TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c42059532-01**
BI Trial No.:	1402.0030
Title:	A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability, and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD) Clinical Trial Protocol c34993667-01
Investigational Product(s):	BI 1358894
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AS	Adherent set
ATC	Anatomical, Therapeutic, Chemical
BI	Boehringer Ingelheim
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CGI-S	Clinical Global Impression – Severity
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Concomitant Therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBLM	Database Lock Meeting
DERS-16	Difficulties in Emotion Regulation Scale – 16 item
DV	Protocol Deviations
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EOT	End of Treatment
EQ-5D-5L	Euro Quality of Life-5 Dimensions-5 Levels
FAS	Full Analysis Set
fMRI	Functional magnetic resonance imaging
FU	Follow-up
ICH	International Conference on Harmonisation
IDEA	International Document Management & Electronic Archiving
IPD	Important Protocol Deviation

Term	Definition / description
IVRS	Integrated Voice Response System
LLT	Lowest Level Term
MCPMod	Multiple Comparison Procedures and Modelling
MMRM	Mixed effects Model Repeated Measures
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
OAA	Overall [redacted] Adherence
PCL-5	PTSD Checklist for DSM-5
PGI-I	Patient Global Impression – Improvement
PGI-S	Patient Global Impression Severity Scale
PHQ-9	Patient Health Questionnaire - 9 items
PK	Pharmacokinetics
PKS	PK parameter analysis set
PPS	Per Protocol Set
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
PD	Pharmacodynamics
QD	Quaque Die (once a day)
RDC	Remote Data Capture
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SDS	The Sheehan Disability Scale
SS	Screened Set
STD	Standard Deviation
STAI	The State-Trait Anxiety Inventory for Adults
TMF	Trial Master File
TOM	Trial Oversight Meeting
TS	Treated Set

Term	Definition / description
TSAP	Trial Statistical Analysis Plan
UDAEC	User-defined AE categories
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organisation

3. INTRODUCTION

The purpose of this TSAP is to provide analysis specifications that is to be reported in the final CTR. Also included in this TSAP are analysis specifications for an interim analysis, the results of which are to be reported in a synoptic report that is separate from the final CTR.

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

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

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

The main analyses of this TSAP will be conducted under the estimand concept. To quote ICH E9 R1, “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, 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.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Change from baseline in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at Week 8

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There is no key secondary endpoint in this trial.

5.2.2 Secondary endpoint(s)

CAPS-5
- Response defined as ≥30% CAPS-5 reduction from baseline at Week 8
- Response defined as ≥50% CAPS-5 reduction from baseline at Week 8

PCL-5
- Change from baseline on the PTSD Checklist for DSM-5 total score at Week 8

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For details on the treatment regimen, assignment of treatment groups, and the selection of doses, refer to Section 4 of the CTP. Below in Table 6.1:1 are the descriptions of the short and long names of the treatments. Next, are the definitions of the study phases for the analysis periods (Table 6.1:2).

Table 6.1: 1 Treatment descriptions

Long Name	**Short Name**
Placebo	Placebo
BI 1358894 125 mg qd	BI 125 mg

Table 6.1: 2 Study analysis phases*

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

* The defined treatment periods are the same for all treatment groups.
REP is the residual effect period which is defined as 28 days after the last dose of trial treatment for safety, and 7 days after last dose for efficacy
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.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., randomized patients). Consistency check listings (i.e., identification of violations of time windows) and a list of CTP deviations will be provided to be discussed at the Report planning meeting (RPM)/Database lock meeting (DBLM)/Medical Quality Review Meeting (MQRM). At these meetings, it will be decided whether a discrepant data value can be used in analyses and/or whether it must be queried in the clinical database. Each CTP deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the current BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (3).

Generally, a protocol deviation is considered as an iPD if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. If any iPDs are identified, they are to be summarized into categories and will be captured in the RPM/DBLM/MQRM minutes via an accompanying DV domain specifications Excel spreadsheet (4). The following table contains the categories which are iPDs in this trial. If the data presents additional iPDs (e.g., based on monitor visits to the sites), then the DV domain specifications will be supplemented accordingly at TOMs or RPMs or through team review of the manual PD log.

The decision whether a subject will be excluded from the analysis will be made at the final RPM prior to Database Lock (DBL). The documentation of the iPD categories and how to handle iPDs in the analysis are listed in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). iPDs will be summarized and listed for the treated set.

6.3 INTERCURRENT EVENTS

The following intercurrent events (ICEs) are of interest:

1. Change in background CNS active medication (e.g., non-SSRI antidepressant, anxiolytics)
2. Change in pharmacological therapy (SSRI)
3. Change in drug test result from negative to positive (Benzodiazepine, Barbiturates, Opiates, Cocaine, Amphetamines, Methadone, PCP)
4. Change in non-pharmacological therapy – trauma-focused psychotherapy
5. Change in non-pharmacological therapy – all other cognitive/behavioral therapy (CBT) (e.g., any other kind of psychotherapy, nicotine withdrawal therapy, diet, etc.)
6. Withdrawal of study medication due to investigator assessed drug-related adverse events (e.g., headache)
7. Withdrawal of study medication due to perceived lack of efficacy or disease worsening
8. Withdrawal of study medication due to other adverse events
9. Withdrawal of study medication due to any other reasons.

Table 6.3:1 lists the handling of the ICEs for the primary estimand and supplementary estimand.

Table 6.3:1 Handling rules for Intercurrent events

	ICE	Primary Estimand	Supplementary Estimand
Handling rules for ICEs	1-4	Treatment policy	Treatment policy
	5	Treatment policy	Treatment policy
	6-7	Hypothetical	Treatment policy
	8-9	Hypothetical	Hypothetical

From the table above we see that that primary estimand estimates the treatment effect when changes to background CNS active medication, pharmacological SSRI therapies and non-pharmacological therapies (ICEs 1-5) are part of the treatment effect, but changes to randomized treatment (ICEs 6-9) are not considered to be part of the treatment effect of interest. ICEs are therefore handled by a hybrid estimand that combines the treatment policy and hypothetical approaches, where ICEs 1-5 are handled using the treatment policy approach, thus measurements taken after the occurrences of these ICEs are included in the primary analysis.

However, ICEs 6-9 are handled using the hypothetical approach, where measurements after their occurrences are therefore censored in the primary analysis. Therefore, this analysis (ICEs 6-9) 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 date of the last dose of trial medication plus 7 days. Any data collected after a patient discontinues trial drug, regardless of reason, will be censored and will not be included in the primary analysis.

6.4 SUBJECT SETS ANALYSED

The following analysis sets are defined for this trial:

- Screened Set (SS): consists of all subjects who signed informed consent.

- Treated Set (TS): consists of all subjects that have been randomized and that 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): consists of all subjects in TS that have a baseline and at least one evaluable post-baseline 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.

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

Table 6.4: 1 Subject sets analyzed

	Subject set					
Class of analyses	TS	SS	FAS	PPS	PKS	AS
Primary and secondary endpoints, compliance			X	X*		
Further endpoints ([redacted]			X			
Disposition		X				
[redacted]					X	
Safety variables and iPDs	X					
Demographics, baseline characteristics, exposure	X			(X)		
Primary endpoint adjusted for overall study [redacted]						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.

(X) An additional PPS presentation of the demographic/baseline endpoints may be provided in the End of Text (EoT) section, if there are a non-negligible number of treated subjects with no post randomization data for the primary endpoint.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing data are not explicitly imputed and remain missing for all main analyses. For efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will ensure that missing data are handled implicitly via a missing at random assumption (MAR) by the statistical model. For the binary efficacy endpoint of CAPS-5 response, missing data will not be imputed.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (5). Missing data and outliers of [redacted] data are handled according to (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last observation at, or prior to Visit 2. Hence, if a subject is randomized at Visit 2, but does not start trial medication until a future 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.

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

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 which have the same difference in days to the planned 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. Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data. Repeated and unscheduled efficacy measurements will be assigned to the nominal visits according to the time windows described in Table 6.7: 1.

For safety measurements, data collected at all visits 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 for which there is no standard reference direction for the safety parameter, the average of all values for the same visit will be used for analysis.

Table 6.7: 1 Planned and actual study days

Visit	Relative to treatment start	
	Planned test day	Actual test day
2	1	Day 1 – Day 2

3	8	Day 3 – 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	43	Day 41 – Day 47
9	50	Day 48 – Day 52
10/EOT	57 for completed subjects	Day 53 – treatment stop date (stopdt) + 7 days
eEOT	N/A (for early discontinued subjects)	Date of the last administration of trial medication + 7 days (for early discontinued subjects). The number of days will be assigned to the visit. Thus, if days to eEOT is 31, it will be mapped to Visit 6. For those that early discontinue treatment but continue with the collection of efficacy data, those data points will be mapped to the later Visits as per the above Visit window. Hence, if this same subject collects CAPS-5 at Day 46, it will be mapped to Visit 8.
End of Trial	EOT + 28 days	[stopdt + 8 days] to [stopdt + 30 days]

- Days are counted relative to the day of randomization, which is defined as Day 1.
- stopdt stands for treatment stop date.

There's no visit window mapping for C-SSRS given that it is collected every week throughout the study.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (7).

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 (see Section 7.8.1 below for details). The listings will be contained in an Appendix of the CTR.

For End-Of-Text 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 are preferred to mean, standard deviation, minimum and maximum. In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places than the raw data. Minima and Maxima are presented to the same number of decimal places as the raw data.

Disposition of the patient population participating in the trial will be analyzed by treatment and presented by the categories in the standard CRF groups and presented in the clinical trial report as a frequency-distribution.

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

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only standard descriptive statistics and summary tables are planned for this section of the report. Data will be summarised by treatment group and a "total" column will be included in the summary table.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases (i.e., baseline conditions) will be coded similarly as AEs using the most recent version of MedDRA. A summary of concomitant diseases will be provided by treatment group, System Organ Class (SOC) and Preferred Term (PT). Concomitant diseases

which are present at start of the study will be descriptively summarized by treatment, except for suicidal ideation, suicidal behavior and non-suicidal self-injurious behavior-. -These shall be removed from the concomitant diseases (baseline condition/medical history) and will be presented as a separate stand-alone table(s).

A medication/therapy will be considered concomitant to treatment if it (1) is ongoing at the start of randomized trial treatment or (2) starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases). A medication/therapy will be considered as prior medication/therapy, if the end date of the medication/therapy is at any time prior to the start of randomized trial treatment.

Concomitant therapies (CTs) are coded according to WHO Drug Dictionary. CTs 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. The most current MedDRA and WHO DD versions will be used.

7.3 TREATMENT COMPLIANCE

7.3.1 CRF Compliance

Only descriptive statistics are planned for this section of the report. Treatment compliance is calculated at Week 2, 4, 6, and 8(EOT) based on the CTP's flow chart.

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

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

For completers: if a subject's observed treatment compliance rates are 80%, 81%, 82%, 83%, at Weeks 2, 4, 6, and 8, then the cumulative treatment compliance percent = (.80*2 + .81*2 + .82*2 + .83*2)/8*100 = 81.5%.

For early discontinued subject: if a subject's observed treatment compliance rates are 80% at Week 2, 81% at Week 4, 50% at eEOT, then the cumulative treatment compliance rate = (0.80*2 + 0.81*2 + 0.5*((eEOT date – drug start date + 1)/7 – 4))/((eEOT date – drug start date + 1)/7) * 100% = 63.6% if the quantity (eEOT date – drug start date + 1) is assumed to be 36 days. In the example above the last regular visit is Week 4, so 4 is subtracted because there is compliance for the first 4 weeks. If the last regular visit is Week 2, then the '4' that's being subtracted would change to 2 to account for having compliance up through 2 weeks.

If at a particular visit a participant did not return the trial drug kits, then the compliance at that visit is zero.

Treatment compliance will be summarised overall and by visit for the treated set (FAS) using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of patients with the following overall compliance categories will be presented using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of patients with the following overall compliance categories will be presented:

- "<80% of planned",
- "80 to <100% of planned",
- ">=100% of planned",
- missing.

7.3.2 Video Confirmed [redacted]

First, we define overall [redacted] (abbreviated as OAA), as the sum of all tablet adherence minus the total number of tablets flagged as red, orange, or yellow alerts, divided by a denominator of 3 times 56. Or, in other words:

- OAA = [[(Sum of all tablet adherence) – (total number of red, orange, and yellow alerts)]/ 3*Treatment duration] *100,
    - Treatment duration is the number of days on treatment = treatment end date - treatment start date +1
        - It is equal to 56 for subjects that adhere to the protocol.
    - 3 is the number of tablets per dose.

Tablet adherence is the successful administration of a pill as captured by [redacted] *Red alerts* are tablet administrations for which the [redacted] 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 behavior, 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 the following method: visually confirmed by the [redacted]

For subjects that discontinue treatment early, 56, 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.

As defined in Section 6.4, the Adherent set (AS) consists of all subjects in FAS that achieved an OAA of at least 60%.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary endpoint is the change from baseline to Week 8 in CAPS-5 total score. Baseline refers to the measurement recorded at randomization (Visit 2), if data at Visit 2 is missing, then data from Visit 1 will be considered baseline. The primary analysis of the primary endpoint will use a hybrid estimand that combines the treatment policy and hypothetical estimands as detailed in Section 6.3.

MMRM analysis
The change from baseline in CAPS-5 total score at Week 8 for each dose group as well as the corresponding variance-covariance matrix are estimated by a mixed effects model repeated measure (MMRM) including the fixed categorical covariates of treatment, and the stratification indicator of presence of significant childhood trauma (yes vs. no), the continuous fixed covariates of baseline CAPS-5 total severity score and time since index event (in years) and the treatment-by-visit interaction. Patient is considered as a random effect. Visit will be treated as a repeated measure with an unstructured covariance matrix used to model the within subject variability. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using SAS 9.4 PROC MIXED. FAS is used for the primary analysis of the primary efficacy endpoint.

More specifically, the change in CAPS-5 total score from baseline (Visit 2), at Visits 2, 6, and 10 (Weeks 0, 4, and 8) will be evaluated using an MMRM accounting for the following sources of variation: ‘treatment’, ‘visit’, ‘presence of significant childhood trauma (yes vs.no), time since index event (in years) and ‘baseline CAPS-5 total score’ as continuous covariates, and treatment-by-visit interaction, as well as the random ‘subject’ effect. The methods described in Section 10.1 will be utilized to resolve model non-convergence.

SAS code for MMRM:
The following SAS code will be used to calculate the MMRM.

```
PROC MIXED DATA=indata cl method=reml;
        CLASS visit trt stratum subject;’
        MODEL ept = stratum visit*trt time_since_index base / ddfm=kr s CL;
        REPEATED visit / subject= subject type=un r rcorr;
        LSMEANS visit*trt / pdiff=all om cl alpha=0.05 slice=visit;
RUN;
```

Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

[redacted]

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

Logistic regression analysis
The binary secondary endpoints of CAPS-5 response (defined as ≥30% CAPS-5 reduction from baseline at Week 8 and defined as ≥50% CAPS-5 reduction from baseline at Week 8) will each be analyzed through a logistic regression model to obtain an estimate of the population odds ratio (OR) and associated confidence intervals between active arms and placebo. This logistic regression will be adjusted for fixed factors of treatment and presence of significant childhood trauma (yes vs. no). The analysis will be performed on the FAS. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing treatment to placebo.

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

```
proc logistic data=indata;
  class trt stratum/ param=GLM; /* include (ref=”placebo”) for trt*/
  model resp = trt base stratum / link=LOGIT covb;
  lsmeans trt / cl;
run;
```

Adjusted odds ratio together with 95% confidence intervals, comparing all treatments to placebo, will be presented.

The secondary endpoint of change from baseline in PTSD Checklist for DSM-5 (PCL-5) total severity score at Week 8 will be analyzed using an MMRM model like that described for the primary analysis of the primary endpoint to obtain the adjusted change from baseline at Week 8 for BI active arm versus placebo.

[redacted]

[redacted]

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 weeks", "2 to <3 weeks", "3 to <4 weeks", "4 to <6 weeks", "6 to <8 weeks", "8 weeks", ">8 weeks", or "missing".

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. AEs will be coded based on the most current version of MedDRA. Analysis will be performed as defined in Section 7.2.6 of the CTP.

7.8.1 Adverse Events

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI guideline (8). AEs will be coded with the most current version of MedDRA.

For analysis 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-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarisation of AE data, please refer to (5,8).

The analysis of AEs will be based on the concept of treatment emergent adverse events, thus, all adverse events occurring between the date of the first administration of trial treatment through the date of the last administration of trial treatment + residual effect period will be assigned to the on-treatment period. Adverse events that occur before first drug intake will be assigned to 'screening', and adverse events that occur within 28 days after the residual effect

period will be assigned to 'follow-up'. For details on the treatment definitions, see Section 6.1.

Adverse events of special interest (AESIs)

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.
- These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

Refer to CTP Section 5.4.6.1.4 for details.

Other significant AE (according to ICH E3)

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

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

AE summaries
An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarized by treatment, primary system organ class (SOC) and preferred term (PT) according to MedDRA. The SOCs will be sorted by default alphabetically and PTs will be sorted by frequency within an SOC. Separate tables will be provided for patients with:

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

AEs suggestive of abuse potential

In support of an evaluation of human abuse potential, user-defined AE categories (UDAEC) are defined in Section 10.4. In addition, frequency of subjects with AEs suggestive of abuse potential will be summarized by treatment, UDAEC, and preferred term. A listing of the AEs and a listing of subjects with >100% compliance or unreturned medication kits will also be provided.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (10). 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. Study visits will be presented by the Visit labels in Table 6.7:1.

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 the average of all the measurements for the corresponding visit.

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 analysed as such. No separate listing or analysis of these ECG data will be prepared.

7.9 OTHER ANALYSIS

This section mainly refers to CTP Section 7.2.7 Other Analyses.

[redacted]

7.9.3 Interim Analyses

An interim analysis is planned when the 120th evaluable subject completes the planned treatment period. An evaluable subject is one that has remained in the study, and has at least one change from baseline CAPS-5 severity score. The purpose of this interim analysis is for internal planning of the PTSD indication with BI 1358894. PoC will be evaluated. The decision to stop or continue the trial will be made by BI based on the totality of evidence - to also include observations from secondary objectives and the safety profile. An independent team will be formed to perform this analysis. Details on whom has access to unblinded data will be specified in an interim analysis logistic plan. Table 7.9.3:1 provides the scope of analysis for the interim analysis package.

Table 7.9.3:1 Interim Analysis Package

Demographics, Disposition and Baseline conditions	
	1. Baseline demographic tables (include HA/migraines)
	2. Comorbidities
	3. Concomitant medications – Background therapies
	4. Disposition Table
Primary and secondary endpoints	
	5. Change from baseline in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at Week 8
	6. Response defined as ≥30% CAPS-5 reduction from baseline at Week 8
	7. Response defined as ≥50% CAPS-5 reduction from baseline at Week 8
	8. Change from baseline on the PTSD Checklist for DSM-5 total score at Week 8
Standard safety	
	9. Overall summary of patients with AEs
	10. Frequency of patients with AEs
	11. Frequency of patients with AEs leading to drug discontinuation
	12. Frequency of patients with serious AEs
	13. Frequency of patients with AEs leading to death
	14. Suicidality as assessed by C-SSRS
	15. AEs suggestive of abuse potential

Exploratory	
	16. Change from baseline in Pittsburgh Sleep Quality Index (PSQI) global scores over time
	17. Change from baseline in the Difficulties in Emotion Regulation Scale (DERS-16) total score at Week 8
	18. Change from baseline in the State Trait Anxiety Inventory (STAI) State and Trait version at Week 8. Specifically, the change from baseline in the STAI-S and STAI-T at Week 8.
	19. Change from baseline in CGI-S at Week 8

The very first part of Table 7.9.3:1, 'Demographics, Disposition and Baseline conditions' will be analyzed as stated in Sections 7.1-7.4. The subsequent analyses that pertain to 'Primary and secondary endpoints' will be analyzed via the methods discussed in Sections 7.4.1 and 7.5.2. Standard safety will be evaluated according to the methods described in Section 7.8. And lastly, Table 7.9.3:1 ends with a set of 'Exploratory' analyses that will be analyzed descriptively, hence the change from baseline at Week 8, as well as the percent change from baseline (across treatment arms and for the total) will be provided.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

This section details the planned time point at which the database will be declared ready for analysis. Further details regarding the timing and disclosure of the interim analyses will be specified in the Logistics and Access plan.

Standard approach:
This approach is the default option for double-blind pivotal trials, or trials that potentially could be pivotal and do not require expedited reporting, or non-pivotal double-blind trials that choose not to use a fast-track approach.

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.

The following plan for an End of Treatment database lock will be implemented if deemed necessary for decision making.

End of Treatment Lock (Interim Database Lock):
This section details the planned time point at which the database will be declared ready for the End of Treatment (interim database) lock. This interim database lock will consist of all data up through the End of Treatment (EoT), Week 8.

The treatment information will be released for this End of Treatment analyses, thus, given that the database will be unblinded with this lock, there is no need for specification in the logistics plan.

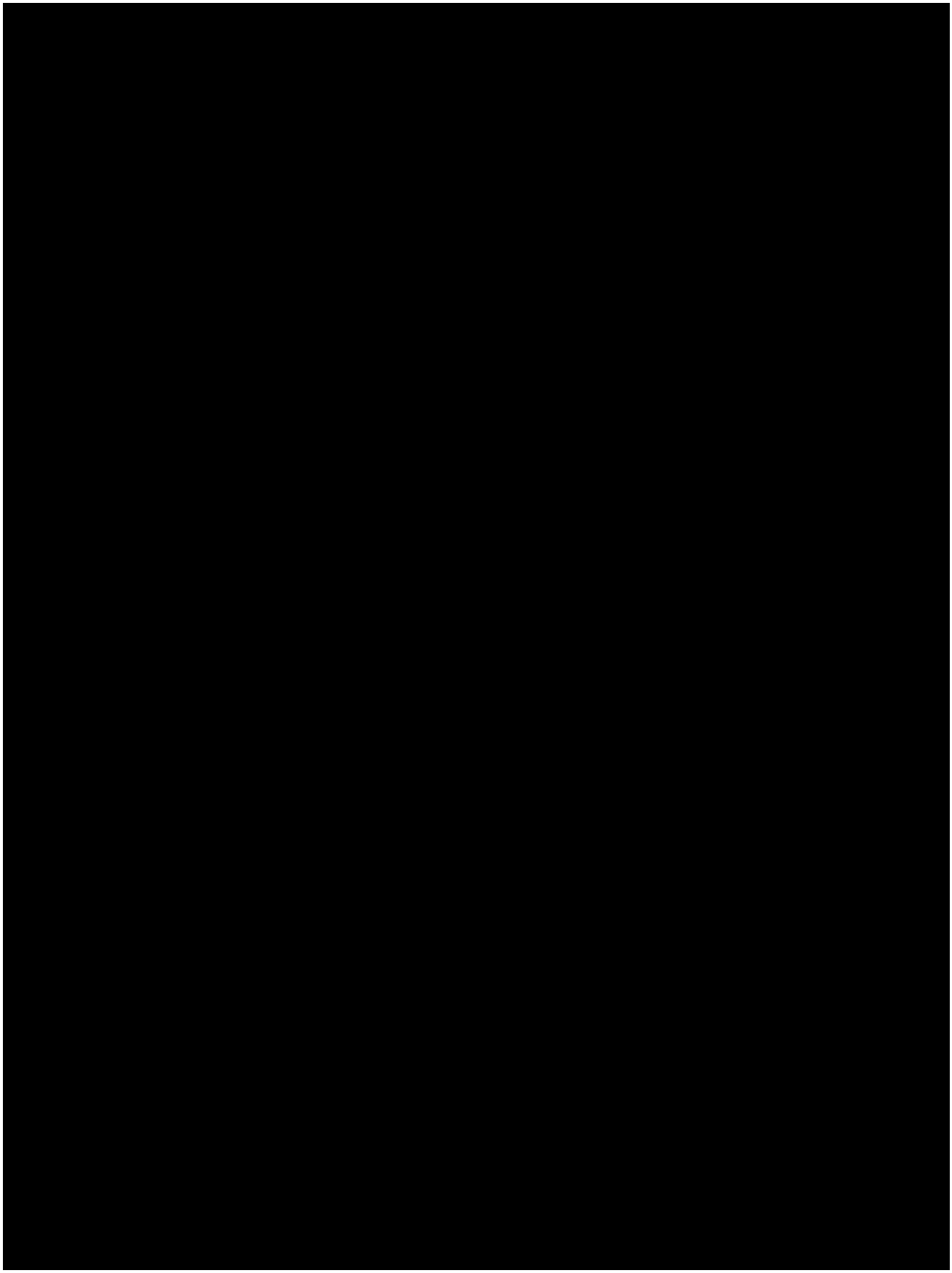
Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.

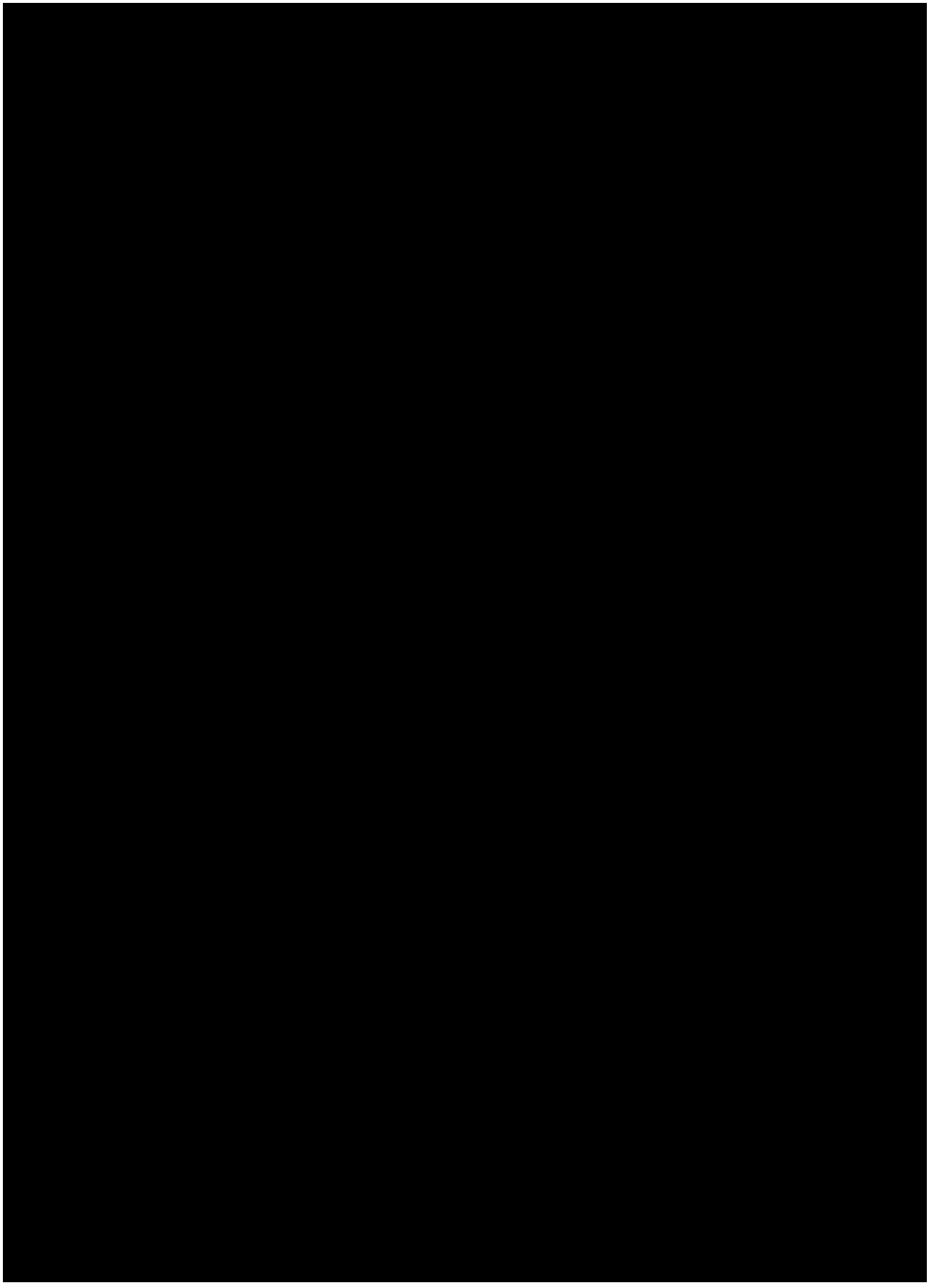
The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

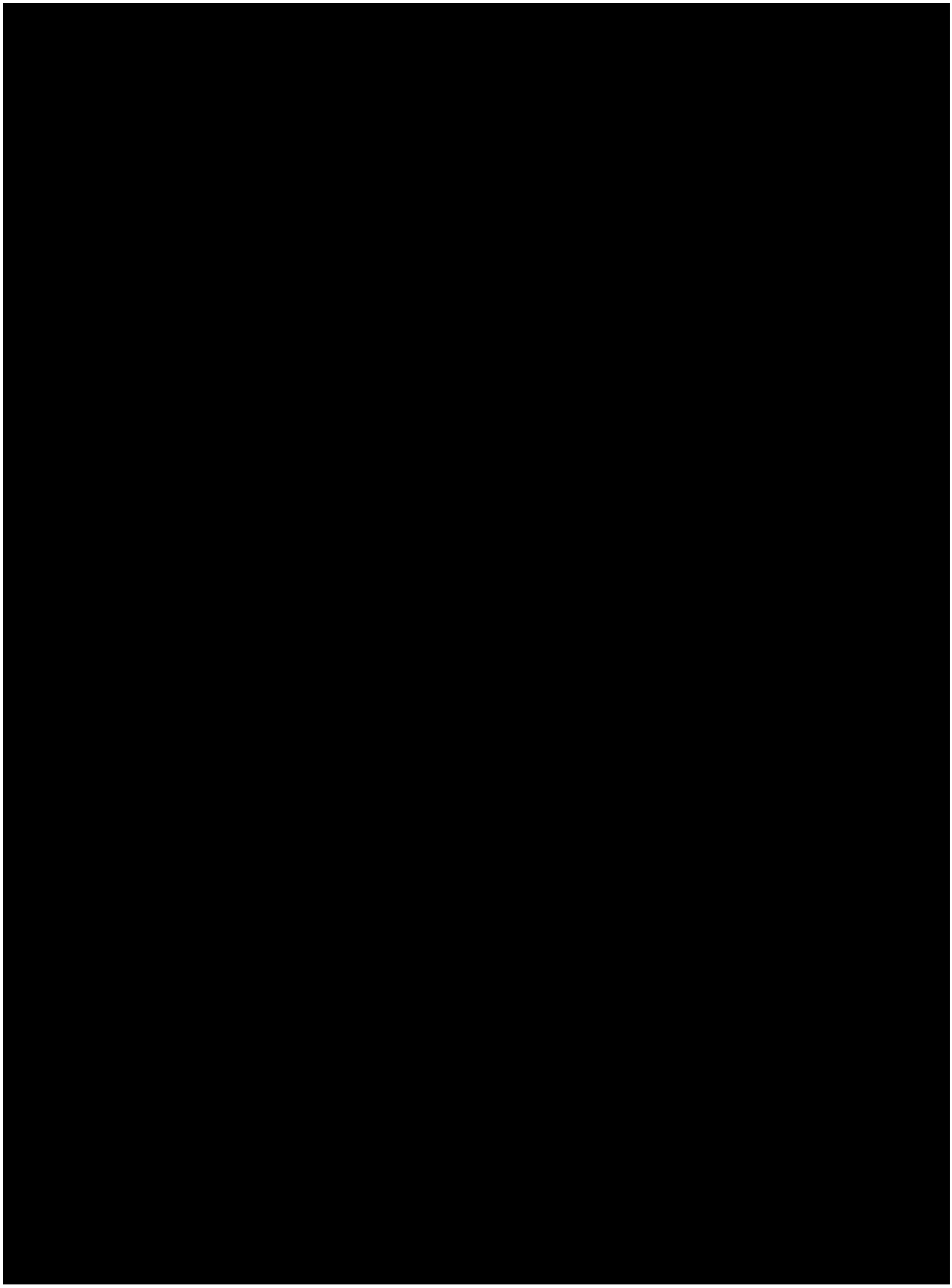
After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit will be documented and summarized in the CTR.

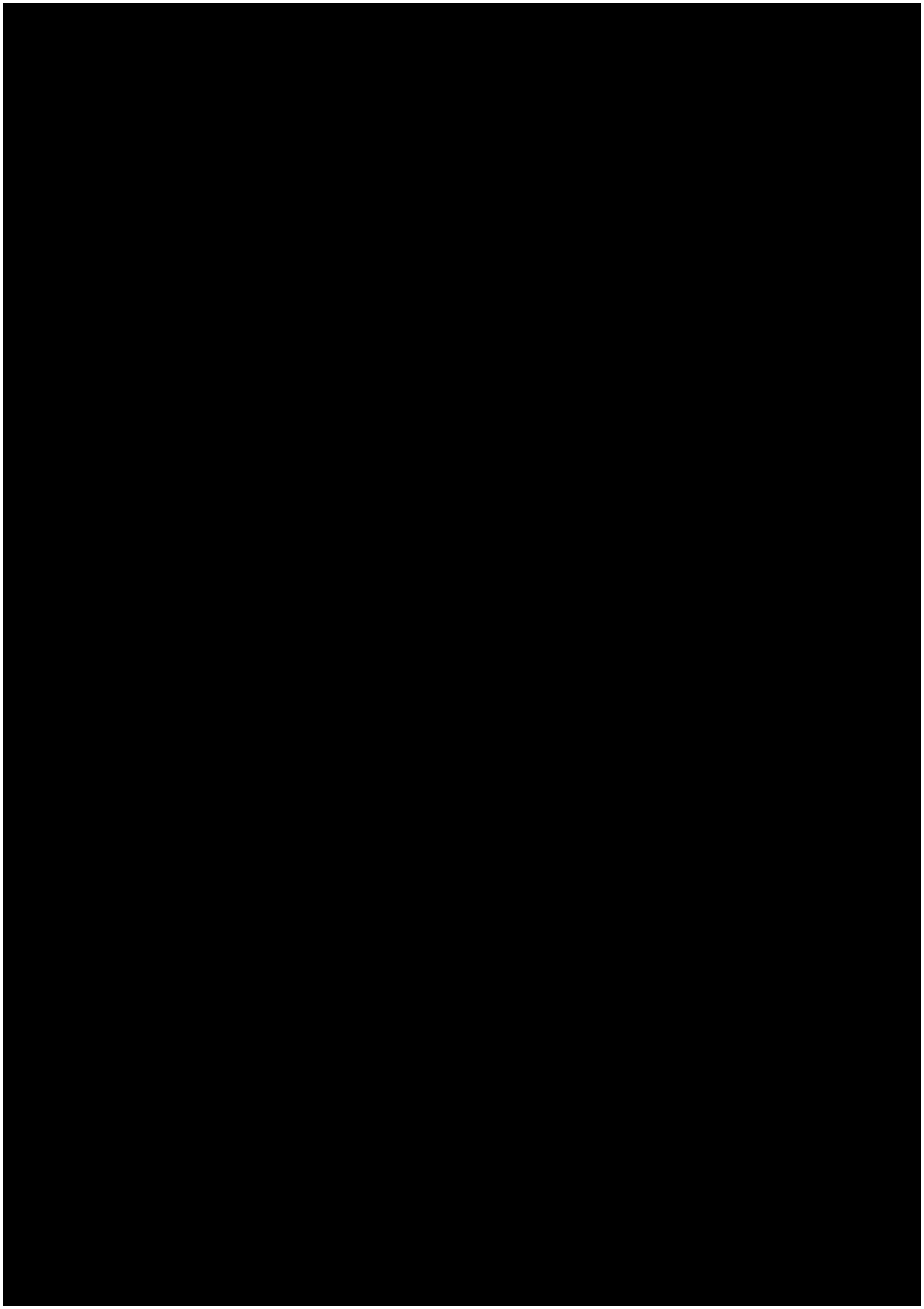
9. REFERENCES

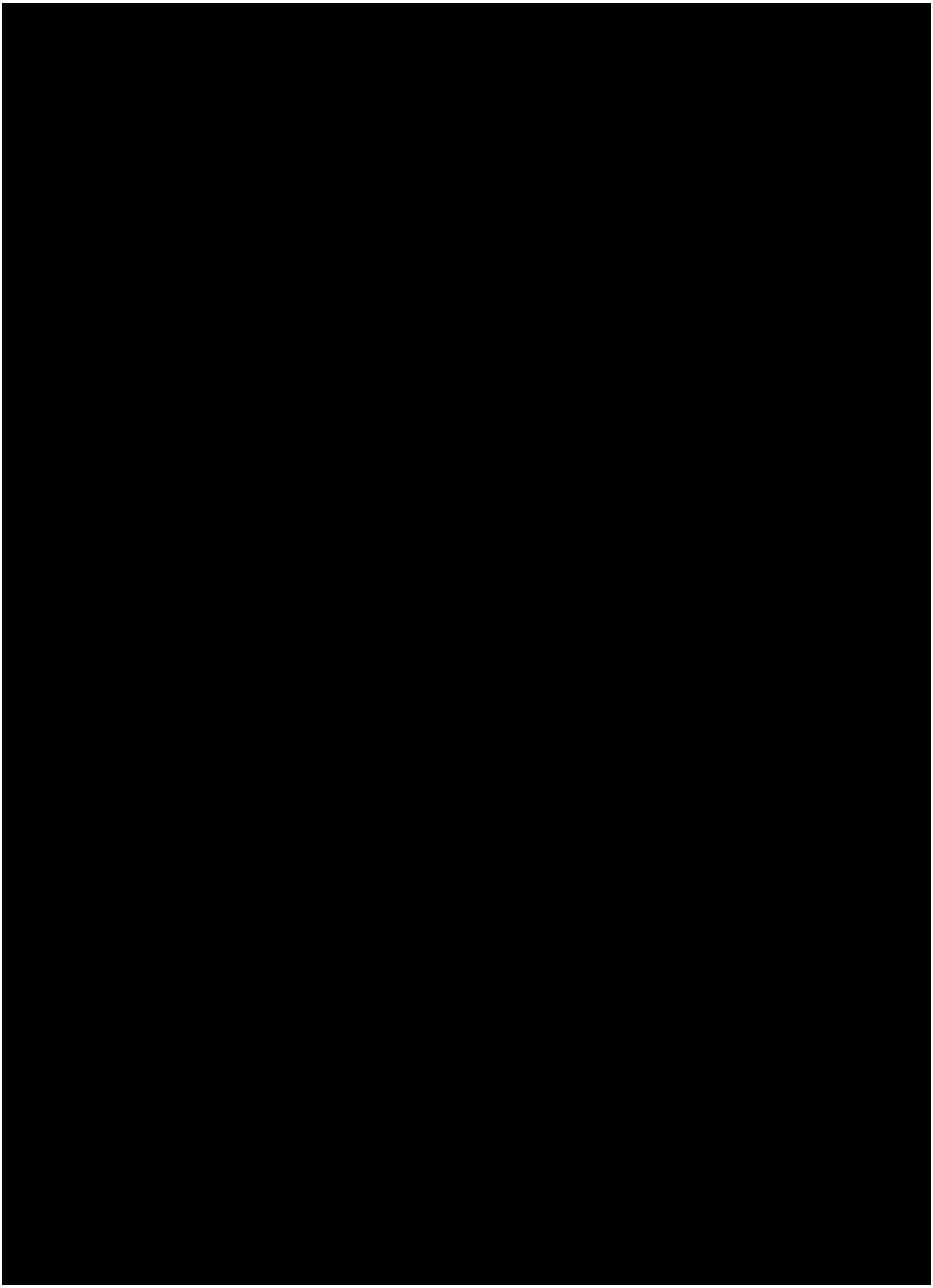
1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding' (February 19, 2015). Comprehensive R Archive Network 2015; [R15-2001]
3.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
4.	*BI-KMED-COPS-TMP-0001:* "Important Protocol Deviation (iPD) log", current version; IDEA for CON
5.	*BI-KMED-BDS-HTG-0035:* "How to Guide: Handling of missing and incomplete AE dates", current version; IDEA for CON.
6.	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
7.	*BI-KMED-BDS-HTG-0045:* "How to Guide: Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
8.	*BI-KMED-BDS-HTG-0041:* "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
9.	*CPMP/ICH/137/95:* "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
10.	*BI-KMED-BDS-HTG-0042:* "How to Guide: Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

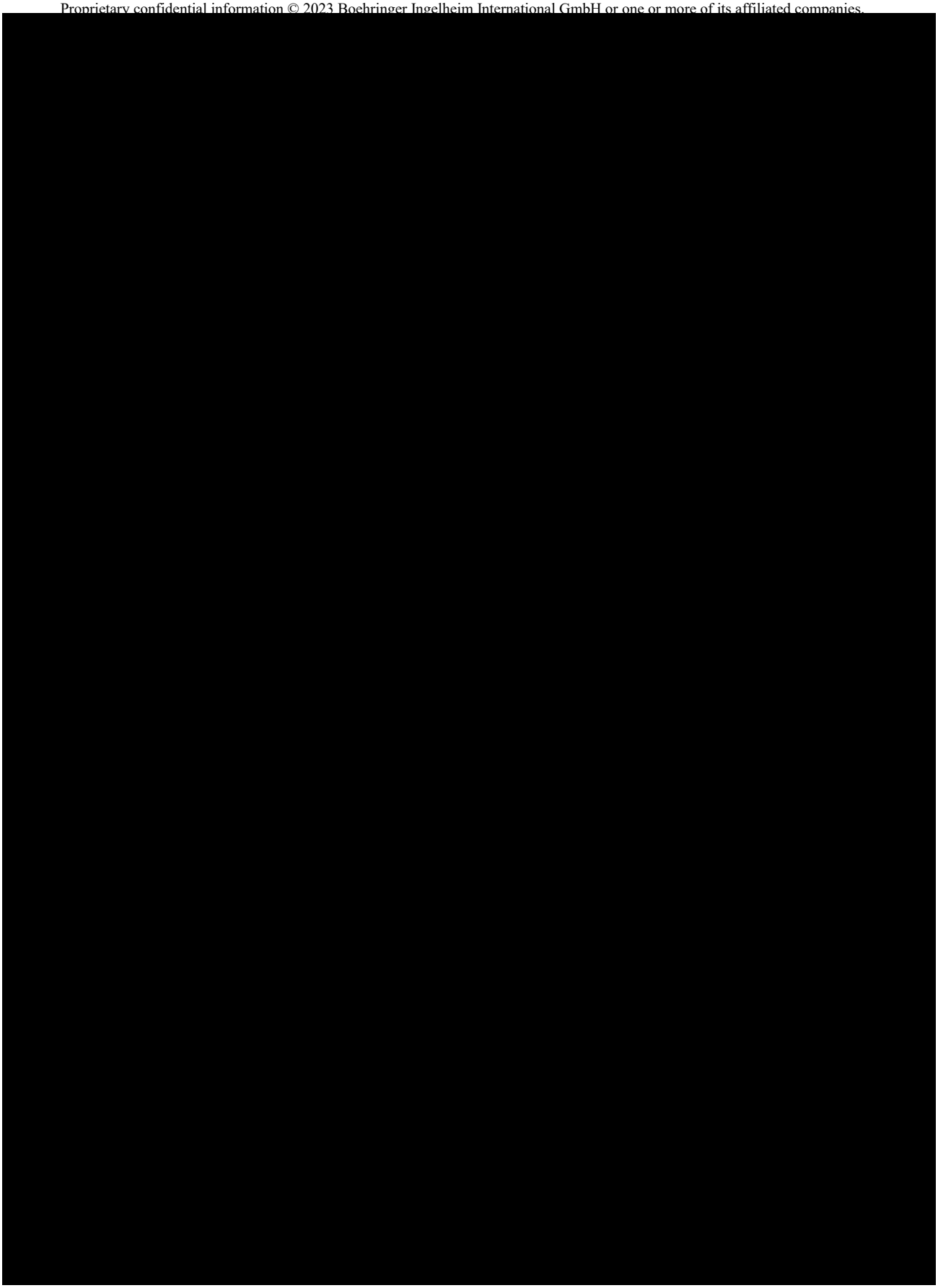


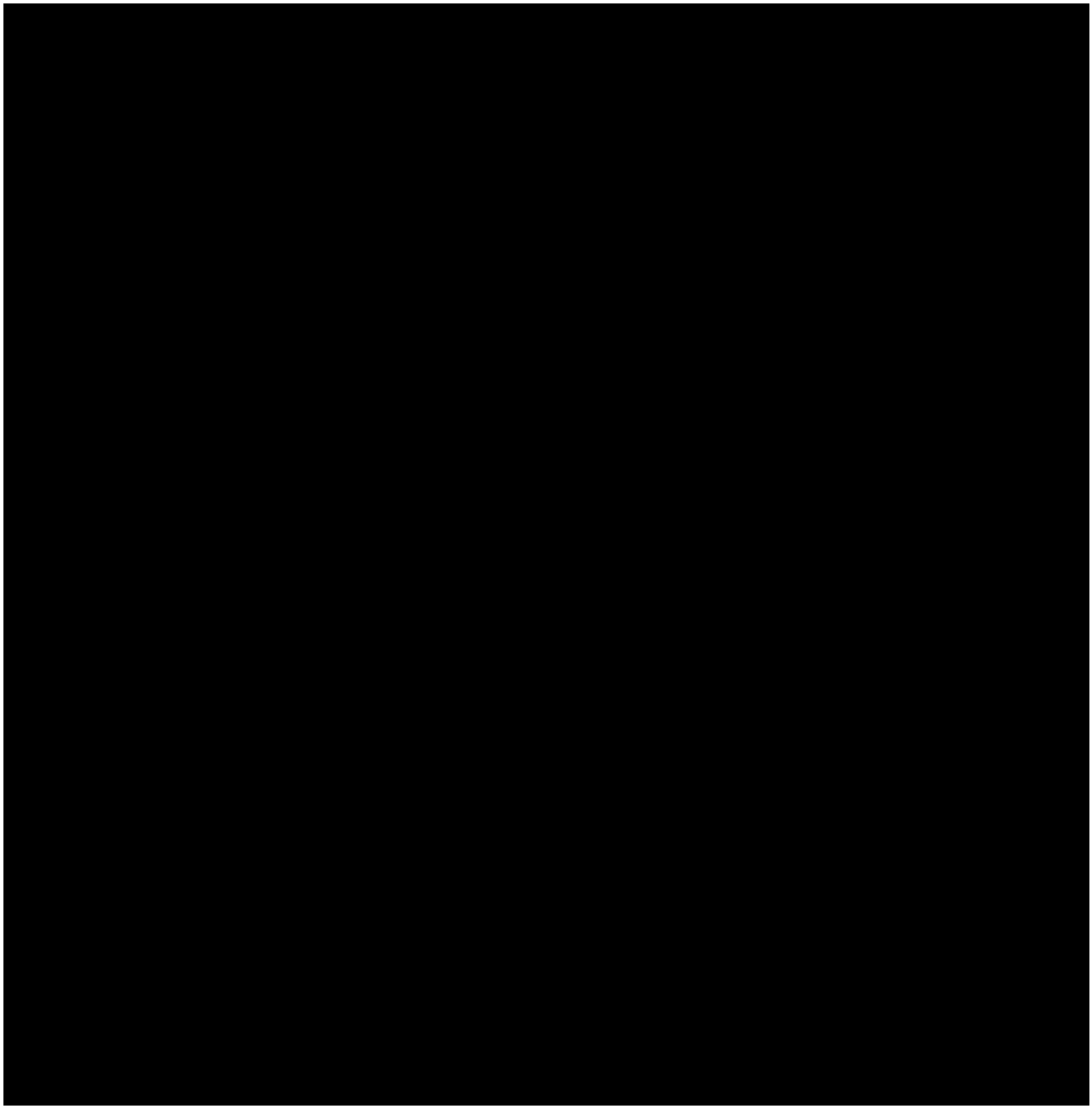












11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**21-JUNE-23**	[redacted]	None	This is the final TSAP.

APPROVAL / SIGNATURE PAGE

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Document Name: 8-01-tsap-core

Title: A Phase II, 8-week-treatment, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, tolerability, and safety of orally administered BI 1358894 in patients with Post-Traumatic Stress Disorder (PTSD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	21 Jun 2023 18:20 CEST
Approval-Clinical Program [redacted]		21 Jun 2023 19:45 CEST
Approval		22 Jun 2023 15:05 CEST
Approval-Clinical Trial Leader		22 Jun 2023 17:25 CEST
Approval-Medical Writer		22 Jun 2023 20:55 CEST
Author-Clinical Pharmacokineticist		23 Jun 2023 08:06 CEST

(Continued) Signatures (obtained electronically)

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