TRIAL STATISTICAL ANALYSIS PLAN

c19184992-01

BI Trial No.:	1305-0011
Title:	Safety, tolerability, and pharmacokinetics of single (Part 1) and multiple rising oral doses (Part 2) of BI 1015550 in healthy male subjects Final Protocol (including protocol revisions 2)
Investigational Product:	BI 1015550
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BMS	Biomarker set
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECGPCS	Electrocardiogram plasma concentration set
EMA	European Medicines Agency
ES	Entered set
gCV	geometric coefficient of variation
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter set
PV	Protocol Violation
$R_{A,Cmax}$	Accumulation ratio based on $C_{max,ss}$
$R_{A,AUC}$	Accumulation ratio based on $AUC_{0-\tau}$

Term	Definition / description
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan

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.

Study data will be stored in a trial database within the Oracle Clinical™ system.

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 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 CTP.

In addition to the analyses described in the protocol,

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

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 ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary PK endpoints will be defined as in Section 5.5.1.2 of the CTP.

5.2.2.1 Part 1

Secondary endpoints in the single dose part of this trial are $AUC_{0-\infty}$ and C_{max} of BI 1015550 in plasma.

5.2.2.2 Part 2

Secondary endpoints in the multiple dose part of this trial are $AUC_{\tau,1}$ and C_{max} of BI 1015550 in plasma after the first dose, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1015550 in plasma after the last dose and the accumulation ratios $R_{A,Cmax}$ and $R_{A,AUC}$.

5.3.2 Safety endpoints

Further safety endpoints will be used as defined in Section 5.2.1 of the CTP:

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 planned to be treated either with

- a single dose of 36 mg or 48 mg of BI 1015550 (test treatment)
  or
- a single dose of placebo (reference treatment)
  or
- multiple doses of 6 mg or 12 mg of BI 1015550 (test treatment)
  or
- multiple doses of placebo (reference treatment).

In part 2, subjects will receive a single dose on Day 1. During the multiple dose segment from Day 3 until Day 13, subjects will be treated twice daily followed by a single dose on Day 14.

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	**Pbo SD**, **Pbo MD,** **36 mg SD**, **48 mg SD**, **6 mg bid MD**, or **12 mg bid MD**, respectively	Date/time of first administration of study drug	Date/time of last administration of BI 1015550 + REP or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up[1]	**F/U Pbo SD**, **F/U Pbo MD**, **F/U 36 mg SD**, **F/U 48 mg SD**, **F/U 6 mg bid MD**, or **F/U 12 mg bid MD**, respectively	Date/time of last administration of BI 1015550 + REP	12:00 a.m. on day after subject's trial termination date

[1] Follow-up phases might not exist, e.g. if the subject's trial termination date is within after last administration of BI 1015550.

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

CTR Appendix 16.1.9.2.8.1 displays will present results for the screening, on-treatment phases and follow-up 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 + follow-up)

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" (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
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
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, C4, C5 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" (1).

6.3 SUBJECT SETS ANALYSED

The following subject sets will be defined for statistical analysis:

- Entered set (ES):
  This subject set includes all entered and randomised subjects, 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. This is the full analysis set population in the sense of ICH-E9.

- 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

	Subject set			
Class of endpoint	ES	TS	PKS	BMS
Disposition	X	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

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). 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.*

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 (3).

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 (4). **CTP**: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) 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).*

CTP: *For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP 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 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 with centralised evaluation

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Comment[1]	Study phase
2	1	-02:00	-02:00 - 00:00	Baseline
		00:30	only in SRD part	On-treatment
		01:00		
		01:30	only in SRD part	
		02:00		
		04:00		
		08:00	only in SRD part	
		10:00	only in SRD part	
		12:00	only in MRD part	
	2	24:00		
	3	48:00	only in SRD part	

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation (cont.)

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Comment[1]	Study phase
2	4	72:00	only in SRD part	On-treatment
	14	311:00	only in MRD part	
		313:00	only in MRD part	
		314:00	only in MRD part	
		316:00	only in MRD part	
		324:00	only in MRD part	
	15	336:00	only in MRD part	
	16	360:00	only in MRD part	
	17	384:00	only in MRD part	

[1] If no comment is given, time point is applicable to all dose groups in this trial

Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all time points with centralised ECG evaluation (as listed in the table above).

The baseline value of an ECG variable is defined as the mean of the 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 1015550 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" (5).

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, biomarkers as well as for all PK and PD 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 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 frequency 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.

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 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.6 FURTHER ENDPOINTS

7.6.1 Safety parameters

Safety and tolerability will be analysed as described in Section 7.8 of this TSAP.

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 "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) and "Handling of missing and incomplete AE dates" (3).

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, on-treatment or follow-up 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, 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.*

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) and drug related SAEs 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 intensity, 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 "Display and Analysis of Laboratory Data" (9).

If possible, analyses will be based on original values. If multiple reference ranges apply for a parameter (e.g. due to different age groups), analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range.

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 (blood pressure, pulse rate, respiratory rate, aural body temperature and body weight (only part 2)) 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 for part 1 and part 2 separately. 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.

7.8.5 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 *001-MCS-50-413_RD-01:* "Protocol Violation Handling Definitions", current version; IDEA for CON

2 *001-MCS-50-413_RD-02:* "Important Manual Protocol Violations Spreadsheet", 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-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON

5 *001-MCG-159:* "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON

6 *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON

7 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON

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

9 *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	**11-APR-2018**		None	This is the final TSAP without any modification