TRIAL STATISTICAL ANALYSIS PLAN

c25706980-02

BI Trial No.:	1346.9
Title:	A phase II randomised, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia Clinical Trial Protocol (c03559983-04), including Global Protocol Amendment 1 (21APR2016), Global Protocol Amendment 2 (13DEC2017), Global Protocol Amendment 3 (28MAR2019)
Investigational Product(s):	BI 425809
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	17 FEB 2020 SIGNED
Version:	REVISED (Version 4)

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical, Therapeutic, Chemical
BCVA	Best Corrected Visual Acuity
BI	Boehringer Ingelheim
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Concomitant Therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
ECG	Electrocardiogram
EOT	End of Treatment
FAS	Full Analysis Set
F-M 100	Farnsworth-Munsel 100
FU	Follow-up
ICH	International Conference on Harmonisation
IDEA	International Document Management & Electronic Archiving
IOP	Intra-Ocular Pressure
IPD	Important Protocol Deviation
IVRS	Integrated Voice Response System
LLT	Lower Level Term
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia

Term	Definition / description
MCCB	MATRICS Consensus Cognitive Battery
MCPMod	Multiple Comparison Procedures and Modelling
MMRM	Mixed effects Model Repeated Measures
MRI	Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
PPS	Per Protocol Set
PT	Preferred Term
QD	Quaque Die (once a day)
RDC	Remote Data Capture
REP	Residual Effect Period
RPM	Report Planning Meeting
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCoRS	Schizophrenia Cognition Rating Scale
SD-OCT	High Definition Ocular Coherence Tomography (SD-OCT)
SOC	System Organ Class
SS	Screened Set
STD	Standard Deviation
TOM	Trial Oversight Meeting
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organisation

3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), 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, randomisation.

R Version 3.3.2 with “DoseFinding” package (2) will be used for analyses based on Multiple Comparison Procedures and Modelling (MCPMod) and SAS® Version 9.4 will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In the third paragraph in the 1346.9 CTP Section 7.1 (on page 65), the second sentence states "Change from baseline in everyday functional capacity as measured by SCoRS global ratings after 12 weeks of treatment is the secondary endpoint". This is inconsistent with the specifications in Section 5.1.2 in the CTP. It is clarified in this TSAP that the secondary endpoint in 1346.9 study is "change from baseline in everyday functional capacity as measured by SCoRS total score after 12 weeks of treatment".

5. ENDPOINTS

The primary objectives of this trial are to establish proof-of-clinical-concept (POCC) with respect to a non-flat dose-response curve together with the definition of one or more suitable doses with respect to the efficacy and safety of orally administered once daily dosing of BI 425809 in patients with schizophrenia on stable antipsychotic treatment. Table 5: 1 below lists the different endpoints and the corresponding measurement time points.

Table 5: 1 Endpoints and time points of measurement

Screening (Visit 1) **Day -28 to -7**	**Baseline (Visit 2)** **Day 1**	**Week 3 (Visit 3)** **Day 22 ± 3 days**	**Week 6 (Visit 4)** **Day 43 ± 3 days**	**Week 9 (Visit 5)** **Day 64 ± 3 days**	**Week 12 (Visit 6) or EOT** **Day 85[#] + 3 days**	**Follow-up 1** **EOT + 7 days ± 3 days**
MCCB	MCCB		MCCB		MCCB	
	SCoRS				SCoRS	
		$C_{pre,ss,3}$	$C_{pre,ss,4}$, $C_{2,ss}$, $C_{3.5,ss}$			
eC-SSRS	eC-SSRS	eC-SSRS	eC-SSRS	eC-SSRS	eC-SSRS	eC-SSRS[†]
BCVA[#]				BCVA		BCVA
F-M 100[#]				F-M 100		F-M 100
Pupil diameter[#]				Pupil diameter		Pupil diameter
Anterior and posterior biomicroscopy exam[#]				Anterior and posterior biomicroscopy exam		Anterior and posterior biomicroscopy exam
IOP[#]				IOP		IOP
SD-OCT[#]				SD-OCT		SD-OCT
Fundoscopy[#]				Fundoscopy		Fundoscopy

[†] eC-SSRS is also measured at the second follow-up visit (end of study visit): FU2 (EOT + 28 days ± 7 days)
[#] Endpoints collected only in subjects participated in the ophthalmology sub-study

5.1 PRIMARY ENDPOINT

Change from baseline in MCCB overall composite score at Week 12 is the primary efficacy endpoint. The MCCB overall composite t-score is derived from the seven domain scores obtained from a total of ten tests (see CTP Table 5.1.1: 1) and is measured at screening (Visit

1), baseline (Visit 2), Week 6 (Visit 4), and Week 12 (Visit 6). See CTP Sections 5.1.1 and 5.2.1 for details. A larger overall composite t-score indicates better cognition.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

There is no key secondary endpoint in this trial.

5.2.2 Secondary endpoints

Change from baseline in SCoRS total score assessed by interviewer at Week 12 is the secondary efficacy endpoint. SCoRS total score is derived as the sum of non-missing responses from 20 interview-based items rated by an interviewer on a 4-point scale with higher rating indicating greater degree of impairment in day-to-day functions due to cognitive deficits. A response of "N/A" to an item is treated as missing. If six or more of the 20 items are missing for a subject at a visit, then the corresponding SCoRS total score is missing for that subject at the visit. If five or less of the 20 items are missing for a subject at a visit, then the item(s) with missing value(s) will be imputed first with the average of the non-missing item values, and then the SCoRS total score for the subject at the visit will be derived as the sum of non-missing item values and the imputed item values. SCoRS total score is measured at baseline (Visit 2) and Week 12 (Visit 6) or End of Treatment (EOT visit). See CTP Sections 5.1.2 and 5.2.1 for details.

For safety, the percentage of subjects with serious adverse event (SAE) (including clinically relevant abnormalities of physical examination, vital signs, electrocardiogram (ECG) test and laboratory tests) are secondary endpoint.

5.4.1 Variables from Ophthalmologic Sub-study

The following variables are collected at baseline (Visit 2), Week 9 (Visit 5) and one week after EOT (Follow-up Visit 1) and analysed for the ophthalmologic sub-study:

- Number of correct letters from the Best Corrected Visual Acuity (BCVA) test in each eye
- Total error score (TES) and level of color vision deficiency classification (i.e. low, average and superior discrimination) from the Farnsworth-Munsel 100 (F-M 100) hue testing in each eye
- Pupil diameter measurement in each eye

- Categorical changes (normal / abnormal) from the anterior and posterior biomicroscopy exam in each eye
- Intra-ocular pressure (IOP) in each eye
- Central retinal thickness in each eye as measured by the High Definition Ocular Coherence Tomography (SD-OCT)
- Categorical changes (normal / abnormal) from the indirect fundoscopy of the retina in each eye.

Changes from baseline to Week 9 and from baseline to follow-up visit 1 are derived for each of the above ocular measurements.

Please refer to Table 5: 1 for the different endpoints and the corresponding measurement time points.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Table 6.1: 1 Treatment descriptions

Long Name	Short Name
Placebo	Placebo
BI 425809 2 mg QD	BI 2mg
BI 425809 5 mg QD	BI 5mg
BI 425809 10 mg QD	BI 10mg
BI 425809 25 mg QD	BI 25mg

Table 6.1: 2 Analysing treatment periods (same for all treatment groups)

Analysing Treatment Period	Start Date	Stop Date
Screening	Date of informed consent	Date of the first treatment administration
On-treatment	Date of the first treatment administration	Date of the last treatment administration + REP + 1 day
Follow-up	Date of the last treatment administration + REP + 1 day	Date of the last per protocol visit

REP is the residual effect period which is defined as 11 days after the last dose of trial treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way.

A list of important PDs (IPDs) is given in Table 6.2: 1. Important PDs will be reviewed at Trial Oversight Meeting (TOM) conducted periodically during the trial. A list of protocol deviations (treatments are blinded) will be discussed at the Report Planning Meetings (RPMs) before data unblinding.

If the data show other important PDs, this table will be supplemented accordingly at TOMs or RPMs or through team review of the manual PD log. The decision whether a subject will be excluded from the analysis will be made at the final RPM prior to Database Lock (DBL).

Table 6.2: 1 Handling of IPDs

Category/Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1	**Inclusion criteria not met**		
	A1.1	No diagnosis of Schizophrenia per DSM-5 or medically and psychiatrically not stable	IN3 in the CTP not met	PPS
	A1.2	Age <17 or >52	IN2 in the CTP not met. Check age in demographic page	None
	A1.3	Not exhibit reliability, physiologic capability or have insufficient educational level	IN6 in the CTP not met	None
	A1.4	No consistent informant identified	IN7 in the CTP not met	None
	A1.5	Violation of IN4	Either one of the first two bullet points in IN4 regarding typical and/or atypical antipsychotics use	None
	A2	**Exclusion criteria met**		
	A2.1	Any exclusion criteria met	EX1-EX29 in the CTP	None
	A2.2	Any of the exclusion criteria for the ophthalmologic sub-study met	See CTP Section 10.8.3.2	EYE
B		**Informed consent**		
	B1	**Informed consent not available/not done**		
	B1.1	Informed consent not available/not done	IN1. No patient signature on ICF. Not follow local law requirement for informed consent.	All
	B1.2	Ocular measurements taken without ICF for ophthalmologic sub-study	Signed ICF for main study available but not for ophthalmologic sub-study, but ocular measurements were taken; not an IPD if consent for the ophthalmologic sub-study was given late	EYE

Table 6.2: 1 Handling of IPDs (cont'd)

Category/Code		Description	Example/Comment	Excluded from
C		**Trial medication and randomisation**		
	C1	**Incorrect trial medication taken**		
	C1.1	Incorrect trial medication taken during study	Any deviation. Check whether the medication packages dispensed (med. numbers entered into RDC) has the correct content (to be seen from the med. number list that was the basis for packaging). If content was correct, the deviation will only be noted. Otherwise, the cases will be described individually and possibly excluded. In addition, check whether the dispensed packages match the randomised treatment of the patient (IVRS assignment). If not, and if treated consistently throughout the trial, analyse as treated.	None
	C2	**Randomisation order not followed**		
	C2.1	Error by the vendor who implemented the randomisation scheme	E.g., the same randomisation number was given to different patients or the assignment of duplicate medication numbers or incorrect medication numbers. Or wrong stratum. Verify by comparing the medication numbers and randomisation numbers from IVRS. If a patient actually receives the correct medication despite the wrong kit, such deviation will only be noted.	None
	C3	**Non-compliance with trial medication**		
	C3.1	<80% cumulative compliance rate with trial medication during the entire treatment period	<80% cumulative compliance rate with trial medication during the entire treatment period is considered as an IPD.	None

Table 6.2: 1 Handling of IPDs (cont'd)

Category/Code		Description	Example/Comment	Excluded from
D		**Concomitant medication**		
	D1	**Prohibited medication (including prohibited procedures) use before the first administration of trial medication**	All medications before first drug administration (those defined in CTP Section 4.2.2). To be determined on a case by case basis.	None
	D2	**Prohibited medication (including prohibited procedures) use during the treatment period (including follow-up period)**	As defined in CTP Section 4.2.2. To be determined on a case by case basis.	None
	D2.1	Used restricted medications within 8 hours before taking MCCB after Visit 1	E.g., anticholinergic agents, antihistamine, benzodiazepine, benztropine, diphenhydramine, sleep medication	PPS
	D3	**Subjects who stopped taking all antipsychotics and refused to re-take antipsychotics during the study**		None
F		**Incorrect timing of endpoint measurements or administration of trial medication**		
	F1	**Primary endpoint performed at incorrect date/time**		
	F1.1	MCCB measured outside the allowed time window	MCCB should be performed at the same time of the day, i.e. within +/- 120 minutes at Visits 4 and / or EOT as compared with Visit 2 MCCB administration time.	None
	F1.2	Baseline MCCB measured after first drug administration	Visit 2 MCCB should be measured before the first drug administration	None
	F1.3	EOT MCCB measured >10 days after last drug administration	E.g. EOT MCCB measured >10 days after last drug administration	None
Z		**Other**		
	Z1	**Serious issue of protocol deviation**	Cases reported from site monitoring	None
	Z2	**Other protocol deviation affecting efficacy and possibly safety**	E.g. substantial change in nicotine consumption; positive drug screening during study	None
	Z3	**Other protocol deviation affecting safety only**	E.g. abnormal hemoglobin measurement; not reported or under-reported suicidal ideation; DILI cases not handled properly	None

6.3 SUBJECT SETS ANALYSED

- Screened Set (SS):

  The screened set consists of all subjects who signed informed consent and were screened for the trial with at least one screening procedure done at Visit 1.

- Randomised Set (RS):

  The randomised set consists of all subjects who were screened for the trial and who were randomised to trial treatment, regardless of whether any trial treatment was administered.

- Treated Set (TS):

  The treated set consists of all subjects who were randomised and treated with at least one dose of trial treatment. The TS is used for the analysis of safety variables.

- Full analysis set (FAS):

  The full analysis set consists of all randomised subjects who were treated with at least one dose of trial treatment and had a baseline and at least one evaluable post-baseline on-treatment measurement of the primary or secondary efficacy endpoints. The FAS is used for the primary and secondary analyses of the efficacy endpoints.

- Per protocol set (PPS):

  The per protocol set is nested within the FAS and only includes subjects in the FAS who do not have any important protocol deviations which are specified to be excluded from the sensitivity analysis of the efficacy endpoints using the PPS (see Table 6.2: 1). If the number of subjects in the PPS is less than 90% of the number of subjects in the FAS, then the PPS is used for the sensitivity analysis of the primary and secondary efficacy endpoints.

- Ophthalmologic Sub-study Set (EYE):

  The ophthalmologic sub-study set consists of all treated subjects who consented to participate in the ophthalmologic sub-study (including late/retrospective consent to the ophthalmologic sub-study) and had evaluable ophthalmologic measurements.

Table 6.3: 1 Subject sets analysed

	Subjects Sets Analysed					
Class of endpoints	**TS**	**FAS**		**PPS**		**EYE**
Primary endpoint – primary analysis using MCPMod & secondary analysis using pair-wise comparisons approach and descriptive statistics		X				
		X (subset)		X*		
(other) Secondary endpoints – primary analysis using MCPMod and secondary analysis using pair-wise comparisons and descriptive statistics		X		X* (only secondary efficacy endpoint)		
Safety variables	X					X
Variables in Ophthalmologic Sub-study						X
Demographic/baseline variables/exposure	X				X	X

* Only if the number of subjects in the PPS is <90% of the number of subjects in the FAS, sensitivity analysis of the primary and secondary efficacy endpoints using PPS will be conducted.

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

Every effort should be taken to collect complete data at each visit for each subject. If not specified otherwise, missing data are not imputed and remain missing. Potential outliers will be reported and analysed as observed.

MCCB

All imputations will be carried out separately for each study visit since there may be differences in test performance at different time points.

For the domains of Working Memory (consisting Letter-Number Span test and Wechsler Memory Scale 3rd ed. Spatial Span subtest) and the Speed of Processing (consisting Trail Making Test Part A, Brief Assessment of Cognition in Schizophrenia – Symbol Coding subtest, and Category Fluency test – animal naming), if one of the tests consisting of a domain has missing value at a visit, the corresponding domain score can still be derived using the observed test raw score for that visit. If more than one of the tests consisting of a domain have missing value at a visit, the corresponding domain score is missing at that visit.

For the other five domains (Verbal Learning, Reasoning and Problem Solving, Visual Learning, Attention / Vigilance, and Social Cognition) which has only one test, if the test has missing value at a visit, the corresponding domain score is missing.

If a domain score is missing at a visit, the missing T-score of this domain can be imputed using the following algorithm:

$$\hat{T}_{ijk} = \bar{T}_{ij+} + \bar{T}_{i+k} - \bar{T}_{i++}$$

Where $\hat{T}_{ijk}$ is the missing T-score at Visit *i* to be imputed for domain *j* of subject *k*

$\bar{T}_{ij+}$ is the mean T-score at Visit *i* on domain *j* from all subjects

$\bar{T}_{i+k}$ is the mean T-score at Visit *i* on all available domains from subject *k*

$\bar{T}_{i++}$ is the mean T-score at Visit *i* of all available domains from all subjects.

In order to produce a more plausible imputed value that reflects the naturally occurring variability around the measure of a subject's cognitive ability, a small amount of random variance will be added to each predicted value $\hat{T}_{ijk}$. Multiplying the square root of the mean square error of $\hat{T}_{ijk}$ by a random value drawn from a standard normal distribution, $Z \sim N(0, 1)$, the final imputed T-score of the missing domain would become:

$$\tilde{T}_{ijk} = \hat{T}_{ijk} + \sqrt{MSE\ (\hat{T}_{ijk})} * Z$$

This will not only preserve the independent nature of the collected data, but also prevent exaggerating the precision of the treatment differences (3).

For baseline assessment, at least two-thirds of the cognitive domains (i.e., a minimum of five out of the seven domains for the MCCB overall composite score and a minimum of four out of the six domains for the MCCB neurocognitive composite score) need to be successfully assessed at baseline for it to be counted as a test occasion with non-missing baseline value.

For post-baseline assessments, at least half of the domains (i.e., a minimum of four out of the seven domains for the MCCB overall composite score and a minimum of three out of the six domains for the MCCB neurocognitive composite score) need to be successfully assessed to be considered a test occasion with non-missing value.

EOT measurement of MCCB endpoints which were collected >10 days after the last trial medication intake date will not be included in the analysis.

SCoRS

For the 20-item SCoRS assessment, if six or more of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the SCoRS total score for that subject at that visit is missing. If five or less of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the item with missing response will be imputed first with the average of the non-missing item values for the subject at the visit, and then SCoRS total score for the subject at the visit will be derived as the sum of the non-missing item values and the imputed item values.

Missing or incomplete AE dates are imputed according to (4).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, baseline values are the measurements taken on the day of the first administration of trial medication (Visit 2), and immediately prior to the first administration of trial medication. If this value is not available, the measurement at the screening visit (Visit 1) is used (PANSS and eC-SSRS), but this does not apply for MCCB measurement.

Visits are labelled according to the flow chart in the protocol: Visit 1 (screening), Visit 2 (randomisation and start of treatment, also baseline), Visit 3 (Week 3), Visit 4 (Week 6), Visit 5 (Week 9), Visit 6 (Week 12), and End of Treatment (EOT), Follow-up 1 (FU1) (7 days after EOT), Follow-up 2 (FU2) (28 days after EOT). Planned and actual test days are included in the analysis data sets and are calculated relative to the beginning of study as indicated in Table 6.7: 1 below.

Table 6.7: 1 Planned and actual study days

Visit	Relative to study start	
	Planned test day	Actual test day
2	1	Day 1 – Day 2
3	22	Day 3 – Day 39
4	43	Day 40 – Day 60
5	64	Day 61 – Day 81
6 / EOT	85 for completed subjects	Day 81 – Day 101
EOT	N/A (for early discontinued subjects)	Date of the last administration of trial medication to date of the last administration of trial medication + 8 days (for early discontinued subjects)
FU1	EOT + 7 days	EOT + 4 days to EOT + 10 days
FU2	EOT + 28 days	EOT + 21 days to EOT + 35 days

For efficacy endpoints with planned measurements at baseline, Week 6 and Week 12, actual measurement collected between Day 3 and Day 60 will be mapped to Week 6 and actual measurement collected between Day 61 and the actual EOT visit date will be mapped to Week 12, and baseline is the measurement collected at Visit 2. If multiple measurements are mapped into the same time point using the time window, then the first measurement will be used in the analysis.

7. PLANNED ANALYSIS

In general the display format of the analysis results follow BI guideline and standards as much as possible.

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

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

In general, means, medians, and percentiles are presented to one more decimal place than the raw data and STDs are presented to two more decimal places than the raw data. Minima and Maxima are presented to the same number of decimal places as the raw data.

Tabulations of frequencies for categorical data include all possible categories defined (even if there is no count in a category) and display the number of observations in a category as well as the percentage (%) relative to the number of subjects in the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages are rounded to one decimal place. The category missing is displayed only if there are actually missing values.

If a table presents only categorical data, "[N (%)]" is displayed in the column header only.

Abbreviations (e.g. Wors.) or acronyms (e.g. PD) will not be displayed in tables and subject data listings without any explanation. They will be either spelled out or explained in footnotes.

If applicable, conversion from days to weeks, months and years will be as follows:

- weeks = days ÷ 7
- months = 12 × days ÷ 365.25
- years = days ÷ 365.25.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only standard descriptive statistics and summary tables are planned for this section of the report based on the treated set and other subject sets as appropriate. Data will be summarised by treatment group and a "total" column will be included in the summary table.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report based on the treated set and other subject sets as appropriate.

Concomitant diseases are coded similarly as AEs based on the most current MedDRA® version. A summary of concomitant diseases will be provided by treatment group, system organ class (SOC), and preferred term (PT).

Concomitant therapies (CTs) are coded according to WHO DD. CTs will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, subjects receiving CTs with more than one possible ATC level-three category will be counted more than once and footnote will clarify this possible multiple counting in tables. CTs will be summarised in two groups: psycho-active and non-psycho-active concomitant medications. CTs of special interest, e.g. antipsychotic CTs, may also be defined and explored in detail.

7.3 TREATMENT COMPLIANCE

Treatment compliance is calculated at Week 3, 6, 9, and 12/EOT using the following formula:

Treatment Compliance = (number of tablets actually taken during a time period) / (number of tablets that should have been taken during a time period) * 100.

For early discontinued subjects, if there is documented evidence for taking the subject off the drug, for example due to an adverse event, then the drug stop date should be used to derive the treatment period for treatment compliance; if there is no documented evidence for taking the subject off the drug, for example a subject came to a planned in-office visit and informed the study investigator that she/he has already stopped taking the drug several days ago because she/he did not want to continue the study, then this in-office visit is the EOT visit and the EOT visit date should be used to derive the treatment period for treatment compliance. The following is an example to illustrate the calculation of treatment compliance.

Scenario 1

- A subject started treatment on June 5, 2019
- This subject had an AE on June 10, 2019
- Study investigator decided to stop the trial medication for this subject on June 11, 2019
- This subject had EOT visit on June 17, 2019 for early discontinuation

Treatment Compliance for Scenario #1 = (number of tablets this subject actually took between June 5 and 11, 2019) / (number of tablets that this subject should have taken between June 5 and 11, 2019) * 100

Scenario 2

- A subject started treatment on June 5, 2019
- This subject decided to stop taking the trial medication on June 10, 2019
- This subject came to office for the planned Visit 3 on June 26, 2019 per CTP flowchart, withdrew consent for continuing with this trial, and then Visit 3 became EOT visit

Treatment compliance for Scenario #2 = (number of tablets this subject actually took between June 5 and 26, 2019) / (number of tablets this subject should have taken between June 5 and 26, 2019) * 100.

The cumulative treatment compliance during the entire treatment period is derived using the following formulas:

For completers: if a subject's observed treatment compliance rates are 85% at Week 3, 90% at Week 6, 100% at Week 9 and 100% at EOT, then the cumulative treatment compliance rate = (0.85*3 + 0.90*3 + 1*3 + 1*3)/12 * 100% = 93.75%.

For early discontinued subject: if a subject's observed treatment compliance rates are 85% at Week 3, 100% at Week 6, 50% at EOT visit, and this subject did not discontinue early due to AE, then the cumulative treatment compliance rate = (0.85*3 + 1*3 + 0.5*((EOT date – drug start date + 1)/7 – 6))/((EOT visit date – drug start date + 1)/7) * 100% = 85.7% if EOT visit date – drug start date + 1 = 50 days. If there is documented evidence of early discontinuation due to AE before the EOT visit date for this subject, then replace EOT visit date with the documented drug stop date in the above formula.

If any one of the by-visit treatment compliance rates is missing, then the cumulative treatment compliance should be non-evaluable.

Only descriptive statistics are planned for this section of the report. Summary statistics of compliance, by-visit and cumulative compliance, in the treated set will be given for the number of subjects as well as the corresponding percentage with compliance in the categories <80%, 80% - 100%, >100% - 120%, >120% for by-visit compliance and <80%, 80% - 100%, >100% for cumulative compliance.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

The MCPMod approach (6, 7) is implemented in two main stages: (1) trial design stage; (2) trial analysis stage. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations are provided in the CTP Section 7.3.1 and 7.7. The procedures for the trial analysis stage are specified below. FAS is used for the primary analysis of the primary efficacy endpoint.

The change from baseline in MCCB overall composite t-score at Week 12 as well as the corresponding variance-covariance matrix are estimated using a mixed effects model repeated measure (MMRM) including the fixed categorical effects of treatment, visit and treatment-by-visit interaction, as well as the fixed continuous covariates of the baseline MCCB overall composite t-score and the baseline-by-visit interaction, and subject is considered as random effect. The unstructured covariance matrix is used to estimate the within subject errors. Then the pair-wise comparison procedure will be implemented using the optimal contrast tests which control the family-wise type I error rate at one-sided α=0.05. The optimal contrasts corresponding to the candidate models are calculated as in the trial design stage and shown in

Table 7.4.1: 1 below. These contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix from the data.

Table 7.4.1: 1 Optimal contrast coefficients

	Optimal Contrast Coefficients for Dose				
Model	**0**	**2mg**	**5mg**	**10mg**	**25mg**
Linear	-0.593	-0.212	-0.085	0.127	0.762
Linear in log	-0.844	-0.012	0.146	0.271	0.439
Emax	-0.773	-0.142	0.083	0.292	0.539
Sigmoid Emax	-0.623	-0.295	-0.078	0.389	0.606
Logistic	-0.542	-0.254	-0.181	0.231	0.745
Beta model	-0.782	0.173	0.358	0.441	-0.190

Proof of concept is established if at least one dose-response model is statistically significant, i.e. the null hypothesis of a flat dose-response curve is rejected indicating a benefit of one BI 425809 dose over placebo.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using the model averaging method. The selected dose-response model(s) is re-fitted to the data without any parameter assumptions to generate a set of new estimates of the model parameters from the data. The final dose-response model is obtained via the weighted model averaging based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). Estimate of the target dose is the smallest dose producing an effect greater than or equal to the target effect size of 0.35 based on the final dose-response model as well as considering safety information and other relevant information.

The MCPMod trial analysis will be implemented by calling an R function/package within SAS.

7.5 SECONDARY ENDPOINT

7.5.1 Key secondary endpoint

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

7.5.2 (Other) Secondary endpoint

7.5.2.1 Primary analysis of the secondary endpoint

The MCPMod approach will be applied to the secondary endpoint of change from baseline in SCoRS total score by interviewer at Week 12 using an ANCOVA model including treatment and baseline SCoRS total score as covariates using the FAS.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarised for the treated set using descriptive statistics for days of exposure as well as number (%) of subjects whose total exposure falls in the defined categories: <30 days, 30 to <42 days, 42 to <60 days, 60 to <90 days, >=90 days.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set and other subject sets as appropriate.

7.8.1 Adverse Events

Unless otherwise specified, 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. The reporting and analyses of AEs will follow the BI guideline (8). AEs will be coded with the most current version of 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 (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarisation of AE data, please refer to (4, 8).

The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between the date of the first administration of trial treatment till the date of the last administration of trial treatment + residual effect period will be assigned to the on-treatment period label with the trial treatment assigned on Day 1 of the first treatment cycle. All AEs occurring before the first administration of trial treatment will be assigned to ‘screening’ and all AEs occurring after the residual effect period will be assigned to ‘follow-up’. For details on the treatment definition, see Section 6.1.

Adverse events of special interest (AESIs)

A hepatic injury is 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 draw sample; and / or
- marked peak aminotransferase (ALT and / or AST) elevations ≥ 10 fold ULN.

See CTP Section 5.3.6.1.

Other significant AE (according to ICH E3)

According to ICH E3 (9), AEs classified as "other significant" needs to be reported and will include those non-serious and non-significant AEs with

1. action taken = discontinuation' or 'action taken = reduced'; or
2. marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor / Investigator during medical quality review at TOM.

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). The SOCs will be sorted by default alphabetically and PTs will be sorted by frequency within an SOC. Separate tables will be provided for patients with

- related AEs
- serious AEs
- serious related AEs
- AESIs
- Other significant AE (according to ICH E3)
- AEs leading to death
- AE leading to discontinuation of trial medication
- AEs occurred with incidence in the preferred term >2%
- AEs occurred with incidence in the preferred term >5%
- AEs occurred during the follow-up period.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow (10).

Descriptive statistics for laboratory values will be displayed using the converted values. Shift tables of change in laboratory measurements between baseline and worst value on treatment, between baseline and last value on treatment, and between worst and last value on treatment will also be presented.

7.8.3 Vital signs

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

7.8.4 ECG

Clinical relevant abnormal ECG findings will be reported and analysed as AEs.

7.8.5 Others

Ophthalmologic variables

Each ophthalmologic variable is measured for both the right eye and the left eye. For the total error score from F-M 100 test, the average of the total error scores from the right and the left eye will be used in the analysis.

For continuous variables, summary statistics including mean, median, standard deviation, minimum, maximum will be presented for the change from baseline measurements. In addition, paired t-test and 95% CI will be derived comparing Week 9 with baseline measurements.

For categorical variables, shift tables will be presented for the categorical changes from baseline.

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	Bomkamp B, Pinheiro J, Bretz F. R Package 'DoseFinding' (February 19, 2015). website:cran.r-project.org/web/packages/DoseFinding/DoseFinding.pdf (access date 28 April 2015); Comprehensive R Archive Network. 2015 [R15-2001]
3.	Little R. and Rubin D. Statistical Analysis with Missing Data. 2nd ed. New York: John Wiley & Sons. 2002
4.	*BI-KMED-BDS-HTG-0035*: "How to Guide: Handling of missing and incomplete AE dates", current version, IDEA for CON
5.	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, IDEA for CON
6.	Pinheiro J, Bomkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006; 16 (5): 639-656 [R10-1424]
7.	Pinheiro J, Bomkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014; 33 (10): 1646-1661 [R15-4293]
8.	*BI-KMED-BDS-HTG-0041*: "How to Guide: Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, IDEA for CON
9.	*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, EMA webpage.
10.	*BI-KMED-BDS-HTG-0042*: "How to Guide: Handling, Display and Analysis of Laboratory Data", current version, IDEA for CON

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Initial (Version 1)	**27-Jun-2016**		All	This is the initial TSAP before study initiation which is planned on 25-Jul-2016.
Initial Revised (Version 2)	**05-Mar-2018**		6.2	This is the revised initial TSAP based on the protocol amendment (protocol version 3.0 dated 13-Dec-2017) after the clinical hold was lifted and before this trial is re-started on 11-Apr-2018.
Final (Version 3)	**20-Nov-2019**		4, 5, 6, 7, 8, 9	This is the revised and final version after the initial TSAP.
Revised (Version 4)	**17-Feb-2020**		4 5.2.2 6.2 6.6 6.7	Correct a typo in a sentence in CTP Section 7.1 for the secondary efficacy endpoint. Clarified derivation of SCoRS total score and missing data handling rule Revised iPD table 6.2: 1 based on decision at RPM and TOM Clarified missing data handling rule for SCoRS total score Clarified time window derivation based decision at RPM and TOM

APPROVAL / SIGNATURE PAGE

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Document Name: 8-01-tsap

Title: A phase II randomised, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 425809 once daily over 12 week treatment period in patients with Schizophrenia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		17 Feb 2020 16:55 CET
Approval-Medical Writer		17 Feb 2020 17:31 CET
Approval-Team Member Medicine		17 Feb 2020 17:57 CET
Approval-Project Statistician		18 Feb 2020 07:39 CET
Approval-Clinical Trial Leader		18 Feb 2020 08:54 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed