TRIAL STATISTICAL ANALYSIS PLAN

c30114925-01

BI Trial No.:	1346-0039
Title:	A study to investigate the effects of memantine on the pharmacokinetics of BI 425809 and vice versa in healthy male and female subjects (nonrandomized, single-arm, open-label, three-period, one fixed sequence cross-over study) Including Protocol Amendment 2 [c26441810-02]
Investigational Product:	BI 425809
Responsible trial statistician:	Phone: + Fax: +
Date of statistical analysis plan:	22 NOV 2019 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{\tau,ss}$	area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BI	Boehringer Ingelheim
BP	Blood pressure
$C_{max,ss}$	maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
C-SSRS	Columbia Suicidal Severity Rating scale
ECG	Electrocardiogram
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
IQRMP	Integrated quality and risk management plan
MedDRA	Medical Dictionary For Regulatory Activities
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter set
PR	Pulse rate
RAGe	Report appendix generator
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
TS	Treated set
TSAP	Trial Statistical Analysis Plan

Term	Definition / description
ULN	Upper limit of normal range

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 CTP, and to include detailed procedures for executing the statistical analysis of the primary 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 Medidata Rave 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; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, Certara USA Inc., Princeton, NJ, 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 revised CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Primary endpoints are PK endpoints of BI 425809 and memantine, as defined in Section 2.1.2 of the CTP:

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

Not applicable.

5.3.2 Safety parameters

Safety and tolerability of BI 425809 will be assessed based on further safety parameters defined in Section 2.2.2.2 of the CTP:

- *Adverse events (including clinically relevant findings from the physical and neurological examination)*
- *Safety laboratory tests*
- *12-lead ECG (only abnormal findings will be reported as AE)*
- *Visual tests (only abnormal findings will be reported as AE)*
- *Vital signs (blood pressure, pulse rate)*
- *Suicidality assessment (C-SSRS)*

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 three subsequent treatment periods in a fixed sequence order. There will be a washout-period of at least 7 days between treatment period 1 and 2. Between treatment period 2 and 3 there will be no washout-period.

All subjects will receive multiple doses of BI 425809 alone in the first period, multiple doses of memantine alone in the second period and then multiple doses of BI 425809 and memantine combined in the third period.

Table 6.1: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R1 (Reference 1)	BI 425809	Tablet	25 mg	1 tablet (Day 1-10, Visit 2) q.d.	250 mg
Up-titration to R2	Memantine	Tablet	5 mg	1 tablet (Day 1-7, Visit 3) q.d.	35 mg
			10 mg	1 tablet (Day 8-14, Visit 3) q.d.	70 mg
			15 mg	1 tablet (Day 15-21, Visit 3) q.d.	105 mg
			20 mg	1 tablet (Day 22-28, Visit 3) q.d.	140 mg
R2 (Reference 2)			20 mg	1 tablet (Day 29-35, Visit 3) q.d.	140 mg
T (Test)	BI 425809	Tablet	25 mg	1 tablet (Day 1-10, Visit 4) q.d.	250 mg
	Memantine	Tablet	20 mg	1 tablet (Day 1-10, Visit 4) q.d.	200 mg

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

Table 6.1: 2 Analysis phases for statistical analysis of AEs, vital signs and safety laboratory data

Study analysis phase	Label	Start	End
Screening	**Screening**	Date of informed consent	Date/time of first administration of BI 425809
On treatment BI 425809	**BI**	Date/time of first administration of BI 425809	Date/time of first administration of memantine
On treatment memantine	**Mem**	Combination of two phases: First phase: Date/time of last administration of BI 425809 alone + (i.e. REP of BI 425809 of Second phase: Date/time of last administration of BI 425809 + memantine (i.e. REP of BI 425809	Combination of two phases: First phase: Date/time of first administration of BI 425809 + memantine Second phase: Date/time of last administration of BI 425809 + memantine + 21*24h (i.e. REP of memantine of 21 days) or 00:00 a.m. on day after subject's trial termination date whatever occurs earlier
On treatment BI 425809+ memantine	**BI + Mem**	Combination of two phases: First phase: Date/time of first administration of memantine Second phase: Date/time of first administration of BI 425809 + memantine	Combination of two phases: First phase: Date/time of last administration of BI 425809 alone (i.e. REP of BI 425809 Second phase: Date/time of last administration of BI 425809 + memantine (i.e. REP of BI 425809
Follow-up	**F/U**	Date/time of last administration of BI 425809 + memantine + 21*24h (i.e. REP of memantine of 21 days)	00:00 a.m. on day after subject's trial termination date

The planned duration of the analysis phase of BI 425809 is at least 17 days, of memantine it is 41 days and of memantine + BI it is 25 days.

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 will present results for the on-treatment phase only.

In AE tables in CTR Section 15.3 (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following total will be provided in addition:

- "**Total on-trt"**, defined as the total over all on-treatment phases
- "**Total BI"**, defined as the total over all on-treatment phases involving BI

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from 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 Report Planning Meeting (RPM). At this meeting, it will be decided whether a discrepant data value can be used in the analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important PD (IPD). For definition of IPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (IPD)" (2).

If any IPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be IPDs in this trial are defined in the integrated quality and risk management plan (IQRMP). If the data show other IPDs, the definition in the IQRMP will be supplemented accordingly by the time of the RPM.

IPDs will be summarized and listed. Table 6.2: 1 below specifies which kind of IPDs could potentially lead to exclusion from which analysis set. The decision on exclusion of subjects from analysis sets will be made at the latest at the RPM, after discussion of exceptional cases and implications for analyses. If the data show other IPDs, this table will be supplemented accordingly by the time of the RPM.

Table 6.2: 1 Handling of IPDs

IPD code	IPD Category & Brief Description	Excluded from which analysis set
A1	Inclusion Criteria Not Met	PKS
A2	Exclusion Criteria Not Met	PKS
B1	Informed consent not available/not done	TS, PKS
B2	Informed consent too late	None
C1	Non-compliance	PKS
C2	Incorrect trial medication taken	PKS
C3	Incorrect intake of trial medication	PKS
C4	Improper washout between treatments	PKS
D1	Prohibited medication use	PKS
D2	Improper washout of concomitant medication	PKS
E1	Certain violations of procedures used to measure primary or secondary data	PKS
F1	Certain violations of time schedule used to measure primary or secondary data	PKS
G1	PDs affecting safety and rights of subjects	None

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in the CTP, Section 7.3.

Table 6.3: 1 Subject sets analyzed

	Subject set	
Class of endpoint	TS	PKS
Primary PK endpoints		X
Safety parameters & treatment exposure	X	
Demographic/baseline endpoints	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.

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 reported in the CTR.

CTP: *It is not planned to impute missing values for safety parameters.*

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

Missing data and outliers of PK data are handled according to BI standards (4) and (5).
CTP: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last available value before first study drug administration.

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

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by sequence group subject number and visit (if visit is applicable in the respective listing). 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

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of plasma 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 actually are 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 CTR.

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. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

A medication will be considered concomitant, if it

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

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

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analyzed as a specific endpoint. Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoints

Primary analysis of the primary endpoints will be performed as defined in Sections 7.3.1 of the CTP.

The statistical model for the primary analysis defined in the CTP is an analysis of variance (ANOVA) model on the logarithmic scale including "treatment" as fixed effects and "subject" as random effect. Relative bioavailability of the study treatments will be estimated by the ratios of the geometric means of (T/R1) and (T/R2) of the primary endpoints.

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. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (5).

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint

The same statistical model as used for the primary analysis (Sections 7.3.1 of the CTP) will be repeated for the primary endpoints but with all sources of variation ("subject", "treatment") considered as fixed effects.

Furthermore, primary PK endpoints will be assessed descriptively. The analysis of standard PK parameters is performed according to BI standards (4).

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

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

7.6.2 Safety parameters

Safety endpoints and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

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 one event provided that all of the following applies:

- All AE attributes are identical (lower level term, 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 "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to screening, on-treatment or follow-up phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 2

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 (8) and for the class of AESIs.

CTP: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

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 SOC 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 SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

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 SOC 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 summarized.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (9).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

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.

Unscheduled measurements of laboratory data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement. Descriptive statistics will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM 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 in an automated manner will not be applied in this study.

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) 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.

Unscheduled measurements of vital signs will be assigned to planned time points in the same way as described above for laboratory data. However, for vital signs, descriptive statistics will

be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Relevant ECG findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of ECG findings will be prepared.

7.8.5 Others

Physical and neurological examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical or neurological examination findings will be prepared.

Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.4 of the CTP, results will only be listed. No further analysis will be prepared. Findings will also be reported as AEs if applicable.

Visual test

Visual test will be performed as described in Section 5.2.3 of the CTP. Abnormal findings during the screening examination will lead to exclusion of the subject.

Any deterioration during the study compared to baseline will be reported as an AE. Results from all measurements will also be listed separately for colour discrimination test, visual acuity test and Amsler grid test and will also be summarized.

Unscheduled measurements of visual tests will be assigned to planned time points in the same way as described above for laboratory data. However, for visual tests, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**22-NOV-19**		None	This is the final TSAP