Trial Statistical Analysis Plan

C28264105-01

BI Trial No.:	1407-0032
Title:	Relative bioavailability of intended commercial formulations (iCF) of BI 730357 versus BI 730357 trial formulation 1 and bioavailability comparison of three different iCF batches following oral administration in healthy subjects (an open-label, single-dose, randomised, 2-way and 3-way crossover trial) including Global Protocol Amendment 1 [c26431910-02]
Investigational Products:	BI 730357 film-coated tablets 50 mg iCF and trial formulation 1 (TF1), 100 mg iCF and TF1, and 100 mg iCF final batch with regularly milled API and iCF side batches with coarse milled or unmilled API.
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	30 JUL 2019 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 transaminase
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
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
$AUC_{0-\infty}$	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
BWC	Bioavailability/Bioequivalence, within-subject design, time-controlled
CI	Confidence interval
CL/F	Apparent clearance of the analyte in the plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRA	Clinical research associate
CRF	Case report form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DILI	Drug induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric coefficient of variation
gMean	Geometric mean

Term	Definition / description
iCF	Intended commercial formulation
ICH	International Conference on Harmonisation
iPD	Important Protocol Deviation
ISF	Investigator site file
IQRM	Integrated quality and risk management
λ_z	Terminal rate constant in plasma
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRT,po	Mean residence time of the analyte in the body after oral administration
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
PK	Pharmacokinetics
PKS	PK parameter analysis set
PR	Pulse rate
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
R	Reference treatment
RAGe	Report Appendix Generator system
RCTC	Rheumatology Common Toxicity Criteria
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
$t_{1/2}$	Terminal half-life of the analyte in plasma

Term	Definition / description
TF1	Trial formulation 1
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
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
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). 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 RAVE EDC 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. No changes compared to the protocol were made.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

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 ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

Pharmacokinetic (PK):

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)*

There are two methods by which $AUC_{0-\infty}$ is calculated:

- AUCINF_obs: Area under the plasma concentration time curve from time zero to time infinity with extrapolated area from time t_z to infinity based on last observed concentration at time t_z

- AUCINF_pred: Area under the plasma concentration time curve from time zero to time infinity with extrapolated area from time t_z to infinity based on the concentration predicted by regression for the time t_z

In this study, both types will be derived and both will statistically be evaluated.

Safety:

Section 2.2.2.2 of the CTP: *Safety and tolerability of BI 730357 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)*

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on investigational products, assignment of treatment sequences, and selection of doses, please see CTP, Sections 3 and 4.

The study will be performed as a randomised, open-label, two-way and three-way crossover trial with 3 parts.

Part 1 is a two-way crossover trial with two treatments (T1 and R1) and two treatment sequences (T1-R1 or R1-T1).

Part 2 is a two-way crossover trial with two treatments (T2 and R2) and two treatment sequences (T2-R2 or R2-T2).

Part 3 is a three-way crossover trial with three treatments (T3c, T3u, and R3) and three treatment sequences (T3c-T3u-R3 or T3u-R3-T3c or R3-T3c-T3u).

In total, it was planned to assign 43 healthy male and female subjects: 14 subjects to the two treatment sequences of Part 1 and 2 in a 1:1 ratio, and 15 subjects to the three sequences of Part 3 in a 1:1:1 ratio.

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	Short label for footnote
T1	BI 730357, 50 mg tablet, iCF, final batch, qd	BI 50mg iCF	BI 730357 50mg iCF
R1	BI 730357, 50 mg tablet, TF1, qd	BI 50mg TF1	BI 730357 50mg TF1
T2	BI 730357, 2*100 mg tablet, iCF, final batch, qd	BI 200mg iCF	BI 730357 200mg iCF
R2	BI 730357, 2*100 mg tablet, TF1, qd	BI 200mg TF1	BI 730357 200mg TF1
T3c	BI 730357, 100mg tablet, iCF side batch coarse milled API, qd	BI coarse	BI 730357 100mg coarse milled API
T3u	BI 730357, 100mg tablet, iCF side batch unmilled API, qd	BI unmilled	BI 730357 100mg unmilled API
R3	BI 730357, 100mg tablet, iCF final batch reg milled API, qd	BI regular	BI 730357 100mg regularly milled API

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** (separately for each treatment described in Table 6.1: 1 above, including residual effect period (REP); i.e. ranging from the time of administration of the respective treatment until 7 days after administration of the respective treatment)
- **Follow-Up** (ranging from end of on-treatment phase until end of follow-up or time of administration of the next treatment)

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

A) Section 15.3 and Appendices 16.1.13.1.8.2 and 16.1.13.1.8.3 (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 will not be included in this analysis.

The following total will be provided in addition (Section 15.3 only):

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

B) Section 15.4 and Appendix 16.1.13.1.8.1 (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

In Section 16.1.13.1.8 AE tables, the following total 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 BRAVE views refer to Technical TSAP ADS 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 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 minutes via an accompanying Excel spreadsheet (3).

For a description of categories which are considered to be iPDs in this trial, please refer to the IQRM plan.

6.3 SUBJECT SETS ANALYSED

Section 7.3 of the CTP:
Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treated set will be used for safety analyses.*

- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (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 (as specified in the following subsection 'Pharmacokinetics'). 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.*

Relevant protocol violations 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 is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

The following Table 6.3: 1 contains the information which subject is used for which class of endpoint:

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	TS	PKS
Analyses of primary and secondary PK endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	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 7.5.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards

Missing data and outliers of PK data are handled according to BI standards

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For vital signs, baseline for each study period is defined as the pre-treatment measurement at -2:00 h.

For overall analysis, the screening visit will be used as baseline for laboratory measurements.

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 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 the trial drug administration.

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.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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.

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 Section 7.4 and Section 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.

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 (7).

The three parts will be reported in separate tables, listings, and figures.

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

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 sequence/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

Exclusion of PK concentrations

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 treatment sequence 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 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 ENDPOINT(S)

Relative bioavailability of BI 730357 is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.1).

Section 7.3.1 of the CTP:

Primary analysis

The statistical model used for the analysis of primary and secondary 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: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation, where p=2 for Part 1 and 2 of the trial and p=3 for Part 3 of the trial:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, *where*

y_{ijkm} = *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ = *the overall mean,*

ζ_i = *the* i^{th} *sequence effect,* $i = 1, \ldots, p$

s_{im} = *the effect associated with the* m^{th} *subject in the* i^{th} *sequence,* $m = 1, 2, \ldots, n_i$

π_j = the j^{th} period effect, j = 1, …, p

τ_k = the k^{th} treatment effect, k = 1, …, p

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

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

Section 7.3.1 of the CTP: *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). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.*

Further exploratory analyses

As a sensitivity analysis, this ANOVA will be repeated for the primary and secondary endpoints with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects. This analysis will be done using PROC GLM.
The following SAS code can be used to fit the model:

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

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

The secondary PK parameter $AUC_{0-\infty}$ will be assessed using the same methods as described for the primary endpoints.

Safety:

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability.

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] (8).

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 case report form (CRF) will be collapsed into one 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] (8,4).

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, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

- *Severe infections (grading according to Rheumatology Common Toxicity Criteria (RCTC) developed by OMERACT)*

- *Opportunistic and mycobacterium tuberculosis infections*

  These include pneumocystis jirovecii, BK virus disease including polyomavirusassociated 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 of BI 730357 (REP, i.e., the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present)*

All adverse events occurring before first drug administration will be assigned to 'screening', those between intake of trial medication and prior to next drug administration or termination date will be assigned to the corresponding treatment ('on treatment') as long as they occur within the REP. Adverse events with onset outside of the REP but prior to next drug administration or termination will be assigned to "follow-up".

Section 7.3.4 of the CTP: *Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.*
For more detail see the TSAP ADS plan.

According to ICH E3 (9), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken with trial drug = 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 summarised 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 (9), 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

Descriptive statistics will be calculated for screening and end-of-trial visits as well as for the difference from screening. The summary statistics will be provided in total.

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 flagged in the data listings.

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

The analyses of laboratory data will be based on BI standards [001-MCG-157] (10).

7.8.3 Vital signs

Descriptive statistics will be calculated for screening and end-of-trial visits. The summary statistics will be provided in total. Furthermore, for each treatment, summary statistics at pre-treatment visit and 24:00 h including change from pre-treatment visit will be provided.

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

This section is not applicable as no other variables have been specified in the protocol.

8. REFERENCES

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**30-JUL-19**		None	This is the final TSAP without any modification