Trial Statistical Analysis Plan

c17248861-01

BI Trial No.:	1346-0018
Title:	Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period, fixed-sequence trial)
Investigational Product:	BI 425809
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted] [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	21 JUL 2017 SIGNED
Version:	Final

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, distribution, metabolism, and excretion
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
a.m.	Ante meridiem
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-168}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 168 h
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
CARE	Clinical data analysis and reporting environment
C_{max}	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ES	Entered set
EudraCT	European union drug regulating authorities clinical trials
F/U	Follow-up
gCV	Geometric coefficient of variation
gMean	Geometric mean

Term	Definition / description
ICH	International Conference on Harmonisation
IPV	Important protocol violation
LLT	Lower level term
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	PK analysis set
PV	Protocol violation
R	Reference treatment
RI	Rifampicin
RAGe	Report appendix generator
REP	Residual effect period
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
T	Test treatment
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range

3. INTRODUCTION

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

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

Study data will be stored in a trial database within the Oracle Clinical™ system.

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; RAGe system for compilation/formatting of the CTR appendices).

PK parameters will be calculated using WinNonlin™ software (professional Network version Phoenix 6.3, Pharsight Corporation, Mountain View, CA 94041-1530, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

Section 5.2.1 of the CTP specifies that safety and tolerability will be assessed based on AEs, safety laboratory tests, vital signs, 12-lead ECG, and physical examination. Because of the requirements for registry and results disclosure (1) [001-MCS-00-131_RD-03], one particular endpoint out of these parameters had to be defined as safety endpoint of this trial. Note that this is not a deviation from the CTP, as all planned analyses of safety and tolerability will be conducted as planned. In order to fulfil the requirements for registry and results disclosure, the frequency [N (%)] of subjects with drug related AEs is defined as safety endpoint in Section 5.3.1 of this TSAP, while all other parameters for assessing safety and tolerability are defined as further criteria of interest.

The CTP states in Section 7.3.3 that events occurring in a certain phase of the study will be summarized as 'post-treatment' events. The BI corporate guideline 001-MCG-156 (6) had been updated to replace the term 'post-treatment' by 'follow-up'. This TSAP follows the updated terminology from the BI corporate guideline.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary PK endpoints will be defined as in Section 5.5.1.1 of the CTP:

- AUC_{0-168} of BI 425809 in plasma with and without co-administration of rifampicin (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 168 h)
- C_{max} of BI 425809 in plasma with and without co-administration of rifampicin (maximum measured concentration of the analyte in plasma)

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Other Secondary endpoints

Secondary PK endpoints will be defined as in Section 5.5.1.2 of the CTP:

- $AUC_{0-\infty}$ of BI 425809 in plasma with and without co-administration of rifampicin (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- $t_{1/2}$ of BI 761036 in plasma without co-administration of rifampicin (terminal half-life of the analyte in plasma)

5.3 FURTHER ENDPOINTS

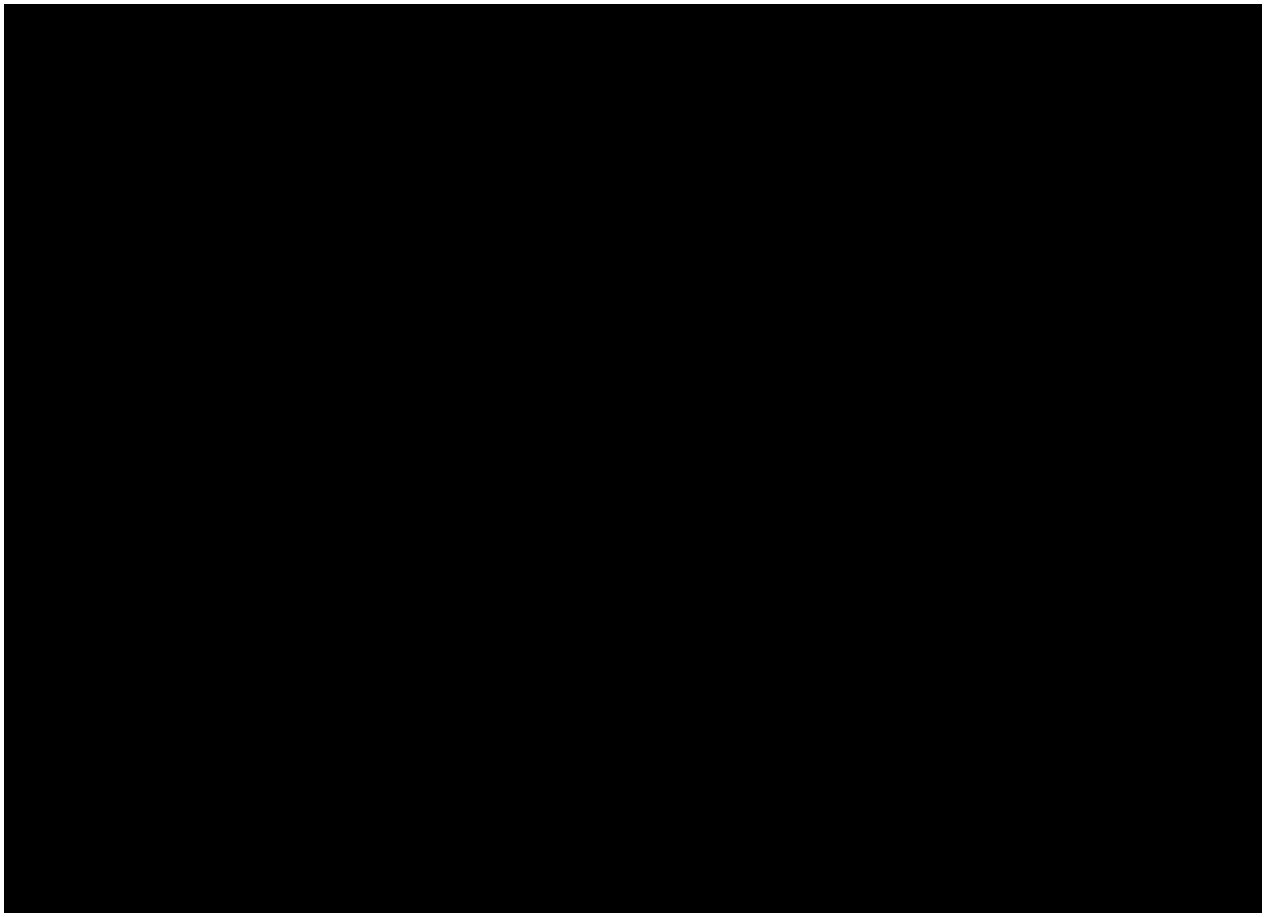
5.3.1 Safety endpoints

Safety and tolerability will be assessed by the frequency [N (%)] of subjects with drug-related AEs. Further criteria of interest will be:

- AEs (including clinically relevant findings from physical examination)
- Safety laboratory tests
- Vital signs (blood pressure, pulse rate)
- 12-lead ECG (occurrences of findings)

[redacted]

[redacted]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

Each subject is planned to be treated in two subsequent treatment periods. In the first treatment period, subjects will receive a single dose of 25 mg of BI 425809 (reference treatment, R). In the second treatment period, subjects will receive treatment with rifampicin 600 mg once daily over 10 days together with an administration of a single dose of 25 mg of BI 425809 on the seventh day of rifampicin treatment (test treatment, T). The sequence of these treatment periods is fixed and the same for all subjects.

For statistical analyses of AEs, laboratory tests, and vital signs, the following separate analysis phases will be defined for each subject:

Table 6.1: 1 Flow chart of analysis phases for statistical analysis of AEs, safety laboratory and vital signs

Study analysis phase	Label	Start	End
Screening	**Screening**	Date of informed consent at 12 a.m.	Date/time of first administration of BI 425809
On treatment BI 425809	**BI 425809**	Date/time of first administration of BI 425809	Minimum of date/time of first administration of BI 425809 + REP (11 days * 24 h) and first administration of loading RI
Follow-up BI 425809 [1]	**F/U BI**	Date/time of first administration of BI 425809 + REP (11 days * 24 h)	Date/time of first administration of loading RI
On treatment RI	**Loading RI**	Date/time of first administration of loading RI	Date/time of second administration of BI 425809
On treatment BI 425809+RI	**BI 425809+RI**	Date/time of second administration of BI 425809	Date/time of second administration of BI 425809 + REP (11 days * 24 h) or 12:00 a.m. on day after trial completion date, whichever occurs earlier
Follow-up BI 425809+RI [1]	**F/U BI+RI**	Date/time of second administration of BI 425809 + REP (11 days * 24 h)	12:00 a.m. on day after trial completion date
Post study[2]	**Post-study**	12:00 a.m. on day after trial completion date	Not defined – a placeholder date is used, e.g. a date after database lock

[1] Follow-up phases might not exist, e.g. if loading RI is administered within 11 days of the time of administration of BI 425809, or the trial completion date is within 10 days of the time of administration of BI 425809+RI.
[2] AE tables will present results for the post-study phase only if at least one AE occurred in the post-study phase.

CTR Section 15, Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE displays will present results for the following study treatments during on-treatment phases:

- BI 425809
- Loading RI
- BI 425809+RI

Screening, follow-up and post-study periods will not be included in these sections/appendices.

In CTR Section 15 AE tables (but not in Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE tables), the following totals will be provided in addition:

- a total over the on-treatment phases of "BI 425809" and "BI 425809+RI" ("**Total BI**")
- a total over all on-treatment phases included in this analysis ("**Total on treatment**"). This includes all BI treatments and loading RI.

CTR Appendix 16.1.9.2.8.1 displays will present results for the screening, on-treatment, follow-up and post-study phases (post-study only if at least one AE occurred in the post-study phase).

Additionally to the totals defined above, the following total will be provided in CTR Section 16.1.9.2.8.1 AE tables:

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

Laboratory analyses will present results by treatment period (i.e., for treatment periods "BI 425809", "BI 425809+RI", and “Loading RI” plus “BI 425809+RI”).

Analyses of vital signs will present results by BI 425809 treatment periods (i.e., for treatment periods "BI 425809", and "BI 425809+RI").

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects). Consistency check listings (for identification of violations 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 RPM/DBLM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be

assessed to determine whether it is an IPV. For definition of IPVs, and for the process of identification of these, refer to the BI reference document "Protocol Violation Handling Definitions" (2) [001-MCS-50-413_RD-01].

If any IPVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet (3) [001-MCS-50-413_RD-02]. The following table contains the categories which are considered to be IPVs in this trial. If the data show other IPVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

IPVs will be summarised and listed.

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	Incorrect dose of trial medication taken
	C3	Non-compliance
	C4	Incorrect intake of trial medication
	C5	Improper washout between treatments
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**[1]
		None
F		**Incorrect timing**
	F1	Certain violations of time schedule used to measure primary or secondary data[2]
G		**Other trial specific important violations**
	G1	Certain violations of procedures used to measure primary or secondary data
	G2	Incorrect intake of meal

Violations C1, C2, C4, G1 and G2 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not PVs
[2] Time deviations will only be flagged as IPV, when leading to exclusion of the entire subject from and analysis set
Source: BI reference document 'Protocol Violation Handling Definitions' (2) [001-MCS-50-413_RD-01].

6.3 SUBJECT SETS ANALYSED

All entered subjects who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP. The analysis sets are defined as follows:

- Entered set (ES):
  This subject set includes all entered subjects, whether treated or not.
  It will be used for analysis of disposition.

- Treated set (TS):
  This subject set includes all subjects from the ES 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. It will be used for analysis of safety, demographic data, baseline characteristics, and disposition.

- PK analysis set (PKS):
  This subject set includes all subjects from the TS who provided in any period at least one primary or secondary PK endpoint value that is judged as PK evaluable and is not affected by PVs relevant to the statistical evaluation of PK endpoints. Thus, a subject will be included in the PKS, even if he contributes only one PK endpoint value for one period to the statistical assessment. Whether a PK endpoint is evaluable or a PV is relevant will be decided no later than at the RPM.
  This subject set will be used for the analysis of BA.

CTP: *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*

A PK endpoint value will be considered as non-evaluable, if for example:

- *The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference product or from median t_{max} for the test product, depending on whether the subject had experienced emesis after taken the test or the reference product. Median t_{max} is to be determined excluding the subjects experiencing emesis.*
- *The subject has a protocol deviation relevant to the evaluation of relative bioavailability*
- *Use of restricted medications*

Violations may lead to exclusion of single measurements or parameters for a subject or even to exclusion of all data of the subject.

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessments.

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to populations will be made at latest at the RPM/DBLM.

Table 6.3: 1 Subject sets analysed

	Subject set		
Class of endpoint	ES	TS	PKS
Disposition	X	X	
IPVs	X		
Demographic/baseline endpoints	X[1]	X	
Exposure		X	
Safety parameters		X	
Primary PK endpoints			X
Secondary PK endpoint			X
[redacted]			[redacted]

[1] only summary of country and age for disclosure in the EudraCT register

[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

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

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded in the CTR.

CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

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 (4) [001-MCG-156_RD-01].

Missing data and outliers of PK data are handled according to BI standards (5) [001-MCS-36-472_RD-01]. **CTP**: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).*

CTP: *For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline for the evaluation of data of the "BI 425809+RI" treatment period will be defined as the last available value at Visit 3 before the second BI 425809 dose.

For an additional laboratory summary, baseline of treatment period 2 ("Loading RI" plus "BI 425809+RI") is defined as the last follow-up assessment during treatment period 1 (i.e., lab value at Day 43).

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the RPM/DBLM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (9) [001-MCG-159].

The individual values of all subjects will be listed, sorted by subject number and visit. AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

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

For plasma 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 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 (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. These will be based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only descriptive statistics are planned for this section of the report.

A medication will be considered concomitant to a treatment, if it

- is ongoing at the time of first administration of this treatment, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint (cf. Section 5.4.2). Any deviations from complete intake will be addressed in the RPM/DBLM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Analysis of relative BA of primary endpoints $AUC_{0\text{-}168}$ and C_{max} of BI 425809 in plasma will be performed as defined in Sections 7.1.3 and 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP is an ANOVA model on the logarithmic scale including "treatment" as fixed effect and "subject" as random effect. In addition, a secondary analysis will be performed, using both, "subject" and "treatment", as fixed effects in the ANOVA model.

Primary PK endpoints will be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (5) [001-MCS-36-472_RD-01].

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 are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to 'Included'.

Exclusion of plasma 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.
CTP: *However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.*

Further details are given in “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) [001-MCS-36-472_RD-01] and “Description of Analytical Transfer Files and PK/PD Data Files” (10) [001-MCS-36-472_RD-03].

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

Analysis of relative BA of secondary endpoint $AUC_{0-\infty}$ of BI 425809 in plasma will be performed in the same way as for the primary endpoints.

No inferential statistical analysis is planned for secondary endpoint $t_{1/2}$ of metabolite BI 761036.

Secondary PK endpoints will be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (5) [001-MCS-36-472_RD-01].

See Section 7.4 of this TSAP for details regarding exclusion of PK parameters and plasma concentrations.

7.6 FURTHER ENDPOINTS

7.6.1 Safety endpoints

Further safety endpoints will be analysed as described in Section 7.8 of this TSAP.

[redacted]

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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. All analyses of AEs 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 eCRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended).

For further details on summarization of AE data, please refer to 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (6) [001-MCG-156] and "Handling of missing and incomplete AE dates" (4) [001-MCG-156_RD-01].

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to the screening, treatment, follow-up or post-study phases as defined in Section 6.1.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 and for the class of AESIs.

CTP: *The following are considered as AESIs 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 investigator had to classify on the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (8), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant AEs
(i) which are marked haematological or other lab abnormalities, or
(ii) which were reported with 'action taken = discontinuation' or 'action taken = reduced', or
(iii) which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (8)). AEs will also be summarized by maximum intensity.

The system organ classes will be sorted according to the standard sort order specified by the EMA, preferred terms will be sorted by total frequency (within system organ class).

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary system organ class and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standard "Display and Analysis of Laboratory Data" (7) [001-MCG-157].

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

The descriptive summary table will be repeated for the treatment period 2 with the last assessment prior to loading RI defined as baseline. This summary will include the assessments during loading RI in addition to the BI 425809+RI on-treatment assessments.

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.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analysis of vital signs will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such. No separate listing or analysis of ECG data will be prepared.

7.8.5 Others

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of first 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 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

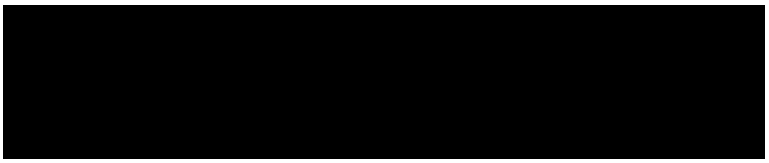
[redacted]

[redacted]

8 *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]

[redacted]



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**21-JUL-17**	[redacted]	None	This is the final TSAP without any modification

APPROVAL / SIGNATURE PAGE

Document Number: c17248861 **Technical Version Number:1.0**

Document Name: 8-01-tsap

Title: Effects of rifampicin on the pharmacokinetics of BI 425809 following oral administration in healthy male subjects (an open-label, two-period,fixed-sequence trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Project Statistician	[redacted]	21 Jul 2017 15:09 CEST
Approval-Trial Clinical Monitor		21 Jul 2017 15:10 CEST
Author-Trial Medical Writer		21 Jul 2017 16:32 CEST
Author-Trial Clinical Pharmacokineticist		21 Jul 2017 17:01 CEST
Verification-Paper Signature Completion		24 Jul 2017 08:55 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed