥ 2 days (48 hours) despite adequate antidiarrhoeal treatment, BIBW 2992 must be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, BIBW 2992 should be resumed at a reduced dose according to the dose reduction scheme outlined in Section 4.1.4.1.1.

The occurrence of diarrhoea and the outcome of treatment will be recorded in the AE section of the CRF. Antidiarrhoeal treatments should be documented in the concomitant medication section of the CRF.

If despite optimal supportive care and a treatment pause, diarrhoea does not resolve to CTC Grade ≤1 within 14 days, the patient must not receive any further BIBW 2992 treatment and the end of treatment (EOT) visit should be performed.

4.4.2 Management of nausea and vomiting following treatment with BIBW 2992 (Arm A)

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated according to the recommendation given in Table 4.4.2:1.

Table 4.4.2:1 Management of nausea and vomiting

CTCAE Grade	**Antiemetic treatment**
Nausea = grade 0 and Vomiting = grade 0	No antiemetic prophylactic treatment
Nausea = grade 1 and Vomiting = grade 0	No antiemetic treatment

Nausea = grade 2 and Vomiting = grade 0 Nausea = grade 0, 1 or 2 and Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause BIBW 2992 treatment if grade 2 vomiting or grade 2 nausea persist for 7 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE grade ≤ 1.
Vomiting ≥ grade 3 or Nausea ≥ grade 3	Antiemetic treatment[1] Pause BIBW 2992 treatment until return to CTCAE grade ≤ 1 or baseline[2].

1 Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).
2 Baseline is defined as the CTCAE grade at the start of treatment.

After a treatment pause the dose of BIBW 2992 should be reduced according to the dose reduction scheme in Table 4.1.4.1.1:1.

The occurrence of nausea and/or vomiting and the outcome of treatment will be recorded in the AE section of the CRF. Antiemetic treatments should be documented in the concomitant medication section of the CRF with the start and end of treatment dates and daily dose.

In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m^2/day plus hydration deficit) must be ensured.

4.4.3 Management of rash following treatment with BIBW 2992 (Arm A)

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and reduce the rash.

The recommendations for management are as follows:

- **General/Prevention**: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.

- **CTCAE Grade 1 rash*:*** mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.

- **CTCAE Grade 2 rash**: relief from major symptoms caused by CTCAE Grade 2 skin-related adverse events should be achieved by a combination of local and systemic therapies including:

  1) Systemic antibiotics (doxycycline or minocycline etc.).
  2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

And / or

1) Antihistamines (diphenhydramine, etc.)
2) Oral prednisone (short term i.e., <14 days treatment) may be added at investigator's discretion.

Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continue until improvement or resolution to CTCAE Grade ≤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 for up to 14 days followed by a reduction in the dose of BIBW 2992 according to the dose reduction scheme in Table 4.1.4.1.1:1.

- **CTCAE Grade 3 (or greater) rash:** may be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade ≥3 rash, treatment with BIBW 2992 should be paused until recovery to CTCAE Grade ≤1. Treatment should be resumed at a reduced dose (see Section 4.1.4.1). If CTCAE Grade ≥3 rash does not resolve to CTCAE Grade ≤1 within 14 days of stopping BIBW 2992 treatment and despite optimal supportive care, the patient should not receive any further treatment with BIBW 2992 and the End of Treatment visit should be performed.

5. OBSERVATIONS

5.1 EFFICACY - CLINICAL PHARMACOLOGY OR PHARMACODYNAMICS

5.1.1 Primary Endpoint

The primary endpoint is progression free survival (PFS) in all randomized patients, defined as time from the date of randomization to the date of progression or to the date of death, whichever occurs first.

5.1.2 Secondary Endpoints

Secondary endpoints are;

- Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) according to RECIST 1.1 (R09-0262)
- Overall survival (OS) defined as the number of days from the date of randomization to the date of death.
- Time to deterioration of body weight (defined as the first occurrence of a decrease from baseline of more than 10 %) and time to deterioration of ECOG performance status.
- Health-related quality of life (HRQOL).
- Pharmacokinetics of BIBW 2992 (see Section 5.5)
- Safety of BIBW 2992 as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 (R04-0474).

5.1.3 Tumour Assessment

Response will be evaluated according to RECIST 1.1 (R09-0262). Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) will be assessed by the investigator and also by a central imaging unit (see Section 5.1.4).

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

One to five target lesions (not exceeding two lesions per organ) should be identified at screening by Computed Tomography (CT). Skin lesions should be measured and photographic documentation should be performed. Individual lesions detected at screening will be numbered and recorded in the CRF. These lesions should be followed up with the same method(s) used at screening and the same numbering should be applied. The size of the target lesions will be recorded in millimetres. The examinations should be performed at screening, after 6 weeks, after 12 weeks and every 6 weeks thereafter. After week 48, assessments should be performed every 12 weeks. If a patient develops an allergy to contrast media, MRI scans can be substituted for CT scans.

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 routine clinical practice within the allowed time window (within 28 days prior to start of treatment).

Target lesions should be selected based on their size (those with the longest diameter) and suitability for accurate repeated measurements. All other lesions should be identified as non-target lesions and will be recorded at baseline. The non-target lesions will be followed during the patients' participation and will be taken into consideration when determining the patients' response.

Full details of RECIST 1.1 assessment can be found in Appendix 4.

A bone scan should be performed at baseline in cases of clinical suspicion of previously unknown bone metastasis (e.g. bone or joint pain associated with relevant increases of calcium and alkaline phosphatase). If the patient has known bone metastases or if bone metastases are detected at screening, correlative imaging (X-ray or CT scan) should be done of the respective lesion(s) at baseline and subsequently correlative imaging of known bone lesions should be performed at every imaging time-point. During study treatment, bone scans should be performed when medically indicated e.g. in case of suspected new bone metastases.

In the event of a delay, interruption or discontinuation of treatment, tumour assessment should continue to follow the original schedule. The schedule should be followed until progression is observed or until the patient commences further treatment for disease, whichever occurs first.

5.1.4 Central imaging

All image data will be sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment based on a uniform interpretation of radiographic image data for all patients enrolled in the trial. Upon receipt, the central imaging unit will log all image data into a tracking system and perform quality control of digitised radiographic images. An independent review of radiographic images including (i) sequential lesion selection and measurement and (ii) incremental radiological response assessment followed by (iii) global review of tumour response or progression will be performed by two blinded (with regard to patient, treatment, and visit) radiologists. In the case of disagreement on the radiological assessment at any time-point between the two primary reviewers, a third adjudicating radiologist will select one of the primary reviewer's interpretations for all time-points. The data will also be reviewed by an oncologist who will provide a final assessment for each patient.

The review of the image data will be performed by independent radiologists, who are not affiliated with the study. All procedures will be done according to the specifications provided in the investigator site file. The purpose of the blinded reading is to independently assess patient response to therapy and disease progression.

Modifications of the conventional RECIST 1.1 lesion measurement criteria will be introduced into the measurement process in an attempt to reduce variability in the measurements for the independent central imaging review.

Eligibility and treatment decisions will be based on the assessment of disease by the investigator. Central imaging will not be used for this purpose and the results of the central imaging review will not be communicated to the investigator.

5.1.5 Health-Related Quality Of Life

Health-Related Quality Of life (HRQOL) will be measured with the following multidimensional questionnaires included in Appendix 3.

- EQ-5D health status self-assessment questionnaire (R96-2382)
- EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (R99-1213, R07-2064)
- EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) (R07-2060, R07-2065)

All three questionnaires will be completed at the time points specified in the Flow Chart. Questionnaires should be completed by patients prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status so that the responses are not influenced (biased). The questionnaires generally take about 5-10 minutes to complete. Once completed, the questionnaires should be handed to the study co-ordinator or nurse. The data will then be transferred into the CRF by the sponsor. The questionnaires represent source documents (please refer to Section 8.2.4). Validated translations exist for all questionnaires for all countries participating in the study and patients will receive the questionnaires in their native language.

Any unsolicited information provided by the patient on the questionnaire and any safety related data obtained from the patient's responses to the standard questions on the questionnaires will be immediately reported to the investigator. Adverse event information from the questionnaire will be appropriately reported in the CRF.

If local regulations require the completed questionnaires to be confidential (i.e. not seen by the site staff) appropriate arrangements will be made to ensure confidentiality.

The patient perspective is considered a supportive contribution to inform physicians on the clinical utility of BIBW 2992 compared to standard chemotherapy in the NSCLC population under investigation. In addition, the EQ-5D, HRQOL assessment will inform a later health economic (cost-effectiveness) analysis.

EQ-5D

The EQ-5D is a disease generic instrument that has been widely used and has been found to capture HRQOL changes in NSCLC (R07-2129, R07-2130). The EQ-5D comprises the following two questionnaires:

1. The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems).

2. The EQ VAS records the respondents self-rated health status on a vertical graduated (0-100) visual analogue scale.

For the EQ-5D the respondent is asked to indicate his/her health state by placing a cross in the box against the most appropriate statement in each of the 5 dimensions. Additional instructions are provided in the ISF.

QLQ-C30 and LC-13

The QLQ-C30 is comprised of 30 questions. The QLQ-C30 incorporates both multi-items scales and single-item measures. These include one global health status/HRQOL scale, five functional scales, three symptoms scales and six single items to assess dyspnea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Each of the multi-item scales includes a different set of items- no item occurs in more than one scale (R07-2064). The QLQ-LC13 module comprises 13 questions. The module is designed for use in patients receiving treatment with chemotherapy and / or radiotherapy. The QLQ-LC13 incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis (R07-2064).

5.2 SAFETY

5.2.1 Adverse Events

During the screening phase of the trial, the patient's condition will be assessed (e.g., documentation of history / concomitant diagnoses and diseases), and subsequently all relevant changes from baseline will be noted.

The definition of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.4.1. A list of expected adverse events with BIBW 2992 can be found in the investigator brochure (U03-3218).

Patients will be required to report spontaneously any adverse events (AEs) as well as the dates of onset and end of these events. Specific questions will be asked wherever required or useful to more precisely describe an AE and to allow a grading according to CTCAE, Version 3 (R04-0474).

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the date of onset, end date and CTCAE grading of the event as well as any treatment or action required for the event and its outcome.

Regular and continuing assessment of safety will be performed at least once per course during the first 6 courses and every 3 weeks thereafter. Dose reduction schemes are provided in Section 4.1.4.1.1 and Section 4.1.4.2 for patients who experience specified adverse events and who, at the discretion of the investigator, could derive benefit from continuing treatment on the protocol.

Adverse events with an onset during therapy with trial medication or within 28 days after discontinuation of drug intake are considered as "on-treatment". Adverse events which are not yet recovered at the End of Treatment visit will be followed up until recovery or in case of persistence sufficient characterisation of the toxic effects has been achieved and the investigator and Boehringer Ingelheim agree not to pursue them further. Adverse events that occur between Follow-up 1 (21 days after End of Treatment) and the final follow-up visit (see Section 6.1.4 for definition) will only be reported if they are considered related to trial medication or procedures by the investigator.

Adverse events occurring after the final follow-up visit (during the observation period) will be reported only if considered serious (SAEs) and related to trial medication. Data regarding deaths which are not related to trial medication will be collected for the purposes of assessing the overall survival endpoint but these deaths will not be reported as SAEs.

A summary of the requirements is given in Table 5.2.1:1.

Table 5.2.1:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
Screening to Follow-up 1 (21 days after End of Treatment (EOT))	Report all AEs and SAEs regardless of relatedness. This includes all deaths.
Follow-up 1 to Final Follow-up (see Section 6.1.4 for definition of final follow-up)	Report AEs and SAEs which are considered related to study treatment or procedures. Death should not be reported as an SAE unless considered related to study treatment or procedures (because death is an endpoint and will be followed-up separately)
Observation Period	Report only SAEs which are considered related to study treatment or procedures. Death should not be reported as an SAE unless considered related to study treatment or procedures (because death is an endpoint and will be followed-up separately).

Definitions and requirements for documentation and reporting of AEs and serious adverse events (SAEs) during a trial in the CRF are provided in Section 8.4.1.

Patients may be hospitalised for administrative reasons during the trial. These and other hospitalisations planned at the beginning of the trial need not be reported as SAEs if they have been documented at the screening visit and have been performed as planned.

Changes observed in safety tests including blood pressure, pulse rate, electrocardiogram (ECG) and laboratory tests will be recorded as AEs and graded according to CTCAE, if they are not associated with an already reported AE, symptom or diagnosis, and meet at least one of the following criteria:

- Action is required and taken with the investigational drug, i.e., dose reduction or treatment discontinuation

- Treatment is required (i.e., a concomitant medication is added or changed).

5.2.2 Worsening of pre-existing conditions

Expected fluctuations or expected deterioration of the underlying disease will not be recorded as an AE. If progressive disease occurs and is associated with symptoms or meets one of the seriousness criteria (see Section 8.4.1), the signs and symptoms of progressive disease will be reported as an adverse event or a serious AE (if applicable).

The only exception to the above is in the event of a death which is attributed to progressive disease but where the signs and symptoms are not available. In this situation it is acceptable to report the progressive disease as the serious AE.

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event. However, any worsening of any pre-existing baseline condition should be reported as an adverse event. Examples of worsening of a preexisting condition that should be recorded as an AE are given below;

- Worsening of condition meets the criteria for an SAE

- Action is taken with the investigational drug (i.e. dose is reduced or treatment is discontinued)

- Treatment is required (concomitant medication is added or changed)

- The investigator believes a patient has shown a clear deterioration from baseline symptoms

5.2.3 Assessment of Healthcare Resource use

If patients are hospitalised due to adverse events, the reason for hospitalisation, the duration of hospital stay, emergency room admission and time in the intensive care unit will be documented in the CRF. Adverse event related outpatient visits and interventions will also be documented in the CRF.

Information on caregiver support (home care), hospital and outpatient visits (other than scheduled visits) collected in the CRF will inform on healthcare resource use required to treat the trial indication and adverse events observed during the trial. The data collected will be used for a later health economic (cost-effectiveness) analysis.

5.2.4 Laboratory investigations

Blood samples will be collected at the time points specified in the Flow Chart and analysed in a laboratory facility at (or close to) 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.

For patients randomized to Gemcitabine/Cisplatin chemotherapy (Arm B) the decision to continue treatment will be based on assessment of laboratory parameters. Therefore the results of these assessments should be available and assessed on the day of treatment prior to commencing treatment.

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

Haematology	Red blood cell count (RBC), neutrophils, haemoglobin, hematocrit, white blood cell count (WBC) and differential, platelets.
Biochemistry	Glucose, sodium, potassium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), bilirubin, urea (BUN), total protein, uric acid, creatine phosphokinase (CPK). In case of pathological CPK further evaluation (e.g., by Troponin assays) should be performed and the findings documented in the CRF. Glomerular Filtration Rate (GFR) will be estimated by the Cockgroft-Gault Formula utilizing serum creatinine values.
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick. In case of abnormal findings, further evaluation (g/24 hrs urine sampling) should be performed and the findings documented in the CRF.
Pregnancy test	β-HCG testing in urine will be performed in women of childbearing potential at screening (SV2).

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

5.2.5 Physical examination, performance score

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.

A limited physical examination should include a cardiopulmonary examination, a clinical tumour assessment, an examination of the regional lymph nodes and an examination of the abdomen.

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

5.2.6 ECG

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart. ECGs will be performed using a digital ECG machine and the data will be sent to a central assessment centre for evaluation.

The investigator should also review the ECG data at the time of the visit and this will be used to make decisions on eligibility for the study and treatment. However, the investigator should also review the results of the central review when received.

5.2.7 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or MUGA scan will be assessed at time points specified in the Flow Chart. The same method of measurement must be used throughout the study.

Echocardiography (ECHO)

Echocardiography will be performed to assess the LVEF according to the standard guidelines of the American Society of Echocardiography (ASE). http://asecho.org/Guidelines.php (R06-1414).

MUGA Scan

The Multiple Gated Acquisition scan (MUGA) is recommended as a non-invasive method for the assessment of diseases of the heart muscle. It is used for the monitoring of the ejection fraction of the cardiac ventricles, especially the left ventricular ejection fraction (LVEF).

5.2.8 Vital signs

Vital signs (blood pressure, pulse and respiratory rate after 2 minutes supine rest) and temperature will be recorded at the screening visit and at the time points specified in the Flow Chart.

5.2.9 Data and Safety Monitoring Committee (DMC)

A Data and Safety Monitoring Committee (DMC) will be set up for this study in order to ensure its ongoing safety. The DMC will include three members, including an independent statistician and two independent oncologists. Safety review meetings will be held according to the DMC charter; approximately every 6 months (depending on the rate of enrolment).

Inclusion of patients in the study will continue during the scheduled meetings of the DMC. Decisions on trial termination, amendment or cessation of patient recruitment, based on safety or outcome findings will be made after recommendations from the DMC have been assessed by the sponsor.

5.3 OTHER

5.3.1 Demographics and history

Demographics (sex, birth date, race), alcohol history, and histological subtype will be collected during the screening 1 visit. The smoking history will be documented as follows;

- Smoking status; never smoker (<100 cigarettes/lifetime), current-smoker or former smoker
- Number of pack years = (number of cigarettes smoked per day x number of years smoked)/ 20 (R08-4072)
- Date of last cigarette

History of NSCLC will be obtained during screening 2 and reported in the CRF:

- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites (bone, brain, liver, pleural effusion, other)

- Tumour Stage according to the TNM-classification at diagnosis
- Previous surgery and radiotherapy for NSCLC
- Previously administered neoadjuvant/adjuvant chemotherapy including start and end dates and the outcome

5.3.2 Concomitant therapies and diagnoses

Concomitant diagnoses and/or therapies present during study participation (between informed consent and the follow-up visit) will be recorded in the CRF..

5.4 APPROPRIATENESS OF MEASUREMENTS

RECIST 1.1 (R09-0262), which will be used for evaluation of tumour response, is well established and scientifically accepted. The US NCI CTCAE criteria (R04-0474) are used in the assessment of adverse events in cancer patients.

5.5 DRUG CONCENTRATION MEASUREMENTS - PHARMACOKINETICS

5.5.1 Methods and timing of sample collection

For patients randomized to arm A (BIBW 2992) blood sampling will be performed to estimate the BIBW 2992 trough (pre-dose) plasma concentrations at steady state. Samples will be taken at the time-points specified in the table below and at each sampling time, 4 ml of venous blood will be collected.

Table 5.5.1:1 Time schedule for pharmacokinetic (PK) sampling

Course	Visit	Visit name	Time of sampling	Allowed time window	CRF Time/ PTM	Sample No.
Course 2	Day 1	C2V1	Just before drug administration	None	-0:05	1
	Day 8	C2V2	Just before drug administration	None	-0:05	2
Course 3	Day 1	C3V1	Just before drug administration	None	-0:05	3

Date and time of pharmacokinetic blood sampling should be recorded in the eCRF. In addition, the dose, date and time of BIBW 2992 administration and time of food intake before and after medication for the four (4) days prior to pharmacokinetic sampling should be recorded in the eCRF.

Correct and complete documentation of drug administration and blood sampling is mandatory to obtain data of adequate quality for the pharmacokinetic analysis.

The PK sample should not be taken if the patient has not taken any BIBW 2992 tablets during the 4 days prior to the visit (due to dose interruption).

Detailed instructions for the collection and shipping of these samples will be provided in the ISF.

5.5.2 Analytical determinations

BIBW 2992 drug concentrations will be determined by a validated by a high performance liquid chromatography-mass spectrometry (HPLC-MS/MS) assay. The procedure and specification of the analytical method are available at the determination site (Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach, Germany).

5.6 BIOMARKER - PHARMACODYNAMIC SAMPLING

5.6.1 Methods and timing of sample collection

The presence of an EGFR mutation, detected by central laboratory analysis, is mandatory for study enrolment. The results of local analysis of EGFR mutation status will not be accepted for study enrolment.

EGFR mutation analysis will be performed at Screening visit 1. Tumour material will be submitted to the central laboratory as at least five (5), but preferably seven (7), 10 µm unstained sections mounted on non-charged microscopic slides as described in the Laboratory Manual and in the Investigator Site File (ISF). If an equivalent quantity of material is available as sections of different thickness, this is acceptable (e.g. 6 x 7.5 µm, 8 x 5 µm). It is recommended that the sections should contain at least 20% tumour pathology.

Tumour tissue should be paraffin-embedded material obtained from initial diagnostic surgery for NSCLC. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. If tissue is available from more than one occasion, the latest obtained tissue should be used wherever possible. The site of biopsy (primary tumour or metastatic site) will be recorded in the eCRF.

DNA extraction, amplification and quantification using real-time PCR will be performed as described in detail in the Laboratory Manual in the ISF. Mutation genotyping of the most common activating EGFR mutations will be conducted using an established quantitative real-time PCR protocol together with fluorescence detection (Therascreen: EGFR29, DxS Limited). In addition, a central pathology review will be performed, including assessment of percentage of tumour involvement, but this will not be reported to investigators.

The following somatic EGFR mutations are detected;

- 19 deletions in exon 19
- L858R
- 3 insertions in exon 20
- L861Q
- G719S, G719A and G719C
- T790M
- S768I

Samples testing positive for one of these mutations will be reported as 'Positive' and the patient will be eligible for Screening Visit 2. The stratification category and the type of mutation will be specified in the report to the investigator. If a mutation is not detected, the result will be reported as 'Negative' and the patient will be recorded as a Screen Failure. In the event that the EGFR mutation test is inconclusive the investigator is allowed to send further material for testing if desired.

In addition, a blood sample will be collected on Course 1 day 1 for EGFR mutation analysis. This sample is compulsory but the results will not be reported to investigators

During follow-up (after progression) a further blood sample and tissue sample for EGFR mutation analysis may be taken but are optional. The sample requirements are the same as those at screening.

Material submitted for EGFR mutation analysis may be used for the validation of alternative methods for detection of EGFR mutations, which may include detection of additional mutations. The results of these analyses will not be reported to investigators. If local regulations allow, any excess material will be shipped and stored at Boehringer Ingelheim, Germany until any required validation has taken place or until it is decided that there is no requirement for validation. Samples will be destroyed at the latest 5 years after the last patient study visit.

If both L858R and a deletion in exon 19 are detected in the same sample, the patient will be allocated to the 'L858R' stratificatkion category. In any other case where more than one mutation is detected, the patient will be allocated to the 'other mutation' stratification category.

5.6.2 Analytical determinations

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

To allow pharmacogenetic analyses, patients will be asked for one extra blood sample after randomization. Donation of this blood sample for pharmacogenetics is voluntary and not a prerequisite for participation in the study. The sample will only be taken and processed or stored after separate informed consent is given in accordance with local ethical and regulatory requirements.

The blood sample for pharmacogenetic analysis will be anonymised. The anonymisation procedure will guarantee the legally required level of data protection for the donor. Once the anonymisation has been carried out, there will be no legal way to trace back to the identity of the donor. The anonymised DNA may be analysed at a later time to identify whether there are genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions. These analyses may include genes related to efficacy, safety and pharmacokinetics. The sample (or the DNA derived from it) will be stored at Boehringer Ingelheim for 15 years after the end of the clinical trial or until there is no more material available for tests.

The pharmacogenetic sampling will not be performed in countries where local regulations prohibit the shipment of biological materials to Germany.

5.6.2.1 Methods and timing of sample collection

If consent is given, the sample for pharmacogenetic testing may be taken at any time after randomization, but preferably on Day 1 of Course 1. A maximum of 8.5 mL blood will be collected in a PaxGene DNA blood sampling tube. The Paxgene Blood DNA tubes can be stored and shipped at room temperature within 14 days. If a longer storage and shipment period for Paxgene Blood DNA tubes is necessary, the blood samples have to be stored at a temperature of -20 centigrade or below. Once frozen, thawing of the samples should be avoided. Detailed instructions for pharmacogenetic sampling, handling and shipment of samples are provided in the ISF

5.6.2.2 Analytical determinations

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analysed by TaqMan® or other standard genotyping technologies.

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Correlation between drug concentration and response may be made if adequate appropriate data are available. In addition, exploratory correlation will also be made between drug concentration and AEs. Correlation between drug concentration and response may be made if adequate appropriate data are available.

5.8 DATA QUALITY ASSURANCE

The trial will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki (see Section 8), local law and according to the principles of GCP and the company standard operating procedures (SOPs). Each investigator will receive an ISF with all information relevant for the performance of the trial.

Investigators will be visited at regular intervals for on-site monitoring by a Boehringer Ingelheim employee or a clinical research associate (CRA) authorised by BI. An audit may be performed if required or if Boehringer Ingelheim decides to perform an audit.

Data quality review meetings will be performed at regular intervals to evaluate the quality of the data collected. The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

6.1.1 Screening and randomization

The screening process is divided into two visits, Screening Visit 1 and Screening Visit 2. At Screening Visit 1, biopsy material will be analysed by a central laboratory for EGFR mutation status. Patients who test positive for an EGFR mutation will proceed to Screening Visit 2, when full assessments will take place.

All Screening Visit 2 procedures must be performed in the 28 days prior to the first administration of study medication.

Patients who meet the eligibility criteria will be randomized and treatment must commence within 2 days after randomization.

6.1.2 Treatment

Patients randomized to arm A (BIBW 2992) will receive continuous daily treatment until the criteria for stopping medication are met (see Section 6.3.1). For administrative purposes treatment is divided into courses, which are each 3 weeks (21 days) in duration.

Patients randomized to arm B (Gemcitabine/Cisplatin chemotherapy) will receive up to 6 courses of treatment, each 21 days in length. Treatment may be discontinued prior to 6 courses if the criteria for stopping medication are met (see Section 6.3.1).

During the treatment phase visits should be performed as scheduled wherever possible, but within 2 days of the scheduled date.

6.1.3 End of Treatment visit

All patients should be evaluated at the end of treatment (EOT).

In arm A (BIBW 2992) the EOT visit should be performed within 14 days of permanent discontinuation of BIBW 2992. If the decision to discontinue BIBW 2992 is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

In arm B (Gemcitabine/Cisplatin chemotherapy) the EOT visit should be performed 21 days (± 7 days) after course 6 day 1. If the patient does not complete 6 courses of treatment, the visit should be performed within 14 days of the decision to end treatment.

6.1.4 Follow-up

All patients should have the first follow-up visit (FU1) 21 days (± 7 days) after the EOT visit. This visit should be performed regardless of whether the patient has commenced further treatment. If the patient has already started another treatment at the first follow-up, the visit

should still be performed and the new treatment should be recorded as concomitant medication.

Patients who have not progressed and not started further treatment at the first follow-up visit should have further follow-up visits every 21 days (± 7 days) until progression or start of further treatment.

Patients will be considered to have completed the study at the follow-up visit where progression is first documented or where further treatment has begun. This follow-up visit will be termed the 'final follow-up visit'.

6.1.5 Observation period

After completion of the study patients will enter an observation period. During the observation period no study visits will be performed, but data regarding progression, further treatment (including best response and reason for stopping treatment) and death will be collected every 60 days (± 15 days) until death. Information will be collected from the patient notes or by telephone contact with the patient.

The observation period will end after all patients have died or 5 years after the last follow up visit, whichever occurs first.

6.1.6 Treatment after the End of Study

Following progression, patients should receive adequate further treatment to prevent a treatment bias between the two arms.

It is recommended that patients who progress after receiving BIBW 2992 in the clinical trial are subsequently treated with standard platinum-based combination chemotherapy if eligible. Licensed single-agent chemotherapy can be considered if patients are unable to tolerate combination chemotherapy.

It is recommended that patients who progress after receiving first-line chemotherapy in the clinical trial should receive standard second line treatment with single agent chemotherapy and/or a licensed EGFR TKI, as long as they are clinically eligible.

Second-line therapy should only be started following an objective and confirmed progression.

6.2 TRIAL PROCEDURES AT EACH VISIT

6.2.1 Screening and run-in in phases

Screening Visit 1 Screening Visit 1 should be performed within 6 weeks of the first administration of study medication	
Informed Consent 1	Written informed consent must be obtained before any study-specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status
Demographics	Sex, birth date, race, alcohol history and smoking history
Tumour biopsy for EGFR mutation analysis	Tumour biopsy will be collected for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Material should be submitted to the central laboratory for analysis as described in Section 5.6.1.

Screening Visit 2 This visit should only be performed by patients who have tested positive for an EGFR mutation. All screening visit 2 procedures should be performed within 28 days of the first administration of study medication.	
Informed Consent 2	Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.
Demographics	Sex, birth date, race, alcohol history and smoking history will be taken for patients who had a tumour biospy performed as routine clinical practice and did not participate Screening Visit 1
Medical history	Oncological and relevant non-oncological history including details of any previous treatment for NSCLC (see Section 5.3.1)
Patient eligibility	Assessment of eligibility according to inclusion and exclusion criteria should be performed..
Randomization	If the patient meets the eligibility criteria, randomization should be performed. Treatment should commence within 2 days after randomization. If the patient is randomized to chemotherapy, pre-medication should commence immediately after randomization (see Appendix 2).
Physical examination	Cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status. Measurement of height and weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG	ECOG performance status will be assessed and documented
ECG	12-lead resting ECG will be performed.
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA
Safety lab	Haematology, Biochemistry, Urinalysis and Creatinine Clearance (see Section 5.2.4 for minimum assessments).
Pregnancy test	β-HCG testing in urine will be performed in women of childbearing potential
Tumour assessment	CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The assessment does not need to be repeated if there are valid results available from assessments which were performed as part of routine clinical practice within the allowed time. 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.
Con meds	Document indication, start and stop date of each concomitant medication
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.

6.2.2 Treatment phases

6.2.2.1 Treatment Arm A (BIBW 2992)

Arm A (BIBW 2992) Day 1 of each course (± 2 days) C1V1, C2V1, C3V1, C4V1, C5V1 etc. N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions
Caregiver support	Collect information on any meal delivery, caregiver support (home care) and healthcare professional support
Physical examination	Cardiopulmonary examination, an examination of the regional lymph nodes and an examination of the abdomen. Measurement of weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG performance status	ECOG performance status will be assessed and documented
ECG	12-lead resting ECG will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.).
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.)
Safety lab	Haematology, Biochemistry and Urinalysis (see Section 5.2.4 for minimum assessments).
Serum sample for EGFR mutation analysis	A serum sample will be collected on Day 1 of Course 1 for analysis of EGFR mutation status.
Blood sample for pharmacokinetic analysis	Pharmacokinetic sampling will be performed on Day 1 of Course 2 and Day 1 of Course 3 (see Section 5.5 for sampling schedule).
Blood sample for pharmacogenetic analysis	If consent is given, a blood sample for pharmacogenetic analysis is taken at any time after randomization, but preferably on Day 1 of Course 1.
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication
Compliance Check	Check number of tablets remaining and check that trial medication taken correctly (not applicable at C1V1).
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit. In particular the presence of diarrhoea, skin related AEs and mucositis has to be assessed and appropriately managed
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Dispense trial drugs	Dispense sufficient medication for the next course of treatment.

Arm A (BIBW 2992) Day 8 of course 1 and course 2 (± 2 days) C1V2, C2V2 N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG performance status	ECOG performance status will be assessed and documented
ECG	12-lead resting ECG will be performed on day 8 of course 1 (C1V2).
Blood sample for pharmacokinetic analysis	Pharmacokinetic sampling will be performed on Day 8 of Course 2 (see Section 5.5 for sampling schedule).
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication
Compliance Check	Check number of tablets remaining and check that trial medication taken correctly.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit. In particular the presence of diarrhoea, skin related AEs and mucositis has to be assessed and appropriately managed
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.

6.2.2.2 Treatment Arm B (Gemcitabine/Cisplatin)

Arm B (Gemcitabine/Cisplatin Day 1 of each course (± 2 days) C1V1, C2V1, C3V1, C4V1, C5V1, C6V1 N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions
Caregiver support	Collect information on any meal delivery, caregiver support (home care) and healthcare professional support
Physical examination	Cardiopulmonary examination, an examination of the regional lymph nodes and an examination of the abdomen. Measurement of weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG performance status	ECOG performance status will be assessed and documented
ECG	12-lead resting ECG will be performed if clinically indicated.
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if clinically indicated
Safety lab	Haematology, Biochemistry and Urinalysis (see Section 5.2.4 for minimum assessments). Results must be available prior to commencing treatment.
Serum sample for EGFR mutation analysis	A serum sample will be collected on Day 1 of Course 1 for analysis of EGFR mutation status.
Blood sample for pharmacokinetic analysis	Pharmacokinetic sampling will be performed on Day 1 of Course 2 and Day 1 of Course 3 (see Section 5.5 for sampling schedule).
Blood sample for pharmacogenetic analysis	If consent is given, a blood sample for pharmacogenetic analysis is taken at any time after randomization, but preferably on Day 1 of Course 1.
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Dispense trial drugs and administer treatment	Dispense and administer chemotherapy. Gemcitabine 1000 mg/m^2 and Cisplatin 75 mg / m^2

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Arm B (Gemcitabine/Cisplatin) Day 8 of each course (± 2 days) C1V2, C2V2 N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG performance status	ECOG performance status will be assessed and documented
ECG	12-lead resting ECG will be performed on day 8 of course 1 (C1V2).
Safety lab	Haematology, Biochemistry and Urinalysis (see Section 5.2.4 for minimum assessments). Results must be available prior to commencing treatment.
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Administer trial drugs	Gemcitabine 1000 mg/m^2

6.2.3 End of trial and follow-up

End of treatment EOT Complete this visit at the following time-point; • 0-14 days after permanent discontinuation of BIBW 2992 • 21 days after Course 6 day 1 of chemotherapy (± 7 days) • If patient does not complete 6 courses of chemotherapy, perform visit 0-14 days after decision to end treatment	
HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions.
Caregiver support	Collect information on any meal delivery, caregiver support (home care) and healthcare professional support
Physical examination	Cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status. Measurement of weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG	ECOG performance status will be assessed and documented
ECG	Arm A (BIBW 2992); A12-lead resting ECG will be performed if not performed in the previous 8 weeks. Arm B (Gemcitabine/Cisplatin); A12-lead resting ECG will be performed if clinically indicated.
ECHO/MUGA	Arm A (BIBW 2992); Cardiac left ventricular function assessment by

	either ECHO or MUGA will be performed if not performed in the previous 8 weeks. Arm B (Gemcitabine/Cisplatin); Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if clinically indicated.
Safety lab	Haematology, Biochemistry, Urinalysis (see Section 5.2.4 for minimum assessments).
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Con meds	Document indication, start and stop date of each concomitant medication
Compliance Check	Arm A (BIBW 2992) only: Check number of tablets remaining and check that trial medication taken correctly.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.

6.2.4 Follow-up (all patients)

Follow-up Every 21 days after EOT visit FU1 is performed 21 days (± 7 days) after EOT visit and is mandatory, even if new treatment has commenced. If patient has not progressed at FU1, perform further follow-up visits every 21 days (± 7 days) until progression or start of further treatment (FU2, FU3, FU4 etc.).	
HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions.
Caregiver support	Collect information on any meal delivery, caregiver support (home care) and healthcare professional support
Physical examination	Cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen. Measurement of weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature
ECOG	ECOG performance status will be assessed and documented
Safety lab	Haematology, Biochemistry, Urinalysis (see Section 5.2.4 for minimum assessments).
Tumour assessment	Ensure that tumour assessments are scheduled at the time-points specified in the flow chart.
Serum sample for EGFR mutation analysis	An optional serum sample for analysis of EGFR mutation status may be collected at Follow-up 1
Tumour biopsy for EGFR mutation analysis	An optional tumour biopsy for analysis of EGFR mutation status may be collected during the Follow-up phase.
Con meds	Document indication, start and stop date of each concomitant medication

Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Study completion	Study completion occurs at the follow-up visit where progression or start of further treatment is first documented.

6.2.5 Observation period

Observation period Collect data every 60 days (± 15 days) after last follow-up visit. A formal study visit is not required; data should be collected from patient notes or by telephone.	
Progression	Collect date of progression.
Further treatment	Collect details of any further treatment for NSCLC, including best response and reason for stopping treatment.
Death	Collect date and cause of death.

6.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

6.3.1 Removal of patients from study treatment

A patient will be withdrawn from further study treatment in the following circumstances:

- The patient withdraws consent to further treatment. For safety reasons it is recommended that the patient is encouraged to return for at least one follow-up visit. Wherever possible patients should be encouraged to return for regular follow-up visits until progression or start of further treatment.

- Documented disease progression (see Section 5.1.3).

- The patient is no longer able to participate in the treatment phase (e.g. surgery, concomitant diagnoses, concomitant therapies or administrative reasons). In these cases the investigator should record the reason for a patients' removal in the CRF.

- Significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made by the Boehringer Ingelheim (BI) clinical monitor in agreement with the investigator.

- Requirement to stop treatment due to adverse events as described in Sections 4.1.4.1.1 and 4.1.4.2.

If during the treatment phase the patient no longer meets the inclusion/exclusion criteria this is not automatically a reason for withdrawal but the investigator should consider the ongoing

safety of the patient and withdraw the patient from further treatment if the safety of the patient is at risk.

The EOT visit should be performed after permanent discontinuation of treatment. In arm A (BIBW 2992) the visit should be performed 0-14 days after permanent discontinuation of BIBW 2992. In arm B (chemotherapy) the visit should be performed 21 days (± 7 days) after Course 6 Day 1 (for patients completing 6 courses) or 0-14 days after the decision to end treatment (for patients not completing 6 courses). For safety reasons all patients should be encouraged to return to the clinic 21 days after the EOT visit for the first follow-up visit.

6.3.2 Removal of patients from trial

A patient will be withdrawn from the trial in the following circumstances:

- Requirement for further treatment of NSCLC after the first follow-up visit (21 days after EOT)
- Patient withdraws consent to all further study procedures and elects to discontinue participation in the trial.
- Termination of the study by the sponsor

The reason for discontinuation must be recorded and if consent is given, patients should be followed up in the observation period until the date of death (Section 6.2.5).

Every effort should be made to follow-up patients in case an adverse event is ongoing at the time of withdrawal.

6.3.3 Replacement of patients

Patients who prematurely discontinue the study treatment or trial will not be replaced.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomised, open-label, active-controlled multi-center trial in Asia. The primary objective of the statistical analysis is to determine whether BIBW 2992 prolongs progression-free survival (PFS) in comparison to chemotherapy.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The alternative hypothesis of the primary analysis is that the progression-free survival time is longer for patients treated with BIBW 2992 than for those who receive chemotherapy. That is

$$H_A: S_{BIBW}(t) > S_{Chemo}(t), \text{ for } t>0$$

The null hypothesis tested by this trial is:

$$H_0: S_{BIBW}(t) \leq S_{Chemo}(t), \text{ for } t>0$$

where S(t) is the probability that a patient passes time t without dying or experiencing disease progression. The subscripts represent the two treatment groups. The null hypothesis will be tested at the one-sided 0.025 level.

If the difference between the treatment groups for the primary efficacy endpoint is statistically significant then formal statistical testing will be performed on the key secondary endpoints. In order to protect the overall type I error rate a closed testing procedure will be employed, whereby each key secondary endpoint will only be formally analysed if the previous endpoint was found to be statistically significant. The key secondary endpoints will be analysed according to the order they are presented in Section 7.3.2 below.

7.3 PLANNED ANALYSES

The primary analyses will include all randomized patients.

7.3.1 Primary analyses

The primary endpoint of this study is progression-free survival, defined as the time from the date of randomisation to the date of disease progression, or to the date of death if a patient died earlier. The analysis will be based upon the evaluation of tumour imaging as reviewed by an independent central unit, blinded to treatment assignments.

The primary analysis of PFS will be conducted when at least 217 patients have progressed or died. This is expected to take approximately 19-20 months, assuming 330 patients are randomised over a period of 9-10 months.

A stratified log-rank test will be used to test for the effect of BIBW 2992. The test will be stratified by EGFR mutation (L858R vs. del 19 vs. other).

A Cox proportional-hazards model will be used to derive the hazard ratio and 95 % confidence interval between the two randomised regimens. Kaplan-Meier estimates and 95% CI will be calculated at the time of each planned imaging assessment.

Disease progression will be evaluated according to the RECIST 1.1 criteria (R09-0262), with adaptations as described in the imaging charter.

For patients with known date of progression (or death):

- PFS [days] = earlier of date of progression or death – date of randomisation + 1.

Patients with unknown disease progression status or date, or who are treated with new anticancer therapy will be handled as described in Section 7.4

7.3.2 Secondary analyses

7.3.2.1 Key Secondary analyses

The following key secondary analyses will be performed according to the statistical testing strategy detailed in Section 7.2

7.3.2.1.1 Best RECIST assessment

Each patient will be assigned to one of the following RECIST 1.1 categories based on independent central review, irrespective of protocol violations or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)
- PD (progressive disease)
- Not evaluable (not assessable, insufficient data)

Objective response is defined as CR and PR. Time to objective response is the time from randomisation to the date of first documented CR or PR. The duration of objective response is the time from first documented CR or PR to the time of progression or death. Disease control is defined as CR, PR, and/or SD.

Logistic regression will be used to test for a difference between regimens for objective response and for disease control. The statistical model will include the same stratification factor used for the analysis of PFS. Nominal significance levels will be reported.

Objective response will be tabulated both overall and within EGFR mutation categories. Descriptive statistics will be calculated for the duration of objective response and duration of disease control.

7.3.2.1.2 Overall survival (OS)

The treatment regimens will be compared in terms of time to death, but unequal treatment after progression is expected to obscure any effect of BIBW 2992 relative to chemotherapy. Similarly to PFS, the stratified log-rank test will be used to test OS.

OS will be analyzed twice. The first analysis will be performed at the time of the primary PFS analysis. A second analysis will be performed somewhat later with the aim of providing as much information as possible on OS. With 330 patients randomised over a period of 9-10 months and a median time to death of 20 months (HR= 1.0), approximately 219 deaths would be expected within 36 months.

To preserve the overall 0.025, one-sided alpha-level, a Haybittle-Peto stopping boundary will be used (p-value <0.0001) for the analysis of OS performed at the time of the primary PFS analysis.

In addition to the formal treatment comparison, the analyses will describe the overall pattern of time to death, together with the extent and influence of post-progression treatment.

The following analyses will examine the pattern of time to death for consistency with the PFS results, while accounting for the extent and influence of post-progression intervention:

- test for a difference between treatment regimens at six, nine, and twelve months,
- describe the cumulative proportion of deaths at each scheduled tumour assessment time point
- tabulate the specific anti-cancer treatments after progression
- describe the effect of additional anti-cancer treatment, by separating patients into the following sub-groups
  - those not eligible for additional treatment
    - patients who did not progress
    - patients who died within one month of progression
  - those eligible for additional treatment
    - did not take additional treatment
    - did take additional treatment

7.3.2.2 Other secondary analyses

The following other secondary analyses will be performed.

7.3.2.2.1 Sensitivity and exploratory analyses for PFS

The timing of imaging assessments will be described. In order to account for the possible effect of mistimed or delayed imaging assessments, a sensitivity analyses will assign the midpoint to PFS failures within time intervals that will be formed around the planned times of imaging assessments.

An additional analysis will assign all patients who progress in the chemotherapy arm to the later assessment of progression (investigator or independent central unit review) and all patients who progress in the BIBW 2992 arm to the earliest assessment of progression.

An exploratory analysis will stratify the log-rank test by each of the EGFR mutations for which there are sufficient randomized patients.

Descriptive methods (e.g. Forest plot) and Cox proportional-hazards will be used to examine the effects of other baseline disease characteristics and demographic factors, including the stratification factor (EGFR mutation category), baseline sum of target lesions, geographical region, ECOG, gender, and age.

7.3.2.2.2 Tumour shrinkage

The two treatment groups will be compared in terms of the minimum sum of target lesion diameters recorded for each patient after randomisation, as measured by central imaging.

The analysis will compare the treatments using analysis of covariance (ANCOVA) for minimum sum of diameters, using baseline sum of diameters as a covariate. The randomization stratum will be included as a classification factor.

7.3.2.2.3 Body weight and ECOG performance status

Analyses will compare the treatment groups in terms of time to deterioration of:

- body weight, defined as the first occurrence of a decrease from baseline of more than 10 %, and
- ECOG performance status, defined as the first instance of an increase in ECOG category.

Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without deterioration will be censored at the time of the last measurement of weight or ECOG performance status.

Time to deterioration will be analysed similarly to PFS i.e. by stratified log-rank test.

7.3.2.2.4 Health-Related Quality of Life (HRQOL)

The relevant HRQOL endpoints are the time to deterioration for the following three symptom scales/items measured on the QLQ-C30 or QLQ-LC13 questionnaire (R99-1213, R07-2060):

- cough (Question 1 on the QLQ-LC13),
- dyspnoea (composite of Questions 3-5 on the QLQ-LC13),
- pain (composite of Questions 9 and 19 on the QLQ-C30)

Scoring of the symptom scales/items will follow the EORTC scoring algorithm. For ease of interpretation, a linear transformation will be used to standardise the raw scores of all items and scales, so that scores range from 0 to 100 (R07-2064). A higher score represents a higher ('better') level of functioning (functional scales, global health status/QOL), or a higher ('worse') level of symptoms (symptom scale/item) (R07-2064).

Time to deterioration for the cough, dyspnoea, pain and symptom scales/items will be defined as the time to a 10-point increase from the baseline score (R07-2064, R99-1223, R07-2061). Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQOL assessments will be censored at day of randomisation. If a HRQOL assessment is missed, but followed by another assessment and deterioration occurs during that period, the time to deterioration will be defined as the midpoint between the two observed assessments. In addition, the three alternative measures of pain (Questions 10-12* in QLQ-LC13) will be examined descriptively for consistency with the composite of questions 9 and 19 from the QLQ-C30, as will dyspnoea (Question 8) from the EORTC QLQ-C30 be compared with the dyspnoea composite (Questions 3-5* on the QLQ-LC13).

Time to deterioration will be analysed similarly to PFS i.e. log-rank test stratified by the stratification factor used at randomisation will be used to test for the effect of BIBW 2992. The individual items of the symptom scales will be examined for consistency with the composites.

In addition, a comprehensive analysis of all subscales/items (where a single item is scored, R07-2064) will estimate the hazard ratio for time to deterioration with 95% confidence. The results of these analyses will be displayed using a Forest plot to summarise the impact of therapy over the entire profile of the EORTC QLQ-C30 and LC13 measures.

Additional analysis will describe the distribution of patients that are improved, stable, or worsened for each of the QLQ-C30 and QLQ-LC13 summary scales and items (where a single item is scored, R07-2061).

* Note that questions on the QLQ-LC13 are numbered consecutively following the QLQ-C30 as shown in Appendix 4. Consequently, Question 1 is numbered as Question 31 and Questions 3-5 as Questions 33-35

7.3.3 Safety analyses

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

The primary analysis of adverse events will be based upon events that start on or after first administration of trial medication and within 28 days after the last administration trial medication. An additional analysis will compare the treatment regimens over a period of time equivalent to six courses of chemotherapy.

Adverse events as well as laboratory parameters will be graded according to CTCAE, Version 3.0 (R04-0474). Key safety measures will include:

- events leading to dose reduction
- events leading to permanent treatment discontinuation
- the overall incidence and intensity of adverse events, as well as relatedness of adverse events to treatment
- causes of death
- gastrointestinal events (diarrhoea, vomiting, nausea)
- cutaneous reactions
- oral irritation
- decreased renal function
- elevated liver function tests,
- haematological abnormalities (anaemia, thrombocytopenia, neutropenia)
- CTCAE Grade 2 with increase by at least one CTCAE grade from baseline, for selected laboratory tests:
  - (high values) INR, PTT, creatinine, AST, ALT, bilirubin, alkaline phosphatase, proteinuria (dipstick or [g/24 hrs])
  - (low values) haemoglobin, neutrophils, platelets, total WBC
- descriptive statistics for change from baseline for all laboratory tests

Additional, more in-depth analyses will be performed as needed. These analyses will examine the influence of extent of exposure and time to event onset.

Key adverse event tables will be reproduced to examine the effect of BIBW 2992 among special populations e.g. elderly, females.

7.3.4 Interim analyses

A Data and Safety Monitoring Committee (DMC) will review the safety data approximately every six months. In order to completely assess the risk-benefit advantage of BIBW 2992, the committee may see the need during such regular meetings to examine survival and PFS. However, the significance level for the primary analysis of PFS will not be adjusted for the interim looks by the DMC. This is because the trial will not be stopped for superiority of BIBW 2992 vs. chemotherapy in terms of PFS prior to the primary analysis, which is scheduled to occur after 217 PFS failures.

7.3.5 Pharmacokinetic methods

BIBW 2992 plasma concentrations will be summarized by time point by descriptive statistics and, if feasible, graphically inspected. A pharmacokinetic correlation plot analysis will be performed on BIBW 2992 plasma concentrations.

Objectives of this analysis will be:

- describe the trough BIBW 2992 plasma concentrations at steady state in the target patient population
- to estimate the inter-individual and intra-individual variability of BIBW 2992 trough plasma concentrations
- to estimate the influence of covariates such as age, gender or weight on the variability of the BIBW 2992 trough plasma concentrations using correlation plot analysis

7.4 HANDLING OF MISSING DATA

The central imaging unit will work with the clinical sites towards a standard implementation of the RECIST 1.1 criteria. An imaging charter will detail all procedures, including quality control and the criteria needed to handle missing assessments.

Patients will continue to be followed for both progression and death after discontinuation of study treatment.

Table 7.4: 1 describes how patients will be classified for the analysis of PFS. Sensitivity analyses will examine the effect of using alternative rules.

Table 7.4: 1 Endpoint determination for PFS

Situation	Outcome (event or censored)	Date of PFS or censoring
No baseline tumour assessment	censored	Date of randomisation
Progressed according to central review (no missed radiological assessments)	event	Date of PD determined by central review
Non-PD from central review[1], death before next scheduled assessment	event	Date of death
Non-PD from central review[1], one missed assessment, death or progression after date of missed assessment, but before a second scheduled assessment	event	Date of PD or death
Non-PD from central review[1], more than one consecutive missed assessment, death or progression after date of second missed assessment	censored	Date of last imaging before missed assessment
New anti-cancer medication before progression or death	censored	Date of last imaging 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	Day of randomisation
No imaging performed post-baseline, vital status is unknown or patient is known to be alive	censored	Day of randomisation
Alive and not progressed according to central review (no missed radiological assessments)	censored	Date of last imaging

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

Table 7.4: 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.

Table 7.4: 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

Patients who are randomised, but never receive randomised treatment will be censored on the day of randomisation (Tables 7.4: 1 and 7.4: 2).

7.5 RANDOMISATION

Two patients will be randomized to BIBW 2992 for each patient randomized to chemotherapy. The randomization will be stratified by EGFR mutation (L858R vs. del 19 vs. other).

Randomization will be performed by IVRS/IWRS. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Support Group or a CRO appointed by the Sponsor will provide the randomization lists using a validated randomization number generating system. Access to the randomization codes will be controlled and documented.

7.6 DETERMINATION OF SAMPLE SIZE

Table 7.6: 1 indicates that 217 PFS failures would be expected to provide 90% power for the log-rank test, presuming a hazard ratio of 0.64 for BIBW 2992 relative to chemotherapy. In a previous trial of gefitinib vs. chemotherapy the upper limit of the 95% confidence limit of the hazard ratio was observed to be 0.64 (R08-5155).

Table 7.6: 1 Number of PFS events required for 90% power

	90% power 0.025, one-sided
BIBW median	11 months
Control median	7 months
	57% increase (0.64 hazard ratio)
# PFS failures	217 failures
# patients with mutations	330 patients

Calculations performed using EAST-5 software using the log-rank test, excluding interim analysis

8. ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

8.1 ETHICS

8.1.1 Independent Ethics Committee or Institutional Review Board

The trial will not be initiated before the protocol and informed consent and patient information form have been reviewed and received approval / favourable opinion from the local Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and approval by / notification to the Competent Authority (CA) / regulatory authority as required according to national regulations.

Should a Clinical Trial Protocol (CTP) amendment be made that needs IRB / IEC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IRB / IEC and the CA / regulatory authority has been notified / provided approval (as required according to local regulations). A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IRB / IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification to the IRB / IEC and CA only.

The constitution of the IRB / IEC must meet the requirements of ICH GCP and of the participating country. A list of the IRB / IEC members who attended the meeting when the CTP / CTP amendment was discussed, including names and qualifications, needs to be provided by the IRB / IEC to the investigator or sponsor (according to local practice). The investigator or sponsor (according to local practice) must provide to the regulatory authorities the name and address of the IRB / IEC along with a statement from the IRB / IEC that it is organised according to GCP and the applicable laws and regulations. The IRB / IEC must perform all duties outlined by the requirements of ICH GCP and of the participating country.

8.1.2 Patient Information and Informed Consent

Prior to patient participation in the trial, a signed and dated written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature

must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

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

Should a CTP amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the investigator or sponsor (according to local practice) to ensure that an amended consent form is reviewed and has received approval / favourable opinion from the IRB / IEC and the CA / regulatory authority has provided approval / has been notified (as required according to local regulations), and that it is signed by all patients subsequently entered in the trial and those currently in the trial, if affected by the amendment.

8.2 RECORDS

8.2.1 Drug accountability

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

The investigator and/or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator / pharmacist will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the sponsor the investigator / pharmacist 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.

8.2.2 Emergency code break

Not applicable.

8.2.3 Case Report Forms (CRFs)

All the clinical data will be captured via electronic data capture (EDC) using the Oracle Clinical Remote Data Capture system, a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification or username and password – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs (eCRFs) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial, narrative statements relative to the patient's progress during the trial will be maintained. The electronic CRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the electronic CRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. While a trial is ongoing and until the access to the database has been terminated, there will be no Documentation of Changes (DOCs). All changes will be requested from the investigator through the EDC system. If a change is necessary once the investigator has no further access to the database, a DOC will be sent to the investigator for confirmation of the change. The investigator's signature or seal is requested to show he/she agrees with the change that was made. The original DOC is kept by the investigator.

Copies of the electronic CRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

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

For eCRFs all data must be derived from source documents, including the following:

- Patients identification (gender, date of birth)
- Patients 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 (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)
- Conclusion of Patient's Participation in the trial

8.2.5 Direct access to source data - documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs 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. sFDA). The Clinical Research Associate (CRA) or on-site monitor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.2.4.

Data collected during the Observation Period will be checked for completeness and plausibility but will not require source data verification.

8.3 QUALITY ASSURANCE AUDIT

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. 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.

8.4 PROCEDURES

8.4.1 Adverse events

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

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent to the final follow-up visit) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, 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 jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

All adverse events, serious and non-serious, will be fully documented on the appropriate CRFs. For each adverse event, the investigator will provide the onset, end, CTCAE grade (R04-0474), treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in the 'Adverse Event Reporting' Section of the Investigator Site File.

There are no events defined as 'significant' for this study. All events will be categorised as either Adverse Event (AE) or Serious Adverse Event (SAE).

The basis for judging the causal relationship between the investigational product and the AE is described below.

Causal relationship

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

- Yes: There is a reasonable causal relationship between the investigational drug administered and the AE.

- No: There is no reasonable causal relationship between the investigational drug administered and the AE.

The investigator has the obligation to report all AEs/ SAEs occurring between informed consent and follow-up visit 1, regardless of causality. From follow-up 1 to final follow-up the investigator should report all AEs/SAEs which are related to the study treatment or procedures. During the observation period, only SAEs considered related to the study treatment should be reported. Deaths occurring after follow-up 1 do not need to be reported as SAEs unless considered related to study treatment or procedures.

SAEs are to be reported to the sponsor using the BI Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. When follow-up information becomes available, all remaining fields on the SAE form are to be completed or updated.

Any serious AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to the sponsor. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to

local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

Following every such telephone / fax report, the Clinical Monitor must provide a written report of the serious AE and any sequelae to Corporate Drug Safety according to the appropriate Corporate SOP(s). These narratives, which confirm the information collected by telephone, may give additional information not available at the time of the initial report.

8.4.2 Emergency procedures

Not applicable.

8.4.3 Contraception and Pregnancy

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

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

Acceptable methods of contraception for females include hormonal contraception and double barrier method. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and IUD (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). If hormonal contraceptives are used, at least one barrier method should also be used. Partner vasectomy, natural 'rhythm' and spermicidal jelly/cream are not acceptable as methods of contraception.

Male patients should use adequate contraception throughout the study (e.g. condom and spermicidal jelly).

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

If a patient is found to be pregnant during study participation, this should be handled as follows;

Table 8.4.3: 1 Pregnancy reporting

Timing of pregnancy	**Action**
Prior to commencing study medication	Patient should be withdrawn from the study immediately. No reporting necessary
During study treatment	Treatment must be stopped immediately and the pregnancy should be reported to the sponsor immediately using the pregnancy form. If the investigator wishes to give any further treatment with study medication, this must be discussed and agreed with the BI clinical monitor. The pregnancy should be followed up to final outcome and the outcome, including any premature termination should be reported to the sponsor on the pregnancy form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death) must be reported as an SAE.
During follow-up (after finishing treatment but before end of study participation).	The pregnancy should be reported to the sponsor immediately using the pregnancy form. The pregnancy should be followed up to final outcome and the outcome, including any premature termination should be reported to the sponsor on the pregnancy form. In addition, any event leading to the termination of pregnancy (i.e. spontaneous, accidental, or induced abortion; as well as miscarriage, intrauterine foetal demise/death) must be reported as an SAE.
Within 28 days of last dose of study medication (even if no longer participating in study	

8.5 RULES FOR AMENDING PROTOCOL

All CTP amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. This also applies to any local amendment that may become necessary. Amendments (excluding those exclusively for administrative or logistical changes) need to be submitted to the IRB / IEC for review/approval and to the competent authority (CA) / regulatory authority for approval / notification according to local regulations. Local Amendments will only be submitted in the countries / centres concerned.

8.6 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

Boehringer Ingelheim reserves the right to discontinue the trial 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 that could significantly affect continuation of the trial,

3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

8.7 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.

8.8 PUBLICATION POLICY

Boehringer Ingelheim is as much as possible dedicated to support process of free exchange of relevant scientific information. Any publication of the result of this trial must be consistent with the Boehringer Ingelheim publication policy. 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.

9. REFERENCES

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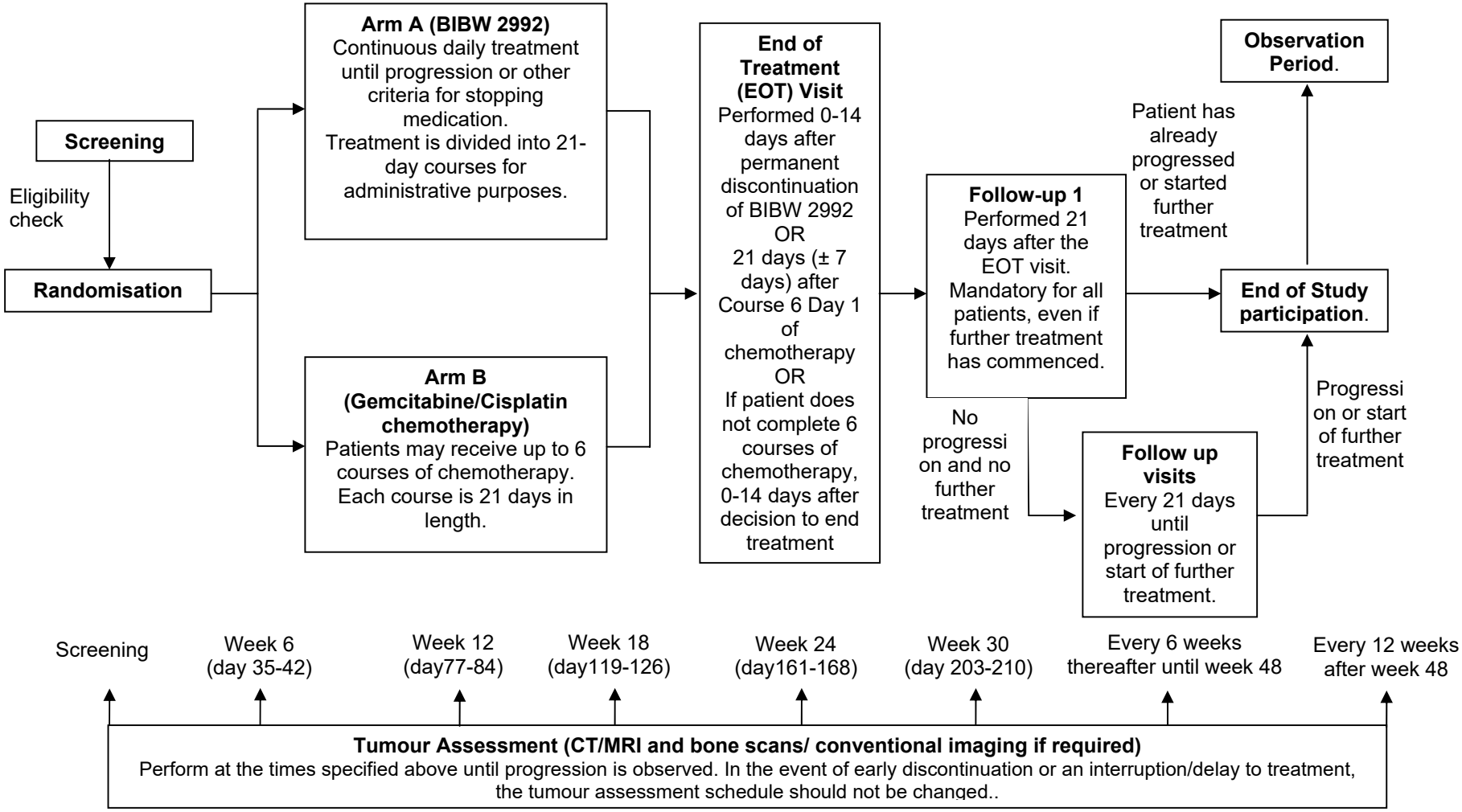
10. APPENDICES

10.1 APPENDIX 1 OVERVIEW OF STUDY VISITS



10.2 APPENDIX 2 RECOMMENDED SUPPORTIVE CARE AND DOSE MODIFICATION SCHEME FOR GEMCITABINE / CISPLATIN CHEMOTHERAPY

The guidance below is taken from the summary of product characteristics (SPC). The guidance given in the latest published SPC should always take precedence over the guidance given below.

Supportive Care

Pre-medication should commence after a patient is randomised to receive chemotherapy. The recommended supportive care for Gemcitabine / Cisplatin chemotherapy is as follows;

- Pre-treatment hydration with 1 - 2 litres of fluid infused for 8 - 12 hours prior to Cisplatin will initiate diuresis. Adequate subsequent hydration should maintain diuresis during the 24 hours following administration.
- Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapyinduced emesis: Results of the Perugia Consensus Conference (R06-0986).

Dose Modification Scheme

Dosage adjustments for hematologic toxicity may be required for gemcitabine and for cisplatin. Gemcitabine dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 10.2:1.

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with gemcitabine plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grade 3/4 serum creatinine toxicity for gemcitabine plus cisplatin was 5% versus 2% for cisplatin alone).

Table 10.2:1 Dosage Reduction Guidelines for Gemcitabine in combination with Cisplatin

Absolute granulocyte count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	% of full dose
≥1000	and	≥100,000	100
500-999	or	50,000-99,999	75
<500	or	<50,000	Hold

10.3 APPENDIX 3 QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

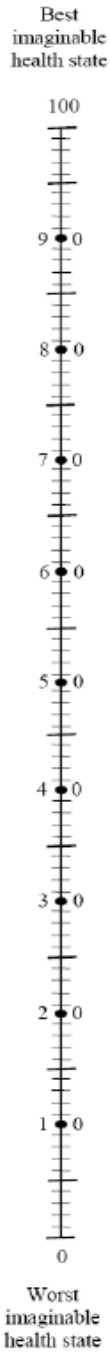
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



10.4 APPENDIX 4 RECIST 1.1 CRITERIA

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

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).

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

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 10.4:1).

Table 10.4:1 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 10.4:2).

Table 10.4:2 Evaluation of non-target lesions and new lesions

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

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

Confirmation

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

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.4:3) 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 10.4:3).

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

Table 10.4:3 Algorithm for evaluation of overall best response*

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

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

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Clinical Trial Protocol Amendment

Doc. No.: U10-3034-01-AM1

Amendment Number:	1		
Date:	Final, 14 May 2010	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
BI Trial No.:	1200.34	x	To be implemented immediately in order to eliminate hazard – *IRB / IEC / Competent Authority* to be notified of change with request for approval
Investigational Product(s):	BIBW 2992	☐	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only

Title:	LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation
Rationale for Amendment:	Since BIBW 2992 is a P-gp substrate, BI performed a phase I trial 1200.79 in healthy volunteers to assess the effects of the potent P-gp inhibitor ritonavir on the pharmacokinetics (PK) of BIBW 2992. The initial results of the study show that, although the median t_{max} and terminal half-life of BIBW 2992 were not affected, the rate and extent of absorption of BIBW 2992 was increased by co-treatment with ritonavir. These results also indicate that an effect of potent P-gp inducers on the PK characteristics of BIBW 2992 cannot be excluded. To ensure continued subject safety, the following amendment have been made in the protocol: 1. Change of exclusion criteria to clarify section listing restricted medications (Change 1) 2. Change of restricted medications to be given together with BIBW 2992 (Change 2)

Change 1: Change of an exclusion criterion in section 3.3.2 Exclusion criteria

21. Requirement for treatment with any of the prohibited concomitant medications listed in section 4.2.2.2

was change to

21. Requirement for treatment with any of the prohibited concomitant medications listed in section 4.2.2

Reason For Change 1:

During the consent process it is not known what medication the patient will be randomised to so it is necessary to have the exclusion criteria cover both arms of treatment.

Change 2: Addition of explanatory paragraph (s) on restrictions regarding BIBW 2992 treatment to section 4.2.2

4.2.2 Restrictions

4.2.2.1 Restrictions for patients randomised to arm A (BIBW 2992)

Patients randomised to treatment with BIBW 2992 should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

4.2.2.2 Restrictions for patients randomised to arm B (Gemcitabine/ Cisplatin chemotherapy)

Patients randomised to treatment with Gemcitabine/ Cisplatin chemotherapy should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate), maintenance therapy for NSCLC or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

Patients should not receive any of the prohibited medications as listed in the current summary of product characteristics (SPC) for the Gemcitabine/ Cisplatin chemotherapy regimen.

was change to

4.2.2 Restrictions

All patients randomised should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit.

In addition patients randomised to treatment with Gemcitabine/ Cisplatin chemotherapy should not receive any maintenance therapy for NSCLC or receive any of the prohibited medications as listed in the current summary of product characteristics (SPC) for the Gemcitabine/ Cisplatin chemotherapy regimen.

BIBW 2992 is a substrate of P-gp and its plasma concentrations can be affected by the use of P-gp inhibitors (data on file) and it is also likely that P-gp inducers could also influence BIBW 2992 plasma concentrations. The use of potent P-gp inhibitors (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil) and potent P-gp inducers (including St John's wort, rifampicin) must be avoided during treatment with BIBW 2992. Any exemptions to this must be discussed with the BI clinical monitor.

In any patient ongoing in the trial receiving BIBW 2992 and a concomitant potent P-gp inhibitor or inducer at the time of amendment 1 being implemented, the decision for continuation of either drug will be based on the individual circumstances of the patient upon discussion with the responsible BI clinical monitor.

Reason For Change 2:

The restriction was added based on the results of a phase 1 trial 1200.79 performed in healthy volunteers. Since BIBW 2992 is a P-gp substrate, BI performed this trial to assess the effects of the potent P-gp inhibitor ritonavir on the pharmacokinetics (PK) of BIBW 2992.

In this open-label, randomised, two-way crossover study the relative exposure after a single oral dose of BIBW 2992 (20 mg), co-administered with multiple oral doses of ritonavir (200 mg bid for 3 days), was compared to the exposure after a single oral dose of BIBW 2992 (20 mg) alone in healthy male volunteers. The study was designed to determine the maximum effect of P-gp inhibition on the PK of BIBW 2992.

The initial results of the study show that, although the median t_{max} and terminal half-life of BIBW 2992 were not affected, the rate and extent of absorption of BIBW 2992 was increased by co-treatment with ritonavir. The exposure to BIBW 2992, when taken in combination with ritonavir ($AUC_{0-\infty}$, AUC_{0-tz} and C_{max}), increased by 50.0%, 47.6%, and 38.5%, respectively (Data on file).

These results also indicate that an effect of potent P-gp inducers on the PK characteristics of BIBW 2992 cannot be excluded.

The data in trial 1200.79 were obtained at a dose of 20 mg BIBW 2992. It is currently unclear whether the results can be extrapolated to higher doses of BIBW 2992 currently used in phase II/III trials. However, considering the dose dependence of adverse events and for safety reasons caution has to be exercised in combining BIBW 2992 with potent P-gp inhibitors and inducers.

In addition guidance for management of patients who already receive BIBW 2992 in combination with Pgp-inhibitors and Pgp-inducers was provided, as in these patients careful

risk-benefit assessment of the individual case may need to be performed upon discussion with the responsible BI clinical monitor.

This is reflected by the modification of an exclusion criterion to all ongoing trials (Change 1), and the addition of restrictions for concomitant medications to be given together with BIBW 2992 (Change 2).

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Clinical Trial Protocol Amendment

Doc. No.: U10-3034-01-AM2

Amendment Number:	2		
Date:	9 May 2011	x	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
BI Trial No.:	1200.34	☐	To be implemented immediately in order to eliminate hazard – *IRB / IEC / Competent Authority* to be notified of change with request for approval
Investigational Product:	BIBW 2992	☐	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only
Title:	LUX-Lung6; A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation		
Rationale for Amendment:	1.Changes and clarifications to adverse event reporting 2. Multiple administrative changes and clarifications 3. Change of Trial Clinical Monitor's information 4. Changes to statistical analyses 5. Changes to collection of demographic data		

Change 1:

Change of TCM's information

Phone: , Fax:

Was changed to:

Phone: , Fax:

Reason For Change 1: Office address moved

Change 2:

Flow Chart: Arm A (BIBW 2992)

"x" in flowchart for Demographics was moved from SV1 to SV2

Reason for change 2: Clarification that demographic information will not be collected prior to signature of informed consent for screening visit 2.

Change 3:

Flow Chart: Arm A (BIBW 2992)

Footnote 1: Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

Was changed to:

Footnote 1: Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

Reason for change3: Informed consent that has been signed by patients at SV1 does not specify that demographic information will be collected.

Change 4:

Flow Chart: Arm A (BIBW 2992)

Footnote 7: Includes haematology, serum biochemistry and urinalysis. Creatinie clearance must be measured at screening for all patients.

Was changed to:

Footnote 7: Includes haematology, serum biochemistry and urinalysis. Creatinie clearance must be measured at screening for all patients. In case of course 1 day 1, assessments do not need to be repeated if the visit is within 2 days of the screening visit 2 assessments.

Reason for change 4: To clarify about assessments that should be performed during the trial.

Change 5:

Flow Chart: Arm A (BIBW 2992)

Was added:

Footnote 14: Adverse events and healthcare usage: Adverse events should be assessed from signature of informed consent until 21 days after end of treatment visit (see table 5.2.1:1). Health care usage is only assessed from course 1 day 1 to end of treatment and is not assessed in screening period.

Reason for change 5: To clarify about assessments that should be performed during the trial.

Change 6:

Flow Chart: Arm B (Gemcitabine/Cisplatin)

“x” in flowchart for Demographics was moved from SV1 to SV2

Reason for change 6: Clarification that demographic information will not be collected prior to signature of informed consent for screening visit 2.

Change 7:

Flow Chart: Arm B (Gemcitabine/Cisplatin)

Footnote 1: Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

Was changed to:

Footnote 1: Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent 1 must include consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.

Reason for change 7: Informed consent that has been signed by patients at SV1 does not specify that demographic information will be collected.

Change 8:

Flow Chart: Arm B (Gemcitabine/Cisplatin)

Footnote 7: Includes haematology, serum biochemistry and urinalysis. Creatinie clearance must be measured at screening for all patients.

Was changed to:

Footnote 7: Includes haematology, serum biochemistry and urinalysis. Creatinie clearance must be measured at screening for all patients. In case of course 1 day 1, assessments do not need to be repeated if the visit is within 2 days of the screening visit 2 assessments.

Reason for change 8: To clarify about assessments that should be performed during the trial.

Change 9:

Flow Chart: Arm B (Gemcitabine/Cisplatin))

Was added:

Footnote 14: Adverse events and healthcare usage: Adverse events should be assessed from signature of informed consent until 21 days after end of treatment visit (see table 5.2.1:1). Health care usage is only assessed from course 1 day 1 to end of treatment and is not assessed in screening period.

Reason for change 9: To clarify about assessments that should be performed during the trial.

Change 10:

4.1.4.1 Selection and timing of doses for each patient: BIBW 2992 (Arm A)

The medication should be taken at the same time each day (± 2 hours) at least one hour before food intake and at least three hours after food intake.

Was changed to:

The medication should be taken at approximately the same time each day at least one hour before food intake and at least three hours after food intake.

Reason for change 10: In light of the long half-life of afatinib (gMean terminal half-life 37,2 hrs), the strict window for drug intake can be removed to accomodate individual patients' daily schedule preference.

Change 11:

4.1.6.1 Packaging, labelling and re-supply: BIBW 2992

Was added:

The patient may take their daily tablet in the morning before coming to the clinic and in this case it is acceptable that the tablet comes from the bottle dispensed at the previous course.

Reason for change 11: To clarify that doses may be taken from bottle not for that course in case of tablet needing to be taken before the patient comes into clinic for day 1 assessments.

Change 12:

4.2 Concomitant Therapy

All concomitant (non-oncological) medications which are taken between informed consent and the last follow-up visit should be recorded in the electronic case report form (eCRF), including anaesthetic agents, vitamins, and homeopathic remedies and nutritional supplements. If a patient requires parenteral nutrition it is not necessary to specify the detail on the eCRF; it will be sufficient to indicate 'parenteral nutrition'.

Was changed to:

All concomitant (non-oncological) medications which are taken between informed consent at screening visit 2 and the last follow-up visit should be recorded in the electronic case report form (eCRF), including anaesthetic agents, vitamins, and homeopathic remedies and nutritional supplements. If a patient requires parenteral nutrition it is not necessary to specify the detail on the eCRF; it will be sufficient to indicate 'parenteral nutrition'.

Reason for change 12: Clarification on when concomitant medications should start to be collected.

Change 13:

4.2.1 Rescue medication and additional treatments

G-CSF use is permitted but not mandated for patients who experience CTCAE Grade 3 or 4 neutropenia or who develop neutropenic fever between cycles of Gemcitabine/Cisplatin chemotherapy. The following doses and schedules are recommended; G-CSF (Filgastrim, 5 µg/kg/day) SC beginning 24 hours after the completion of Gemcitabine and continued daily until the neutrophil count is >10,000/µL in two successive analysis or G-CSF (Pentagastrim, 6 mg) SC once per chemotherapy cycle at least 24 hours after completion of Gemcitabine.

Was changed to:

G-CSF use is permitted but not mandated for patients who experience CTCAE Grade 3 or 4 neutropenia or who develop neutropenic fever between cycles of Gemcitabine/Cisplatin chemotherapy. The following doses and schedules are recommended; G-CSF (Filgastrim, 5 µg/kg/day) SC beginning 24 hours after the completion of Gemcitabine and continued daily until the neutrophil count is >10,000/µL in two successive analysis or G-CSF *(PegFilgastrim,* 6 mg) SC once per chemotherapy cycle at least 24 hours after completion of Gemcitabine.

Reason for change 13: The incorrect name for PegFilgastrim was used in original protocol.

Change 14:

5.1.5 Health-Related Quality of Life

Any unsolicited information provided by the patient on the questionnaire and any safety related data obtained from the patient's responses to the standard questions on the questionnaires will be immediately reported to the investigator. Adverse event information from the questionnaire will be appropriately reported in the eCRF.

Was changed to:
Any unsolicited information provided by the patient on the questionnaire and any safety related data obtained from the patient's responses to the standard questions on the questionnaires will be immediately reported to the investigator *and as such the medical records will be the primary source for adverse event information.*

Reason for change 14: To clarify how data in the quality of life questionnaires should be handled in terms of adverse event reporting.

Change 15:

5.2.1 Adverse Events

During the screening phase of the trial, the patient's condition will be assessed (e.g., documentation of history / concomitant diagnoses and diseases), and subsequently all relevant changes from baseline will be noted.

Was changed to:
During the first screening phase of the trial (screening visit 1 to screening visit 2) no medical history will be collected. No adverse event data will be collected (unless related to the patient's participation in the trial).

During the second screening phase of the trial (after informed consent is signed for screening visit 2), the patient's condition will be assessed (e.g., documentation of history / concomitant diagnoses and diseases), and subsequently all relevant changes from baseline will be noted.

Reason for change 15: To clarify adverse event reporting in the screening period of the trial.

Change 16:

Table 5.2.1: 1 AE/SAE reporting requirements

Time period	**Reporting requirements**
Screening to Follow-up 1 (21 days after End of Treatment (EOT))	Report all AEs and SAEs regardless of relatedness. This includes all deaths.

Was changed to:

Table 5.2.1: 1 AE/SAE reporting requirements

Time period	**Reporting requirements**
Screening Visit 1 to Screening Visit 2	Report only AEs or SAEs related to the patients participation in the trial.
Screening Visit 2 to Follow-up 1 (21 days after End of Treatment (EOT))	Report all AEs and SAEs regardless of relatedness. This includes all deaths.

Reason for change 16: To clarify adverse event reporting in the screening period of the trial.

Change 17:

5.2.4 Laboratory investigations

Was added:

At course 1 day 1, safety laboratory assessments (haematology, biochemistry and urinalysis) do not need to be repeated if visit date is within 2 days from screening visit 2 assessments)

Reason for change 17: Clarification that assessments do not need to be repeated.

Change 18:

5.3.1 Demographics and history

Demographics (sex, birth date, and race), alcohol history, and histological subtype will be collected during the screening 1 visit. The smoking history will be documented as follows;

- Smoking status; never smoker (<100 cigarettes/lifetime), current-smoker or former smoker
- Number of pack years = (number of cigarettes smoked per day x number of years smoked)/ 20 (R08-4072)
- Date of last cigarette

History of NSCLC will be obtained during screening 2 and reported in the eCRF:

- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites (bone, brain, liver, pleural effusion, other)
- Tumour Stage according to the TNM-classification at diagnosis
- Previous surgery and radiotherapy for NSCLC
- Previously administered neoadjuvant/adjuvant chemotherapy including start and end dates and the outcome

Was changed to:

Consent date and histological subtype will be collected during the screening 1 visit.

Demographics, history of NSCLC as well as alcohol and smoking history will be obtained during screening 2 and reported in the eCRF:

- Demographics (sex, birth date, race, ethnicity)
- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites (bone, brain, liver, pleural effusion, other)
- Tumour Stage according to the TNM-classification at diagnosis
- Previous surgery and radiotherapy for NSCLC
- Previously administered neoadjuvant/adjuvant chemotherapy including start and end dates and the outcome

- Alcohol history,
- Smoking history, to be documented as follows;
    - Smoking status; never smoker (<100 cigarettes/lifetime), current-smoker or former smoker
    - Number of pack years = (number of cigarettes smoked per day x number of years smoked)/ 20 (R08-4072)
    - Date of last cigarette

Reason for change 18: Informed consent signed at screening visit 1 does not clearly document the collection of demographic information and therefore this will only be collected for patients who have signed the informed consent at screening visit 2.

Change 19:

5.3.2 Concomitant therapies and diagnoses

Concomitant diagnoses and/or therapies present during study participation (between informed consent and the follow-up visit) will be recorded in the eCRF.

Was changed to:

Concomitant diagnoses and/or therapies present during study participation (between informed consent at screening visit 2 and the follow-up visit) will be recorded in the eCRF.

Reason for change 19: To clarify the collection of information during the screening phase of the trial.

Change 20:

6.1.5 Observation Period

After completion of the study patients will enter an observation period. During the observation period no study visits will be performed, but data regarding progression, further treatment (including best response and reason for stopping treatment) and death will be collected every 60 days (± 15 days) until death. Information will be collected from the patient notes or by telephone contact with the patient.

The observation period will end after all patients have died or five years after the last follow-up visit, whichever occurs first.

Was changed to:

After completion of the study patients will enter an observation period. During the observation period no study visits will be performed, but data regarding progression, further treatment (including best response and reason for stopping treatment) and death will be collected every 60 days (± 15 days) until death. Information will be collected from the patient notes or by telephone contact with the patient.

The observation period will end after all patients have died or five years after the last follow-up visit, whichever occurs first. However, the observation period may end earlier depending upon the timing of analyses requested by regulatory authorities.

Reason for change 20: To give the option of ending the study earlier if the timing of requested analyses by regulatory authorities have been met.

Change 21:

6.2.1 Screening and run-in in phases

Screening Visit 1 Screening Visit 1 should be performed within 6 weeks of the first administration of study medication	
Informed Consent 1	Written informed consent must be obtained before any study-specific screening assessments are performed. Informed Consent 1 must include consent to collection of demographic data and consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status.
Demographics	Sex, birth date, race, alcohol history and smoking history.
Tumour biopsy for EGFR mutation analysis	Tumour biopsy will be collected for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Material should be submitted to the central laboratory for analysis as described in section 5.6.1.

Was changed to:

Screening Visit 1 Screening Visit 1 should be performed within 6 weeks of the first administration of study medication	
Informed Consent 1	*Written informed consent must be obtained before any study-specific screening assessments are performed. Informed Consent 1 must include consent to obtaining a biopsy and testing of biopsy material for EGFR mutation status as well as provision of histological classification.*
Tumour biopsy for EGFR mutation analysis	Tumour biopsy will be collected for analysis of EGFR mutation status. If a tumour biopsy is performed as part of routine clinical practice prior to trial participation and material is available for analysis, the biopsy does not need to be repeated. Material should be submitted to the central laboratory for analysis as described in section 5.6.1.

Reason for change 21: To clarify the collection of information during the screening phase of the trial. Demographic information will not be collected for patients only signing consent at screening visit 1

Change 22:

6.2.1 Screening and run-in phase

Screening Visit 2 This visit should only be performed by patients who have tested positive for an EGFR mutation. All screening visit 2 procedures should be performed within 28 days of the first administration of study medication.	
Informed consent 2	Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.
Demographics	Sex, birth date, race, alcohol history and smoking history will be taken for patients who had a tumour biospy performed as routine clinical practice and did not participate Screening Visit 1
Medical history	Oncological and relevant non-oncological history including details of any previous treatment for NSCLC (see section 5.3.1).
Patient eligibility	Assessment of eligibility according to inclusion and exclusion criteria should be performed.
Randomisation	If the patient meets the eligibility criteria, randomisation should be performed. Treatment should commence within 2 days after randomisation. If the patient is randomised to chemotherapy, pre-medication should commence immediately after randomisation (see appendix 2).
Physical examination	Cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status. Measurement of height and weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature.
ECOG	ECOG performance status will be assessed and documented.
ECG	12-lead resting ECG will be performed.
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA.
Safety lab	Haematology, Biochemistry, Urinalysis and Creatinine Clearance (see section 5.2.4 for minimum assessments).
Pregnancy test	B-HCG testing in urine or serum will be performed in women of childbearing potential.
Tumour assessment	CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The assessment does not need to be repeated if there are valid results available from assessments which were

	performed as part of routine clinical practice within the allowed time. 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.
Con meds	Document indication, start and stop date of each concomitant medication.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.

Was changed to:

Screening Visit 2 This visit should only be performed by patients who have tested positive for an EGFR mutation. All screening visit 2 procedures should be performed within 28 days of the first administration of study medication.	
Informed consent 2	Informed Consent 2 will be obtained for patients who have positive EGFR mutation status and must include consent to all study procedures including a blood sample for analysis of EGFR mutation status. The only exception is that consent to collection of a blood sample for DNA banking is optional.
Demographics	*Sex, birth date, race, alcohol history and smoking history.*
Medical history	Oncological and relevant non-oncological history including details of any previous treatment for NSCLC (see section 5.3.1).
Patient eligibility	Assessment of eligibility according to inclusion and exclusion criteria should be performed.
Randomisation	If the patient meets the eligibility criteria, randomisation should be performed. Treatment should commence within 2 days after randomisation. If the patient is randomised to chemotherapy, pre-medication should commence immediately after randomisation (see appendix 2).
Physical examination	Cardiopulmonary examination, examination of the regional lymph nodes, examination of the abdomen and an assessment of the mental and neurological status. Measurement of height and weight.
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature.
ECOG	ECOG performance status will be assessed and documented.
ECG	12-lead resting ECG will be performed.
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA.
Safety lab	Haematology, Biochemistry, Urinalysis and Creatinine Clearance (see section 5.2.4 for minimum assessments).
Pregnancy test	B-HCG testing in urine or serum will be performed in women of childbearing potential.
Tumour assessment	CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The assessment does not need to be repeated if there are valid results available from assessments which were performed as part of routine clinical practice within the allowed time.

	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.
Con meds	Document indication, start and stop date of each concomitant medication.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.

Reason for change 22: Demographic information to be collected at screening visit 2 once the informed consent for screening visit 2 is signed.

Change 23:

6.2.2.1 Treatment Phase: Treatment Arm A (BIBW 2992)

Safety lab: Haematology, Biochemistry, and Urinalysis, (see section 5.2.4 for minimum assessments)

Was changed to:

Safety lab: Haematology, Biochemistry, and Urinalysis, (see section 5.2.4 for minimum assessments) (Note: For course 1 day 1 the assessments do not need to be repeated if within 2 days of screening visit 2 assessments)

Reason for change 23: To clarify that repeated tests do not need to be done if course 1 day 1 is within 2 days of laboratory assessments for screening visit 2.

Change 24:

6.2.2.2 Treatment Arm B (Gemcitabine/Cisplatin)

Arm B (Gemcitabine/Cisplatin) Day 8 of each course (± 2 days) C1V2, C2V2 N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature.
ECOG performance status	ECOG performance status will be assessed and documented.
ECG	12-lead resting ECG will be performed on day 8 of course 1(C1V1).
Safety lab	Haematology, biochemistry and Urinalysis (see Section 5.2.4 for minimum assessements). Results must be available pior to commencing treatment
Tumour assessment	Ensure that tumour assessments are scheduled at the timepoints specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Administer trial drugs	Gemcitabine 1000mg/m^2

Was changed to:

6.2.2.2 Treatment Arm B (Gemcitabine/Cisplatin)

Arm B (Gemcitabine/Cisplatin) **Day 8 of each course (± 2 days)**C1V2, C2V2, C3V2, C4V2, C5V2, C6V2 N.B. In the event of progression or decision to end treatment, please complete the EOT visit instead.	
Vital signs	Blood pressure, pulse rate, respiratory rate and temperature.
ECOG performance status	ECOG performance status will be assessed and documented.
ECG	12-lead resting ECG will be performed if clinically indicated.
Safety lab	Haematology, biochemistry and Urinalysis (see Section 5.2.4 for minimum assessements). Results must be available pior to commencing treatment
Tumour assessment	Ensure that tumour assessments are scheduled at the timepoints specified in the flow chart.
Concomitant medications	Document indication, start and stop date of each medication.
Adverse events	Document details of any new AEs and obtain any new information about AEs ongoing at the last visit.
Healthcare usage	Collect information on any unscheduled outpatient visits and hospitalisations.
Administer trial drugs	Gemcitabine 1000mg/m^2

Reason for change 24: Table for day 8 assessments corrected to state that day 8 visit needs to be done for all 6 cyles. ECG will be performed if clinically indicated for Arm B.

Change 25

7.3.2.2.4 Health-Related Quality of Life (HRQOL)

The relevant HRQOL endpoints are the time to deterioration for the following three symptom scales/items measured on the QLQ-C30 or QLQ-LC13 questionnaire (R99-1213, R07-2060):

- cough (Question 1 on the QLQ-LC13),
- dyspnoea (composite of Questions 3-5 on the QLQ-LC13),
- pain (composite of Questions 9 and 19 on the QLQ-C30)

Scoring of the symptom scales/items will follow the EORTC scoring algorithm. For ease of interpretation, a linear transformation will be used to standardise the raw scores of all items and scales, so that scores range from 0 to 100 (R07-2064). A higher score represents a higher ('better') level of functioning (functional scales, global health status/QOL), or a higher ('worse') level of symptoms (symptom scale/item) (R07-2064).

Time to deterioration for the cough, dyspnoea, pain and symptom scales/items will be defined as the time to a 10-point increase from the baseline score (R07-2064, R99-1223, R07-2061). Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQOL assessments will be censored at day of randomisation. If a HRQOL assessment is missed, but followed by another assessment and deterioration occurs during that period, the time to deterioration will be defined as the midpoint between the two observed assessments. In addition, the three alternative measures of pain (Questions 10-12* in QLQ-LC13) will be examined descriptively for consistency with the composite of questions 9 and 19 from the QLQ-C30, as will dyspnoea (Question 8) from the EORTC QLQ-C30 be compared with the dyspnoea composite (Questions 3-5* on the QLQ-LC13).

Time to deterioration will be analysed similarly to PFS i.e. log-rank test stratified by the stratification factors used at randomisation will be used to test for the effect of BIBW 2992. The individual items of the symptom scales will be examined for consistency with the composites.

In addition, a comprehensive analysis of all subscales/items (where a single item is scored, R07-2064) will estimate the hazard ratio for time to deterioration with 95% confidence. The results of these analyses will be displayed using a Forest plot to summarise the impact of therapy over the entire profile of the EORTC QLQ-C30 and LC13 measures.

Additional analysis will describe the distribution of patients that are improved, stable, or worsened for each of the QLQ-C30 and QLQ-LC13 summary scales and items (where a single item is scored, R07-2061).

* Note that questions on the QLQ-LC13 are numbered consecutively following the QLQ-C30 as shown in Appendix 4. Consequently, Question 1 is numbered as Question 31 and Questions 3-5 as Questions 33-35.

Was changed to:

7.3.2.2.4 Health-Related Quality of Life (HRQOL)

The analyses will focus on cough, dyspnea, and pain measured on the EORTC QLQ-C30 and QLQ-LC13 questionnaires (R99-1213, R07-2060).

For each of summary scales and items measuring cough, dyspnea, and pain, the treatments will be compared in terms of:

- the distribution of patients that are improved, stable, or worsened

  Improvement is defined as scores that improve by at least 10 points at any time during the study. If a patient does not improve, worsening is defined as a 10 point worsening in EORTC scores at any time. Otherwise, a patient would be considered stable if they neither improve nor worsen.

- time to deterioration

  Time to deterioration will be defined as the time to a 10-point increase from the baseline score (R07-2064, R99-1223, R07-2061).

  Patients who die before deteriorating will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQOL assessments will be censored at day of randomisation. If a HRQOL assessment is missed, but followed by another assessment and deterioration occurs during that period, the time to deterioration will be defined as the midpoint between the two observed assessments.

  Time to deterioration will be analysed similarly to PFS i.e. log-rank test stratified by the stratification factors used at randomisation will be used to test for the effect of BIBW 2992.

- change in cough, dyspnea and pain scores over time

  The change in cough, dyspnea and pain will be assessed using a mixed-effects growth curve model with the average profile over time for each endpoint described by a piecewise linear model adjusted for baseline EGFR mutation category and ethnicity (R10-4359).

The results of the time to deterioration analyses and the longitudinal analysis will be displayed using Forest plots.

These analyses will be repeated in subgroups defined by:

- baseline ECOG: 0 vs. 1
- presence of symptoms at baseline: no vs. yes

In addition, similar analyses will be summarized for all QLQ-C30 and QLQ-LC13 subscales/items (where a single item is scored, R07-2064).

Finally, the usage of cough, dyspnea and pain medication will be described.

Reason for change 25:

The focus of the analysis of HRQOL was broadened to include all summary scales and items measuring cough, dyspnea, and pain measured on the EORTC QLQ-C30 and QLQ-LC13 questionnaires. This change was made to more comprehensively characterize the treatment effects on the signs and symptoms of NSCLC.

Change 26:

8.4.1 Adverse Events

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent to the final follow-up visit) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

Was changed to:

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent *at screening visit 2* to the final follow-up visit) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File. *In addition only trial related adverse events will be collected between screening visit 1 and screening visit 2.*

Reason for change 26: To clarify collection of safety data during the screening phase of the trial.

Change 27:

Was added:

8.9 COMPLETION OF TRIAL

The trial will be considered complete when the last patient completes the last follow-up visit.

Reason for change 27: To clarify the defination of completion of trial.

Change 28: Appendix 4: RECIST 1.1 Criteria

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

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).

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

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, and 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 characterise the objective tumour response of the measurable dimension of the disease (see Table 10.4:1).

Table 10.4: 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 10.4:2).

Table 10.4: 2 Evaluations of non-target lesions and new lesions

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is

recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

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

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.4:3) 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 10.4:3).

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

Table 10.4: 3 Algorithms for evaluation of overall best response*

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

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

Was changed to:

(please note that due to size of this section all changes are italicised to clearly show differences)

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

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). *Lymph nodes must be ≥15mm in short axis when assessed by CT scan*

Measurable disease

Measurable disease requires the presence of at least one measurable lesion.

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, and 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 for all lesions except lymph node and shortest diameter = ShD for lymph nodes) 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 diameters (SoD) for all target lesions will be calculated and reported as the baseline SoD. The baseline SoD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.4:1).

Table 10.4: 1 Evaluation of target lesions

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

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.4:2).

Table 10.4: 2 Evaluations of non-target lesions and new lesions

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

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

Confirmation

In the case of SD, follow-up measurements must have met SD criteria at least once after study entry at a minimum interval of 35 days.

Evaluation of Best Response to Study Treatment

The best response to study treatment (Table 10.4:3) 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 10.4:3).

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

Table 10.4: 3 Algorithms for evaluation of overall best response*

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

** In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of thirty five (35) days.*

Reason for change 28: To update protocol appendix to match RECIST 1.1 criteria and ensure consistency with the imaging charter for central analysis of the images.

Change 29:

APPENDIX 5: COCKROFT-GAULT FORMULA

Was added:

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

Reason for change 29: To document the formula in protocol to calculate creatinine clearance.

Boehringer Ingelheim

Clinical Trial Protocol Amendment

Doc. No.: U10-3034-01-AM3

Amendment Number:	3		
Date:	9 Aug 2011	☐	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
BI Trial No.:	1200.34	☐	To be implemented immediately in order to eliminate hazard – *IRB / IEC / Competent Authority* to be notified of change with request for approval
Investigational Product(s):	Afatinib (BIBW2992)	■	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only

Title:	LUX-Lung 6: A randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation
Rationale for Amendment:	The protocol stipulates that this trial is a multinational study and we are including patients from 3 countries; China, Thailand and South Korea. Since patients in Thailand and South Korea are enrolling toward the end of the study and to ensure an adequate representation of patients from Thailand and South Korea, we are amending the protocol to allow for a slight increase in the total number of randomized patients in the trial to approximately 360 patients rather than 330 patients.

Change 1: The total number of randomized patients in the trial changes to approximately 363 patients rather than 330 patients.

Page 2 No. of Patients:

Total:

330 randomized

Was changed to:

Total:

Approximately 360 randomized

And

Page 26 3.1 OVERALL TRIAL DESIGN AND PLAN-DESCRIPTION

It is estimated that approximately 1366 patients will be screened for the trial in order to find 330 eligible patients.

Was changed to:

It is estimated that approximately 1366 patients will be screened for the trial in order to find approximately 360 eligible patients.

And

Page 27 3.3 SELECTION OF TRIAL POPULATION

It is estimated that approximately 1366 patients will be screened in order to find 330 eligible patients.

Was changed to:

It is estimated that approximately 1366 patients will be screened in order to find approximately 360 eligible patients.

Reason For Change 1:

The protocol stipulates that this trial is a multinational study and we are including patients from 3 countries; China, Thailand and South Korea. Since patients in Thailand and South Korea are enrolling toward the end of the study and to ensure an adequate representation of patients from Thailand, and South Korea, we are amending the protocol to allow for a slight increase in the total number of randomized patients in the trial to approximately 363 patients rather than 330 patients

Boehringer Ingelheim

Clinical Trial Protocol Amendment

Doc. No.: U10-3034-01-AM4

Amendment Number:	4		
Date:	16 Oct 2013	■	To be implemented only after documented approval of the *IRB / IEC / Competent Authorities*
BI Trial No.:	1200.34	□	To be implemented immediately in order to eliminate hazard – *IRB / IEC / Competent Authority* to be notified of change with request for approval
Investigational Product:	BIBW2992	□	Can be implemented without *IRB / IEC / Competent Authority* approval as changes involve logistical or administrative aspects only

Title:	LUX-Lung6; A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation
Rationale for Amendment:	1. Reschedule the trial procedures to reduce or omit unnecessary ECG, ECHO/MUGA measurements, and clinic visit for on-going patients, since the available data of afatinib does not show any cardiotoxicity risk. 2. Define a timepoint for the termination of independent image review as the primary PFS analysis has already been performed. 3. Redefine the trial completion timeline to allow a flexible completion time point in the future based on regulatory authority requirements. 4. Stop collecting follow-up biopsy sample and blood sample of EGFR mutation as the data is unlikely to be of additional value. 5. Stop the collection of HRQOL data as sufficient long term data has already been collected. 6. Update the latest information of afatinib from the IB and implement newly introduced procedures and SOPs according to the company procedural changes: • concomitant use of PgP inhibitors and inducers. • DILI related content and appendix. • management of keratitis. • adverse events considered “always serious”. 7. Other administrative changes.

TABLE OF CONTENTS

Change 1: Change of Trial Clinical Monitor

Phone: , Fax:

Was changed to:

Phone: , Fax:

Reason for Change 1

change of trial clinical monitor

Change 2: Coordinator Investigator's name

Was changed to:

Reason for Change 2

correct the format of the coordinator investigator's name

Change 3: Synopsis: Trial site(s)

Multi-centre trial in Asia (China, India and Korea）

Was changed to:

Multi-centre trial in Asia (China, Thailand and Korea）

Reason for Change 3

Thailand replace India attended this trial

Change 4: Flow Chart: Arm A (BIBW2992)

*** All courses are 3 weeks in duration (21 days). Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met (see Section 6.3.1).
***** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment.

Was changed to:

*** All courses are 3 weeks in duration (21 days). Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), the clinic visit of an on-treatment patient will be extended from every 3 weeks to every 9 weeks. Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met (see Section 6.3.1).
***** All patients should have a follow-up visit 21 days after the EOT visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 21 days until progression or start of further treatment, following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), patients who have not progressed and not started further treatment should have further follow-up visits every 9 weeks until progression or start of further treatment.
****** Following the second (primary) analysis of overall survival (see section 7.3.2.1.2), the collection of observation period data may be reduced in frequency as appropriate, as communicated by the Trial Clinical Monitor.

Reason for Change 4

To reduce the monitoring frequency to avoid the unnecessary clinical monitoring to patients with long time stable disease and good medication tolerance.

Change 5: Flow Chart: Arm A (BIBW2992)

Was added to footnote5:

Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), ECG assessment will be performed as clinically indicated.

Reason for Change 5

ECG data has been collected and centrally assessed for at least 18 months for all randomised patients. Clinical trial data shows afatinib does not have an effect on QTc interval or other

ECG parameters, and therefore routine monitoring is no longer indicated. This is further supported by results from dedicated QTc trial. Patients who have been previously identified with abnormal findings will continue ECG assessment if investigator judges that it is clinically indicated.

Change 6: Flow Chart: Arm A (BIBW2992)

Was added to footnote 6:

Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), ECHO or MUGA will be performed only as clinically indicated.

Reason for Change 6

Available clinical trial data shows afatinib does not have an effect on LVEF, and therefore routine monitoring is no longer indicated.

Change 7: Flow Chart: Arm A (BIBW2992)

Was added to footnote 8:

After approval of amendment 4, no further follow-up biopsy samples will be collected.

Reason for Change 7

Available data already collected has indicated that the collection of further samples is unlikely to be of additional value.

Change 8: Flow Chart: Arm A (BIBW2992)

Was added to Footnote 9:

After approval of amendment 4, no further follow-up blood samples for EGFR mutation testing will be collected.

Reason for Change 8

Available data already collected has indicated that the collection of further samples is unlikely to be of additional value.

Change 9: Flow Chart: Arm A (BIBW2992)

Was added to footnote 12:

Following the second (primary) analysis of overall survival (see section 7.3.2.1.2), assessment will be performed every 18 weeks.

Reason for Change 9

Following the second (primary) analysis of overall survival, patients will have been on treatment for over 2 years and such frequent tumour assessment is no longer required now that the primary endpoint of PFS has been assessed.

Change 10: Flow Chart: Arm A (BIBW2992)

Was added to footnote 15:

The assessment and collection of HRQOL data will be ceased after the second (primary) analysis of overall survival (see section 7.3.2.1.2).

Reason for Change 10

Sufficient long term HRQOL data will have been collected by the second (primary) analysis of OS; it is expected that there will only be 10-20 patients still being treated in the afatinib arm.

Change 11: Flow Chart: Arm B (GEMCITABINE/CISPLATIN)

A new footnote will be added as follows:

***** added next to OP

***** Following the second (primary) analysis of overall survival (see section 7.3.2.1.2), the collection of observation period data may be reduced in frequency or stopped as appropriate, as decided and communicated by the Trial Clinical Monitor.

Reason for Change 11

To allow flexibility in collection of vital status data after the second (primary) analysis of overall survival.

Change 12: ABBREVIATIONS

Was added:

DILI Drug induced liver injury

MDR1 MultiDrug-Resistance Protein 1

Reason For Change 12

Addition of new abbreviations introduced by other changes

Change 13: Section 1.1 Pharmacology and toxicology profile

Was added after paragraph 2:

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

Reason for Change 13

Addition of latest clinical data on the concomitant use of PgP inhibitors and inducers

Change 14: Section 1.4 BENEFIT - RISK ASSESSMENT

Was added after paragraph 4:

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

Reason for Change 14

To be compliant to the new corporate standard for monitoring and assessment of drug – induced liver injury.

Change 15: Section 3.1 OVERALL TRIAL DESIGN AND PLAN-DESCRIPTION

The trial will be performed by investigators specialised in the treatment of lung cancer in Asia countries (China, India and Korea). It is estimated that approximately 1366 patients will be screened for the trial in order to find approximately 360 eligible patients.

Was changed to:

The trial will be performed by investigators specialised in the treatment of lung cancer in Asia countries (China, Thailand and Korea). It is estimated that approximately 1366 patients will be screened for the trial in order to find approximately 360 eligible patients.

Reason for Change 15

India was replaced by Thailand for patient recruitment.

Change 16: Section 3.1 OVERALL TRIAL DESIGN AND PLAN-DESCRIPTION

All patients will visit the investigator at regular intervals for assessment of safety parameters and adverse events as outlined in the flow chart. Assessments of response will be made at 6 weeks, 12 weeks and every 6 weeks thereafter until progression or withdrawal for another reason. After week 48, assessment of response will be performed every 12 weeks until progression of withdrawal for another reason. Tumour response and progression will be assessed using RECIST 1.1 (R09-0262) and assessment at the investigator site will be sufficient for decisions on continuation of treatment. An independent analysis of response will also be performed by a Central Imaging Unit (see Section 5.1.4) but this will not be used to make treatment decisions.

Was changed to:

All patients will visit the investigator at regular intervals for assessment of safety parameters and adverse events as outlined in the flow chart. Assessments of response will be made at 6 weeks, 12 weeks and every 6 weeks thereafter until progression or withdrawal for another reason. After week 48, assessment of response will be performed every 12 weeks until progression or withdrawal for another reason. Following the second (primary) analysis of overall survival (see section 7.3.2.1.2), assessment will be performed every 18 weeks. Tumour response and progression will be assessed using RECIST 1.1 (R09-0262) and assessment at the investigator site will be sufficient for decisions on continuation of treatment. An independent analysis of response will also be performed by a Central Imaging Unit (see Section 5.1.4) but this will not be used to make treatment decisions. After the second (primary) analysis of overall survival (see Section 7.3.2.1.2) images will no longer be sent to the central imaging unit for independent review.

Reason for Change 16

To change frequency of visits. Following the second (primary) analysis of overall survival, patients will have been on treatment for over 2 years and such frequent monitoring is no longer required. There is also no longer the requirement for central analysis of imaging as primary endpoint of PFS has been assessed.

Change 17: Section 3.3 SELECTION OF TRIAL POPULATION

A log of all patients who have signed the informed consent form will be maintained in the ISF at the investigational site. The trial will be conducted in multiple centres in Asia (China, India and Korea). It is estimated that approximately 1366 patients will be screened in order to recruit approximately 360 eligible patients.

Was changed to:

A log of all patients who have signed the informed consent form will be maintained in the ISF at the investigational site. The trial will be conducted in multiple centres in Asia (China, Thailand and Korea). It is estimated that approximately 1366 patients will be screened in order to recruit approximately 360 eligible patients.

Reason for Change 17

India was replaced by Thailand for patient recruitment.

Change 18: Section 3.3.1 Inclusion criteria

Patients are eligible for inclusion (enrolment) if they fulfill the following criteria

Was changed to:

Patients are eligible for inclusion (enrollment) if they fulfill the following criteria

Reason for Change 18

Typo is corrected.

Change 19: Section 4.1.1 Identity of investigational product

Substance (INN): BIBW 2992

Was added in section: Duration of use:

Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), treatment will be divided into courses which are 9 weeks (63 days) in duration.

Reason for Change 19

Change in visit frequency.

Change 20: Section 4.1.4.1 Selection and timing of doses for each patient

BIBW 2992 (ARM A)

For administrative purposes treatment will be divided into treatment courses, which are each 3 weeks (21 days) in duration. Patients will take a single oral dose of 40mg BIBW 2992 each day for the first course (21 days).

Was changed to:

For administrative purposes treatment will be divided into treatment courses, which are each 3 weeks (21 days) in duration. Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), treatment will be divided into courses which are 9 weeks (63 days) in duration. Patients will take a single oral dose of 40mg BIBW 2992 each day for the first course (21 days).

Reason for Change 20

Change in visit frequency

Change 21: Section 4.1.4.1 BIBW 2992 (Arm A)

The medication should be taken at approximately the same time each day at least one hour before food intake and at least three hours after food intake. The tablet should be swallowed with a glass of water. BIBW 2992 tablets are film-coated and therefore should not be chewed or crushed, but may be administered via G-tube after dispersing the BIBW 2992 tablets according to the following procedure: Place the tablet into a glass containing 50 mL isotonic sodium chloride solution. Stir until the tablet is broken up into very fine particles (about 15 minutes). Drink the suspension immediately or administer via a gastric tube. Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the gastric-tube again (to pick up any drug remaining in the glass/gastric-tube).

Was changed to:

The medication should be taken at approximately the same time each day at least one hour before food intake and at least three hours after food intake.

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.

Reason for Change 21

To be compliant to new corporate standard description on administration of afatinib for patients unable to take whole tablets.

Change 22: Section 4.1.6.1 Packaging, labelling and re-supply BIBW 2992

Was added at end of section:

After the second (primary) analysis of overall survival, patients may switch BIBW2992 from trial supplies to marketed product, an expanded-access program, named patient use program, or compassionate use protocol. This may mean a change in packaging and labelling.

Reason for change 22

To ensure an on-going supply of BIBW2992 to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial.

Change 23: Section 4.2.1 Rescue medication and additional treatments

Was added after paragraph 4:

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.

Reason for Change 23

Added additional guidance for management of keratitis according to the IB update.

Change 24: Section 4.2.2 Restrictions

BIBW 2992 is a substrate of P-gp and its plasma concentrations can be affected by the use of P-gp inhibitors (data on file) and it is also likely that P-gp inducers could also influence BIBW 2992 plasma concentrations. The use of potent P-gp inhibitors (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil) and potent P-gp inducers (including St John's wort, rifampicin) must be avoided during treatment with BIBW 2992. Any exemptions to this must be discussed with the BI clinical monitor.

In any patient ongoing in the trial receiving BIBW 2992 and a concomitant potent P-gp inhibitor or inducer at the time of amendment 1 being implemented, the decision for continuation of either drug will be based on the individual circumstances of the patient upon discussion with the responsible BI clinical monitor.

Was changed to:

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 7

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

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

Acceptable methods of contraception include surgical sterilisation and double barrier method, and must be in accordance with local regulations where applicable. Double barrier method of contraception is defined as two barrier methods used simultaneously each time the patient has intercourse. Accepted barrier methods include diaphragm, female condom, cervical cap, male condom and intrauterine device (UID) (the diaphragm and cervical cap must be used in conjunction with spermicidal jelly/cream). Those using hormonal contraceptives, or with partners using hormonal contraceptives, must also be using an additional approved method of contraception (as described above). Partner vasectomy, natural "rhythm" and spermicidal jelly/cream are not acceptable methods of contraception.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in section 5.2.2.3

Reason For Change 24

Update to incorporate latest guidance on the use of concomitant medications.

Change 25: Section 4.3.1 TREATMENT COMPLIANCE BIBW 2992 (Arm A)

…. At the end of each course remaining medication should be collected. If the patient is eligible for a further course of treatment a new bottle should be dispensed.

Was changed to:

…. At the end of each course remaining medication should be collected. If the patient is eligible for a further course of treatment a new bottle**/new bottles** should be dispensed.

Reason for change 25

As courses will change to 9 weekly after the second (primary) analysis of overall survival, 3 bottles of medication will need to be dispensed to patient.

Change 26: Section 4.4 MANAGEMENT OF ADVERSE EVENTS

4.4.1 Management of diarrhoea following treatment with BIBW 2992 (Arm A)

Close monitoring and proactive management of diarrhoea is essential for successful treatment of patients with BIBW 2992. Early and appropriate intervention can prevent the development of more severe diarrhoea. In most cases, loperamide controls diarrhoea caused by BIBW 2992. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating treatment with BIBW 2992.

The recommendations for management are as follows:

- If any diarrhoea is experienced (CTCAE Grade 1), two 2 mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).
- In the event of diarrhoea patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.
- Oral hydration is essential regardless of severity; appropriate rehydration (1.5 l/m2/day plus equivalent of actual fluid loss) and electrolyte replacement has to be ensured in the event of CTCAE Grade 2 and Grade 3 adverse events.
- For CTCAE Grade 3 diarrhoea or CTCAE Grade 2 diarrhoea lasting ≥ 2 days (48 hours) despite adequate antidiarrhoeal treatment, BIBW 2992 must be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, BIBW 2992 should be resumed at a

reduced dose according to the dose reduction scheme outlined in Section 4.1.4.1.1.

The occurrence of diarrhoea and the outcome of treatment will be recorded in the AE section of the CRF. Antidiarrhoeal treatments should be documented in the concomitant medication section of the CRF.

If despite optimal supportive care and a treatment pause, diarrhoea does not resolve to CTC Grade ≤1 within 14 days, the patient must not receive any further BIBW 2992 treatment and the end of treatment (EOT) visit should be performed.

4.4.2 Management of nausea and vomiting following treatment with BIBW 2992 (Arm A)

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated according to the recommendation given in Table 4.4.2:1.

Table 4.4.2:1 Management of nausea and vomiting

CTCAE Grade	**Antiemetic treatment**
Nausea = grade 0 and Vomiting = grade 0	No antiemetic prophylactic treatment
Nausea = grade 1 and Vomiting = grade 0	No antiemetic treatment
Nausea = grade 2 and Vomiting = grade 0 Nausea = grade 0, 1 or 2 and Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause BIBW 2992 treatment if grade 2 vomiting or grade 2 nausea persist for 7 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE grade ≤ 1.
Vomiting ≥ grade 3 or Nausea ≥ grade 3	Antiemetic treatment[1] Pause BIBW 2992 treatment until return to CTCAE grade ≤ 1 or baseline[2].

1 Antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference (R06-0986).
2 Baseline is defined as the CTCAE grade at the start of treatment.

After a treatment pause the dose of BIBW 2992 should be reduced according to the dose reduction scheme in Table 4.1.4.1.1:1.

The occurrence of nausea and/or vomiting and the outcome of treatment will be recorded in the AE section of the CRF. Antiemetic treatments should be documented in the concomitant medication section of the CRF with the start and end of treatment dates and daily dose.

In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m^2/day plus hydration deficit) must be ensured.

4.4.3 Management of rash following treatment with BIBW 2992 (Arm A)

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and reduce the rash.

The recommendations for management are as follows:

- **General/Prevention**: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.
- **CTCAE Grade 1 rash*:*** mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.
- **CTCAE Grade 2 rash**: relief from major symptoms caused by CTCAE Grade 2 skin-related adverse events should be achieved by a combination of local and systemic therapies including:

  1) Systemic antibiotics (doxycycline or minocycline etc.).
  2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

  And / or

  1) Antihistamines (diphenhydramine, etc.)
  2) Oral prednisone (short term i.e., <14 days treatment) may be added at investigator's discretion.

  Systemic and topical treatment should be initiated at the start of CTCAE Grade 2 rash and continue until improvement or resolution to CTCAE Grade ≤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 for up to 14 days followed by a reduction in the dose of BIBW 2992 according to the dose reduction scheme in Table 4.1.4.1.1:1.

- **CTCAE Grade 3 (or greater) rash:** may be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade ≥3 rash, treatment with BIBW 2992 should be paused until recovery to CTCAE Grade ≤1. Treatment should be resumed at a reduced dose (see Section 4.1.4.1). If CTCAE Grade ≥3 rash does not resolve to CTCAE Grade ≤1 within 14 days of stopping BIBW 2992 treatment and despite optimal supportive care, the patient should not receive any further treatment with BIBW 2992 and the End of Treatment visit should be performed.

Was changed to:

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.

4.4.1 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 4.4.1: 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 4.4.1: 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	Life-threatening consequences (e.g.	Dose interruption until recovered to ≤Grade 1	See Grade 3

(Grade 4)	haemodynamic collapse)	followed by dose reduction*	

* 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.

4.4.2 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 4.4.2: 1 and grade-specific treatment recommendations are summarized in Table 4.4.2: 2. For dose adjustment of afatinib refer to Table 4.1.4.1.1:1.

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

Table 4.4.2: 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 4.4.2: 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)
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
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 4.1.4.1.1:1		

4.4.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.4.3:1. For dose adjustment refer to Section 4.1.4.1.1 and for restrictions on concomitant therapies refer to Sections 4.2.2 and 10.7.

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 modification 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 4.4.3:1 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 4.4.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations	Intervention concerning afatinib treatment/ dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution .	No change .
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.

Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4

Reason for Change 26

Update to incorporate latest guidance on the management of adverse events.

Change 27: Section 5.1.3 Tumor assessment

One to five target lesions (not exceeding two lesions per organ) should be identified at screening by Computed Tomography (CT). Skin lesions should be measured and photographic documentation should be performed. Individual lesions detected at screening will be numbered and recorded in the CRF. These lesions should be followed up with the same method(s) used at screening and the same numbering should be applied. The size of the target lesions will be recorded in millimetres. The examinations should be performed at screening, after 6 weeks, after 12 weeks and every 6 weeks thereafter. After week 48, assessments should be performed every 12 weeks. If a patient develops an allergy to contrast media, MRI scans can be substituted for CT scans.

Was changed to:

One to five target lesions (not exceeding two lesions per organ) should be identified at screening by Computed Tomography (CT). Skin lesions should be measured and photographic documentation should be performed. Individual lesions detected at screening will be numbered and recorded in the CRF. These lesions should be followed up with the same method(s) used at screening and the same numbering should be applied. The size of the target lesions will be recorded in millimetres. The examinations should be performed at screening, after 6 weeks, after 12 weeks and every 6 weeks thereafter. After week 48, assessments should be performed every 12 weeks. Following the second (primary) analysis of overall survival (see Section 7.3.2.1.2), the assessments should be performed every 18 weeks. If a patient develops an allergy to contrast media, MRI scans can be substituted for CT scans.

Reason for Change 27

To modify the tumor assessment frequency according to the modified clinical visit following the second (primary) analysis of overall survival.

Change 28: Section 5.1.4 Central imaging

Was added after paragraph 4:

After the second (primary) analysis of overall survival (see Section 7.3.2.1.2) images will no longer be sent to the central imaging unit for independent review.

Reason for Change 28

The primary PFS analysis of independent data has already been performed and will be re-analysed at the time of the second (primary) analysis of overall survival. Additional independent review data after this time will be of little value. Investigator tumour response assessments will continue to be performed.

Change 29: Section 5.1.5 Health-Related Quality Of Life

Was added at last:

The assessment of Health-Related Quality Of life (HRQOL) will be stopped after the second (primary) analysis of overall survival (see section 7.3.2.1.2).

Reason for Change 29

Sufficient long term HRQOL data will have been collected by the second (primary) analysis of OS; it is expected that there will only be 10-20 patients still being treated in the afatinib arm.

Change 30: Section 5.2.1 Adverse Events

Was added at paragraph 6

Regular and continuing assessment of safety will be performed at least once per course during the first six courses and every three weeks thereafter….

Was changed to:

Regular and continuing assessment of safety will be performed at least once per course during the first six courses and every three weeks thereafter until after the second (primary) analysis of overall survival. After the second (primary) analysis of overall survival (see section 7.3.2.1.2), safety will be assessed at least every nine weeks unless an unscheduled visit is required for safety reasons.

Reason for change 30

Updated frequency of visits.

Change 31: Section 5.2.6 ECG

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart. ECGs will be performed using a digital ECG machine and the data will be sent to a central assessment centre for evaluation.

Was changed to:

A 12-lead resting ECG will be performed at the time points specified in the Flow Chart. ECGs will be performed using a digital ECG machine and the data will be sent to a central assessment centre for evaluation. Central evaluation of ECG data will end after the second (primary) analysis of overall survival (see section 7.3.2.1.2).

Reason for Change 31

Available clinical trial data shows afatinib does not have an effect on QTc interval or other ECG parameters, and therefore routine monitoring is no longer indicated. Patients who have been previously identified with abnormal findings will continue ECG assessment if investigator confirms that it is clinically indicated.

Change 32: Section 5.2.7 Left ventricular function

Was added in paragraph 1:

After the second (primary) analysis of overall survival, the LVEF measurement would be performed only as clinical indicated.

Reason for Change 32

Available clinical trial data shows afatinib does not have an effect on LVEF, and therefore routine monitoring is no longer indicated. Patients who have been previously identified with abnormal findings will continue LVEF assessment if investigator confirms that it is clinically indicated.

Change 33: Section 5.6.1 Methods and timing of sample collection

During follow-up (after progression) a further blood sample and tissue sample for EGFR mutation analysis may be taken but are optional. The sample requirements are the same as those at screening.

Was changed to:

During follow-up (after progression) a further blood sample and tissue sample for EGFR mutation analysis may be taken but is optional. The sample requirements are the same as those at screening. After approval of amendment 4, no further follow-up tissue or blood samples will be collected.

Reason for Change 33

Available data already collected has indicated that the collection of further samples is unlikely to be of additional value.

Change 34: Section 5.6.1 Methods and timing of sample collection

If both L858R and a deletion in exon 19 are detected in the same sample, the patient will be allocated to the 'L858R' stratificatkion category.

Was changed to:

If both L858R and a deletion in exon 19 are detected in the same sample, the patient will be allocated to the 'L858R' stratification category.

Reason for Change 34

Typo is corrected.

Change 35: Section 6.1.2 Treatment

Patients randomized to arm A (BIBW 2992) will receive continuous daily treatment until the criteria for stopping medication are met (see Section 6.3.1). For administrative purposes treatment is divided into courses, which are each 3 weeks (21 days) in duration.

Was changed to:

Patients randomized to arm A (BIBW 2992) will receive continuous daily treatment until the criteria for stopping medication are met (see Section 6.3.1). For administrative purposes treatment is divided into courses, which are each 3 weeks (21 days) in duration. After the second analysis of overall survival (see section 7.3.2.1.2), clinic visit for mandated assessments will be prolonged to each 9 weeks (63 days).

Reason for Change 35

To align with modified flowchart.

Change 36: Section 6.1.4 Follow-up

Patients who have not progressed and not started further treatment at the first follow-up visit should have further follow-up visits every 21 days (± 7 days) until progression or start of further treatment.

Was changed to:

Patients who have not progressed and not started further treatment at the first follow-up visit should have further follow-up visits every 21 days (± 7 days) until progression or start of further treatment. After the second (primary) analysis of overall survival, Patients who have not progressed and not started further treatment should have further follow-up visits every 9 weeks (± 7 days) until progression or start of further treatment.

Reason for Change 36

To align with modified flowchart.

Change 37: Section 6.1.5 Observation period

After completion of the study patients will enter an observation period. During the observation period no study visits will be performed, but data regarding progression, further treatment (including best response and reason for stopping treatment) and death will be collected every 60 days (± 15 days) until death. Information will be collected from the patient notes or by telephone contact with the patient.

Was changed to:

After completion of the study patients will enter an observation period. During the observation period no study visits will be performed, but data regarding progression, further treatment (including best response and reason for stopping treatment) and death will be collected every 60 days (± 15 days) until death. Information will be collected from the patient notes or by telephone contact with the patient. Following the second (primary) analysis of overall survival (see section 7.3.2.1.2), the collection of observation period data may be reduced in frequency or stopped as appropriate, as communicated by the Trial Clinical Monitor.

Reason for Change 37

To allow flexibility in collection of vital status data after the second (primary) analysis of overall survival.

Change 38: Section 6.2.1 EGFR mutation analysis

During follow-up (after progression) a further blood sample and tissue sample for EGFR mutation analysis may be taken but are optional. The sample requirements are the same as those at screening.

Was changed to:

During follow-up (after progression) a further blood sample and tissue sample for EGFR mutation analysis may be taken but are optional. The sample requirements are the same as those at screening. After approval of amendment 4, no further follow-up tissue or blood samples will be collected.

Reason for Change 38

Available data already collected has indicated that the collection of further samples is unlikely to be of additional value. Therefore, this change has been implemented to prevent ongoing patients from being exposed to unnecessary procedures.

Change 39: Section 6.2.2.1 Treatment Arm A (BIBW2992)

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions.
ECG	12-lead resting ECG will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.).
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO or MUGA will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.).

Was changed to:

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions. After the second (primary) analysis of overall survival, this is no longer required.
ECG	12-lead resting ECG will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.). After the second (primary) analysis of overall survival, ECG assessment will be performed as clinically indicated.
ECHO/MUGA	Cardiac left ventricular function assessment by either ECHO

	or MUGA will be performed on day 1 of every third course (C4V1, C7V1, C10V1 etc.). After the second (primary) analysis of overall survival, ECHO or MUGA will be performed only as clinically indicated.

Reason for Change 39

To align with modified flowchart.

Change 40: Section 6.2.3 End of trial and follow-up

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions.
ECG	Arm A (BIBW 2992); A12-lead resting ECG will be performed if not performed in the previous 8 weeks. Arm B (Gemcitabine/Cisplatin); A12-lead resting ECG will be performed if clinically indicated.
ECHO/MUGA	Arm A (BIBW 2992); Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if not performed in the previous 8 weeks. Arm B (Gemcitabine/Cisplatin); Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if clinically indicated.

Was changed to:

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions. After the second (primary) analysis of overall survival, this is no longer required.
ECG	Arm A (BIBW 2992); A12-lead resting ECG will be performed if not performed in the previous 8 weeks. After the second (primary) analysis of overall survival, ECG assessment will be performed as clinically indicated. Arm B (Gemcitabine/Cisplatin); A12-lead resting ECG will be performed if clinically indicated.
ECHO/MUGA	Arm A (BIBW 2992); Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if not performed in the previous 8 weeks. After the second (primary) analysis of overall survival, ECHO or MUGA will be performed only as clinically indicated. Arm B (Gemcitabine/Cisplatin); Cardiac left ventricular function assessment by either ECHO or MUGA will be performed if clinically indicated.

Reason for Change 40

To align with modified flowchart.

Change 41: Section 6.2.4 Follow-up (all patients)

If patient has not progressed at FU1, perform further follow-up visits every 21 days (+/- 7 days) until progression or start of further treatment (FU2, FU3, FU4 etc.)

Was changed to:

If patient has not progressed at FU1, perform further follow-up visits every 21 days (+/- 7 days) until progression or start of further treatment (FU2, FU3, FU4 etc.)
After the second (primary) analysis of overall survival, if patient has not progressed at FU1, perform further follow-up visits every 9 weeks (63 days) +/- 7 days until progression or start of further treatment (FU2, FU3, FU4 etc.)

Reason for change 41

Change in frequency of visits.

Change 42: Section 6.2.4 Follow-up (all patients)

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions.
ECOG	ECOG performance status will be assessed and documented.
Serum sample for EGFR mutation analysis	An optional serum sample for analysis of EGFR mutation status may be collected at Follow-up 1
Tumour biopsy for EGFR mutation analysis	An optional tumour biopsy for analysis of EGFR mutation status may be collected during the Follow-up phase.

Was changed to:

HRQOL	Ask patient to complete HRQOL questionnaires prior to any other assessments or discussions. After the second (primary) analysis of overall survival, this is no longer required.
ECOG	ECOG performance status will be assessed and documented. After the second (primary) analysis of overall survival, ECG will be performed only as clinically indicated.
Serum sample for EGFR mutation analysis	An optional serum sample for analysis of EGFR mutation status may be collected at Follow-up 1. After approval of amendment 4, no further serum samples will be collected.
Tumour biopsy	An optional tumour biopsy for analysis of EGFR mutation status may

for EGFR mutation analysis	be collected during the Follow-up phase. After approval of amendment 4, no further biopsy samples will be collected.

Reason for Change 42

To align with modified flowchart and omit unnecessary procedures.

Change 43: Section 6.2.5 Observation period

Observation period Collect data every 60 days (± 15 days) after last follow-up visit. A formal study visit is not required; data should be collected from patient notes or by telephone.

Was changed to:

Observation period Collect data every 60 days (± 15 days) after last follow-up visit. A formal study visit is not required; data should be collected from patient notes or by telephone. Following the second analysis of overall survival (see section 7.3.2.1.2), the collection of observation period data may be reduced in frequency, as communicated by the Trial Clinical Monitor.

Reason for Change 43

To allow flexibility in collection of vital status data after the second analysis of overall survival.

Change 44: Section 6.3.2 Removal of patients from trial

Was added at end of section:

The sponsor may remove patients from the study, after the second (primary) analysis of overall survival, if the patient has access to BIBW2992 through marketed product, an expanded-access program, named patient use program, or compassionate use protocol. If a patient is removed from the study as communicated by TCM, an end of treatment and follow up 1 visit will need to be performed to ensure all adverse events are followed up. No observational visits will be required.

The cost of any on-going supply of BIBW2992 will be incurred by the Sponsor.

Reason for change 44

To ensure an on-going supply of BIBW2992 to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial

Change 45: Section 7.3.2.1.2 Overall survival (OS)

OS will be analyzed twice. The first analysis will be performed at the time of the primary PFS analysis. A second analysis will be performed somewhat later with the aim of providing as much information as possible on OS. With 330 patients randomised over a period of 9-10 months and a median time to death of 20 months (HR= 1.0), approximately 219 deaths would be expected within 36 months.

Was changed to:

OS will be analyzed twice. The first analysis will be performed at the time of the primary PFS analysis. A second (primary) analysis will be performed somewhat later with the aim of providing as much information as possible on OS. With 360 patients randomised over a period of 9-10 months and a median time to death of 20 months (HR= 1.0), approximately 237 deaths would be expected within 36 months.

Reason for Change 45

Section updated in line with increase in sample size implemented in the protocol amendment 3.

Change 46: Section 8.4.1 Adverse events

Was added after paragraph 3:

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

Reason for Change 46

To be compliant to new corporate standard for events considered “always serious”.

Change 47: Section 8.4.1 Adverse events

There are no events defined as 'significant' for this study. All events will be categorised as either Adverse Event (AE) or Serious Adverse Event (SAE).

Was replaced with:

Protocol-specified significant events

Although rare, drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified significant adverse event. Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the underlying malignancy on liver function from other causes is important for patient safety. The following are considered as Protocol-specified significant events:

Hepatic injury defined by the following alterations of liver parameters:

- For patients with normal liver function (ALT, AST and bilirubin within normal limits) at baseline an elevation of AST and/or ALT >3 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to section 10.6 of this clinical trial protocol and the "DILI checklist" provided in the ISF.
- For patients with abnormal liver function at baseline an elevation of AST and/or ALT >5 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample. Patients showing these lab abnormalities need to be followed up according to section 10.6 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

Protocol-specified significant events are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

If the investigator determines any protocol-specific significant event is related to study drug, the administration of the study drug must be managed according to section 4.1.4 of the protocol.

Reason for Change 47

To be compliant to new corporate standard for monitoring and assessment of drug induced liver injury.

Change 48: Section 8.9 COMPLETION OF TRIAL

The trial will be considered complete when the last patient completes the last follow-up visit.

Was changed to:

The trial will be considered complete when the last patient completes the last follow-up visit. An earlier trial completion may occur if BIBW2992 is approved and available locally,

whereby patients still taking trial medication will be switched to marketed product and complete the trial. Such a scenario will only take place if adequate trial data has been collected for analysis.

After mandatory follow-up visits required for each patient's trial completion, each patient will enter the observation period. The observation period of the trial will end after all patients have died or five years after the last follow-up visit, whichever occurs first. However, the observation period may end earlier depending upon the timing of analyses requested by regulatory authorities or communicated by TCM.

Reason for Change 48

To be consistent with section 6.1.5, and allow trial termination when the trial drug is approved by local authority and trial data is adequate for analysis.

Change 49: APPENDIX 1

Arm A (BIBW2992)

Continuous daily treatment until progression or other criteria for stopping medication. Treatment is divided into 21-day courses for administrative purposes.

Was changed to:

Continuous daily treatment until progression or other criteria for stopping medication. Treatment is divided into 21-day courses for administrative purposes. After the second (primary) analysis of overall survival, treatment is divided into 9 week (63 day) courses for administrative purposes.

Reason for change 49

Change in visit frequency.

Change 50: APPENDIX 1

Follow up visits

Every 21 days until progression or start of further treatment.

Was changed to:

Every 21 days until progression or start of further treatment. **After the second (primary) analysis of overall survival, every 9 weeks (63 days) until progression or start of further treatment.**

Reason for change 50

Change in visit frequency.

Change 51: APPENDIX 1

Was added:

* added next to "Every 12 weeks after week 48"

* After the second (primary) analysis of overall survival, imaging will be performed every 18 weeks.

Reason for change 51

Change in frequency of imaging.

Change 52: Addition of new appendix

10.6 APPENDIX 6 Clinical Evaluation of Liver Injury

10.6.1 Introduction

Alterations of liver laboratory parameters, as described in section 8.4.1 (Protocol-specified Significant Events), are to be further evaluated using the following procedures:

10.6.2 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.

Reason for Change 52

To be compliant to new corporate standard for monitoring and assessment of drug induced liver injury.

Change 53: Additon of new appendix

10.7 APPENDIX 7 List of potent inhibitors and inducers of PGP

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

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

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

Reason For Change 53

Addition of latest guidance on the concomitant use of P-gp inhibitors and inducers.