Trial Statistical Analysis Plan

c23833856-01

BI Trial No.:	1289-0025
Title:	Absolute bioavailability and pharmacokinetics of BI 409306 using a single oral dose of BI 409306 co-administered with an intravenous stable labeled isotope BI 409306 (C-13/N-15) in healthy male and female subjects (Non-Randomised, open-label, single arm, single period design)
Investigational Products:	BI 409306
Responsible trial statisticians:	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	26 JUN 2018 SIGNED
Version:	FINAL

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BWU	Bioavailability/Bioequivalence, within-subject design, uncontrolled w.r.t time
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
DILI	Drug induced liver injury
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference on Harmonisation
iv	intravenous
LLT	Lower level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number non-missing observations
O*C	Oracle Clinical

Term	Definition / description
PK	Pharmacokinetics
PKS	PK parameter analysis set
PM	Poor metabolizer
po	Per os
PT	Preferred term
PV	Protocol violation
qd	Quaque die (daily)
R	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
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary
XPKISTAT	Library of SAS® Macros for PK analysis

3. INTRODUCTION

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

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

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

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3, 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 5.5.1.1 of the CTP: *The following primary endpoints will be determined for BI 409306 and BI 409306 (C-13/N-15):*

- *$AUC_{0-\infty}$ and C_{max}*

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

Secondary endpoints are pharmacokinetic parameters. For more details see CTP Section 5.5.1.2.

5.3 FURTHER ENDPOINTS

Safety:

Section 5.2.1 of the CTP: *Safety and tolerability of the investigational drug 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)*
- Local tolerability

Section 5.2.1 of the CTP: *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.*

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* […].

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.

5.4.2 Pharmacogenomic evaluation

Section 5.3.1 of the CTP: *[..] a sample of at most 10 mL of blood will be taken at the screening examination if a subject's CYP2C19 genotype has not been previously determined. Pharmacogenetic results of CYP2C19 will be included in the final report.*

If a separate informed consent is signed, the extracted DNA of this sample will be used to determine a panel of genes coding for proteins that are involved in the Absorption, Distribution, Metabolism and Excretion (ADME) of drugs. The panel contains a list of known and likely functional variations present in key genes and covers more than 90% of the current ADME related genetic markers as defined by the PharmaADME group (website.pharmaadme.org). It is not intended to include these data in the final report. However, the data may be part of the report if necessary.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

The study will be performed as a non-randomised, open-label, single arm, single period trial with 2 treatments (T and R).

In total, it was planned to assign up to 12 healthy male and female subjects (6 subjects with CYP 2C19 non-PM status and up to 6 subjects with 2C19 PM status).

For details of dosage and formulation see Table 6.1: 1 and Table 6.1: 2 below:

Table 6.1: 1 Treatments and labels used in the analysis of AEs, safety laboratory data and vital signs as well as demographics

Treatment		**Short label**
A	BI 409306 50mg tab + 0.1mg i.v.	BI tab + iv

Table 6.1: 2 Overview of treatments for intra-individual comparison

Treatment		**Short label**
T	BI 409306, 50 mg tablet, qd	BI 50mg tab
R	BI 409306 (C-13/N-15), 0.1 mg/mL i.v. solution 0.1 mg, qd	BI 0.1mg iv

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** (including residual effect period (REP);

- **Follow-up** (ranging from end of on treatment phase until 0:00 h on the day after trial termination date)

Displays of AEs will be presented without differentiation of intravenous or oral administration during on treatment phase.

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.

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

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

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

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

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS plan. In particular, AEs will be counted for treatment if they occur up to the end of the residual effect period (REP) of 24 hours after oral administration.

6.2 IMPORTANT PROTOCOL VIOLATION

Data discrepancies and deviations from the CTP will be identified for all randomised subjects. Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the combined report planning and database lock meeting (RPM/DBLM), e.g. deviations in drug administration, in blood sampling etc. At this meeting, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation. A protocol violation (PV) is important if it affects the rights or safety of the study subjects or if it can potentially influence the primary outcome measure(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. This last category of important PV forms the basis for the decision of whether a subject does or does not belong to an analysis set. PVs that do not influence the subject's rights and safety or the evaluability of the subjects for the main study objectives are called non-important PVs. These are only considered when checking the trial quality in general.

If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet [001-MCS-50-

413_RD-02] (2). The following table contains the categories which are considered to be important protocol violations in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

Table 6.2: 1 Important protocol violations

Category /Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Non-compliance
D		**Concomitant medication**
	D1	Concomitant medication with the potential to affect the assessment of the trial medication
E		**Missing data**
	E1	Certain violations of procedures used to measure primary data
F		**Incorrect timing**[1]
	F1	Certain violations of time schedule used to measure primary data
G		**Other trial specific important violations**
	G1	PVs affecting safety and rights

[1] Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (3)

6.3 PATIENT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects who were documented to have received 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) analysis if they are not flagged for exclusion due to a protocol violation 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 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 experiences emesis that occurred at or before 2 times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),*
- *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 from the TS who provide at least one primary 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 formulation to the statistical assessment.

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

Table 6.3: 1 Subject sets analysed

	Analysis set	
Class of endpoint	TS	PKS
Analyses of PK endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	X	
Important protocol violations	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

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR.

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 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

For vital signs and laboratory parameters the baseline is defined as the last measurement prior to first study drug administration.

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 oral drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min for the first 4 hours after oral drug administration and ± 45 min thereafter.

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 BI and presented in Section 15.6 of the CTR.

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

The individual values of all subjects will be listed, sorted by treatment, subject number and visit. The listings will be included in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For analyte concentrations as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

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

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 APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is 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" (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 for both formulations together (BI tab + iv).

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 and/or urinary excretion 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

Absolute bioavailability is to be determined on the basis of the dose normalized primary pharmacokinetic endpoints (see Section 5.1).

Primary analysis

The statistical model used for the analysis of the primary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'subjects' and 'formulation'. The effect 'subjects' will be considered as random, whereas 'formulation' 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 (dose normalized primary endpoint, see Section 5.1) measured on subject m receiving formulation k,*

μ = *the overall mean,*

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

τ_k = *the* k^{th} *formulation effect (either tablet or i.v.), k = 1, 2,*

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

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).

Section 7.3.1 of the CTP: […] *the dose normalized PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model […] For each endpoint, the difference*

between the expected means for log(T)-log(R), will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval (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.

The response variables used in the ANOVA model are the following:

for C_{max}*:* $C_{max,\ norm,\ po}$ *and* $C_{max,\ norm,iv}$

for AUC: $AUC_{0-\infty,\ norm,\ po}$ *and* $AUC_{0-\infty,\ norm,iv}$

Further analysis

Section 7.3.2 of the CTP: *As a sensitivity analysis, the ANOVA performed as primary analysis will be repeated with subject as fixed effect instead of random effect. The results will be presented in the same manner as for the primary analyses.*

Furthermore, the input dataset will be restricted in such a way that treatments not relevant for the comparison of interest will be deleted. 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;
        MODEL logkp = treatment subject;
        LSMEANS treatment / PDIFF=CONTROL("Ref_trt") CL ALPHA=0.1;
RUN;
```

Section 7.3.2 of the CTP: *If an adequate number of PM subjects is reached within the study a subgroup analysis will be done for the primary PK endpoints to compare PM subjects with non-PM subjects.*
This subgroup analysis will be done using the same model and parameters as for the primary analysis but including the PM status as a covariate (fixed effect).

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

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

Descriptive statistics of plasma concentrations and PK endpoints will be done by department Translational Medicine and Clinical Pharmacology at BI and will be presented in Section 15.6 of the CTR.

The analysis of PK parameters as well as the tables and graphs for the pharmacokinetic non-compartmental analyses will follow specific definitions of this TSAP or, otherwise, the BI standard procedure "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" [001-MCS-36-472] (7).

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 CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (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 2 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 and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or*

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

  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.

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

Section 5.2.2.2 of the CTP:

The REP refers to the oral drug administration. The REP of the BI 409306 (13-C/15-N) is considered to be negligible. Therefore, all AEs that occur through the treatment phase and throughout the REP will be considered as on treatment (without differentiation of intravenous or oral administration) […].

All adverse events occurring before first drug administration will be assigned to 'screening', those between intake of trial medication and end of the 24-hour REP will be assigned to treatment ('on treatment'). AEs occurring after the REP but prior to termination date will be assigned to 'follow-up'.
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 (BI tab + iv), 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. 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 post examination visits as well as for the difference from baseline (=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 clinically relevant will be flagged in the data listings.
Frequency tables of changes with respect to the reference range between screening and post examination will be presented.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments on the eCRF or at the RPM/DBLM at the latest. It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal

or not. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

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

7.8.3 Vital signs

Descriptive statistics over time and for the changes from baseline will be performed for vital signs (blood pressure and pulse rate) for both formulations together (BI tab + iv).

Section 7.3.3 of the CTP: *For vital signs, the differences from baseline (last value before oral drug administration) will be evaluated.*

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 adverse events (when they occurred during treatment).

7.8.5 Others

Local tolerability

Local tolerability at the injection site will be assessed by the investigator according to ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or ‘other findings’.

A frequency table using the worst assessment will be provided.

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-50-413_RD-02:* "Important Manual Protocol Violations Spreadsheet", current version, IDEA for CON.
3	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version, IDEA for CON.
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*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
8	001-MCG-156: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
9	*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.
10	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
11	001-MCS-36-472_RD-03: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**26-JUN-18**		None	This is the final TSAP without any modification