Trial Statistical Analysis Plan

c01946576-03

BI Trial No.:	1200.98
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 (including protocol revisions 1-7 1200-0098--protocol-revision-07 [c02103088]).
Investigational Product(s):	Giotrif®. afatinib
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Date of statistical analysis plan:	20 OCT 2014 SIGNED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BSA	Body Surface Area
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ICH	International Conference on Harmonisation
IPV	Important protocol violation
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
Q1	Lower quartile
Q3	Upper quartile
RECIST	Response Evaluation in Solid Tumours
SD	Stable disease
StD	Standard deviation
SOC	System Organ Class
TRT A	Treated set (Part A)
TRT B	Treated set (Part B)
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

3. INTRODUCTION

As per the International Conference on Harmonisation (ICH E9) guideline (3), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the Clinical Trial Protocol (CTP), and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the CTP, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

SAS® Version 9.2 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Not applicable.

5. ENDPOINTS

All endpoints in this study, except where specified, will be assessed separately for the monotherapy part of the study (Part A) and for the combination part of the study (Part B). These parts are defined in Section 6.1.

5.1 PRIMARY ENDPOINT

Objective response (with confirmation):

Best overall response of confirmed complete response (CR) or confirmed partial response (PR) recorded since first administration of trial medication and until the earliest of disease progression, death or start of next treatment (either Part B combination therapy or new anti-cancer therapy) in each part separately. Best overall response is the best overall response to trial medication (without clinical disease assessment) according to Response Evaluation in Solid Tumours (RECIST) version 1.1 (see Appendix 10.3 of the CTP) and is calculated relative to the baseline of each respective part.

Criteria for confirmation of best overall response are described by RECIST version 1.1 and in Section 5.1.2 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Best overall response (with and without confirmation)

Defined as for objective response. For both confirmed and unconfirmed best overall response, stable disease (SD) needs to be observed >=35 days after the first dose in each part respectively.

See Section 6.6 for details on how missing or incomplete data (due to missed visits or blurred/unclear images) are handled for best overall response.

Progression-Free Survival (PFS)

Assessed for three time intervals (see Section 6.1 for the start of monotherapy and combination therapy definitions):

- Part A: time from the date of the start of monotherapy to the date of 1st disease progression or death
- Part B: time from the date of the start of combination therapy to the date of 2nd disease progression or death
- Whole study (Part A + Part B): time from the date of the start of monotherapy to the date of 2nd disease progression or death.

And defined for patients presenting with disease progression (according to RECIST version 1.1) or death before start of new anti-cancer therapy, as the shortest duration of the following:

- Date of disease progression - date of first administration of trial medication + 1,
- Date of death - date of first administration of trial medication + 1;

where date of disease progression is the earliest of the following:

- Date of imaging documenting progressive disease (PD),
- Date of progression of disease, recorded at the follow-up visits, occurring prior to commencement of other anti-cancer therapy.

For patients not presenting with disease progression according to RECIST version 1.1 or death before start of new anti-cancer therapy, censoring will be applied according to the following:

- Date of last assessment where patient was known to be progression-free and alive before start of new anti-cancer therapy - date of first administration of trial medication + 1.

For patients not presenting with disease progression according to RECIST version 1.1 or death and lost to follow-up before start of new anti-cancer therapy, censoring will be applied according to the following:

- Date of last assessment where patient was known to be progression-free - date of first administration of trial medication + 1.

Further censoring information with regards to missing or incomplete data (due to missed visits or blurred/unclear images) values is given in Section 6.6 of this document.

PFS will only be based on tumour imaging data, i.e. clinical disease progression will not be considered.

Duration of objective response (without confirmation) [days]:

For patients presenting with unconfirmed objective response, the shortest duration of the following:

- Date of disease progression - date of first assessment indicating objective response + 1,
- Date of death - date of first assessment indicating objective response + 1,
- Date of censoring for PFS - date of first assessment indicating objective response + 1

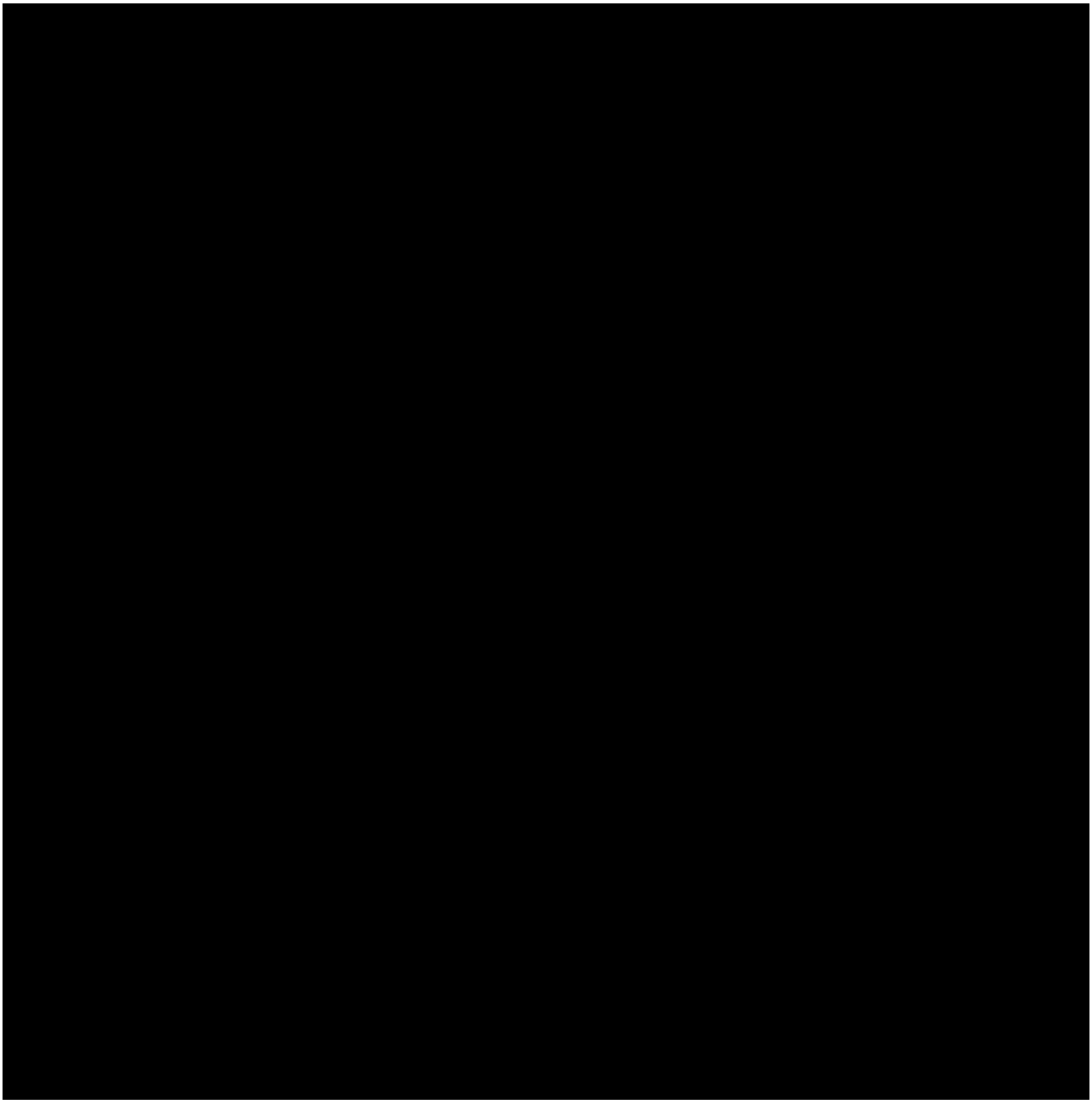
where objective response, date of disease progression and censoring details for PFS are defined earlier on in this section of this document.

5.2.2 Other Secondary endpoints

Safety endpoints

- Number of patients with highest CTCAE grade of 3 or higher
- Change from baseline to end of treatment in SBP
- Change from baseline to end of treatment in DBP

- Number of patients with possibly clinically significant laboratory values by functional group (Haematology, Differentials, Coagulation, Electrolytes, Enzymes and Substrates)



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

The following study periods based on actual start and stop dates of study treatment administration are defined:

- Screening: day of informed consent to day prior to starting afatinib monotherapy.
- **Part A:** On-treatment (monotherapy): day of first administration of afatinib monotherapy to day of last administration of afatinib monotherapy.
- Post-treatment (monotherapy): day after last administration of afatinib monotherapy to either the 28th day after last administration of afatinib monotherapy or the day before the first administration of study paclitaxel/vinorelbine, whichever occurs first.
- **Part B:** On-treatment (combination therapy – if applicable): day of first administration of study paclitaxel/vinorelbine to day of last administration of afatinib or study paclitaxel/vinorelbine (whichever is later) in Part B.
- Post-treatment (combination therapy – if applicable): day after last administration of afatinib or study paclitaxel/vinorelbine (whichever is later) in Part B to the 28th day after last administration of afatinib or study paclitaxel/vinorelbine (whichever is later) in Part B.
- Post-study: 29th day after last administration of study treatment onwards. This includes patients in long-term follow-up.

For safety summaries data recorded up to and including 28 days after last administration of study treatment will be considered as on-treatment (i.e. the actual on-treatment and post-treatment periods defined above will be combined into one ‘on treatment’ analysing treatment for mono- and combination therapy separately).

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations (IPVs). The final column describes which PVs will be used to exclude patients from the different patient analysis sets. Since a per-protocol analysis set is not defined for the analysis of this trial, patients are either excluded from “All” or “None” of the analysis sets.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1.1	Age out of range or patient not female	Inclusion criterion 1 answered 'No' or *demography* eCRF page indicates patient is male and/or <18 years old.	None
	A1.2	Patient does not have proven diagnosis of trial disease or archived tissue sample available for reassessment of HER2 status	Inclusion criterion 2 answered 'No'.	None
	A1.3	Patient does not have stage IV metastatic disease	Inclusion criterion 3 answered 'No'.	None
	A1.4	Patient does not have at least one measurable lesion according to RECIST 1.1	Inclusion criterion 4 answered 'No' or patient doesn't have at least one target lesion ≥ 10 mm if non-lymph node or ≥ 15 mm if lymph node on *tumour evaluation (target lesions part A – monotherapy) according to RECIST 1.1* eCRF page.	None
	A1.5	Patient does not have ECOG score of 0, 1, or 2	Inclusion criterion 5 answered 'No' or 'ECOG performance status' > 2 on screening *physical examination* eCRF page.	None
	A1.6	Patient does not have required life expectancy	Inclusion criterion 6 answered 'No'.	None
	A1.7	Patient has not failed on trastuzumab and/or lapatinib in the neoadjuvant and/or adjuvant setting.	Inclusion criterion 8 answered 'No' or neither 'Was trastuzumab taken?' nor 'Was lapatinib taken?' on the *previous other anti-cancer therapies* eCRF page answered 'Yes' with corresponding 'Therapy mode' neoadjuvant or adjuvant.	None
	A1.8	Patient has not failed on trastuzumab and/or lapatinib in the neoadjuvant and/or adjuvant setting and afatinib monotherapy in the 1st line metastatic setting (only applicable to patients entering part B)	Inclusion criterion 9 answered 'No' or 'date of progression' is missing from *completion part A* eCRF page.	None

Table 6.2: 1 Important protocol violations (cont.)

	A1.9	Patient is not eligible for re-treatment with either paclitaxel or vinorelbine	Inclusion criterion 10 answered 'No' or database indicates patient not eligible at entry to Part B for re-treatment with either paclitaxel or vinorelbine using *previous systemic chemotherapies* eCRF page: • the preferred term for the previous compound is 'PACLITAXEL', 'PACLITAXEL LIPOSOME' or 'PACLITAXEL POLIGLUMEX' but the date of last administration is ≤ 12 months prior to the VPC1V1 date AND • the preferred term for the previous compound is 'VINORELBINE' or 'VINORELBINE TARTRATE'	None
	A2.1	Patient has a requirement for treatment with prohibited concomitant medications	Exclusion criterion 1 answered 'Yes'.	None
	A2.2	Previous or current excluded medical condition	Exclusion criterion 2, 3, 8, 9, 10, 11, 13 or 21 answered 'Yes' or medical review of *baseline conditions* eCRF page indicates excluded medical condition.	None

Table 6.2: 1 Important protocol violations (cont.)

	A2.3	Previous excluded treatment or therapy	Exclusion criterion 4, 5, 6, 25, 26 or 28 answered 'Yes' or indication of excluded prior treatment or therapy by medical review of: • date of last chemotherapy (*other anti-cancer therapies* eCRF page) greater or equal to date of first appearance of metastasis (*screening oncology/breast cancer* eCRF page), or trastuzumab or lapatinib (*previous other anti-cancer therapies* eCRF page) given as first line metastatic therapy • radiotherapy within 4 weeks prior to trial treatment (*previous radiotherapies* eCRF page) • chemotherapy within 4 weeks prior to trial treatment (*previous systemic chemotherapies* eCRF page) • immunotherapy within 4 weeks prior to trial treatment (*previous other anti-cancer therapies* eCRF page where therapy type=1 (immunotherapy)) • trastuzumab or lapatinib taken within 4 weeks prior to trial treatment (*previous other anti-cancer therapies* eCRF page) • surgery (other than biopsy) within 4 weeks prior to trial treatment (*previous surgeries for trial disease* eCRF page) • hormone therapy within 2 weeks prior to trial treatment (*previous other anti-cancer therapies* eCRF page where therapy type=2 (hormone therapy)) • EGFR/HER2-targeted small molecules or antibodies other than trastuzumab and lapatanib in the neoadjuvant and/or adjuvant setting (based on medical review of *previous other anti-cancer therapies* eCRF page where therapy type=1 (immunotherapy) or 3 (other))	None
	A2.4	Active brain metastases	Exclusion criterion 7 answered 'Yes' or 'brain metastases status' on *screening oncology/breast cancer* eCRF page = active.	None
	A2.5	Cardiac left ventricular function with resting ejection fraction of less than 50%.	Exclusion criterion 12 answered 'Yes' or 'LVEF' < 50% on *left ventricular ejection fraction* eCRF page.	None

Table 6.2: 1 Important protocol violations (cont.)

	A2.6	Abnormal laboratory measurement at Screening.	Exclusion criterion 14, 15, 16, 17, 27 or 31 answered 'Yes' or database indicates criterion not met due to one of the following at screening, with no subsequent eligible value prior to first study drug administration: • Absolute neutrophil count (ANC) < 1.5 x 10^9/L • Calculated Creatinine clearance < 60 ml / min (Cockcroft formula – Appendix 1 CTP) • Serum creatinine > 1.5 times upper limit of normal • Bilirubin > 1.5 times upper limit of normal (ULN) • Aspartate amino transferase (AST) or alanine amino transferase (ALT) > 3 times the ULN where patient does not have liver metastases (*oncology/breast cancer history* eCRF page) • AST or ALT > 5 times the ULN where patient has liver metastases (*oncology/breast cancer history* eCRF page) • Platelet count < 100 x 10^9/L or the following at the VPC1V1 visit (part B baseline): • Platelet count < 100,000/mm^3 for afatinib combination treatment with study paclitaxel • Platelet count < 75,000/mm^3 for combination treatment with study vinorelbine. Platelet counts which are ≥75,000/mm^3 and <100,000/ mm^3 prior to treatment with study vinorelbine will be compared against the local CTP approval dates to confirm whether a violation has taken place.	None
	A2.7	Contraception, pregnancy or breast-feeding exclusion criteria met	Exclusion criterion 18 or 19 answered 'Yes' or pregnancy result at screening.is 'positive' or 'Not done (although childbearing potential)'.	None
	A2.8	Other exclusion criteria met	Exclusion criterion 20, 22, 23 or 24 met.	None
	A2.9	Patient treated with study paclitaxel in Part B when eligibility criterion not met	Exclusion criterion 29 answered 'Yes' or the preferred term for the previous compound is 'PACLITAXEL', 'PACLITAXEL LIPOSOME' or 'PACLITAXEL POLIGLUMEX' but the date of last administration is ≤ 12 months prior to the date of first administration of study paclitaxel in Part B	None

Table 6.2: 1 Important protocol violations (cont.)

	A2.10	Patient treated with study vinorelbine in Part B when eligibility criterion not met	Original exclusion criterion 30 answered 'Yes' or the preferred term for the previous compound is 'VINORELBINE' or 'VINORELBINE TARTRATE '	None
B		**Informed consent**		
	B1	Informed consent not available	Inclusion criterion 7 answered 'No' or informed consent date missing	All
	B2	Informed consent too late	Date of informed consent was after screening visit date	None
C		**Trial medication and randomisation**		
	C1.1	Incorrect dose level of afatinib taken at first administration	At Visit C1V1: Dose level from *administration of BIBW 2992* eCRF page not '40' or 'medication number' from *medication dispensed record BIBW 2992* eCRF page indicates 'unit strength' is not '40'.	None
	C1.2	Afatinib dose reduction scheme not followed or treatment not paused appropriately	Based on medical review of the *trial medication compliance (BIBW 2992)* and *medication dispensed record BIBW 2992* eCRF pages for patients who had the AE type and grade as specified in Table 4.1.4: 1 in the CTP.	None
	C1.3	Increase in afatinib dose	Dose of afatinib increased after dose reduction has already occurred.	None
	C2.1	Incorrect trial chemotherapy taken	In part B, study vinorelbine administered instead of study paclitaxel or vice versa. This will be assessed using 'drug administered' and 'medication number' from *(first) administration of paclitaxel or vinorelbine* eCRF page.	None
	C2.2	Incorrect dose level of chemotherapy taken	From *(first) administration of paclitaxel or vinorelbine* eCRF page: Actual dose ≠ (planned dose level x body surface area [BSA] (m^2)) ± 10%	None
	C2.3	Incorrect exposure to combination therapy	Patient stopped afatinib more than 4 weeks before or after chemotherapy or no afatinib taken in Part B	None

Table 6.2: 1 Important protocol violations (cont.)

	C3	Trial medication non-compliance	Medical review of 'administration according to the protocol?'='No' and any associated comments from either of the following eCRF pages: • *Administration of BIBW 2992* • *Trial medication compliance (BIBW 2992)* Review of 'infusion according to the protocol?'='No' and any associated comments from either of the following eCRF pages: • *First administration of paclitaxel or vinorelbine* • *Administration of paclitaxel or vinorelbine*	None
D		**Concomitant medication**		
	D1	Prohibited medication use or radiotherapy during treatment period	Based on medical review of concomitant therapy.	None
G		**Trial specific**		
	G1	Incorrect timing of baseline tumour evaluation	Baseline tumour assessment is >4 weeks prior to study drug administration in Part A.	None
	G2	Patient not withdrawn as per protocol	Patient met at least one of the withdrawal criteria identified in Section 3.3.4.1 of the CTP but was not withdrawn.	None
	G3	Laboratory measurements out of range but chemotherapy not delayed	Most recent platelet count < 75,000/mm^3 or most recent neutrophil count < 1500/mm^3 prior to treatment with study vinorelbine Platelet counts which are ≥75,000/mm^3 and <100,000/ mm^3 prior to treatment with study vinorelbine will be compared against the local CTP approval dates to confirm whether a violation has taken place. OR Most recent platelet count < 100,000/mm^3 immediately prior to treatment with study paclitaxel.	None
	G4	Gap between progression on Part A and start of Part B greater than 28 days with no radiotherapy.	Check 'date of progression' from *completion part A* eCRF page vs date of first administration of study chemotherapy in Part B, taking start and end dates of radiotherapy into account.	None
	G5	Other protocol violations affecting patients' rights or safety		None

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial:

- SCR – Screened patients set
  All patients screened for the trial who completed at least some screening procedures.
- TRT A – Treated set (Part A)
  This patient set includes all patients who were documented to have taken at least one dose of afatinib in Part A.
- TRT B – Treated set (Part B)
  This patient set includes all patients who were documented to have had at least one dose of afatinib and one infusion of either study paclitaxel or study vinorelbine in Part B.

The treated sets for Part A and Part B will be used for all efficacy and safety analyses in parts A and B respectively.

6.5 POOLING OF CENTRES

All centres will be analysed together, with any centre effects being ignored. Country or region effects will also not be considered.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, missing efficacy data will not be imputed and all reasonable efforts will be taken during the study to obtain such data. If missing data do occur though, they will be handled as follows:

For PFS, patients will be censored using date of first administration of trial medication in the following situations:

- Baseline tumour assessment missing,
- First two post-baseline tumour assessments immediately preceding disease progression or death missing or not evaluable.

For PFS and duration of objective response, patients will be censored using date of last post-baseline assessment where patient was known to be progression-free in the following situation:

- Two consecutive post-baseline tumour assessments missing or not evaluable (not including first two) immediately preceding disease progression or death.

A patient's best overall response will be set to not evaluable (NE) in the following situations:
- Missing baseline tumour evaluations,
- No post-baseline tumour evaluations prior to or on day of PD, last dose+1 or death,
- No protocol-specified post-baseline tumour evaluations (unless unscheduled tumour evaluation indicates PD in which case patients will be assigned a best overall response of PD),
- Two consecutive protocol-specified post-baseline tumour evaluations missing or NE (unless prior tumour evaluation indicates CR, PR or SD or subsequent tumour evaluation indicates PD).

If a patient has died and the death date is missing or incomplete, then the earliest conceivable date will be imputed, given the available information.

If day of first histological diagnosis or first appearance of metastases is missing it will be imputed using '15'. If month of first histological diagnosis or first appearance of metastases is missing it will be imputed using 'June'.

Missing or incomplete AE dates are imputed according to BI standards (see reference document 001-MCG-156 "Handling of missing and incomplete AE dates").(1)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values for Part A will be the measurements taken most recently prior to first administration of afatinib in Part A. For patients entering Part B, baseline values will be the measurements taken most recently prior to first administration of study paclitaxel or study vinorelbine on day 1 of the combination treatment period. Note that for some procedures (e.g. ECOG performance status, vital signs, laboratory tests), this may be the measurement taken on the same day the patient starts their treatment in each part, but since the assessments are made before study drug administration, these are acceptable to use as baseline measurements.

Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'; therefore 'Day 0' will not exist. This will be performed separately for Parts A and B.

All data collected at a visit level will be presented according to the actual protocol visit it was measured at.

7. PLANNED ANALYSIS

All analyses, except where specified, will be performed on the TRT A and TRT B analysis sets for parts A and B respectively.

Patient disposition (number of patients screened, treated in Part A etc.) will be presented for all patients in the screened set. If applicable, the number of patients who will continue treatment at the time of reporting will be reported in the disposition table, separately. A patient is deemed to have completed the trial once they show progressive disease according to RECIST in Part B.

The frequency of patients with IPVs will be presented.

Descriptive statistics for continuous variables will generally be n (number of patients with non-missing values), mean, standard deviation (StD), minimum, Q1 (lower quartile), median, Q3 (upper quartile), maximum. In general, means, StDs, medians, Q1 and Q3 will be presented to one more decimal place than the raw data. Minima and maxima will be presented to the same number of decimal places as the raw data.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective population. As there are fewer than 100 patients in the study, percentages will generally be rounded to the nearest integer. A missing category will be displayed if there are actually missing values. Percentages will generally be based on all patients in the respective patient set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics and/or frequency counts as described in Section 7 will be presented for the following eCRF pages:

- *Demographics*
- *Oncology/breast cancer history*
- *Target lesions (baseline sum) according to RECIST 1.1*
- *Previous systemic chemotherapies Previous radiotherapies*
- *Previous other anti-cancer therapies*
- *Tumour biopsy*

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

The frequency of patients with different concomitant diseases (baseline conditions) will be presented. This presentation will be categorised as follows:

- Baseline conditions

- Sign/Symptom of trial disease
- ECG finding

Concomitant medications will be summarised according to whether they are concomitant with Part A or Part B. Medications which are prior to first study drug administration will be listed only.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

Compliance with afatinib will be calculated for parts A and B separately as follows:

$$\left(1-\frac{\text{Number of tablets missed not in accordance to the CTP}}{\text{Number of days in respective part of study *}}\right)\times 100$$

*Since posology is one tablet per day.

7.4 PRIMARY ENDPOINT

An exact binomial 95% confidence interval (Clopper-Pearson) will be calculated for the proportion of patients who achieve confirmed objective response (see Section 5.1) in each part separately. These point estimates and confidence intervals will be further presented by the subgroups defined in Section 6.4.

The objective response rate, determined without confirmation, will also be presented along with an exact 95% Clopper-Pearson confidence interval.

Additionally, confirmed objective response rates will be evaluated by a Bayesian approach. Further details are given in Appendix 9.1.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

None of the secondary endpoints which use RECIST 1.1 require confirmation, except for SD.

Best overall response

Frequency tables and exact binomial 95% confidence interval (Clopper-Pearson) 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): CR, PR, SD, PD, NE. This will be presented for both confirmed and unconfirmed responses.

Progression-Free Survival (PFS)

PFS (as described in Section 5.2.2) will be assessed based on the Kaplan-Meier method for each part separately and point estimates together with confidence intervals (based on Greenwood's method) will be provided for median PFS.

See Section 6.6 for censoring rules.

Duration of objective response

Descriptive statistics will be produced for the duration of objective response (see Section 5.2.2) for parts A and B separately. The duration will only be calculated for those patients with an objective response. Duration of objective response will also be summarised using Kaplan-Meier plots.

Frequency counts of time to objective response by planned imaging week will also be presented.

7.5.2 Other Secondary endpoints

Safety endpoints: See Sections 7.8.1, 7.8.2 and 7.8.3.

7.7 EXTENT OF EXPOSURE

Calculated in days for each part separately and overall:

Date of last administration of trial medication – date of first administration of trial medication + 1.

Total treatment time therefore includes time when treatment was temporarily discontinued and subsequently reintroduced. Categorisations for total treatment time are defined for Part A as follows:

- 1 - 21 days,
- 22 - 42 days,
- 43 - 84 days,
- 85 - 126 days,
- 127 - 168 days,
- >168 days

For Part B:

- 1 - 21 days,
- 22 - 42 days,
- 43 - 84 days,
- >84 days

And for the overall summary:

- 1 - 21 days,
- 22 - 42 days,
- 43 - 84 days,
- 85 - 126 days,
- 127 - 168 days,
- 169 - 210 days,
- 211 – 252 days,
- >252 days

If there is discordance between the date of last intake of afatinib and study chemotherapy, the latest date will be used for the calculations in Part B and the overall summary.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the respective treated set and presented for parts A and B separately.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). For this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, AE occurrences, i.e. AE entries on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same Medical Dictionary for Regulatory Activities (MedDRA) lowest level term was reported for the occurrences.

- The occurrences were time-overlapping or time-adjacent (the second occurrence started before or one day after the end of the first occurrence).
- Treatment did not change between the onset of the occurrences or treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence.

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarisation of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (2)

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake until 28 days after last drug intake will be assigned to either mono- or combination therapy (depending on the date of onset). Since times are not collected for AEs, any AEs occurring on the first day of Part B will be assigned to combination therapy. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after last drug intake + 28 days will be assigned to ‘post-treatment’ and presented in listings only. For details on the treatment definitions, see Section 6.1.

An overall summary of AEs will be presented. This summary will exclude the rows ‘Severe AEs’, ‘Significant AEs’ and ‘Other significant AEs’ but will include additional rows for ‘AEs leading to dose reduction’ and ‘AEs by maximum CTCAE’ grade.

The frequency of patients with adverse events will be summarised by maximum CTCAE grade (and overall), treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- AEs overall.
- Drug related AEs.
- AEs leading to dose reduction.
- AEs leading to treatment discontinuation.
- Serious AEs.
- Drug related AEs leading to treatment discontinuation.
- Drug related and serious AEs
- AEs leading to death.
- Non-serious AEs

The PTs will be sorted by descending incidence within SOC.

The above tables except for AEs leading to death will be repeated replacing SOC and PT with project defined grouping of AE terms for selected incidence rates. Details of the project defined groupings are defined in the technical TSAP.

Additional AE tables showing time at risk, frequency counts and 95% confidence intervals, outcomes, consequences, maximum CTCAE grade, time to first onset and time to discontinuation will be produced for three of the project defined groupings (diarrhoea, rash

and stomatitis), and for AEs of special interest including 'Renal insufficiency', 'Leukopenia', 'Neutropenia' and 'Neuropathy'. Note that the leukopenia group will not contain cases of neutropenia since these are being presented separately.

All of the tables described above will be produced separately for AEs assigned to parts A and B. See Section 6.1 for the treatment period definitions.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4). CTCAE grades will be applied to laboratory parameters using the current BI oncology standard as detailed in the document 'Conversion of laboratory parameters to CTCAE grades within BI' (5).

Descriptive statistics of all laboratory values by visit will be provided including changes from baseline. Frequency tables of transitions relative to the reference range and of possible clinically significant abnormalities will be produced. For those parameters that have CTCAE grading, possible clinically significant abnormalities are defined as those laboratory values with a CTCAE grade ≥ 2 that have had an increase of ≥ 1 grade from baseline. For those parameters for which no CTCAE grade has been defined, standard BI project definitions will be used to decide on clinical significance.

Three further frequency tables will show:

- the transition of CTCAE grade from baseline to worst value
- the transition from baseline to last value on treatment
- the transition from worst value to last value on treatment.

In order to assess potential Hy's law cases, scatter plots will be produced of peak ALT values versus peak total bilirubin values within 30 days of the ALT value. The following algorithm will be applied:

- Identify all ALT values >= 3*ULN
- Do any of these have a bilirubin value >= 2*ULN within 30 days of the observed peak ALT value?
  → if YES then keep the patient observation with the highest ALT value (along with the highest bilirubin value within 30 days).
  → if NO then keep the patient observation with the highest bilirubin value (along with the highest ALT value 30 days prior to this).

Similar plots will be produced for peak AST versus total bilirubin.

The focus of the laboratory data analysis will be on the following laboratory parameters:

- Low values: haemoglobin, neutrophils, platelets, white blood cell count, magnesium, potassium.
- High values: International Normalised Ratio, creatinine, AST, ALT, total bilirubin, alkaline phosphatase.

The tables described above will be produced for laboratory data recorded during parts A and B separately.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

No data. Any clinically relevant findings were to be reported as AEs.

7.8.5 Others

Left ventricular ejection fraction:

Only descriptive statistics are planned for this section of the report.

8. REFERENCES

1 001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

2 001-MCG-156: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

3 CPMP/ICH/137/95: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

4 001-MCG-157: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

5 BI Guidance document ‘Conversion of laboratory values to CTCAE grades within Boehringer Ingelheim’

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP:

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**13-Jul 12**	[redacted]	None	This is the final TSAP without any modification
Revised	**20-Oct-14**	[redacted]	Title page	Date and referenced protocol version updated. [redacted]
			3	Clarified SAS® version 9.2 *or higher*
			5.1	Efficacy was only to be assessed until the end of treatment in each respective part but to fully utilise all data collected, efficacy will now be assessed from start of treatment in each part to the start of next treatment (Part B or new anti-cancer therapy). Missing data detail removed since covered in Section 6.6.
			5.2.1 and 5.2.2	Moved endpoints from Secondary to Key Secondary in accordance with Section 7.3.2.1 of the CTP. Added detail on confirmation for SD. Removed 'date of detection of new lesions' from PFS section since this is covered by the 'progressive disease' bullet. Removed "Date of last administration of trial medication-date of first assessment indicating objective response+1" bullet from "Duration of objective response" section since covered by censoring for PFS bullet. Made other secondary endpoint definitions more specific.
			[redacted]	[redacted]
			6.1	Removed reference to radiotherapy period since it's not a study treatment and the data are very limited.

Table 10: 1 History table (cont)

			6.2.1	Removed check for stage IV metastatic disease based on TNM classification at study inclusion (PV A1.3), for consistency within project and between projects for this compound. Corrected limits for measurable disease according to RECIST 1.1 (PV A1.4). Added PVs C2.3 "incorrect exposure to combination therapy" and G5 "Other protocol violations affecting patients' rights or safety". Altered platelet count limit in G3 from 75,000 to 100,000 /mm^3 for treatment with vinorelbine in accordance with CTP amendment 5 (06 Nov 2012).
			6.3	Removed requirement to have been dispensed study medication since this is implied by the documentation of administration.
			6.6	Added details on when a patient's best overall response will be 'not evaluable'. Added detail on imputation of date of death.
			6.7	Removed summaries during radiotherapy period. Removed detail on visit labelling – more appropriate for technical TSAP.
			7	Added definition of patients who complete the trial. Changed number of decimal places for percentages.
			7.3	Removed calculation for treatment compliance since this is how they calculate compliance at site and only the percentage is provided on the database.
			7.4	Removed analysis of best overall response since covered later in the document.
			7.5	Moved endpoints from Secondary to Key Secondary in accordance with Section 7.3.2.1 of the CTP.

Table 10: 1 History table (cont)

			7.5.1	Added 95% Clopper-Pearson confidence interval for best overall response for consistency within project. Removed text stating that a proportional hazards model will explore the subgroups since only one treatment group in each part. Added Kaplan-Meier plots for duration of objective response and frequency counts by planned imaging week.
			7.7	Added an extra qualitative exposure category.
			7.8.1	Removed summaries based on the radiotherapy period. Added detail on AEs of special interest and project-defined groupings.
			7.8.2	Added detail on Hy's law assessments.
			7.8.4	Clarified that clinically relevant ECG findings were to be reported as AEs and no specific ECG data were to be collected.
			All	Administrative changes.

APPROVAL / SIGNATURE PAGE

Document Number: c01946576 **Version Number**: 3.0

Document Name: 8-01-tsap

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 (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	20 Oct 2014 21:50 CEST
Approval-Trial Clinical Monitor	[redacted]	21 Oct 2014 10:06 CEST
Approval-Project Statistician	[redacted]	28 Oct 2014 08:07 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed