



TRIAL STATISTICAL ANALYSIS PLAN

c22093092-01

BI Trial No.:	1399-0001
Title:	Safety, tolerability and pharmacokinetics of single rising inhaled doses of BI 1265162 in healthy male volunteers in a partially randomised, single blind, placebo-controlled trial Final Protocol (including protocol revision 1 (c15848245-02))
Investigational Product(s):	BI 1265162
Responsible trial statistician(s):	
	Phone: Fax:
	Phone: Fax:
Date of statistical analysis plan:	10 APR 2018 SIGNED
Version:	“Final”
Page 1 of 27	
Proprietary confidential information © 2018 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.	

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 ENDPOINT	9
5.2 SECONDARY ENDPOINTS	9
5.2.1 Key secondary endpoint	9
5.2.2 Secondary endpoints.....	9
	9
	9
	9
	10
	10
	10
6. GENERAL ANALYSIS DEFINITIONS	12
6.1 TREATMENTS.....	12
6.2 IMPORTANT PROTOCOL VIOLATIONS	13
6.3 SUBJECT SETS ANALYSED.....	14
	14
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	18
7.4 PRIMARY ENDPOINT	18
7.5 SECONDARY ENDPOINTS	18
7.5.1 Key secondary endpoint	18
7.5.2 Secondary endpoints.....	18
	19
	19
	19
7.7 EXTENT OF EXPOSURE	19
7.8 SAFETY ANALYSIS.....	19
7.8.1 Adverse events.....	19
7.8.2 Laboratory data	21
7.8.3 Vital signs.....	21

7.8.4	ECG	22
7.8.7	Others	23
8.	REFERENCES	24
		...25
		...25
10.	HISTORY TABLE	27
		...25

LIST OF TABLES

Table 6.1: 1	Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, vital signs, and ECG.....	12
Table 6.2: 1	Important protocol violations	13
Table 6.3: 1	Subject sets analysed	14
Table 6.7: 1	Time schedule of 12-lead ECG recordings with centralised evaluation	16
Table 10: 1	History table	27

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC _{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
C _{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
gCV	geometric coefficient of variation
HR	Heart rate
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter set
PR	Pulse rate
PV	Protocol Violation
QRS complex	Combination of the Q, R, and S waves

Term	Definition / description
QT interval	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
RAGe	Report appendix generator
RPM	Report Planning Meeting
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range

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 revised CTP, 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 CTP and its 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 system.

The statistical analyses will be performed within the validated working environment CARE, including SASTM (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SASTM-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).

PK parameters will be calculated using Phoenix WinNonlinTM software (version Phoenix 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 revised CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number of subjects with drug-related AEs, as defined in Section 5.2.1 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary endpoints of this trial are AUC_{t1-t2} and C_{max} of BI 1265162 in plasma, as defined in Section 5.5.1.1 of the CTP.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

Subjects were planned to be treated either with

- a single dose of 3, 10, 30, 100, 300, 600, or 1200 µg of BI 1265162 (test treatments)
or
- a single dose of placebo (reference treatment)

All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made for placebo subjects).

Analysis phases for statistical analysis of AEs, safety laboratory data, vital signs, and ECG are defined for each subject as described in the table below.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, vital signs, and ECG

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	Screening	Date of informed consent	Date/time of first administration of study drug
On-treatment	Pbo, 3 ug BI, 10 ug BI, 30 ug BI, 100 ug BI, 300 ug BI, 600 ug BI, or 1200 ug BI, respectively	Date/time of administration of study drug	12:00 a.m. on day after subject's trial termination date

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- "**Total BI**", defined as the total over all on-treatment phases involving BI
- "**Total on-trt**", defined as the total over all on-treatment phases, including placebo

CTR Appendix 16.1.13.1.8.1 displays will present results for the screening and on-treatment phases.

Additionally to the totals defined above, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "Total", defined as the total over all study phases (screening + on-treatment)

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Consistency check listings (for identification of violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the RPM/DBLM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an IPV. For definition of IPVs, and for the process of identification of these, refer to the BI reference document "Protocol Violation Handling Definitions" (2).

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	Incorrect intake of trial medication
D	Concomitant medication
D1	Prohibited medication use
E	Missing data
	None ¹
G	Other trial specific important violations
G1	Certain violations of procedures used to measure secondary PK data

Violations C1, C2 and G1 can only be detected at the trial site.

¹ Missing visits, evaluations, and tests will be considered missing data, not PVs

Source: BI reference document "Protocol Violation Handling Definitions" (2).

If any IPVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet (3) The table above

contains the categories which are considered to be IPVs in this trial. If the data show other IPVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

IPVs will be summarised and listed.

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.

The following subject sets will be defined for statistical analysis:

- Treated set (TS):
This subject set includes all subjects who received at least one dose of study drug. This is the full analysis set population in the sense of ICH-E9. It will be used for analysis of safety, demographic data and baseline characteristics.
- Pharmacokinetic parameter set (PKS):
This subject set includes all subjects in the TS who provide at least one PK parameter that was not excluded because of PVs relevant to the statistical evaluation of PK endpoints as defined in Section 7.3 of the CTP.

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to analysis sets will be made at latest at the RPM/DBLM.

Table 6.3: 1 Subject sets analysed

Class of endpoint	Subject set	
	TS	PKS
Disposition	X	
Exposure	X	
IPVs	X	
Demographic/baseline endpoints	X	
Primary endpoint	X	
Other safety parameters	X	
Secondary PK endpoints		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.

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded in the CTR.

CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

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 (4).

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic mean per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

Missing data and outliers of PK data are handled according to BI standards (5).

Plasma / Urine concentration-time tables

CTP: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).*

Pharmacokinetic parameters

CTP: *Drug concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

There will be a centralised evaluation of 12-lead ECG recordings at the time points specified in [Table 6.7: 1](#).

Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all on-treatment time points with centralised ECG evaluation.

At predose, 3 triplicate ECGs (9 single ECGs) will be recorded within 10 minutes (planned time -1:30 on Day 1). The baseline value of an ECG variable is defined as the mean of the

first triple ECG measurements prior to first drug administration. For all on-treatment assessments, only the first of the three replicate ECG at a single assessment time will be evaluated.

In all other analyses (except for analyses of ECG variables), the last non-missing value determined prior to the first dosing of BI 1265162 will be defined as baseline.

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Study phase
2	1	-01:30	Baseline
		00:05	On-treatment
		00:15	
		01:00	
		00:30	
		01:00	
		02:00	
		04:00	
		06:00	
		12:00	
	2	24:00	
	3	48:00	

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM/DBLM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will generally be sorted by dose group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see [Section 7.8.1](#) below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

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 plasma 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

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10 th percentile
Q1	1 st quartile
Q3	3 rd quartile
P90	90 th percentile

The data format for descriptive statistics of plasma 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 (%) 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 actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

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

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

- is ongoing at the time of first administration of the respective treatment or
- starts within the analysis phase of the respective treatment (see [Section 6.1](#) for a definition of treatments and analysis phases).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the RPM/DBLM (cf. [Section 6.2](#)) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to [Section 7.8.1](#) for a description of the analysis of AEs, and in particular the analysis of the number of subjects with drug related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

The analysis of secondary endpoints will be based on the PKS.

Descriptive statistics are regarded as the main analysis and the analysis
is regarded as further analysis.

Exclusion of PK parameters

The 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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

Exclusion of plasma 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. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" ([5](#)) and "Description of Analytical Transfer Files and PK/PD Data Files" ([5](#)).

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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. All analyses of AEs 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 eCRF will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended)

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (8) and "Handling of missing and incomplete AE dates" (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to the screening or on-treatment phase as defined in [Section 6.1](#). AEs will be analysed based on actual treatments, as defined in [Table 6.1: 1](#).

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 (9) and for the class of AESIs.

CTP: *The following are considered as AESIs in this trial:*

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 investigator had to classify on the eCRF whether an observed AE was an AESI or not.

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

- (i) which are marked haematological or other lab abnormalities, or
- (ii) which were reported with "action taken = discontinuation" or "action taken = reduced", or
- (iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related (primary endpoint) will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (9)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

The system organ classes and preferred terms within system organ classes will be sorted by descending frequency overall treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" ([10](#)).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Descriptive statistics of laboratory values over time and for the difference from baseline (see [Section 6.7](#)) will be provided. In addition, median urine and plasma electrolytes over time will be presented graphically. 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 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 in an automated manner will not be applied in this study.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see [Section 6.7](#)) will be provided.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluation of ECG data will be based on the TS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. Occurrences of notable findings will be flagged.

For all subjects with any notable finding in quantitative ECG recordings, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

Comments regarding the ECGs will be listed.

Analysis of central tendency

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time in all ECG variables.

For QTcF, QT and HR, a repeated measurements analysis of the changes from baseline with baseline as a covariate will be performed. The model will include the fixed effects "baseline", "treatment", "time", "baseline*time" interaction, and "treatment*time" interaction. The covariance model for the repeated effect "time" will be unstructured (i.e. TYPE=UN or UNR); in case of convergence problems refer to [Additional Section 9.2](#). For each dose group and each time point, the contrast of the means for "treatment-placebo" will be estimated by the difference in the corresponding adjusted means (Least Squares Means); two-sided 90% CIs based on the t-distribution will also be computed. For each of the above ECG variables, the time profiles of the mean differences to placebo in the changes from baseline and the corresponding 90% CIs will be presented in a figure.

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

```
PROC MIXED DATA=indata CL METHOD=REML;
  CLASS subject treat time;
  MODEL ECGep = treat time base treat*time base*time / DDFM=KR CL ALPHA=0.1;
  REPEATED time / TYPE=UN SUBJECT=subject;
  LSMEANS treat*time / DIFF CL ALPHA=0.1;
  SLICE treat*time / SLICEBY=time DIFF CL ALPHA=0.1 NOF PLOT=none;
  RUN;
```

For PR, QRS, RR as well as QTcB, the time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

For subjects with notable findings, the individual time courses of QTcF, QT, HR, PR and QRS of these subjects will be presented in figures.

7.8.7 Others

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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
- 2 *001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version; IDEA for CON
- 3 *001-MCS-50-413_RD-02*: "Important Manual Protocol Violations Spreadsheet", 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-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*: "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	10-APR-18		None	This is the final TSAP without any modification