Trial Statistical Analysis Plan

c09176328-02

BI Trial No.:	1200.261
Title:	LUX-Bladder 1: Phase II open label single arm exploratory trial of oral afatinib monotherapy following platinum failure for patients with advanced/metastatic urothelial tract carcinoma with genetic alterations in ERBB receptors. Including protocol amendment version 2.0 [c03510257-02]
Investigational Product:	Afatinib (Giotrif, Gilotrif)
Responsible trial statistician:	Telephone: Fax: Email:
Date of statistical analysis plan:	01 Oct 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
BRPM	Blinded Report Planning Meeting
CR	Complete Response
CRF	Case Report Form
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
DCR	Disease Control Rate
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor, also known as ERBB1
EMEA	European Agency for the Evaluation of Medicinal Products
ERBB2	Second member of the ERBB family of proteins
ERBB3	Third member of the ERBB family of proteins
HLT	High Level Term
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IPV	Important Protocol Violations
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NCI	National Cancer Institute
NE	Not Evaluable
NN	Non-CR/Non-PD
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDL1	Programmed Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetics
PSTAT	Project Statistician
PR	Partial Response
PT	Preferred Term

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Term	Definition / description
PV	Protocol Violation
RECIST	Response Criteria for Solid Tumours
SD	Stable Disease
SMQ	Standardised MedDRA query
TOC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

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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., study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

The validated SAS® version will be used that is in place on the BI system at the time of analyses. Currently Version 9.3 is being used.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The protocol was amended to modify the futility analysis criterion to assess ORR as well as PFS6. This amendment is reflected in Sections 7.4 and 7.5.1 of this document.

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5. ENDPOINTS

5.1 PRIMARY ENDPOINT

This is an open label, uncontrolled, exploratory phase II trial with two patient cohorts. The purpose of this trial is to assess the anti-tumour activity and safety of afatinib monotherapy in patients with urothelial tract carcinoma carrying ERBB2 or ERBB3 mutations or ERBB2 amplifications (Cohort A), and EGFR amplification positive tumours (Cohort B), progressing despite previous platinum based chemotherapy, and thereby to improve their prognosis.

Cohort A of the study follows a two stage design where an analysis for futility will be performed at the end of stage 1 to determine if the stage 2 of cohort A will be carried out. Cohort B of the study will include up to 10 patients with EGFR amplification. Analysis will be conducted in parallel to, and independent of cohort A.

The primary endpoint of this study is progression-free survival rate at six months (PFS6), as assessed at the investigative sites, in the ERBB2/ERBB3 cohort (Cohort A). Patients who are alive and progression-free at the 24-week assessment will be considered successes.

RECIST 1.1 (2) will be used to determine all response and progression endpoints.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

- The key secondary endpoint for the ERBB2/ERBB3 cohort (Cohort A) is confirmed objective response rate (best overall response of CR or PR) by investigator review.

5.2.2 Other secondary endpoints

Refer to Section 5.1.2 of the CTP.

Other secondary endpoints for the ERBB2/ERBB3 cohort are:

- Progression-free survival (PFS)
    - Defined as the time from the treatment start date to the date of disease progression, or to the date of death if a patient died earlier
- Overall survival (OS)
    - Defined as the time from the date of treatment start date to the date of death

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- Disease control rate (best overall confirmed response of CR, PR, or SD)
- Duration of confirmed objective response
- Tumour shrinkage

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For reporting purposes, patients in the ERBB2/ERBB3 cohort will be presented separately from those in the EGFR cohort.

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

- Screening: day of informed consent to day prior to starting afatinib.
- On-treatment: day of first administration of afatinib to the last administration of afatinib.
- Residual effect period: day after last administration of afatinib to the 30th day after last administration of afatinib.
- Post-study: on or after the 31st day after last administration of afatinib.

Data from the on-treatment and residual effect periods will be included in the safety analyses.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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	Manual/ Automatic
A		**Entrance criteria not met**		
	A1	Diagnosis of urothelial tract carcinoma questionable	Refer to IN 2,3	Automatic
	A2	Prior treatment for urothelial tract carcinoma does not meet entrance criteria	Refer to IN 4,5, EX 1,2 Should have received one line of prior systematic chemotherapy in metastatic set up. This needs to be platinum based therapy. Check for patients with no prior systematic platinum based therapy or more than one line of prior systematic therapies as well. Also check exclusion criterion 1 and 2.	Manual/Automatic
	A3	Prior surgery and radiotherapy do not meet entrance criterion	Refer to EX 3, 4. Major Surgery within 4 weeks before starting study treatment, Radiotherapy within 4 weeks prior to start of study treatment in non-palliative setting.	Manual/Automatic
	A4	No measurable disease according to RECIST 1.1 at screening	Refer to IN6	Automatic

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Table 6.2: 1 Important protocol violations (Contd.)

Category/code		Description	Comment	Manual/ Automatic
	A5	No evaluable biopsy obtained at screening	Refer to IN9	Manual
	A6	Patients not correctly classified according to EGFR, ERBB2, and ERBB3 status at screening	Refer to IN10	Manual
	A7	Abnormal screening values	Refer to IN11	Automatic
	A8	ECOG PS is not 0 or 1	Refer to IN7	Automatic
	A9	Other deviation from entrance criteria	Refer to in/exclusion criteria	Manual
B		**Informed consent**		
	B1	Informed consent not available	Signed informed consent not available	Manual
	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, and version signed did not receive prior IRB/IEC approval).	Manual
C		**Trial medication**		
	C1	Incorrect medication dose taken	e.g., starting dose is not 40 mg for afatinib; dose was not paused, resumed, reduced, or discontinued according to protocol	Manual
	C2	Non-compliance	Check MQRM listings for extreme non-compliance only	Manual
D		**Concomitant medication**		
	D1	Use of prohibited concomitant medications	Review concomitant medications for prohibited medication use.	Automatic
E		**Trial specific**		
	E1	Week 24 response assessment not performed according to protocol	Week 24 imaging and response assessment expected but not performed OR Week 24 imaging and response assessment performed before Day 140	Automatic
	E2	Procedures not performed according to protocol	Check applicable data.	Manual
	E3	Prohibited anticancer interventions	Patient received therapeutic radiation or another anti-cancer treatment before termination of afatinib	Manual

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6.3 PATIENT SETS ANALYSED

Treated set: this includes all patients who received at least one dose of afatinib.

The treated set will be used for all efficacy and 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

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 or time to progression 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”). (3)

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6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the measurements taken most recently prior to first dose of afatinib.

Study day will be calculated relative to the date of the first administration of afatinib. The day prior to first administration of afatinib will be 'Day -1' and the day of first administration of afatinib will be 'Day 1'; therefore 'Day 0' will not exist.

Imaging will be performed at 8, 16 and 24 weeks, and in 12-weekly intervals thereafter; images will be slotted to the planned time based on their relative day and using a ±4 week window as appropriate (images taken in the first 4 weeks from afatinib initiation 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.

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7. PLANNED ANALYSIS

In general the display format of the analysis results will follow BI guideline (7, 8) as much as possible.

This is an open label, uncontrolled, exploratory phase II trial with two patient cohorts. The purpose of this trial is to assess the anti-tumour activity and safety of afatinib monotherapy in patients with urothelial tract carcinoma carrying ERBB2 or ERBB3 mutations or ERBB2 amplifications (Cohort A), and EGFR amplification positive tumours (Cohort B), progressing despite previous platinum based chemotherapy, and thereby to improve their prognosis.

Cohort A of the study follows a two stage design where an analysis for futility will be performed at the end of stage 1based on first 25 treated patients to determine if the stage 2 of cohort A will be carried out. Cohort B of the study will include up to 10 patients with EGFR amplification. Analysis will be conducted in parallel to, and independent of cohort A.

If the trial is continued into Stage 2 for the ERBB2/ERBB3 cohort (cohort A), an analysis will be prepared to document the efficacy results among the first 25 patients. This analysis will be restricted to the first 25 treated patients in cohort A, and will be conducted after no more of these 25 patients are eligible to be assessed for progression at 24-weeks (6 months).

The primary report will be produced after there are no more patients eligible to be assessed for progression at 24-weeks.

A final report will be produced when all patients have discontinued afatinib and none remain to be assessed for progression at 24-weeks. The data for this report may be included in the primary report, if the gap in time between the last 24-week assessment and the final discontinuation is not too long.

If central radiological reviews are performed, differences in PFS6 outcome and response between the central and investigator reviews will be tabulated for each patient and summarized for all patients. If there are differences, the analyses of PFS6 and response might be repeated using the central assessments.

Company standard displays will be used whenever possible.

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. 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.

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7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics using standard summary tables for all treated 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 afatinib 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 progression free survival rate at 6 months (PFS6), determined as being alive and progression-free at the 24-week assessment.

Patients who are alive and progression-free at the 24-week (168-day) assessment will be considered successes for PFS6. The following rules are required for PFS6 to be considered a success:

1) Consider only valid assessments done before starting of any new anticancer therapy. Also do not consider any assessments done after EOT date+ 30 days.

2) Patient has at least one valid assessment demonstrating non-progression on or after day 168 with reference to treatment start day.

3) Patient who did not meet the second criterion but has at least one valid non-PD assessment on or after day 154 (22 weeks) and has progression documented after day 182 (26 weeks) is considered as success for PFS6.

   Examples:

   i) With SD at Day 156 followed by PD at Day 183 will be considered as success for PFS6.

   ii) With SD at Day 146 followed by PD at Day 170 will not be considered as success for PFS6.

   iii) With SD at Day 156 followed by PD at Day 170 will not be considered as success for PFS6.

For Cohort A, at the end of stage 2, final goal is to test $H_{0:}$ PFS6 $\leq 40\%$ vs alternative: $H_{a:}$ PFS6 $> 40\%$. **If we observe fewer than 12 PFS6 successes and fewer than 2 objective responses among the first 25 patients in Stage 1, enrollment for Cohort A will be terminated, and the null hypothesis will be accepted.**

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At the end of Stage 2, the significance level for testing the null hypothesis will be calculated as the exact binomial probability i.e. $\mathrm{Prob}(X > s|\, n, p = 0.40)$, where 's' is the observed number of patients achieving PFS6 and 'n' is the total number of patients. A Wilson 90% confidence interval will be provided also.

If trial stops at stage 1, for cohort A, PFS6 will be analysed descriptively and no formal statistical testing will be performed.

PFS6 for Cohort B patients will be analysed descriptively when all patients in Cohort B have completed the 24-week tumour assessment.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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, with confirmation as specified by RECIST 1.1.

A summary of confirmed objective response rate (ORR) using the investigator assessment of best overall response will be produced.

The null hypothesis for this key secondary endpoint ORR is H_0: ORR ≤ 5% and the alternative Ha: ORR >5%.

At the end of the second stage, for cohort A, the significance level for testing the null hypothesis H_0: ORR ≤ 5% will be calculated as the exact binomial probability i.e. $\mathrm{Prob}(X > s|\, n, p = 0.05)$, where 's' is the observed number of patients achieving a confirmed objective response and 'n' is the total number of patients. A Wilson 90% confidence interval will be provided also.
A Hochberg multiple adjustment procedure will be used to control the family-wise error rate at 0.05 (one-sided) for testing PFS6 and ORR.

7.5.2 Other Secondary endpoints

PFS is determined as the time (months) from the date of first administration of Afatinib to the date of disease progression, or date of death (if a patients dies without progressing). The date of progression for the primary analyses will be determined based on assessments made by the investigators. All treated patients will be included.

Table 7.5.2: 1 describes rules that can be used for sensitivity analyses 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).

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These censoring rules will be used as a sensitivity analysis. Any additional sensitivity analyses that relax part of the rules will be determined later and will be mentioned in technical SAP.

Kaplan–Meier curve and associated tables will be produced for overall survival.

A summary of disease control rate using the investigator assessment of response will be produced. Disease control rate (DCR) is defined as the proportion of patients with best overall response as complete response (CR), partial response (PR) or stable disease (SD)

Following analysis for time to response, duration of response, tumor shrinkage will be done after completion of stage 2.

Time to objective response (TTR) is the time from first afatinib administration to the date of first documented CR or PR. This analysis will be based on treated set.

The duration of objective response (DOR) is the time from first documented CR or PR to the time of progression or death. This analysis will be based on responders set only.

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.

Waterfall plots (and associated tables) of the maximum percentage reduction from baseline sum of target lesion diameters will be presented for each cohort.

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Table 7.5.2: 1 Rules to determine events and censoring for sensitivity analyses of 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 the start of afatinib
2	Progressed from imaging (no missed radiologic assessments)	event	Date of PD
3a	Non-PD from imaging[1], death before next scheduled assessment	event	Date of death
3b	Non-PD from 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 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 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 the start of afatinib
6c	No imaging performed post-baseline, vital status is unknown or patient known to be alive	censored	Date of the start of afatinib
7	Alive and not progressed from imaging (no missed assessments)	censored	Date of last imaging

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

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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 of these data will be provided for the treated set of patients.

Further summaries will also be produced:

- Treatment time (days) broken down by each dose level (40 mg, 30 mg and 20 mg for afatinib.
- 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.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs 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. The reporting and analyses of AEs will follow the BI guideline (4). AEs will be coded with the most recent version of MedDRA®. The severity of AEs will be scaled according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

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- 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'. (4)

For further details on summarization of AE data, please refer to (3, 4).

The analysis of AEs will include all events with onset in the on-treatment period (between treatment start date and (last date of trial medication + 30 days)) and residual effect period. Events occurring before first drug intake will be assigned to ‘screening', and all events occurring after the residual effect period will be assigned to ‘Post-study/follow-up’.

- An overall summary of AEs will be presented.

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

- AEs by treatment, highest CTCAE, using SOC and PT
- Drug related AEs, as assessed by investigators, by treatment, highest CTCAE, using SOC and PT
- AEs leading to dose reduction by treatment, highest CTCAE, using SOC and PT
- AEs leading to afatinib discontinuation by treatment, highest CTCAE, using SOC and PT
- Serious AEs by treatment, highest CTCAE, using SOC and PT
- Drug related serious AEs by treatment, highest CTCAE, using SOC and PT
- AEs leading to death by treatment, highest CTCAE, using SOC and PT
- other significant AEs using SOC and PT (see definition below)
- AEs of special interest (discussed below)

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

Grouped terms

In order to most accurately characterize those AEs related to different mechanism, MedDRA SMQ and HLT (with some modification) will be used to group MedDRA PT for

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- rash/acne,
- stomatitis,
- paronychia.

As a first step in the analysis of grouped AE, all constituent PT will be presented in a separate table for each grouped AE. 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. The following tables with grouping terms will be provided:

- AEs by treatment, highest CTCAE, using grouped terms and PT

- Drug-related AEs by treatment, highest CTCAE, using grouped terms and PT
- AEs leading to dose reduction by treatment, using grouped terms and PT
- AEs leading to treatment discontinuation by treatment, using grouped terms and PT
- AEs leading to death by treatment, using grouped terms and PT
- SAEs by treatment, highest CTCAE, using grouped terms and PT
- Drug-related SAEs by treatment, highest CTCAE, using grouped terms and PT

Additional tables will be produced to describe the frequency, intensity, time to onset, and clinical consequences for

- diarrhea,
- rash/acne.
- stomatitis

Pre-defined adverse events of special interest

Some pre-defined AEs are considered to be of special interest (AESIs).

Separate listings will be prepared for patients who are identified as having experienced any of the following AEs. Identification will be based upon modified MedDRA SMQ and HLT groupings. If sufficient events occur within the trial, analyses similar to those for diarrhea rash/acne and stomatitis may be performed.

- Diarrhoea
- Rash/ acne
- stomatitis
- Dehydration

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- Renal insufficiency
- hepatic impairment
- Interstitial Lung Disease (ILD-like events)
- heart failure
- Keratitis
- Pancreatitis
- Severe cutaneous adverse reactions (Severe skin reaction)
- Gastrointestinal perforation
- Hypersensitivity reaction
- Developmental toxicity

Other significant AEs

Other significant AEs are defined as serious and non-serious AEs that lead to dose reduction or permanent discontinuation of study medication. Their incidence will be reported by severity according to CTCAE grades. A listing of patients who developed 'other significant' AEs will be provided and a flag for serious and non-serious will be included.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). CTCAE version 4.03 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).

Primary laboratory tests are defined as:

- Low values (-):Red blood cell count (RBC), haemoglobin, total white blood cell (WBC), platelets, neutrophils (only at baseline), lymphocytes, , sodium, potassium, calcium, and glomerular filtration rate (GFR)

High values (+): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, activated partial thromboplastin time (aPTT), international normalized ratio (INR), creatininetotal bilirubin, LDH, uric acid
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
- 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.

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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.

Note: Section 5.3.3 in protocol has detailed list of lab parameters which will be summarized beside important lab parameter mentioned above.

7.8.3 Vital signs

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

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8. REFERENCES

1	*CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.*
2	*R09-0262: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al., New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247 [R09-0262].*
3	*001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.*
4	*001-MCG-156: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.*
5	*BI Guidance document 'Conversion of laboratory values to CTCAE grades within Boehringer Ingelheim'.*
6	*001-MCG-157: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.*
7	*001-MCG-159: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.*
8	*001-MCG-159_RD-03:* "Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)", current version; IDEA for CON.
9	*001-MCS-60-113: "Clinical Trial Report", current version; IDEA for CON.*

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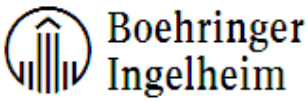
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(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed