SIGNATURE INFORMATION

Document: 1200-0125--tsap

Document No.: T12-3007-01

Title LUX-Lung 8: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy

SIGNATURES (ELECTRONICALLY OBTAINED)

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SIGNATURE INFORMATION (continued)

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SIGNATURES (ELECTRONICALLY OBTAINED)
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Trial Statistical Analysis Plan

T12-3007-01

BI Trial No.:	1200.125
Title:	**LUX-Lung 8**: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy
Investigational Product:	Afatinib, BIBW 2992
Responsible trial statistician:	Telephone: Fax:
Date of statistical analysis plan:	18 APR 2012 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ANCOVA	Analysis of Covariance
BRPM	Blinded Report Planning Meeting
CI	Confidence Interval
CR	Complete Response
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DMC	Data Monitoring Committee
EMEA	European Agency for the Evaluation of Medicinal Products
HLT	High Level Term
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not Evaluable
NN	Non-CR/Non-PD
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PSTAT	Project Statistician
PR	Partial Response
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
s.d.	Standard Deviation
SD	Stable Disease
SMQ	Standardised MedDRA query

Term	Definition / description
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TOC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (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, randomization.

SAS® Version 9.2 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Tumour shrinkage measurement is changed to the maximum decrease of sum of target lesion diameters (i.e. the minimum sum of target lesion diameters after randomisation minus baseline) for better interpretability.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint of this study is progression-free survival, as determined by RECIST 1.1 (1).

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

The key secondary endpoint is overall survival.

5.2.2 Other secondary endpoints

Refer to Section 5.1.1 of the CTP.

Other secondary endpoints of this trial are:

- Objective response (CR, PR) according to RECIST 1.1 (1)
- Disease control (CR, PR, SD) according to RECIST 1.1 (1)
- Tumour shrinkage
- Health-related Quality of Life (HRQoL)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, all randomised patients will be classified into either 'Afatinib' or 'Erlotinib' as randomised. For efficacy analyses patients will be analysed as randomised. For safety analyses, treated patients will be analysed according to the initial treatment taken.

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

- Pre-screening: for any data recorded prior to day of informed consent.
- Screening: day of informed consent to day prior to starting study treatment.
- On-treatment: day of first administration of study treatment to the 28th day after last administration of study treatment.
- Post-treatment: day after last administration of study treatment to the 28th day after last administration of study treatment.
- Post-study: on or after the 29th day after last administration of study treatment.

For safety summaries data recorded up to 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), unless otherwise specified according to the protocol Section 5.2.2.2 and protocol Appendix 10.7.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol set (PPS) will be defined for this study; however patients with potentially important protocol violations (IPVs) will be documented. The following list of potentially IPVs will be used; note that this is a working list and may not be finalised until the final Blinded Report Planning Meeting (BRPM) prior to database lock.

Table 6.2: 1 Important protocol violations

Category/code		Description	Comment
A		**Entrance criteria not met**	
	A1	Diagnosis of NSCLC questionable	Refer to IN 1
	A2	Prior treatment for NSCLC does not meet entrance criteria	Refer to IN 2,3, EX 1,2
	A3	No measurable disease according to RECIST 1.1 at screening	Refer to IN4
	A4	Abnormal screening values	Refer to IN7
	A5	Other deviation from entrance criteria	Refer to in/exclusion criteria
B		**Informed consent**	
	B1	Informed consent not available	Signed informed consent not available
	B2	Inadequate informed consent	Informed consent obtained but not adequately done (e.g., obtained after the study specific activities were done, patient signed the wrong version of the ICF, version signed did not receive prior IRB/EC approval).
C		**Trial medication & randomization**	

	C1	Incorrect medication dose taken	e.g., starting dose is not 40 mg for afatinib or 150 mg for erlotinib; dose was not paused, resumed, reduced, or discontinued according to protocol, including incorrect dose interruptions during concomitant treatment
	C2	Randomization not followed	e.g., randomized to afatinib but received erlotinib or vice versa.
	C3	Non-compliance	Check MQRM listings for extreme non-compliance only
D		**Concomitant medication**	
	D1	Use of prohibited concomitant medications	Review concomitant medications for prohibited medication use.
E		**Trial specific**	
	E1	Procedures not performed according to protocol	Check applicable data.
	E2	Prohibited on study interventions given	Patient received therapeutic radiation or another anti-cancer treatment during on study period

6.3 PATIENT SETS ANALYSED

- Randomised set:
  This patient set includes all randomised patients, whether the patient received study medication or not.

- Treated set:
  This patient set includes all patients who received at least one dose of investigational treatment.

Ranomised set will be used for all efficacy analyses and treated set will be used for all safety analyses.

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

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. Patients with unknown vital status, missing tumour imaging data and missing HRQOL assessments will be censored for time to event analyses; further details are provided in Section 7.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (2)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first administration of study drug.

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.

For the presentation of tumour response data which will follow a calculated visit approach based on the protocol specified tumour imaging schedule. Imaging will be performed at week 8, 12 and 16, and in 8-weekly intervals thereafter from the date of randomisation; images will be slotted to Week 8, 12, 16, 24, … XX based on their relative day and using a ± 2, ±4 week window as appropriate (images taken in the first 4 weeks from randomisation will be slotted to Week 8). If two or more images for a patient are assigned to one interval then the last assessment will be used to ensure progressive disease is not missed. Note German sites only will have an X-ray completed instead of a CT or MRI for the week 12 assessment. If disease progression is suspected, a follow-up CT or MRI will then be completed. In the case where a CT or MRI is not completed for the week 12 assessment, it will be handled as missing assessment.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max. For appendix tables, the set of summary statistics is: N / Mean / s.d. / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

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 treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics using standard summary tables for the randomised set of patients are planned for this section of the report.

7.3 TREATMENT COMPLIANCE

Descriptive statistics using standard summary tables for the treated set of patients are planned for this section of the report. A summary of whether patients took their treatment according to the protocol and whether they missed any doses will be produced for each planned visit. In addition a summary of overall percentage compliance will be produced using visit dates and the total number of doses missed during the study.

7.4 PRIMARY ENDPOINT

The primary endpoint of this study is PFS, defined as the time (weeks) from the date of randomisation to the date of disease progression, or date of death whichever is earlier, subjected to the censoring rule (see Table 7.4: 1). The date of progression for the primary analyses will be determined based on an independent central imaging review incorporating both radiologist and oncologist reviews, blinded to treatment assignments. The primary endpoint analysis will be performed on the randomised set of patients.

A stratified log-rank test will be used to test the effect of afatinib on PFS compared to erlotinib. The test will be stratified by race (Eastern Asian and Non-Eastern Asian). An interim analysis is planned using Haybittle-Peto stopping boundary (p-value < 0.0001). The details of the interim analysis are described in the DMC SAP. The final significance level need not be adjusted in the case of one interim look. The final significance level will be adjusted as necessary in case additional interim looks are requested by the DMC.

A Cox proportional hazard model, stratified by race will be used to estimate the hazard ratio and 95% confidence interval (CI) between the two treatment groups. Kaplan-Meier estimates and 95% CIs (using Greenwood's standard error estimate) will be tabulated at time points of

every 12 weeks and will include a comparison of the treatment groups using a z-test (approximation of the normal distribution). Kaplan-Meier curves for the two treatment groups will also be produced.

A descriptive analysis of PFS will be performed at the time of the final analysis.

The rules to determine whether or not patients have had a PFS event (progression or death) along with the date of event or date of censoring (for those with no event) are specified in Table 7.4: 1. These rules will be applied to both the independent central review and investigator assessed data prior to analysis. A summary table of the reasons for censoring will be produced by treatment group.

Table 7.4: 1 Rules to determine events and censoring for PFS

Rule #	Situation	Outcome (event or censored)	Date of PFS event or censoring
1	No baseline tumour assessment (no death before second scheduled assessment)	censored	Date of randomisation
2	Progressed from central imaging (no missed radiologic assessments)	event	Date of PD
3a	Non-PD from central imaging[1], death before next scheduled assessment	event	Date of death
3b	Non-PD from central imaging[1], one missed assessment, death or progression after date of missed assessment, but before a second scheduled assessment	event	Date of PD or death
3c	Non-PD from central imaging[1], more than one consecutive missed assessment, death or progression after date of second missed assessment	censored	Date of last imaging before missed assessment
3d	Non-PD from central imaging[1], more than one consecutive missed assessment, non-PD according to imaging after missed assessments	censored	Date of last non-PD imaging
4	New anti-cancer medication before progression or death	censored	Date of last imaging before new anti-cancer medication
5	Death before the scheduled date of first imaging	event	Date of death
6a	No imaging performed post-baseline, patient dies between first and second scheduled assessments	event	Date of death
6b	No imaging performed post-baseline, patient dies after second scheduled assessment	censored	Date of randomisation
6c	No imaging performed post-baseline, vital status is unknown or patient known to be alive	censored	Date of randomisation
7	Alive and not progressed from central imaging (no missed assessments)	censored	Date of last imaging

[1] - From the last assessment at which CR, PR or SD was assessed.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Overall survival, defined as the time from randomization to death, is the key secondary endpoint.

A Cox proportional hazard model, stratified by race, will be used to estimate the hazard ratio and the corresponding 95% confidence interval. Additionally, a stratified log-rank test will be performed. Kaplan-Meier estimates of OS and 95% CIs (using Greenwood's standard error estimate) will be tabulated at 12-week interval and compared at each time point with z-test. Kaplan- Meier curves will be presented graphically.

OS will be analysed twice. The first analysis will be performed at the time of the primary PFS analysis using a Haybittle-Peto stopping boundary (p-value <0.0001). The primary analysis of survival is planned at 632 deaths. However, if the futility analysis of PFS curtails accrual at 500 patients, the primary analysis of OS will be performed after 80% of the randomized patients have died.

7.5.2 Other Secondary endpoints

7.5.2.1 Best RECIST assessment

Each patient will be assigned to one of the following RECIST categories, CR, PR, SD, Non-CR/Non-PD (NN), PD or Not Evaluable (NE), irrespective of protocol violations or missing data.

Objective response is defined as CR or PR. Time to objective response is the time from randomization to the date of first documented CR or PR. The duration of objective response is the time from first documented CR or PR to the time of progression or death. Disease control is defined as CR, PR, SD or NN. The duration of disease control is the time from randomization to progression or death defined only for those patients with disease control.

Logistic regression, stratified by the same stratification factors used for the analysis of PFS, will be used to test for a difference between regimens for objective response and for disease control based on central imaging assessment. Nominal significance levels will be reported.

Time to response will be summarised by the planned imaging time points. Descriptive statistics will be calculated for the duration of objective response and duration of disease control, where applicable patients will be censored as for the PFS primary analysis.

A summary of objective response rate and disease control rate using the investigator assessment of best overall response will also be produced, along with a table comparing the investigator best overall RECIST assessment with the corresponding central imaging assessment.

The impact on objective response for each of the subgroups defined in Section 6.4 will be explored. The logistic model detailed above but without the stratification factors will be used. A 'forest plot' will be provided presenting the odds ratio (Afatinib vs. Erlotinib) and corresponding 95% CI for each subgroup category. Subgroup analyses will only be performed on the independent central imaging assessments.

The RECIST 1.1 guidelines state that confirmation of response is not required for randomized Phase III studies that have PFS as the primary endpoint; hence the above summaries will be produced without the requirement for confirmation. However, for completeness all the above

summaries and analyses will be repeated with the requirement for confirmation, these will be considered secondary in nature.

7.5.2.2 Tumour shrinkage

Tumour shrinkage for each patient, measured (via central imaging review) as the maximum decrease from baseline (i.e. minimum sum of target lesion diameters after randomisation minus baseline), will be compared for the two treatment groups. An analysis of covariance (ANCOVA) for the minimum sum of diameters, with the baseline sum of diameters fitted as a covariate and the randomisation strata fitted as factors will be performed.

In addition waterfall plots of the maximum percentage reduction from baseline sum of target lesion diameters will be presented for each treatment group.

7.5.2.3 Patient-reported Outcomes

HRQOL questionnaires as measured by the EORTC QLQ-C30 and QLQ-LC13 at baseline, during treatment and follow-up will be included in the analysis. All scoring of the symptom scales/items will follow the EORTC scoring algorithm.

The analyses will focus on cough, dyspnea and pain; specifically:

- Cough: Q31 - How much did you cough? (QLQ-LC13)

- Dyspnoea: Composite of: Q33 - Were you short of breath when you rested? Q34 - Were you short of breath when you walked? Q35 - Were you short of breath when you climbed stairs? (QLQ-LC13). Individual item from QLQ-C30, Q8 - Were you short of breath?

- Pain: Composite of: Q9 - Have you had pain? Q19 - Did pain interfere with your daily activities? (QLQ-C30). Individual items from QLQ-LC13, Q40 - Have you had pain in your chest? Q41 - Have you had pain in your arm or shoulder? Q42 - Have you had pain in other parts of your body?

For each of the summary scales and items measuring the above the treatment groups will be compared for the following:

<u>Distribution of patients improved, stable or worsened</u>

Improvement will be defined as a score that improves from baseline by at least 10 points (on the 0-100 point scale) at anytime during the study. If a patient has not improved, worsening will be defined as a 10 point worsening at anytime during the study. Otherwise, a patient will be considered as stable.

The number and percentage of patients falling into each of these three categories will be summarised by treatment group. All randomized patients will be included in the denominator. A logistic regression model, stratified by stratification factor race will be used

to compare the distribution of patients improving/not improving across the two treatment groups.

Time to deterioration

Time to deterioration (months) is defined as the time from randomisation to an increase (worsening) from the baseline score of at least 10 points on the 0-100 point scale. Patients who die before deteriorating and before the end of follow-up will be analysed as having deteriorated at the time of death. Disease progression without scale deterioration will be censored at the time of the last scale measurement. Patients with no HRQoL assessments will be censored at day of randomisation. Patients who are alive with no disease progression and no scale deterioration at the end of the follow-up will be censored at the date of last questionnaire.

This time to event data will be analysed and summarised using the same methodology as for the primary efficacy endpoint, refer to Section 7.4. The hazard ratios will be displayed using Forest plots.

Change in scores over time

Changes in scores over time will be assessed using longitudinal models; these will be mixed-effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects race. The models will allow the slope to change at 8, 12, and 16 weeks. Each model will also include the two random effects of intercept and slope (time from randomisation). The area under the estimated growth curve (AUC) up to the median follow-up time will be calculated as a summary measure for each treatment group; this will be divided by the median follow-up time so that it can be interpreted as the mean HRQOL score up to the median follow-up time. The treatment effect will be estimated as the average difference between the treatment group means scores, together with a 95% confidence interval and associated p-value based on a t-statistic with degrees of freedom calculated using the Kenward-Roger method. The results of the analyses will be displayed using Forest plots.

In addition, all single items and subscales (functional and symptom) from both questionnaires will be analysed in a similar fashion to summarise the impact of therapy over the entire profile of the measures, and to examine the consistency of component items with the composite measures.

Note as higher scores represent a ‘better’ level of functioning; deterioration in scales/items related to functioning will be defined as a decrease from baseline score of at least 10 points.

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

7.7 EXTENT OF EXPOSURE

Total treatment time (days and number of courses) will be calculated for each patient; off-drug periods due to non-compliance or toxicity prior to permanent discontinuation will be included as treatment time. In addition the total treatment time will be summed over all patients and transformed to patient years. Standard descriptive summaries, by treatment group, of these data will be provided for the treated set of patients.

A Kaplan-Meier plot showing the number of patients at risk (exposed) during the study treatment period will also be produced.

Further summaries will also be produced:

- Treatment time (days) broken down by each dose level (50 mg, 40 mg, 30 mg and 20 mg for afatinib; 150 mg, 100 mg and 50 mg for erlotinib).
- Number and proportion of patients on each dose level over time.
- Time to first dose reduction and duration (days) of off-drug periods prior to first dose reduction.
- Plot of proportion of patients with the first dose reduction over time

Summary of time to dose escalation will be produced only for afatinib treatment group.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the 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

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 summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries'. (7)

The analysis of adverse events will be based on the concept of treatment emergent adverse events (TEAE). That means that all adverse events occurring between first drug intake till 28 days after last drug intake will be assigned to the randomised treatment. 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' (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented. This summary will include the first 5 categories from the list below and AEs by highest CTC grade.

The frequency of patients with adverse events will be summarised by highest CTC grade (grade 3, 4, 5 and all grades to allow both treatment groups to fit on one page), treatment, primary system organ class and preferred term. Separate tables will be provided for patients with each of the following AE categories:

- All AEs.
- Drug related AEs.
- AEs leading to dose reduction.
- AEs leading to treatment discontinuation.
- Serious AEs.
- Drug related serious AEs.
- AEs leading to death.
- AEs in Afatinib patients who dose escalate from 40 mg to 50 mg.

The system organ classes will be sorted according to the standard sort order specified by EMEA, preferred terms will be sorted by frequency (within system organ class).

In order to most accurately characterize those adverse events related to different mechanism, MedDRA SMQ and HLT (with some modification) will be used to group MedDRA PT for rash/acne, stomatitis, ocular effects, lip effects, nail effects and fatigue. As a first step in the analysis of grouped AE, all constituent PT will be presented in a separate table for each grouped AE. The first 5 standard tables will be supplemented with tables using the grouped AE. Groupings will follow the project standard and details are defined in the technical TSAP. In these tables the grouped AEs will replace the original PTs for all AEs that are included within the grouped term. The grouped AE categories will then be tabulated along with all remaining MedDRA PTs, sorted by descending frequency. A reference table presenting all project defined groupings and MedDRA PTs within each grouping will also be produced.

Additional tables will be produced to describe the frequency, intensity, time to onset, and clinical consequences for AE of special interest, diarrhea and rash/acne.

Separate listings will be prepared for patients who are identified as having experienced any of the following AE. For AE other than the single PT dehydration, identification will be based upon modified MedDRA SMQ and HLT groupings. If sufficient events occur within the trial, analyses similar to those for diarrhea and rash/acne may be performed.

- dehydration
- renal insufficiency
- hepatic impairment
- ILD-like events
- heart failure

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). CTCAE version 3.0 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' (9).

Primary laboratory tests are defined as:

- Low values (-): haemoglobin, total WBC, platelets, neutrophils(only at baseline), potassium, magnesium, sodium, and GFR
- High values (+): AST, ALT, alkaline phosphatase, aPTT, INR, creatinine, and total bilirubin

The following analyses will be presented for the primary laboratory tests:

- descriptive statistics at each planned assessment,
- frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment, and
- frequency of patients with possible clinically significant abnormalities.

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

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

7.8.3 Vital signs

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

A summary table of left ventricular ejection fraction (LVEF) values will be produced by each scheduled visit along with the change from baseline. An additional summary will be

produced of the baseline along with the minimum on treatment value, change from baseline to minimum value, last LVEF on treatment and the change from baseline to last LVEF on treatment. The number of patients with a significant LVEF event will also be presented; a significant event is defined as a decrease of ≥20% relative to baseline that is also below the institutional lower limit of normal or 50%.

7.8.4 ECG

Not applicable.

7.8.5 Others

ECOG performance score:

A descriptive summary of ECOG performance score will be produced by each scheduled visit along with the change from baseline.

8. REFERENCES

1 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247 [R09-0262].

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3 P Korhonen and J Palmgren 'Effect modification in a randomized trial under non-ignorable non-compliance: an application to the alpha-tocopherol beta-carotene study', Applied Statistics (2002) 51, Part 1: 115-133 [R10-4999]

4 P Korhonen, N Laird and J Palmgren 'Correcting for non-compliance in randomized trials: An application to the ATBC study', Statistics in Medicine (1999). 18, 2879-2897 [R10-5000]

5 J Robins and D Finkelstein 'Correcting for Noncompliance and Dependent Censoring in an AIDS Clinical Trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests', Biometrics (Sept 2000), 56, 779-788 [R10-4487]

6 J Robins 'Information recovery and bias adjustment in proportional hazards regression analyses of randomized trials using surrogate markers' Proceedings of the Biopharmaceutical Section, American Statistical Association (1993), 24-33 [R10-4484]

7

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	18-APR-12		None	This is the final TSAP without any modification