SIGNATURE INFORMATION

Document: 1200-0098--protocol-revision-07

Document No.: U10-2538-07

Title LUX-Breast 2. An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting

SIGNATURES (ELECTRONICALLY OBTAINED)

Meaning of Signature:	Signed by:	Date signed: (GMT)
Author-Trial Clinical Monitor	[redacted]	7/1/2013 09:22:48
Approval-Team Member Medicine	[redacted]	7/1/2013 09:25:48
Author-Trial Statistician	[redacted]	7/1/2013 11:44:19
Approval-Therapeutic Area [redacted]	[redacted]	7/1/2013 12:47:26
Verify Paper Signature Completion	[redacted]	7/10/2013 10:07:16

SIGNATURE INFORMATION (continued)

Document 1200-0098--protocol-revision-07

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Title LUX-Breast 2. An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting

SIGNATURES (ELECTRONICALLY OBTAINED)
(There are no entries on this page if there are up to seven signatures.)

Meaning of Signature:	**Signed by:**	**Date signed: (GMT)**

Clinical Trial Protocol

Doc. No.: U10-2538-07

EudraCT No.:	2010-021945-29
BI Trial No.:	1200.98
BI Investigational Product(s):	BIBW 2992 (afatinib)
Title:	LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting
Clinical Phase:	II
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Co-ordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status, Version, and Date of Protocol:	Final Protocol, Version 1.0, 5th October 2010
Status, Version, and Date of Revised Protocol:	Revised Protocol, Version 2.0, 22 December 2010 Revised Protocol, Version 3.0, 27 April 2011 Revised Protocol, Version 4.0, 29 July 2011 Revised Protocol, Version 5.0, 6 December 2011 Revised Protocol, Version 6.0, 6 November 2012 **Revised Protocol, Version 7.0, 27 June 2013** **Page 1 of 101**

CO-ORDINATING
INVESTIGATOR SIGNATURE

Trial Title: LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting

Trial Number: 1200.98

Revised Protocol based upon Global Protocol Amendment 6, 27 June 2013

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

Name: [redacted] **Signature**:_____

Signed signature page is located in the electronic Clinical Trial Master File

Affiliation: [redacted]

Date: _____

LOCAL SIGNATURES
(PRINCIPAL INVESTIGATOR OF SITE AND CLINICAL MONITOR LOCAL)

Revised Protocol based upon Global Protocol Amendment 6, 27 June 2013

Clinical Monitor Local:

Date Name

Full name

Organisation/Department

<Add other signatories if applicable.>

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

Principal Investigator (site):

Date Name

Full name

Organisation/Department

Signed signature page is located in the electronic Clinical Trial Master File

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Afatinib			
Name of active ingredient: BIBW 2992 (afatinib)			
Protocol date: 05 October 2010	**Trial number:** 1200.98		**Revision date:** **27 June 2013**

Title of trial:	LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting
Co-ordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s) :	Multicentre trial, international
Clinical phase:	II
Objectives:	To investigate the efficacy and safety of • BIBW 2992 (afatinib) alone and of • BIBW 2992 (afatinib) in combination with weekly paclitaxel or vinorelbine upon progression on BIBW 2992 (afatinib) monotherapy in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the adjuvant and/or neoadjuvant setting
Methodology:	Open-label, Phase II study
No. of patients: **total entered:**	120 patients will be entered. Approximately 150 patients will be enrolled **With protocol amendment 6 the sponsor will stop enrolment into the trial (part A), pending approval by IRBs and IECs.** **At the time point of implementation approximately 80 patients are expected to have been entered**
Diagnosis :	Metastatic HER2 over-expressing breast cancer after prior HER2 targeted treatment in the adjuvant and/or neoadjuvant setting

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Afatinib			
Name of active ingredient: BIBW 2992 (afatinib)			
Protocol date: 05 October 2010	**Trial number:** 1200.98		**Revision date:** **27 June 2013**

Main criteria for inclusion:	• patients with histologically confirmed HER2-overexpressing breast cancer • patients with metastatic disease (stage IV) • patients must have received prior HER2-targeted treatment, i.e. trastuzumab and/or lapatinib in the adjuvant or neoadjuvant setting • paclitaxel treatment can only be repeated after a treatment free interval for paclitaxel of at least 12 months • no prior vinorelbine treatment allowed **(only for patients entered in part B in the Afatinib + Vinorelbine combination before the 3rd May 2013 as per protocol amendment 6)** • patients with quickly progressing visceral disease will be excluded
Test products :	
dose:	BIBW 2992 (afatinib) dose 40 mg daily
mode of admin. :	Oral
Combination product:	
dose:	Paclitaxel 80 mg/m2 weekly upon treatment failure on BIBW 2992 (afatinib) monotherapy
mode of admin. :	Intravenous infusion over 60 min
Combination product:	
dose:	Vinorelbine 25 mg/m2 weekly upon treatment failure on BIBW 2992 (afatinib) monotherapy **No new patient entered in this treatment combination after 3 May 2013**
mode of admin. :	Intravenous infusion of about 10 minutes
Duration of treatment:	Continuous treatment in the absence of disease progression or undue adverse events
Criteria for efficacy:	Objective Response (OR) consisting of Complete Response (CR) and Partial Response (PR), Best Overall Response using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1), Progression-Free Survival (PFS), [redacted]
Criteria for safety:	Incidence and severity of adverse events to Common Terminology Criteria for Adverse Events (CTC s, AE Version 3.0), cardiac left ventricular function, changes in vital signs and safety laboratory parameters
Statistical methods:	Exploratory data analysis, calculate objective tumour response rate with 95% Clopper-Pearson confidence interval, descriptive statistics. Futility analysis based on objective response in first 20 evaluable patients.

FLOW CHART A (BIBW 2992 (AFATINIB) MONOTHERAPY)

Follow this flow chart if patient continues on BIBW 2992 (afatinib) Monotherapy	**Screening**	**Treatment Course 1 ****		**Treatment Course 2 and subsequent courses****	**End of Treatment *****	**Follow-up ******	**Additional Follow- up visits *******
Visit abbreviation	**SV***	**C1V1**	**C1V2**	**C2V1 to CnV1**	**EOT**	**FU 1**	**FU Vn**
Days	**Up to 14 days before treatment**	**Day 1**	**Day 15 (± 2 days)**	**Day 1 (± 2 days)**	**0-14 days after permanent discontinuation of BIBW 2992 #**	**28 days after EOT visit (± 7 days) #**	**Every 6 weeks after first FU Visit #**
Informed Consent [1]	X						
Demographics	X						
Medical History	X						
Review of In-/Exclusion criteria (For Part A – Monotherapy part of study)	X						
Complete physical examination [2]	X				X		
Limited physical examination[2]		X		X		X	X
Vital Signs	X	X	X	X	X	X	X
ECOG performance status	X	X		X	X	X	X
12 Lead ECG [3]	X		X	X[3]	X[3]		
ECHO or MUGA scan [4]	X[4]			X[4]	X[4]		
Safety lab [5]	X	X		X	X	X	X
Pregnancy test [6]	X	X		X	X		
Archived tissue sample available for central re-assessment of HER2-status.	X [7]						
Tumour assessment[8]	X			See schedule below	X[8]		
[redacted]		[redacted]			[redacted]		
Concomitant medications	X	X	X	X	X	X	X
Compliance Check BIBW 2992 (afatinib)			X	X	X		
Adverse events	X	X	X	X	X	X	X[9]
Dispense Trial drug		X		X			
BIBW 2992 (afatinib) treatment[10]		Continuous					
Termination of active treatment					X		
Trial Completion						X	X

Abbreviations for Visit types: SV = Screening Visit, C = Treatment course, V = Visit, EOT = End of Treatment Visit, FU = Follow-up Visit

* HER2-retesting on archived biopsies will be performed by a central laboratory. Inclusion into the trial will be based on documented HER2-status (see #7 below) –**No more patients will be screened after approval of amendment 6**

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

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

**** Patients who discontinue BIBW 2992 (afatinib) monotherapy trial treatment permanently should have a follow-up visit 28 days after the EOT visit. **See section 5.2.2.2** for AEs reporting during this period.

***** Patients who have not progressed and not started further treatment (i.e. not started on combination treatment as described in Flowchart B, or other antitumour treatment outside of this trial) should have further follow-up visits every 6 weeks until progression or start of further treatment.

The EOT, FU and all subsequent follow-up visits in Flow Chart A are only applicable to patients who are permanently withdrawn from the study during BIBW 2992 (afatinib) monotherapy.

1. Written informed consent must be obtained before any protocol specific screening assessments are performed. Informed Consent must include consent to collection of demographic data and consent to obtaining and re-testing of archived biopsy material for HER2-status and blood samples for tumour markers. Inclusion will be allowed on documented HER2-positive status in patient's files- **All patients who signed the written informed consent before the approval of amendment 6 by IRBs and IECs may continue in the trial- After approval of protocol amendment 6, no new informed consent must be signed as patient recruitment in part A will be stopped.**
2. Includes height (at screening only), respiratory rate, weight and body temperature. See section 5.2.5.1 for difference between a complete and limited physical examination
3. A 12-lead resting electrocardiogram (ECG) will be performed at Screening, on Day 15 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).
4. ECHO or MUGA will be performed at Screening, on Day 1 of Course 4 and then at every third course (Course 7, 10, 13 etc.), and at EOT (if not performed in the previous 8 weeks). Note: LVEF assessment does not need to be repeated at the Screening Visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment and the patient has given consent to utilising these results.
5. Includes haematology, serum biochemistry, coagulation and urinalysis (Baseline and EOT Visits only). See Section 5.2.3.
6. Pregnancy test is only to be performed if patient is of child bearing potential (See Section 3.3.3 exclusion criterion # 19). Also refer to Sections 5.2.2.2 Pregnancy and 3.3.4 Removal of patients from therapy or assessments
7. Archived tumour biopsy material to be collected at Screening Visit. The following tests will be done by the central laboratory: HER2 IHC and reflex FISH testing, HrR (ER and PgR) IHC including Allred.
8. 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. breast, pelvis, brain) using an appropriate method (CT scan, MRI). The same radiographic procedure must be used throughout the study (See Section 5.1.2). Bone scans and correlative imaging should be performed when clinically indicated. Assessment will be performed at screening and then every 6 weeks, calculated from the start of treatment (i.e. 2 courses). In the event of early discontinuation or an interruption/delay to treatment, the tumour assessment schedule should not be changed. Brain metastases are considered as non-target lesions. A brain MRI should be performed at baseline in cases of clinically known, stable brain metastases. Brain MRI should be done of the respective lesion(s) at baseline and subsequently at every

imaging time-point. Tumour assessment does not need to be repeated at the screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to the start of treatment and the patient has given consent to utilising these results. Tumour assessment is not required at EOT visit if progressive disease has already been documented at scheduled imaging assessment.

9. Only if treatment related or not resolved during 1st FU
10. If patient has shown disease progression (based on the clinical judgement of the investigator) on BIBW 2992 (afatinib) monotherapy the patient must commence combination therapy (i.e. VPC1V1) as soon as possible but within 21 days of documented progression (unless radiotherapy is required – see section 3.2). Refer to Flow Chart B below.

FLOW CHART B (BIBW 2992 (AFATINIB) & PACLITAXEL/VINORELBINE COMBINATION TREATMENT)

Follow this flow chart if paclitaxel or vinorelbine treatment added	**Treatment Course 1 ***			**Treatment Course 2 and subsequent treatment courses ***			**End of Treatment ****	**Follow-up *****	**Additional Follow- up visits ********
Visit abbreviation	**VPC1V1**	**VPC1V2**	**VPC1V3**	**VPC2V1 to VPCnV1**	**VPC2V2 to VPCnV2**	**VPC2V3 to VPCnV3**	**EOT**	**FU 1**	**FU Vn**
Days	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 1 (± 2 days)**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**0-14 days after permanent discontinuation of BIBW 2992 and Paclitaxel/ Vinorelbine #**	**28 days after EOT visit (± 7 days) #**	**Every 6 weeks after first FU Visit #**
Complete physical examination	X						X		
Limited physical examination [1]				X				X	X
Review Inclusion /exclusion criteria (for Part B – combination therapy part of study)	X								
Vital Signs	X	X	X	X	X	X	X	X	X
ECOG performance status	X			X			X	X	X
12 Lead ECG [2]	X			X[2]			X[2]		
ECHO or MUGA scan [3]	X			X[3]			X[3]		
Safety lab[4]	X			X			X[4]	X	X
Pregnancy test[5]	X			X			X		
Tumour assessment [6]	X[7]			See schedule below			X[6]		
[redacted]	[redacted]						[redacted]		
Concomitant medications	X	X	X	X	X	X	X	X	X
Compliance Check BIBW2992	X			X			X		
Compliance check Paclitaxel/Vinorelbine	X	X	X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X[9]

CBC assessment prior to administering chemotherapy	X	X	X	X	X	X			
Dispense Trial drugs	X	X	X	X	X	X			
BIBW 2992 (afatinib) treatment	Continuous								
Paclitaxel/Vinorelbine weekly[8]	X	X	X	X	X	X			
Termination of active treatment							X		
Trial Completion								X	X

Abbreviations for Visit types: VPC = Course of combination treatment with BIBW 2992 (Afatinib) + either Paclitaxel or Vinorelbine **before the 3rd May 2013 or Course of combination treatment with BIBW 2992 (Afatinib) + Paclitaxel only for patient starting in part B after the 3rd May 2013** or, V = Visit, EOT = End of Treatment, Visit, FU = Follow-up Visit

* All courses are 3 weeks in duration (21days). Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met**- All patients who have been screened in the trial before protocol amendment 6 approval by IRBs and IECs will be able to enter in part B of the trial if they meet the inclusion/exclusion criteria for part B**

** If the decision to permanently discontinue trial treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. **From May 3rd, 2013, patients who will switch from the combination treatment Vinorelbine+Afatinib to Paclitaxel +Afatinib will have to undergo an EOT visit before the switch. Those patients will have a second EOT visit when they will permanently discontinue part B. See Section 3.1**

*** All patients should have a follow-up visit 28 days after the EOT visit. See section 5.2.2.2 for AEs reporting during this period.

**** Patients who have not progressed and not started further treatment should have further follow-up visits every 6 weeks until progression or start of further treatment.

\# The EOT, FU and all subsequent follow-up visits in Flow Chart B, are only applicable to patients who are permanently withdrawn from BIBW 2992 (Afatinib) and vinorelbine/paclitaxel combination treatment.

1. Includes height (at screening only), weight and body temperature. See section 5.2.1 for difference between a complete and limited physical examination
2. A 12-lead resting ECG will be performed on Day 1 of Course 1 of combination therapy and then on Day 1 of every third course (Day 1 of Course 4 (VPC4V1), 7 (VPC7V1), 10 (VPC10V1) etc.), and at EOT (if not performed in the previous 8 weeks).
3. ECHO or MUGA will be performed within 2 weeks of Day 1 of Course 1 of combination therapy and then on Day 1 of Course 4 (VPC4V1) and then at every third course (Course 7 (VPC7V1), 10 (VPC10V1), 13 etc.), and at EOT (if not performed in the previous 8 weeks).
4. Includes haematology, serum biochemistry, coagulation and urinalysis (Baseline and EOT Visits only. See Section 5.2.3). Once patients are treated with paclitaxel or vinorelbine combination, weekly CBC need to be taken and results available and assessed prior to treatment.
5. Pregnancy test is only to be performed if patient is of child bearing potential. Also refer to Sections 5.2.2.2 Pregnancy and 3.3.4 Removal of patients from therapy or assessments

6. Tumour assessments should include CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. breast, pelvis, brain) using an appropriate method (CT scan, MRI). The same radiographic procedure must be used throughout the study (See Section 5.1.2). Bone scans and correlative imaging should be performed when clinically indicated. During combination therapy assessment will be performed every 6 weeks calculated from the start of combination therapy (i.e. 2 courses). In the event of early discontinuation or an interruption/delay to treatment, the tumour assessment schedule should not be changed. Brain metastases are considered as non-target lesions. A brain MRI should be performed at baseline in cases of clinically known, stable brain metastases. Brain MRI should be done of the respective lesion(s) at baseline and subsequently at every imaging time-point. Tumour assessment is not required at EOT visit if progressive disease has already been documented at scheduled imaging assessment.
7. A tumour assessment is not required to be repeated at VPC1V1 if it has already been performed at the point when PD was determined on BIBW 2992 (afatinib) (Monotherapy) in Flow Chart A and is within 3 weeks prior to starting combination treatment. If radiotherapy is given prior to commencing combination therapy, a tumour assessment must be performed at VPC1V1 to document the baseline status at start of combination therapy.
8. Paclitaxel 80mg/m^2 i.v. or Vinorelbine 25 mg/m^2 i.v. will be administered weekly once a patient progressed on BIBW 2992 (Afatinib) monotherapy. Special inclusion /exclusion criteria apply. Each administration should be preceded by CBC assessment and measurement of weight and body temperature. Pre-medications should be applied per product labelling. Refer to Section 4.
9. Only if treatment related or not resolved during 1st FU

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Amino Transferase
ALTTO	The Adjuvant Lapatinib and/Or Trastuzumab Treatment Optimisation study
AUC	Area under the Curve
BC	Breast Cancer
CA	Competent Authority
CBC	Complete Blood Count
CI	Confidence Interval
CK-ELPR	Creatinine Kinase Electrophoresis
CPK	Creatinine Phosphokinase
CR	Complete Response
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DMC	**Data Monitoring Committee**
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ELPR	Electrophoresis
EOT	End of Treatment
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen Receptor
EU	Europe
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HPC	Human Pharmacology Centre
HER2	Human Epidermal Growth Factor Receptor
HR	Hazard Ratio

HrR	Hormone Receptor
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IHC	Immunochemistry
INR	International Normalised Ratio
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LVEF	Left Ventricular Ejection Fraction
MAB	Monoclonal antibody
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
MOA	Mode of Action
MRI	Magnetic Resonance Imaging
MST	Medical Subteam
MUGA	Multiple Gate Acquisition
NeoALTTO	The Neo Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation study
NIMP	Non Investigational Medicinal Product
NSCLC	Non Small Cell Lung Cancer
OPU	Operative Unit
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PI	Prescribing Information
PK	Pharmacokinetic
PR	Partial Response
p.o.	per os (oral)
PCC	Protocol Challenge Committee
q.d.	quaque die (once a day)
QLQ	Quality of Life Questionnaire
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
s.c.	subcutaneous
SD	Stable Disease
SmPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor

TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TKI	Tyrosine Kinase Inhibitor
TMM	Team Member Medicine
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TNM	Tumour (lymph) Nodes, Metastasis
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
US	United States

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Breast cancer is the most common malignant disease in women in the Western world. In the US, more than 200,000 women will be diagnosed with breast cancer every year, and approximately a fifth will eventually die of the disease (R09-5656).

Aberrant Epidermal Growth Factor Receptor (EGFR) and Human Epidermal Growth Factor Receptor (HER2) signalling has been causally associated with cancer cell proliferation and decreased survival (R08-1376, R08-1380, R08-1386). The HER2 proto-oncogene encodes a 185 kDa transmembrane receptor kinase which is amplified and/or overexpressed in 25% - 30% of human breast cancers. Tyrosine phosphorylation of the HER2 receptor leads to activation of specific signal transduction pathways including the ras/MAP kinase cascade with transduction pathways ultimately converging on the cell nucleus with activation of the receptor (R01-0299). The association between HER2-overexpression and poor prognosis in node-positive and advanced breast cancer has been shown by a number of studies (R06-0964, R08-1382, R08-1384, R08-1392, R08-1393, R08-1394, R08-1395, and R08-1396). Recent studies have also shown the prognostic value of HER2-overexpression in patients with node-negative breast cancer (R08-1397).

Based on this association between the members of EGFR/HER2 family and worse clinical outcome, antibodies and small molecules that specifically target these receptor tyrosine kinases were developed for therapeutic use.

1.2 DRUG PROFILE

BIBW 2992 (afatinib) is a novel oral EGFR/HER2 inhibitor that offers the chance to control both recurrent as well as distant metastatic disease on an outpatient basis with continuous treatment. It is a potent, irreversible, combined EGFR/HER2 inhibitor both in vitro and in vivo[1]. Receptor tyrosine kinases other than the ErbB (Class I) family and non-receptor type tyrosine kinases were not inhibited. Continuous treatment with BIBW 2992 (afatinib) has the potential to provide significant benefit to patients with advanced malignancies by inducing tumour responses or slowing of tumour progression and metastasis. Due to its mechanism of action, treatment with BIBW 2992 (afatinib) will result in a more selective antitumour activity than classical cytotoxic chemotherapeutics which have an indiscriminate effect on all proliferating cells. BIBW 2992 (afatinib) final formulation is available in 20, 30, 40 and 50 mg film-coated tablets to be used for clinical trials up to Phase III.

The available clinical efficacy data for BIBW 2992 (afatinib) is based on phase I and phase II studies and indicate that patients with advanced solid tumours may benefit from BIBW 2992 (afatinib). Three phase IIb/III and phase III trials in patients with advanced non-small cell lung cancer (NSCLC) and a phase III trial in breast cancer are currently ongoing. Objective responses have been observed to date in patients with metastatic NSCLC, breast cancer (BC),

[1] Since this clinical trial protocol was produced, the mechanism of action of BIBW 2992 (afatinib) has been updated (P12-09544)

oesophageal cancer, cholangiocarcinoma and others in monotherapy and combination treatment in phase I and phase II trials (P09-10056, P08-11756, P10-01317 and P09-10626). Ongoing and recently completed phase II studies show clinical activity of BIBW 2992 (afatinib) in patients with EGFR mutation positive NSCLC and patients with HER2 positive breast cancer (U10-3047-01, U10-2018-01, U10-1598-01, U09-2463-03)

Overall 14 patients with metastatic breast cancer were included in the Phase I BIBW 2992 (afatinib) monotherapy trials. Of these 4 patients showed stable disease (SD) as best response to treatment with duration of at least 12 weeks in 3 patients and duration of 24 weeks in 1 patient. Another five patients with metastatic breast cancer (mBC) were entered into Study 1200.20, a Phase I BIBW 2992 (afatinib) trial in combination with docetaxel. BIBW 2992 (afatinib) was administered on days 2-4 following a docetaxel administration on day 1, in a 21 day course. One mBC patient showed a complete response (CR), two a partial response (PR) while on BIBW 2992 (afatinib) treatment and another patient had stable disease.

Full details of the clinical pharmacology, toxicology, clinical pharmacokinetics and safety data can be found in the current Investigator Brochure for BIBW 2992 (afatinib) (U03-3218)

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Patients who received neo-adjuvant and/or adjuvant HER2-targeted treatment will be recruited into this trial. Trastuzumab is currently registered as HER2-targeted treatment in the adjuvant and 1st line metastatic setting in combination with chemotherapy and as monotherapy in later lines of treatment of BC (R10-4385). Lapatinib is registered as 2nd line treatment in combination with capecitabine in HER2-pos. mBC patients after failure of 1st line trastuzumab therapy. Nevertheless both compounds are used outside of their registered indications (off-label) in earlier lines. One recently published trial showed benefit for the combination of both targeted agents even in heavily pre-treated mBC patients (U10-1491-01). The working hypothesis behind the combination of two targeted agents, trastuzumab, a monoclonal antibody (MAB) and lapatinib, a tyrosine kinase inhibitor (TKI), is the different mode of action (MOA) leading to additive efficacy on different levels of signal transduction pathways, thus causing total HER2-inhibition. Most recently several trials used trastuzumab and lapatinib alone or in combination in the neo-adjuvant setting (NeoALTTO, Gepar-Quatro – R10-5364) or in the adjuvant setting (ALTTO – R10-5362) in combination with paclitaxel. If HER2-positive BC-patients already receive taxanes and both registered targeted agents early on in therapy, treatment options in the metastatic setting are limited. Once these patients relapse, they have a high unmet medical need for innovative therapeutics and treatment algorithms. Currently there are no therapies available for patients who failed total HER2-blockade and little is known about the pathological mechanisms involved. Accordingly there is an urgent need to develop treatments for this patient population.

BIBW 2992 (afatinib) is a dual irreversible EGFR/HER2-inhibitor and has shown clinical efficacy in HER2-overexpressing patients with metastatic breast cancer who failed prior trastuzumab treatment. This trial provided proof of concept to further evaluate BIBW 2992 (afatinib) in a larger cohort of HER2-positive metastatic breast cancer patients, who failed prior trastuzumab treatment. Moreover BIBW 2992 (afatinib) unlike lapatinib is an irreversible EFGR/HER2 inhibitor with clinical efficacy in EGFR driven tumours (P09-06809). Preclinical data further support the efficacy of BIBW 2992 (afatinib) in trastuzumab resistant, HER2-positive (SUM 190 PT) breast cancer cell lines and HER2-negative SUM 149 PT): The latter suggests that heterodimerisation of ErbB receptors (HER2/EGFR) even in HER2-positive disease plays an important role (P09-08104, U09-1454-01, U09-1455-01) in tumour growth suppression of HER2-positive/trastuzumab resistant cell lines. BIBW 2992 (afatinib) combines well with paclitaxel and vinorelbine preclinically and clinically (U03-3218, U10-1491-01, P09-10626, and P09-05119)

As BIBW 2992 (afatinib) has a different MOA from trastuzumab and lapatinib, shows monotherapy efficacy in heavily pre-treated patients comparable to that of trastuzumab/lapatinib combinations in the Blackwell trial (R09-4140) and clinically truly is a dual EGFR/HER2 inhibitor, BIBW 2992 (afatinib) monotherapy provides an interesting and rational treatment to these patients in 1st line mBC and the proposed trial design provides an interesting and rational alternative. In case patients don't respond or relapse on monotherapy they may be "rescued" by addition of chemotherapy, i.e. paclitaxel weekly if the prior

paclitaxel-free interval is more than 12 months or vinorelbine in all other cases **(only for patients commencing treatment with this combination prior to 03 May 2013)**. The latter is based on oncogene addiction which has let to the use of "Herceptin beyond progression" over the past two decades (R09-2787). The current trial will investigate the use of BIBW 2992 (afatinib) beyond progression in breast cancer.

2.2 TRIAL OBJECTIVES

This open label phase II study will investigate the efficacy and safety of BIBW 2992 (afatinib) alone and in combination with weekly treatment with paclitaxel or vinorelbine (in patients who progress on BIBW 2992 (afatinib) monotherapy only) as a new treatment algorithm in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the neoadjuvant and/or adjuvant setting.

2.3 BENEFIT - RISK ASSESSMENT

HER2-positive breast cancer still has a poor prognosis despite recent advances which came with the introduction of targeted trastuzumab treatment into therapy. Trastuzumab is a standard component of HER2 positive breast cancer treatment although its use is associated with cardiotoxicity. Patients develop resistance to trastuzumab or display primary resistance to trastuzumab during therapy or upfront, but still most patients continue trastuzumab beyond progression in combination with other cytotoxic drugs with some therapeutic benefit as there are not many options available. Lapatinib, a small molecule reversible, dual EGFR/HER2-TKI is registered in combination with capecitabine for the treatment of 2nd-line HER2-positive mBC.

Both trastuzumab and lapatinib seem to complement each other by a slightly different MOA thus combination of both targeted treatments is supposed to give added benefit to patients. Still lapatinib clinically is not being developed in EGFR-driven malignancies whereas BIBW 2992 (afatinib), a small molecule irreversible, dual EGFR/HER2 RTKI not only showed preclinical and clinical efficacy in trastuzumab resistance, but also showed clinical efficacy in EGFR-driven malignancies (P09-06809). In trastuzumab resistance, alternative pathways, among those the EGFR-pathway, play an important role. In patients, who received various targeted treatment options early in treatment once relapse/resistance develops, targeting these alternative pathways may become crucial for patients' prognosis. As such BIBW 2992 (afatinib) monotherapy treatment may provide a reasonable therapeutic approach in a scenario, where patients early on in therapy have received both registered HER2-targeted treatments and nonetheless relapse: For these patients at present there are no treatment recommendation/ algorithms available.

BIBW 2992 (afatinib) combines well with paclitaxel ~~and vinorelbine~~. Side effects observed for this combination are consistent with what is known for either compound alone (see IB, U03-3218, ~~to vinorelbine interim report (U10-1491-01)~~ and to SmPC).**The Data Monitoring Committee (DMC) of the LUX-Breast 1* trial (EUDRA CT No.: 2009-015476-98, NCT01125566) conducted a benefit-risk analysis as pre-specified in the clinical trial protocol. A DMC recommendation which was issued on 26 April 2013 concluded, that based on the benefit-risk analysis, treatment in the experimental arm (afatinib 40 mg + vinorelbine 25 mg/m^2 weekly i.v.) should be discontinued.**

The benefit-risk analysis was based on data from over half of the planned number of patients enrolled. The DMC concluded that there is a low likelihood of study 1200.75 meeting the pre-defined criteria for increased efficacy in terms of PFS. In addition, a high rate of treatment discontinuations and dose reductions as well as a higher rate of serious adverse events and deaths was observed in the experimental arm compared to the control arm trastuzumab + vinorelbine.

Boehringer Ingelheim and the Executive Committee of the trial agreed to follow the DMC's recommendation and decided to stop further randomisation into trial 1200.75 and to discontinue further treatment with the combination of afatinib and vinorelbine.

Since one of the treatment options in Part B of Trial LUX-Breast 2 is the combination of afatinib + vinorelbine, and in light of the unfavourable benefit-risk observed in 1200.75 Boehringer Ingelheim decided as a precautionary measure to stop the inclusion of new patients into the afatinib + vinorelbine combination in Part B of LUX-Breast 2 on the 3rd May 2013. Continuation of vinorelbine+ BIBW2992 (afatinib) can only be allowed for patients already on treatment before the 3rd May 2013 and benefitting from the treatment combination. For new patients this combination will no longer be offered after the 3rd May 2013. Part A of the trial and continuation of treatment with paclitaxel in Part B were not affected.

Furthermore a decision has been made to stop further enrolment of new patients in Part A:

-Afatinib+VNR Treatment in part B is no longer an option, as the latter showed an unfavourable benefit/risk ratio in trastuzumab pre-treated patients leading to termination of the pivotal trial 1200.75. As a consequence the eligible patient population to be included in part A will narrow down, as patients receiving adjuvant/neoadjuvant paclitaxel are not readily rechallenged with paclitaxel when receiving 1st line mBC treatment. This will generate further difficulties for recruitment.

- In addition since the trial 1200.98 started, pertuzumab/trastuzumab + docetaxel intended for patients who have not received prior treatment for metastatic breast cancer with an anti-HER2 therapy or chemotherapy, has been approved in 2012 and is becoming standard of care wherever available. This will establish further hurdles for a timely recruitment into part A of trial 1200.98.

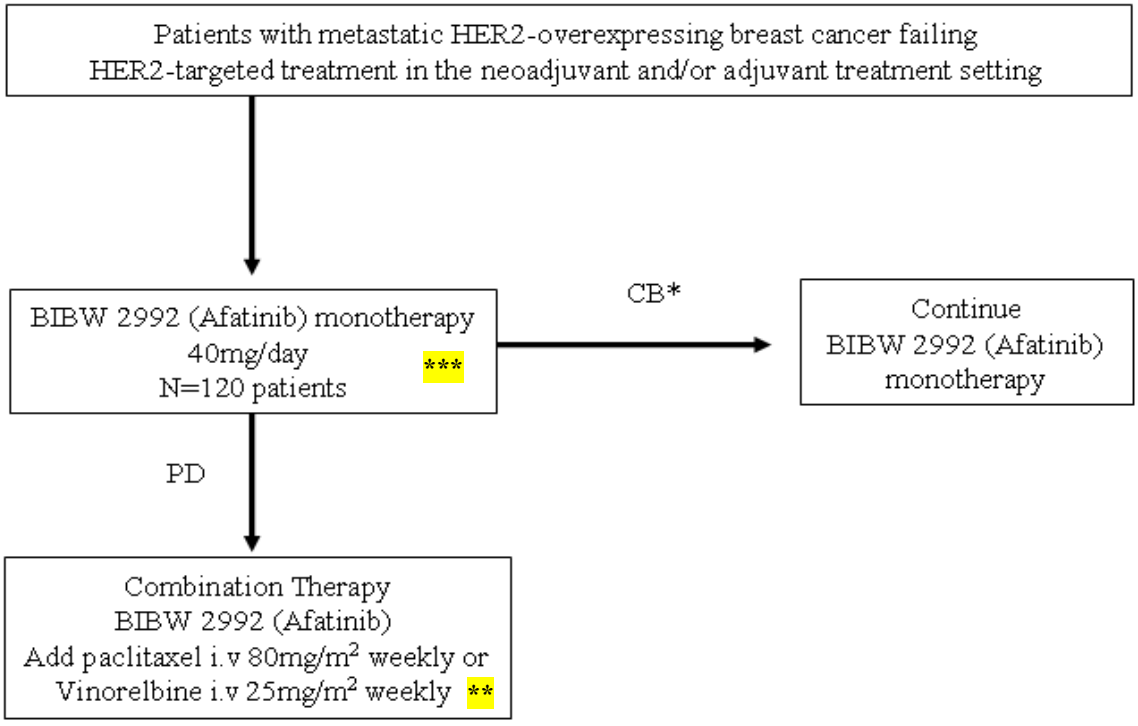
-Approximately 60 out of 69 patients enrolled to date in this trial have received trastuzumab only based regimens as prior treatment in the adjuvant and neoadjuvant setting. By the time of approval of amendment 6, it is expected that approximately 80 patients will have been treated in this trial. As only 9 patients have received lapatinib or a combination of lapatinib and trastuzumab as prior treatment so far, the efficacy analysis will be driven by trastuzumab pretreated patients. 80 patients will address the efficacy of afatinib in the trastuzumab-pretreated patients with a high statistical probability (see section 7.6 for details)

~~**In conclusion, the potential benefits to be expected from BIBW 2992 (afatinib) monotherapy or its combination with paclitaxel weekly or vinorelbine weekly are likely to outweigh its risks in the population described.**~~

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open label study designed to investigate the efficacy and safety of BIBW 2992 (afatinib) alone and in combination with weekly paclitaxel or weekly vinorelbine as treatment in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the neoadjuvant and/or adjuvant setting. All patients will start on BIBW 2992 (afatinib) monotherapy. In case of progression of disease on monotherapy they will commence combination therapy as described above (also compare Figure 3.1:1 below).



CB* = CR+PR+SD

**** From the 3rd May 2013, patients will only be able to enter in the combination therapy BIBW2992 (Afatinib) and Paclitaxel i.v 80mg/m² weekly**

*****patient recruitment will be stopped after approval of protocol amendment 6, however patients who signed PIC before that date will proceed as per schedule described below**

Figure 3.1: 1 Schematic of Trial Design

All patients will initially undergo a 2 week screening period during which time their eligibility will be confirmed. Eligible patients will receive 40 mg/day BIBW 2992 (afatinib) monotherapy in 3-weekly treatment courses for treatment of HER2-overexpressing metastatic breast cancer (mBC) (1st line patients), until progression of disease (PD) assessed by RECIST (1.1) Refer to Flow Chart A and Figure 3.1:1 above. In the event of treatment-

related adverse events, BIBW 2992 (afatinib) doses will be reduced according to Dose reduction scheme (Table 4.1.4: 1).

Patients showing disease progression on BIBW 2992 (afatinib) monotherapy (then eligible for 2nd line mBC treatment) will then receive:

- **before the 3rd May 2013: chemotherapy, i.e. paclitaxel or vinorelbine weekly as decided by the investigator, which will be added to BIBW 2992 (afatinib).**
- **after the 3rd May 2013: paclitaxel weekly, which will be added to BIBW 2992 (afatinib).**

See Flow Chart B and Figure 3.1:1 above. Chemotherapy must commence as soon as possible but within 21 days of documented progression (unless radiotherapy is required – see section 3.2).

For patients on treatment with the combination of vinorelbine + BIBW 2992 (afatinib) in Part B of the trial on the 3rd May 2013, the investigator should perform a thorough benefit-risk analysis to assess whether the patients may continue on this combination. The investigator should then discuss and agree this with the patient whether the combination will be continued:

- **Should the decision be to continue treatment with vinorelbine + BIBW 2992 (afatinib) or to change the chemotherapy regimen from vinorelbine to paclitaxel, the patients will remain on trial and the investigator should document this in the patient's notes (the patients will need to met the inclusion and exclusion criteria for paclitaxel to be able to switch treatment regimen).**

- **Should the decision be to discontinue treatment with the combination, the investigator should document this in the patient's notes and an EOT visit should be conducted. Patients will need to be followed up as per protocol after the EOT visit.**

With protocol amendment 6 the sponsor will stop recruitment into the trial (part A), pending approval by IRBs and IECs. (See section 3.3.4.2 and Section11section 11). All patients who already signed the PIS/PIC when the recruitment is stopped will proceed as planned per protocol

An early stopping rule will be implemented to minimise the number of patients treated if BIBW 2992 (afatinib) was ineffective in the given therapeutic setting. See Section 7.3.4.1 for further details.

All patients will attend an End of Treatment (EOT) Visit when they discontinue the study treatment permanently. All patients will then have a follow-up visit 28 days after the EOT Visit. Following this, patients who still have not experienced disease progression and not started further treatment, will have further follow- up visits every 6 weeks until disease progression or start of further treatment.

After a patient has completed participation in the trial, information on post-trial treatment, best response and vital status will be collected, if available.

The end of the study is when the last patient entered has either experienced a second disease progression or started further treatment.

3.1.1 Administrative structure of the trial

The investigators participating in the trial must have experience in this type of trial and investigations.

The co-ordinating investigator, who will sign the clinical trial report of this trial, has been appointed by Boehringer Ingelheim. The co-ordinating investigator has experience in this type of trial and investigations.

Safety laboratory assessments and tumour marker assessments are performed at the investigator site. Analysis of HER2- and HrR status will be performed centrally by an authorized laboratory. The results of HER2-analysis don't need to be available to confirm the eligibility of the patient for trial participation. They will be used for retrospective analyses only.

Tumour images have to be assessed by the investigator at the site and will be used for clinical decisions on whether or not to continue treatment on study.

There will be no Steering Committee or Data Monitoring Committee for this trial.

All trial relevant documentation is stored in Boehringer Ingelheim's Clinical Trial Master File (CTMF). Trial relevant documentation which has to be at the trial site is filed in the investigator site file (ISF) at the investigator site.

On-site monitoring will be performed by Boehringer Ingelheim or a CRO appointed by Boehringer Ingelheim. It is intended to have a discussion on the early stopping of the trial and that this will not be based on a discussion with all investigators.

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

The primary objective of this trial is to investigate the efficacy and safety of BIBW 2992 (afatinib) alone and in combination with weekly treatment with paclitaxel or vinorelbine (in patients who progress on BIBW 2992 (afatinib) monotherapy only) as first line treatment in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the neoadjuvant and/or adjuvant setting. Patients must be HER2-positive by documented HER2-status in their files, have been treated with prior HER2-targeted treatment and have archived tissue samples available for central re-assessment of HER2-status.

Patients meeting the eligibility criteria will receive BIBW 2992 (afatinib) monotherapy at a dose of 40 mg/d until progression of their disease whereupon patients will additionally receive either paclitaxel weekly at a dose of 80 mg/m^2 or vinorelbine at a weekly dose of 25 mg/m^2. **From the 3rd May 2013 after progression on BIBW 2992 (afatinib) monotherapy, patients will only be allowed to additionally receive paclitaxel weekly at a dose of 80**

mg/m^2 in part B of the trial. Patients will not be able to enter in the combination part of the trial (part B) and receive vinorelbine treatment (section 2.3). With protocol amendment 6 the sponsor will stop recruitment into the trial (part A), pending approval by IRBs and IECs. (See section 3.3.4.2 and section 11)

Disease status will be assessed clinically by the investigator at the end of the first treatment course and each following treatment course. At the time of progression the investigator will decide which study chemotherapy treatment to add (i.e. paclitaxel or vinorelbine). Patients allocated to paclitaxel treatment must not have received paclitaxel treatment within a year of re-starting. Patients allocated to vinorelbine treatment should not have previously received vinorelbine treatment.

If any metastatic sites associated with the first disease progression (i.e. progression on first line treatment with afatinib) require short course palliative radiotherapy, patients should continue on the afatinib monotherapy schedule (part A) whilst radiotherapy is administered. Details of the radiotherapy treatment administered should be documented on the CRF. Treatment with combination therapy (part B) should commence 3-4 weeks after completion of radiotherapy. Visit VPC1V1 should be performed prior to commencing combination therapy and should include a tumour assessment.

Patients with clinical benefit will continue to receive BIBW 2992 (afatinib) monotherapy. If patients experience further disease progression after treatment with BIBW 2992 (afatinib) and chemotherapy i.e., paclitaxel, or vinorelbine, they will be withdrawn from the study. All patients will have a Follow-up Visit, 28 days after the End of Treatment Visit. Patients who have not progressed and not started further treatment should have further follow-up visits every 6 weeks until disease progression or start of further treatment.

After a patient has completed participation in the trial, information on post-trial treatment, best response and vital status will be collected, if available.

3.3 SELECTION OF TRIAL POPULATION

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

All patients that will be included into the trial must have been diagnosed with histologically confirmed HER2-overexpressing disease breast cancer and must have stage IV metastatic disease.

3.3.2 Inclusion criteria

These inclusion criteria apply to both mono and combination therapy (Parts A and B)

Inclusion criteria for Part A (Flow Chart A)

1. Female patients ≥18 years.

2. Proven diagnosis of HER2-overexpressing, histologically confirmed breast cancer. Patients must have an archived tissue sample available for central re-assessment of HER2-status. (The results of this analysis are not required to be available to confirm the eligibility of the patient to take part in the study).

3. Stage IV metastatic disease.

4. At least one measurable lesion according to RECIST 1.1. Skin, bone and brain lesions are considered non-target lesions.

5. Eastern Cooperative Oncology Group (ECOG) score of 0,1 or 2 (See Appendix 2).

6. Life expectancy of at least six (6) months.

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

8. Must have failed or progressed on either trastuzumab or lapatinib or trastuzumab and lapatinib treatment in the neoadjuvant and/or adjuvant setting.

Inclusion criteria for Part B (Flow Chart B) – BIBW 2992 (afatinib) combination therapy with paclitaxel ~~and vinorelbine only~~

9. Must have failed or progressed trastuzumab or lapatinib or trastuzumab and lapatinib treatment in the neoadjuvant and/or adjuvant setting and on BIBW 2992 (afatinib) monotherapy in the 1st line metastatic setting.

10. Must be eligible for re-treatment with paclitaxel, refer to exclusion criterion (29). ~~or vinorelbine, refer to exclusion criterion (30)~~

3.3.3 Exclusion criteria

These exclusion criteria apply to both monotherapy and combination therapy (Parts A and B)

Exclusion criteria for Part A – BIBW 2992 (afatinib) monotherapy only (See Flow Chart A)

1. Requirement for treatment with any of the prohibited concomitant medications listed in Section 4.2.2 (restrictions).

2. Must not have quickly progressing visceral disease.

3. Known pre-existing interstitial lung disease.

4. Prior first line therapy for metastatic breast cancer

5. Radiotherapy, chemotherapy, immunotherapy, trastuzumab or lapatinib treatment or surgery (other than biopsy) within 4 weeks prior to trial treatment. Treatment with palliative radiotherapy (short course to non-target lesions) is allowed.

6. Hormone therapy for breast cancer within 2 weeks prior to trial treatment.

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

8. Any other current malignancy or malignancy diagnosed within the past five (5) years (other than bilateral primary breast cancer, metastases to the contralateral breast, non-melanomatous skin cancer and in situ cervical cancer).

9. 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.

10. 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.

11. Myocardial infarction within 6 months prior to trial treatment.

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

13. 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.

14. Absolute neutrophil count (ANC) < 1.5 x 10^9/L

15. Calculated Creatinine clearance < 60 ml / min (Cockcroft formula – Appendix 1) or serum creatinine > 1.5 times upper limit of normal (Note that both values must be checked and both must be within the limits for inclusion)

16. Bilirubin > 1.5 times upper limit of normal.

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

18. Women of childbearing potential, unwilling to use a medically acceptable method of contraception during the trial. Acceptable methods of contraception include surgical sterilisation (tubar ligation/hysterectomy), 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 intra-uterine device (IUD) (female and male condom, diaphragm and cervical cap must all 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 methods of contraception.

    NOTE: Women of child bearing potential, must also continue to use effective contraception for at least 1 month after treatment has ended if they have been treated with BIBW 2992 monotherapy, for at least 3 months after treatment has ended if they have been additionally treated with vinorelbine and for at least 6 months after treatment has ended, if they have been additionally treated with paclitaxel during the study.). In any case continuing measures after ceasing study medication should be done based on the latest information available for the study drugs: IB (U03-3218) for BIBW2992 and SPC/PI for paclitaxel and vinorelbine.

19. Pregnancy or breast-feeding (lactation).

20. Patients unable to comply with the protocol.

21. Known Hepatitis B infection, known hepatitis C infection or known HIV carrier.

22. Known or suspected active drug or alcohol abuse.

23. Any contraindications for therapy with paclitaxel ~~**or vinorelbine.**~~

24. Known hypersensitivity to BIBW 2992 (afatinib) or the excipients of any of the trial drugs including paclitaxel ~~**and vinorelbine.**~~

25. Treatment with an investigational drug within the previous 4 weeks prior to study or concurrent participation in another clinical trial.

26. Prior treatment with EGFR/HER2-targeted small molecules or antibodies other than trastuzumab and lapatinib in the neoadjuvant and/or adjuvant setting.

27. Platelet count < 100 x 10^9/L for BIBW 2992 (afatinib) monotherapy.

Exclusion criteria for Part B – BIBW 2992 (afatinib) combination therapy only (see Flow Chart B) – Exclusion criteria 12 and 14 has to be rechecked before starting treatment in part B

28. Prior treatment with EGFR/HER2-targeted small molecules or antibodies other than trastuzumab and lapatinib in the neoadjuvant and/or adjuvant setting, and/or BIBW 2992(afatinib) in the 1st line setting.

29. ~~If treatment with paclitaxel is planned,~~ Patient must not have received prior treatment with paclitaxel in the past 12 months. The timeframe between paclitaxel treatments needs to be 12 months to allow re-start of paclitaxel.

~~30. If treatment with vinorelbine is planned, patient must not have received prior vinorelbine treatment.~~

30 Platelet count of < 100000/mm^3 for BIBW 2992 (afatinib) combination treatment with paclitaxel ~~or BIBW2992 (afatinib) combination with vinorelbine.~~

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient has to be withdrawn from study therapy in case any of the following applies:

1. The patient withdraws consent to further study treatment.
2. Documented progressive disease (see Appendix 3) on combination treatment of BIBW 2992 (afatinib) and paclitaxel/vinorelbine, i.e. documented 2nd progression whilst on trial
3. The patient is no longer able to receive any of the study treatments (e.g. adverse events, pregnancy, concomitant diagnoses, concomitant therapies or administrative reasons).
4. Significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made after discussion between the local clinical monitor of the sponsor and the investigator
5. Diagnosis of interstitial lung disease
6. If a patient experiences deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥3.
7. Further dose reductions considered necessary but not allowed according to the protocol (for exceptions, refer to Section 4.1.4.)
8. The patient receives any of the prohibited medications listed in the current SmPC or prescribing information (PI) for paclitaxel and vinorelbine (See Section 4.2)

Except for reasons 1, 2, 5 and 6, it should be attempted to retain the patient in the study and to perform additional follow-up visits at the tumour assessment schedule until progression of disease or start of new treatment.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial if applicable **(See section 2.3)**
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).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Patients will initially be treated with BIBW 2992 (afatinib) 40mg/day monotherapy until 1st disease progression on trial. Upon the latter, patients will additionally receive either paclitaxel weekly at a dose of 80 mg/m^2 or vinorelbine at a weekly dose of 25 mg/m^2 **(See section 3.1)**. ~~**In case there is a timeframe of less than 12 months between paclitaxel treatments, patients can only receive vinorelbine, otherwise it will be investigator's choice of combination treatment.**~~ The manufacturers for each of the products are listed in Section 4.1.1. All three study treatments will be supplied by Boehringer Ingelheim to the investigator for this study.

4.1.1 Identity of BI investigational product and comparator products

Substance (INN):	**BIBW 2992 (afatinib)**
Pharmaceutical form:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20mg, 30mg and 40mg film-coated tablets (the dose of BIBW 2992 (afatinib)) in the film-coated tablets is related to the free base equivalent of BIBW 2992 (afatinib).
Daily Dose:	40mg
Duration of use:	Continuous daily dosing until disease 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

Substance (INN) Paclitaxel

Paclitaxel is a registered commercially available cytotoxic drug. Paclitaxel will be provided by the sponsor

Pharmaceutical form:	Vial containing 6mg/ml concentrate for solution for infusion
Source:	Commercially available paclitaxel will be provided by the sponsor
Unit strength:	Paclitaxel vials containing 30 mg and 150 mg paclitaxel as 6 mg/ml solution for infusion

Weekly Dose:	Paclitaxel 80 mg/m^2 once weekly upon treatment failure on BIBW 2992 (afatinib) monotherapy in case there is a timeframe of $\geq$ 12 months between this and any previous paclitaxel treatment
Duration of use:	Weekly in a 3-weekly course (21 days). Patients will be eligible for repeated treatment courses in the absence of clinical disease progression or undue adverse events.
Route of administration:	Intravenous
Posology:	Intravenous infusion over a period of 60 minutes.
Additional information:	Paclitaxel should be administered according to the Summary of Product Characteristics (SmPC). The SmPC recommendations for pre-administration laboratory assessments and supportive care should be followed. In the study Paclitaxel 80mg/m^2 i.v. may be given in the combination treatment part.

Substance (INN): **Vinorelbine (Navelbine®)**

Vinorelbine is a registered commercially available cytotoxic drug. Vinorelbine will be provided by the sponsor. **Patients will not receive vinorelbine after the 3rd May 2013 unless they are already receiving vinorelbine treatment on that date and are showing benefit from the treatment in the opinion of the investigator.**

Pharmaceutical form:	Concentrate for intravenous infusion
Source:	Pierre Fabre, Germany
Unit strength:	Vial containing 50mg as 10mg/ml solution for infusion
Duration of use:	Patients will be eligible for repeated treatment courses in the absence of clinical disease progression or undue adverse events.
Route of administration:	Intravenous, short infusion of about 10 minutes
Vinorelbine reconstitution:	Vinorelbine must be diluted prior to administration in a 20-50 ml volume of normal saline solution for injection or in 5 % glucose solution for injection
Posology:	25 mg/m² once weekly
Additional information:	Vinorelbine should be administered according to the SmPC. In the study Vinorelbine 25 mg/m² i.v. once weekly may be given in the combination treatment part. The SmPC recommendations for pre-administration laboratory assessments and supportive care should be followed.

4.1.2 Method of assigning patients to treatment groups

All patients will initially receive first line monotherapy with BIBW 2992 (afatinib) until disease progression **(With protocol amendment 6 the sponsor will stop recruitment into the trial (part A), pending approval by IRBs and IECs. (See section 3.3.4.2 and section 11)).**

If disease progression occurs at any time, then patients will receive additional paclitaxel (providing the patient has not received paclitaxel in the past 12 months) or vinorelbine treatment (providing patient has not previously received Vinorelbine) as second line therapy. The decision to treat the patient with either paclitaxel or vinorelbine is left to investigator judgement. Disease progression can occur at any time during the trial and the decision to commence combination therapy is always based on investigator judgement. It may be based on clinical assessment only (e.g. at the end of course 1) or on both clinical judgement and tumour imaging. In any case before combination treatment is started tumour imaging should take place. Combination therapy should commence as soon as possible but within 21 days of documented progression on monotherapy (unless radiotherapy is required – see section 3.2). If there are no signs of PD patients will continue on BIBW 2992 (afatinib) monotherapy.

After the 3rd May 2013 after progression on BIBW2992 (afatinib) monotherapy, patients will only be able to additionally receive paclitaxel weekly at a dose of 80 mg/m^2 Patient will not be able to enter in the combination part of the trial (part B) and receive vinorelbine treatment.

Patients are withdrawn from study treatment if their metastatic disease shows further progression whilst on the combination of BIBW 2992 (afatinib) and paclitaxel or BIBW 2992 (afatinib) and vinorelbine (2nd progression on trial) and/or in case of undue AEs.

4.1.3 Selection of doses in the trial

The Maximum Tolerated Dose (MTD) and recommended phase II dose for BIBW 2992 (afatinib) in combination with either paclitaxel 80 mg/m^2 or vinorelbine 25 mg/m^2 weekly was determined at 40 mg in a continuous regimen. The decision to administer weekly paclitaxel is based on publications which demonstrate the efficacy of this regimen (R11-0902).

The starting dose of BIBW 2992 (afatinib) in this trial was determined at 40 mg/day for monotherapy. 20 mg and 30 mg tablets of BIBW 2992 (afatinib) are available in case a patients need to undergo dose reduction. See Section 4.1.4 below. (U03-3218, U10-1491-01)

4.1.4 Drug assignment and administration of doses for each patient

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 40 mg BIBW 2992 (afatinib) every day for the first course (21 days).

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 (afatinib) tablets are film-coated and therefore should not

be chewed or crushed, but may if necessary, be administered via G-tube after dispersing the BIBW 2992 (afatinib) 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).

Missed doses of BIBW 2992 can be made up if taken within 6 hours of the regularly schedule time. Otherwise, the dose should be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis should not take a replacement dose.

In the event of treatment-related adverse events, the treatment with BIBW 2992 (afatinib) should be handled according to the schedule in Table 4.1.4: 1

Table 4.1.4: 1 BIBW 2992 (afatinib) Dose Reduction Scheme

AE type and grade	Action	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 anti-emetic 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 (afatinib) 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 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 (afatinib).

1 Baseline is defined as the CTCAE grade at 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 for drug related event. 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, 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.In the event of adverse events or serious adverse events which are not related to treatment, the investigator may choose to pause the trial 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 trial medication for more than 7 days, the afatinib doses and/or vinorelbine doses and/or paclitaxel doses will be missed and reasons will need to be documented in the eCRF. Treatment will be resumed at regular schedule thereafter and no dose reduction should occur.

Vinorelbine & Paclitaxel

Paclitaxel and Vinorelbine chemotherapy will be administered at the investigator site and will be prepared and administered in accordance with the respective current SmPC.

Weekly chemotherapy will be administered within treatment courses of 3 weeks. Haematology should be checked prior to commencing each weekly infusion and treatment should be delayed if platelet count < 100,000/mm^3 for combination treatment with vinorelbine or <100,000/mm^3 for combination treatment with paclitaxel.

The patient must be given supportive care during chemotherapy in accordance with the current SmPC and institutional guidelines for both paclitaxel and vinorelbine.

In the event of treatment related adverse events, the treatment dose of vinorelbine/paclitaxel will be missed (see below) in accordance with the guidance in the current SmPC. A summary of the current SmPC is provided in the ISF.

In the event of a missed dose due to adverse events, subsequent infusions and assessments will be done according to schedule (see Flow Chart B).

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 (i.e. to skip one dose of chemotherapy as well as BIBW 2992 (Afatinib) doses) allow the patient to recover, but no dose reduction should occur. If the investigator chooses to delay the medication for more than 7 days, the dose (one chemotherapy dose as well as BIBW 2992 (Afatinib) doses) will be missed and reasons will need to be documented in the eCRF. Treatment will be resumed at regular schedule thereafter.

In the event of treatment related adverse events, the treatment dose of vinorelbine or paclitaxel will be skipped in accordance with the guidance in the current summary of product characteristics (SmPC). A summary of the current SmPC for paclitaxel and vinorelbine is provided in the ISF. In the event of a skipped infusion due to adverse events, subsequent infusions and assessments should be resumed according to the original schedule and the tumour assessment should be performed according to the original schedule. In case of myelotoxicity, administration of chemotherapy will be skipped until recovery, i.e. neutrophil counts >1500/mm³ and thrombocyte counts > 100000/mm³ for vinorelbine or for paclitaxel. In general, for vinorelbine no dose adaptations for liver metastases or renal insufficiency are needed. In cases of severe hepatic impairment a dose reduction of vinorelbine to 20 mg/m² is recommended per SPC/PI and may be applied after causes for severe hepatic impairment on trial have been discussed between the Sponsor and the investigator. Paclitaxel treatment needs to be adapted in case of hepatic impairment (see SmPC). Growth factor support will be allowed, following ASCO Guidelines (R09-0871). Treatment should be continued within the regular schedule.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable in this trial.

4.1.5.2 Procedures for emergency unblinding

Not applicable in this trial.

4.1.6 Packaging, labelling, and re-supply

4.1.6.1 BIBW 2992 (afatinib)

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

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

- Study number (1200.98)
- 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. 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 reduction is necessary the patient will return to the clinic and new medication will be dispensed.

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

4.1.6.2 Paclitaxel

Paclitaxel will be supplied as a vial containing 6mg/ml concentrate for solution for infusion.

Vials/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number (1200.98)
- Product name (Paclitaxel)
- 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

4.1.6.3 Vinorelbine

Vinorelbine will be supplied as a vial containing 10mg/ml solution. This is a concentrate for the preparation of a solution for infusion.

Vials/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number (1200.98)
- Product name (Vinorelbine)
- 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

4.1.7 Storage conditions

BIBW 2992 (afatinib) must be stored in the original packaging. 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.

Paclitaxel and vinorelbine will be stored in accordance with the instructions on the current local label.

4.1.8 Drug accountability

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

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

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,
- If applicable, availability of the proof of appropriate licence(s) for the principal investigator

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

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

Symptomatic treatments of tumour-associated symptoms are allowed. Treatment with corticosteroids and bisphosphonates are allowed. Concomitant medications, or therapy to provide adequate care, may be given as clinically necessary. Restrictions in Section 4.2.2 apply.

All concomitant (non-oncological) therapies starting or changing during the trial are allowed but should be recorded in the e-CRF except for vitamins, appetisers or nutrient supplements. Trade name, indication, dose and dates of administration will be documented. If patients receive parenteral nutrition during the trial, the components need not be specified in detail. It should just be indicated as "parenteral nutrition". If a patient requires anaesthesia, it will be sufficient to indicate "anaesthesia" without specifying the details.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude Interstitial Lung Disease (ILD).

Rescue medications to reverse the actions of BIBW 2992 (afatinib), paclitaxel and vinorelbine are not available. Please refer to the current SPC for paclitaxel and vinorelbine and to the IB (U03-3218) for BIBW 2992 (afatinib) for further information. Side effects of trial medications should be treated symptomatically. Growth factor support, if required, will be used following ASCO Guidelines (R09-0871).

The investigator brochure lists the AEs expected for treatment with BIBW 2992 (afatinib) (U03-3218). Always refer to the most recent IB. Suggested treatments for diarrhoea, nausea, vomiting and rash/acne are described in Sections 4.2.2.3, 4.2.2.4 and 4.2.2.5.

During study participation symptomatic treatment of tumour associated symptoms is allowed. Concomitant medications or therapy to provide adequate care may be given as clinically necessary. All concomitant (non-oncological) medications which are taken between trial informed consent and the last follow-up visit should be recorded in the electronic case report form (eCRF) with the start and end of treatment dates, the total daily dose, the respective unit and the reason for use.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment, maintenance therapy for metastatic breast cancer or radiotherapy within 4 weeks (within 2 weeks for hormone treatment) prior to receiving trial drug until the EOT Visit. Treatment with palliative radiotherapy (short course to non-target lesions) is allowed (see also section 3.2).

Patients should not receive any of the prohibited medications listed in the current SmPC or prescribing information (PI) for paclitaxel and vinorelbine.

For BIBW 2992 (afatinib)**:** 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 4).

For paclitaxel: Refer to current SmPC/PI (see ISF)

For vinorelbine: Refer to current SmPC/PI (see ISF), special care should be taken when administered with inducers or inhibitors of CYP 3A4 (see Appendix 4)

4.2.2.2 Restrictions on diet and lifestyle

For BIBW 2992 (afatinib):

In the event of diarrhoea, patients should be advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.

To prevent skin related adverse events: It is currently proactively recommended to avoid intense irradiation with UV light, e.g., sunbathing or visiting a solarium during the treatment period of the study and strict sun protection should be used. In case of sun exposure a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide should be used, preferably a thick, alcohol-free emollient cream. Harsh detergents should be avoided.

For paclitaxel:

Refer to the current SmPC/PI for details of any restrictions on diet and lifestyle.

For vinorelbine:

Refer to the current SmPC/PI for details of any restrictions on diet and lifestyle.

4.2.2.3 Management of diarrhoea following treatment with BIBW 2992 (afatinib)

Close monitoring and proactive management of diarrhoea is essential for successful treatment of patients with BIBW 2992 (afatinib). Early and appropriate intervention can prevent the development of more severe diarrhoea. In most cases, loperamide controls diarrhoea caused by BIBW 2992 (afatinib). 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 (afatinib). Loperamide is considered as a Non Investigational Medicinal Product (NIMP). For loperamide use, please refer to the current SmPC/ PI

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).

- 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 2 or 3 diarrhoea lasting ≥ 2 days (48 hours) despite adequate antidiarrhoeal treatment, BIBW 2992 (afatinib) must be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, BIBW 2992 (afatinib) should be resumed at a reduced dose according to the dose reduction scheme outlined in Table 4.1.4:1.

The occurrence of diarrhoea and the outcome of treatment will be recorded in the AE section of the eCRF.

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 (afatinib) treatment. Restrictions given in Table 4.1.4:1, footnote 2 may apply.

4.2.2.4 Management of nausea and vomiting following treatment with BIBW 2992 afatinib)

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 4.2.2.4: 1.

Table 4.2.2.4: 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	Antiemetic treatment if deemed necessary by the investigator
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 (afatinib) 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 (afatinib) 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 (afatinib) should be reduced according to the dose reduction scheme in Table 4.1.4:1.

The occurrence of nausea and/or vomiting and the outcome of treatment will be recorded in the AE section of the eCRF.

In case of nausea and/or vomiting ≥ CTCAE grade 2, appropriate hydration (1.5 L/m²/day plus hydration deficit) must be ensured.

4.2.2.5 Management of rash following treatment with BIBW 2992 (afatinib)

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: see Section 4.2.2.2
- 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 (e.g. doxycycline or minocycline etc.).

  2) Topical treatment (e.g. hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

  And / or

  1) Antihistamines (e.g. diphenhydramine, etc.)

  2) Oral corticosteroid (low dose and short term i.e., <10 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 continued 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 (afatinib).

- 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 (afatinib) should be paused until recovery to CTCAE Grade ≤1. Treatment should be resumed at a reduced dose (see Table 4.1.4:1). If CTCAE Grade ≥3 rash does not resolve to CTCAE Grade ≤1 within 14 days of stopping BIBW 2992 (afatinib) treatment and despite optimal supportive care, the patient should not receive any further treatment with BIBW 2992 (afatinib). Restrictions given in Table 4.1.4:1, footnote 2 may apply.

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 (afatinib)

BIBW 2992 (afatinib): Patients treated with BIBW 2992 (afatinib) should take the first dose of BIBW 2992 (afatinib) treatment at the trial site and subsequent doses will be taken at home. A compliance check of trial medication should be performed on Day 15 of Treatment Course 1 and Day 1 of each subsequent course to ensure that the medication is being taken correctly. 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 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 (afatinib) should not be taken more than once a day under any circumstances.

Paclitaxel and vinorelbine: Chemotherapy will be administered at the trial site under the supervision of the investigator and in accordance with the current SmPC for both products. In the event that the patient does not receive the full dose of chemotherapy or a dose of chemotherapy is skipped this should be documented and a reason given. The compliance check for both treatments will include the infusion dose, time and date trial medication administered.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - *CLINICAL PHARMACOLOGY OR PHARMACODYNAMICS*

5.1.1 Endpoints of efficacy

5.1.1.1 Primary endpoint

The primary endpoint of this study for BIBW 2992 (afatinib) monotherapy and combination therapy is:

- Objective Response (OR) assessed by RECIST 1.1

5.1.1.2 Secondary endpoints

The secondary endpoints for this study are:

- Best overall response during each treatment period according to RECIST 1.1
- Duration of objective response, defined as the time from first objective response to the time of progression or death.
- Progression-Free Survival (PFS) will be defined for three time intervals: time from the date of the start of monotherapy to the date of 1st disease progression; time from the date of the start of combination therapy to the date of 2nd disease progression and the time from the date of the start of monotherapy to the date of 2nd disease progression. In each case, the date of death will be used if a patient died before the appropriate progression. The analysis will be based upon the evaluation of tumour imaging performed by the investigator using RECIST Version 1.1.
- Safety assessed by the severity and incidence of adverse event according to Common Terminology Criteria for Adverse Events (CTC s, AE Version 3.0), changes in vital signs and safety laboratory parameters

5.1.2 Assessment of efficacy

Efficacy 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 (Ref: Appendix 3 for RECIST 1.1 criteria)

Every effort should be made to objectively evaluate tumour response and confirm this at a minimum of 4 weeks later using RECIST (1.1) tumour progression with radiological tumour imaging for all patients who enter into the trial, including those who discontinue prematurely. (Ref: Appendix 3 for RECIST 1.1 criteria)

One to five target lesions (not exceeding two lesions per organ) should be identified at screening by Computed Tomography (CT) or MRI.

Individual lesions detected at screening will be numbered and recorded in the eCRF. 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.

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. breast, pelvis, brain) using an appropriate method (CT scan, MRI). The same radiographic procedure should be used throughout the study. Assessment will be performed at screening and every six weeks (i.e. 2 courses) thereafter. If a patient develops a condition that does not allow to continue tumour assessment with CT scans, these scans may be substituted by MRI. Tumour assessment (CT scans) does not need to be repeated at the Screening Visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment and the patient has given consent to utilising these results. In the event of early discontinuation or an interruption/delay to treatment, the tumour assessment schedule should not be changed. Brain metastases are considered as non-target lesions.

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 patient's participation and will be taken into consideration when determining the patient's response. Skin, brain and bone lesions should not be regarded as target lesions in this study.

In case of skin lesions, these should be measured with a calliper and photographic documentation should be performed. However, skin lesion should not be considered as target lesions in this study. Patients exclusively showing skin metastasis will not be eligible for this study.

Bone metastases are considered as non-target lesions. 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 phosphates). 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 (Appendix 3).

Brain metastases are considered as non-target lesions. A brain MRI should be performed at baseline in cases of clinically known, stable brain metastases. The brain MRI of the respective lesion(s) at baseline must be repeated subsequently at every imaging time-point.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety of BIBW 2992 (afatinib), paclitaxel and vinorelbine will be evaluated as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 (R04-0474).

Safety endpoints include:

- Events leading to permanent dose reduction
- Events leading to permanent treatment discontinuation
- The overall incidence and CTC criteria grade of adverse events, as well as relatedness of adverse events to treatment
- Causes of death

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

Serious adverse event

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

Intensity of adverse event

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

Causal relationship of adverse event

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

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

The causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug (BIBW 2992 (afatinib)) and for all other trial drugs IMP or NIMP (paclitaxel, vinorelbine, loperamide).

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE in the (e)CRF, if they are judged clinically relevant by the investigator.

Planned Hospitalizations
Patients may be hospitalized during selected phases of the study as required per protocol, e.g., monitoring of trial drug administration or for administrative reasons. Hospitalizations for administrative reasons and other hospitalizations already planned at the Screening Visit need not be reported as an SAE in cases where they are performed "as planned".

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 10.5.2 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 10.5.2 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 – for details please see section 5.2.2.2.

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.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, CTCAE grade, 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 Section 5.2.2.1.

Adverse events with onset within first administration of trial treatment and 28 days after last administration of chemotherapy and/or BIBW 2992 (afatinib) will be considered as on treatment. All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterised or the clinical monitor and the investigator agree to not further pursue them.

Serious and non-serious adverse events occurring later than 28 days after last administration of trial drug will only be reported in case they are considered drug-related or trial (procedure) related.

The investigator also has the responsibility to report AEs occurring in a certain period (within 28 days after last dose of trial medication or any drug related events) after a patient completes the trial. Any AEs reported to the sponsor during this phase must be documented in the safety database.

If not stipulated differently in the ISF, the investigator must report the following events via telephone/fax or, if available in the trial, by Remote Data Capture (RDC) using the SAE form immediately (within 24 hours or the next business day whichever is shorter) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically

related to the SAE(s), and protocol-specified significant events. With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

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

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified significant events becomes available.

No significant AEs have been defined for this trial

Pregnancy

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. In case of any doubt estradiol, LH and FSH levels should be assessed.

All other patients are considered to have childbearing potential and should use effective contraception throughout the study (i.e. from screening until the following time points after end of study drug treatment: for at least 1 month after treatment has ended if the patient has received BIBW 2992 (afatinib) monotherapy, for at least 3 months after treatment has ended if the patient has been additionally treated with vinorelbine and for at least 6 months after treatment has ended if the patient has been treated with paclitaxel during the study). In any case continuing measures after ceasing study medication should be done based on the latest information available for the study drugs: IB (U03-3218) for BIBW 2992 (afatinib) and SPC/PI for paclitaxel and vinorelbine.

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. The study drug should be stopped and drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. Only if pregnancy is accompanied by a SAE the Pregnancy Monitoring Form and the SAE form must be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Blood samples will be collected at the time points specified in Flow Chart A and Flow Chart B 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 all patients receiving paclitaxel or vinorelbine, the decision to receive the next paclitaxel or vinorelbine infusion 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 blood sampling should be taken within 48hrs prior infusion.

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

Haematology (CBC)	Red blood cell count (RBC), neutrophils, haemoglobin, white blood cell count (WBC) and differential, platelets.
Biochemistry	Sodium, potassium, calcium, magnesium, creatinine, aspartate amino-transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, urea, uric acid, creatine phosphokinase (CPK). In case of pathological CPK further evaluation (e.g., by Troponin assays, CK-ELPR and ECG exam) should be performed and the findings documented in the eCRF. Creatinine clearance will be estimated by the Cockcroft-Gault Formula utilising serum creatinine values (directly imputed in eCRF by data management).
Coagulation	International Normalised ratio (INR)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick at baseline and EOT only. In case of abnormal findings, further evaluation (g/24 hrs urine sampling) should be performed and the findings documented in the eCRF.
Pregnancy test	β-HCG testing in urine or serum will be performed in women of childbearing potential.

5.2.4 Electrocardiogram

A standard 12-lead resting ECG will be performed at the time-points specified in Flow Chart A and Flow Chart B i.e. at Screening, on Day 15 of Monotherapy Course 1, on Day 1 of every third monotherapy course (i.e. Day 1 of Course 4, 7, 10 etc.), on Day 1 of combination course 1 (VPC1V1), on Day 1 of every third combination therapy course (i.e. VPC4V1, VPC7V1 etc.) and at EOT (if not performed in the previous 8 weeks). The investigator should 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.

5.2.5 Assessment of other safety parameters

5.2.5.1 Physical examination, ECOG performance score

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

A full physical examination serves as a clinical tumour assessment and should include a cardiopulmonary examination, examination of the regional lymph nodes, abdomen, and an assessment of the mental and neurological status of the patient. 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), body weight (in kg), respiratory rate and body temperature and the evaluation of the ECOG performance score will be performed at the time points specified in Flow Chart A and Flow Chart B.

5.2.5.2 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography or Multi Gated Acquisition Scan (MUGA) 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). (R06-1414)

MUGA scan: The MUGA scan is recommended 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).

Cardiac left ventricular ejection fraction assessment will be performed at screening. Further ECHO or MUGA scans will be performed on Day 1 of Monotherapy Course 4 and then at every third course during monotherapy (Course 7, 10, 13 etc.), at the start of combination therapy (VPC1V1) and then at every third course during combination therapy (VPC4V1, VPC7V1 etc.) and at EOT (if not performed in the previous 8 weeks).

LVEF assessment does not need to be repeated at the Screening Visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment and the patient has given consent to utilising these results.

5.2.5.3 Vital signs

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

5.3 OTHER

[redacted]

5.3.2 Other assessments

Not applicable to this protocol

5.3.3 Pharmacogenomic evaluation

No pharmacogenomic evaluation is planned in this protocol

5.4 APPROPRIATENESS OF MEASUREMENTS

The RECIST criteria 1.1 (R09-0262) to be used for evaluation of tumour response are well established and scientifically accepted. The US NCI CTCAE criteria version 3.0 (R04-0474) are used in the assessment of adverse events.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable to this protocol

5.5.1 Pharmacokinetic endpoints

Not applicable to this protocol

5.5.2 Methods of sample collection

Not applicable to this protocol

5.5.3 Analytical determinations

Not applicable to this protocol

5.6 BIOMARKERS

There will be no on-trial biopsies. All biomarker evaluations will be used to retrospectively confirm the patient's HER2/hormone receptor status and are performed on archival tissue samples. The results of these tests are not required to confirm the patients' eligibility to take part in the study.

[redacted]

Archived tissue:

Earlier studies showed that there are discrepancies of up to 23% when comparing HER2-ICH and FISH analyses between local and central labs (R09-6008; R09-6009; R09-6011). To assure that patients who had received and failed prior HER2-targeted treatment were truly HER2-positive when they received this, confirmatory HER2-tests will be performed on archival tissue by a central laboratory. The hormone receptor status will also be determined.

Formalin Fixed Paraffin Embedded (FFPE) tumour slides from the primary tumour or metastasis should be provided to confirm the patient segment. The following tests will be done by a central laboratory: HER2 IHC and reflex FISH testing using a FDA -approved DAKO kit.

5.6.1 Endpoints based on biomarkers

There are no clinical trial endpoints based on biomarkers.

5.6.2 Methods of sample collection

[redacted]

The FFPE tumour slides (minimum of 10 slides) from the primary tumour or metastasis should be provided and sent to the central laboratory for retesting to confirm the patient's HER2 status. This is not required for screen failures.

The following tests will be done:

- HER2 IHC and reflex FISH testing using a Food and Drug Administration (FDA) -approved DAKO kit

- HrR (ER and PgR) IHC including Allred

All tests will be performed by a central laboratory according to standard procedures. For HER2 IHC, FDA approved kits will be used. Details will be provided in the ISF

The method of sampling are described in the laboratory manual (see ISF)

5.6.3 Analytical determinations

HER2 IHC/FISH, HrR IHC and Allred, will be performed according to standard procedures by the central lab. Details to be provided in the laboratory manual in the ISF.

5.7 PHARMACODYNAMICS

5.7.1 Pharmacodynamic endpoints

No pharmacodynamic endpoints planned

5.7.2 Methods of sample collection

Not applicable to this protocol

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable to this protocol

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This is an open-label study in patients with metastatic breast cancer. Patients meeting the inclusion and exclusion criteria and who have given their written informed consent are eligible for participation in the study.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Written informed consent must be obtained before any protocol specific screening assessments are performed.

A treatment course lasts 21 days. Visit 1 takes place on the first day of each treatment course and will occur on the day after the preceding 21 day course. For BIBW 2992 (afatinib) monotherapy (see Flow Chart A) an intermediary visit is to be performed on Day 15 (+/- 2 days) of the first treatment course only. If patients receive combination therapy with either paclitaxel or vinorelbine due to treatment failure on BIBW 2992 (afatinib) monotherapy, the timing of the treatment courses re-starts at VPC1V1 and subsequent visits will occur weekly for administration of these treatments (see Flow Chart B). When progression on monotherapy is documented, combination therapy should commence as soon as possible but within 21 days (unless radiotherapy is required – see section 3.2).

Note: Patients will not receive vinorelbine after the 3rd May 2013 unless they are already receiving vinorelbine treatment on that date and are showing benefit from the treatment in the opinion of the investigator (section 2.3).

Patients may continue on treatment for unlimited courses, until the criteria for stopping medication are met (see Section 3.3.4).

If the decision to permanently discontinue the study treatment is taken during a scheduled visit, the End Of Treatment (EOT) Visit should be performed as soon as possible instead of the scheduled visit (within 0 to 14 days after last treatment administration).

All entered and treated patients should have a follow-up visit 28 days (+/-7 days) after the EOT visit.

If a patient misses a visit and the patient reports to the investigator between the missed visit and the next scheduled visit, the missed visit should be performed. The current date and the reason for the delayed visit should be noted in the patients chart. The next visit, however, should take place at the scheduled time after the first administration of the trial drug in the respective treatment course. In the event of any interruption/delay of treatment, the tumour assessment schedule should not be changed (Vinorelbine or paclitaxel infusions in this case may need to be skipped).

The investigations, as outlined in the Flow Charts, will be performed at the respective visits as described in detail in the following sections. Flow Chart A refers to treatment with BIBW 2992 (afatinib) monotherapy. Flow Chart B refers to: the combination of BIBW 2992

(afatinib) and either paclitaxel or vinorelbine treatment. The switch from Flow Chart A (monotherapy) to Flow Chart B (combination therapy) occurs when the patient has disease progression on BIBW 2992 (afatinib) monotherapy, which may occur at any stage during the patients' participation in the study.

PD on BIBW 2992 (afatinib) monotherapy must always be documented by imaging, regardless of when PD occurs. When PD is documented, combination therapy should commence as soon as possible but within 21 days (unless radiotherapy is required – see section 3.2) and the assessments performed at start of combination treatment should be for VPC1V1 (Flow Chart B).

6.2.1 Screening and run-in period(s) (Up to 14 days before start of treatment)

Refer to Flow Chart A.

All patients who signed the written informed consent before the approval of amendment 6 by IRBs and IECs (See section 3.3.4.2 and section 11) may continue in the trial- After approval of protocol amendment 6, no new informed consent must be signed as patient recruitment in part A will be stopped.

Assessments to perform at this visit:

- Written informed consent
- Patient demographics
- Medical history and relevant non-oncological history.
- Review patient eligibility to participate in study
- Complete physical examination including body weight and height
- Vital signs
- Performance status (ECOG scale)
- ECG
- Echocardiogram or MUGA scan. Note: LVEF assessment does not need to be repeated at the Screening Visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment and the patient has given consent to utilising these results.
- Blood and urine sample for safety laboratory assessment
- Provide archived tissue sample for HER2-retesting/ biomarker analysis
- Obtain a urine or serum sample for pregnancy test (if woman is of child bearing potential).
- Tumour assessments (CT Scan) Note: Tumour assessment does not need to be repeated at the screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to the start of treatment and the patient has given consent to utilising these results.
- Record all concomitant therapies
- Record AEs
- Schedule next patient appointment in 0-14 days time (Visit C1V1)

6.2.2 Treatment periods

Course 1, Visit 1, Day 1 (Visit C1V1)

Refer to Flow Chart A - (BIBW 2992 (afatinib) monotherapy)

Assessments to complete at this visit:

- Confirm patient eligibility
- Limited physical examination including measurement of body weight
- Vital signs
- Performance status (ECOG scale)
- Blood and urine sample for safety laboratory tests
- [redacted]
- Urine or serum for pregnancy test (if applicable)
- Record all concomitant therapies
- Record AEs
- Dispense sufficient trial drug BIBW 2992 (afatinib) for 21 days (3 week treatment course)
- Schedule next patient appointment in 14 days time (On Course 1 Day 15)

Course 1, Visit 2, Day 15 (± 2 days) (Visit C1V2)

Assessments to complete at this visit:

- Vital signs
- Performance status (ECOG scale)
- ECG
- AEs since last visit
- Record all concomitant therapies
- BIBW 2992 (afatinib) medication compliance check
- Schedule next patient appointment in 7 days time (Day 22)

Treatment Course 2 (C2V1) and all subsequent treatment courses (CnVn) with BIBW 2992 (afatinib) Monotherapy

Assessments to complete at this visit (on day 1 of each course):

- Limited physical examination including body weight
- Vital signs
- Performance status (ECOG scale)
- ECG (Perform on Day 1 of every third course (i.e. Day 1 of Course 4, 7, 10 etc.) and at EOT (if not performed in the previous 8 weeks)

- Echocardiogram or MUGA scan (Perform on Day 1 of every third course (i.e. Day 1 of Course 4, 7, 10 etc.) and at EOT (if not performed in the previous 8 weeks)
- Blood and urine sample for safety laboratory assessments
- Urine or serum sample for pregnancy test (if applicable)
- Tumour assessments (CT scan) every 6 weeks calculated from start of treatment
- Record all concomitant therapies
- BIBW 2992 (afatinib) medication compliance check
- AEs since last visit
- Dispense sufficient BIBW 2992 (afatinib) trial drug for 21 days
- Schedule next patient appointment in 21 days time
- Assess patient for Disease progression:
    - If a patient has not shown disease progression on BIBW 2992 (afatinib) monotherapy then continue to refer to Flow Chart A.
    - If a patient has shown disease progression on BIBW 2992 (afatinib) monotherapy at any time *(based upon the clinical decision of the investigator*) and treatment with either paclitaxel or vinorelbine is added **(only Paclitaxel after the 3rd May 2013)**, then refer to Flow Chart B for visit scheduling and procedures (see below). If the patient subsequently shows disease progression whilst on the combination treatment, then the patient is to be withdrawn from study treatment.

Combination Therapy Treatment Course 1 and all subsequent combination treatment courses (where paclitaxel or vinorelbine treatment have been added to BIBW 2992 (afatinib)) (See Flow Chart B)

Refer to Flow Chart B

Visit VPC1V1 - Day 1(± 2 days)

Assessments to complete at this visit are the same as those for Treatment Course 2 (C2V1) above with the addition of the following:

- Tumour assessments (CT scan) at the start of combination treatment (VPC1V1) and every 6 weeks calculated from start of combination treatment. Note that a tumour assessment is not required to be repeated at VPC1V1 if it has already been performed at the point when PD was determined on BIBW 2992 (afatinib) (Monotherapy) and is within 3 weeks of starting combination treatment.
- ECHO or MUGA at the start of combination treatment (VPC1V1) and then at every third course (Course 4 (VPC4V1), Course 7 (VPC7V1), 10 (VPC10V1), 13 etc.). Note: ECHO or MUGA can be performed within 2 weeks of Day 1 of Course 1 of combination therapy.
- Complete physical examination including body weight and height
- [redacted]
- Administer paclitaxel or vinorelbine:

- Before the 3rd May 2013: Paclitaxel 80mg/m^2 i.v. or vinorelbine 25 mg/m² i.v. ~~**once weekly**~~ will be administered once weekly once a patient experiences disease progression whilst being treated with BIBW 2992 (afatinib) monotherapy.
- After the 3rd May 2013: Paclitaxel 80mg/m^2 i.v. will be administered once weekly once a patient experiences disease progression whilst being treated with BIBW 2992 (afatinib) monotherapy. Patients will not receive vinorelbine after the 3rd May 2013 unless they are already receiving vinorelbine treatment on that date and are showing benefit from the treatment in the opinion of the investigator. Should the decision be to change the chemotherapy regimen from vinorelbine to paclitaxel, the patient will remain on trial and undergo an EOT visit before the switch. Those patients will have a second EOT visit when they will permanently discontinue part B.

Each administration should be preceded by CBC assessment and measurement of weight and body temperature. Pre-medications should be applied in accordance with the current SmPC

- Perform paclitaxel or vinorelbine compliance check (See Section 4.3.1)
- Schedule next patient appointment in 7 days time

Visit VPC1V2 - Day 8 (± 2 days)

Assessments to complete at this visit:

- Administer paclitaxel or vinorelbine.
  - for patients who performed VPC1V1 before the 3rd May 2013: Paclitaxel 80mg/m^2 i.v. or vinorelbine 25 mg/m² i.v. once weekly
  - for patients who performed VPC1V1 after the 3rd May 2013:: Paclitaxel 80mg/m^2 i.v. once weekly ~~will be administered weekly once a patient experienced disease progression whilst being treated with BIBW 2992 (afatinib) monotherapy~~.
  Each administration should be preceded by CBC assessment and measurement of weight and body temperature. Pre-medications should be applied in accordance with the current SmPC
- Vital signs
- Paclitaxel or vinorelbine compliance check
- Record all concomitant therapies
- Record occurrence of AEs since last visit
- Schedule next patient appointment in 7 days time

Visit VPC1V3 - Day 15 (± 2 days)

Same procedures as for Visit VPC1V2 above and in addition:

- Schedule next patient appointment in 7 days time (Day 22)

- Note: On day 22 the patient will commence the next Treatment Course (i.e. Visit VPC2V1) should patient continue treatment with study medications. The same applies to all subsequent treatment courses.

6.2.3 End of trial and follow-up period

All patients should have an EOT visit when trial medication is permanently discontinued.

Assessments to be performed at the EOT Visit are described below.

End of Treatment Visit (EOT) - 0-14 days after permanent discontinuation of BIBW 2992 (afatinib) monotherapy or combination therapy - See Flow Chart A and Flow Chart B

Assessments to complete at this visit:

- Complete physical examination including body weight
- Vital signs
- Performance status (ECOG scale)
- ECG (if not performed in previous 8 weeks)
- Echocardiogram or MUGA scan. (if not performed in the previous 8 weeks)
- Blood and urine sample for safety assessments
- [redacted])
- Blood or urine sample for a pregnancy test (if applicable)
- Tumour assessment (not required at EOT visit if progressive disease has already been documented at scheduled imaging assessment). In case progressive disease is suspected, CT/MRI imaging needs to be done at any time when active treatment ends. (See Appendix 3) Bone scans and correlative imaging should be performed when clinically indicated
- Record all concomitant therapies
- AEs since last visit
- BIBW 2992 (afatinib) medication compliance
- Paclitaxel or vinorelbine compliance check (if applicable)
- Termination of study medication – Record date of last administration of study drugs and reason for discontinuation

All patients should have a follow-up visit 28 days after the End of Treatment (EOT) visit. Patients who have not experienced disease progression and not started further treatment should have further follow- up visits every 6 weeks after the first FU until disease progression or start of further treatment. See below for assessments to be performed at these visits.

First follow-up visit (FU V1): 28 days after EOT visit (± 7 days) - See Flow Chart A and Flow Chart B

All patients should have a follow-up visit 28 days after the EOT visit and the following assessments should be completed:

- Limited physical examination including body weight
- Vital signs
- Performance status (ECOG scale)
- Blood and urine sample for safety assessments
- Record all concomitant therapies
- AEs since last visit. Follow-up on AEs which were ongoing at EOT. Please refer to section 5.2.2.2 for specific safety reporting obligations
- Trial completion - If applicable (patients who have progressed or who have started new treatment)

Additional Follow-Up Visit (where applicable) (FU Vn – every 6 weeks)

Patients who have not shown disease progression and not started further treatment should have further follow-up visits every 6 weeks until disease progression or start of further treatment. The assessments performed and information collected are the same as that for the first Follow-Up Visit above, with the exception that new AEs are only recorded if they are serious and/or trial drug-related.

Collection of data after patient has ended participation in the study

Follow up information on further post-trial treatment, best response and vital status will be collected, if available, but no visits will be performed for study purposes.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The trial will be performed as a single arm open label study. Patients will receive BIBW 2992 (afatinib) monotherapy until disease progression according to RECIST 1.1. Afterwards they will be treated with BIBW 2992 (afatinib) in combination with either paclitaxel or vinorelbine until a further disease progression according to RECIST 1.1. (See Figure 3.1:1)

Note: Patients will not receive vinorelbine after the 3rd May 2013 unless they are already receiving vinorelbine treatment on that date and are showing benefit from the treatment in the opinion of the investigator (section 2.3).

Patients will not be screened after protocol amendment 6 approvals by IRBs and IECs (See section 3.3.4.2 and section 11).

7.2 NULL AND ALTERNATIVE HYPOTHESES

All analyses in this study are descriptive and exploratory by nature. Any statistical tests are performed only to provide a statistical framework from which to view the results and providing aid for planning further studies. No formal statistical inferences are foreseen.

7.3 PLANNED ANALYSES

Treated analysis sets (TRT) are defined for mono- and combination-therapy separately. The TRT for monotherapy comprises all patients who received at least one single dose of BIBW 2992 (afatinib), and the TRT for combination therapy comprises all patients who received at least one dose each of BIBW 2992 (afatinib) and paclitaxel or BIBW 2992 (afatinib) and vinorelbine.

Separate baselines will be defined for mono- and combination therapy and no pooling will be performed across the two parts of the study unless otherwise stated.

No per protocol population will be used for analyses. However important protocol violations will be described.

7.3.1 Primary analyses

Objective Response

The primary analysis will estimate the proportion of patients who achieve objective response according to the RECIST 1.1 criteria for mono- and combination therapy separately. The individual response criteria will be relative to the respective baselines in each part and the rates will be presented using the respective TRTs. Objective response is defined as CR or PR and only confirmed responses will be considered. An exact 95% Clopper-Pearson confidence

interval will be calculated for the proportion of responders (R06-1080). Also, similar point estimates and exact confidence intervals will be calculated for each category (CR, PR, SD, PD and NE).

Each patient will be assigned to one of the following categories based upon their best response during treatment in each part, as determined according to RECIST 1.1.

- 1 = CR (complete response)
- 2 = PR (partial response)
- 3 = SD (stable disease)
- 4 = PD (progressive disease)
- 9 = Not evaluable

Objective response, determined without requiring confirmation, will be tabulated separately.

7.3.2 Secondary analyses

None of the secondary endpoints which use RECIST 1.1 require confirmation.

7.3.2.1 Key secondary analyses

Best overall response

Frequency tables will be presented for the best RECIST assessment achieved by each patient during each of the treatment periods in the order (from best to worst): complete response, partial response, stable disease, disease progression.

Duration of objective response

Time to objective response is defined as the number of days from the start of treatment to the first recorded objective response in each part. Duration of objective response is measured from the time of first objective response to the time of progression or death (or date of censoring for PFS).

Descriptive statistics will be produced for the duration of objective response for mono- and combination-therapy separately.

Progression-free survival

Disease progression will be evaluated according to the RECIST 1.1 criteria (R09-0262).

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

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

Date of progression and date of first administration is referring to the respective part of the study (mono- or combination therapy).

PFS will also be defined for the following time interval:

- PFS [days] = earlier of date of death or second progression – date of first administration of monotherapy + 1.

PFS will be assessed based on the Kaplan-Meier method for each part separately. Point estimates together with confidence intervals (based on Greenwood's method) will be provided for median PFS. Details of time points and censoring rules will be provided in the TSAP.

Safety endpoints : see section 7.3.3

7.3.4 Interim analyses

7.3.4.1 Early stopping rule

An early stopping rule will be implemented in order to minimise the number of patients treated if BIBW 2992 (afatinib) were ineffective.

When 20 evaluable patients (according to RECIST 1.1) have completed at least two courses of BIBW 2992 (afatinib) (or progressed during the first course), a meeting will be held to evaluate the objective tumour response rate and to decide whether to proceed with the trial or stop for futility. If at least 1 unconfirmed objective response is witnessed from all available information at the time, then the trial will continue to full accrual. If no unconfirmed responses are witnessed, the benefit-risk of continuing with the trial will be discussed. Details of the evaluation and decisions made at this meeting will be fully documented. The attendees at the meeting will be members of the BI trial team and the National Co-ordinating study investigators of each country. As only one responder is required it is possible that this meeting may be held earlier.

As long as assessment of the early stopping condition is still pending, recruitment of further patients will continue.

Table 7.3.4.1: 1 shows that a minimal requirement of at least one responder (CR or PR) out of 20 patients provides a chance greater than 87% of continuing to full accrual, if the underlying objective response rate is at least 10%. On the other hand, there would be a less than 19% chance of falsely continuing to full accrual, if the underlying objective response rate is below 1%.

Table 7.3.4.1: 1 Operating characteristics of first-stage criteria

20 patients in the first stage	Number of responders required to continue to second stage		
Underlying **response rate** [%]	1	2	3
	Probability for stopping*		
0.01	**0.8179**	0.9831	0.9990
0.05	0.3585	0.7358	0.9245
0.08	0.1887	0.5169	0.7879
	Probability for continuing*		
0.10	**0.8784**	0.6083	0.3231
0.15	0.9612	0.8244	0.5951
0.20	0.9885	0.9308	0.7939

*Probabilities are based on the binomial distribution, Bin (20, p), where p is the underlying response rate

7.3.5 Pharmacokinetic analyses

Not applicable to this protocol

7.3.6 Pharmacodynamic analyses

Not applicable to this protocol

7.3.7 Pharmacogenomic analyses

Not applicable to this protocol

7.4 HANDLING OF MISSING DATA

Patients will continue to be followed for progression after discontinuation of study treatment until they start new treatment.

7.5 RANDOMISATION

This is an open-label non-randomised trial without a control group. No randomisation is involved in this trial. Eligible patients will be sequentially entered into the trial.

7.6 DETERMINATION OF SAMPLE SIZE

40 patients would be expected to provide more than a 90% probability of observing at least 2 responders and a nearly 80% probability of observing at least 3. This is based on a binomial probability with an assumed underlying ORR of 10%.

Taking into account the additional condition that at least one responder needs to be among the first 20 patients, the probabilities change to approximately 85% for having at least 2 responders among 40 patients overall and approximately 74% for having at least 3 responders overall.

Taking into consideration the three lines of previous therapy from which patients are entered into this study (trastuzumab, lapatinib and trastuzumab +lapatinib), in order to have sufficient numbers to identify whether there is a previous therapy for which BIBW 2992 (afatinib) is a successful follow-on medication, **it was planned that** 120 patients ~~will~~ **would** be recruited. **However, given that patients will not be enrolled/screened after protocol amendment 6 approvals by IRBs and IECs (See section 3.3.4.2 and section 11), the total sample size is anticipated to be approximately 80 patients.**

A total sample size of 80 is expected to give an 82% probability of observing at least 6 responders and a 91% probability of observing at least 5.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

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

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

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

The sponsor must retain the essential documents according to the sponsor's SOPs. When it is no longer necessary for the trial site to retain the source documents and essential documents the sponsor must notify the head of the trial site.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BIBW 2992 (afatinib), this is the current version of the Investigator's Brochure (U03-

3218). For paclitaxel/ vinorelbine this is the current SmPC. The current versions of these reference documents are to be provided in the ISF.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities, *i.e. the CA*.

8.6 COMPLETION OF TRIAL

The trial will be considered complete when the last patient completes the last follow-up visit.For EU countries: The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 APPENDIX 1 COCKCROFT-GAULT FORMULA

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

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

Or when serum creatinine is measured in µmol/L

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

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

10.2 APPENDIX 2 ECOG SCALE

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

10.3 APPENDIX 3 TUMOUR RESPONSE ASSESSMENT ACCORDING TO RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of a least 5mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

Time-point 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 all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.4 APPENDIX 4 LIST OF CYP3A4 SUBSTRATES, INHIBITORS, AND INDUCERS AND LIST OF POTENT INHIBITORS AND INDUCERS OF P-GLYCOPROTEIN

10.4.1 List of CYP3A4 substrates, inhibitors, and inducers

Summary of CYP 3A4 Substrates, Inhibitors, and Inducers

Chart of Human CYP-450 3A4 Isoenzyme Selective Substrates, Inhibitors, & Inducers		
Substrates	Inhibitors	Inducers
acetominophen, alfentanil, alprazolam, amiodarone, aminopyrine, amitriptyline, amlodipine, amprenavir, antipyrine, astemizole, atorvastatin, benzphetamine, budesonide, busulfan, cannabinoids, carbamazepine, celecoxib, cisapride, clarithromycin, clindamycin, clomipramine, clozapine, codeine, cortisol, cyclobenzaprine, cyclophosphamide, cyclosporin A, dapsone, delavirdine, dexamethasone, dextromethorphan, diazepam, digoxin, diltiazem, disopyramide, docetaxel, donepezil, doxorubicin, dronabinol, erythromycin, ethinylestradiol, ethosuximide, etopside, felodipine, fentanyl, fexofenadine, flutamide, granisetron, haloperidol, hydrocortisone, ifosfamide, imipramine, indinavir, isradipine, ketoconazole, lansoprazole, lidocaine, loratadine, losartan, lovastatin, methadone, mibefradil, miconazole, midazolam, navelbine, nefazodone, nelfinavir, nicardipine, nifedipine, nimodipine, nisoldipine, omeprazole, ondansetron, paclitaxel, pravastatin, prednisone, propafenone, quinidine, quinine, retinoic acid, rifampin, ritonavir, ropivacaine, saquinavir, sertraline, sufentanil, tacrolimus, tamoxifen, temazepam, teniposide, terfenadine, testosterone, THC, theophylline, triazolam, troleandomycin, verapamil, vinblastine, vincristine, (R)-warfarin	amiodarone, amprenavir, cannabinoids, cimetadine, clarithromycin, clotrimazole, cyclosporin, delavirdine, diltiazem, ethinylestradiol, erythromycin, fluconazole, fluoxetine, fluvoxamine, indinavir, intraconazole, ketoconazole, metronidazole, mibefradil, miconazole, nefazodone, nelfinavir, nicardipine, norfloxacin, propafol, quinine, ritonavir, saquinavir, sertraline, troleandomycin, verapamil, zafirlukast	carbamazepine, dexamethasone, ethosuximide, glutethimide, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, St. John's Wort, sulfadimidine, sulfinpyrazone, troglitazone, troleandomycin

10.4.2. List of potent inhibitors and inducers of P-glycoprotein

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 the status of each concomittant therapies and in case of questions contact BI clinical monitor.

While caution needs to continue to be exercised in concomitant use of P-gp inhibitors/inducers with afatinib, based on new data from two drug-drug interaction (DDI) trials (U03-3218 version 13) investigating the effect of ritonavir and rifampicin, respectively, on 40 mg afatinib, their use in patients needing such therapies is no longer prohibited. It cannot be excluded that the plasma exposure to afatinib may increase under concomitant treatment with strong P-gp inhibitors. Conversely, strong P-gp inducers may decrease the plasma concentrations of afatinib. However, maximum observed effects are rather mild to moderate and could even be avoided for the potent inhibitor ritonavir when given simultaneously or 6 h after afatinib. Therefore caution has to be exercised when combining afatinib with potent P-gp modulators.

10.5 APPENDIX 5 CLINICAL EVALUATION OF LIVER INJURY

10.5.1 Introduction

Alterations of liver laboratory parameters, as described in section 5.2.2.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures.

10.5.2 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" and results 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), Anti-nuclear 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*
    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).

and report these via the eCRF.

11. SUMMARY OF CLINICAL TRIAL PROTOCOL MODIFICATIONS

Summary of Clinical Trial Protocol Modifications Sheet (SOMS)

Number of CTP modification		1
Date of CTP modification		*22nd December 2010*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product(s)		*BIBW 2992 (afatinib)*
Title of protocol		*An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. *Flow Charts A and B* 2. *Abbreviations* 3. *Section 3.3.3 Exclusion Criterion 17* 4. *Section 3.3.3 Exclusion Criterion 30* 5. *Section 3.3.4.1* 6. *Section 4.1.1* 7. *Section 5.2.2.2* 8. *Section 5.2.2.1*
Description of change		1. *Clarified schedule for tumour assessments* 2. *Corrected SmPC abbreviation* 3. *Defined use of contraception post study for each of the trial medications used*

		4. Defined threshold values for platelet counts for combination treatment with paclitaxel and vinorelbine *5. Included reason 1 as exception* *6. Vinorelbine infusion time* *7. Added requirements for post treatment requirement for contraception for BIBW 2992, vinorelbine and paclitaxel* *8. Added explanation regarding handling of hospitalisations for administrative reasons*
Rationale for change		*1. Clarification* *2. Corrected typographical error* *3. Change required by regulatory authority to align with SmPC for vinorelbine and paclitaxel* *4. Corrected typographical error* *5. Corrected typographical error* *6. Clarification* *7. Change required by regulatory authority to align with SmPC for vinorelbine and paclitaxel and to align with Exclusion Criterion 17* *8. Clarification*

Number of CTP modification		2
Date of CTP modification		*27th April 2011*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product		*BIBW 2992 (afatinib)*
Title of protocol		*An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		*1. Title page* *2. Flow charts A and B* *3. Section 3.1* *4. Section 3.2* *5. Section 3.3.3* *6. Section 4.1.1* *7.Section 4.1.2* *8. Section 4.1.3* *9. Section 4.1.4* *10. Section 4.2.2.1* *11.Section 5.2.2.2* *12. Section 5.2.4* *13. Section 5.2.5.2* *14. Section 5.6.2* *15. Section 6.2* *16. Section 6.2.1, 6.2.2, 6.2.3* *17. Section 8.4.1* *18. Section 11*

Description of change		*1. Change of Trial Clinical Monitor* *2. Clarification of timing of ECG, LVEF evaluation and tumour assessments. Clarification of timing of transition from part A to part B. Clarification that CBC results required prior to chemotherapy.* *3. Clarification of transition from part A to part B. Clarification of data collection after trial participation.* *4. Clarification of transition from part A to part B. New guidance on the use of radiotherapy during the trial. Clarification of data collection after trial participation.* *5. Exclusion criteria 4 amended to allow palliative radiotherapy. Exclusion criteria 14, 17, 28 and 29 clarified.* *6. Vial size added for vinorelbine* *7. Clarification of transition from part A to part B.* *8. Addition of reference publications for weekly paclitaxel.* *9. Correction to the guidance on timing of study medication intake. Correction to footnote in table 4.1.4: 1.Addition of platelet count value required for treatment with paclitaxel. Clarification of handling of chemotherapy dosing in the event of treatment-related adverse events.* *10. Palliative radiotherapy is now allowed.* *11. Correction to adverse event reporting periods.* *12. Clarification of timing of ECG assessments.* *13. Clarification of timing of LVEF assessments.* *14. Clarification of timing of sample collection.* *15. Clarification of timing of visits and of transition from part A to part B. Clarification of requirement to document progressive disease on BIBW 2992 monotherapy.* *16. Clarification on timing of visits, timing of assessments and assessments to perform. Clarification of data collection after trial participation.* *17. Clarification that the reference SmPC is not the local version.* *18. Correction to date of CTP modification 1 and addition of change number 8.*
Rationale for change		*1. Personnel change*

		2. *Clarification* 3. *Clarification* 4. *Clarification and addition of guidance on use of radiotherapy in response to investigator request.* 5. *Clarification and investigator request to allow palliative radiotherapy to non-target lesions.* 6. *Omission from original protocol* 7. *Clarification* 8. *Investigator request for reference publication.* 9. *Incorrect information in original protocol. Clarification required.* 10. *Investigator request to allow palliative radiotherapy to non-target lesions.* 11. *Incorrect information in original protocol.* 12. *Clarification* 13. *Clarification* 14. *Clarification* 15. *Clarification* 16. *Clarification* 17. *Clarification* 18. *Incorrect and missing information*

Number of CTP modification		3
Date of CTP modification		*29th July 2011*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product		*BIBW 2992 (afatinib)*
Title of protocol		*LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		*Title page*
Description of change		*Addition of LUX-Breast 2 to trial title*
Rationale for change		*To indicate that this trial is part of the LUX-Breast program*

Number of CTP modification		4
Date of CTP modification		*06th December 2011*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product		*BIBW 2992 (afatinib)*
Title of protocol		*LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*

To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		*1 Abbreviations* *2. Section 2.1* *3. Section 2.3* *4. Section 3.2* *5. Section 3.3.2* *6. Section 3.3.3* *7. Section 4.1.2* *8. Section 4.1.4* *9. Table 4.1.4: 1* *10. Section 4.2.2.1* *11. Section 5.1.2* *12. Section 5.2.2.1* *13. Section 5.2.2.2* *14. Section 7.3.1* *15. Section 7.3.2.3* *16. Section 7.3.2.4* *17. Section 7.3.2.7* *18. Addition of Appendix 10.5*
Description of change		*1. Addition of abbreviations CK-ELPR and DILI* *2. Addition of sentence to clarify treatment setting in trial* *3. Addition of text regarding drug-induced liver injury* *4. Clarification that study treatment is first line and that part A schedule is followed during radiotherapy* *5. Correction of cross-references to exclusion criteria.* *6. Addition of new exclusion criteria 4. Addition*

		of guidance to exclusion criteria 8 regarding bilateral breast cancer and metastases to the contralateral breast. *7. Clarification of line of treatment in study* *8. Addition of guidance on missed doses* *9. Removal of '≥' sign* *10. Clarification of time window* *11. Clarification that confirmation of tumour response must be at least 4 weeks after original assessment of response.* *12. Addition of text regarding drug-induced liver injury* *13. Addition of paragraph regarding adverse events which are considered to be 'always serious'* *14. Clarification of analyses to be performed* *15. Clarification of analyses to be performed* *16. Correction of cross-reference* *17. Clarification of analyses to be performed* *18. Addition of text regarding drug-induced liver injury*
Rationale for change		*1. Omission from original protocol* *2. Clarification* *3. New corporate standard for monitoring and assessment of drug-induced liver injury* *4 Clarification* *5 Correction* *6. Clarification that the intent of the protocol is to include patients requiring first-line treatment for metastatic breast cancer. Clarification regarding the inclusion of patients with bilateral breast cancer or metastases to the contralateral breast.* *7. Clarification* *8. Additional guidance added* *9. Removal of redundant symbol to clarify meaning* *10. Clarification* *11. Clarification in accordance with RECIST (1.1)* *12. New corporate standard for monitoring and assessment of drug-induced liver injury* *13. New corporate standard for events considered 'always serious'* *14. Clarification* *15. Clarification*

		16. Correction *17. Clarification* *18. New corporate standard for monitoring and assessment of drug-induced liver injury*

Number of CTP modification		*5*
Date of CTP modification		*06 Nov 2012*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product		*BIBW 2992 (afatinib)*
Title of protocol		*LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		*1. Title page* *2. Flow chart A and B* *3. Flow chart B, Section 6.2.2* *4. Abbreviations* *5. Section 1.2 and 9.3* *6. Section1.2, 3.3.4.1, 4.2.2.1 and appendix 10.4* *7. Section 2.3* *8. Section 3.1* *9. Section 3.3.2* *10. Section 3.3.3* *11. Section 3.3.3 and 4.1.4* *12. Section 4.1.1*

		13. Section 4.1.4 *14. Section 5.2.2.1* *15. Section 5.2.2.2* *16. Section 5.2.3* *17. Section 6.2.3* *18. Section 7.3.2.1 and 7.3.2.2* *19. All protocol*
Description of change		*1. Change of Clinical Trial Monitor* *2. Clarification that the coagulation test is part of the safety assessment as described in section 5.2.3 and addition of reference to section 5.2.2.2 for safety reporting during the follow up period* *3. Clarification of time of Echo or MUGA during the combination therapy* *4. Addition of abbreviation DDI* *5. Addition of reference on new publication on the mode of action of BIBW 2992* *6. Updated guidance on the concomitant use of P-gp inhibitors and inducers- Deletion of withdrawal criteria 9 – addition in appendix 4 of the list of potent inhibitors and inducers of P-glycoprotein (MDR1) in line with updated P-gp information (appendix 4.2).* *7. Information about incidence of Keratitis in licensed EGFR inhibitors.* *8. Clarification* *9. Clarification on inclusion criteria to be rechecked at the start of part B* *10. Clarification on exclusion criteria to be rechecked at the start of part B and clarification on pregnancy monitoring after the end of the trial* *11. Exclusion criteria amended: requirement for updated platelet count prior to the start of each vinorelbine infusion - Addition of a statement on vinorelbine dose adjustment for severe hepatic impairment due to the release of the updated vinorelbine SPC* *12. Removal of manufacturer name of Paclitaxel in the trial and updated dilution volume for vinorelbine* *13. Clarification on how to proceed with study treatment when patients do not have drug related adverse events.*

		14. Modification regarding the reporting of worsening of underlying disease or other pre-existing conditions, change in vital signs, ECG, physical examination and laboratory test results. *15. Clarification on pregnancy monitoring after the end of the trial.* *16. Clarification.* *17. Addition of reference to section 5.2.2.2 for safety reporting during the follow up period* *18. Alignement between section 5.1.1 (endpoints and efficacy) and Section 7.3 (planned analyses)* *19. Spell check (English UK)*
Rationale for change		*1. Personnel change* *2. Clarification* *3. Clarification and addition of guidance for the time of Echo or MUGA during the combination therapy* *4. New abbreviation added in the amendment text* *5. Update on the mechanism of action of BIBW 2992(afatinib)* *6. Updated guidance on the concomitant use of P-gp inhibitors and inducers (IB(U03-3218) version 13)* *7. Update* *8. Clarification* *9. Clarification* *10. Clarification* *11. Update following the release of the updated Vinorelbine SPC* *12. Following a shortage of Paclitaxel from Hospira UK on the market and in order to be able to provide Paclitaxel to the patients in the study, Boehringer-Ingelheim may need to purchase Paclitaxel from a different manufacturers - Update on vinorelbine dilution due to SPC changes.* *13. Clarification* *14. Alignment with project standard definition* *15. Clarification* *16. Clarification* *17. Clarification* *18. Clarification*

		19. Spelling check

Number of CTP modification		6
Date of CTP modification		*27 June 2013*
EudraCT number		*2010-021945-29*
BI Trial number		*1200.98*
BI Investigational Product		*BIBW 2992 (afatinib)*
Title of protocol		*LUX-Breast 2; An open label, phase II trial of BIBW 2992 (afatinib) in patients with metastatic HER2-overexpressing breast cancer failing HER2-targeted treatment in the neoadjuvant and/or adjuvant treatment setting*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐

<u>Changes related to Urgent Safety Information released on 03 May 2013 which were implemented at this time:</u>

Section to be changed		*1. Protocol synopsis* *2. Flow chart B* *3. Abbreviations* *4. Section 2.1* *5. Section 2.3* *6. Section3.1* *7. Section3.2* *8. Section 3.3.2 and 3.3.3* *9. Section 3.3.4.2* *10. Section 4.1and 4.1.1* *11. Section 4.1.2*

		12. Section 6.2 *13. Section 6.2.2* *14. Section 7.1* *15 Section 7.6*
Description of change		*1 to 15. Stop the inclusion of new patients into the afatinib + vinorelbine combination in Part B of LUX-Breast 2*
Rationale for change		*1 to 15. The Data Monitoring Committee (DMC) of the 1200.75 trial (LUX-Breast 1 - EudraCT # 2009-015476-98, NCT01125566) conducted a benefit-risk analysis as pre-specified in the clinical trial protocol. A 1200.75 DMC recommendation which was issued on 26 April 2013 concluded, that based on the benefit-risk analysis, treatment in the experimental arm (afatinib 40 mg + vinorelbine 25 mg/m^2 weekly i.v.) should be discontinued.* *The benefit-risk analysis in trial 1200.75 was based on data from over half of the planned number of patients enrolled. The DMC concluded that there is a low likelihood of the study meeting the pre-defined criteria for increased efficacy in terms of PFS. In addition, a high rate of treatment discontinuations and dose reductions as well as a higher rate of serious adverse events and deaths was observed in the experimental arm compared to the control arm trastuzumab + vinorelbine. The sponsor and the Executive Committee of the trial agreed to follow the DMC's recommendation and decided to stop further randomisation into the study and to discontinue further treatment with the combination of afatinib and vinorelbine.* *Since one of the treatment options in Part B of Trial LUX-Breast 2 is the combination of afatinib + vinorelbine, BI decided as a precautionary measure to stop the inclusion of new patients into the afatinib + vinorelbine combination in Part B of LUX-Breast 2. Part A of the trial and continuation of treatment with paclitaxel in Part B was not affected by this urgent safety measure*

Changes NOT related to Urgent Safety Information released on 03 May 2013 and only to be implemented after approval of this amendment:

Section to be changed		*1. Protocol synopsis* *2. Flow chart A and B* *3. Section 2.3* *4. Section3.1* *5. Section3.2* *6. Section 3.3.4.2* *7. Section 4.1.2* *8 Section 6.2.1* *9 Section 7.1* *10. Section 7.6* *11 Section 4.1.6.1*
Description of change		*1 to 10 Stop enrolment into the trial after protocol amendment 6 approval by IRBs and IECs* *11 Remove description of Afatinib bottle*
Rationale for change		*1 to 10 In addition the decision has been made to stop further enrolment of new patients in Part A as:* *-Afatinib+Vinorelbine Treatment in part B is no longer an option. This combination showed an unfavourable benefit/risk ratio in trastuzumab pre-treated patients leading to termination of the pivotal trial 1200.75. As a consequence the eligible patient population to be included in part A of trial 1200.98 will narrow down, as patients receiving adjuvant/neoadjuvant paclitaxel are not readily rechallenged with paclitaxel when receiving 1st line mBC treatment. This will generate further difficulties for recruitment.* *- In addition since the trial 1200.98 started, pertuzumab/trastuzumab + docetaxel intended for patients who have not received prior treatment for metastatic breast cancer with an anti-HER2 therapy or chemotherapy, has been approved in 2012 and is becoming standard of care wherever available. This will establish further hurdles for a timely recruitment even into part A of trial 1200.98.* *-Approximately 60 out of 69 patients enrolled to date in this trial have received Trastuzumab only based regimens as prior treatment in the adjuvant and neoadjuvant*

		setting. By the time of approval of amendment 6, it is expected that approximately 80 patients will have been treated in this trial. As only 9 patients have received lapatinib or a combination of lapatinib and trastuzumab as prior treatment so far, the efficacy analysis will be driven by trastuzumab pretreated patients. 80 patients will address the efficacy of afatinib in the Trastuzumab-pretreated patients with a high statistical probability (see section 7.6 for details) *11 In the future, afatinib supplies for clinical trials might be switched to the marketed product. The bottle type might be different from an HDPE bottle (e.g. PP-bottle with more desicant)*