Trial Statistical Analysis Plan

c21117747-01

BI Trial No.:	1305-0020
Title:	Relative bioavailability of BI 1015550 following oral administration under fed and fasted conditions in healthy male subjects
Investigational Products:	BI 1015550
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	19 JAN 2018 SIGNED
Version:	"Final"

1. TABLE OF CONTENTS

TITLE PAGE 1
1. TABLE OF CONTENTS 2
LIST OF TABLES 4
2. LIST OF ABBREVIATIONS 5
3. INTRODUCTION 7
4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY 8
5. ENDPOINTS 9
5.1 PRIMARY ENDPOINTS 9
5.2 SECONDARY ENDPOINTS 9
5.2.1 Key secondary endpoints 9
5.2.2 Secondary endpoints 9
..... 9
..... 10
..... 10
6. GENERAL ANALYSIS DEFINITIONS 11
6.1 TREATMENTS 11
6.2 IMPORTANT PROTOCOL VIOLATION 12
6.3 PATIENT SETS ANALYSED 14
..... 15
6.5 POOLING OF CENTRES 15
6.6 HANDLING OF MISSING DATA AND OUTLIERS 15
6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS 15
7. PLANNED ANALYSIS 17
7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 18
7.2 CONCOMITANT DISEASES AND MEDICATION 18
7.3 TREATMENT COMPLIANCE 19
7.4 PRIMARY ENDPOINTS 19
7.5 SECONDARY ENDPOINTS 20
7.5.1 Key secondary endpoints 20
7.5.2 Secondary endpoints 20
..... 21
7.7 EXTENT OF EXPOSURE 21
7.8 SAFETY ANALYSIS 21
7.8.1 Adverse events 21
7.8.2 Laboratory data 23
7.8.3 Vital signs 23
7.8.4 ECG 24
7.8.5 Others 24
8. REFERENCES 25
..... 26

10. HISTORY TABLE..... 27

LIST OF TABLES

Table 6.1: 1 Treatments and labels used in the analysis 11
Table 6.2: 1 Important protocol violations 13
Table 6.3: 1 Subject sets analysed 15
Table 10: 1 History table 27

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BMI	Body mass index
BWC	Bioavailability/Bioequivalence, within-subject design, time-controlled
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DILI	Drug induced liver injury
ECG	Electrocardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference on Harmonisation
ISF	Investigator site file
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations

Term	Definition / description
O*C	Oracle Clinical
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK parameter set
PT	Preferred term
PV	Protocol violation
qd	Quaque die (daily)
R	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual effect period
RPM	Report planning meeting
SAS®	Statistical Analysis System
SD	Standard deviation
SOC	System organ class
T	Test treatment
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary
XPKISTAT	Library of SAS® Macros for PK analysis

3. INTRODUCTION

As per ICH E9 (1), 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 Trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP). 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.

Study data will be stored in a trial database within the Oracle ClinicalTM (O*C) system.

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS®-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP. The following change compared to the protocol will be made:

No ‘Entered set’ will be defined in the TSAP as data of subjects entered and randomised but discontinued before first administration of trial medication will not be entered in the case report form. A correct display of the ‘Entered set’ would not be possible.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 5.5.1.1 of the CTP: *The following primary endpoints will be determined for BI 1015550:*

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 5.5.1.2 of the CTP: *The following secondary endpoint will be evaluated for BI 1015550:*

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatment sequences and selection of doses, please see CTP, Sections 3 and 4.

The study will be performed as a randomised, open-label, single dose, two-way crossover trial with 2 treatments (T and R) and 2 treatment sequences (TR or RT).

In total, it was planned to assign 12 healthy male subjects to the two treatment sequences in a 1:1 ratio.

For details of dosage and formulation see Table 6.1: 1 below:

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
T	BI 1015550, 4*6 mg tablet, fed, qd	BI 24mg fed
R	BI 1015550, 4*6 mg tablet, fasted, qd	BI 24mg fast

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00 h on day of informed consent until first administration time of study drug)
- **On treatment** (including residual effect period (REP); i.e. ranging from the time of administration of the respective treatment until thereafter)
- **Follow-up** (ranging from end of on treatment phase until next drug administration or 0:00 h on the day after trial termination date, according to previous treatment (labelled "**FU-Test**", "**FU-Ref**"))

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 above.

Two types of AE displays will be provided in the report:

A) Section 15.3 and Appendix 16.1.9.2.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and follow-up periods will not be included in this analysis. The following total will be provided in addition (Section 15.3 only):

- a total over all on treatment phases included in this analysis ("**Total on treatment**")

B) Section 15.4 and Appendix 16.1.9.2.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up ("FU-Test" and "FU-Ref")

In Section 16.1.9.2.8 AE tables, the following totals will be provided in addition:

- a total over all study phases ("**Total**")

Tables of vital signs and laboratory values will present results by the above mentioned on treatment phase.

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS plan. In particular, AEs will be counted for test or reference treatment if they occur up to the end of the residual effect period

6.2 IMPORTANT PROTOCOL VIOLATION

Data discrepancies and deviations from the CTP will be identified for all randomised subjects. Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the combined report planning and database lock meeting (RPM/DBLM), e.g. deviations in drug administration, in blood sampling etc. At this meeting, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation. A protocol violation (PV) is important if it affects the rights or safety of the study subjects or if it can potentially influence the primary outcome measure(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. This last category of important PV forms the basis for the decision of whether a subject does or does not belong to an analysis set. PVs that do not influence the subject's rights and safety or the evaluability of the subjects for the main study objectives are called non-important PVs. These are only considered when checking the trial quality in general.

If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet [001-MCS-50-413_RD-02] (2). The following table contains the categories which are considered to be important protocol violations in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

Table 6.2: 1 Important protocol violations

Category /Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Medication code broken inappropriately
	C5	Incorrect intake of trial medication
	C6	Improper washout between treatments
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
E		**Missing data**
	E1	Certain violations of procedures used to measure primary or secondary data
F		**Incorrect timing**[1]
	F1	Certain violations of time schedule used to measure primary or secondary data
G		**Other trial specific important violations**
	G1	Incorrect intake of meal
	G2	PVs affecting safety and rights

[1] Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (3)

6.3 PATIENT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were documented to have received one dose of study drug.
  This is the full analysis set population in the sense of ICH-E9 (1).
  It is used for safety analyses.

Section 7.3 of the CTP: *Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.*

Relevant protocol violations may be:

- *Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma concentrations and/or PK parameters of a subject will be considered as non-evaluable, if for example:

- *The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis)*
- *Missing samples/concentration data at important phases of PK disposition curve*
- *Use of restricted comedication*

- PK parameter analysis set (PKS):
  This subject set includes all subjects in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment.

The descriptive analysis of PK concentrations will be based on the analysis data set (ADS) ADPC as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

	Analysis set	
Class of endpoint	TS	PKS
Analyses of primary and secondary PK endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	X	
Important protocol violations	X	
Disposition	X	

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR. Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before trial drug administration in each treatment period.
For laboratory parameters the baseline is defined as the last measurement prior to first administration of study drug.

Section 6.1 of the CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration and prior to predose meal intake.

The acceptable deviation from the scheduled time for post-dose vital signs, ECG and laboratory tests will be ± 30 min.

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by
and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.9.2.

Inferential statistical analyses of PK endpoints (refer to Section 7.4 and Section 7.5.2) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK parameters and concentrations will be performed by BI and presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of Clinical Trials and Project Summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations.

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate). The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10th percentile
Q1	1st quartile
Q3	3rd quartile
P90	90th percentile

The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

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 (%) for each

treatment group. Percentages will be rounded to one decimal place and will be based on all subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The analysis data set (ADS) ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is APEXCO is equal to “Included”.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’ the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (11).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

The data will be summarised by treatment sequence and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study center under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.1).

The PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model (see below).

Primary analysis

The statistical model used for the analysis of primary and secondary PK endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale (see below).

Section 7.3.1 of the CTP: *This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:*

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

y_{ijkm} = *logarithm of response (*$AUC_{0\text{-}tz}$, C_{max}, $AUC_{0\text{-}\infty}$*) measured on subject m in sequence i receiving treatment k in period j,*

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect, i = 1, 2*

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence, m = 1, 2, ..., 6, i=1, 2*

π_j = *the* j^{th} *period effect, j = 1, 2*

τ_k = the k^{th} treatment effect, k = 1, 2

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

The difference between the expected means for test treatments (tablets under fed conditions, T) and reference treatment (tablets under fasted conditions, R) ln(T)-ln(R), will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

The analysis will be accomplished by using the XPKISTAT macro, based on PKS (design BWC).

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

The secondary PK endpoint $AUC_{0-\infty}$ will be assessed using the same methods as described for the primary endpoints but will not be interpreted in a confirmatory sense.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by actual treatment.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [001-MCG-156] (8).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

For analysis, multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)

- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started within one hour after end of the first occurrence).

For further details on summarization of AE data, please refer to [001-MCG-156] (8,4).

Section 5.2.2.1 of the CTP: *The following are considered as AESIs in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*

    - *an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or*

    - *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy,unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

With the exception of DILI, no AESIs have been defined for this trial.

The analysis of adverse events will be based on the concept of treatment emergent adverse events.

Section 5.2.2.2 of the CTP: *The Residual Effect Period (REP) for BI 1015550, when measurable drug levels or PD effects are still likely to be present, is defined as after the last administration of BI 1015550. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment […].*

All adverse events occurring before first drug administration will be assigned to 'screening', those between intake of trial medication and end of the will be assigned to the corresponding treatment ('on treatment'). AEs occurring after the REP but prior to next drug administration or termination date will be assigned to 'follow-up'. The follow-up will be summarized according to previous treatment.

According to ICH E3 (9), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant adverse events with

(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the Report Planning Meeting.

An overall summary of AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with other significant AEs according to ICH E3 (9), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.
The SOC and PTs will be sorted by frequency. The MedDRA version number will be displayed as a footnote in the respective output.

In addition, for disclosure of AE data on ClinicalTrials.gov, frequencies of subjects with non-serious AEs that had an incidence of > 5% (in preferred term) for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (10).

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the data listings.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments on the CRF or at the RPM/DBLM at the latest. It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate).

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as AEs (when they occurred during treatment).

7.8.5 Others

This section is not applicable as no other variables have been specified in the protocol.

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 *001-MCS-50-413_RD-02:* “Important Manual Protocol Violations Spreadsheet”, current version, IDEA for CON.
3 *001-MCS-50-413_RD-01*: “Protocol Violation Handling Definitions”, current version, IDEA for CON.
4 *001-MCG-156_RD-01*: “Handling of Missing and Incomplete AE Dates”, current version; IDEA for CON.
5 *001-MCS-36-472_RD-01*: “Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies”, current version; IDEA for CON.
6 *001-MCG-159*: “Reporting of Clinical Trials and Project Summaries”, current version; IDEA for CON.
7 *001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8 001-MCG-156: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version; IDEA for CON.
9 *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.
10 *001-MCG-157*: “Handling, Display and Analysis of Laboratory Data”, current version; IDEA for CON.
11 001-MCS-36-472_RD-03: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**19-JAN-18**		None	This is the final TSAP without any modification