TRIAL STATISTICAL ANALYSIS PLAN

c36743592-01

BI Trial No.:	1402-0014
Title:	A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	[redacted] [redacted] Phone: +[redacted]
Date of statistical analysis plan:	01 JUL 2022 SIGNED
Version:	1

1. TABLE OF CONETNTS

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Variance
App	(Smartphone) Application
AST	Aspartate Aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
AUC	Area Under the Curve
BA	Bioavailability
BI	Boehringer Ingelheim
BPD	Borderline Personality Disorder
CA	Competent Authority
CCK-4	Cholecystokinin Tetrapeptide
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
CGI-S	Clinical Global Impression Severity Scale
ClinRO	Clinician Reported Outcome
Cmax	Maximum Concentration
Cmin	Minimum Plasma Concentration
CNS	Central Nervous System
CRA	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
C-SSRS	Columbia Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CYP	Cytochrome P450

Term	Definition / description
DBL	Database Lock
DCT	Decentralized Clinical Trial
D/C	Discontinue
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, v5
EC	Ethics Committee
EC50	Half Maximal Effective Concentration
eCDF	Empirical Cumulative Distribution Function
ECG	Electrocardiogram
[redacted]	[redacted]
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
EDMS	Electronic Document Management System
eDC	Electronic Data Capture
EGFR	Estimated Glomerular Filtration Rate
EoStudy	End of Study
eEOT	Early End of Treatment
EOT	End of Treatment
[redacted]	[redacted]
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDA	Food and Drug Administration
FUP	Follow Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GMP	Good Manufacturing Practice
HA	Health Authority
HDL	High Density Lipoprotein

Term	Definition / description
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LPLT	Last Patient Last Treatment
LS	Least Square
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at Random
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
MGH	The Massachusetts General Hospital
MMRM	Mixed Effects Model for Repeated Measurements
MQRM	Medical Quality Review Meeting
MRD	Multiple Rising Dose
nM	Nanomole
NIMH	National Institute for Mental Health
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporter Protein
OPU	Operative Unit
[redacted]	[redacted]
P-gp	P-Glycoprotein
PGI-C	Patient Global Impression of Change Scale
PGI-S	Patient Global Impression Severity Scale

Term	Definition / description
PK	Pharmacokinetics
p.o	Per Os
PoCP	Proof of Clinical Principle
PRO	Patient Reported Outcomes
PV	Pharmacovigilance
QD	Quaque Die (once a day)
[redacted]	[redacted]
QTcF	Corrected QT interval by Fredericia
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RSI	Random Slope and Intercept Model
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5
SD	Standard Deviation
[redacted]	[redacted]
SIB	Suicidal Ideation and Behavior
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
STAR*D	Sequenced-Treatment-Alternatives to Relieve Depression
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMS	Transcranial Magnetic Stimulation
TOM	Trial Oversight Meeting
TRPC	Transient Receptor Potential Channel
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UGT	UDP-Glucuronosyltransferase
ULN	Upper Level of Normal
VAS	Visual Analogue Scale

Term	Definition / description
VCT	Verified Clinical Trial
WHO	World Health Organization
WOCBP	Woman of Child Bearing Potential

3. INTRODUCTION

As per ICH E9 (11), 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 will be used for all analyses.

The main analyses of this TSAP will be conducted under the estimand concept. To quote ICH E9 R1 (11), “An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared.” So, an estimand is a way for the clinical trial protocol to address how intercurrent events will be handled. And according to ICH E9 R1 (11), intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Or in other words, intercurrent events are occurrences after randomization that involve a change in treatment regimen.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The analyses will be performed as planned. However, results will be interpreted in descriptive manner since the trial was terminated early and the specified number of patients required for the analyses was not obtained.

Due to early termination and the small sample size, the analysis for within-patient SMDDS will be challenging. Therefore, it will not be performed.

5. ENDPOINT(S)

The primary objective of this trial is to evaluate the efficacy and safety of oral BI 1358894 compared to placebo over a 6-week treatment period in MDD participants with inadequate response to antidepressants (selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI)).

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is the change from baseline at Week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There is no key secondary endpoint in the trial.

5.2.2 Secondary endpoint(s)

Montgomery-Asberg Depression Rating Scale (MADRS)

- Response defined as ≥ 50% reduction in MADRS total score from baseline at Week 6

State-Trait Anxiety Inventory (STAI)

- Change from baseline in STAI state and trait version scores at Week 6

Clinical Global Impression Severity Scale (CGI-S)

- Change from baseline in CGI-S at Week 6

Symptoms of Major Depressive Disorder Scale (SMDDS)

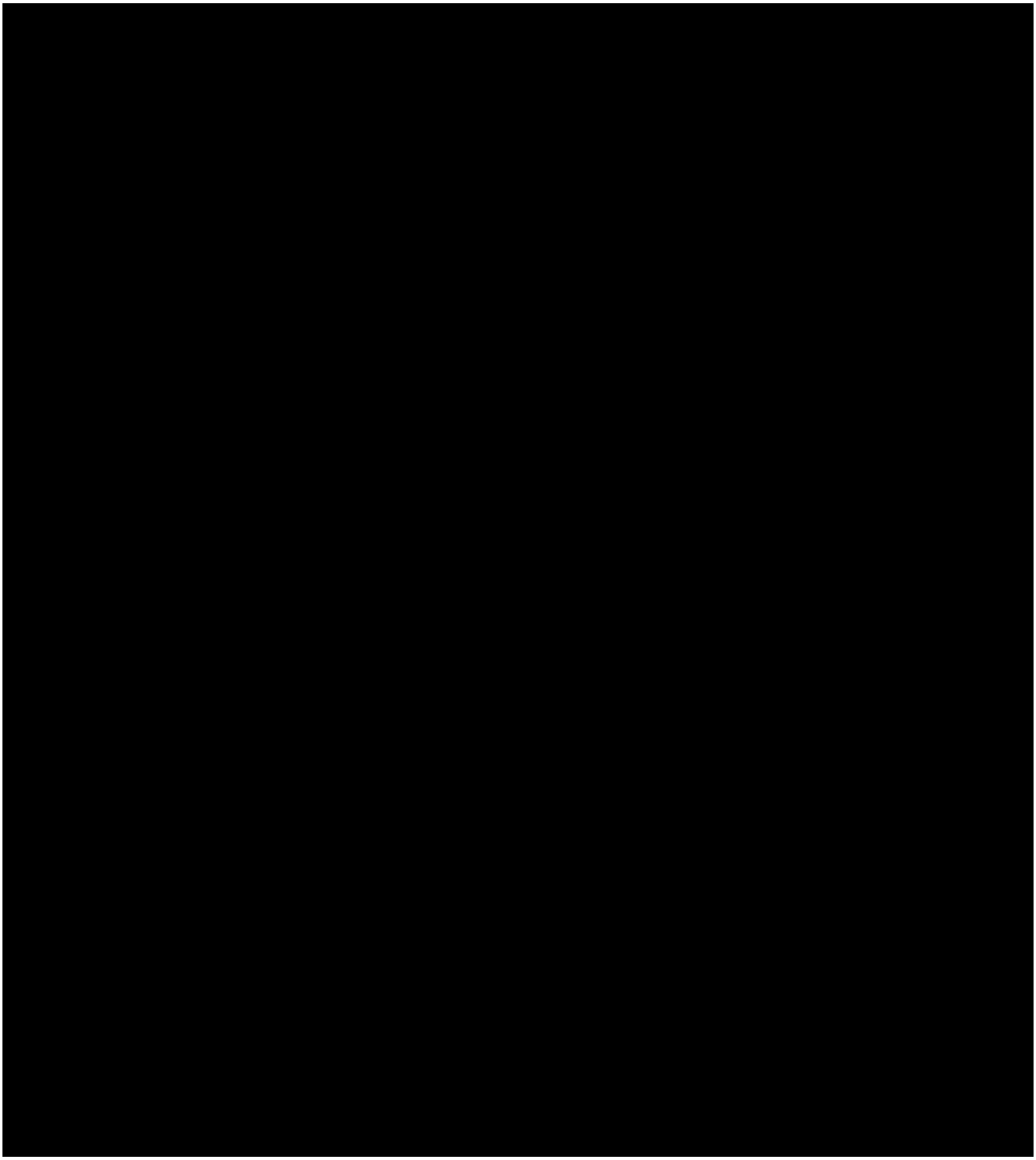
- Change from baseline in SMDDS total score at Week 6

Patient Global Impression Severity Scale (PGI-S)

- Change from baseline in PGI-S score at Week 6

Patient Global Impression of Change Scale (PGI-C)

- PGI-C score at Week 6



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Participants who meet all in- and exclusion criteria will be enrolled into the trial. These participants will be randomized to the following treatment groups for the 6-week double blind treatment period with allocation ratio of 1:1:

- 125 mg BI 1358894 once daily

- Placebo matching BI 1358894 once daily

The randomization will be handled by IRT. Details about the participants randomization, drug assignment, dose selection and administration can be found in the Section 4 of study protocol.

Participants will be analyzed according to the treatment to which they were treated. The study periods based on actual start and stop dates of study treatment administration are defined as follow:

Table 6.1: 1 Analyzing Treatment Periods*

Study analysis phase	Description	Start Date (included)	End Date (included)
Screening	Screening (prior to enrollment)	Date of informed consent	Date of first treatment administration minus 1 day
Treatment and residual effects	On-treatment period	Date of first treatment administration	Date of last treatment administration + REP
Follow-up	Off-treatment period	Date of last treatment administration + REP + 1 day	Date of last protocol visit

*The defined treatment periods are the same for all treatment groups.
REP stands for Residual Effect Period, which is defined as 28 days for safety analysis and 7 days for efficacy analysis.
Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

Participants who discontinue trial medication prior to the completion of protocol-specified end of treatment visit are still encouraged to remain in the trial if medically safe. They will ideally be observed until the end of study as if they were still receiving blinded trail treatment. Their study periods will be defined the same as the participants who complete all the study procedures. For participants who refuse to complete all further visits after early treatment discontinuation, refer the Section 6.2.3 of study protocol for visit schedule and study period definition.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled subjects). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided and will be discussed at the Report Planning Meeting (RPM) / Database Lock Meeting (DBLM) / Medical Quality Review Meeting (MQRM). Decisions regarding whether a discrepant data value can be used in analyses and / or whether it must be quired in the clinical database will be made during these meetings. Each protocol deviation must be assessed to determine if it is an important Protocol Deviation (iPD). Refer to the BI reference document “Identify and Manage Important Protocol Deviations (iPD)” (7) for definition of iPDs and their identification

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

If any iPDs are identified, they will be summarized into categories and will be captured in the RPM / DBLM / MQRM minutes via an accompanying DV domain specifications Excel spreadsheet (14). It contains all the iPD categories in this trial. If the data present any additional iPDs, the DV domain specifications will be supplemented accordingly at Trial Oversight Meetings (TOMs) or RPMs or through team review of the manual PD log.

The decision whether a subject will be excluded from the analyses will be made at the final RPM prior to Database Lock (DBL). The documentation of the iPD categories and how to handle iPDs in the analyses are listed in the DV domain specifications and are stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). IPDs leading to exclusion from analysis sets are indicated by the DV domain specifications. IPDs will be summarized and listed for the treated set. IPDs from patients in the screened set will be listed but not be summarized.

6.3 SUBJECT SETS ANALYSED

The following analysis sets have been defined for this trial:

- Screened Set (SS): This subject set includes all subjects who signed informed consent and were screened for the trial with at least one screening procedure done at Visit 1.

- Treated Set (TS): This set includes all subjects in SS which are randomized and have received at least one administration of study drug. The TS will be the main analysis set for the evaluation of safety. Subjects are analysed according to the actual received treatment.

- Full Analysis Set (FAS): This set includes all subjects in TS that have a baseline and at least one evaluable post-baseline on-treatment measurement for the primary endpoint. This is the main analysis set for the evaluation of efficacy data.

- Per Protocol Set (PPS): This is a subset of FAS, for subjects with adequate protocol compliance. It consists of all subjects in FAS without any important protocol deviations that impact efficacy assessments.

- Adherence Set (AS): This set includes all subjects in FAS that are at least 60% overall [redacted] adherent to study medication. See Section 7.3.2 for further information.

[redacted]

The safety analyses will be conducted on the TS. Data collected from patients in SS will be included in the disposition table and listings. The SS will not be included in any other summaries or inferential statistics.

Table 6.3: 1 Subject Sets Analyzed

	Subject Set				
Class of Endpoints	SS	TS	FAS	[redacted]	AS
Primary endpoints			X		
Secondary endpoints			X		
Further endpoints			X		
Disposition	X				
iPD		X			
Demographics, baseline characteristics		X			
Exposure, adherence		X	X		
Safety		X			
[redacted]				[redacted]	
Primary endpoint adjusted for overall study [redacted] adherence					X

If the percentage of subjects in FAS with iPD that lead to the exclusion from the PPS is > 10%, then sensitivity analysis of the primary and secondary efficacy endpoints using PPS may be conducted.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study is a decentralized clinical trial.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing data are not explicitly imputed and remain missing for all main analyses. Most efficacy endpoints are continuous and will be analysed by a restricted maximum likelihood (REML)-based mixed model known as Mixed Effect Model with Repeated Measurements

(MMRM). This model assumes data are missing at random (MAR) and can handle the missingness implicitly. For the calculation of summary statistics and the binary endpoint MADRS response and remission, missing data will not be imputed.

Missing or incomplete AE dates will be imputed according to "Handling of missing and incomplete AE dates" (12). [redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline refers to the last non-missing value recorded prior to first dose of trial medication and is typically recorded at Visit 2. If data from Visit 2 are missing, the last value recorded prior to Visit 2 will be considered as the baseline value. If a subject is randomized at Visit 2 but does not get trial medication until further visit (e.g., Visit 4), then his / her baseline is the latest assessment performed at Visit 2.

However, for laboratory safety measurements, the last value prior to the first drug administration will be considered as the baseline value.

The visit schedule with accompanying details can be found in Flow Chart in the study protocol. The midpoint between two on-treatment visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit.

Planned and actual visit days are included in the analysis data sets and are calculated relative to the beginning of study as indicated in Table 6.7: 1.

Repeated and unscheduled efficacy measurements will be assigned to the nominal visits according to the time windows described in Table 6.7: 1.

For efficacy measurements, only one observation per time window will be selected for statistical analysis – the first one in the corresponding time window. If there are two observations having the same difference in days to the planned visit day, or if there are two observations on the same day, the first value will be selected. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window. Non-imputed (observed) data will be utilized to assign efficacy observations to nominal visits which are defined based on time window.

For safety measurements, collected visit numbers will be used. For repeated and unscheduled safety measurements for the same visit on treatment, the worst of these will be selected for analysis. In the case where there is no standard reference direction for the safety parameter, the average of all values for the same visit will be used for analysis.

Repeated and unscheduled efficacy, safety, and biomarker measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Table 6.7: 1 Planned and actual visit days

Visit	Relative to study start	
	Planned visit day	Actual visit day
2	1	Day 1 – Day 5
3	8	Day 6 – Day 12
4	15	Day 13 – Day 19
5	22	Day 20 – Day 26
6	29	Day 27 – Day 33
7	36	Day 34 – Day 40
8/EoT	43	Day 41 – Day 47
eEoT	N/A	Date of last administration of trial medication + 7 days (for early discontinued subjects)
EoStudy	EoT / eEoT + 28 days + 4 days	(EoT + 30 days) to (EoT + 32 days)

Days are counted relative to the day of first trial medication administration, which is defined as Day 1.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Standards for Reporting of Clinical Trials and Project Summaries” (13).

The individual values of all subjects will be listed, sorted by dose group, subject number and visit. AE listings will be sorted by assigned treatment. The listings will be contained in Appendix of the CTR.

For continuous data summarized in End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard Deviation (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. In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places as the raw data.

For categorical data, tabulations of frequencies 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 percentages should be rounded to one decimal place, 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.

Disposition of patient population participating in the trial will be analyzed by treatment and presented by the categories defined in the standard CRF groups. The results will be reported in form of frequency tables in CTR to show the distribution of trial population.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only 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 summarized by treatment group, and a "total" column will be included in the summary table. The results will be presented by the categories defined in the standard CRF groups.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diagnoses (concomitant diseases) will be coded using the latest version of MedDRA. A summary of concomitant diagnoses will be provided by treatment group, System Organ Class (SOC), and Preferred Term (PT). Frequency tables will be utilized to summarize the concomitant diagnoses recorded at baseline and throughout the study.

A medication / therapy is considered as concomitant to treatment if it (1) is ongoing at the start of randomized trial treatment or (2) starts within the on-treatment period. A medication / therapy is considered as a prior medication / therapy if its end date is at any time prior to the start of randomized trial treatment.

Concomitant therapies (CTs) are coded according to WHO Drug Dictionary. CT will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorize 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.

Non-drug concomitant therapies are handled similar to concomitant therapies and are classified into general non-drug therapies and psychotherapies.

Summary of certain concomitant medications will be presented in addition to the forementioned analyses, which include SSRI, SNRI, Benzodiazepines, and Non-Benzodiazepines hypnotics.

7.3 TREATMENT COMPLIANCE

7.3.1 Treatment compliance

Only descriptive statistics are planned for this section of the report. Treatment compliance will be summarized on the TS and will be reported basing on the calculation defined in CTP section 4.3 and shown below.

$$Total\ compliance\ (\%) = \frac{Number\ of\ tablets\ actually\ taken}{Number\ of\ tablets\ which\ should\ have\ been\ taken\ as\ directed\ by\ the\ investigator} * 100\%$$

According to the study protocol, mobile nurses will collect all unused remaining trial medications at home visits (Week 0, Week 2, Week 4, and Week 6 / EOT / eEOT) and report treatment compliance. The overall compliance will be calculated basing on the compliance rates from all the visits. For patients who discontinued the study treatment prematurely, only the visits on or before premature discontinuation will be used for the calculation of overall compliance.

If at a particular visit a participant did not return the trial medication kits, and if there is no other reasonable evidence to suggest that the participant did take trial medication as specified in the protocol, then the compliance at that visit is zero.

Summary statistics of overall compliance rates as well as rates at each home visit (Week 0, Week 2, Week 4, and Week 6 / EOT / eEOT) will be presented for patients in the treated set. In addition, the percentages with compliance in the following categories will be reported for overall compliance and home visits:

- < 80% of planned
- 80 - 100% of planned
- > 100% of planned
- Missing

7.3.2 Treatment adherence

The Overall [redacted] Adherence, abbreviated as OAA, is defined as the adjusted percentage of pills taken by an individual, i.e.,

$$OAA = \frac{Sum\ of\ all\ tablet\ adherence - Number\ of\ red,\ orange, and\ yellow\ alerts}{3 * 42} * 100\%$$

- 42 = Number of days on treatment
- 3 = Number of tablets per dose

Tablet adherence is the successful administration of a pill as captured by [redacted] video. *Red alerts* are tablet administrations for which the [redacted] video captures the dosing process but includes strong visual proof of deceptive behaviors, non-adherence, and / or overdose of study drug. Examples include removing study drug from the mouth, 'cheeking', spitting out the drug, or using non-IP to dose. Also, in cases for which more than one pill was ingested simultaneously, a red alert is flagged. For *orange alerts*, the video captures the dosing

process, but contains suggested visual proof of potentially deceptive behaviors, potential non-adherence, or shows potential overdose of study drug. And lastly, for *yellow alerts* the video is missing visual information necessary to confirm adherence.

Note that tablet adherence is the administration of a tablet by visually confirmed via [redacted] app.

The adjustment in OAA definition is made to exclude pills that are flagged as red, orange, and yellow alerts by the app. For subjects that discontinue treatment early, 42, which is the number of days from randomization to the planned treatment end, will be replaced by the total number of days from randomization to the respective date of early treatment discontinuation.

Like the treatment compliance, summary statistics of OAA will be displayed in tables by different treatment groups. Additionally, the percentages with OAA in different levels (<80%, 80-100%, >100%, missing) will be reported in the table.

As defined in Section 6.3, the Adherent Set (AS) consists of all subjects in FAS that achieved an OOA of at least 60%. Within these subjects, flags (or classifications) will be built to denote increasing thresholds of adherence. Hence, it may be of interest to evaluate the effect of varying levels (≥60%, ≥70%, ≥80%, ≥90%, 100%) of overall adherence on efficacy.

An evaluation of the primary endpoint to varying levels of adherence to treatment may be of interest. If so, the AS will be used to re-evaluate the primary endpoint, and of course, using the same MMRM methods.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint in this study is change from baseline in MADRS score at Week 6. Due to the premature termination of the trial, the specified number of patients required for the analyses was not obtained. Therefore, the results will be interpreted in a descriptive manner in the CTR.

Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication and is typically recorded at Visit 2. If data from Visit 2 are missing, the last value recorded prior to Visit 2 will be considered as the baseline value. The investigator reported MADRS total scores will be used for the primary analysis.

The primary estimand of interest is the treatment effect assuming all subjects remained adherent to the assigned trial medication and the trial protocol using a hypothetical approach, i.e., trial drug is taken as directed. The primary analysis of the primary endpoint will include all data collected while on treatment, which is defined as the time from the date of the first dose of trial medication until the last date of last dose of trial medication plus 7 days (3 times the estimated elimination half-life). Any data collected after a participant discontinues trial drug, regardless of reason, will be censored and not included in the primary analysis.

The primary analyses will be the restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) will be applied to compare the change from baseline of MADRS score at Week 6.

The analysis will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, as well as the continuous fixed covariates of baseline MADRS score and baseline by visit interactions.

Participants will be considered as random effects. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within patient measurements error. Additional covariates identified prior to database lock may be included in the MMRM model as applicable.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be performed based on least-square (LS) means using a two-sided $\alpha = 0.1$.

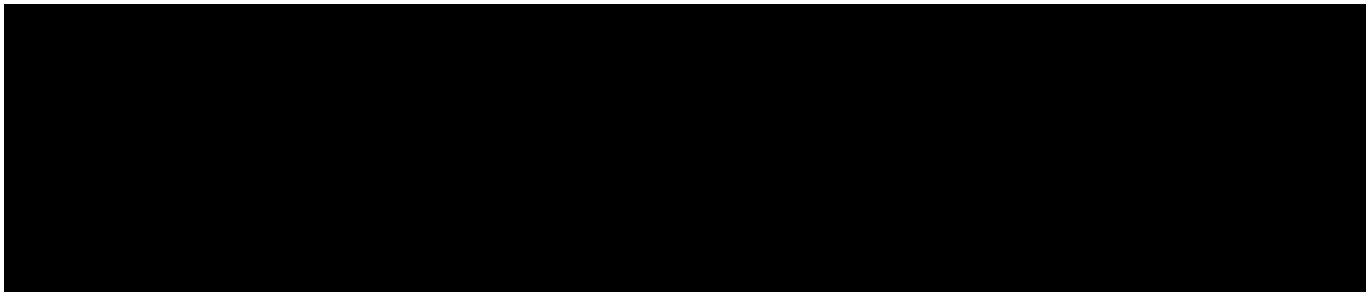
Analyses will be implemented using SAS (version 9.4) PROC MIXED. The following SAS code may be used with some modifications to calculate the MMRM

```
PROC MIXED DATA=indata cl method=reml;
        CLASS visit trt subject;
        MODEL madrs_change = trt visit visit*trt base base*visit / ddfm = kr s CL;
        REPEATED visit/subject = subject type = un r rcorr;
        LSMEANS visit*trt / pdiff=all om cl alpha = 0.10 slice = visit;
RUN;
```

Results of the MMRM will presented in tables and displayed graphically.

The primary treatment comparisons will be between BI1358894 and placebo with respect to the mean change from baseline in the MADRS total score at week 6. Adjust mean change from baseline as well as treatment contrasts will be presented together with the 90% confidence intervals. The treatment contrast at Week 6 is the primary treatment comparison between our study drug and placebo.

In addition to the MADRS total score, the scores of the individual MADRS items at baseline, Week 1, Week 2, Week 4, and Week 6 will be summarized by treatment groups. The changes from baseline in these individual items at the forementioned time points will also be summarized similarly. The results will be presented in tables.



[redacted]

[redacted]

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)

Analyses for different secondary endpoints are listed below and will be performed on the FAS. Like the primary analysis, there will be limited interpretation for the analysis results included in the CTR because of the premature termination of the trial.

The definition of baseline measurements for the secondary endpoints is the same as that for the primary endpoint. Baseline score is the last non-missing value recorded prior to first dose of trial medication and is typically observed at Visit 2. If data from Visit 2 are missing, the last value recorded prior to Visit 2 will be considered as the baseline value.

For endpoints that will be analyzed with MMRM model, the SAS implementation and display plan are similar to the primary analysis (refer to Section 7.4.1) and would not be included in the following description. Implementation for other statistical analyses will still be included.

MADRS Response

Response over the 6-week treatment period will be assessed using the MADRS total score. Participants with ≥ 50 % reduction in MADRS total scores from baseline to Week 6 are considered as responders. Participants experiencing < 50% reduction in MADRS total score are considered as non-responders. Percent reduction from baseline at a specific post-baseline visit (Visit X) is calculated as:

$$\%\,reduction = \frac{(MADRS\ total\ score\ at\ baseline - MADRS\ total\ score\ at\ visit\ X)}{MADRS\ total\ score\ at\ baseline} * 100$$

The proportions of participants achieving response at Week 6 will be summarized as the frequency and percentage of participants in each treatment arm. In addition, if sufficient number of responders is observed, a logistic regression model adjusted for treatment (BI 1358894 or placebo) and baseline MADRS severity will be used to calculate the odds ratio for response between each of the BI treatment arms and placebo and corresponding 90 % confidence intervals. The likelihood ratio test will be used to test for differences between each active treatment arm and placebo.

A logistic regression model adjusted for treatment will be used to calculate the odds ratio for response between the treatment and placebo arms if enough responders are observed. The logistic regression model would include all the covariates in the MMRM model from primary analysis as well as additional variables identified prior to database lock.

The SAS code for the logistic regression model is as follow:

```
PROC LOGISITC DATA=indata;
        CLASS trt   / param=GLM; /* include (ref="placebo") for trt */
        MODEL resp = trt base / link=LOGIT covb;
        LSMEAN trt / cl;
RUN;
```

The above SAS code may be used with some modifications, if necessary. Estimate including point estimates for the model parameters, adjusted odds ratios, and 90% confidence intervals will be summarized and presented in tables.

STAI

Change from baseline to Week 6 in STAI state and trait scores will be analyzed using an MMRM model similar to the model described for the primary endpoint analysis. A comparison between study medication and placebo will also be performed.

CGI-S

CGI-S will be summarized by treatment arm as both a continuous variable and an ordinal variable. Mean CGI-S change from baseline to Week 6 and its standard deviation will be presented. In addition, the frequency and proportion of participants reporting each response category at baseline and at Week 6 will be displayed. The results will be included in a single table which includes both numerical summary statistics and frequencies.

To compare change in depression severity as assessed by the CGI-S between the BI 1358894 treatment arm and placebo, an MMRM model similar to the model described for the primary efficacy analysis will be used. CGI-S change from baseline at Week 6 will be the model response variable, and covariates will be those used in the primary analysis. Same model assumptions will be used here.

PGI-S

The secondary endpoint of change from baseline in PGI-S at Week 6 will be analyzed in the same way as CGI-S.

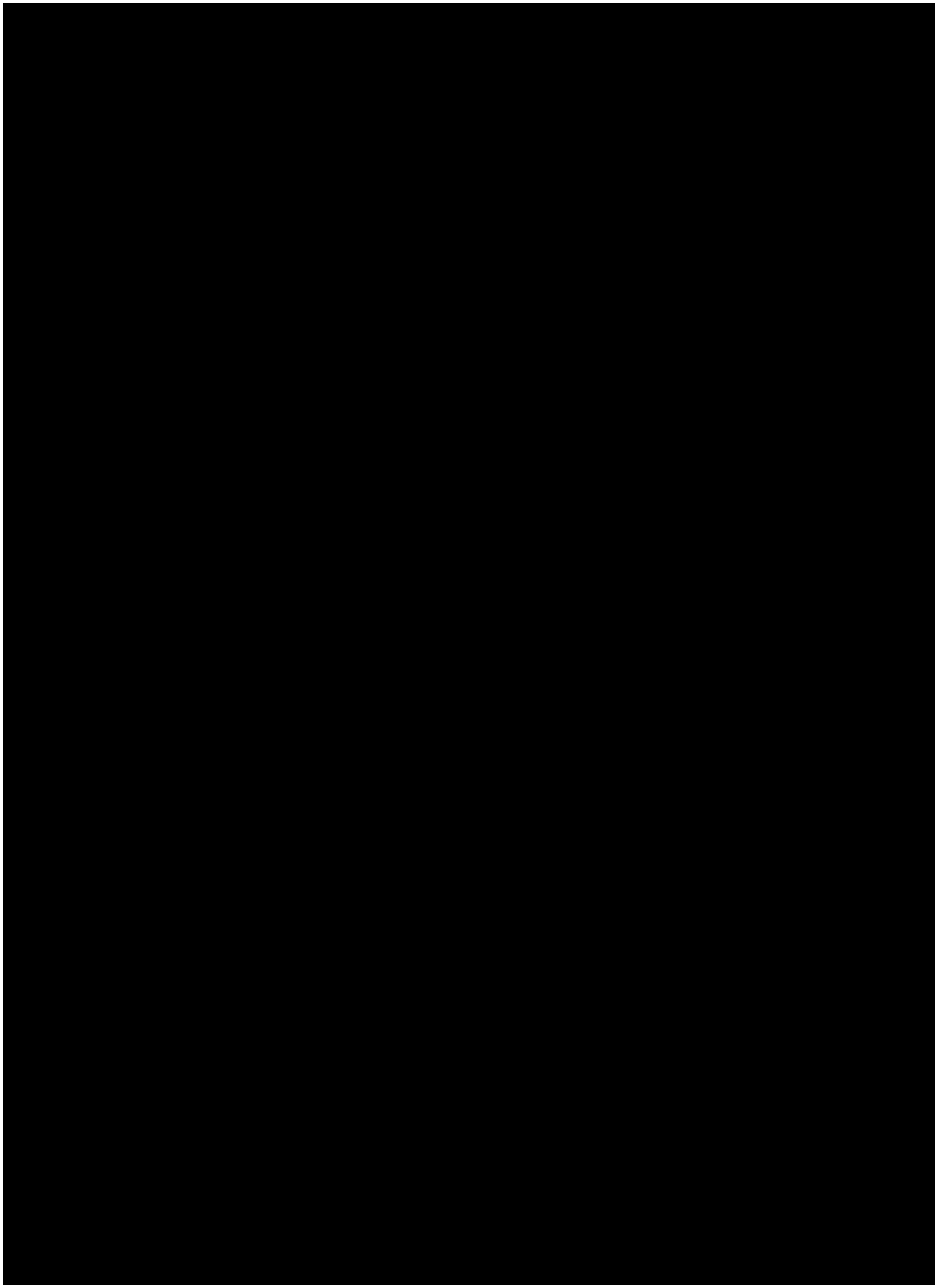
PGI-C

PGI-C at Week 6 will be analyzed as both a continuous variable and an ordinal variable. A single summary table will be presented and includes: (1) mean PGI-C score and SD at the end of treatment; and (2) frequency and proportion of patients reporting each category of response defined in the CRF.

SMDDS

The analysis for SMDDS includes both a descriptive part and a MMRM-based inferential part. The descriptive analysis includes: (1) summary of SMDDS total score change from baseline at Week 6 (as a continuous variable); and (2) frequency and proportion of patients reporting each category of response in every individual domain. Responses to all 16 domains at baseline and Week 6 will be summarized in the tables and aggregated by visit.

A MMRM model will also be used to compare change in SMDDS total score from baseline to Week 6 between treatment and placebo arms. The model response variable will be SMDDS change from baseline at Week 6, and covariates are those used in the primary analysis. Same model assumptions will be used in this analysis.



7.7 EXTENT OF EXPOSURE

Extent of exposure will be calculated as the difference between last intake of study drug and the first administration of the study drug plus one day. Descriptive statistics will be provided for number of days of exposure for each treatment arm. Also, cumulative exposure of number and percentage (N, %) of subjects will also be displayed as

- < 1 week
- 1 to < 2 week
- 2 to <3 weeks
- 3 to <4 weeks
- 4 to <6 weeks
- 6 to <8 weeks
- 8 to <10 weeks
- 10 to <12 weeks
- 12 weeks
- Missing

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. Analysis will be performed as defined in Section 7.2.5 of the CTP.

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. AEs will be coded based on the latest version of Medical Dictionary for Drug Regulatory Activities (MedDRA) at the specified in the database lock process.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake and the day of last drug intake + residual effect period will be assigned to the "on-treatment". All AEs occurring before first drug intake will be assigned to "screening", and all AEs occurring after last drug intake + residual effect period will be assigned to "follow-up" (for listings only). For details on the treatment period definition, see Section 6.1.

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF will be collapsed into one AE event if all the following apply:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, and outcome)
- The occurrences were time-overlapped or time-adjacent (time-adjacency of two 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 (12) and (16).

According to ICH E3 (10), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g., discontinuation or dose reduced or interrupted).

AE summaries

An overall summary of adverse events will be presented. The frequency of subjects with AEs will be summarized by treatment, primary system organ class and PT (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for subjects with:

- Serious AEs
- AEs leading to treatment discontinuation
- AEs of at least moderate severity
- Drug related AEs.
- AE of special interest (AESI)
- AE leading to death
- Other significant AEs (according to ICH E3)

The system organ classes (SOC) will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g., SOC 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 (15). Baseline for safety laboratory parameters will be the last available measurement before the start of randomized study drug. Laboratory measurements taken up to the residual effect period of 28 days after the last administration of randomized study drug 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. Laboratory values of particular interest include:

- Assessments of CRP and erythrocyte sedimentation rate
- Lipid panel (triglyceride, cholesterol, HDL-C, LDL-C)
- Central hematology laboratory values including RBC, Hct, Hb levels, Reticulocytes, WBC and differential
- Hormone panel (TSH, LH, FSH, Testosterone)

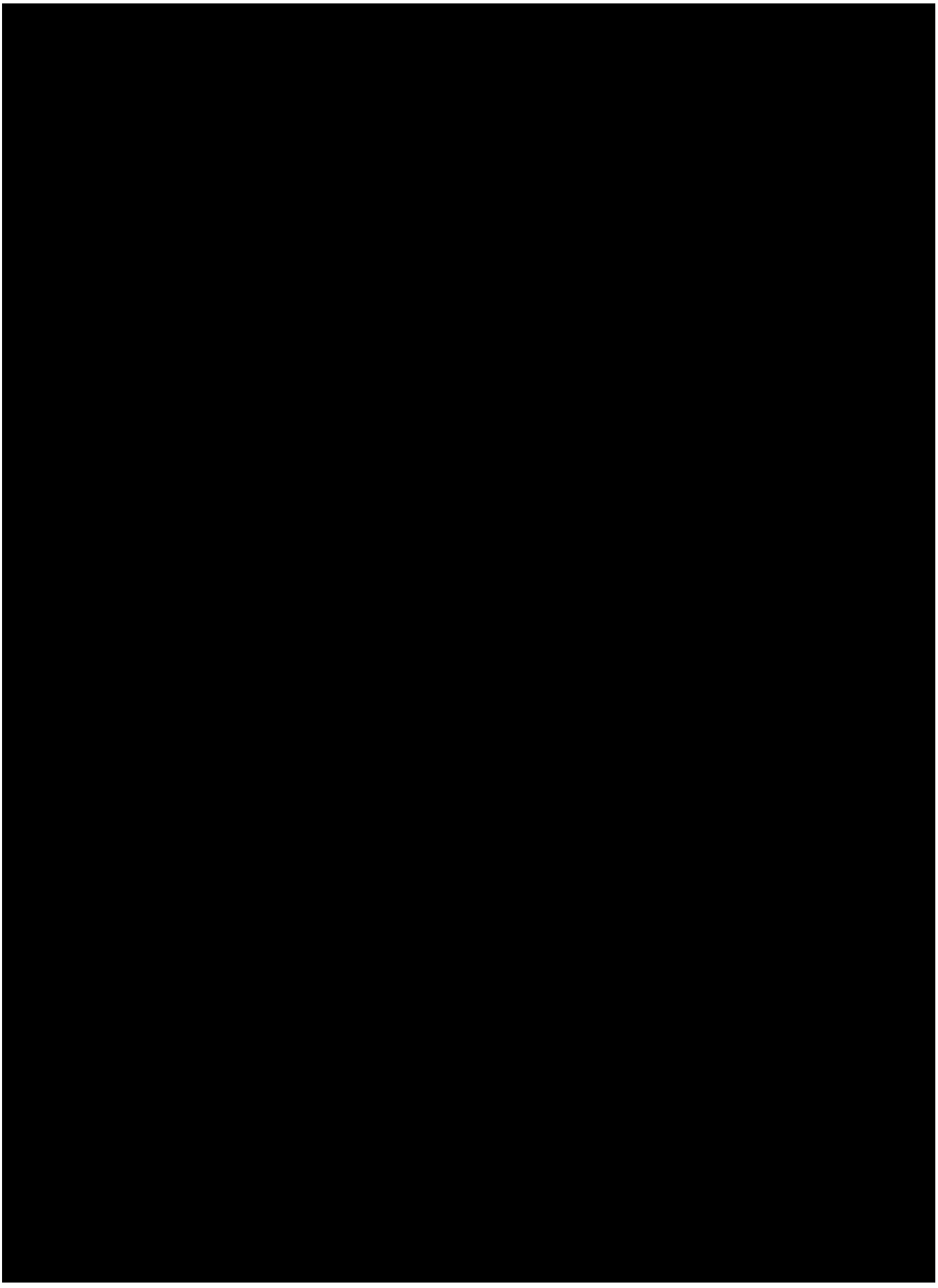
7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. In case of multiple measurements including unscheduled visits, the value for the vital sign measurement will be average of all measurements for the corresponding visit. Vital signs of particular interest include mean Systolic Blood Pressure (SBP), Diastolic BP, pulse rate over time, and weight change over time.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. 12-lead ECG-findings before first intake of trial drug will be considered as baseline condition or as AEs (during the trial) if judged clinically relevant by the investigator and will be analyzed as such. No separate listing or analysis of ECG data will be prepared.

[redacted]



8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study / Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

9. REFERENCE

1.	*001-MCS-50-415_RD-02:* “Project Analysis Dataset (PADS) Template (template) “, current version, Group “Biostatistics & Data Sciences”, IDEA for CON.
2.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

3.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
4.	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
5.	*001-MCS-40-106_RD-03:* "Clinical Trial Protocol general template for Phase I-IV", current version, Group "Clinical Operations", IDEA for CON.
6.	*001-MCS-80-60*6: "Management of Non-Compliances", current version, Group "Quality Medicine", IDEA for CON.
7.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
8.	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version, Group "Clinical Operations", IDEA for CON.
9.	REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, European Commission webpage.
10.	*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.
11.	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9,Note For Guidance on Statistical Principles for Clinical Trials, current version.
12.	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version, Group "Med Biostatistics & Data Sciences", Vault Quality
13.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries" current version, Group "Med Biostatistics & Data Sciences", Vault Quality
14.	*BI-KMED-COPS-TMP-0001:* "Important Protocol Deviation (iPD) log", current version; IDEA for CON
15.	*BI-KMED-BDS-HTG-0042:* "How to Guide: Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
16.	*BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**01-JUL-22**	[redacted]	None	Creation of the TSAP

APPROVAL / SIGNATURE PAGE

Document Number: c36743592 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: A phase II 6-week, randomized, double-blinded, placebo-controlled, parallel group decentralised clinical trial to evaluate efficacy and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	01 Jul 2022 16:30 CEST
Approval-Project Statistician		01 Jul 2022 16:38 CEST
Approval-Clinical Program Leaders		01 Jul 2022 16:58 CEST
Approval-Medical Writer		04 Jul 2022 03:38 CEST
Approval-Clinical Trial Leader		04 Jul 2022 08:28 CEST
Author-Trial Clinical Pharmacokineticist		04 Jul 2022 08:35 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**