Trial Statistical Analysis Plan

c17748273-01

BI Trial No.:	1386.7
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1467335 in healthy Japanese male volunteers with multiple oral doses at the highest dose in Caucasian for comparison (randomised, double-blind, placebo-controlled trial)
Investigational Product:	BI 1467335
Responsible trial statisticians:	Phone: , Fax:
Date of statistical analysis plan:	29 JAN 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, distribution, metabolism, and excretion
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of the first dose
$AUC_{0-24,28}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after administration of the 28^{th} dose
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
C_{max}	Maximum measured concentration of the analyte in plasma after administration of the first dose
$C_{max,28}$	Maximum measured concentration of the analyte in plasma following administration of the 28^{th} dose
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CTP	Clinical trial protocol
CTR	Clinical trial report

Term	Definition / description
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECGPKS	Electrocardiogram pharmacokinetic set
eCRF	Electronic case report form
EMA	European Medicines Agency
EudraCT	European union drug regulating authorities clinical trials
gCV	Geometric coefficient of variation
gMean	Geometric mean
HR	Heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPV	Important protocol violation
MedDRA	Medical Dictionary for Regulatory Activities
on-trt	on-treatment
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PR interval	ECG interval from the onset of P wave to the beginning of the QRS
PV	Protocol violation
QRS complex	Combination of the Q, R, and S waves
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave
QTcB	QT interval, heart rate corrected according to Bazetts formula
QTcF	QT interval, heart rate corrected according to Fridericias formula
QTcN	QT interval, heart rate corrected according to study population formula
R	Reference treatment
RAGe	Report appendix generator
RPM	Report planning meeting

Term	Definition / description
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SOC	System organ class
T	Test treatment
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the 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.

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).

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

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoint is the number [N (%)] of subjects with drug-related AEs, as defined in Section 5.2.1 of the CTP.

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoint

Secondary endpoints are the PK parameters for BI 1467335, as defined in Section 5.5.1.1 of the CTP.

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

These variables that are defined as medical examinations in the CTP, Section 5.2.5.2 will be used.
Derived variables are defined as follows:
Age [years] will be determined as the difference between year of birth and year of informed consent.

BMI will be calculated as weight [kg] / (0.01 * height [cm]^2).

5.4.2 Ophthalmological examination

Ophthalmological examination findings will be presented as defined in Section 5.2.5.3 of the CTP. Descriptive statistics will be provided.

5.4.3 Treatment compliance and treatment exposure

Treatment compliance will be based on data from the subject diary. The subjects will report whether they took study medication during the treatment period. For each subject, percent compliance will be calculated as the number of times they reported taking study medication (i. e. number of non-missing actual administration date on CRF) divided by the number of tablets which should have been taken was given times 100. If subjects discontinued study, denominator is defined as the number of the dates from day 1 to day of discontinuation.
Treatment exposure is defined as the number of days taking medication and the total dose of BI 1467335 per subject.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Subjects were treated with 3 mg, 6 mg or 10 mg of BI 1467335 (test treatment, T) or placebo (reference treatment, R) once daily over 28 days. Three placebo groups will be defined: Placebo for Japanese, Placebo for Caucasians and Total placebo. Placebo for Japanese will be defined as a pooled group of the Japanese subjects receiving placebo treatment in the three dose groups. Placebo for Caucasians will be defined as the placebo subjects in the 10 mg dose group for Caucasians (which comprises all placebo-treated Caucasian subjects). Total placebo will be defined as one pooled placebo group (i.e. no distinction between dose groups and ethnicity will be made for placebo subjects).

For statistical analysis of AEs, safety laboratory data, vital signs and ECG, the following analysis phases are defined for each subject:

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	Placebo, 3 mg BI for Japanese, 6 mg BI for Japanese, 10 mg BI for Japanese or 10 mg BI for Caucasians, respectively	Date/time of first administration of study drug	0:00 on day after subject's trial termination date

CTR Section 15, Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE tables), the following totals will be provided in addition:

- "**Total BI**", defined as the total over all on-treatment phases involving BI, i.e., "3 mg BI for Japanese" + "6 mg BI for Japanese" + "10 mg BI for Japanese"+ "10 mg BI for Caucasians "

- "**Total BI for Japanese**", defined as the total over all on-treatment phases involving BI, i.e., "3 mg BI for Japanese" + "6 mg BI for Japanese" + "10 mg BI for Japanese"

- **"Total on-trt"**, defined as the total over all on-treatment phases, i.e., "Placebo" + "3 mg BI for Japanese" + "6 mg BI for Japanese" + "10 mg BI for Japanese"+ "10 mg BI for Caucasians"

CTR Appendix 16.1.9.2.8.1 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 16.1.9.2.8.1 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

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects). 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" (1).

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 (2). The following table 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.

Table 6.2: 1 Important protocol violations

Category/Code		Description	Example/Comment
A		**Entrance criteria not met**	
	A1	Inclusion criteria not met	Inclusion criteria not met as specified in the protocol
	A2	Exclusion criteria met	Exclusion criteria met as specified in the protocol
B		**Informed consent**	
	B1	Informed consent not available/not done	Informed consent date missing
	B2	Informed consent too late	Informed consent date was after screening visit
C		**Trial medication and randomization**	
	C1	Incorrect trial medication taken	The contents of medication kit do not match with the randomisation
	C2	Randomisation order not followed	Subject received trial medication from medication kit assigned to another subject
	C3	Non-compliance	Medication not taken as scheduled by protocol
	C4	Medication code broken inappropriately	Medication code was broken with no valid reason
D		**Concomitant medication**	
	D1	Any prohibited concomitant medications/therapies use	Intake of medications/therapies that might reasonably influence the results of the trial
E		**Missing data**	
	E1	Certain violations of procedures used to measure secondary PK endpoint	Violations of PK sampling which may cause no secondary PK endpoint. Handling for violation relating PD sampling will be discussed on RPM.
F		**Incorrect timing**	
	F1	Certain violations of time schedule used to measure secondary PK endpoint	PK sample taken too early/too late[1] Handling for violation relating PD sampling will be discussed on RPM.
G		**Other trial specific important violations**	
	G1	Incorrect intake of food	The subject who eats food within 10 hours before the medication intake on the visit days

[1] Time deviations will only be flagged as iPV, when one of the secondary endpoint of the subject cannot be evaluated

6.3 SUBJECT SETS ANALYSED

The following subject sets will be defined for statistical analysis:

- Randomised set (RS):
  This subject set includes all subjects who were randomised, i.e., who have been assigned a subject number, whether treated or not.

- Treated set (TS):
  This subject set includes all subjects who received at least one dose of study drug, as defined in Section 7.3.1 of the CTP. This is the full analysis set population in the sense of ICH-E9.

- Pharmacokinetic parameter analysis set (PKS):
  This subject set includes all subjects of the TS who provide at least one PK parameter that was not excluded due to relevant PVs or due to PK non-evaluability, as defined in Section 7.3.1 of the CTP.

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.

- ECG PC set (ECGPCS):
  This subject set consists of all subjects in the TS who provide a baseline value and at least one post-baseline value for at least one ECG variable used in the exposure-response analysis, and a corresponding (i.e. time-matched) valid drug plasma concentration. Since placebo subjects will be included in the exposure-response analyses with plasma concentration set to 0, a plasma concentration BLQ is considered a valid drug plasma concentration for placebo subjects.

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

	Subject set			
Class of endpoint	RS	TS	PKS	ECGPCS
Disposition	X	X		
Exposure		X		
IPVs	X			
Demographic/baseline endpoints		X		
Primary endpoint		X		
ECG endpoints and plasma concentrations used in exposure-response analysis				X
ECG endpoints in other analyses		X		
Other safety parameters		X		
Secondary PK endpoints			X	

6.5 POOLING OF CENTRES

This section is not applicable because centre is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

The endpoint will be derived taking account for handling of missing data as defined in the CTP, Section 7.4.

CTP: *If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). The only exception to this rule is when the subject had an AESI and/or SAE that the investigator considers related to the screening procedure. If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR.*

Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (3)).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

There will be a centralised evaluation of all 12-lead ECG recordings at the time points specified in Table 6.7: 1 below:

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

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase
2	1	00:15	On-treatment
		00:30	
		00:45	
		01:00	
		01:30	
		02:00	
		04:00	
		08:00	
		12:00	
	2	23:55	

Table 6.7: 1 Time schedule of 12-lead ECG recordings (continued)

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase
2	14	310:00	On-treatment
		312:15	
		312:30	
		312:45	
		313:00	
		313:30	
		314:00	
		316:00	
		320:00	
		324:00	
	15	336:00	
		337:00	
	28	646:00	
		648:15	
		648:30	
		648:45	
		649:00	
		649:30	
		650:00	
		652:00	
		656:00	
		660:00	
	29	672:00	

Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all time points on Day 1, Day 2, Day 14, Day 15, Day 28 and Day 29. On all other time points, single ECGs will be recorded.

The value of an ECG variable at each of the time points with triple ECG is defined as the arithmetic mean of the 3 single ECG measurements. In particular, the baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to first drug administration.

In all other analyses (except for analyses of ECG variables), the last non-missing value determined prior to the first dosing of BI 1467335 will be defined as baseline.

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" (001-MCG-159) (9).

The individual values of all subjects will be listed. Listings will generally be sorted by dose group, ethnicity, 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 and biomarker 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 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. 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.

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.

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 be analysed using descriptive statistics and also using frequency tables for categories of treatment compliance. Categories will be defined as <80%, 80% - 100% and >100%.

Any deviations from complete intake will be addressed in the RPM/DBLM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the frequency of subjects with drug related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

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

Dose proportionality of secondary endpoints will be evaluated as defined in the CTP, Section 7.3.1, by use of the power model. The assessment of dose proportionally will be performed for Japanese subjects only. 2 type placebo groups, Placebo for Japanese and Total placebo, will be used for dose proportionality analysis. If steady state will already be reached after 14 days of treatment, dose proportionality will also be investigated for $AUC_{0\text{-}24,14}$ and $AUC_{0\text{-}24,28}$ together (and for $C_{max,14}$ and $C_{max,28}$ together, respectively) by use of a repeated measurements model.

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.

Further details are given in 001-MCS-36-472_RD-01 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and 001-MCS-36-472_RD-03 "Description of Analytical Transfer Files and PK/PD Data Files" (5).

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the CTR based on the TS. The number of days taking medication will be analysed with standard descriptive statistical parameters and also using frequency tables for categories "<28 days", “28 days” and "> 28 days".

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.

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 [CTCAE grade Version 4.03], 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 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (6) [001-MCG-156] and "Handling of missing and incomplete AE dates" (3) [001-MCG-156_RD-01].

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 phase or on-treatment phase as defined in Section 6.1.

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 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 upper limit normal (ULN) combined with an elevation of total bilirubin > 2 fold ULN measured in the same blood draw sample, and/or*
- *marked peak 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 (8), 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 (8). 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 grade of CTCAE (version 4.03), primary SOC and preferred term.

The SOCs will be sorted according to the standard sort order specified by the EMA, preferred terms will be sorted by total frequency (within SOC).

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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (7). Laboratory analyses will be based on normalised values, i.e., for a given laboratory parameter, values will be transformed to a standard unit and a standard reference range before statistical analysis.

CTP: *Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated.*

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) 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 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 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.

7.8.5 Others

Physical examination findings and ophthalmological examination findings (exclusion of cataract) 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 or ophthalmological examination findings will be prepared.

8. REFERENCES

8	*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	*R17-0553:* Garnett C, Needleman K, Liu J, Brundage R, Wang Y; Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther 100 (2), 170 - 178 (2016)
11	*R10-2920:* Ring A: Statistical models for heart rate correction of the QT interval; Stat Med 29, 786 - 796 (2010)

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**31-MAY-17**		None	This is the initial TSAP with necessary information for trial conduct
Final	**29-JAN-18**		None	This is the final TSAP without any modificaton