TRIAL STATISTICAL ANALYSIS PLAN

c25432470-01

BI Trial No.:	1386-0002
Title:	Pharmacokinetics, safety and tolerability after multiple dose administration of BI 1467335 in subjects with moderate renal impairment and subjects with normal renal function (a mono-centric, open-label study in matched-group design) Including Protocol Amendment 1 and 2 [c17401132-03]
Investigational Product:	BI 1467335
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	10 OCT 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_{0-24}	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
$AUC_{\tau,14}$	Area under the concentration-time curve of the analyte in plasma following administration of the 14th dose
$AUC_{\tau,28}$	Area under the concentration-time curve of the analyte in plasma following administration of the 28th dose
BI	Boehringer Ingelheim
BWU	Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,14}$	Maximum measured concentration of the analyte in plasma following administration of the 14^{th} 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
CV	Arithmetic Coefficient of Variation
DB	Dose Proportionality, Between-Subject Design
DBLM	Database Lock Meeting
ECG	Electrocardiogram
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
LLT	Lower Level Term

Term	Definition / description
iPD	Important Protocol Deviation
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
O*C	Oracle Clinical
PK	Pharmacokinetic(s)
PKS	PK analysis set
PKS-stat	PK statistical analysis set
PO	Per Os (oral)
PT	Preferred Term
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
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary
XPKISTAT	Library of SAS® Macros for PK analysis

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 or higher, 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. The following change compared to the protocol will be made:

No ‘Randomised set’ will be defined in the TSAP as data of subjects randomised but discontinued before first administration of trial medication will not be entered in the case report form. A correct display of the ‘Randomised set’ would not be possible.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 5.5.1.1 of the CTP:

After the first dose (Day 1), for BI 1467335:

- *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)*

- *C_{max} (maximum measured concentration of the analyte in plasma after administration of the first dose)*

After the last dose (Day 28), for BI 1467335:

- *$AUC_{\tau,28}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 28^{th} dose)*

- *$C_{max,28}$ (maximum measured concentration of the analyte in plasma following administration of the 28^{th} dose)*

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:

After the 14th dose (Day 14), for BI 1467335:

- *$AUC_{\tau,14}$ (area under the concentration-time curve of the analyte in plasma over the dosing interval after administration of the 14^{th} dose)*

- *$C_{max,14}$ (maximum measured concentration of the analyte in plasma following administration of the 14^{th} dose)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Section 3.1 of the CTP: It is planned to include altogether 20 participants in the trial, of which up to 10 subjects with moderate renal impairment. All subjects will receive over 4 weeks 10 mg of BI 1467335 once daily […]. Each renally impaired subject will have a healthy subject matched for gender, race, smoking status, age (within ±10%) and BMI (within ±10%). They will build a pair for later evaluation.

For details of dosage and formulation, see Table 6.1:1 below.

Table 6.1: 1 Labels for treatments for use in the CTR

Treatment		Short label
A	BI 1467335, 2*5mg tablet, po, qd, renal impaired	Moderate
B	BI 1467335, 2*5mg tablet, po, qd, healthy volunteer	Normal

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 1467335))
- **On treatment**
  - **Normal** (ranging from the time of first administration of BI until 0:00h on the day after the trial termination date for subjects with normal renal function)
  - **Moderate** (ranging from the time of first administration of BI until 0:00h on the day after the trial termination date for subjects with moderate renal impaired function)

Please note that all AEs reported between start of trial drug administration and the last per-protocol contact will be considered on treatment (i.e. no follow-up period is considered in this trial).

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 will not be included in this analysis.
The following totals will be provided in addition:

- a total over all on treatment phases included in this analysis ("**Total on treatment**") (Section 15.3 only)

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))

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

- a total over all study phases ("**Total**")

Tables of vital signs and laboratory values will present results by the above mentioned on treatment phase.

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 DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects.

Consistency check listings (for identification of deviations 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 combined report planning and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identifyed at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (3).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM minutes via an accompanying Excel spreadsheet (2). The following table 6.2: 1 contains the categories which are considered to be iPDs in this trial. If the data show other iPDs, this table will be supplemented accordingly by the time of the RPM/DBLM at the latest.

Table 6.2: 1 Important protocol deviations

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
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
E		**Missing data**
	E1	Certain deviations of procedures used to measure primary or secondary data
F		**Incorrect timing**[1]
	F1	Certain deviations of time schedule used to measure primary or secondary data
G		**Other trial specific important deviations**
	G1	Appropriate fasting condition not met prior to study drug administration
	G2	Protocol deviations affecting safety and rights

[1] Time deviations will only be flagged as iPD, when leading to exclusion of the entire subject from an analysis set

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). It is used for safety analyses.

Plasma and urine concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be:

- Incorrect dose of trial medication taken
- Use of restricted medications.

Plasma and urine concentrations and/ or parameters of a subject will be considered as non-evaluable, if for example:

- the subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- missing samples/ concentration data at important phases of PK disposition curve.

- PK analysis set (PKS):
  The PK analysis set (PKS) includes all subjects in the TS who provide at least one PK parameter that was defined as primary or secondary endpoint and was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value to the statistical assessment.

- PK statistical analysis set (PKS-stat):
  This subject set includes all subjects from the PKS who built a subject pair of renal impaired subject and his matching healthy volunteer control and provide at least one PK parameter that was defined as primary or secondary endpoint and was not excluded according to the description above.

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 Analysis sets for endpoints/data description

	Analysis set		
Endpoint/data description	TS	PKS	PKS-stat
Safety assessments	X		
Primary and secondary analyses of primary, secondary and further PK endpoints			X
Further analyses of primary and secondary PK endpoints		X	
Descriptive evaluations of primary, secondary and further PK endpoints		X	
Demographic/baseline data	X		
Important Protocol Deviations	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 is defined as the last measurement before first administration of BI 1467335.

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 on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (only on Day 1 this includes blank values for PK in urine and plasma).

On Day 14 and 28, same time windows apply except of the plasma PK sample which will be collected 5 minutes before drug administration.

The acceptable deviation from the scheduled time for vital signs […] *will be ± 30 min for the first 4 h after trial drug administration and ± 60 min thereafter when not already stated otherwise in the* CTP *Flow Chart.*

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 7.4 and 7.5.2) 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 the department Translational Medicine and Clin. Pharmacology at BI 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 renal function 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 renal function 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 by renal function group and 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 monitored by either administration of all trial medication in the study centre under supervision of the investigating physician or a designee or during ambulatory period subjects confirm drug intake by phone contact with the study site. 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

The effect of moderate renal impairment is to be determined on the basis of the primary endpoints C_{max}, AUC_{0-24} of BI 1467335 on Day 1, and $C_{max,28}$ and $AUC_{\tau,28}$ of BI 1467335 on Day 28 as well as the secondary pharmacokinetic endpoints $C_{max,14}$ and $AUC_{\tau,14}$ of BI 1467335 on Day 14.

These analyses will be based on the PKS-stat.

Section 7.1.3 of the CTP:

The statistical model used for the analysis will be an ANOVA (analysis of variance) model on the logarithmic scale including the effect "degree of renal impairment" as a fixed effect as well as subject pair as a random effect. The model is described by the following equation:

$y_{ik} = \mu + \tau_k + s_i + \varepsilon_{ik}$, *where*

y_{ik} *logarithm of response (endpoint for relative bioavailability evaluation, measured on the degree of renal impairment k for subject pair i),*

μ *the overall mean,*

s_i *the ith subject pair (each renal impaired subject has his own matching healthy control), i=1,…,10,*

τ_k *the kth degree of renal impairment, k = 1 for normal and k=2 for moderate renal impaired,*

ε_{ik} *the random error associated with the kth degree of renal impairment for subject pair i.*

Point estimates of the ratios of the geometric means (T/R) for the endpoints and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

The analysis will be accomplished by using the XPKISTAT macro, based on PKS-stat (design BWU).

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 same analyses as for the primary endpoints will be performed for the secondary endpoints $C_{max,14}$ and $AUC_{\tau,14}$ of BI 1467335 on Day 14 (refer to Section 7.4).

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.

If not stated otherwise, the safety results will be sorted by renal function group.

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).

The intensity (severity) of adverse events will be performed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (12).
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 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*
  - *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 REP for BI 1467335, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this clinical trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered 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 the Report Planning 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). This table will also be shown by maximum CTCAE grade. 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 SOC). 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). Differences from baseline will be evaluated descriptively.

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 possible clinically significant will be highlighted in the data listings.

It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not (at the RPM/DBLM at the latest).

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate).
Body weight at screening and post examination will be listed only.

7.8.4 ECG

12-lead 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 AEs (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.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
3.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS
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.
12.	Common terminology criteria for adverse events (CTCAE): version 4.0 (NIH publication no. 09-5410, published: May 28, 2009 (v4.03: June 14, 2010), revised June 2010, reprinted June 2010). http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf; 2010. [R10-4848]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	10-OCT-18		None	This is the final TSAP without any modification