TRIAL STATISTICAL ANALYSIS PLAN

c24908067-01

BI Trial No.:	1305-0015
Title:	Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (including Protocol Amendment No.1 [**c19245536-03**])
Investigational Product:	BI 1015550
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	21 AUG 2018 SIGNED
Version:	Final

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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_{0-119}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 119 h
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BWU	Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
ECG	Electrocardiogram
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
Itra	Itraconazole
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
O*C	Oracle Clinical
PK	Pharmacokinetic(s)

Term	Definition / description
PKS	Pharmacokinetic Set
PT	Preferred Term
PV	Protocol Violation
QD	Quaque die, once daily
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organization- Drug Dictionary
XPKISTAT	SAS® Macro for analysis of PK data

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

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.

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_{0-119} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 119 h)*
- *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)*

5.3 FURTHER ENDPOINTS

Safety:

Section 5.2.1 of the CTP:

Safety and tolerability of the investigational drugs will be assessed based on:

- *Adverse events (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate)*

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'further parameters of interest'. A confirmatory analysis is not planned.

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 was performed as an open-label, fixed-sequence trial with 2 treatments (T and R). It was planned to assign 16 healthy male subjects (at least 12 completed).

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
R	BI 1015550, 1*6 mg tablet, qd	BI
T	BI 1015550, tablet, 6mg + Itraconazole 20ml, 10mg/ml, qd	BI + ITZ

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 (BI)
- **On treatment**
  - **BI treatment** (including residual effect period (REP); i.e. ranging from the time of first administration of BI 1015550 until
  - **Itraconazole "**ITZ**"** (ranging from the time of first administration of Itraconazole until time of second administration of BI 1015550)
  - **BI + ITZ** (ranging from time of second administration of BI 1015550 until 9 days after the last administration of Itraconazole (up to 18 days)
- **Follow up**
  - **Follow-up BI** (ranging from end of BI treatment phase until next drug administration or alternatively, 0:00h on the day after trial-termination date in case of no further treatment)
  - **Follow-up BI+ITZ** (ranging from end of BI+ITZ phase until 0:00h on the day after trial termination date)

Displays of AEs will be presented separately for the following treatments during on treatment phase:

- BI 1015550, 6 mg tablet, qd (labelled “BI“)
- Itraconazole, 200 mg oral solution, qd (labelled “ITZ”)
- BI 1015550, 6 mg tablet, qd + Itraconazole, 200 mg oral solution, qd (labelled “BI + ITZ”)

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

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) 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, Follow-up BI and Follow-up BI+ITZ will not be included in this analysis.
The following totals will be provided in addition (Section 15.3 only):

- a total over all on treatment phases involving BI (“Total on treatment BI”)
- a total over all on treatment phases included in this analysis ("Total on treatment")

B) Section 15.4 and Appendix 16.1.13.1.8 (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 BI (labelled “FU BI”)
- Follow-up BI+ITZ (labelled “FU BI+ITZ”)

In Section 16.1.13.1.8 AE tables, the following totals will be provided in addition:

- a total over all on treatment phases involving BI (“Total BI”)
- a total over all study phases ("Total")

Tables of vital signs and laboratory values will present results by study period including baseline of the respective period.

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS (analysis data set) plan and Data Reviewers guide.

6.2 IMPORTANT PROTOCOL VIOLATIONS

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 summarized 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	Non-compliance
	C3	Incorrect intake of trial medication
	C4	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	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 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This is the full analysis set population in the sense of ICH-E9 (1). The TS is used for safety analyses.

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken from the median t_{max} for BI 1015550, depending on whether the subject had experienced emesis after intake of study medication. Median t_{max} is to be determined excluding the subjects experiencing emesis
- Time deviations
- Use of restricted medications

Violations may lead to exclusion of single measurements/parameters for a subject (e.g. only data of one study period) or even to exclusion of all data of the subject.

- Pharmacokinetic set (PKS):
  The Phamacokinetic set (PKS) includes all subjects from 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.
  It is used for the analysis of PK endpoints.

The descriptive analysis of PK concentrations will be based on the 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 PK endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	X	
Important PVs	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

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exceptions where imputation might be necessary for safety evaluation are 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 for period 1 is defined as the last measurement before first administration of BI 1015550 (Day 1, -3:00 of period 1 for vital signs or Day -5, -122:00 of period 1 for laboratory). The baseline value for period 2 is defined as the last measurement before first administration of Itraconazole (Day -3, -76:00 of period 2 for both vital signs and laboratory).

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 are to be performed and completed within a 3 h-period prior to the trial drug administration as indicated in the Flow Chart.

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

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.

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.

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 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Sections 7.5.2 and 7.6) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by and will be 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 group, subject number, and visit.
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	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. 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 ADS ADPP (PK parameters) 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 APEXC 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 (and, as a consequence, any calculation that relies on λ_z) 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” (7).

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 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

Primary analysis

Relative bioavailability is to be determined on the basis of the primary PK endpoints (AUC_{0-119}, C_{max}). Those parameters will be ln-transformed (natural logarithm) prior to fitting the ANOVA model (see below).

Section 7.1.3 of the CTP: *The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'subjects' and 'treatment'. The effect 'subjects' will be considered as random, whereas the treatment effect will be considered as fixed. The model is described by the following equation:*

$Y_{ij} = \mu + s_i + \tau_j + e_{ij}$, *where*

y_{ij} = *logarithm of response (*AUC_{0-119}, C_{max} and $AUC_{0-\infty}$*) measured on subject i receiving treatment j,*

μ = *the overall mean,*

s_i = the effect associated with the i^{th} subject, i = 1, 2, ..., n

τ_j = the j^{th} treatment effect, j = 1, 2,

e_{ij} = the random error associated with the i^{th} subject who received treatment j.

The difference between the expected means for test treatments and reference treatment ln(T)-ln(R), 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 implementation for this analysis will be accomplished by using the XPKISTAT macro, based on PKS, and option BWU (Bioavailability/Bioequivalence, within-subject design, uncontrolled w.r.t. time).

Further analysis

Section 7.1.3 of the CTP: *In addition, the same analysis will be applied using subject as fixed effect.*

Furthermore, the input dataset will be restricted in such a way that treatments not relevant for the comparison of interest will be deleted. This analysis will be done using PROC GLM.

The following SAS code can be used to fit the model:

```
PROC GLM DATA=indata;
        CLASS subject treatment;
        MODEL logkp = treatment subject;
        LSMEANS treatment / PDIFF=CONTROL("Ref_trt") CL ALPHA=0.1;
RUN;
```

Further analysis of primary endpoints is explorative.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have 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.

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] (9).

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 (lower 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 two 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] (9).

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

- *Hepatic injury*
  A hepatic injury is 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*
  - *aminotransferase (ALT, and/ or AST) elevations ≥10 fold ULN*

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 7 days after the administration of BI 1015550 for the mono-therapy (Treatment R). In Treatment T, the REP of itraconazole is about 9 days after last administration of itraconazole on day 9, i.e. up to day 18 (Treatment T). Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment […].*

According to ICH E3 (10), 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.

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

The frequency of subjects with AEs will be summarized 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 (10), 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 (within system organ class). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% 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] (11). Original laboratory values will be listed and summary statistics will be reported.

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). In the listing the difference from baseline will also be displayed.

Clinically relevant findings in vital signs will be reported as AEs.

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 adverse events (when they occurred during treatment).

7.8.5 Others

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-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_RD-03:* “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON.
8.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
9.	001-MCG-156: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version; IDEA for CON.
10.	*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
11.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", 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	21-AUG-2018		None	This is the final TSAP without any modification