TRIAL STATISTICAL ANALYSIS PLAN

c26812923-01

BI Trial No.:	1407-0014
Title:	Relative bioavailability of a single oral dose of BI 730357 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, one way crossover study) (including Protocol Amendments No.1[c24616632 -02] and No. 2 [c24616632 -03])
Investigational Product:	BI 730357
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	08APR2019 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-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BMI	Body Mass Index
BP	Blood Pressure
BWU	Bioavailability/Bioequivalence, Within-Subject Design, uncontrolled
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
ECG	Electrocardiogram
EDC	Electronic Data Capture
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FU	Follow-up
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
iPD	Important Protocol Deviation
ITZ	Itraconazole

Term	Definition / description
LLT	Lower Level Term
Max	Maximum
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing observations
O*C	Oracle Clinical
P10	10th percentile
P90	90th percentile
PK	Pharmacokinetic(s)
PKS	PK Parameter Analysis Set
PR	Pulse Rate
PT	Preferred Term
PV	Protocol Violation
Q1	1st quartile
Q3	3rd quartile
QD	Quaque die, once daily
R / Ref	Reference treatment
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
T	Test treatment
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
t_z	Time of last measurable concentration of the analyte in plasma
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

Term	Definition / description
WHO-DD	World Health Organization- Drug Dictionary
XPKISTAT	SAS® Macro for analysis of PK data

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

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

Study data will be stored in a trial database within the Oracle Clinical™ (O*C) system.

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

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Section 2.1.2 of the CTP:

The following pharmacokinetic parameters will be determined for BI 730357:

- *AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *C_{max} (maximum measured concentration of the analyte in plasma)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameter will be determined for BI 730357:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)*

Safety:

Section 2.2.2.2 of the CTP:

Safety and tolerability of BI 730357 and itraconazole will be assessed based on:

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

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on investigational products, assignment of treatment sequences and selection of doses, please see CTP, Section 4.

The study was performed as an open-label, one-way crossover trial with 2 treatments (T and R). It was planned to assign 14 healthy male subjects (at least 12 completed).

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

Table 6.1: 1 Treatments and labels used in the analysis

Treatment		Short label
R	BI 730357, tablet, 50 mg, qd (Day 1)	BI
T	BI 730357, 50 mg tablet, qd (Day 1) + Itraconazole 200 mg, qd (Day -3 to Day 9)	BI + ITZ

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00 h on day of informed consent until first administration time of study drug)
- **On treatment**
  - **BI treatment** (including residual effect period (REP); i.e. ranging from the time of first administration of BI 730357 until 7 days thereafter)
  - **Itraconazole** (ITZ) (ranging from the time of first administration of Itraconazole until time of BI 730357 administration in treatment period 2)
  - **BI + ITZ (**including residual effect period (REP); i.e. ranging from time of BI 730357 administration in treatment period 2 until 9 days after the last administration of Itraconazole (up to 18 days))
- **Follow up**
  - **Follow-up BI** (ranging from end of BI treatment phase until next drug administration (of itraconazole) or alternatively, 0:00h on the day after trial-termination date in case of no further treatment, labelled **"FU-BI"**)
  - **Follow-up BI+ITZ** (ranging from end of BI+ITZ phase until 0:00h on the day after trial termination date, labelled **"FU-BI+ITZ"**)

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

- BI 730357, 50 mg tablet, qd (labelled **"BI"**)
- Itraconazole, 200 mg oral solution, qd (labelled **"ITZ"**)
- BI 730357, 50 mg tablet, qd + Itraconazole, 200 mg oral solution, qd (labelled **"BI + ITZ"**)

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

A) Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening and follow-up periods will not be included in this analysis.
The following totals will be provided in addition (Section 15.3 only):

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

B) Section 15.4 and Appendix 16.1.13.1.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up BI (labelled "**FU BI**")
- Follow-up BI+ITZ (labelled "**FU BI+ITZ**")

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

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

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

Section 7.3 of the CTP: *Important protocol deviations* (iPD) *categories will be suggested in the integrated quality and risk management* (IQRM) *plan,* iPDs *will be identified no later than in the Report Planning Meeting, and the* iPD *categories will be updated as needed.*

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 Report Planning Meeting and database lock meeting (RPM/DBLM). At this meeting, all manual deviations identified 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)" (2).

If any iPDs 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 iPDs will be summarised and listed.

6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were entered and treated with at least one dose of study drug.
  This is the full analysis set population in the sense of ICH-E9 (1).
  The TS is used for safety analyses.

Section 7.3.1 of the CTP: *Plasma 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 trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Plasma 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),*
- *A predose concentration of BI 730357 is >5% C_{max} value of that subject in the respective treatment period*
- *Missing samples/concentration data at important phases of PK disposition curve*

- PK parameter analysis set (PKS):
  This subject set includes all subjects in the TS who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Analyses of PK endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	X	
Important PDs	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 7.5.

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 administration of BI 730357 in each period.

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 the end of trial examination are provided in the* CTP *Flow Chart.*

Study measurements and assessments scheduled to occur 'before' trial medication administration are to be performed and completed within a 3h-period prior to BI 730357 administration in Visit 2, and within a 2h-period prior to the next itraconazole administrationin Visit 3, if not indicated otherwise in the Flow Chart.

Following administration of trial drugs in Visits 2 and 3, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1, ± 45 min on Day 2, and ± 60 min from Day 3 onwards.

[…]

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

Starting from 119 hours after BI 730357 administration (and beyond), a time window of ± 60 min will be allowed for PK blood sampling times.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

Adherence to time windows will be checked via the consistency check listings at the RPM/DBLM.

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) will be performed by and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Sections 7.4 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 endpoints will be performed by and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of Clinical Trials and Project Summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations (8).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number, visit and actual treatment (if appropriate).
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, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all

subjects in the respective subject set whether they have non-missing values or not. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

Exclusion of PK parameters

The ADS ADPP (PK parameters) contains column variables 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 APEXCO is equal to “Included”.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’, the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’, the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’, the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λ_z) only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The data will be summarised in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM/DBLM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

Primary analysis

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

Section 7.3.1 of the CTP: *The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:*

$y_{km} = \mu + s_m + \tau_k + e_{km}$, *where*

y_{km} = *logarithm of response measured on subject m receiving treatment k,*

μ = *the overall mean,*

s_m = *the effect associated with the* m^{th} *subject, m = 1, 2, ..., n*

τ_k = *the* k^{th} *treatment effect, k = 1, 2,*

e_{km} = *the random error associated with the* m^{th} *subject who received treatment k.*

The difference between the expected means for test treatments and reference treatment ln(T)-ln(R), estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution, will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

The implementation for this analysis will be accomplished by using the XPKISTAT macro, based on PKS, and option BWU (Bioavailability/Bioequivalence, within-subject design, uncontrolled w.r.t. time).

Further analysis

Section 7.3.1 of the CTP: *The same statistical model as stated above will be repeated for the primary endpoints but with 'subject' considered as fixed effects.*

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

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

Further analysis of primary endpoints is explorative.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 Secondary endpoints

The secondary PK endpoint $AUC_{0-\infty}$ will be assessed using the same methods as described for the primary endpoints but will not be interpreted in a confirmatory sense.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated subjects who failed to complete the study (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [001-MCG-156] (9).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

For analysis, multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started within one hour after end of the first occurrence)

For further details on summarization of AE data, please refer to [001-MCG-156] (9).

Section 5.2.6.1.4 of the CTP: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/ or ALT (alanine transaminase) ≥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*
- *Severe infections (grading according to Rheumatology Common Toxicity Criteria (RCTC) developed by OMERACT [R13-3515](12))*
- *Opportunistic and mycobacterium tuberculosis infections*
  These include pneumocystis jirovecii, BK virus disease including polyomavirus-associated nephropathy, cytomegalovirus, posttransplant lymphoproliferative disorder (Epstein-Barr virus), progressive multifocal leukoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), hepatitis B virus reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi Infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus progression.

The analysis of adverse events will be based on the concept of treatment emergent adverse events.

Section 1.2.3 of the CTP: *The Residual Effect Period (REP, i.e., the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 730357 is 7 days for the mono-therapy (Treatment R). When given together with itraconazole (Treatment T), it is expected that plasma exposure of BI 730357 could be increased (albeit within the range explored in the clinical trial 1407-0001), and the time of*

relevant plasma exposure could be prolonged, which in turn could result in a prolonged period in which adverse effects could potentially occur.

For the use of itraconazole in Treatment T, the REP is defined as 9 days after last administration of itraconazole on Day 9 in Period 2. Therefore, the follow-up period will start earliest on Day 18 following BI 730357 dosing in Period 2, as this is expected to cover the period in which any potential adverse effects could reasonably occur.

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 Trial Leader/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). Separate tables will be provided for subjects with other significant AEs according to ICH E3 (10), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.

The SOC and PTs will be sorted by frequency (within system organ class). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (11).

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

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

7.8.4 ECG

ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be listed under 'Relevant Medical History / Baseline Conditions' (when they occurred during screening) or will be reported as 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.	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, IDEA for CON.
3.	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; IDEA for GEN.
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.	Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 34:6. 1401-1414. 2007 [R13-3515].

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	08APR2019		None	This is the final TSAP without any modification