TRIAL STATISTICAL ANALYSIS PLAN

c17518576-03

BI Trial No.:	1289.32
Title:	A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 52-week treatment period as an early intervention in patients with attenuated psychosis syndrome.
Investigational Product(s):	BI 409306
Responsible trial statistician(s):	[redacted] Telephone: [redacted]
Date of statistical analysis plan:	21 MAY 2021 SIGNED
Version:	"Final"

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1. TABLE OF CONTENTS

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LIST OF TABLES

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
[redacted]	
APS	Attenuated Psychosis Syndrome
AR(1)	Autoregressive covariance matrix of order 1
BAC App	Tablet based Brief Assessment of Cognition
BACS	Brief Assessment of Cognition in Schizophrenia
BACS SC	Brief Assessment of Cognition in Schizophrenia: Symbol Coding
BCVA	Best Corrected Visual Acuity
BDNF	Brain-derived neurotrophic factor
BI	Boehringer Ingelheim
[redacted]	
C-SSRS	Columbia- Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DRA	Drug Regulatory Affairs
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Exclusion Criteria
ECG	Electrocardiogram
EOT	End of Treatment
eCRF	Electronic Case Report Form
[redacted]	
FAS	Full Analysis Set
FU	Follow Up
H_0	Null Hypothesis
H_a	Alternative Hypothesis
HR	Hazard Ratio

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Term	Definition / description
IC	Inclusion Criteria
ICH	International Conference On Harmonisation
ICF	Informed Consent Form
ICH E9	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use, E9-Statistical Principles for Clinical Trials
iPD	Important Protocol Deviation
ITT	Intent To Treat
Max	Maximum
Min	Minimum
[redacted]	
MMRM	Mixed Model with Repeated Measurements
MedDRA	Medical Dictionary For Regulatory Activities
N	Sample Size
NAPLS	North American Prodromal Longitudinal Study
PANSS	Positive and Negative Syndrome Scale
[redacted]	
PK	Pharmacokinetic
PSP	Personal and Social Performance
PT	Preferred Term
RS	Randomized Set
SAE	Serious Adverse Event
SCoRS	Schizophrenia Cognition Rating Scale
SD	Standard Deviation
SOC	System Organ Class
SOPS	Scale of Prodromal Symptoms
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
VAS	Visual Analogue Scale

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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.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Due to recruitment challenges, the trial has a much smaller sample size than originally intended. The following are the changes in the analyses due to the limited sample size:

- No subgroup analyses.
- No evaluation of psychometric properties of SIPS/SOPS.
- No additional sensitivity analyses excluding patients who were recruited from the enriched population prior to amendment 3.

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5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is time to remission from APS within a 52 week timeframe (please see **section 5.1.1** of the CTP).

Per DSM-V, the proposed diagnostic criteria for APS are:

A. At least one of the following of symptoms is present in attenuated form, with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention:

- Delusions
- Hallucinations
- Disorganized speech.

B. Symptom(s) must have been present at least once per week in the last 1 month

C. Symptom(s) must have begun or worsened in the past year

D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention

E. Symptom(s) is not better explained by another mental disorder, including: Depressive or bipolar disorder with psychotic features and is not attributable to physiological effects of a substance or another medical condition

F. Criteria for any psychotic disorder have never been met.

A diagnosis of APS is defined by the presence of recent attenuated positive symptoms that meet ALL of 5 criteria: sufficient **severity** (criterion A), sufficient **frequency** (criterion B), **recency** of onset or worsening (criterion C), associated with sufficient distress or disability to warrant clinical attention ("**warrant attention** criterion," criterion D), and not likely due to another disorder ("**attribution** criterion," criterion E).

A patient in remission is defined as someone who no longer meets the severity criterion.

Remission from APS is defined as a score of <3 on all of the P1-P5 Positive Symptom items of the SOPS and maintained until the end of treatment.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable.

5.2.2 Secondary endpoint(s)

The following are the secondary endpoints as defined in **section 5.1.2** of the CTP.

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- Time to first episode of psychosis within a 52 week timeframe as adjudicated by the Central Rating Committee.

  First episode of psychosis defined as:
  - One or more SOPS P1- P5 rated a 6
  - *AND* either a symptom is seriously disorganizing or dangerous
  - *OR* one of the symptoms above occurred at least one hour per day at an average frequency of four days/week over the past month
  - *OR* a new prescription or increase in dose of an ongoing antipsychotic medication.

  Time of onset of first episode psychosis is defined using the rater's best estimate as determined in the SOPS interview or when the patient began taking a new prescription or increased the dose of antipsychotic medication.

- Change from baseline in everyday functional capacity as measured by Schizophrenia Cognition Rating Scale (SCoRS) total score after 24 and 52 weeks of treatment.

- Change from baseline in the BAC App composite T score after 52 weeks of treatment.

- Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive items score, negative items score, and total score after 52 weeks of treatment.

[redacted]

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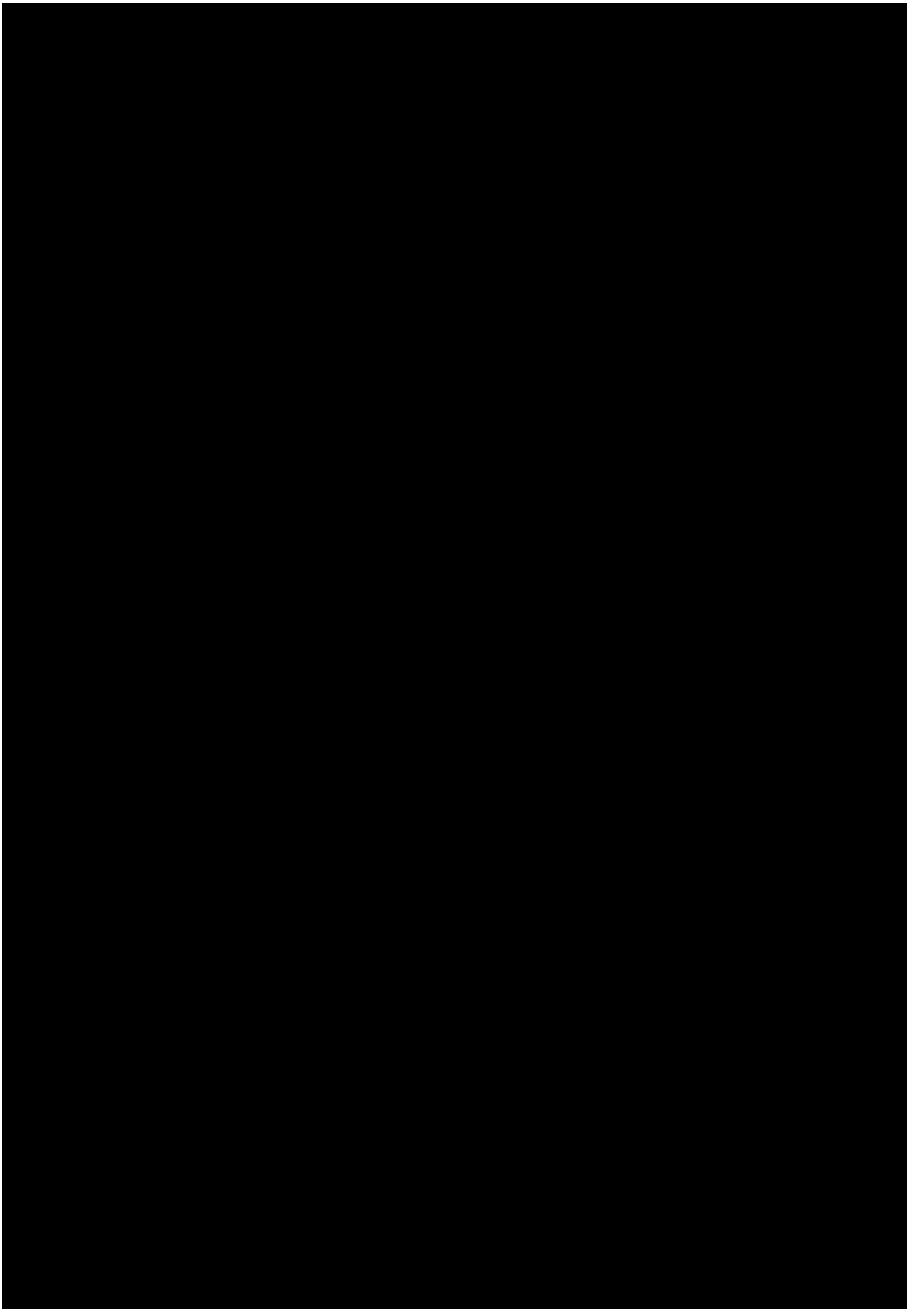

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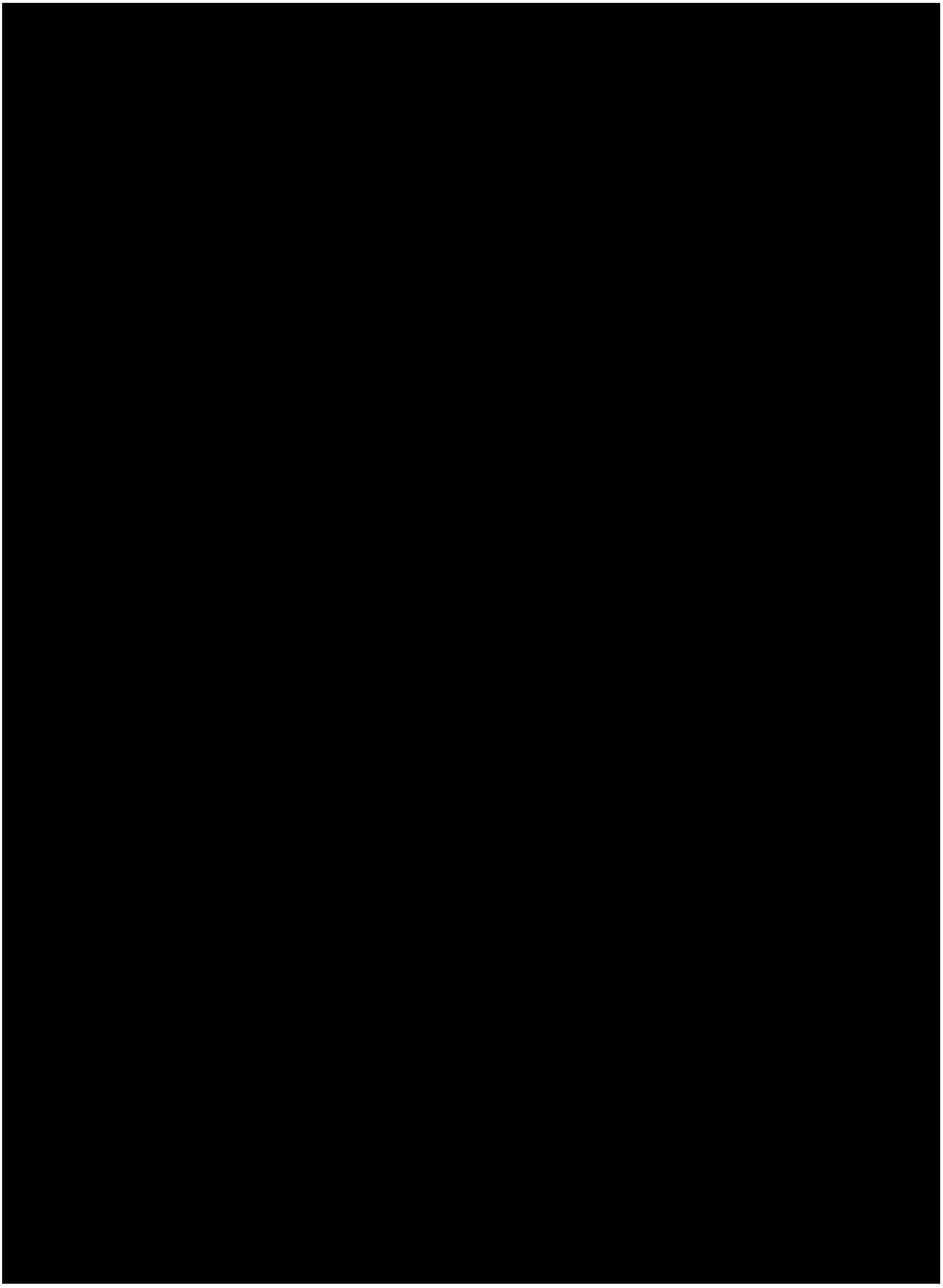

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

As described in **Section 3** of the CTP, patients will be randomized in equal allocation to one of two treatment dosage groups (50 mg and placebo) for analysis purposes.

For randomization purposes 2 arms have been defined:

- BI 409306 50 mg q.d. for 52 weeks.
- Placebo for 52 weeks.

Table 6.1: 1 Treatments and their labels per randomization list

Treatment	**Short label**
BI 409306 50 mg q.d.	BI 409306 50 mg
Placebo	Placebo

The trial consists of a 28 day screening period, followed by a 52 week treatment period (after randomization), and a 28 day residual effect period for follow-up.

For analysis purposes two periods have been defined in **section 7.3.1** of the CTP:

- Full follow-up
  This is the entire study period, beginning with randomization until the end of the follow-up period (or date of last contact), including the residual effect period.

- On-treatment
  This includes the time period from treatment start date until drug discontinuation + 7 days.

Patients who discontinue early will be followed up according to the **section 3.3.4.1** of the CTP.

6.2 IMPORTANT PROTOCOL VIOLATIONS

According to latest iPD HTG, important protocol deviations are recorded in the DV template.

6.3 SUBJECT SETS ANALYSED

Screened/Enrolled Set
The screened set includes all patients who were screened for the trial, gave informed consent and had at least one screening procedure at Visit 1.

Randomized Set (RS)
The RS consists of all patients who were screened for the trial and who were randomized to study drug, regardless of whether any study drug was taken.

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Treated Set (TS)
The TS includes all patients who were randomized and were documented to have taken at least one dose of study drug.

Full Analysis Set (FAS)
The FAS includes all patients in the TS with at least one baseline and post-baseline measurement of any type. The FAS will be used for the primary and secondary analyses.

The screened set, RS and TS will be used to populate patient disposition and the TS will be used for demographics, baseline characteristics, treatment exposure and safety analyses (including adverse events, laboratory measurements, vital signs and ECG).

Efficacy data will always be analyzed according to the randomized treatment following the intention-to-treat (ITT) principle. If a patient erroneously received a medication kit that included a treatment different from what they were randomized to, the patient's efficacy data will be analyzed according to the treatment they were originally randomized to.

Table 6.3: 1 Subject sets analyzed

	Subject set	
Class of endpoint	TS	FAS
Primary and key secondary endpoints		X
(other) Secondary and further endpoints		X
Safety endpoints	X	
Demographic/baseline endpoints	X	

Analysis periods are defined in the revised CTP and in section 6.1.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because country is not included in the statistical model.

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6.6 HANDLING OF MISSING DATA AND OUTLIERS

Assessment of remission data (primary endpoint):

All patients will be followed up for remission from APS. As specified in section 5.1, remission from APS has to be maintained until the end of treatment to satisfy the primary endpoint.

Any patient who has not remitted will be censored in the analysis of the primary endpoint at the time of their planned completion of 52-week treatment period or at the time of discontinuation.

Any patient who has remitted but relapsed to APS will be also censored in the analysis of primary endpoint at the time of their planned completion of 52-week treatment period or at the time of discontinuation.

Any patient who has an episode of psychosis will be censored at the time point of psychosis.

Patients who begin taking a new prescription or increase in dose of ongoing antipsychotics will not be considered eligible for remission. Such patients will be censored at the start of new prescription or increase of dose of ongoing antipsychotics.

No missing data will be imputed for primary and secondary analyses.

SCoRS:
For the SCoRS, if an individual item is missing, it should be imputed with the average of the patient's non-missing item scores.

PANSS positive symptoms (secondary analysis)
Change from baseline in PANSS positive symptoms will be evaluated using Mixed effect Model for Repeated Measures (MMRM) approach. This approach allows for missing data, assuming they are missing at random. All patients can be included in the model and missed visits will not be imputed. If a PANSS item is missing, the missing score on that individual PANSS item will not be imputed; if individual PANSS item is missing within a PANSS subscale, this subscale cannot be included in the calculation of the overall PANSS total score. Therefore, patients with missing individual PANSS items will also have a missing PANSS total score at that visit. However, subscale scores will be used for analysis if none of the individual items is missing.

AE dates
Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (3).

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6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all efficacy endpoints, "baseline" is defined as the assessments done at Visit 2, prior to administration of first dose. If this value is not available, the latest measurement before the first time drug administration (at screening (Visit 1), or an unscheduled visit) will be used.

For demographics, medical history, ECG, concomitant antipsychotic medication, AEs, concomitant therapies and vital signs, Visit 1 (screening) will be considered as "baseline".

Visit will be labelled according to the flow chart in the protocol: Visit 1 (for screening), Visit 2 (randomization and start of treatment), Visits 3-23, End of Treatment (EOT), Follow Up (FU) (28 days after Visit 23 for completed patients; 28 days after EOT for early discontinued patients). Planned and actual test days will be calculated relative to the beginning of study as indicated in the following table.

Table 6.7: 1 Visit calculation relative to study start

Visit	**Relative to study start**	
	Planned test day (every 14 days)	**Actual test day**
2	1	1
3	8	Visit 3 date – first dose date +1
4	15	Visit 4 date – first dose date +1
5	22	Visit 5 date – first dose date +1
Etc...	...	...
23	365	Visit 23 date – first dose date +1
EOT	Visit 23 + (7 days)	EOT– first dose date + 1
FU	Visit 23 + 28 days	FU date – first dose date + 1

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7. PLANNED ANALYSIS

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

For tables 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).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. 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 treated set.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report, based on the treated set. A summary of concomitant diseases will be provided by treatment group, System Organ Class (SOC) and Preferred Term (PT).

Concomitant medications will be summarized by two groups: schizophrenia and non-schizophrenia. Both baseline and on-treatment mediations will be summarized.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Summary statistics will be given for percent compliance along with the number (%) of patients with compliance in the categories <50%, 50% - <80%, >80% (cf. section 5.4.2 for calculation of treatment compliance). Similar table with the same categories will be prepared for patient adherence obtained via [redacted]. A patient level listing comparing traditional treatment compliance with patient adherence from [redacted] will also be included to facilitate patient level insights.

7.4 PRIMARY ENDPOINT(S)

The hypothesis testing strategy for primary endpoint is described in **Section 7.2 of the CTP:**

The hypothesis for the superiority testing of the primary endpoint time to remission from APS is (HR = hazard ratio):

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H_o: $HR_{BI\ 409306\ /\ placebo} = 1$ vs. H_a: $HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the active treatment arms (i.e. BI 409306 50 mg q.d.), over 52 weeks.

Superiority will be declared if the hazard ratio between BI 409306 vs. placebo is statistically significantly less than 1 at the two-sided type I error level $\alpha = 0.1$.

7.4.1 Sensitivity Analyses

The following sensitivity analyses will be conducted: (1) on the primary endpoint that includes only patients from the TS during the time of the full follow-up period and (2) Patients who have [redacted] adjusted adherence over 80%.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

Secondary endpoints will be analyzed as described in **section 7.3.2 in the revised CTP**:

Time to First Episode of Psychosis:

Time to event endpoint will be analyzed using Cox proportional hazard model as described for the primary endpoint analysis.

Change from baseline SCoRS (at time points 24 weeks, 52 weeks respectively), BAC App (composite T score), PANSS (positive items score, negative items score and total score respectively):

All change from baseline endpoints specified in Section 5.2.2 will be analyzed using the restricted maximum likelihood (REML) based mixed effects model with repeated measurements (MMRM). The model will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, and baseline NAPLS risk score, and baseline use of antipsychotic medication, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, compound symmetry covariance structure might be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using [redacted]® PROC MIXED. The primary treatment comparisons will be between the placebo and BI 409306 with respect to the mean change from baseline. Adjusted mean change from baseline as well as treatment contrasts will be presented together with the 95% confidence intervals.

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[redacted]

7.7 EXTENT OF EXPOSURE

Exposure will be analyzed on the treated set. Extent of exposure will be summarized using descriptive statistics for days of exposure as well as number (%) of patients whose total exposure falls in the categories specified in section 5.4.2.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. Analyses are specified in **section 7.3.4** of the CTP.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events 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 analysis of adverse events will be based on the concept of treatment emergent adverse events. That means all adverse events with an onset between start of treatment and end of the on-treatment period, which is 7 days after the last dose of trial medication, will be assigned to the treatment period for evaluation. All adverse events occurring before first drug intake will be assigned to ‘screening’ and all adverse events occurring after the residual effect period will be assigned to ‘post-treatment’ (for listings only).

According to ICH E3 (5), AEs classified as ‘other significant’ need 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.

An overall summary of adverse events will be presented. The frequency of subjects with adverse events, and will be summarized by treatment, primary system organ class and

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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 (only if defined) and for subjects with serious adverse events.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). Planned analyses are detailed in **section 7.3.4** of the CTP.

Baseline for safety laboratory parameters will be the last available measurement before the start of randomized treatment. Laboratory measurements taken up to 7 days after the last administration of randomized treatment will be considered as on-treatment.

Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings. If there are multiple safety laboratory values at one visit, the worst of these will be assigned to that visit date measurement.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. See **section 7.3.4** of the CTP.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. ECG findings before first intake of study drug will be considered as baseline condition. Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AE and analyzed as planned in section 7.8.1.

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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.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCG-156*: "Handling and summarization 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*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

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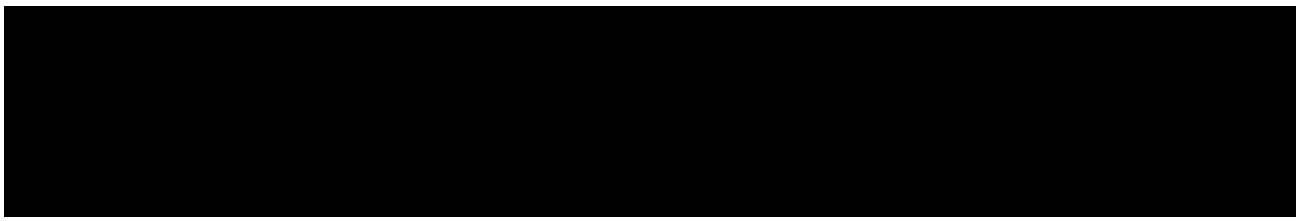

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10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**13-DEC-17**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**21-MAY-21**		All were updated.	This is the final TSAP