TRIAL STATISTICAL ANALYSIS PLAN

c14388870-01

BI Trial No.:	1386.17
Title:	Relative bioavailability of a BI 1467335 tablet compared to a BI 1467335 oral solution and the effect of food on the bioavailability of the tablet following oral administration (a randomised, open-label, single dose, three-way crossover trial in healthy male subjects)
Investigational Product(s):	BI 1467335
Responsible trial statistician(s):	[redacted] Phone: Fax: [redacted] Phone: Fax:
Date of statistical analysis plan:	15MAY2017 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
[redacted]	[redacted]
[redacted]	[redacted]
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable data point
[redacted]	[redacted]
AE	Adverse Event
BI	Boehringer Ingelheim
BMI	Body mass index
[redacted]	[redacted]
CARE	Clinical data Analysis and Reporting Environment
CDR	Clinical Data Repository
CI	Confidence interval
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CV	Arithmetic coefficient of variation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug induced liver injury
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of trial
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
ISF	Investigator site file

Term	Definition / description
[redacted]	[redacted]
LLT	Lowest level term
log	Natural logarithm
Max	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
[redacted]	[redacted]
N	Number of non-missing observations
O*C	Oracle Clinical
PK	Pharmacokinetics
PKS	PK analysis set
PV	Protocol Violation
R	Reference treatment
RAGE	Report Appendix Generator system
REP	Residual effect period
RPM/DBLM	Report planning and database lock meeting
RS	Randomised set
SD	Standard Deviation
SDL	Subject data listing
T	Test treatment
[redacted]	[redacted]
[redacted]	[redacted]
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
[redacted]	[redacted]
WHO-DD	World Health Organisation – Drug Dictionary

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 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."

Study data will be stored in a trial database within the Oracle Clinical™ (O*C) system. Laboratory data will additionally be loaded and stored in the CDR.

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

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP version 1.0.

5. ENDPOINTS

The endpoints will be as defined in the CTP.

5.1 PRIMARY ENDPOINTS

The following primary pharmacokinetic endpoints given in the CTP in Section 5.5.1.1 will be determined for BI 1467335:

- *$AUC_{0\text{-}tz}$ (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 ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable as no key secondary endpoints have been specified in the protocol.

5.2.2 Secondary endpoint(s)

Not applicable as no secondary endpoints have been specified in the protocol.

[redacted]

5.3.2 Safety endpoints

General

The following safety assessments will be evaluated as further endpoints (see CTP, Section 5.2.1):

- AEs (including clinically relevant findings from physical examination)
- Safety laboratory tests
- 12-lead ECG (abnormal findings documented as AEs or baseline conditions)
- Vital signs (systolic and diastolic blood pressure, pulse rate)

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignments of treatment groups, and selection of doses, see CTP Section 4. Subjects will be randomly allocated to one of 3 treatment sequences (ABC, BCA and CAB). The study has a single dose, randomised, three-way crossover, open-label design.
Subjects will be randomized to one of the 3 treatment sequences. Treatments to be evaluated are outlined in Table 6.1: 1 below.

Table 6.1: 1 Treatment regimens

Description of treatment regimen	Label	Short Label
BI 1467335, 2*5mg tablet, po, qd, fasted	A	BI 10 mg tab, fasted
BI 1467335, 0.5 mg/mL solution, 10mg, po, qd, fasted	B	BI 10 mg sol, fasted
BI 1467335, 2*5mg tablet, po, qd, fed	C	BI 10 mg tab, fed

tab= tablet, sol= solution

CTP (Section 6.2.2 Treatment periods): *Each subject is expected to participate in each of the three treatment periods (drug administration on Day 1 of each period, see [CTP] Table 4.1.4:1). Treatment periods will be separated by at least 21 days between drug administrations.*

On Day -1 of each treatment period, study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration on Day 1. Subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. Within the time window Day -5 to -1 of Visits 3 and 4, safety laboratory will be taken and AE/ concomitant questioning will be done.

For details on time points and procedures for collection of plasma samples for PK [redacted] *analysis, refer to Flow Chart and [CTP] Sections 5.5.2 and 5.6.3.*
The safety measurements performed during the treatment period are specified in [CTP] Section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, see Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

For the statistical analyses of AEs, laboratory data and vital signs, the following phases of the study will be defined:

Table 6.1: 2 Study phases

Label	Start	End*
Screening	Date of informed consent	Date/time of first drug administration
BI 10mg tab fasted or BI 10mg sol fasted or BI 10mg tab fed	Date/time of BI 1467335 administration	Date/time of BI 1467335 administration [redacted] days
F/U BI 10mg tab fasted F/U BI 10mg sol fasted F/U BI 10mg tab fed	Date/time of BI 1467335 administration [redacted] days	Date/time of BI 1467335 administration in next period or End of trial (EOT) examination

* For all defined study phases, the end date/time itself does not belong to the study phase

Vital signs will be presented for each assessment time point.

CTP (Section 5.2.2.2 Adverse event collection and reporting*):* [redacted]

Therefore, all AEs which will occur throughout the treatment phases and the [redacted] *REP will be considered as 'on treatment' (see [CTP] Section 7.3.3). Events which occur after the* [redacted] *REP and prior to the next drug administration will be considered as 'follow-up' events.*

Based on these definitions, two types of analyses will be provided in the report, as appropriate.

A) High-level analysis (for Section 15 and Appendix 16.1.9.2.8.2 &3 displays)

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). The screening and follow-up periods will not be included.
For AE tables, a total over the active treatments ("Total BI 1467335") will be provided.

B) Low-level analysis (for Appendix 16.1.9.2.8.1 displays)

The separate phases, as defined in the table above, will be used in this analysis.
In addition, a total over the active treatments ("Total BI 1467335) and a total over all study phases ("Total overall") will be provided.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all randomized 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).

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 (PV).

For definition of important PVs, and for the process of identification of these, please refer to the Boehringer Ingelheim (BI) reference document 'Protocol Violation Handling Definitions' (7).

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 (9). The following table contains the categories in which important PVs are classified. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

If substantial numbers of PVs are reported at the RPM/DBLM, a decision about summarising the PVs in a tabular format will be made. Otherwise, only a PV listing will be provided.

Additionally, consistency checks will be prepared for identifying violations of time windows.

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	Prohibited medication use
	D2	Mandatory medication not taken
	D3	Improper washout of concomitant medication
E		**Missing data**
	E1	Certain violations of procedures used to measure primary or secondary data

Table 6.2: 1 Important protocol violations (cont'd)

Category / Code		Description
F		**Incorrect timing**
	F1	Certain violations of time schedule used to measure primary or secondary data.
G		**Other trial specific important violations**
	G1	Incorrect intake of meal

6.3 SUBJECT SETS ANALYSED

All entered subjects who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP.

Populations (analysis sets) and the criteria for inclusion are defined as follows:

- Randomised set (RS):
  This subject set includes all randomised subjects. It will be used for disposition displays.

- Treated set (TS):
  This subject set includes all subjects who received at least one dose of study drug. It will be used for analysis of safety, demographic data and baseline characteristics.

- Pharmacokinetic set (PKS):
  This subject set includes all subjects in the Treated Set (TS) who provide at least one primary PK parameter that is not excluded due to a relevant protocol violation or non-evaluable plasma concentrations.

  According to CTP Section 7.3.1, plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example:
  - The subject experienced emesis at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding subjects having experienced emesis)
  - Pre-dose concentration is >5% of the C_{max} value of that subject
  - Samples/concentration data at critical phases of the PK disposition curve are missing

  A subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment.

[redacted]

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to populations based on other data than PK, PD or Biomarkers will be made at latest at the RPM/DBLM. Other decisions based on PK, PD or Biomarkers data have to be made once the corresponding data are assessed.

Table 6.3: 1 Subject sets analysed

	Subject set			
Class of endpoint	RS	TS	PKS	[redacted]
Primary and further PK endpoints			X	
Safety endpoints		X		
[redacted]				[redacted]
Demographic/baseline endpoints		X		
Disposition	X			

Note that the number of subjects with available data for an endpoint may differ. For details, see Section 6.6 “Handling of missing data and outliers”.

[redacted]

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

According to section 7.4 of the CTP:

- Missing or incomplete AE times are imputed according to BI standards (see 001-MCG-156_RD-01 (3). BI-SDTM does not contain date/time imputations, all such imputations are done during ADS generation.

- With respect to other safety evaluations, it is not planned to impute missing values.

- Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01 (2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, the baseline value is defined as the last measurement before the first intake of study medication.

For laboratory data, the baseline value will be derived for each treatment to be the last value before intake of study medication in the respective study period. For repeated laboratory data, baseline will be the last repetition before intake of study medication in the respective study period.

Similar for vital signs, [redacted] the baseline value will be derived for each treatment.

Time windows are defined in the CTP. Adherence to time windows will be checked at the RPM/DBLM.

CTP (Section 6.1 Visit schedule): *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, Visits 3 and 4 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 3h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min on Day 1, and ± 60 min on Day 2.

If scheduled in the [CTP] Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture, are scheduled at the same time, venipuncture should be the last due to its inconvenience to subjects and possible influence on physiological parameters.

For planned sampling times of the PK [redacted] blood samples, see [CTP] Flow Chart. While these nominal times should be adhered to as closely as possible, actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

7. PLANNED ANALYSIS

Subjects will be assigned to treatment groups according to their randomised treatment.

Inferential statistical analyses of PK endpoints [redacted] will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK endpoints will be performed by BI ClinPK/PD group and presented in Section 15.6 of the CTR. [redacted]

The format of the listings and tables will follow the BI guideline 'Reporting of clinical trials and project summaries' [001-MCG-159] (7).

The individual values of all subjects will be listed, sorted by sequence group, subject number and visit. All listings will be contained in Appendix 16.2 of the Clinical Trial Report (CTR). Additionally, PK [redacted] data will be listed in Sections 15.6 [redacted].

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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

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

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations and its descriptive statistics will be displayed according to SOP MCS-36-472_RD1 (8).

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

All subject data listings (SDLs), except for AE listings, will be sorted by sequence group and subject number.

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS presented by sequence group and overall. The following variables will be displayed: gender, race, ethnicity, age, height, weight, body mass index (BMI), smoking and alcohol status.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD).

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

A medication will be considered concomitant to a treatment, if it

- is ongoing at the time of administration of the respective treatment or
- starts within the on-treatment phase (see Section 6.1).

Hence a medication may be considered as concomitant to more than one actual treatment. In the listing of concomitant therapies, a record will be created for each actual treatment in which the therapy is present.

7.3 TREATMENT COMPLIANCE

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

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly.

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed and documented at the RPM/DBLM and described in the CTR.

7.4 PRIMARY ENDPOINT(S)

To investigate the relative bioavailability of the two formulations (tablet/oral solution) and to investigate the effect of food on the primary PK parameters as defined in Section 5.1, the following comparisons will be made:

(1) T1 (tablet, fasted) vs. R1 (oral solution, fasted), to investigate the relative bioavailability of the tablet and solution formulations

(2) T2 (tablet fed) vs. R2 (tablet fasted) , to investigate the effect of food on the tablet formulation

These comparisons will be performed separately on the PKS. For further details about treatments see Table 6.1: 1.

The primary PK endpoints (see CTP Section 5.5.1 and TSAP Section 5.1) will be log transformed (natural logarithm) prior to fitting the ANOVA model. For each endpoint, the difference between the expected means for log(T (fasted))-log(R) and log(T (fed))-log(T (fasted)) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% confidence intervals (CIs) for each endpoint. Since the main focus is on estimation (and not testing), an acceptance range was not specified, i.e. no hypothesis will be tested.

CTP (Section 7.1.3 Model): *The statistical model used for the analysis of primary endpoints will be an analysis of variance (ANOVA)) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects nested 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:*

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

y_{ijkm} = *logarithm of response (endpoint, see [CTP] Section 5.5.1) 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, 3*

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

π_j = *the* j^{th} *period effect, j = 1, 2, 3*

τ_k = *the* k^{th} *treatment effect, k = 1, 2, 3*

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

The analysis will be accomplished using the XPKISTAT macro, based on PKS, and the option BWC (Bioavailability/Bioequivalence, within subject design, time-controlled).

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

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

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. The analyses will be done by 'treatment at onset'(concept of 'treatment emergent AEs').

CTP (Section 7.3.3 Safety analyses): *Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.*

7.8.1 Adverse events

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

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

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

- All AE attributes are identical (lowest level term (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 in the same hour in which the first occurrence ended)

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) [001-MCG-156].

CTP (Section 5.2.2.1 Definitions of adverse events): *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 that these parameters are analysed, 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.

According to ICH E3 (5) AEs classified as 'other significant' needs 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 a Medical Quality Review Meeting.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all adverse events occurring between first drug intake till last drug intake + residual effect period 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 the residual effect period will be assigned to "follow-up" (for listings only). For details on the treatments and the definition of study phases, see Section 6.1.

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for subjects with serious AEs, subjects with AESIs, and subjects with other significant AEs (according to ICH E3 (5)). AEs which were considered by the investigator to be drug related will be summarised separately. AEs will also be summarised by maximum intensity. The system organ classes will be sorted

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

Separate listings will be provided for all AEs, for serious AEs, for AESIs, for other significant AEs (according to ICH E3), for serious AEs, AESIs or other significant AEs, and for non-serious AEs that had an incidence of > 5% for at least one treatment.

The analysis of AEs will be based on the concept of treatment emergent AEs. For details on the treatments and the definition of study phases, see Section 6.1.

An overall summary of AEs will be presented.

7.8.2 Laboratory data

CTP (Section 7.3.3 Safety analyses): *Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.*

The analyses of laboratory data will be based on BI standards (6). Descriptive statistics of laboratory values over time and for the difference from baseline will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments on the database 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. Possibly clinically significant abnormal laboratory values will only be presented within the scope of the listing of investigator comments.

7.8.3 Vital signs

CTP (Section 7.3.3 Safety analyses): *Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.*

Only descriptive statistic of vital signs over time and for the difference from baseline are planned for this section of the report.

Clinically relevant findings in vital signs data will be reported as AEs and will be analysed as part of the AE analysis.

7.8.4 ECG

CTP (Section 7.3.3 Safety analyses): *Relevant ECG findings will be reported as AEs.*

No separate listing or tables will be prepared.

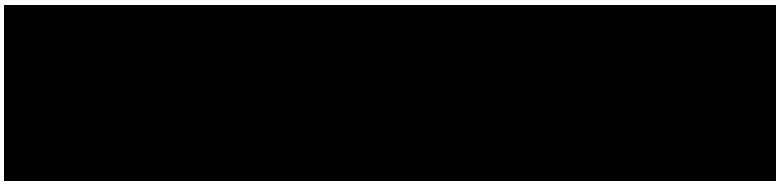
7.8.5 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

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-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5.	*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
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-MCS-36-472_RD1: "Noncompartmental Pharmacokinetic Pharmacodynamic Analyses of Clinical Studies"*
9.	*001-MCS-50-413_RD-02: "Important Manual Protocol Violations Spreadsheet", current version, BIRDS*



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**15-MAY-2017**	[redacted]	None	This is the final TSAP without any modification.