Trial Statistical Analysis Plan

c03413910-02

BI Trial No.:	1289.27
Title:	Randomised, parallel-group, double-blind study of systemic and ocular safety and pharmacokinetics of BI 409306 in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers Including Protocol Amendment 3 1289.27-revised-protocol-03 [c02218444-07]
Investigational Product:	BI 409306
Responsible trial statistician:	 TEL: FAX:
Date of statistical analysis plan:	08 August 2017 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AD	Alzheimer's Disease / Alzheimer's Dementia
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Curve
BDS	Biostatistics & Data Sciences
BI	Boehringer Ingelheim
BP	Blood Pressure
BPM	Beats Per Minute
BRPM	Blinded report planning meeting
CARE	Clinical data Analysis and Reporting Environment
CDR	Clinical Data Repository
CIAS	Cognitive Impairment Associated with Schizophrenia
$C_{max,ss}$	Maximum concentration of the analyte in plasma at steady state
conc.	concentration
CPPL	Clinical Pharmacology Program Leadership
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
eCFR	electronic Case Report Form
ECG	Electrocardiogram
EMEA	European Agency for the Evaluation of Medicinal Products
EoT	End-of-Text
EOT	End of Trial
EX	Exclusion criteria from CTP
geom.	geometric
HR	Heart Rate
HV	Healthy Volunteer(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDC	International Development Committee
IMC	International Medical Committee
IN	Inclusion criteria from CTP
IPV	Important Protocol Violation
iPROG	independent Programmer

Term	Definition / description
iSTAT	independent Statistician
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
O*C	Oracle Clinical
PAC	Premature Atrial Complexes
PCPK	Project Clinical PharmacoKineticist
PDM	Project Data Manager
PK	Pharmacokinetics
PKA	Pharmacokinetics Analyst
PKProg	PK Programmer
PKS	Pharmacokinetic Set
PMW	Project Medical Writer
PPROG	Project Programmer
PR	Pulse Rate
PSTAT	Project Statistician
PVC	Premature Ventricular Contraction
QD	quaque die (once a day)
QRS	Combination of Q, R and S waves
RAGe	Report Appendix Generator
R on T	refers to the R wave of the premature beat being so premature that it coincides with the T wave of the previous beat
RR	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAS	Statistical Analysis System (SAS® System, SAS Institute Inc., Cary, North Carolina)
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
STATANA	Statistical analysis
SVT	Supraventricular
TA	Therapeutic Area
TAC	Therapeutic Area Committee
TAH	Therapeutic Area Head
TALT	Therapeutic Area Leadership Team
TCM	Trial Clinical Monitor
TCPK	Trial Clinical PharmacoKineticist
TCPKa	Trial Clinical PharmacoKinetics Analyst
TDM	Trial Data Manager
$t_{max,ss}$	time from dosing to maximum measured concentration of the analyte in plasma at steady-state
TME	Team Member
TMM	Team Member Medicine

Term	Definition / description
TMW	Trial Medical Writer
TProg	Trial Programmer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSTAT	Trial Statistician
V	Visit
VT	Ventricular
WHO	World Health Organization

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 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.

SAS® Version 9.4 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There are no changes to the planned analysis described in the CTP.

5. ENDPOINTS

This trial is designed to evaluate the ocular and systemic safety and pharmacokinetics during a 14-day treatment period in patients with schizophrenia, Alzheimer's disease, and age-comparable healthy volunteers treated with oral film-coated tablet of BI 409306 25 or 100 mg. .

5.1 PRIMARY ENDPOINT

The primary endpoint is:

- The number (%) of subjects with AEs, coded to the MedDRA-SOC 'Eye disorders', as determined by the investigator at End of Trial

5.2 SECONDARY ENDPOINTS

5.2.1 (Other) Secondary endpoints

Secondary endpoints include:

- The number (%) of subjects with drug-related AEs as determined by the investigator at End of Trial

The following two pharmacokinetic parameters of BI 409306 are also secondary endpoints:

- $C_{max,ss}$ - maximum measured concentration of the analyte in plasma at steady-state
- $t_{max,ss}$ - time from dosing to maximum measured concentration of the analyte in plasma at steady-state.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of subjects to dose group, and selection of doses, see CTP, Section 4.

The two dose levels for this trial are described as following:

Long label	***Short label***
BI 409306 25 mg QD	BI 25mg QD
BI 409306 100 mg QD	BI 100mg QD

The populations for this trial are described as: Alzheimer's Dementia (AD), cognitive impairment associated with schizophrenia (CIAS), and healthy volunteers (HV). Populations will be determined using 'Group under which subject is entering trial' captured on the demographics page at visit 1. For some displays, HV will be split into two groups: healthy volunteers comparable in age to AD subjects (HV_AD) and healthy volunteers comparable in age to CIAS subjects (HV_CIAS). HV_CIAS are all HV subjects from site . HV_AD are all HV subjects from sites and .

Short label *unblinded*	***Interval*** *blinded*	***Sort order***	***CRF field***
AD	AD	01	Group under which subject is entering trial
CIAS	CIAS	03	
HV	HV	05	
HV_AD	HV_AD	02	
HV_CIAS	HV_CIAS	04	
Total	Total	06	

The following column headers will be used in the CTR displays.
The 7-column display shows population by dose and Total.

AD		CIAS		HV		Total
BI 25mg QD	BI 100mg QD	BI 25mg QD	BI 100mg QD	BI 25mg QD	BI 100mg QD	

The 4-column display shows populations and Total

AD	CIAS	HV	Total

Tables displaying HV split into two groups will have the following layouts:

AD	HV_AD	Total

and

CIAS	HV_CIAS	Total

The 3-column display shows dose and Total

BI 25mg QD	BI 100mg QD	Total

The following treatment phase definitions will be applied to the analyses of data except adverse events:
The **screening phase** will be defined as the time from informed consent to the date of Visit 2 (sites and) or Visit 2 minus 1 day (site).
The **baseline phase** will be defined as the date of Visit 2 (sites and) or Visit 2 minus 1 day (site) to (one minute before) the first administration of trial medication.
The **on-treatment phase** will be defined as the time from first administration of trial medication to last visit with trial medication intake.
The **post-treatment phase** will be defined as starting on the day after the last visit with drug intake to end of trial visit.
The **post-study phase** will be defined as starting from 0:00 a.m. on the day after the end of trial visit onwards.

Table 6.1: 1 Treatment regimens / study intervals

Short label *unblinded*	***Interval*** *blinded*	***Sort order+***	***Start date*** *(CRF)*	***Start time*** *(CRF/derived)*
Screening	Screening	01	V1, Date of informed consent	00:00
Baseline For site *	Baseline	02	V2, Date of visit – 1 day	00:00
For sites & #	Baseline	02	V2, Date of visit	00:00
25 mg QD or 100 mg QD	Treat	03	V3, Date of study drug intake	V3, Time of study drug intake
Post-treatment	Post-treat	04	From EOT page, Date of last administration of trial drug + 1 day	V16, Time of study drug intake
Post-study	Post-study	05	EOT visit, Date of visit + 1 day	00:00

+ The sort order refers to the unblinded regimens.
* Site (subjects) is using the date of randomization to populate the visit 2 date (Using the CTP flowchart notation, this is Day -1). The date that the subject checked into the site is Day -2. This will be the start of the Baseline period and will be derived by subtracting one day from the visit 2 date.
# Sites & (subjects) are not admitting any patients for in-patient stays. At these sites, the date of randomization is the visit 2 date and is the start of the Baseline period.

Table 6.1: 2 Adverse events analysing treatment: 'Active + 7 days'

Label	***Sort order***	***Start date** (CRF)*	***Stop date***
Screening	01	V1, Date of informed consent	V2, Date of visit 2 – 1 day* or V2, Date of visit 2[#]
Baseline		V2, Date of visit 2 – 1 day* or V2, Date of visit 2[#]	V3, Date of study drug intake
Treatment	02	V3, Date of study drug intake	From EOT page, Date of last administration of trial drug + 1 day + 7 days
Post-treatment	03	From EOT page, Date of last administration of trial drug + 1 day + 7 days	EOT visit, Date of visit + 1 day
Post-study	04	EOT visit, Date of visit + 1 day	Date of data base lock

*Site
[#]Sites &

The treatment phase definitions for adverse events analyses are described above in Table 6.1: 2. All adverse events occurring from informed consent until the day before visit 2 (site) or the day of visit 2 (sites &) will be assigned to "screening". All adverse events occurring the day before visit 2 (site) or the day of visit 2 (sites &) until first dose of study drug will be assigned to "baseline". All adverse events occurring between first dose of study drug until 7 days (inclusive) after last treatment administration will be assigned to "treatment". Adverse events occurring after this period and prior to end-of-trial will be assigned to "post-treatment". Adverse events occurring after end-of-trial will be considered "post-study".

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations (IPVs). The final column describes which IPVs will be used to exclude subjects from the different subject analysis sets.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Potentially excluded from
A		**Entrance criteria not met**		
	A1	**Inclusion criteria not met**		
	A1.1	Diagnoses of schizophrenia not established	IPV if any of the clinical features defining the population (IN1) are not met.	None
	A1.2	Diagnosis of AD not established	IPV if any of the clinical features defining the population (IN1) are not met	None
	A2	**Exclusion criteria met**		
	A2.1	Presence of active ocular conditions	Any of EX1-EX4 are met.	None
	A2.2	Suicidal ideation or behavior	Any of EX13-EX14	None
	A2.3	Other clinically relevant baseline conditions	Any of EX12, 15, 17-22, 24-26, 28	None
B		**Informed consent**		
	B1	**Informed consent not available/not done**	Informed consent date missing; no signature on ICF	All
	B2	**Informed consent too late**	Informed consent date <actual consent date> was after Visit 1 date <Visit 1 date>	None
C		**Trial medication and randomisation**		
	C1	**Incorrect trial medication kit assigned**	Medication (kit) number assigned is not from the correct group (AD, CIAS etc.). OR Medication number was not assigned in sequential order (as subjects were randomized).	None
	C2	**Incorrect trial medication administered**		
	C2.1	Incorrect trial medication administered on any of days 2-13.	Trial medication administered on any of days 2-13 was not from the medication kit assigned to subject.	None
	C2.2	Incorrect trial medication administered on PK day 1 or 14.	Subject was administered medication from kit assigned to another subject on days 1 or 14 (PK visit)	PKS
	C3	**Medication code broken inappropriately**	Medication code broken inappropriately - reason for medication code break <reason>	None
D		**Concomitant medication**		
	D1	**Prohibited medication use 3 days prior to Day 1 and/or Day 14.**	Use of St. Johns wort, Carbamazepine, extracts from Gingko, artemisinin, enzalutamide, efavirenz, lopinavir, ritonavir, tipranavir, & rifampicin.	None
F		**Incorrect timing**		
	F1	**Peak exposure visual procedures performed outside time range.**	Visual procedures were not completed during estimated peak exposure time range (between Day 5 and Day 10 (except Day 7), 20-90 minutes after dosing).	None
Z		**Other**		
	Z3	**Other protocol violations affecting safety only**		None

PKS: PK set

Note: Missing visits, evaluations, and tests will be considered missing data, not protocol deviations. All final decisions as to whether any deviation is relevant will be taken at the BRPM.

6.3 SUBJECTS SETS ANALYSED

- Randomised set:
  This subject set includes all randomised subjects, whether treated or not.

- Treated set (TS):
  This subject set includes all subjects who were documented to have been administered at least one dose of investigational treatment.

- Pharmacokinetic set (PKS):
  This subject set includes all subjects in the treated set who provide at least one evaluable observation for at least one PK endpoint without important protocol violations relevant to the evaluation of PK.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	**Treated set**	**Pharmacokinetics set**
Primary endpoint	X	
(other) Secondary and further endpoints	X	X
Safety endpoints	X	
Demographic/baseline endpoints	X	
Pharmacokinetics analysis		X

In addition, the population group is defined as Alzheimer's Dementia group, schizophrenia group and healthy volunteer group. The ophthalmological assessment will be done by population group.

6.5 POOLING OF CENTRES

This section is not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

With respect to safety evaluations, it is not planned to impute missing values other than AE start dates and times. Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (1)

For handling of missing data in PK evaluation, refer to CTP Appendix Section 10.1.2 and 029-DCP-102. (2)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, the baseline is the last available measurement before the first trial medication intake. For laboratory data that were repeatedly measured, baseline is defined to be the last available measurement before the first trial medication intake.

7. PLANNED ANALYSIS

No statistical hypothesis testing is planned. Variables will be evaluated by descriptive statistical methods in this trial.

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For displays that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum

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 (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS. The following variables will be displayed: gender, age, race, ethnicity, height, weight, body mass index, smoking and alcohol status.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. The concomitant disease will be summarized by MedDRA primary system organ class and preferred term. The concomitant medications taken at baseline and those while on treatment will be coded using the WHO Drug coding dictionary. Concomitant medications will be summarized by WHO Drug ATC coding.

7.3 TREATMENT COMPLIANCE

On each treatment day, study drug is administered to the subject at the study centre or at the ophthalmology site. Date and time of study drug intake is documented on day 1-14 of the treatment interval.

7.4 PRIMARY ENDPOINT

Ocular adverse events will be those events coded to the SOC ‘Eye disorders’ determined by the investigator at end of trial. The assessment of ocular adverse events will be done on treated set. Ocular adverse events analyses will be performed in accordance with BI standards, essentially, tabulations of frequencies will be displayed. Refer to Section 7.8.1 for a description of the analysis of adverse events.

7.5 SECONDARY AND FURTHER 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 (Other) Secondary endpoints

Summary of drug-related AEs as determined by the investigator at end of trial will be performed in accordance with BI standards, essentially, tabulations of frequencies will be displayed. Refer to Section 7.8.1 for a description of the analysis of adverse events.

The analysis of standard PK parameters, $C_{max,ss}$ and $t_{max,ss}$, will be performed as described in CTP Section 7.3.5 and also according to 029-DCG-103 (3). Descriptive analyses are planned.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarized by treatment group using descriptive statistics for days of exposure as well as number (percent) of patients whose total exposure falls in the following categories:

1 day, 2 days, 3 days, 4 days, etc. until 14 days, and >=15 days

Exposure to treatment will be calculated as study drug stop date minus study drug start date plus 1. Total exposure will summarize exposure to both doses.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events (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. AEs will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA).

For analysis, multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)**.**
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started ≤ 24 hours from the end of the first occurrence).

For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (4) [001-MCG-156].

The relationship of an AE to the study drugs treatments will be assessed by the investigator.

The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs occurring between first study drug intake till 7 days (inclusive) after last study drug intake will be considered "treatment-emergent" and be assigned to the randomised treatment.. AEs occurring before first study drug intake will be assigned to 'screening' or 'baseline'; AEs occurring after last study drug intake + 7 days till end-of-trial visit will be assigned to 'post-treatment' (for listings only). AEs occurring after the end-of-trial visit will be assigned to 'post-study' (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 (5), 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.

Overall summaries of adverse events will be presented to summarise any AEs, severe AEs, drug-related AEs, AEs leading to treatment discontinuation, serious AEs, drug-related serious AEs, and AEs leading to death.

The frequency of subjects with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for subjects with other significant adverse events according to ICH E3 (5), for subjects with adverse events of special interest (AESI) and for subjects with serious adverse events. The AESI are described in Section 5.2.2.1 of the CTP. There is a field on the eCRF for the site to designate that an AE is an AESI. This variable will be used to identify the AESI.

The system organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6).

7.8.3 Vital signs

Descriptive statistics of vital signs (BP and PR) observed values and change from baseline will be provided for both supine and standing positions separately. Orthostatic BP and PR will also be summarized descriptively. Orthostatic changes in BP are flagged for falls in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg. Orthostatic changes are calculated as standing − supine.

Baseline values for vital signs will be the observations taken at Visit 2

7.8.4 ECG

Clinically significant findings for ECG will be recorded as baseline conditions or AEs and will be analyzed accordingly.

7.8.5 Others

24-hour Holter Monitoring

The 24-hour Holter monitoring will be analyzed using descriptive statistics.

8. REFERENCES

1 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
2 *029-DCP-102*: "Noncompartmental Pharmacokinetic Analyses of Clinical Studies", current version; IDEA for CON.
3 *029-DCG-103*: "Noncompartmental Pharmacokinetic Analyses using WinNonlin®", current version; IDEA for CON.
4 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5 *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.
6 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

This is a revised TSAP including the following modifications to the final TSAP

Version	**Date (DD-Mmm-YY)**	**Author**	**Sections changed**	**Brief description of change**
Final	**21-Apr-16**		None	This is the final TSAP without any modification
Revised	**08-Aug-17**		Title page	To indicate that the TSAP covers CTP Amendments 1-3.
			Section 6.1	In selected AE tables, HV will be split out to display results for HV_AD and HV_CIAS groups.
			Section 6.1	The definition of the start of the baseline period was revised to reflect study conduct differences at the new sites (Subjects at site were in-patients; subjects at sites & were not.)
			Section 6.2	CTP Amendment #3 allowed subjects > age 85 to participate in the trial. Exclusion of PK data for subjects outside the original age cut-offs was no longer deemed necessary. The IPV 'Age criteria not met' was removed.
			Section 7.8.1	Section now correctly describes analysis & presentation of AE data based on Version 8 of the guideline.
			Multiple sections	CTP Amendment #1 changed terminology from 'End of Study' to 'End of Trial' for the last study visit.