TRIAL STATISTICAL ANALYSIS PLAN c20537098-04

BI Trial No.:	1289-0049
Title:	A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 28-week treatment period as adjunctive therapy to antipsychotic treatment for the prevention of relapse in patients with schizophrenia. **[c14883409-02]**
Investigational Product(s):	BI 409306
Responsible trial statistician(s):	[redacted] Telephone: [redacted]
Date of statistical analysis plan:	17 MAR 2021 SIGNED
Version:	V4

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
[redacted]	
AR(1)	Autoregressive covariance matrix of order 1
BI	Boehringer Ingelheim
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity
C-SSRS	Columbia- Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
EC	Exclusion Criteria
ECG	Electrocardiogram
EOS	End of Study
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
IC	Inclusion Criteria
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
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

Term	Definition / description
LLT	Lower Level Term
LTFU	Lost to Follow-up
Max	Maximum
Min	Minimum
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed Model with Repeated Measurements
N	Sample Size
PANSS	Positive and Negative Syndrome Scale
PGI-I	Patient Global Impressions-Improvement
PK	Pharmacokinetic
PSP	Personal and Social Performance
PT	Preferred Term
RRR	Relative Risk Reduction
RS	Randomized Set
SD	Standard deviation
SOC	System Organ Class
TOEPH	Toeplitz with Heterogeneous Variances
TOEP	standard Toeplitz matrix
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
T/W	Taper/Withdrawal
VAS	Visual Analogue Scale

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

CTP section 7.5 specifies: *All patients will be followed up for relapse* […]. *Any patient who has not relapsed will be censored in the analysis of the primary endpoint at the time of last patient contact.* In fact, the primary endpoint analysis is the ITT analysis, which is indicated in CTP section 7.3 to include relapses only during the 28-week planned on-treatment period. See Section 6.6 for corrections.

The following additional analyses, which were not mentioned in the CTP, were added:

- Time to Discontinuation was added as a further endpoint.
- Time to Treatment Discontinuation or Relapse was added as a sensitivity analysis to the primary endpoint

Recruitment to this study was stopped early by the Sponsor due to slow enrolment. As a result, statistical power is reduced because of sample size reduction, analyses remain the same as planned, see more details in Section 7.4. A fast-track approach will be taken in order to expedite decision making and for preparation of the planned phase III trials, see more details in Section 9.2.

Details surrounding the planned assessment of the impact of the COVID-19 pandemic on the trial, are specified in section 9.3.

Hazard ratio calculated from the Cox proportional hazard model and a 95% confidence interval around the HR will be provided for primary and secondary endpoint; relative risk reduction and a 95% confidence interval around the RRR will be provided for further endpoints.

Due to the fact that there were cases where the site was not able to enter the data into the iPad in a timely manner and [redacted] was unable to confirm with the site the actual date the assessment was completed, visit start date as recorded on the CRF will be used as the analysis date. [redacted] confirmed that all assessments started on the visit date and therefore it is a reasonable assumption to use the CRF recorded visit date as the analysis date.

5. ENDPOINTS

The overall objective of this study is to evaluate the efficacy and safety of BI 409306 during a 28-week period in patients with schizophrenia, who are on stable background antipsychotic treatment. Refer to Sections 2 and 7 of the CTP for more details on the endpoints of the study.

5.1 PRIMARY ENDPOINT(S)

The primary endpoint will be used as defined in the revised **CTP, Section 2.1.2**:

The primary endpoint is time to first relapse until study end (planned at 28 weeks). Time of relapse will be obtained by selecting the earliest date from any, or all of the following 6 criteria:

- *Time to hospitalization (involuntary or voluntary admission), intensive outpatient therapy or use of home treatment, as an alternative to hospitalization, for decompensation of schizophrenia symptoms*

- *Time to an assessment on the Clinical Global Impressions - Severity (CGI-S) of ≥ 5 (markedly ill) and either:*

  - *an increase on any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content - to a score > 4 with an absolute increase of ≥2 on that specific item since randomisation*

  or

  - *an increase on any of the following individual PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content - to a score > 4 and an absolute increase of ≥4 on the combined 4 PANSS items since randomisation*

  or

  - *PANSS total score increase of ≥25% relative to baseline score or an increase of ≥10 points if baseline score was ≤40*

- *Time to a prescription for a new antipsychotic or time to an increase in dose of an ongoing antipsychotic medication for significant worsening of schizophrenia symptoms*

- *Time to clinically significant homicidal ideation, in the investigator's judgement*

- *Time to suicidal behavior, or time to assessment of suicidal ideation type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS)*

- *Time to deliberate self-injury and/or violent behaviour resulting in suicide or in clinically significant injury to the patient or another person or property damage, in the investigator's judgement*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint

The key secondary endpoint as described in **Section 2.1.3 in the revised CTP** is:

Change from baseline in Positive and Negative Symptom Score (PANSS) positive symptoms score after 28 weeks of treatment.

See section 6.7 for details regarding the definition of "baseline".

5.2.2 Secondary endpoints

The secondary endpoints are described in **Section 2.1.3 in the revised CTP**:

- *Time to new prescription or increase in dose of an ongoing antipsychotic medication.*
- *Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment.*
- *Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment.*
- *Suicidal ideation and behaviour as assessed by C-SSRS after 28 weeks of treatment.*
- *Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment.*

See section 6.7 for details regarding the definition of "baseline".

5.4 OTHER VARIABLES

5.4.1 Demographic and other baseline characteristics

Demographics:

- Sex
- Race
- Ethnicity
- Region (North America, Europe, Asia)
- Country (Canada, USA, France, Japan, Taiwan, South Korea)
- Age [years]
- Age in classes (18-<35; 35-<50; >=50)
- Weight (kg)
- Height (cm)
- Body Mass Index [kg/m^2]: Weight [kg]/(Height[m]*Height[m]), as continuous variable and in classes (<18.5; >=18.5 to <25; >=25 to <30; >=30)
- Ethnicity
- Smoking history
- Alcohol Consumption
- Cannabis usage
- Time since diagnosis of schizophrenia [years]

- Education (self) [years]
- Education (childrearing mother) [years]
- Student (within past 6 months)
- Living arrangements
- Employment status

Other baseline characteristics:

- Baseline conditions/Medical history
- Baseline clinical assessments (CGI-S, C-SSRS, PANSS (total, conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content positive, negative, general), PSP (total, socially useful activity, personal and social relationships, self-care, disturbing and aggressive behaviour) AIMS, EQ-5D-5L)
- Concomitant Antipsychotic Medication
- Concomitant Medication
- Concomitant Non-Drug Therapy
- Psychotherapy

Pharmacogenomic data:

- CYP2C19 (UM, EM, IM, PM, ND, Missing)

5.4.2 Treatment compliance and treatment exposure

Treatment compliance:
Treatment compliance is assessed via the use of the AICURE device and the eCRF. Average adjusted compliance will be calculated and displayed. Compliance will be categorized into classes: <80%, >=80% to <=100%, >100%.

Treatment exposure:

- Exposure is calculated as (drug stop date) – (drug start date) +1

- Treatment exposure classes (<=102 days, 103 days to <=204 days, >204 days)

The Taper/Withdrawal (T/W) period is included in the treatment exposure calculation.

Study observation periods:

- Each patient's observation time contribution, for the Intent to Treat (ITT) follow-up, and Full follow-up period, will be summarized, for more details see Section 6.1.

5.4.3 Pharmacokinetic assessments

As described in **Section 5.3.1 of the CTP**:

- *$C_{0:45h}$: measured plasma concentration of BI 409306 in plasma 0:45h after a single dose of BI 409306*

- *$C_{1.5h}$: measured plasma concentration of BI 409306 in plasma 1.5h after a single dose of BI 409306*

- *C_{2h}: measured plasma concentration of BI 409306 in plasma 2h or more after a single dose of BI 409306*

From the individual pharmacokinetic parameters $C_{0:45h}$ and $C_{1.5h}$, mean pharmacokinetic parameters will be calculated by descriptive statistics if data allow.

At the post-randomisation visits, the following pharmacokinetic parameters will reported for each analyte:

- *C_{press}: residual concentration of BI 409306 and metabolites CD 13896 and CD 14084 in plasma after last dose of BI 409306*

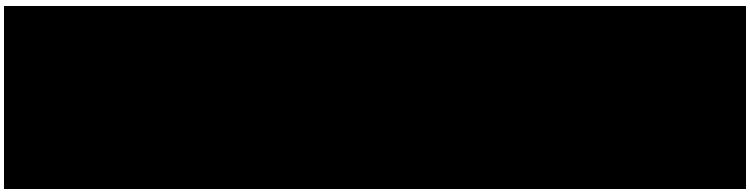
Per CTP flow-chart, pharmacokinetic sampling will be performed at Visits 8 and 16.

5.4.4 Pharmacogenomic evaluation

As specified in the **Section 5.4.2 of the CTP**:

One blood sample will be taken at the screening visit for genotyping of CYP2C19 from all patients taking medication known to be strong or moderate inhibitors of CYP1A2.
[…]
In case of a positive study outcome, the sample may be used for DNA extraction and subsequent genotyping for variants in genes involved in absorption, distribution, metabolism and elimination of the compound. It is not intended to include these data in the final report. However, the data may be part of the report if necessary.

In case of a positive study outcome as determined based on topline results, samples from all subjects will be genotyped for CYP2C19. The influence of CYP2C19 variations on pharmacokinetics will be explored descriptively and if applicable by population pharmacokinetic methods. The parameters $C_{0.45h}$ and $C_{1.5h}$ of BI 409306 in plasma will be compared in exploratory figures by CYP2C19 diplotype and predicted phenotype, if applicable; these analyses will be presented in section 15.6 of the CTR.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

As described in Section 3 of the revised CTP, patients will be randomized in equal allocation to one of three treatment dosage groups (50 mg, 25 mg and placebo) for analysis purposes.

For randomization purposes 6 arms have been defined:

- BI 409306 50 mg q.d for 28 weeks and 7 days of withdrawal from treatment
- BI 409306 50 mg q.d for 28 weeks and 7 days of tapering from treatment
- BI 409306 25 mg q.d for 28 weeks and 7 days of withdrawal from treatment
- BI 409306 25 mg q.d for 28 weeks and 7 days of tapering from treatment
- Placebo for 28 weeks and 7 days of withdrawal from treatment
- Placebo for 28 weeks and 7 days of tapering from treatment

Table 6.1: 1 Treatments and their labels per randomization list

Treatment	**Short label**
BI 409306 50 mg q.d. taper	BI 409306 50 mg taper
BI 409306 50 mg q.d. withdraw	BI 409306 50 mg withdraw
BI 409306 25 mg q.d. taper	BI 409306 25 mg taper
BI 409306 25 mg q.d. withdraw	BI 409306 25 mg withdraw
Placebo taper	Placebo taper
Placebo withdraw	Placebo withdraw

The treatment period is defined as 28 weeks, hence for most analyses the taper/withdrawal period will not be considered and the arms corresponding to the same doses of treatment will be pooled, resulting in the following treatment labels for displays.

Table 6.1: 2 Treatments and their labels in specified analyses

Treatment (per rand list)	**Short label (in displays)**
BI 409306 50 mg q.d. taper	BI 409306 50 mg
BI 409306 50 mg q.d. withdraw	
BI 409306 25 mg q.d. taper	BI 409306 25 mg
BI 409306 25 mg q.d. withdraw	

Treatment (per rand list)	Short label (in displays)
Placebo taper	Placebo
Placebo withdraw	

The trial consists of a 28 day screening period, followed by a 28 week treatment period (after randomization), followed by a 7 day taper/withdraw (T/W) period and a 21day follow-up.

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

- Intent to Treat (ITT) follow-up
  This is the intended 28 week treatment period. It does not include the T/W period. For patients who discontinue early, their follow-up information until the end of the planned 28 week treatment period is included.

- 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 T/W period and follow-up period. (Sensitivity for ITT follow-up analysis)

- On-treatment
  This includes the time period from treatment start date until drug discontinuation + 7 days.
  - *Patients randomized to withdrawal period/early discontinued patients:*
    Time on treatment prior to withdrawal (or early discontinuation) + 7 days

  - *Patients randomized to taper period:*
    Time on treatment + 7 days taper period + 7 days

Patients who discontinue early will be followed up according to the CTP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in the electronic Document Management System (eDMS).

6.3 SUBJECT SETS ANALYZED

Screened 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.

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, and treated set 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, and vital signs). Safety analyses will assign patients to the treatment group based on the treatment they received at the time the AE occurred.

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.

6.5 POOLING OF CENTRES

The randomization was stratified by country.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Assessment of relapse data (primary endpoint):
All patients will be followed up for relapse […]. Any patient who has not relapsed will be censored in the analysis of the primary endpoint at the time of their planned complete 28-week treatment period. This does not include the T/W period. For AEs that meet the primary endpoint criteria, missing or incomplete AE dates are imputed according to BI standards.

The sensitivity analysis will use the Full Follow-up period to demonstrate the robustness of the results of the main analysis. See revised CTP Section 7.3

PANSS positive symptoms (key 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 are missing.

Relative Risk Reduction (RRR)
Per revised CTP Section 7.5.:
All patients in the FAS will be included […] *regardless of drop-out.*

For

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

PK data
Missing data and outliers of PK data are handled according to Reference (2) and as described in Section 10 of the revised CTP.

In December 2019, during the conduct of the trial, a Visit 8 eCRF page was added to capture the date and time of the last dose of BI drug intake before the PK sampling performed at Visit 8. For patients who had completed the trial at that time, or patients for whom the visit 8 date had passed, the [redacted] data will be used to inform the date and time of the last BI drug intake.
Sensitivity analysis: the date and time of the last dose of BI drug intake at Visit 8 collected in the eCRF will be compared to the information recorded in [redacted] This will be done for patients for whom both sources of information are available (eCRF and [redacted].

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 prior to treatment administration will be used.

For demographics, medical history, concomitant antipsychotic medication, AEs, concomitant therapies, vital signs and C-SSRS, Visit 1 (screening) will be considered as "baseline". If this value is not available, the earliest value prior to treatment administration will be used.

Visit will be labelled according to the flow chart in the protocol: Visit 1 (for screening), Visit 2 (randomization and start of treatment), Visits 3-19, End of Treatment (EOT), Follow Up (FU) (28 days after Visit 16 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

Visit	**Relative to study start**	
	Planned test day (every 14 days)	**Actual test day**
3	15	Visit 3 date – first dose date +1
4	29	Visit 4 date – first dose date +1
5	43	Visit 5 date – first dose date +1
Etc...	...	...
16	197	Visit 16 date – first dose date +1
T/W 17	Visit 16 + 2 days	T/W 17 date – first dose date + 1
T/W 18	Visit 16 + 4 days	T/W 18 date – first dose date + 1
EOT (T/W 19)	Visit 16 + 7 days	EOT (T/W 19 date) – first dose date + 1
FU	Visit 16 + 28 days	FU date – first dose date + 1

All time to event analyses will use the visit start date as recorded on the CRF as the analysis date.

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. And depending on if concomitant medication is started before or after trial medication, baseline and on-treatment concomitant medication use will be summarized separately.

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 <80%, 80% - 100%, >100%, see more details in Section 5.4.2.

7.4 PRIMARY ENDPOINT(S)

The hypothesis testing strategy for primary and key secondary endpoints is described in **Section 7.2 of the CTP:**

The trial will follow a hierarchical testing strategy. The first hypothesis for the superiority testing of the primary endpoint time to first relapse is (HR = hazard ratio):

> *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 pooled active treatment arms (i.e. BI 409306 50 mg q.d. and BI 409306 25 mg q.d.), over 28 weeks (excluding the withdrawal/taper period)*

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 $\alpha = 0.05$.

If the first hypothesis test is determined to be statistically significant, the individual doses will be tested for superiority using Hochberg's step-up test. The method will be to perform the statistical tests and rank the p-values for the individual doses vs. placebo. Let $p_{(1)} \geq p_{(2)}$ be the two-sided p-values. The corresponding null hypotheses are $H_{0(1)}$ and $H_{0(2)}$.

> ***$H_{0(1)}$:*** *$HR_{BI\ 409306\ /\ placebo} = 1$ vs.* ***$H_{a(1)}$:*** *$HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the BI 409306 dose with the highest p-value*

> ***$H_{0(2)}$:*** *$HR_{BI\ 409306\ /\ placebo} = 1$ vs.* ***$H_{a(2)}$:*** *$HR_{BI\ 409306\ /\ placebo} \neq 1$, where $HR_{BI\ 409306}$ is the hazard ratio for the BI 409306 dose with the lowest p-value*

Step 1: If $p_{(1)} \leq 0.05$ then both hypotheses are rejected and both doses are declared statistically significant and testing ends. If $p_{(1)} > 0.05$, then $H_{0\ (1)}$ is not rejected and the testing proceeds to Step 2.

Step 2: If $p_{(2)} \leq 0.025$, then $H_{0\ (2)}$ is rejected and this dose is declared statistically significant. If $p_{(2)} > 0.025$, then all doses fail.

7.4.1 Primary efficacy analysis

The primary analysis will be conducted on the FAS using the ITT follow-up period as defined in Section 6.1. Because the ITT covers the 28 weeks of planned treatment and not the T/W period, the treatment arms will be pooled according to dose and disregarding the T/W randomization.

Revised CTP in Section 7.3.1:
The equality of the hazard rates will be tested by the Wald test for the treatment effect in a stratified Cox proportional hazards model at the two-sided 5% significance level. The model includes the treatment effect as the only covariate and is stratified by country. Breslow's method for handling ties will be used.

The same stratified Cox proportional hazards model will be used to estimate the hazard ratio of BI 409306 vs. placebo and the asymptotic 95% Wald confidence interval. A hazard ratio of less than one favors BI 409306. The analysis will be implemented using SAS® PROC PHREG. Cox proportional hazard model assumptions will be verified.

In early discontinued patients, if the occurance of a relapse cannot be determined between the time of discontinuation and last contact, it is assumed that no relapse has occurred. Patients who discontinue study medication will be followed until the end of the trial for the primary endpoint. Patients who are lost-to-follow up will be censored for the primary endpoint at the date of last known patient contact.

According to the CTP, we have specified more details regarding efficacy analysis using ITT FU and Full FU:

Definition of last at-risk date:

The last at-risk date determined as the latest date among: the date of first dose of study medication, the date of last drug administration, all the visit start dates (including phone contact dates in which the patient was reached and follow-up contact dates) and start or stop dates of events reported on the adverse event forms.

If a patient dies, the date of death is their last at-risk date.

Definition of Visit 16 date:

The date of Visit 16 for the determination of the ITT FU period end date will be the start date recorded on eCRF.

Time to event calculations:

A. Patients completing treatment period and study period (for ITT analysis):

Events (relapses) are counted in the ITT time to event analysis whenever they occur between the first dose of randomized treatment and the patient's Visit 16 date or the date of last dose if this occurred after visit 16. (In SDTM this is EPOCH=TREATMENT1)

- Patients with event counted: <date of event> – <date of first drug administration> +1 day
- Patients without event counted: <date of last dose of study drug or date of Visit 16> – <date of first drug administration >+1 day

B. Patients completing treatment period and study period (for Full FU analysis):
Events (relapses) are counted in the FU time to event analysis whenever they occur between the first dose of randomized treatment and the patient's EOS date.

- Patients with event counted: <date of event> – <date of first drug administration> +1 day

- Patients without event counted: <date of EOS> – <date of first drug administration >+1 day

C. Patients who chose Early Discontinuation Option 1 or Option 2 per CTP (ITT and Full FU analysis):

1. And completed required study period: Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the patient's EOS date.
   - Patients with event counted: <date of event> – <date of first drug administration> +1 day
   - Patients without event counted: <date of EOS> – <date of first drug administration >+1 day
2. And discontinued or did not complete required study period: Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the patient's last at-risk date.
   - Patients with event counted: <date of event> – <date of first drug administration> +1 day
   - Patients without event counted: <date of last at-risk date > – <date of first drug administration >+1 day

D. Patients who chose Early Discontinuation Option 3 or Option 4 per CTP (ITT and Full FU analysis):

1. And completed required study period: Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the patient's End of Study Date.
   - Patients with event counted: <date of event> – <date of first drug administration> +1 day
   - Patients without event counted: < date of EOS > – <date of first drug administration >+1 day
2. And discontinued or did not complete required study period: Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the date of last at-risk date.
   - Patients with event counted: <date of event> – <date of first drug administration> +1 day
   - Patients without event counted: < date of last at-risk date > – <date of first drug administration >+1 day

E. Patients who chose Early Discontinuation Option 5, i.e. withdrew consent per CTP (for ITT and Full FU analysis): Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the patient's date of consent withdrawal.
   - Patients with event counted: <date of event> – <date of first drug administration> +1 day
   - Patients without event counted: <date of consent withdrawal> – <date of first drug administration >+1 day

F. Patients who are Lost-to-Follow-up (for ITT analysis): Events (relapses) are counted in the time to event analysis whenever they occur between the first dose of randomized treatment and the last at-risk date.

- Patients with event counted: <date of event> – <date of first drug administration> +1 day
- Patients without event counted: <date of last at-risk> – <date of first drug administration >+1 day

*Please note: Patients who are LTFU during the study (regardless of initial Early Discontinuation choice), but were successfully found towards the end of study via a vital status call, will be included in the Full-FU analysis period by replacing as follows:

- Patients without event counted: <date of vital status/date of EOS> – <date of first drug administration >+1 day

The following SAS code will be used:

```
proc phreg data= primary;
   CLASS &trt.(ref="Placebo") / order=internal;
   model aval*cnsr(1) = &trt./ties=breslow;
   strata countrdc;
   hazardratio 'HR' &trt. /diff=ref cl=both ;
run;
```

Subgroup analyses will be performed on the subgroups specified in Section 6.4. Definition of Japanese patients is provided in Section 9.1. The same model as described above for the primary efficacy analysis, will be used for these analyses.

The following SAS code will be used for survival plot:

```
proc lifetest data=primary method=km plots=survival(failure test
atrisk);
time aval*cnsr(1);
id usubjid;
strata &trt. /test=logrank;
run;
```

7.4.2 Sensitivity analysis

The sensitivity analysis to the primary analysis, will be performed on the Treated Set (TS) using the Full follow-up period.

An additional sensitivity analysis of Time to Treatment Discontinuation or Relapse will be performed using the same model as the primary analysis and using the same subject sets, i.e. FAS using the ITT follow-up period. This endpoint is a composite endpoint as defined above in the primary analysis, however it includes discontinuation as an outcome event.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

The hypothesis testing strategy for key secondary endpoints is described in **Section 7.2 of the revised CTP:**

The remaining alpha after the testing of the primary endpoint (Steps 1 and 2) will be used to test the key secondary endpoint of change from baseline in PANSS positive symptoms. The hypotheses to be tested are:

> ***$H_{0(3)}$:*** *Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with BI 409306 ≥ Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo*
>
> *vs.*
>
> ***$H_{a(3)}$:*** *Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with BI 409306 < Mean change from baseline of PANSS positive symptom score after 28 weeks of treatment with placebo*

The first of the key secondary hypothesis to be tested will be based on the pooled active treatment arms (i.e. BI 409306 50 mg q.d. and BI 409306 25 mg q.d.), over 28 weeks (excluding the withdrawal/taper period).

Similar to the primary endpoint, if the first hypothesis test (on the pooled doses) is determined to be statistically significant, the individual doses will be tested for superiority using Hochberg's step-up test as described above.

The key secondary analysis will be performed on the FAS, and is described in **Section 7.3.2 of the revised CTP:**

The key secondary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline of PANSS positive symptoms score after 28 weeks of treatment (Section 7.2).
The analysis will include the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
The statistical model will be as follows:

$$y_{ijkm} = \beta_j S_i + \tau_{jk} + \phi_m + e_{ij}$$
$$e_{ij} \sim N_Z (\mathbf{0}, \boldsymbol{\Sigma}).$$

y_{ijkm} = response variable for subject i in country m at visit j receiving treatment k
S_i = the baseline measurement of subject i, i=1,2,…
β_j = coefficient of baseline effect at visit j
τ_{jk} = the effect of treatment k at visit j, j=1,…,Z and k=1,…,Y

ϕ_m = the effect of country m, m=1,…,X
e_{ij} = the random error associated with the j^{th} visit of the i^{th} subject. Errors are independent between subjects.
Σ *= an unstructured covariance matrix.*

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided α = 0.05 or the remaining alpha (two-sided ((1- α)% confidence intervals).The treatment comparison will be the contrast between treatments at the endpoint visit.

The key secondary analysis will be performed on the FAS. Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

[…]

To assess the homogeneity of the treatment effect on the key secondary endpoint across the levels of the country stratification, the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-country-by-visit term. A descriptive p-value of treatment effect homogeneity at 28 weeks will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

The following SAS code will be used:

```
ODS OUTPUT LSMEANS=lsmeans DIFFS=diffs TESTS3=tests3;

PROC MIXED DATA=alldata cl method=reml order=formatted;
      CLASS ptno treatment country timepoint;
      MODEL ept = country treatment*timepoint baseline*timepoint
            / ddfm=kr solution;
      REPEATED timepoint / subject=ptno type=un r rcorr;
      LSMEANS timepoint*treatment / pdiff=all om cl alpha=0.05
slice=timepoint;
RUN;

ODS OUTPUT CLOSE;
```

In case the model described in the revised CTP fails to converge, the following methods will be attempted (in order) to overcome it:

1. Add the ‘singular=1e-10’ option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2. Set ‘maxiter=100’ in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.
3. Set ‘scoring=4’ to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Include the statement ‘performance nothread’ – this removes multi-threading from the calculations.

5. Provide starting values for covariance parameters using a 'parms' statement.
6. Use a simpler covariance matrix: Should none of the previous methods work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances (TOEPH). Should this also not converge, a standard Toeplitz matrix (TOEP) will be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) will be fitted.
   In this case, the final choice of covariance matrix will be documented in the CTR.

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 change in antipsychotic medication will be analysed in the same manner as the primary endpoint using the stratified Cox proportional hazards model.

Additionally, the analyses for suicidal ideation and behaviour as assessed by C-SSRS will be analysed by calculating a relative risk reduction and providing a 95% confidence interval around the RRR.

The following SAS code will be used for RRR:

```
proc freq data=patdata;
  tables trtp*avalc /chisq  RELRISK ;
  ods output
RelativeRisks=rr(where=(lowcase(STUDYTYPE)=' Cohort (Col1 Risk)')
rename=(value=compestimate lowercl=complower uppercl=compupper))
ChiSq=chi(where=(lowcase(STATISTIC)='chi-square') rename=prob=comppvalue);
run;
```

The PGI-I score, change in CGI-S and PSP will be summarized descriptively.

For the secondary endpoints summary, the worse case scenario data will be analyzed if multiple assessments are completed during the same visit window.

[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.

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 on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (3, 4).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till last drug intake + residual effect period will be assigned to the randomised treatment. 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). For details on the treatment definition, see Section 6.1.

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 will be summarized 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 (detailed in section 5.2.6.1 of the revised CTP) and for subjects with serious adverse events.

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). Planned analyses are detailed in section 7.3.4 of the revised 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. The latest measurement will be analyzed if multiple assessments are completed during the same visit window.
See section 7.3.4 of the revised CTP.

7.8.4 ECG

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.

7.8.5 Others

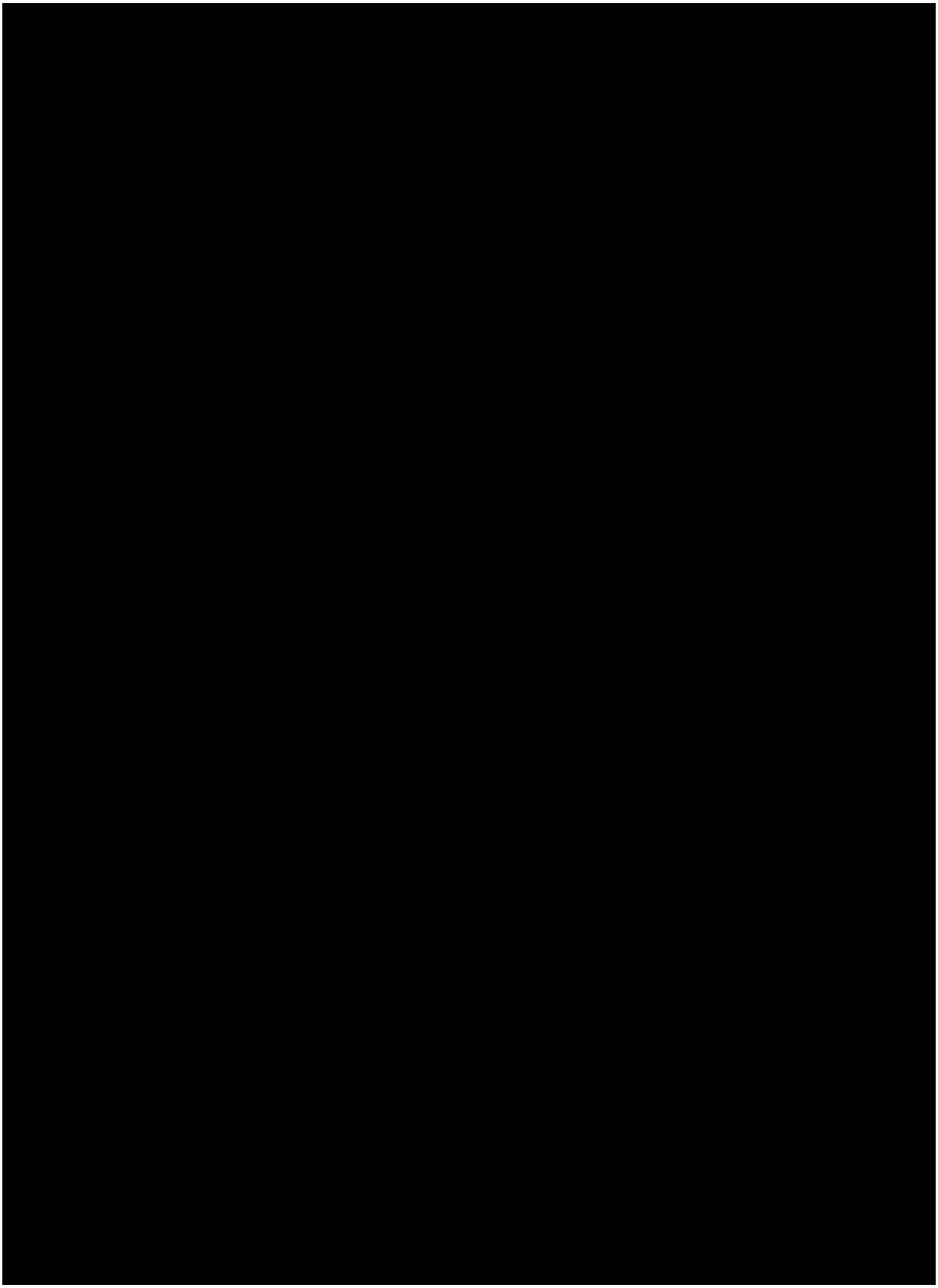
Taper/withdrawal (T/W) period

The 7-day, post 28 week treatment T/W period will not be analyzed as part of the primary analyses. Planned analyses on the T/W period will be descriptive only

Vital signs, suicidality and adverse events will be closely monitored during this period T/W. Only data obtained during the T/W period will be included in the analyses, and only of those patients randomized to the active treatment arms will be included in comparisons, which include all tapering comparing to all withdrawal as well as comparisons between the individual doses.

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.



[redacted]

9.3 ADDITIONAL ANALYSIS FOR IMPACT OF THE COVID-19 PANDEMIC ON THE TRIAL

9.3.1 Start and end of COVID-19 disruption

The trial specific start date of COVID-19 disruption is defined as the date of earliest COVID-19 related event, including COVID-19 related protocol deviation, discontinuation of a subject's treatment with study drug or trial participation due to COVID-19, or onset of a SARS-CoV-2 related AE. In this trial, start date of COVID-19 disruption is 13-Mar-2020 as it is the date of first occurrence of COVID-19 related protocol deviation.

As of now, end of the impact is not foreseeable so it will not be defined for this trial.

9.3.2 Additional analysis

Additional outputs will be included in CTR to assess the impact of COVID-19 on the trial, and it will include analyses of the following:

- Disposition
- Premature discontinuation
- COVID-19 related iPD
- Study medication exposure
- Compliance with study medication
- Adverse events

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**01-DEC-17**	[redacted]	Initial	This is the initial TSAP with necessary information for trial conduct
V2	**27-NOV-18**	[redacted]	Initial sections were only modified to change “iPV” to “iPD”; All other sections were populated	This is the final TSAP
V3	**26-Feb-2021**	[redacted]		Updated version to reflect sponsor’s decision to stop trial earlier, implement fast-track approach to expedite decision making and for preparation of the planned phase III trials. and add more analysis to assess COVID-19 impact.
V4	**17-Mar-2021**	[redacted]		Updated a typo in the date of signature