Trial Statistical Analysis Plan

c26433851-01

BI Trial No.:	1361-0011
Title:	Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomised, single-dose, two-period, two-sequence crossover study) Including Protocol Amendment 1 [c22769951-02]
Investigational Products:	Empagliflozin/linagliptin/metformin extended release fixed dose combination
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	06 DEC 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 transaminase
ANOVA	Analysis of variance
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_{0-72}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 hours
$AUC_{0-\infty}$	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
BWC	Bioavailability/Bioequivalence, within-subject design, time-controlled
CI	Confidence interval
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
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDC	Fixed dose combination
FU	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean

Term	Definition / description
ICH	International Conference on Harmonisation
iPD	Important Protocol Deviation
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
P10	10th percentile
P90	90th percentile
PK	Pharmacokinetics
PKS	PK parameter set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
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
T	Test treatment
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
XR	Extended release

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 Amendment. 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,).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4,), 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: *The following primary endpoints will be determined:*

- *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) for empagliflozin and metformin*
- *AUC_{0-72} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 72 h) for linagliptin*
- *C_{max} (maximum measured concentration of the analyte in plasma) for empagliflozin, linagliptin, and metformin*

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

Pharmacokinetic (PK):

Section 5.5.1.2 of the CTP: *The following secondary endpoints will be evaluated for empagliflozin, linagliptin, and metformin:*

- *$AUC_{0-\infty}$ (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 5.2.1 of the CTP: *Secondary endpoint to assess safety and tolerability of the investigational drugs is the number [N (%)] of subjects with drug-related adverse events.*

Safety:

Section 5.2.1 of the CTP: *Further criteria of interest:*

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

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

Section 5.2.5.2 of the CTP: *At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination.*

Age [years] will be determined as the difference between year of informed consent and year of birth.

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

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, Sections 3 and 4.

The study will be performed as a randomised, open-label, two-way crossover trial with two treatments (T and R) and two treatment sequences (TR or RT).

In total, it was planned to assign 30 healthy male and female subjects to the two treatment sequences in a 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
T	Empagliflozin 5 / Linagliptin 2.5 / Metformin XR 1000, 2* FDC fed	2 x FDC 5/2.5/1000	2 x FDC Empa5/Lina2.5/Met1000 fed
R	Empagliflozin 10 + Linagliptin 5 + Metformin XR 4*500, fed	E10+L5+4xM500	Empa10+Lina5+4xMet500 Tab fed

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, including residual effect period (REP); i.e. ranging from the time of administration of the respective treatment until 7 days thereafter)
- **Follow-up** (ranging from end of on treatment phase until next drug administration or 0:00 h on the day after trial termination date, according to previous treatment (labelled "**FU-Test**", "**FU-Ref**"))

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 above.

For detailed information on the handling of the treatments in the BRAVE views refer to Technical TSAP ADS plan and Data Reviewers guide. In particular, AEs will be counted for test or reference treatment if they occur up to the end of the residual effect period (REP) of 7 days.

6.2 IMPORTANT PROTOCOL DEVIATION

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)" (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).

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	Randomisation not followed
	C3	Non-compliance
	C4	Medication code broken inappropriately
	C5	Incorrect intake of trial medication
	C6	Improper washout between treatments
D		**Concomitant medication**
	D1	Prohibited medication use
	D2	Mandatory medication not taken
	D3	Improper washout of concomitant medication
E		**Missing data**
	E1	Certain deviations from procedures used to measure primary or secondary data
F		**Incorrect timing**[1]
	F1	Certain deviations from time schedule used to measure primary or secondary data
G		**Other trial specific important deviations**
	G1	Incorrect intake of meal
	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 study drug.
  This is the full analysis set population in the sense of ICH-E9 (1).
  It 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 clinical trial report.*

Relevant protocol deviations *may be:*

- *Incorrect trial medication taken, that is, 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 experiences emesis that occurred at any time during 24 hours after drug administration*
- *A pre-dose concentration is >5% C_{max} value of that subject*
- *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 primary or secondary PK parameter that 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 for one period to the statistical assessment.

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

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	

6.4 SUBGROUPS

A subgroup analysis is not planned.

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 exception where imputation might be necessary for safety evaluation is 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

For vital signs and laboratory parameters the baseline is defined as the measurement at screening.

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 3 h-period prior to the trial drug administration.

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.

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 (7).

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

For 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

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 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

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 and 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 λz) 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” (11).

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 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

Bioequivalence is to be determined on the basis of the primary pharmacokinetic endpoints (see Section 5.1).

Section 7.1.3 of the CTP: *For the bioequivalence analyses, pharmacokinetic endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA (analysis of variance) model* (see below).

Primary analysis

The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA model on the logarithmic scale. 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:

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

y_{ijkm} = *logarithm of response (endpoint) 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, 2

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

π_j = the j^{th} period effect, j = 1, 2

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

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

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 7.1.3 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), and a two-sided 90% confidence interval (CI) 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.*

Bioequivalence is considered established if the 90% CIs of the ratios of the geometric means for the primary endpoints (see Section 5.1) are contained in the pre-defined acceptance range of 80.00 – 125.00 %.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

The secondary PK parameter $AUC_{0-\infty}$ 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] (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 5.2.2.1 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.

- *Pancreatitis*

- *Hypersensitivity defined as angioedema, severe cutaneous adverse reactions or anaphylactic responses*
- *Ketoacidosis*
- *Lactic acidosis*

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

Section 1.2.5 of the CTP: *The residual effect period (REP) for the combined treatment with empagliflozin, linagliptin, and metformin, when measurable drug levels or PD effects are still likely to be present, is defined as 7 days after the last administration of trial medication.*

Therefore, all AEs which occur through the treatment phase and throughout the REP will be considered as on treatment.

All adverse events occurring before first drug administration will be assigned to 'screening', those between intake of trial medication and end of the 7-day REP will be assigned to the corresponding treatment ('on treatment'). AEs occurring after the REP but prior to next drug administration or termination date will be assigned to 'follow-up'. The follow-up will be summarized according to previous treatment.

Section 7.3.3 of the CTP: *AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety 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 = 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

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 only) 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 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 (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 ("FU-Test" and "FU-Ref")

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

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

7.8.2 Laboratory data

Descriptive statistics will be calculated for screening and end-of-trial visits as well as for the difference from baseline (=screening). The summary statistics will be provided in total. Laboratory data assessed within 7 days prior to the drug administration in the second treatment period will only be listed.

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 including change from baseline will be performed for vital signs (blood pressure and pulse rate) for both treatment sequences together (in total).

As vital signs are just measured at screening and post examination only these differences from screening will be calculated and presented in a table. In the listing the difference from screening 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).

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**06-DEC-2018**		None	This is the final TSAP without any modification