TRIAL STATISTICAL ANALYSIS PLAN

c40434427-01

BI Trial No.:	1289-0057
Title:	A randomized, placebo controlled, double-blind, double-dummy three-way cross over trial to investigate the effect of BI 409306, BI 425809 and lamotrigine on ketamine-induced cognitive deficits in healthy male subjects Including Protocol Amendment 1 [c26985010-02] Including Protocol Amendment 2 [c26985010-03]
Investigational Product:	BI 409306, BI 425809
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	14-Oct-2022 SIGNED
Version:	1

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	[redacted]
BI	Boehringer Ingelheim
BP	Blood pressure
CADSS	Clinician Administered Dissociative States Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
[redacted]	[redacted]
[redacted]	[redacted]
COVID	Coronavirus disease
C-SSRS	Columbia Suicidal Severity Rating scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
[redacted]	[redacted]
FU	Follow-up
[redacted]	[redacted]
gCV	Geometric coefficient of variation

Term	Definition / description
gMean	Geometric mean
ICH	International Conference On Harmonisation
IPD	Important protocol deviations
IQRMP	Integrated Quality and Risk Management Plan
MedDRA	Medical Dictionary For Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PAL	Paired Associates Learning
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic set
[redacted]	[redacted]
PR	Pulse rate
RAGe	Report appendix generator
REP	Residual effect period
RPM	Report Planning Meeting
RVP	Rapid Visual Information Processing
SAE	Serious adverse event
SaO_2	Oxygen saturation
SD	Standard Deviation
SFST	Standardized Field Sobriety Test
SOC	System Organ Class

Term	Definition / description
SWM	Spatial Working Memory
[redacted]	[redacted]
[redacted]	[redacted]
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range
VA	Visual acuity
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9 (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the revised CTP, 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 CTP and its 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 revised CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

Study data as collected in the eCRF will be stored in a trial database within the RAVE EDC system. All study data also including external data will then be uploaded to the CDR data warehouse.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3, [redacted].

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In addition to the CTP-described analysis summary statistics as well as profile plots will be provided for the primary and secondary endpoint.

All other analyses described in this TSAP are in accordance with the statistical methods described in the revised CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoint of BI 409306, BI 425809, lamotrigine and placebo is as named in Section 2.1.2 and defined in Section 5.4.1.1 of the CTP:

- *PAL Total Errors Adjusted (PALTEA28) on ketamine*

5.2 SECONDARY ENDPOINT

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 Secondary endpoint

The secondary endpoints of BI 409306, BI 425809, lamotrigine and placebo are as named in Section 2.1.3 and defined in Sections 5.4.1.2 and 5.4.1.3 of the CTP:

- *SWM Between Errors (SWMBE468) on ketamine*
- *RVP A' Prime (RVPA) on ketamine*

[redacted]

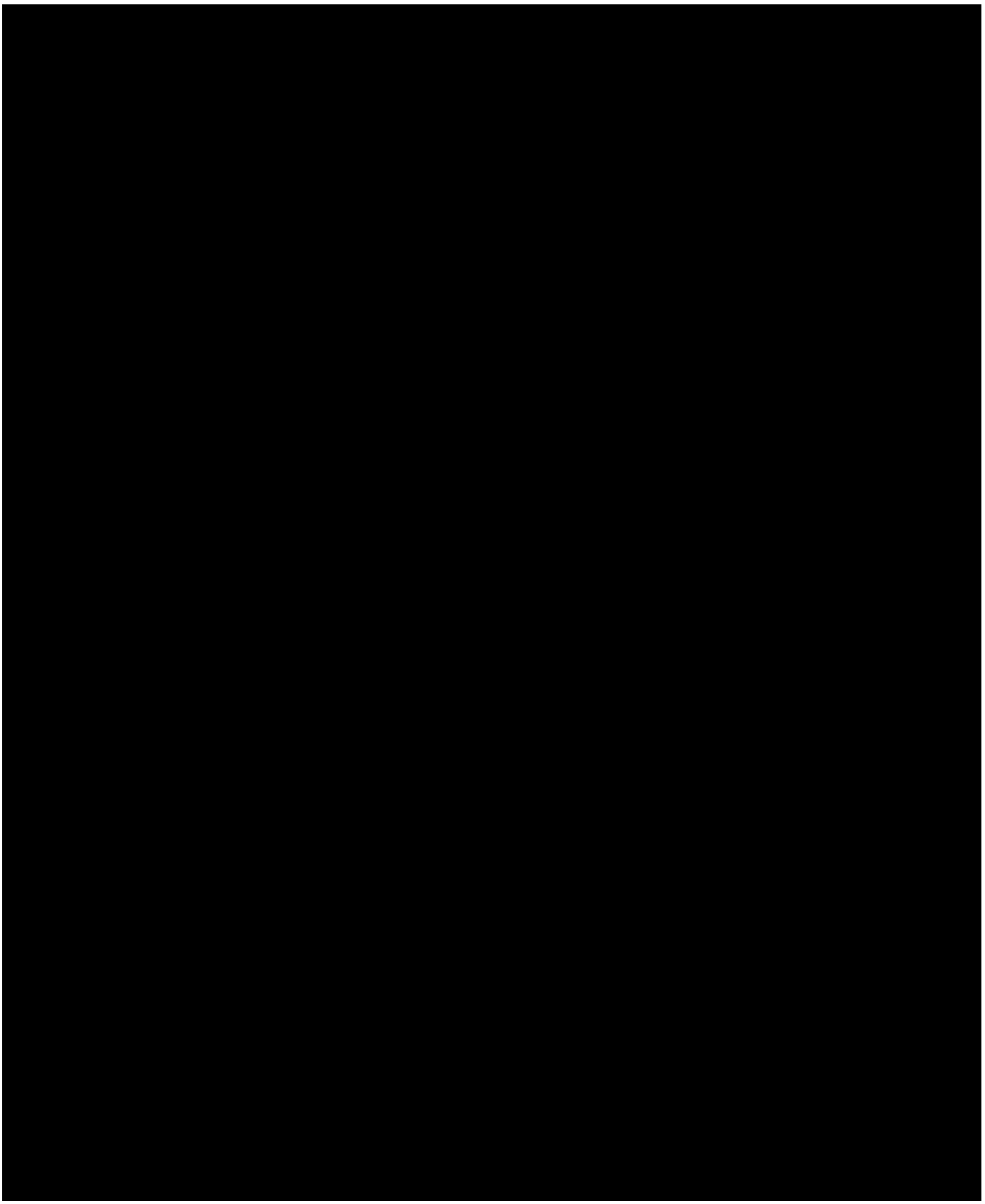
5.3.1 Safety parameters

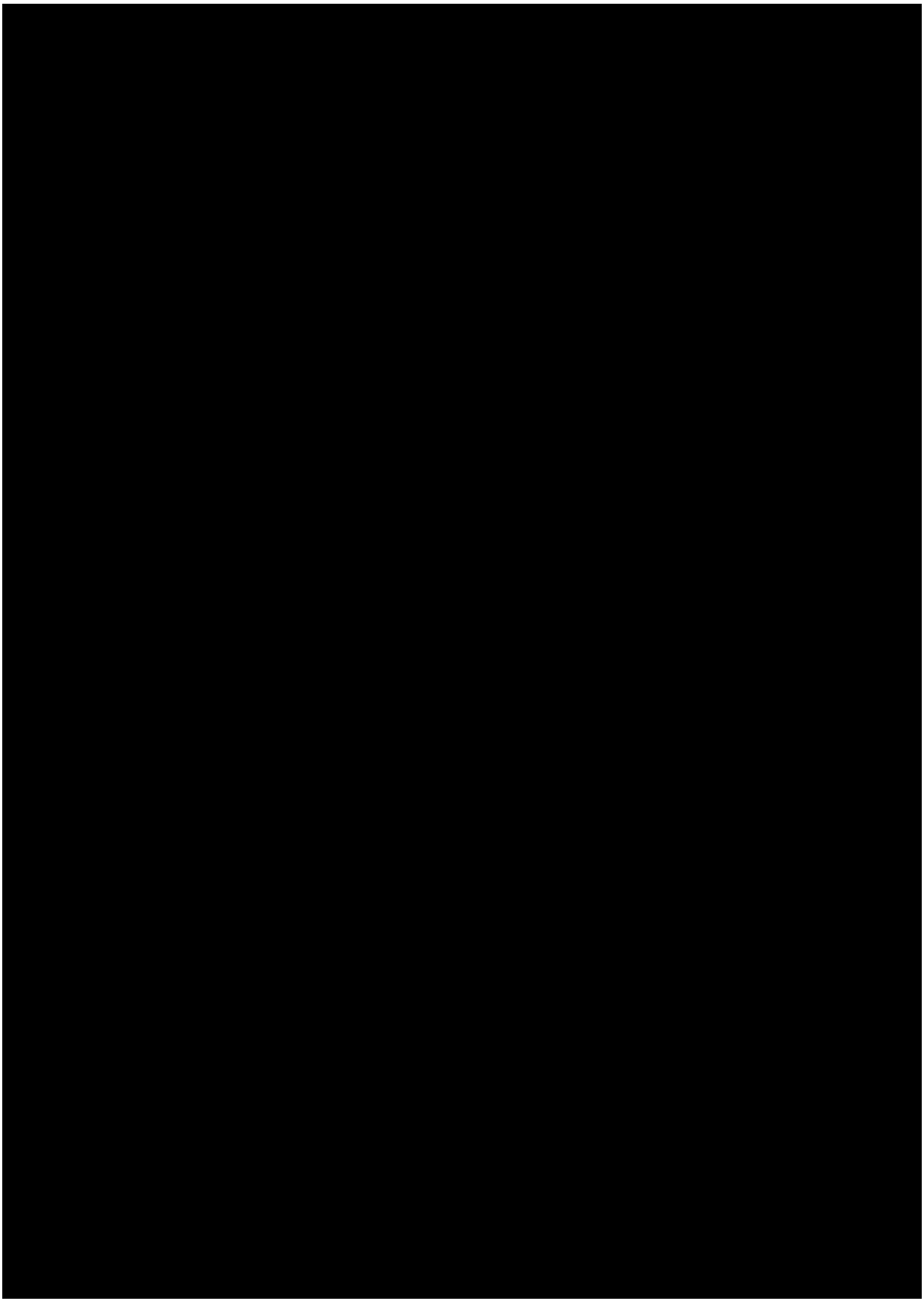
Safety and tolerability of BI 409306, BI 425809, lamotrigine, placebo and ketamine will be assessed based on further safety parameters named in Section 2.2.2.3 and defined in Section 5.2 of the CTP:

- *Adverse events (including clinically relevant findings from the physical examination incl. targeted examination, visual acuity test, vital signs; as well as clinically relevant abnormal results in C-SSRS and safety tests (DSST, MOAA/S, CADSS and SFST))*
- *Safety laboratory tests (only abnormal findings will be reported as AEs)*[1]
- *12-lead ECG and continuous ECG monitoring (only abnormal findings will be reported as AEs)*
- *Vital signs (BP, PR, SaO_2)*[2]
- *Suicidality assessment (C-SSRS)*

[1] According to the CTP Section 5.2.3 safety laboratory test results will only be kept in the source data but not collected in the CRF. Clinically relevant abnormal findings will be reported as AEs.

[2] According to the CTP Section 5.2.2 SaO_2 will only be kept in the source data but not collected in the CRF. Clinically relevant abnormal findings will be reported as AEs.





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

Each subject is planned to be treated in three subsequent treatment periods with one single dose at Day 1 in each treatment period:

- Test treatment 1 (T1):
  300 mg of Lamotrigine as tablet
- Test treatment 2 (T2):
  [redacted] of BI 409306 as film-coated tablet
- Test treatment 3 (T3):
  [redacted] of BI 425809 as film-coated tablet
- Reference treatment (R):
  Placebo as film-coated tablet

Each subject is planned to be randomly allocated to one of 18 3-period sequences including placebo in one of the periods and 2 out of 3 active treatments in the remaining periods:

T1–T2–R, T1–R–T2, T1–T3–R, T1–R–T3, T2–T1–R, T2–R–T1, T2–T3–R, T2–R–T3, T3–R–T1, T3–T1–R, T3–T2–R, T3–R–T2, R–T1–T2, R–T2–T1, R–T1–T3, R–T3–T1, R–T2–T3, R–T3–T2.

Each treatment period is separated by a washout period of at least 11 days.

[redacted]**:** *The Residual Effect Period (REP)* [redacted]*, for lamotrigine 10 days, and for ketamine 24 hours. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.*

For statistical analyses of AEs and vital signs, the following separate analysis phases will be defined for each subject:

Table 6.1: 1 Analysis phases for statistical analysis of AEs and actual treatment for analysis of vital signs

Study analysis phase	Label of analysing treatment	Label of actual treatment	Start	End
Screening	**Screening**	**Screening**	Date of informed consent	Start date/time of screening ketamine infusion
		Screening+Ketamine	Start date/time of screening ketamine infusion	End date/time of screening ketamine infusion + 24 h
		Screening	End date/time of screening ketamine infusion + 24 h	Start date/time of first administration of study treatment (Planned time: 00:00h) in the respective treatment period
On treatment [1, 2, 3]	**Placebo, [redacted] BI 409306, [redacted] BI 425809** or **300mg Lamotrigine,** respectively	**Placebo, [redacted] BI 409306, [redacted] BI 425809** or **300mg Lamotrigine,** respectively	Start date/time of administration of the first study treatment (Planned time: 00:00h) in the respective treatment period	Start date/time of on-treatment ketamine infusion or 12:00 a.m. on day after subject's trial completion date, whatever comes first
		Placebo+Ketamine, [redacted] BI 409306+Ketamine, [redacted] BI 425809+Ketamine or **300mg Lamotrigine+Ketamine,** respectively	Start date/time of on-treatment ketamine infusion	End date/time of on-treatment ketamine infusion + 24 h or 12:00 a.m. on day after subject's trial completion date, whatever comes first
		Placebo, [redacted] BI 409306, [redacted] BI 425809 or **300mg Lamotrigine,** respectively	End date/time of on-treatment ketamine infusion + 24 h	Start date/time of administration of the second study treatment (Planned time: 03:00h) in the respective treatment period + 11 days * 24 h/day (for BI 409306, BI 425809, lamotrigine and placebo) or Date/time of administration of study drug in the next treatment period or 12:00 a.m. on day after subject's trial completion date, whatever comes first
Follow-up	**F/U Placebo, F/U [redacted] BI 409306, F/U [redacted] BI 425809** or **F/U 300mg Lamotrigine,** respectively	**F/U Placebo, F/U [redacted] BI 409306, F/U [redacted] BI 425809** or **F/U 300mg Lamotrigine,** respectively	Start date/time of administration of the second study treatment (Planned time: 03:00h) in the respective treatment period + 11 days * 24 h/day (for BI 409306, BI 425809, lamotrigine and placebo)	Date/time of administration of the respective treatment in the next treatment period, if applicable, or 12:00 a.m. on day after subject's trial completion date, whatever comes first.

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of vital signs.
[2] A REP of 11 days will be used for all study treatments (BI 409306, BI 425809, lamotrigine and placebo) to avoid any bias which might occur due to different observation times. This may lead to an overestimation of AEs in the treatment periods in which subjects received a study treatment with considerably lower REP.

[3] The on-treatment phase extends from Day 1 00:00h (planned time) to Day 11 03:00h (planned time) to include AEs which occur after the start of the first study drug (or corresponding placebo) administration (which is not necessarily the analysing treatment of the respective treatment period) as well as AEs which occur within the REP of the second study drug (or corresponding placebo).

Analysis phases for statistical analysis of AEs are defined for each subject as described in Table 6.1: 1.

AE summary tables will present results for the on-treatment phase only. All AEs will be listed.

In AE tables in CTR Section 15.3 (but not in displays for ClinicalTrials.gov) the following total will be provided in addition:

- **"Total on-trt"**, defined as the total over all on-treatment phases

Listings of AEs presented in Section 15.4 will display results for the screening, on-treatment and follow-up phases (labelled with the name of the study treatment (short label)).

AE tables and listings will be displayed by analysing treatment. Beyond that, listings will include an additional column for the actual treatment (defined in Table 6.1: 1).

Vital signs, ECG, CANTAB, [redacted] will be analysed based on the respective treatment (Placebo, BI 409306, BI 425809 or Lamotrigine) with clear differentiation between baseline (cf. Section 6.7) and post-baseline measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 1. ECG measurements are considered to be on-treatment if they were measured between the first administration of the respective treatment and the corresponding residual effect period after the last administration of the respective treatment.

Vital signs listings will include an additional column for the actual treatment (defined in Table 6.1: 1).

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of deviations from time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Report Planning Meeting. At this meeting, it will be decided whether a discrepant data value can be used in analyses, must be corrected in the clinical database or constitutes a PD.

Each protocol deviation must be assessed to determine whether it is an important PD (IPD). For definition of IPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (IPD)" (2).

If any IPDs are identified, they are to be summarised into categories and will be captured in the decision log. Categories which are considered to be IPDs in this trial are defined in the DV domain template. If the data show other IPDs, the definition in the DV domain template will be supplemented accordingly by the time of the Report Planning Meeting.

CTP Section 7.2.1: *Important protocol deviations (IPD) categories will be suggested in the IQRMP and specified in more detail in the TSAP, IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.*

IPDs will be summarized and listed. Which kind of IPDs could potentially lead to exclusion from which analysis set is specified in the DV domain template. The decision on exclusion of subjects from analysis sets will be made at the latest at the Report Planning Meeting, after discussion of exceptional cases and implications for analyses. If the data show other IPDs, this table will be supplemented accordingly by the time of the Report Planning Meeting.

Non-important COVID-19 related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

Subject sets will be used as defined in Section 7.2.1 of the CTP:

- Treated set (TS):
  The treated set includes all subjects who were randomized and treated with at least one dose of study drug or ketamine. The treated set will be used for safety analyses.

- Pharmacodynamic set (PDS):
  PD analyses will be based on the PDS which is defined as all randomised patients who performed the post ketamine tests in at least one period.

The following additional subject sets will be used:

- Screened set (SCS):
  This set includes all subjects who signed the informed consent form.

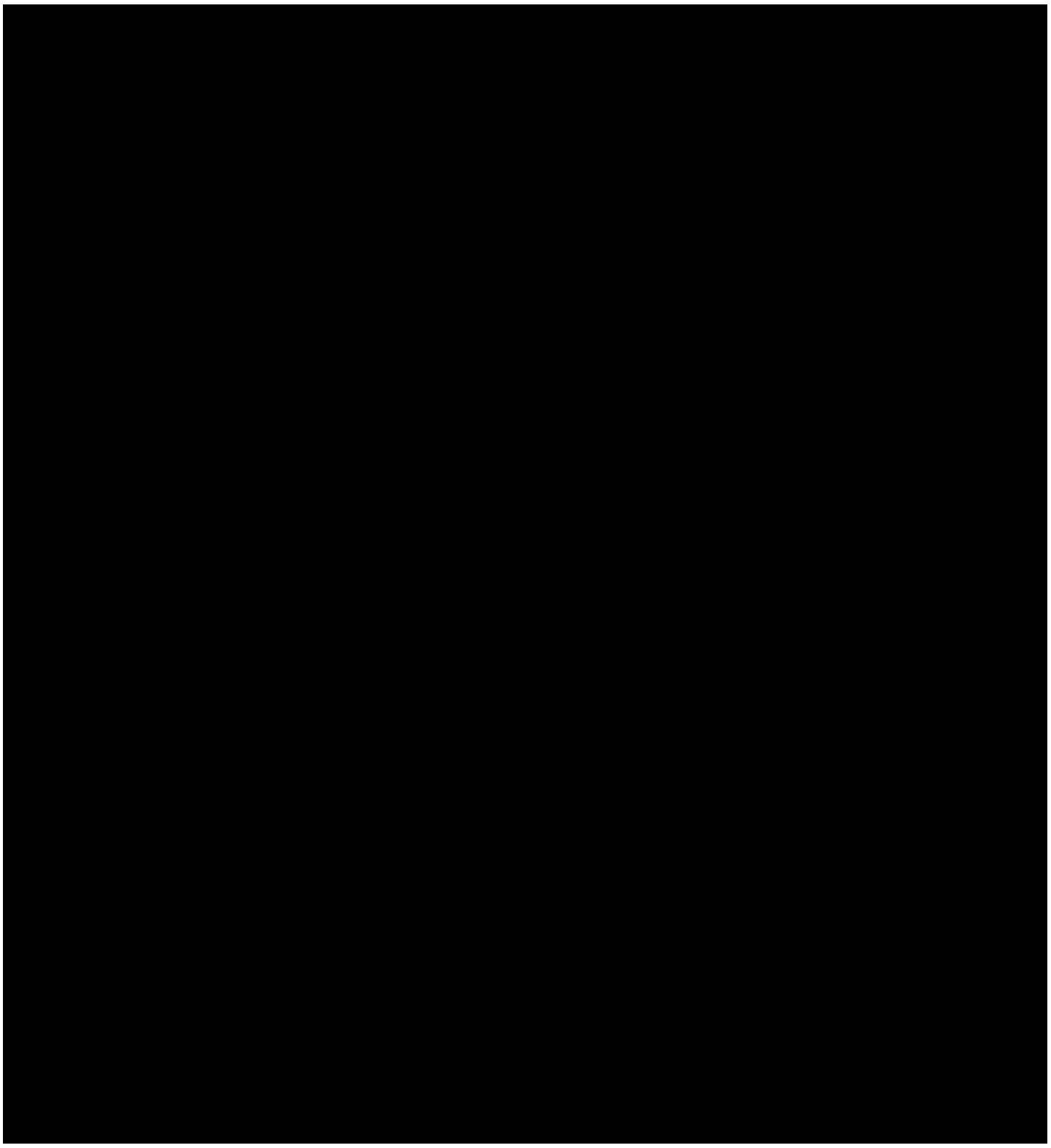


Table 6.3: 1 Subject sets analysed

	Subject set								
Class of endpoint	SCS	TS	PDS	[redacted]					
Disposition	X								
iPDs		X							
Primary endpoint – PALTEA28			X						
Secondary endpoint – SWMBE468			X						
Secondary endpoint – RVPA			X						
[redacted]			X						
			X						
			X						
			X						
			X						
			X						
Safety parameters		X							
Demographic/baseline characteristics		X							
Treatment exposure		X							

[redacted]

6.5 POOLING OF CENTRES

Data from both centers involved in this trial will be pooled.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

CTP Section 3.3.4: "*If a subject is removed from or withdraws from the trial prior to the first administration of trial medication (BI 425809 or BI 409306 or lamotrigine or placebo) or ketamine, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.*"

CTP Section 7.3: "*It is not planned to impute missing values."*

One exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Due to the different analysing approaches with regard to the consideration of ketamine, baselines for pharmacodynamic and safety endpoints are defined separately.

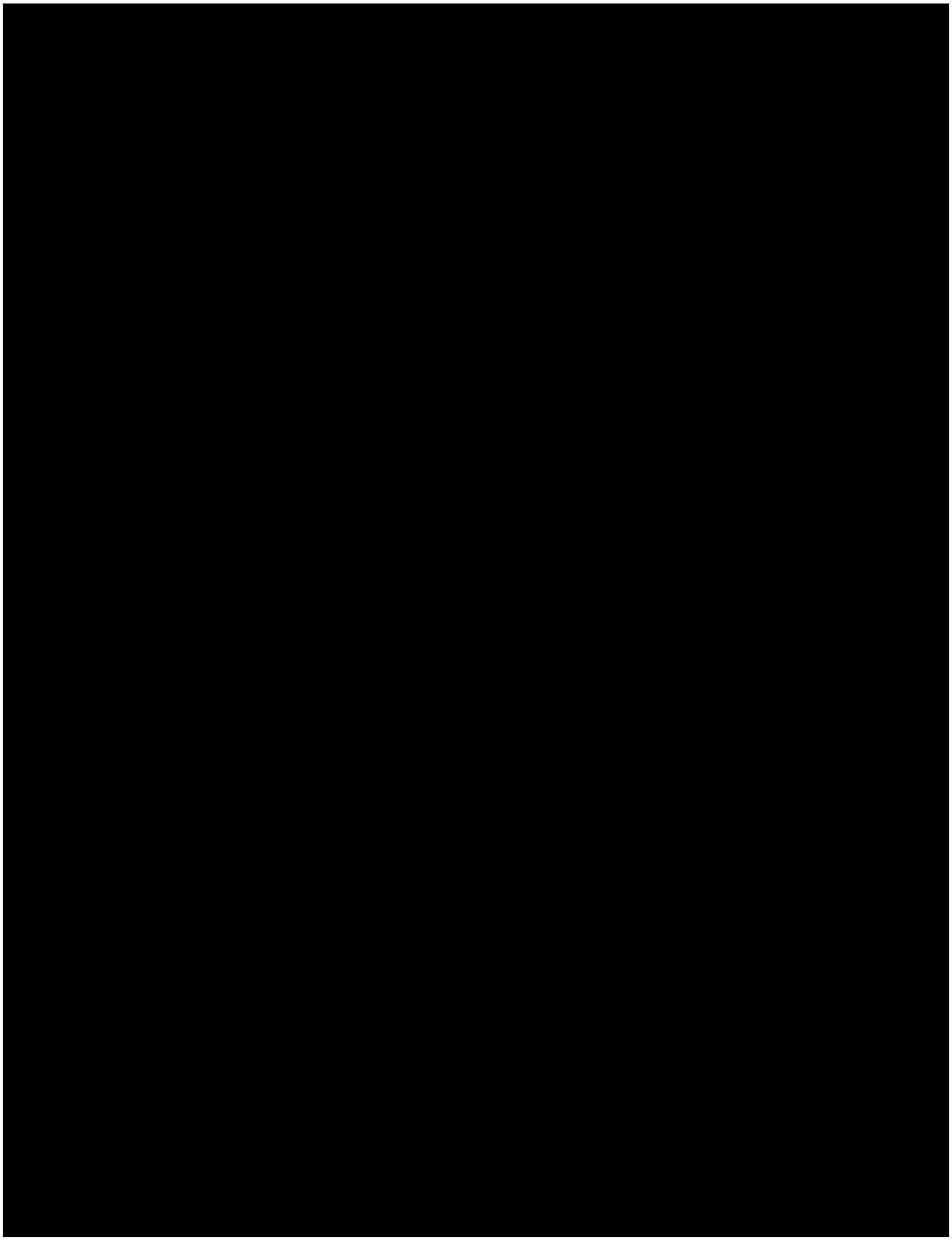
On-ketamine analysis of CANTAB, [redacted] parameters (according to Section 2.2.2.2 of the CTP):

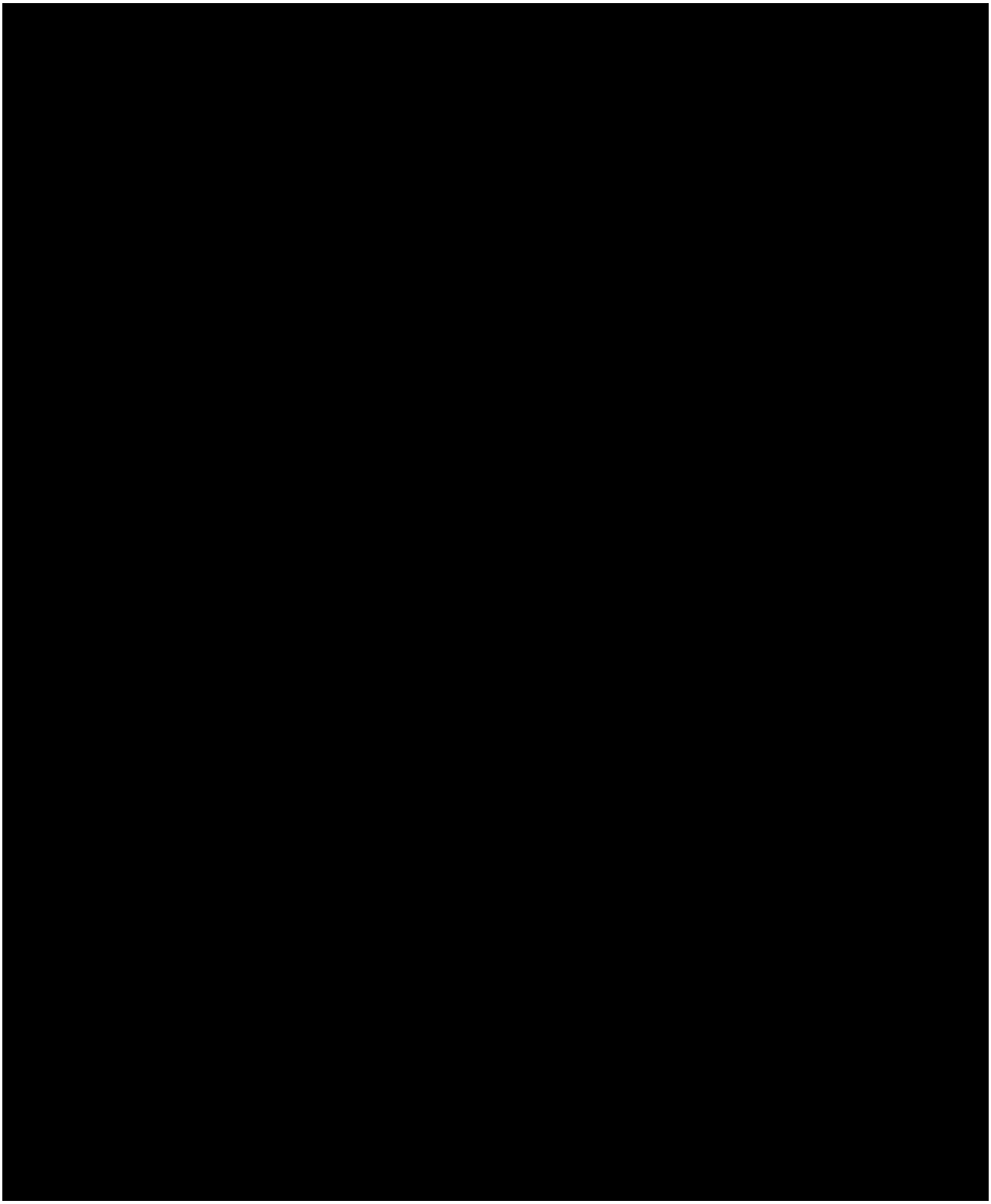
CTP Section 6.2.1: "*For the Screening Ketamine Challenge eligible subjects will come to the clinic in the morning of the test day, where they will participate in two assessment-sessions:*

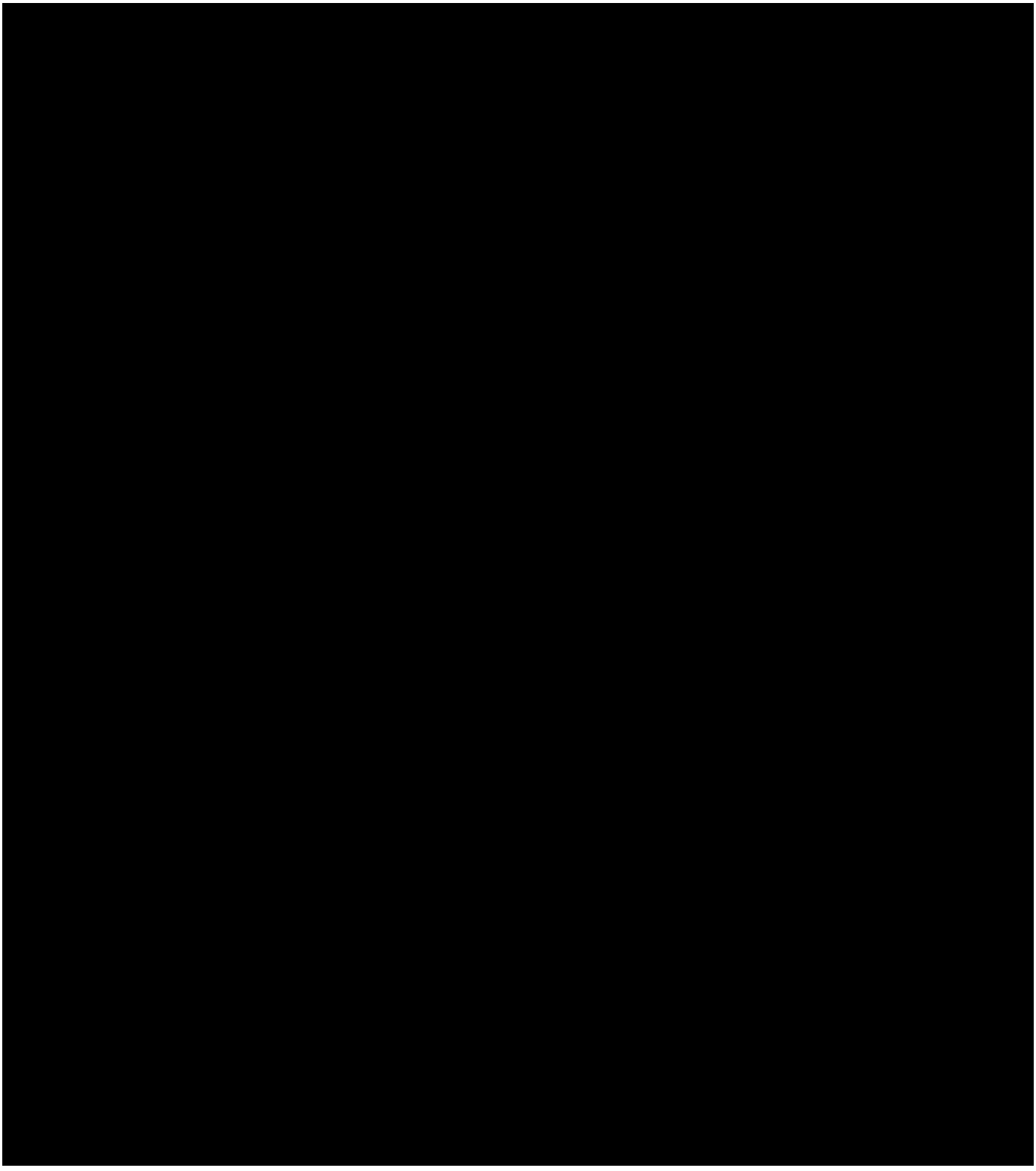
- *Screening Baseline (= SCR BL)*
  CANTAB tests, [redacted] *will be done without any treatment, i.e. with no ketamine infusion*
- *Screening Ketamine (= SCR KET)*
  CANTAB tests, [redacted] *will be done during ketamine infusion*
  […]

The assessments of SCR KET will also be used as baseline for the assessments performed on the test days of the treatment periods, i.e. under treatments T1, T2, T3 and R."

For the analysis of the pharmacodynamic endpoints (CANTAB tests, [redacted] two baselines exist. The pre-ketamine baseline is defined as the last non-missing value prior to start of ketamine infusion at screening. The during-ketamine baseline is defined as the first non-missing value during ketamine infusion at screening.







[redacted]

Safety analyses:

For safety analyses the baseline is defined as the last available value prior to administration of the respective treatment.
For ECG as well as vital signs a separate baseline can be defined for each treatment period as a pre-dose assessment on Day 1 (at Visit 3/4/5) is available.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the Report Planning Meeting.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (6).

The individual values of all subjects will be listed. Listings will be sorted by treatment or sequence group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

For plasma concentrations as well as for all PK parameters the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject set whether they have non-missing values or not.

7.1 DISPOSITION, DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. Whereas disposition will be based on the SCS, demographics and other baseline characteristics will be presented based on the TS.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. Concomitant non-drug therapies will be coded according to the most recent version of MedDRA.

Only descriptive statistics based on the TS are planned for this section of the CTR.

CTP Section 4.2.2.1: "*In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.*"

A medication will be considered concomitant to a treatment period, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

Concomitant medications as well as their time relative to the previous and subsequent study drug administration will be listed.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the Report Planning Meeting (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis of the primary endpoint

The analysis of the primary endpoint will be based on the PDS.

CTP Section 7.2.2: "*A linear mixed effects model will be used for the analysis of the primary endpoint. This model will include effects for sequence, subject within sequence, period, baseline values (obtained at screening visit 2 prior to and on ketamine) and treatment. The*

effect 'subject within sequence' will be considered as random, whereas the other effects will be considered as fixed. All three periods (if available) will be included in the analysis."

The corresponding baseline values are described in Section 6.7 of this TSAP (see baseline definition for 'On-ketamine analysis of CANTAB, [redacted] parameters (according to Section 2.2.2.2 of the CTP)').

The model is described by the following equation:

$y_{ijklmp} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + \vartheta_p + \alpha_l + e_{ijklmp}$, where

y_{ijklmp} = response measured on subject m in sequence i receiving treatment k in period j with pre-ketamine baseline p and during-ketamine baseline l

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2, …, 18

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., n_i

π_j = the j^{th} period effect, j = 1, 2, 3

τ_k = the k^{th} treatment effect, k = 1, 2, 3, 4

ϑ_p = the p^{th} pre-ketamine baseline effect, p = 1, …, 40

α_l = the l^{th} during-ketamine baseline effect, l = 1, …, 40

e_{ijklmp} = the random error associated with subject m in sequence i who received treatment k in period j with pre-ketamine baseline p and during-ketamine baseline l

where $s_{im} \sim N(0,\sigma_2)$ i.i.d., $e_{ijklmp} \sim N(0,\sigma_2)$ i.i.d. and s_{im}, e_{ijklmp} are independent random variables.

CTP Section 7: *The primary and secondary PD endpoints will be compared between BI 409306 and placebo as well as BI 425809 and placebo. The Lamotrigine (T1) treatment period acts as a positive control group. It is not planned to compare PD effects between Lamotrigine, BI 425809 and BI 409306. The primary and secondary PD endpoints will be compared between Lamotrigine and placebo to investigate the sensitivity of the design.*

In addition the primary endpoint will be analysed descriptively for each study treatment.

N, mean, SD, median, minimum and maximum will be provided for absolute values as well as for the change from baseline. Additionally placebo-corrected values will be presented as difference between the value of the respective study treatment and the value of placebo.

Profile plots will be provided to display absolute pre- and during-ketamine values at baseline as well as for each treatment period.

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 Secondary endpoints

The analysis of the secondary endpoints will be based on the PDS. [redacted]

7.5.2.1 Secondary endpoint analysis

According to the CTP Section 7.2.3 the secondary endpoints will be assessed statistically using the same methods as described for the primary endpoint (see also Section 7.4.1 of this TSAP).

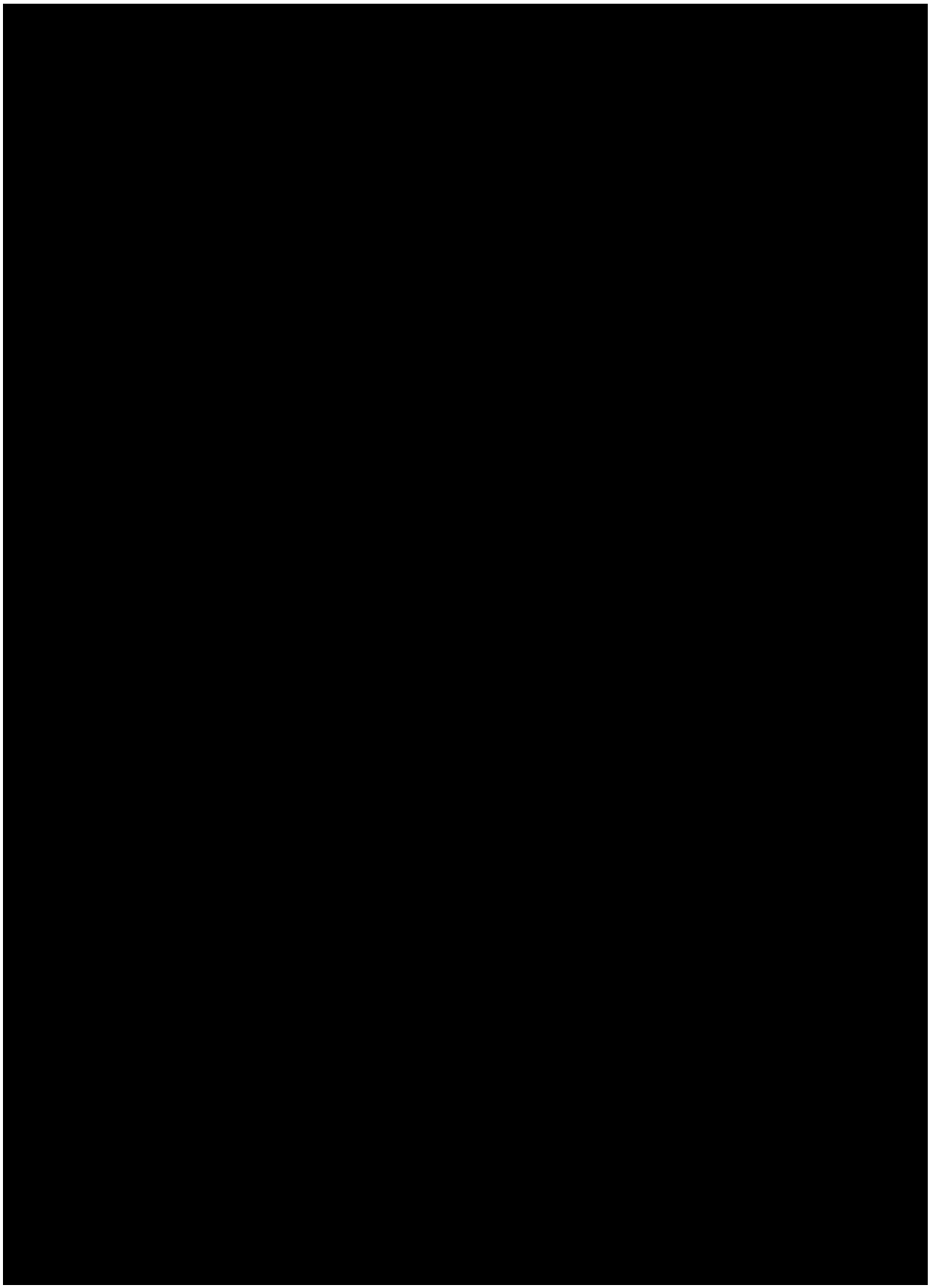
[redacted]

[redacted]

7.6.1 Safety parameters

Safety and tolerability endpoints will be analysed as described in Section 7.8 of this TSAP.

[redacted]



7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report.

7.8 SAFETY ANALYSIS

All safety analyses for BI 409306, BI 425809, lamotrigine and ketamine will be performed on the TS.

CTP Section 7.2.5: "*The safety analysis will be done by 'treatment at onset'.*"

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

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.

For further details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

All AEs will be assigned to the screening, on-treatment or follow-up phase as defined in Section 6.1. AEs will be analysed based on treatments as actually received, defined in Table 6.1: 1.

CTP Section 7.2.5: "*Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.*"

The longest REP, i.e. 11 days will be taken for all study treatments (Placebo, BI 409306, BI 425809 and Lamotrigine) to avoid any bias which might occur due to different observation times. This may lead to an overestimation of AEs in the treatment periods in which subjects received a study treatment with considerably lower REP.

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of AESIs.

CTP Section 5.2.6.1.4: *The following are considered as AESIs:*

- *Hepatic injury*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

According to ICH E3 (8), 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).

The frequency of subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs will also be summarized by maximum intensity. AEs which were considered by the investigator to be drug related will be presented separately. Separate tables will also be provided for subjects with SAEs, related SAEs and subjects with AESIs.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarized.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

All AEs occurring in screening, on-treatment and follow-up phase will be listed.

7.8.2 Laboratory data

No analyses are planned as safety laboratory test results will only be kept in the source data but not collected in the CRF (according to the CTP Section 5.2.3). Clinically relevant abnormal findings will be reported as AEs.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Unscheduled measurements of vital signs will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement. However, for vital signs, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point). If the time of measurement is missing for a scheduled post-baseline measurement, the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed).

If the time of measurement is missing for an unscheduled measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics.

Clinically relevant findings in vital signs data will be reported as baseline conditions (prior to first administration of study treatment) or as AEs (after first administration of study treatment) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

Abnormal findings in ECG will be reported as baseline conditions (at screening) 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.

7.8.5 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (if a condition already exists before first administration of study treatment) or as AE (if condition emerges after first administration of study treatment) and will be summarized as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Body weight

Body weight will only be listed.

7.8.5.3 Suicidality assessment

Suicidality monitoring will be performed as described in Section 5.2.5.2 of the CTP, results will be listed. Additionally, the frequency of subjects categorized by any question answered with 'Yes' (or all answered with 'No' or missing) will be presented. Results for subjects who answered any question with 'Yes' will additionally be listed. Findings will also be reported as AEs.

[redacted]

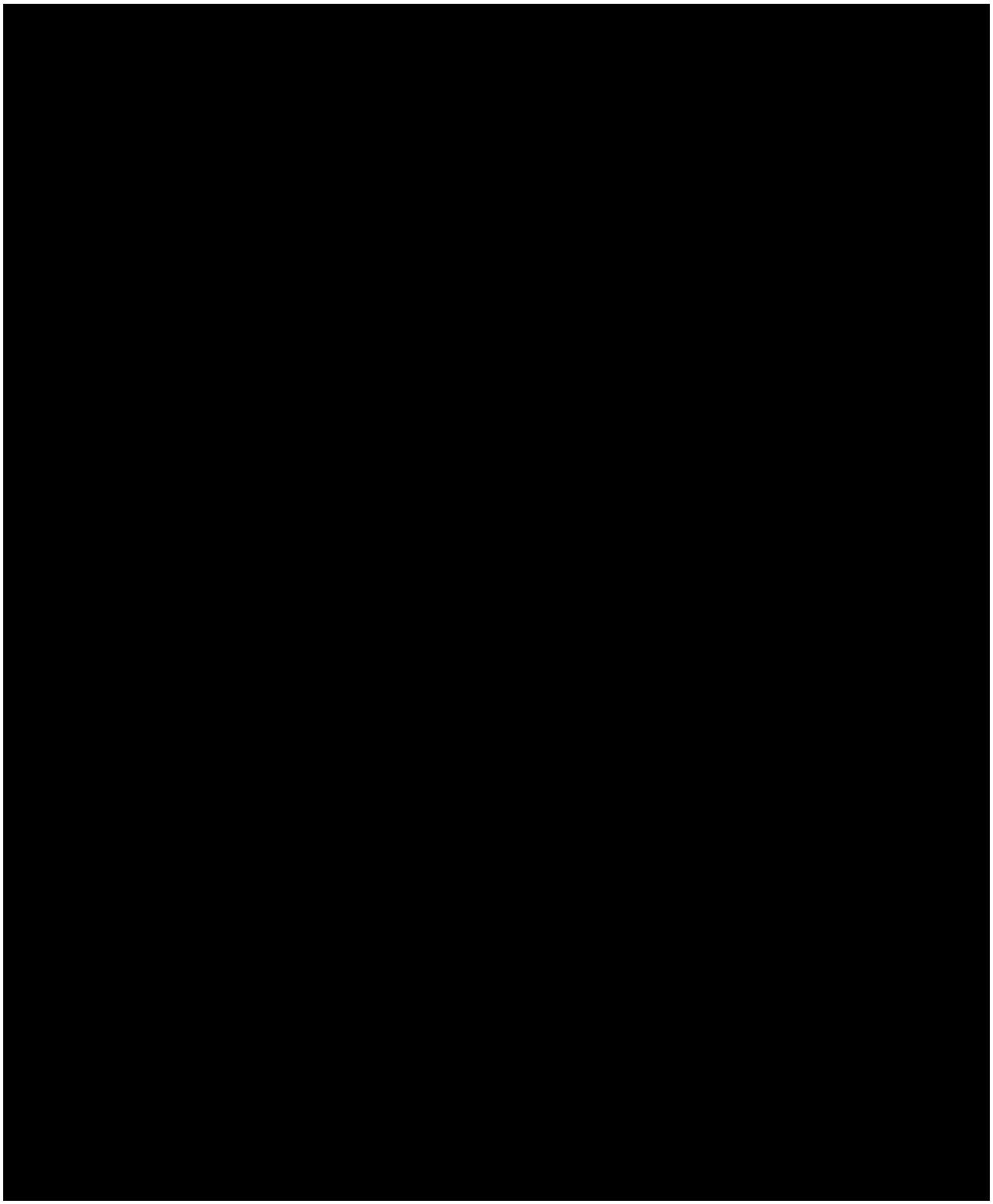
7.8.5.5 Visual acuity test

The visual acuity test will be performed as described in Section 5.2.5.4 of the CTP.
Any deterioration occurring during the study will be documented as an AE.

[redacted]

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrollment, i.e. the randomization has completed.



11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**14-Oct-2022**	[redacted]	None	First final TSAP version