TRIAL STATISTICAL ANALYSIS PLAN

c27997646-01

BI Trial No.:	1402-0005
Title:	A double-blind, randomised, two-way cross-over, single-dose, placebo-controlled trial to investigate the effects of BI 1358894 on cholecystokinin tetrapeptide (CCK-4) induced panic symptoms in healthy male subjects Including Protocol Amendment 2 [c26426667-03]
Investigational Product:	BI 1358894
Responsible trial statistician:	Phone: Fax:
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
CCK-4	Cholecystokinin tetrapeptide
CDR	Clinical Data Repository
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
E_{max}	Maximum effect
ENTS	Entered Set
ES	Enrolled Set
FDA	Food Drug Administration
eCRF	Electronic case report form

Term	Definition / description
gCV	geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference On Harmonisation
iPD	Important protocol deviation
IQRMP	Integrated quality and risk management plan
MedDRA	Medical Dictionary For Regulatory Activities
NIMP	Non-investigational medicinal product
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic parameter set
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PSS	Panic symptom scale
R	Reference treatment
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial Statistical Analysis Plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal range
VAS	Visual Analogue Scale

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 TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol 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, randomization.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

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 by means of noncompartmental analysis using Phoenix WinNonlin™ software (current version Phoenix 6.3 or higher, Certara USA Inc., Princeton, NJ, USA). Outputs for the CTR will be generated using SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

The following changes compared to the protocol will be made:

No ‘Enrolled set (ES)’ will be defined in the TSAP as data of subjects discontinued before first administration of investigational trial medication will not be entered in the CDR. A correct display of the ES is therefore not possible. Due to the same reason, the ‘Entered set (ENTS)’ will be similar to the ‘Treated set (TS)’. Therefore, no ‘Entered set (ES)’ will be defined in the TSAP as well.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is a PD endpoint, as defined in Section 2.1.2 of the CTP:

- *Maximum change from baseline of Panic symptom scale (PSS) sum intensity score after CCK-4 injection.*

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoints

Not applicable.

5.3.3 Safety and Tolerability endpoints

Safety and tolerability of BI 1358894 will be assessed based on parameters defined in Section 2.2.2.2 and Section 2.2.2.3 of the CTP:

- *Adverse events (including clinically relevant findings from the physical and neurological examinations)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Continuous ECG monitoring*
- *Vital signs (blood pressure, pulse rate)*
- *Suicidality assessment (C-SSRS)*

Local tolerability of CCK-4 injections (absence or presence of "swelling", "induration", "heat", "redness", "pain", or "other findings") will be summarized with counts and percentages overall (i.e. subject-wise worst case over all injections and time points) as well as listed by injection and time point.

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, with one single dose of BI 1358894 or placebo in each treatment period:

- Test treatment (Treatment T):
  4 x 25 mg BI 1358894 film-coated tablet in the fed state

- Reference treatment (Treatment R):
  4 x placebo film-coated tablets in the fed state

Each subject is planned to be randomly allocated to one of the two treatment sequences (T-R or R-T) in a 1:1 ratio.

In addition to the two investigational treatments stated above, the following non-investigational provoking agent will be used:

- provoking agent (NIMP)
  50 µg CCK-4 (cholecystokinin tetrapeptide) as i.v. bolus injection

For the selection of subjects included in the trial, subjects able and willing to participate will be exposed to the provoking agent CCK-4 at screening. After identification of CCK-4 sensitive subjects (cf. Section 3.3 of the CTP), trial subjects will be exposed to CCK-4 again within each treatment period.

For statistical analyses of AEs, the following separate analysis phases will be defined for each subject:

Table 6.1: 1 Analysis phases for statistical analysis of AEs

Study analysis phase	Label	Start	End
Screening	**Screening**	Date of informed consent	Date/time of first administration of BI 1358894 or placebo
On treatment	**BI 1358894** or **Placebo**, respectively	Date/time of administration of BI 1358894 or placebo, respectively	Date/time of administration of BI 1358894 or placebo in the next treatment period, if applicable, otherwise 12:00 a.m. on day after subject's end of study participation date.

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15, AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

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

CTR Appendix 16.1.13.1.8.1 displays will present results for the screening and on-treatment phases.

Additionally to the total defined above, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total**", defined as the total over all study phases (screening + on-treatment)

Statistical analyses of safety laboratory tests and vital signs will be conducted by treatment period (BI 1358894 or Placebo), with clear differentiation between baseline (cf. Section 6.7) and on-treatment measurements.

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. 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 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 minutes of the Report Planning Meeting via an accompanying Excel spreadsheet (3). 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 Report Planning Meeting.

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 patients from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses.

Table 6.2: 1 Handling of iPDs

iPD code	iPD Category & Brief Description	Excluded from which analysis set
iPD B1	Informed consent not available/not done	All
iPD B2	Informed consent too late	None
iPD A1	Inclusion Criteria not met	PDS, PKS
iPD A2	Exclusion Criteria violated	PDS, PKS
iPD C2	Randomisation not followed	PDS, PKS
iPD C3	Non-compliance	PDS, PKS
iPD C4	Medication code broken inappropriately	PDS, PKS
iPD C5	Incorrect intake of trial medication	PDS, PKS
iPD C6	Improper washout between treatments	PDS, PKS
iPD D1	Prohibited medication use	PDS, PKS
iPD E1	Certain violations of procedures used to measure primary or secondary data	PDS, PKS
iPD E2	Certain violations of procedures (e.g. C-SSRS)	PDS, PKS
iPD F1	Certain violations of time schedule used to measure primary or secondary data	PDS, PKS
iPD G1	Certain violations of procedures used to measure primary or secondary data	PDS, PKS
iPD G2	PDs affecting safety and rights of subjects	None

6.3 SUBJECT SETS ANALYSED

As stated in Section 4 of this TSAP, the ES and ENTS will not be used, as the data of these subjects are not in the CDR. The PDS and PKS will be used as defined in the CTP, Section 7.3. In this Section, the treated set was defined as:

Treated set (TS):
This subject set includes all subjects from the ENTS who were documented to have received at least one dose of study drug.

For clarification, the definition of the TS will be specified further as:

Treated set (TS):
This subject set includes all subjects that underwent screening procedures, entered the trial and were documented to have received at least one dose of *investigational* study drug.

The following Table 6.3: 1 contains the information which subject is used for which class of endpoint:

Table 6.3: 1 Subject sets analyzed

	Subject set		
Class of endpoint	TS	PDS	PKS
Primary PD endpoint		X	
Further PD endpoints		X	
Further PK endpoints			X
Safety parameters & treatment exposure	X		
Demographic/baseline endpoints	X		
Important protocol deviations	X		

6.5 POOLING OF CENTRES

This section is not applicable, because the study is 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 investigational study drug will not be reported in the CTR.

Data of subjects who drop out or withdraw from the trial 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.

Handling of missing PD data will be done as described in **CTP Section 7.5.3**:
For the PD endpoints PSS , if the period baseline value is missing in treatment period 1, it will be imputed by the corresponding value measured in treatment period 2. If the period baseline value is missing in treatment period 2, it will be imputed by the

corresponding value measured in treatment period 1. If a value is missing after CCK-4 injection, this value will not be imputed. If all four assessments after CCK-4 injection are missing for a subject, this subject is not evaluable for this endpoint in this period.

CTP Section 7.5.1: *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.

CTP Section 7.5.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*
Missing data and outliers of PK data are handled according to BI standards (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

A separate baseline is defined for each study treatment. The baseline is the last available value before administration of the CCK-4 challenge in the respective treatment period. E.g. for PSS sum intensity score baseline is the value measured 15 minutes before administration of the CCK-4 challenge within the respective treatment period.

In addition, for vital signs displays where PTM -2:00 are considered as baseline will be provided.

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

Unscheduled measurements of laboratory data or vital signs 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 of laboratory data 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).
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).

7. PLANNED ANALYSIS

The format of the listings and tables will follow the standards defined in the BI standards with the exception of those generated for PK-calculations (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment sequence, 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 report.

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 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 ENDPOINT

CTP Section 7.3.1: "*The derivation of the primary endpoint PSS sum intensity score per time point is outlined in Section 5.6.3. The maximum CfB is defined as the maximum of the differences of the PSS sum intensity score measured at each time point after the CCK-4 challenge minus the PSS sum intensity score measured at baseline.*"

7.4.1 Primary analysis of the primary endpoint

The primary endpoint will be analyzed based on the PDS.

Descriptive statistics and boxplots of the primary endpoint by treatment will be provided.

As main analysis, the following model will be applied:

Statistical model

CTP Section 7.3.1: *"The statistical model used for the investigation of the primary endpoint PSS sum intensity score will be a mixed effects model given by*

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b_i' + s_i + e_{imj},$$

where

y_{imj}	*Maximum CfB (absolute change from period baseline) in PSS sum intensity score for the ith subject and the mth period, receiving randomised treatment j,*
μ	*overall intercept,*
π_m	*mth period effect, m = 1,2,*
τ_j	*jth treatment effect, j = 1,2,*
b_{im}	*baseline value for subject i in period m (period baseline),*
γ	*associated covariate effect of period baseline,*
b_i'	*the subject baseline value (mean of the 2 period baselines) for subject i,*
γ'	*associated covariate effect of subject baseline,*
s_i	*the random effect of subject i,*
e_{imj}	*the random error associated with subject i who received treatment j in period m.*

The last value before administration of the CCK-4 challenge in each period is considered as the corresponding period baseline measurement. The PSS sum intensity score mean value of the two period baseline values is considered as the subject baseline.

The treatment comparison will be the difference between active treatment and placebo. Adjusted means (Least Squares Means) as well as 2-sided 90% CIs will be calculated. Additionally, the difference in adjusted means relative to placebo will be provided. To support this analysis, listings and graphical displays may be generated if appropriate.

As a sensitivity analysis, the same statistical model as stated above will be repeated for the primary endpoint but with all sources of variation considered as fixed effects."

For the random 'subject' effect in the above model a Variance Components (VC) covariance structure will be used; in case of convergence problems refer to Additional Section 9.2. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in Kenward and Roger (8).

Programming details are provided in Section 9.1.1.

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

CTP Section 7.3.1: *As a sensitivity analysis, the same statistical model as stated above will be repeated for the primary endpoint but with all sources of variation considered as fixed effects.*

7.5 SECONDARY ENDPOINTS

Not applicable.

7.6.1 Safety parameters

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

7.7 EXTENT OF EXPOSURE

Treatment exposure will be listed by means of the date and time of drug administration.

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)

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to screening or on-treatment phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 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 (7) and for the class of AESIs.

CTP, Section 5.2.6.1.6: "*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 (7), 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 (7)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

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.

If the subject reports headaches during the treatment period further information about the duration of headache, headache severity (NRS), location, characteristics, and signs and symptoms were recorded. The information will be summarized with descriptive statistics.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards.

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.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the Report Planning Meeting 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.

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

7.8.5.1 Physical examination

Physical 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 examination findings will be prepared.

7.8.5.2 Neurological examination

Clinically relevant findings of the neurological examination 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 neurological examinations will be prepared.

7.8.5.3 Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.2 of the CTP, results will only be listed: No further analysis will be prepared.

8. REFERENCES

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**29-AUG-2019**		None	This is the final TSAP