TRIAL STATISTICAL ANALYSIS PLAN

c19227171-01

BI Trial No.:	1289-0044
Title:	Effect of rifampicin on the pharmacokinetics of BI 409306 following oral administration in healthy male subjects (an open-label, two-period, fixed sequence trial)
Investigational Product:	BI 409306
Responsible trial statisticians:	[redacted] Phone: Fax: [redacted] Phone: Fax:
Date of statistical analysis plan:	18 AUG 2017 SIGNED
Version:	FINAL

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Data Set
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable 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
BWU	Bioavailability/Bioequivalence, within-subject design, time-uncontrolled
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
ECG	Electrocardiogram
ES	Entered Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
ICH	International Conference On Harmonisation
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
PT	Preferred Term
PV	Protocol Violation
qd	Quaque Die, Once Daily
R	Reference Treatment
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^{TM} software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SASTM (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SASTM-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*

- *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

5.2.1 Key secondary endpoint

As no key secondary endpoint has been specified in the CTP, this section is not applicable.

5.2.2 Secondary endpoint

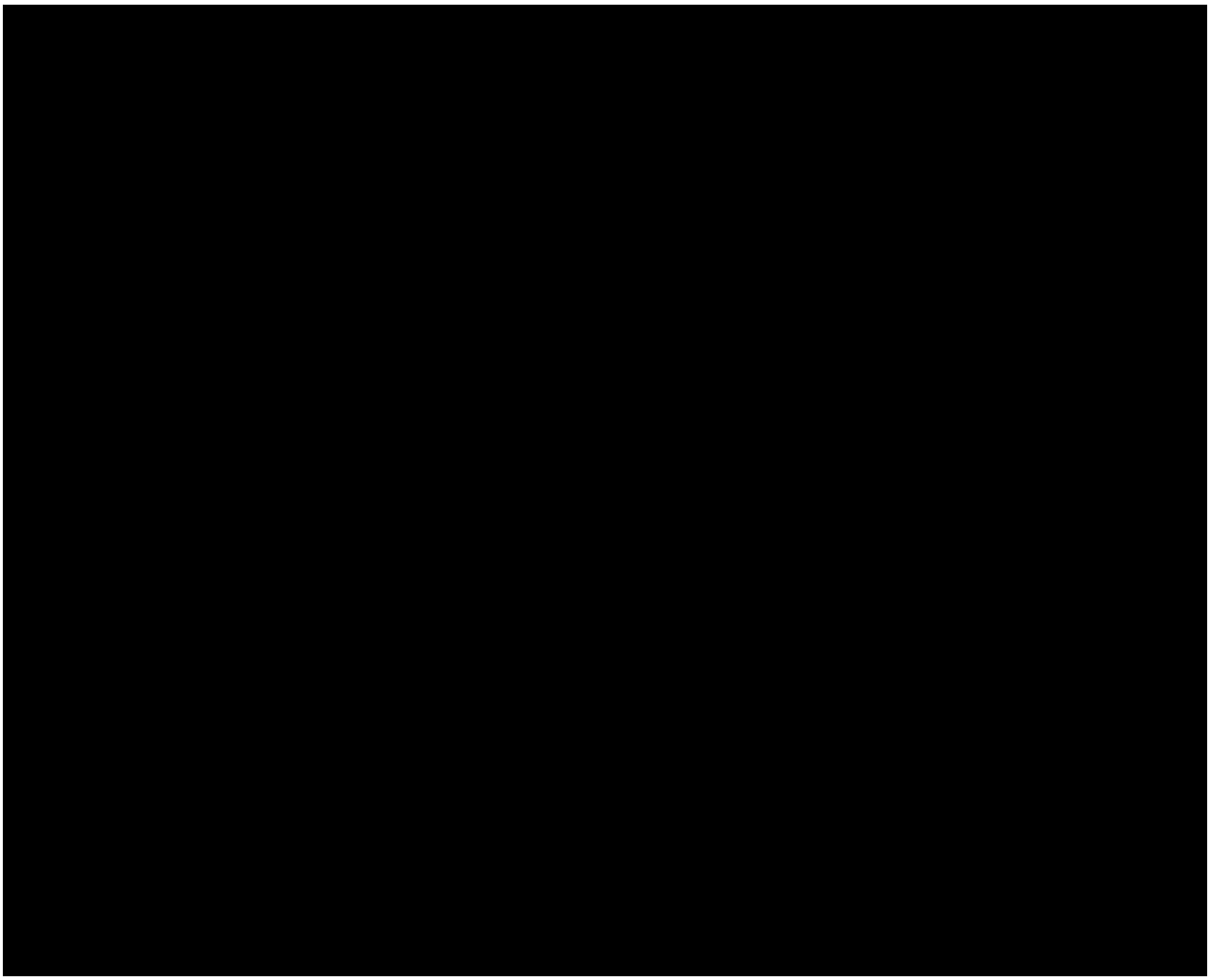
Section 5.5.1.2 of the CTP: *The following secondary endpoint will be evaluated for BI 409306:*

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

[redacted]

Safety:

There is no specific endpoint regarding safety. The safety assessments, see CTP Section 5.2.1, will be evaluated in a descriptive way only.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Section 3 of the CTP: *This clinical phase I study will be conducted as an open-label, two period, fixed-sequence trial with 2 treatments in order to compare the test treatment (T) to the reference treatment (R) in a single centre.*
[…] It is planned that 16 healthy male subjects will enter the study.

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

Table 6.1: 1 Labels for treatments for use in the Clinical Trial Report (CTR)

Treatment		Short label
R	BI 409306, 50 mg tablet, qd	BI
T	BI 409306, 50 mg tablet, qd + Rifampicin, 600 mg tablet, qd	BI + Rifa

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

- **Screening** (ranging from day of informed consent until first administration of study drug)
- **BI treatment** [redacted]
- **Follow-up BI** (ranging from end of BI treatment period until next drug administration or alternatively, trial-termination date in case of no further treatment)
- **Rifa treatment** (ranging from the time of first administration of rifampicin until time of second administration of BI 409306 and
  ranging from end of BI+Rifa treatment period until last Rifa administration + 6 days (Rifa REP))
  OR
  in case of study discontinuation, until last Rifa administration + 6 days (Rifa REP)
- **BI+Rifa treatment** (ranging from time of BI 409306 administration in Visit 3 until 24 hours thereafter (BI REP))
- **Follow-up Rifa** (ranging from end of Rifa treatment period until trial termination date + one day)

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

- BI 409306, 50 mg tablet, qd (labelled “BI“)
- Rifampicin, 600 mg tablet, qd (labelled “Rifa“)
- BI 409306, 50 mg tablet, qd + Rifampicin, 600 mg tablet, qd (labelled “BI + Rifa“)

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

A) Section 15.3 and Appendix 16.1.9.2.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays:

In these displays, the on treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening, Follow-up BI and Follow-up Rifa 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 involving BI (“**Total BI**”)
- a total over all on treatment phases included in this analysis ("**Total on treatment**")

B) Section 15.4 and Appendix 16.1.9.2.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On treatment (labelled with the name of the study treatment (short label))
- Follow-up BI (labelled “FU BI”)
- Follow-up Rifa (labelled “FU Rifa”)

In Section 16.1.9.2.8 AE tables, the following totals will be provided in addition:

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

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

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS (analysis data set) plan.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all 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 summarized 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 combined 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 randomization**
	C1	Incorrect trial medication taken
	C2	Non-compliance
	C3	Incorrect intake of trial medication
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**
	E1	Certain violations of procedures used to measure primary and secondary data
F		**Incorrect timing**[1]
	F1	Certain violations of time schedule used to measure primary and secondary data
G		**Other trial specific IPVs**
	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 SUBJECT SETS ANALYSED

Entered set (ES):
This subject set includes all entered subjects, whether treated or not.

Treated set (TS):
This subject set includes all subjects from the ES who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
This is the full analysis set population in the sense of ICH-E9 (1). It is used for safety analysis.

Section 7.3.1 of the CTP: *Primary and secondary pharmacokinetic parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses 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 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 pre-dose concentration is >5% of the C_{max} value of that subject*
- *missing samples/concentration data at important phases of PK disposition curve.*

PK parameter analysis set (PKS):
The PK parameter analysis set (PKS) 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.
It is used for the PK analysis.

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	ES	TS	PKS
Analyses of primary and secondary PK endpoints			X
Safety endpoints		X	
Demographic/baseline endpoints		X	
Important PVs	X		
Disposition	X		

[redacted]

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

The baseline value is defined as the last measurement prior to study drug administration, i.e. the measurement on day 1 of period 1.

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 -4, Day -1, and Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs and laboratory tests will be ±60 min.

The time window for rifampicin administration from Day -7 to Day -2 is ± 60 min.

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 [redacted] and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendices 16.2 and 16.1.9.2.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) will also be performed by [redacted] and will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK endpoints will be performed by BI and will be presented in Section 15.6 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of clinical trials and project summaries" [001-MCG-159] (6) with the exception of those generated for PK-calculations.

The individual values of all subjects will be listed, sorted by 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

For PK parameters, P10, P90, Q1 and Q3 will be calculated.

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

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

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

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

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion; that is APEXC is equal to “Included”.

Exclusion of PK concentrations

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

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

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

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

7.3 TREATMENT COMPLIANCE

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

To investigate whether and to what extent co-administration of multiple doses of rifampicin affect single dose pharmacokinetics of BI 409306 in healthy male subjects, point estimates of the intra-subject ratios of the geometric means (test/reference) for the primary endpoints (see Section 5.1), and their two-sided 90% confidence intervals (CI) will be provided.

Section 7.1.3 of the CTP: *The statistical model used for the analysis of 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 'treatment'. The effect 'subjects' will be considered as random, whereas the treatment effect 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 (endpoint, see Section 5.1) measured on subject m receiving treatment k,*

μ = *the overall mean,*

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

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

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

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

In addition, a sensitivity analysis will be performed by fitting the model described above, but using all effects as fixed. This analysis will be done using PROC GLM.

The PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model.

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), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoint

The secondary PK parameter will be analysed in the same manner as the primary endpoints (see Section 7.4).

[redacted]

Safety:

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 409306.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by actual treatment.

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

7.8.1 Adverse events

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

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: "Analysis and presentation of adverse event data from clinical trials" [001-MCG-156], (9).

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

For analysis multiple AE occurrence data on the case report form (CRF) will be collapsed into an AE provided that all of the following applies:
- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 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 (4, 9).

Section 5.2.2.1 of the CTP: *The following are considered as* adverse events of special interest (*AESI) in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*
  - *an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or*
  - *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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

Section 5.2.2.2 of the CTP: [redacted]*. The REP for rifampicin is defined as 6 days after the last administration of rifampicin. Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3* of CTP.

All adverse events occurring prior to drug administration will be assigned to 'screening', those between intake of trial medication and end of the REP will be assigned to the corresponding treatment. AEs occurring after the REP but prior to next treatment or to termination date will be assigned to the corresponding follow-up phase. For more detail see the TSAP ADS plan.

For details on the treatment definition, see Section 6.1.

According to ICH E3 (10), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of adverse events 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 (10), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.

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

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

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

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

7.8.2 Laboratory data

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

Section 7.3.3 of the CTP: *Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline (day 1 of period 1) will be evaluated.*

With respect to evaluations of laboratory data, 'baseline' is understood as last measurement before first drug administration. The 'last value on treatment' is defined as the last

measurement before the end of the 6 days REP for rifampicin and 'post examination' is the measurement at the end-of-trial examination.

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

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate). In the listing the difference from baseline will also be displayed. With respect to evaluations of vital signs, baseline is understood as last measurement before the first drug administration.

7.8.4 ECG

ECG findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of ECG findings will be prepared.

7.8.5 Others

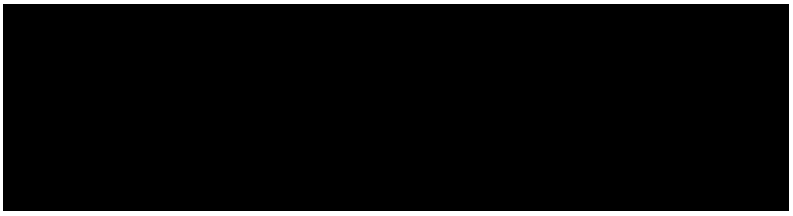
Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
[redacted]	
10.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version

[redacted]



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	18 Aug 2017	[redacted]	None	This is the final TSAP