TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_3722045_1.0**
BI Trial No.:	1447-0012
Title:	A 6-week, multi-centre, randomised, double-blind (participant and investigator), placebo-controlled, dose-finding trial to evaluate the efficacy, tolerability, and safety of different doses of oral BI 1569912 in patients with major depressive disorder
Investigational Product(s):	BI 1569912
Responsible trial statistician(s):	[redacted]
Date of statistical analysis plan:	10 JUN 2025
Version:	1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criteria
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
[redacted]	
CI	Confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	
DBL	Database lock
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDMS	Electronic Document Management System
EMA	European Medicines Agency
EoS	End of Study
EoT	End of Treatment
[redacted]	
FCS	Fully conditional specification
FDA	Food and Drug Administration
[redacted]	
HDRS-17	Hamilton Depression Rating Scale-17
HR	Heart rate
ICE	Intercurrent event

Term	Definition / description
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
iPD	Important protocol deviation
IRT	Interactive response technology
[redacted]	
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOi	Monoamine Oxidase Inhibitors
Max	Maximum
MCPMod	Multiple Comparison Procedures and Modelling
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
[redacted]	
PAS	Primary analysis set
[redacted]	
PN	Preferred name
PoCC	Proof of clinical concept
PRO	Patient-reported Outcome
PT	Preferred term
Q1	First quartile
Q3	Third quartile
[redacted]	
REML	Restricted maximum likelihood estimation
REP	Residual effect period

Term	Definition / description
RPM	Report Planning Meeting
RS	Randomised set
RUN	Data Ready to be Unblinded and/or Final Trial Closure Notification
SAE	Serious adverse event
SCS	Screened set
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
[redacted]	
SDG	Standardized Drug Grouping
[redacted]	
SNRI	Serotonin and norepinephrine reuptake inhibitor
SoA	Schedule of assessments
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic Antidepressants
TEAE	Treatment-emergent adverse event
[redacted]	
TMF	Trial master file
TS	Treated set
TSAP	Trial Statistical Analysis Plan
[redacted]	
WHO	World Health Organization Drug Dictionary
[redacted]	

Term	Definition / description
[redacted]	
PR	Pulse rate
[redacted]	

Term	Definition / description
[redacted]	

3. INTRODUCTION

As per ICH E9 [ref. 9.1, ref 9.2], 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 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, randomisation.

R version 4.2.2 or higher will be used for analyses based on Multiple Comparison Procedures and Modelling (MCPMod), with DoseFinding R-package 1.2-1. or higher, and SAS® Version 9.4 or higher will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

- Throughout the TSAP, text was updated compared to the protocol, to clarify that data will be analysed under the time points as defined in Section 6.7, rather than under the scheduled visits.
- [redacted]
- The description of participants included in the Mixed Model for repeated Measures (MMRM) was updated to clarify that the analysis method automatically excludes observations of participants without a baseline and at least one post-baseline value from analysis, as this restriction does not lead to an additional analysis set.
- [redacted]
- [redacted]
- [redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

CTP section 2.1.2:

- *Change from baseline in MADRS total score at Week 6*

5.1.1 MADRS - Montgomery-Åsberg Depression Rating Scale

CTP section 5.1.1.1:

The MADRS is a clinician-reported interview guide designed to assess the severity of symptoms in depressive illness and to be sensitive to treatment effects […]. The MADRS consists of 10 items:

1. *reported sadness*

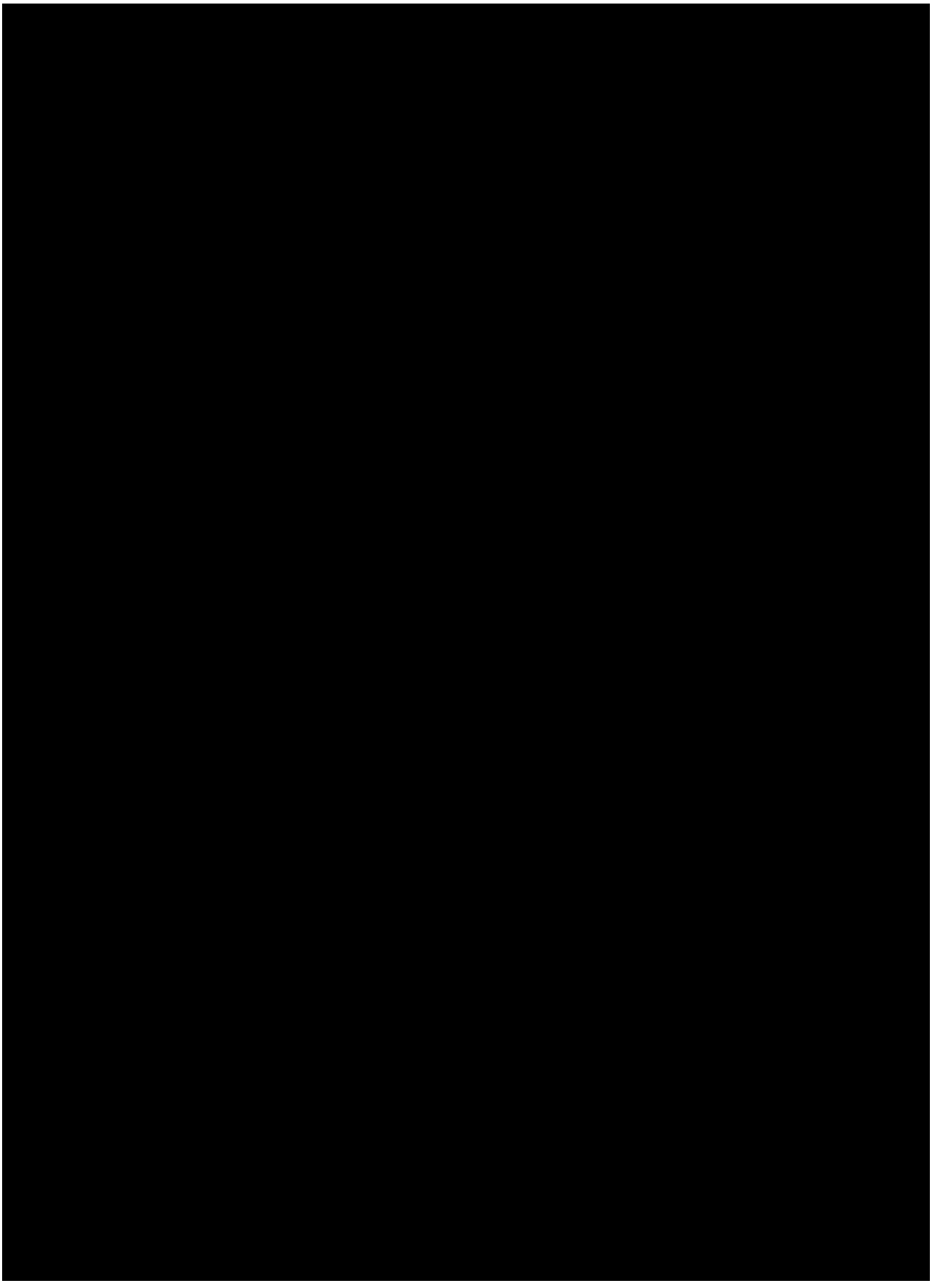
2. *apparent sadness*
3. *inner tension*
4. *reduced sleep*
5. *reduced appetite*
6. *concentration difficulties*
7. *lassitude*
8. *inability to feel*
9. *pessimistic thought*
10. *suicidal thoughts*

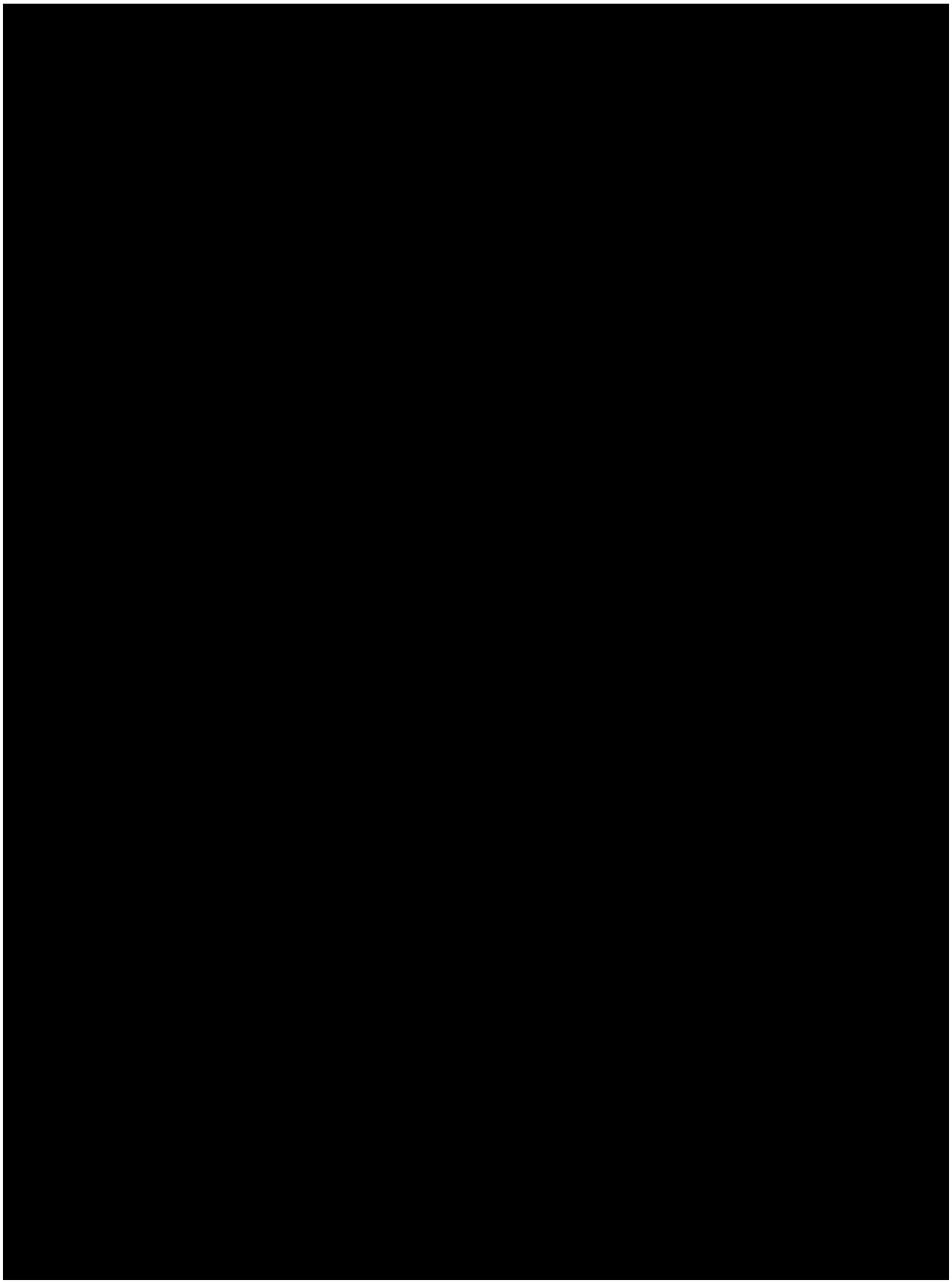
Symptoms are rated on a 7-point Likert scale from 0 (no symptom) to 6 (severe symptom). Definitions of severity are provided at 2-point intervals. The possible total score could range from 0 to 60 (from normal with absence of symptoms to severe depression). A recall period of 7 days will be used at all visits.

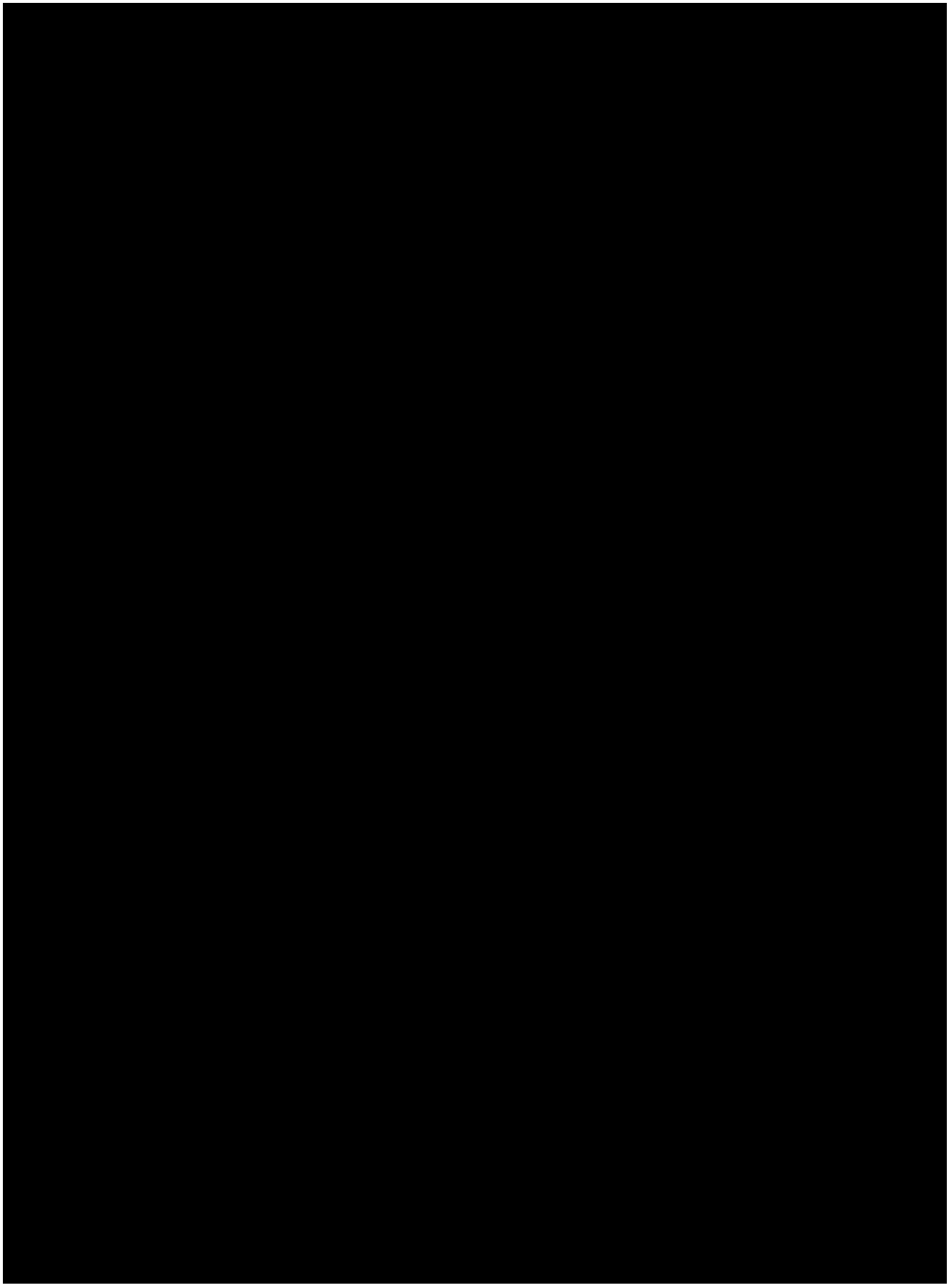
5.2 SECONDARY ENDPOINT(S)

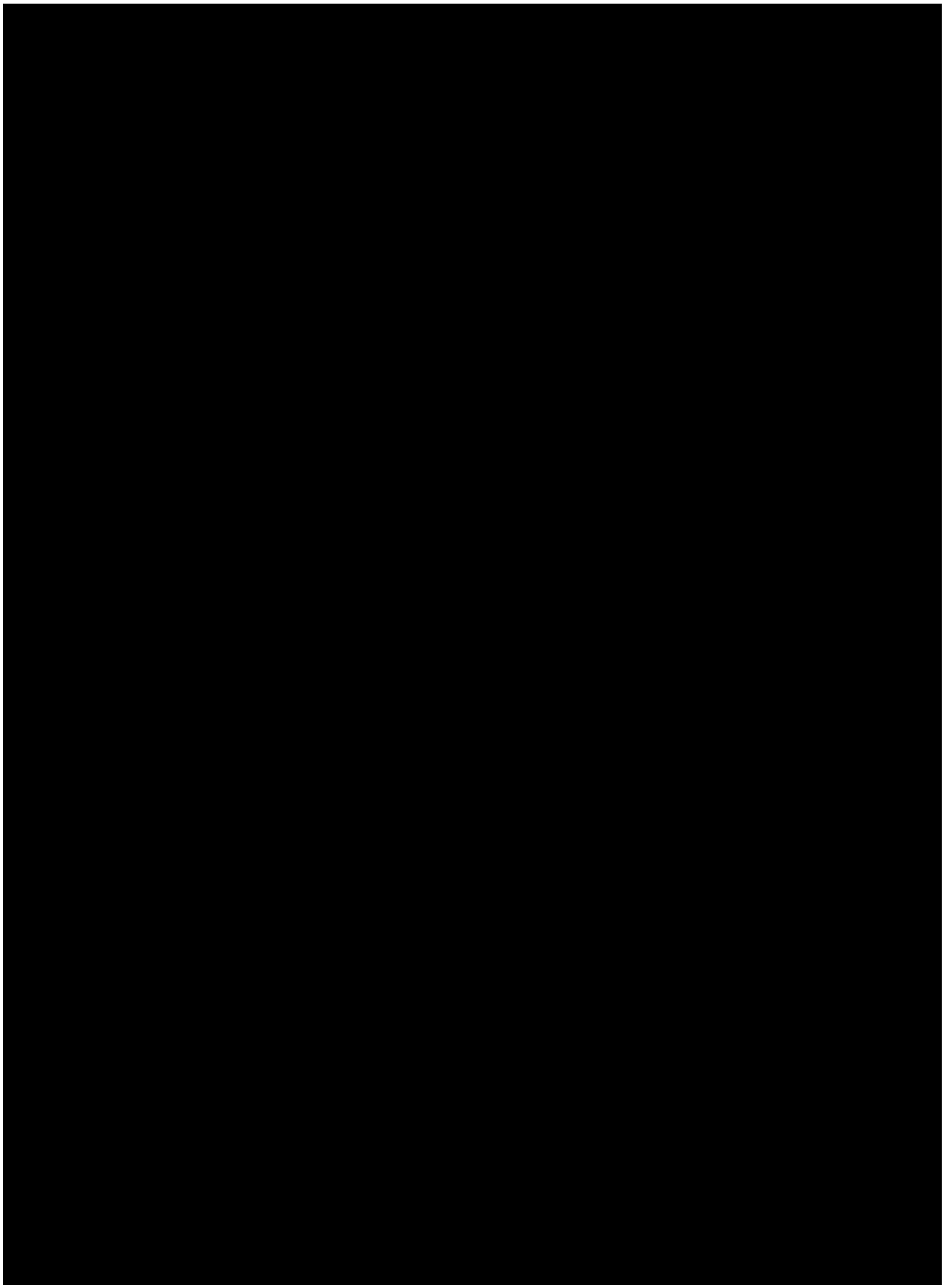
CTP Section 2.1.3:

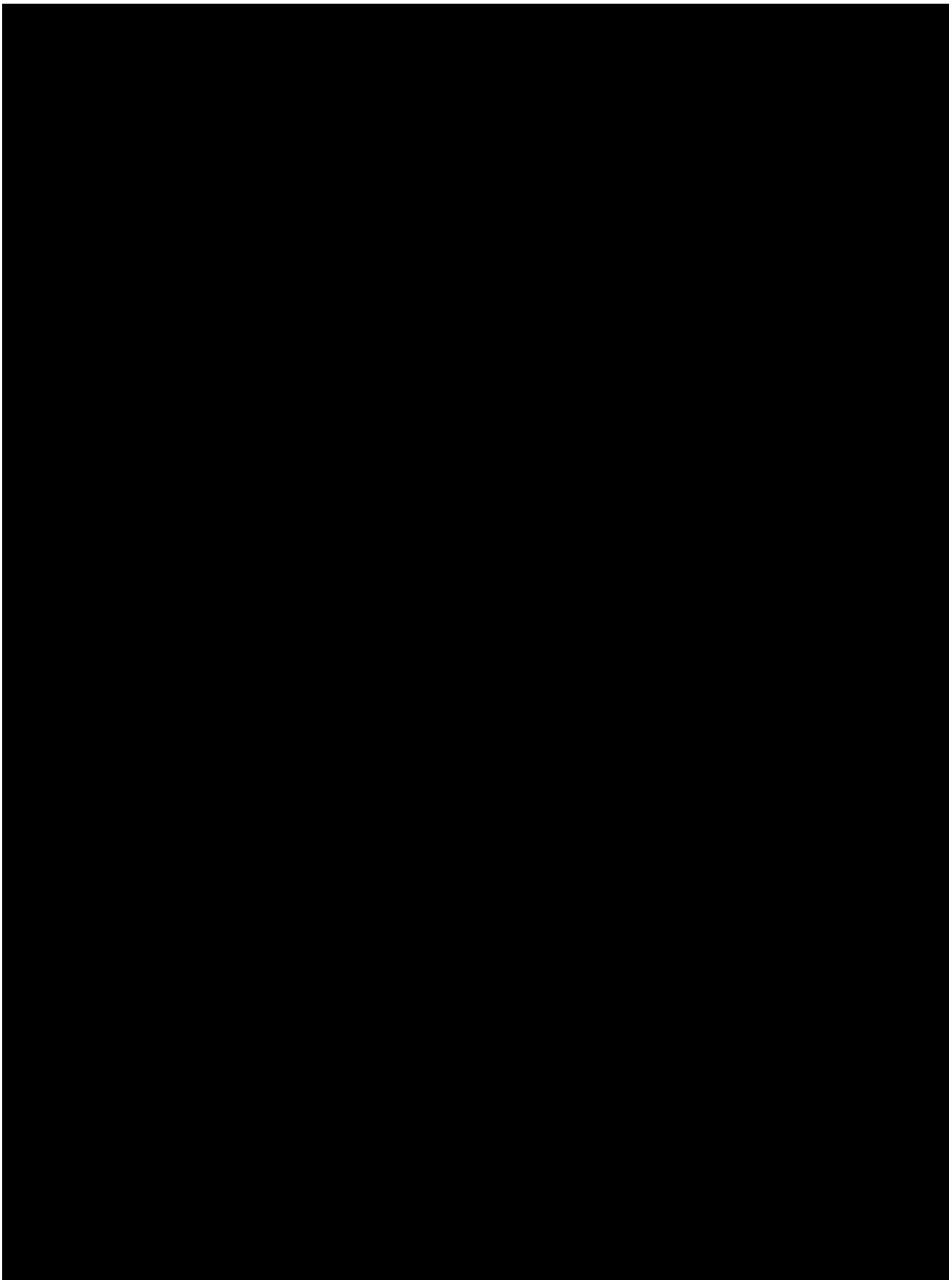
No secondary endpoints have been defined for this trial.

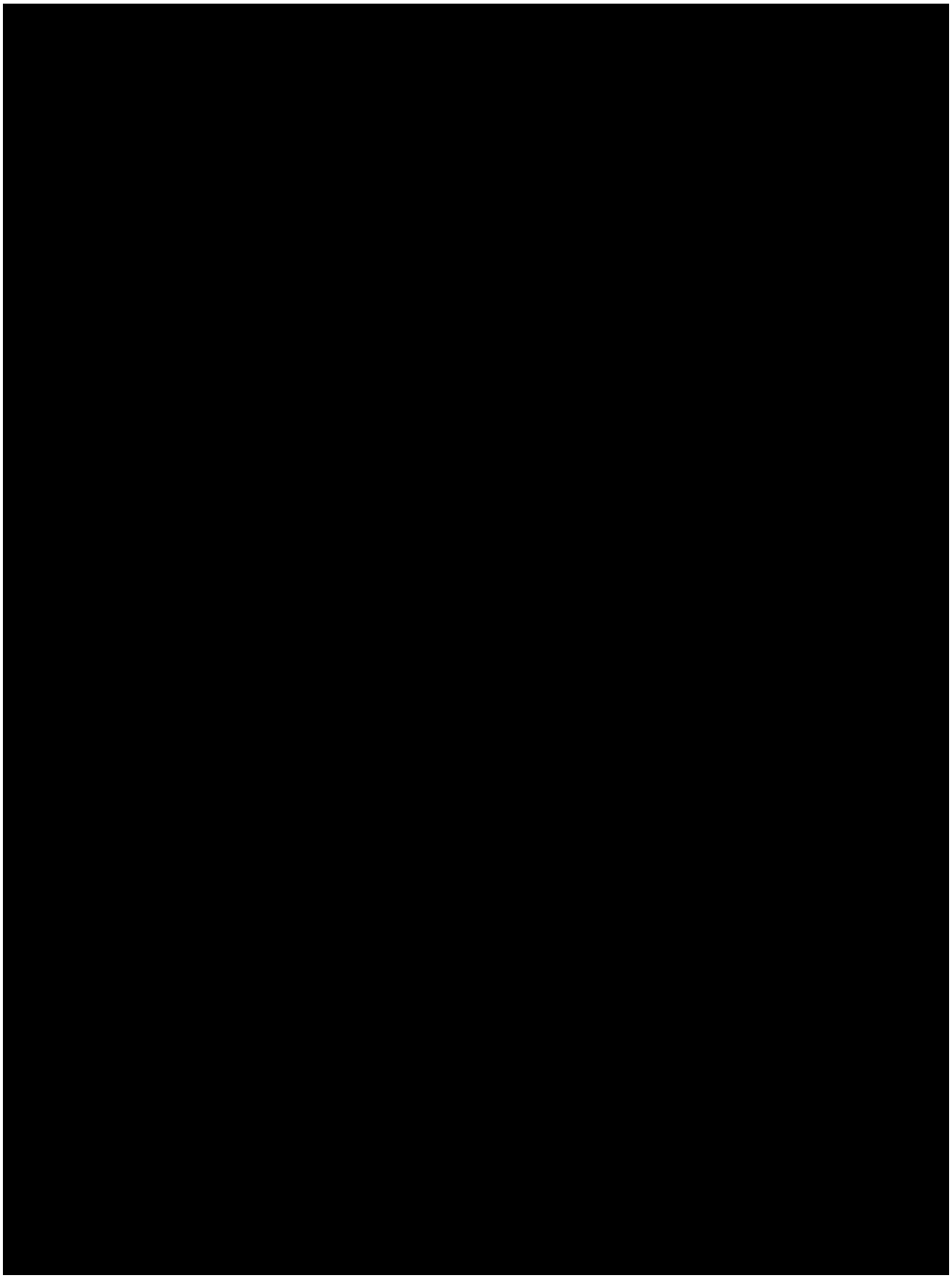


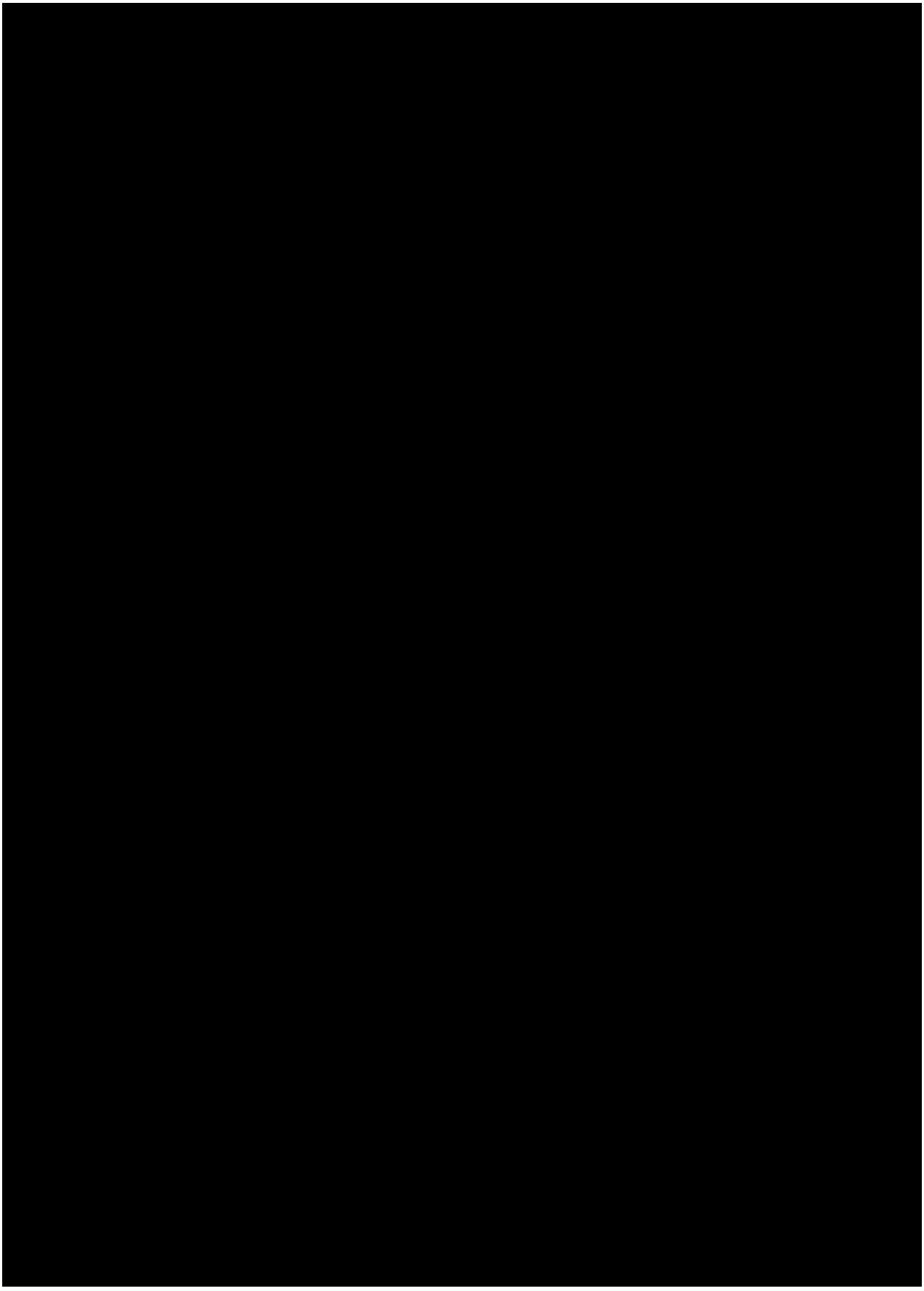












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Section 4. The Residual Effect Period (REP) is discussed in CTP Section 1.2 and set to 8 days for this study's analyses.

For statistical analysis, the following analysis phases are defined for each participant:

Table 1: Study analysis phases

Study analysis phase	Label	Start	End[1]
Screening	**Screening**	Date of informed consent	Date/time of first administration of trial drug
On-treatment	**Placebo, 5 mg BI, 10 mg BI, 20 mg BI**	Date/time of first administration of trial drug	Date/time of last administration of trial drug + REP or 00:00:00 on day after last contact date[2] (whichever occurs first)
Follow-up	**F/U Placebo, F/U 5 mg BI, F/U 10 mg BI, F/U 20 mg BI,**	Date/time of administration of trial drug + REP	00:00:00 on day after last contact date

Note: The defined study analysis phases may or may not exist for a participant. If the derived start of an analysis phase is on or after the derived end of the analysis phase, the phase will be considered missing.
[1] Phases are defined excluding the respective end date/time.
[2] Last contact date is the end of study participation date as recorded on the CRF for most of the patients; if the patient was lost to follow-up, it is the date the patient was last successfully contacted by the site or known to be alive; if the patient died, it is the date of death

6.2 IMPORTANT PROTOCOL DEVIATIONS

A [redacted] is important if it affects the rights or safety of the study participant, or if it can potentially influence the data integrity in a non-negligible way. The documentation of the important [redacted] (i[redacted]) categories and how to handle iPDs in the analysis are done in the iPD Specification Document, which is stored within the trial master file (TMF) in Electronic Document Management System (EDMS). The decision on exclusion of participants or data points from the analysis will be made at the Report Planning Meeting (RPM) at the latest after discussing exceptional cases and implications for the analyses.

6.3 INTERCURRENT EVENTS

The intercurrent events (ICE) of interest in this trial are:

- Death, with date and time of death as recorded on the EoS / Adverse Event eCRF pages.
- Treatment discontinuation, with date/time of last IMP intake as the date/time of the intercurrent event,
  - due to reasons related to IMP (any treatment discontinuation with reason "Perceived lack of efficacy" or reason "Adverse Event", with the corresponding AE indicated as being related to study treatment),
  - due to reasons unrelated to IMP (all other reasons).
- Change in (pharmacological or non-pharmacological) antidepressant treatment:
  - Introduction of further antidepressant treatments: Cases will be identified via manual review. Final decisions will be made during the last RPM. All identified cases will be documented in the Clinical Trial Analysis Decision Log [ref. 9.3].
  - Change in existing background psychotherapy (stop of baseline psychotherapy, start of new psychotherapy after first IMP intake, change in frequency and/or session settings of baseline psychotherapy), with date/time defined as the

minimum of the end date/time of respective psychotherapy recorded at baseline and start date/time of a newly initiated psychotherapy

CTP Section 7.2.2:

The primary treatment effect of interest is the effect obtained at the primary time point if the participant had stayed on randomised IMP, i.e. cases of treatment discontinuation, regardless of reason [(including death)*], will be handled using a hypothetical approach […]. Data collected after treatment discontinuation + [*residual effect period (]*REP[)] will be censored and will not be included in the analysis.*

Changes in antidepressant treatment [including changes in background psychotherapies] *will be disregarded in the primary analysis of treatment effect, i.e. they will be handled using the treatment policy approach as defined in ICH E9(R1).*

[redacted]

Table 2: Strategies for handling ICEs

ICE	**Primary**	[redacted]
Death	Hypothetical	
Treatment discontinuation related to IMP	Hypothetical	
Treatment discontinuation unrelated to IMP	Hypothetical	
Change in pharmacological or non-pharmacological) antidepressant treatment	Treatment policy	
Analysis flags to be used (REP = 8 days)	*ANL01FL='Y'*	

Each analysis will reference the strategy for handling ICEs that was used.

For the handling of efficacy assessments after the REP within the different strategies, please see Section 6.6.4.

6.4 PARTICIPANT SETS ANALYSED

CTP Section 7.2.1:
Statistical analyses will be based on the following main analysis sets:

- *Treated set (TS):*

  *The TS includes all participants who were randomized and treated with the IMP. The TS will be used for safety and most of the efficacy analyses. Safety analyses will be conducted using actual treatment received. [*Participants to whom medication from kits with varying medication was dispensed will be included in the safety analyses with their randomised treatment. For these participants as well as for participants who received medication different from the one assigned for the entire trial, additional listings will be created to support review of safety-related data in relation to the actual treatment received.] *For efficacy analyses, treatment assignment will be as randomised, unless specified otherwise.*

- *Primary analysis set (PAS)*

  The PAS comprises all randomised participants who received at least one dose of IMP during the trial and had a baseline MADRS total score ≥24. The primary analysis [and all MADRS-based analyses] *will be performed on the PAS and will be based on assigned treatment.*

Additionally, for participant disposition, the following analysis sets will be considered:

- Screened set (SCS):

  The SCS includes all participants who have signed informed consent.

- Randomised set (RS):

  The RS includes all randomised participants, whether treated or not.

For analyses of disposition, iPDs, demographic data and baseline characteristics based on the SCS, RS or PAS, the treatment assignment will be as randomised; respective analyses based on the TS will be conducted using actual treatment received.

Table 3: Participant Sets Analysed

	Participant set				
Class of endpoint	SCS	RS	TS	PAS	[redacted]
Disposition	X				
iPDs		X			
Demographic data/baseline characteristics			X	X	
Primary endpoint			X	X	
[redacted]					
Treatment exposure			X		
Other safety parameters			X		
[redacted]					
[redacted]					

[redacted]

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Questionnaire-based data

As all questionnaires except for MADRS and HDRS-17 are captured electronically, it is expected that, for a time point, the questionnaire is either fully completed or completely missing – missing single items or multiple answers for one item are not expected for the electronically captured questionnaires. In the unlikely case that such events occur, [redacted] missing values will not be imputed and summary scores derived from these items will be missing.

6.6.1.1 MADRS Total Score [redacted]

In case a single item of the questionnaire is missing at a time point, the total score will be set to missing for this time point, too. [redacted]

Considering analysis of change from baseline in MADRS total score [redacted] the MMRM used for these analyses implicitly imputes missing data, assuming they are missing at random.

[redacted]

6.6.1.2 Other Questionnaire-based Endpoints

[redacted]

In analysis of endpoints based on MMRM, the analysis implicitly imputes missing data, assuming they are missing at random. No other imputation of missing data will be performed for these endpoints.

6.6.2 AE [redacted]

Missing or incomplete AE dates are imputed according to Boehringer Ingelheim standards [ref 9.10].

[redacted]

[redacted]

6.6.4 Handling of efficacy assessments after REP

The primary characterisation of efficacy will be on treatment which will assume all participants took randomised treatment for the duration of the trial.

Consequently, analyses using the primary analysis approach, with the primary strategy for handling ICEs (see Section 6.3) will be on treatment, i.e. data observed after last IMP intake + REP will generally be excluded from these analyses.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, the last non-missing value within the pre-dose time window will be defined as baseline. [redacted] If the time of an assessment/measurement (except for ECG) was not captured, and it was on the same day IMP administration started, it will be assumed that it was taken prior to first IMP; for ECG, which was planned to be performed after first IMP intake at Visit 2 as per CTP, such assessments will not be considered for baseline.

Time windows will be used as described in the following tables, in order to assign data to the relevant visit/time point based on the actual date/time of the assessment. Data will then be analysed using these assigned analysis visits/time points in the statistical tables. Assignment of values to time windows is thereby in general irrespective of the analysis phase (Screening, On-treatment, or Follow-up) they fall into. Consequently, if analyses require participants with at least one non-missing post-baseline value to be included, then this refers to available values within the analysis time windows and for the relevant analysis phase (if applicable).

However, in the listings, all assessments performed will be displayed (even if outside the analysis time windows), along with the assigned analysis visits/time points (if applicable).

Analysis time windows for different assessments are defined in Table 4, Table 5, Table 6, and Table 7, with Day 1 referring to the day of first IMP intake in all cases. [redacted]

If after assignment of analysis time windows, two or more values fall within the same post-dose analysis time window, then the measurement closest to the planned time point will be used for analysis. In case two measurements are equidistant from the planned time point, then the later one will be picked. For Day 1 (post-dose for ECG), Day 8, Week 2, Week 4, and Week 6, in the above, on-treatment values will generally be prioritized over follow-up values. I.e. if there is one or more on-treatment values in the respective time window, the analysis value will be selected from the available on-treatment values. Follow-up values will only be considered if there are no on-treatment values within the respective time window.

Consequently, if statements are made regarding ‘all post-baseline values to be included’ for an analysis considering analysis time windows, then this includes only the respectively flagged values within the time windows (and analysis phase).

Adherence to time windows will be checked at the last RPM at the latest. Any handling of assessments differing from the described general rules will be documented in the Clinical Trial Analysis Decision Log [ref. 9.3]. [redacted]

Table 4: Analysis time windows for MADRS, [redacted]

Assessments	Label	Target day	Analysis time windows	
			Start	End
MADRS, [redacted]	Pre-dose	1		Day 1, prior to IMP
	Day 8	8	Day 6	Day 9
	Week 2	15	Day 11	Day 22
	Week 4	29	Day 23	Day 36
	Week 6	43	Day 37	
[redacted]				
[redacted]				

Table 5: Analysis time windows for [redacted], Safety lab (blood/urine), and vitals

Assessments	Label	Target day	Analysis time windows	
			Start	End
[redacted], Safety lab (blood/urine/drug screening), vitals	Pre-dose	1	Day -35	Day 1, prior to IMP
	Day 8	8	Day 6	Day 10

Assessments	Label	Target day	Analysis time windows	
			Start	End
(excluding weight, BMI, height)	Week 2	15	Day 11	Day 22
	Week 4	29	Day 23	Day 36
	Week 6	43	Day 37	Day 47
	Week 8	51	Day 48	
Weight, BMI	Pre-dose	1	Day -35	Day 1, prior to IMP
	Week 6	43	Day 37	Day 47
Height	Pre-dose	1		Day 1, prior to IMP

Table 6: Analysis time windows for ECG

Assessments	Label	Target day	Analysis time windows	
			Start	End
ECG	Pre-dose	1	Day -35	Day 1, prior to IMP
	Day 1	1	Day 1, post IMP	Day 1, 23:59
	Day 8	8	Day 6	Day 10
	Week 4	29	Day 23	Day 36
	Week 6	43	Day 37	Day 47
	Week 8	51	Day 48	

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	1st quartile
Median	median
Q3	3rd quartile
Max	maximum

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the

respective treatment group (unless otherwise specified, all participants in the respective participant set whether they have non-missing values or not).

The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.

Any p-value presented will be from two-sided tests and confidence intervals (CI) will be two-sided 95% CI, unless otherwise specified. Apart from the p-values from the primary test for a flat dose response relationship on change from baseline in MADRS total score at Week 6, all p-value presented will be considered descriptive (nominal) in nature.

Analyses performed by treatment group will consider the following treatment groups:

- Placebo,
- 5 mg BI,
- 10 mg BI,
- 20 mg BI,
- BI total (where applicable), and
- Total (where applicable).

Thereby, summary tables of disposition, demographics and other baseline characteristics data, as well as descriptive summaries of safety data, including treatment compliance and treatment exposure data, and descriptive summaries of efficacy data will in general include a BI total and a total column.

For model-based analyses, unless stated otherwise, the actual strata “number of antidepressants used for the current episode” (0 vs 1) and “baseline MADRS total score” (< 24 vs ≥24)) as documented in the eCRF will be used, as applicable. If erroneous data was documented and used for randomisation in IRT, this will be described accordingly – but these erroneous data will in general not be used for the model-based analyses.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Unless otherwise stated, summaries will be provided for the TS.
Substance use data will be summarised by visit, using the number of patients at each visit as the denominator for percentage calculation.
A summary of suicidal ideation and suicidal behaviour data from the C-SSRS as collected at screening will be provided.

Furthermore, demographic data, baseline conditions, and additional medical history of study indication will be displayed for the PAS, as well as by subgroup for the subgroups defined in Section 6.5, also based on the PAS. An overview of the number of patients in the different subgroups will also be provided for the PAS.

Additionally, a listing of participants who were re-screened, including reason for initial screen failure and status following the final screening (i.e. screen failed or randomized) will be provided.

7.2 CONCOMITANT DISEASES AND MEDICATION

Baseline conditions (ongoing at the date of informed consent) / medical history (not ongoing after date of informed consent) will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at Boehringer Ingelheim at the time of database lock (DBL). They will be summarised descriptively, separately by MedDRA system organ class (SOC) and preferred term (PT).

Concomitant medications will be coded using the current World Health Organization Drug Dictionary (WHO-DD) version in use at Boehringer Ingelheim at the time of database lock.

Concomitant non-drug therapies will be coded using the current MedDRA version in use at BI at the time of DBL.

A medication/non-drug therapy will be considered concomitant to treatment, if

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

A medication/non-drug therapy will be considered concomitant to follow-up, if

- it is ongoing at the start of the follow-up analysis phase, or
- starts within the follow-up analysis phase (see Section 6.1 for a definition of analysis phases).

In case of missing or incomplete date/time information, a medication/non-drug therapy will be considered concomitant to treatment and follow-up, unless the available information (including the flag indicating that a medication/non-drug therapy was ongoing at the end of study) clearly indicates that the medication/non-drug therapy was not concomitant to treatment or follow-up, respectively.

Concomitant medications (concomitant to treatment, and concomitant to treatment or follow-up) will be summarised by Anatomical Therapeutic Chemical (ATC) classification and preferred name (PN), using the ATC3 levels for the TS. These summaries will be sorted alphabetically by ATC class, and by decreasing frequency in “Total”-column within ATC class.

Medications concomitant to treatment will additionally be displayed for the PAS, as well as by subgroup for the subgroups defined in Section 6.5, also based on the PAS.

Psychotherapy for the primary indication (MDD) at baseline (i.e. ongoing at time of first IMP intake) will be summarised descriptively, via frequency tables for frequency and session setting for the TS. The number and percentage of participants with on-treatment changes in psychotherapy will also be provided within the overview of ICE.

Other non-drug therapy data will only be listed.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Summaries will be provided by visit, based on the number of patients per visit for the TS.

7.4 INTERCURRENT EVENTS

Intercurrent events will be summarised as number and percentage of participants with each ICE. By-participant-listings of all ICEs will be created.

7.5 PRIMARY OBJECTIVE ANALYSIS

7.5.1 Main analysis

CTP Section 7.2.3.1:

[…] *the primary endpoint is the change from baseline to Week 6 in MADRS total score.*

[MCPMod is used for the primary analysis of the primary endpoint – to test the null hypothesis that there is a flat dose response curve comparing placebo and the BI 1569912 dose groups on the primary endpoint.]

MCPMod (multiple comparison and modelling techniques) [ref. 9.17] *is used to evaluate several possible dose response models (patterns). As a basis for the MCPMod analysis, a restricted maximum likelihood estimation (REML) based on a mixed model for repeated measures (MMRM) analysis will be used to generate covariate adjusted estimates of mean change from baseline in MADRS total score at Week 6 and associated covariance matrices. The model will include fixed categorical effects of treatment at each visit and number of antidepressant treatments taken for current episode (0 versus 1), and fixed continuous effects of baseline MADRS total score at each visit.*

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors (SEs). Least-squares mean estimates per dose group and differences to placebo at each time point, corresponding two-sided 95% CIs and p-values will be presented in tables. Further, for the differences to placebo at each time point, standardized effect sizes will be calculated based on the results/estimates of this analysis (standardized effect size = (adjusted mean difference in change from baseline between treatment groups) / (SE / sqrt(1/n + 1/m)), where n and m are the number of participants in the respective treatment group).

Additionally, adjusted means and corresponding SEs will be presented graphically over time.

For the MMRM, an unstructured covariance matrix will be assumed. In case of non-convergence the following steps will be taken (in that order) to overcome convergence issues:

1. Add the ‘singular=1e-10’ option in the model statement
   (This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).)
2. Set ‘maxiter=100’ in the Proc Mixed statement
   (This increases the number of convergence iterations used from a default of 50.)
3. Set ‘scoring=4’ to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Include the statement ‘performance nothread’
   (This removes multi-threading, possibly improving stability, but may also slow down calculations.)
5. Provide starting values for covariance parameters using a ‘parms’ statement.

6. Should none of the previous methods work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances (TOEPH). Should this also not converge, a standard Toeplitz matrix (TOEP) will be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) will be fitted.

CTP Section 7.2.3.1:

Participants from the PAS with a baseline and at least one post-baseline value with their MADRS values of all post-baseline visits, will be included in the model, according to the considered strategy for handling intercurrent events [(see Section 6.3*)* Note that the MMRM automatically excludes observations of participants without a baseline and at least one post-baseline value from analysis.]

The primary treatment comparisons will be the contrasts between each BI 1569912 treatment arm and placebo at Week 6.

The dose-response relationship of these estimates from the MMRM will then be analysed using MCPMod. Thereby, several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error at 10%, one-sided) to identify the best-fitting model or subset of models.

*A monotone dose-response relationship is assumed. For the PoCC testing and for the sample size calculations the following model assumptions (*Table 8*) and resulting graphs [*Figure 1*] have been selected to cover both the plausible and a diverse range of potential dose response patterns.*

Table 8: Dose response pattern assumptions and rationale

Model	***Description***
Linear	*Linear dose response*
Emax1	*50% of the maximum effect (ED50) is achieved at the 5 mg dose*
Emax2	*95% of the maximum effect (ED95) is achieved at the 10 mg dose*
Exponential	*5% of the maximum effect is achieved at the 5 mg dose,* *i.e. high effect only at a high dose*
Sigmoid Emax	*20% of the maximum effect (ED20) is achieved at the 5 mg dose,* *80% of the maximum effect (ED80) is achieved at the 10 mg dose,* *i.e. effect of 5 mg and 10 mg are further apart* *(fixed hill parameter h=4)*

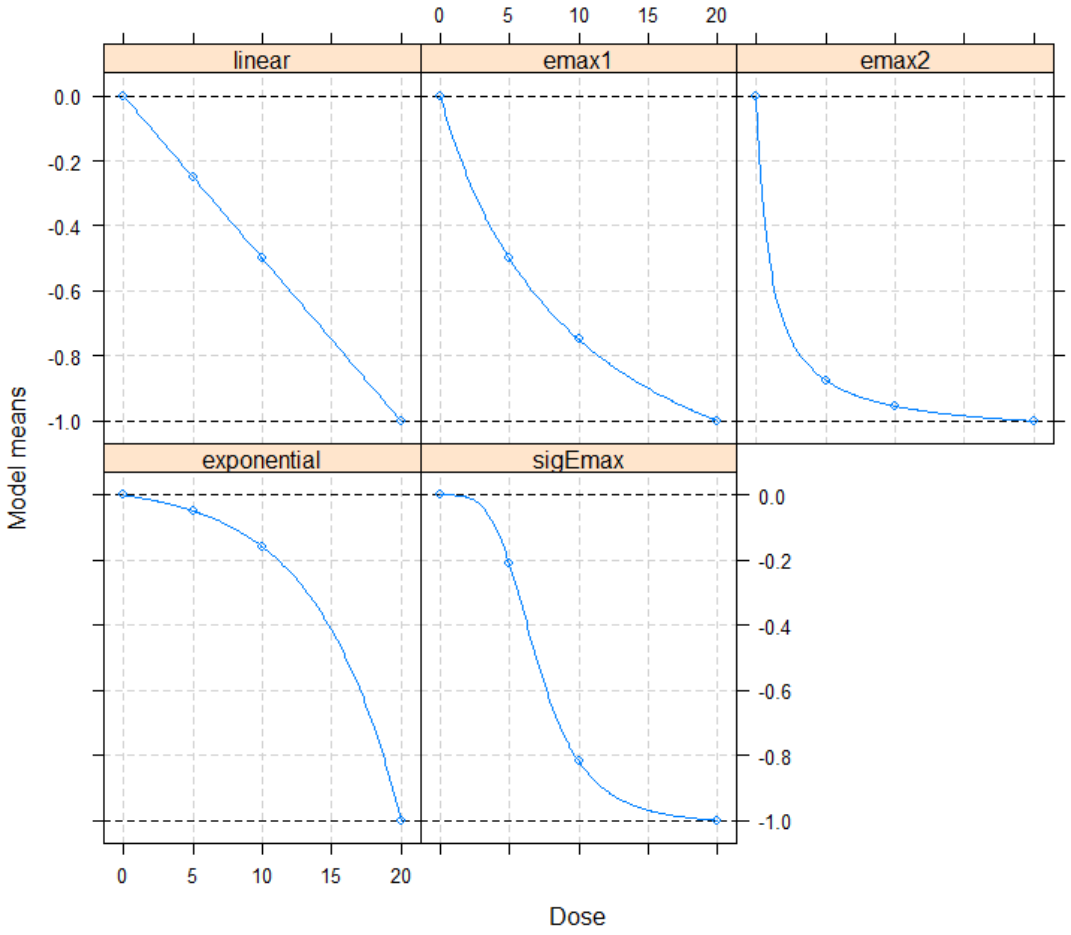


Figure 1: Shape and considered dose response patterns for the MCPMod analysis

The optimal contrasts corresponding to the candidate models [are shown in the following table (see Section 10.5 for the R code used for the calculation)].

Table 9: Contrast coefficients

	Contrast coefficients			
Model	**Placebo**	**5 mg BI**	**10 mg BI**	**20 mg BI**
Linear	0.639	0.145	-0.029	-0.755
Emax1	0.755	0.029	-0.145	-0.639
Emax2	0.840	-0.156	-0.208	-0.476
Exponential	0.487	0.211	0.138	-0.836
Sigmoid Emax	0.683	0.200	-0.212	-0.670

For the final evaluation, these contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model.

A non-flat dose response is established if at least one dose response pattern is statistically significant, rejecting the null hypothesis of a flat dose response relationship on change from baseline in MADRS total score at Week 6 jointly for each of the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at a one-sided $\alpha = 10\%$.

If a non-flat dose response is established, the statistically significant (i.e. best fitting) model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters. The dose-response curve is then obtained via model averaging across the significant models based on Akaike Information Criteria (AIC). [The predicted change from baseline in MADRS total score at Week 6 and difference to Placebo based on data fit via MCPMod to each model shape will be calculated for significant shapes.]

The target dose(s) for further clinical development can be estimated from each significant model by incorporating information on the minimum clinically relevant effect. The totality of evidence, including secondary and further efficacy and safety parameters, will be taken into account in the selection of dose(s) for pivotal studies.

[redacted]

[redacted]

7.6 SECONDARY OBJECTIVE ANALYSIS

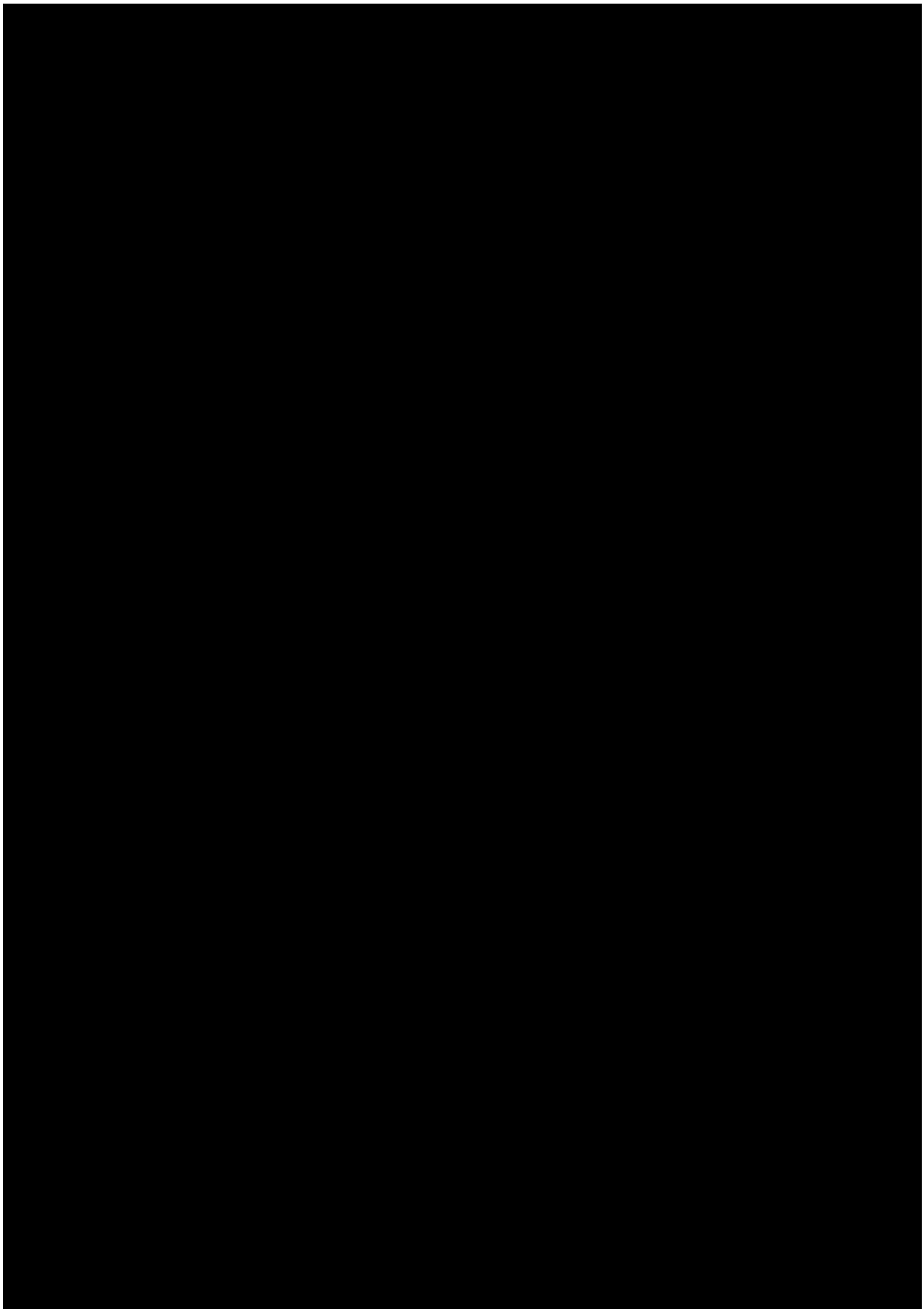
7.6.1 Key secondary objective analysis

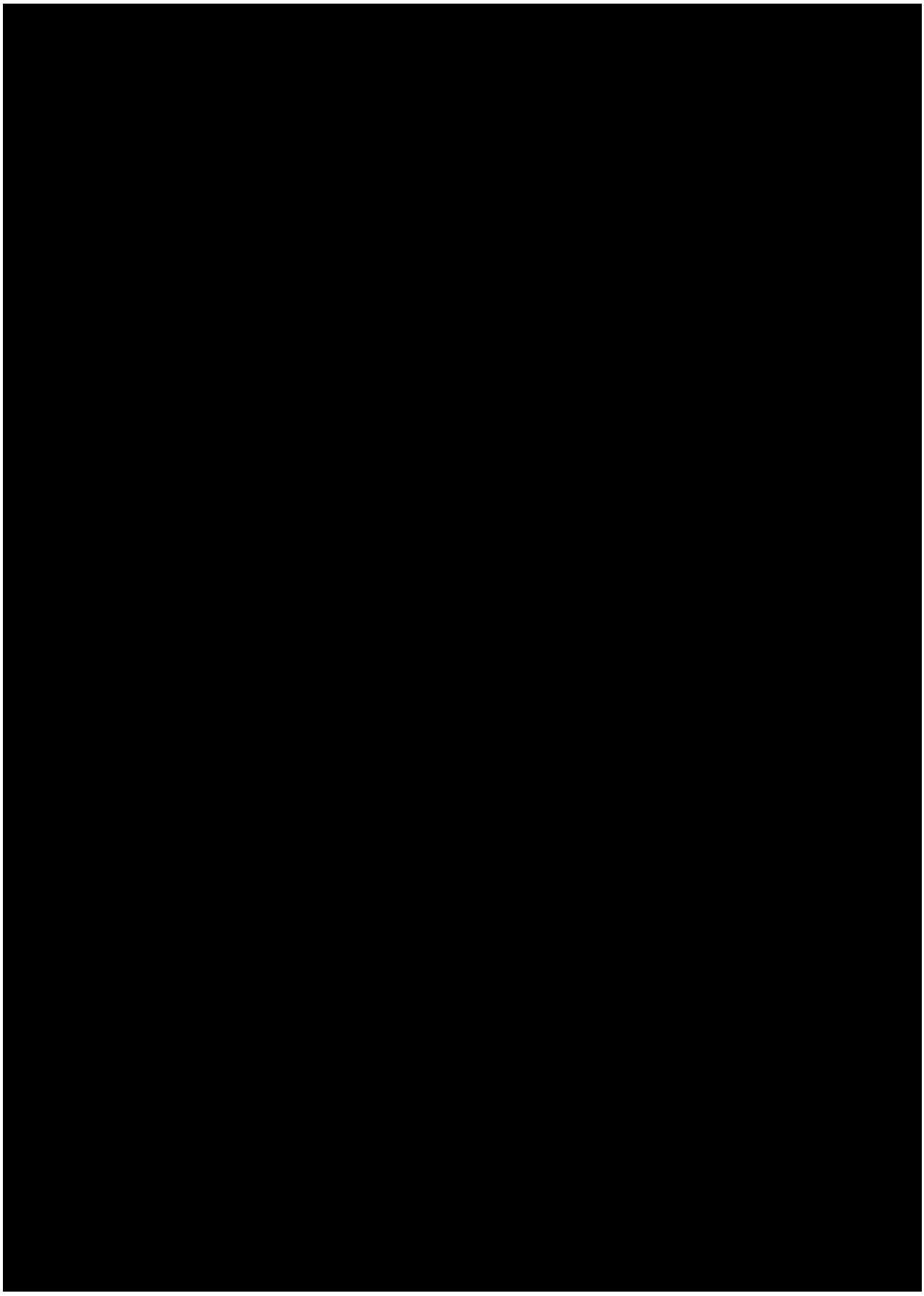
This section is not applicable as no key secondary endpoint has been specified in the protocol.

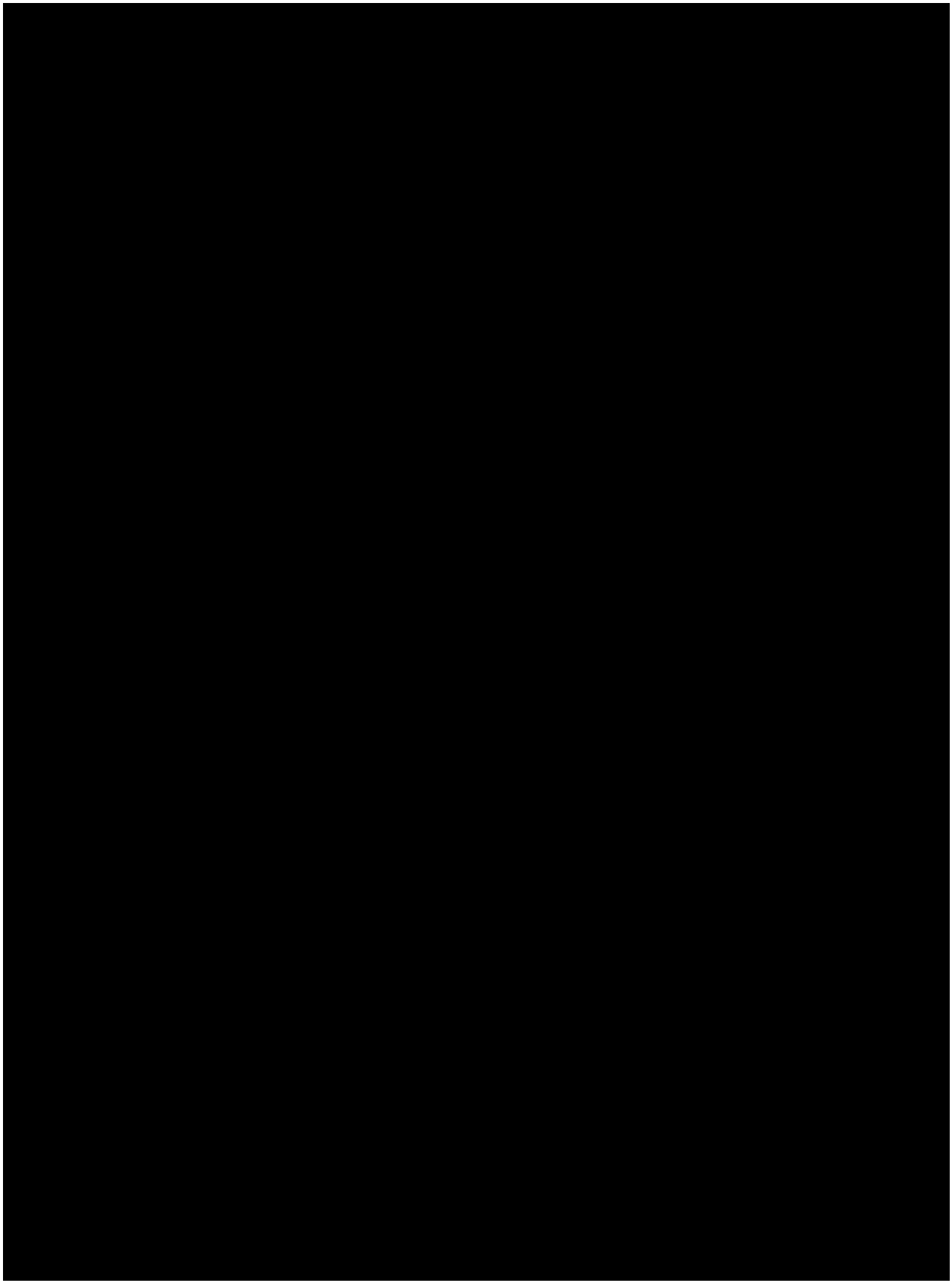
7.6.2 Secondary objective analysis

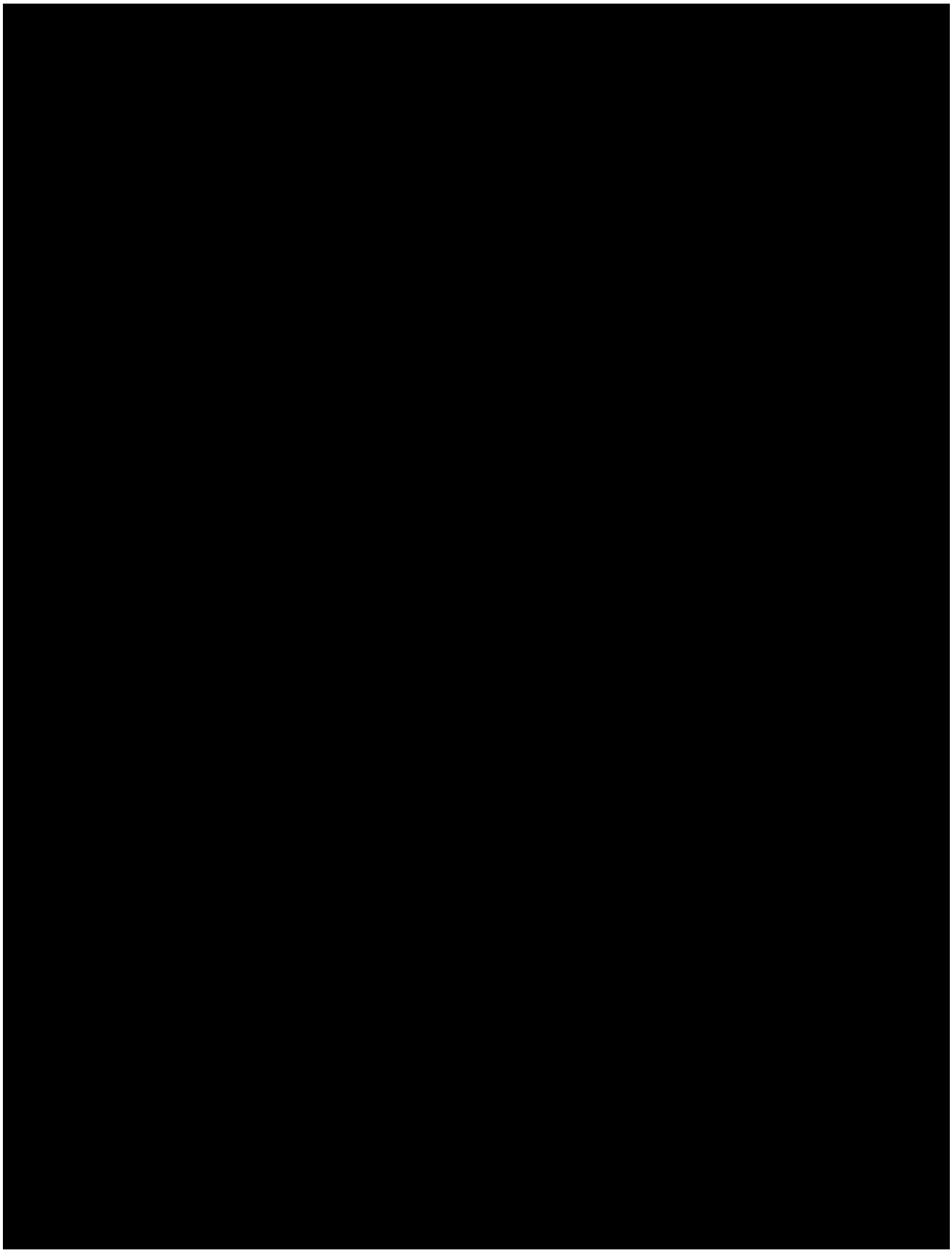
This section is not applicable as no secondary endpoints have been specified in the protocol.

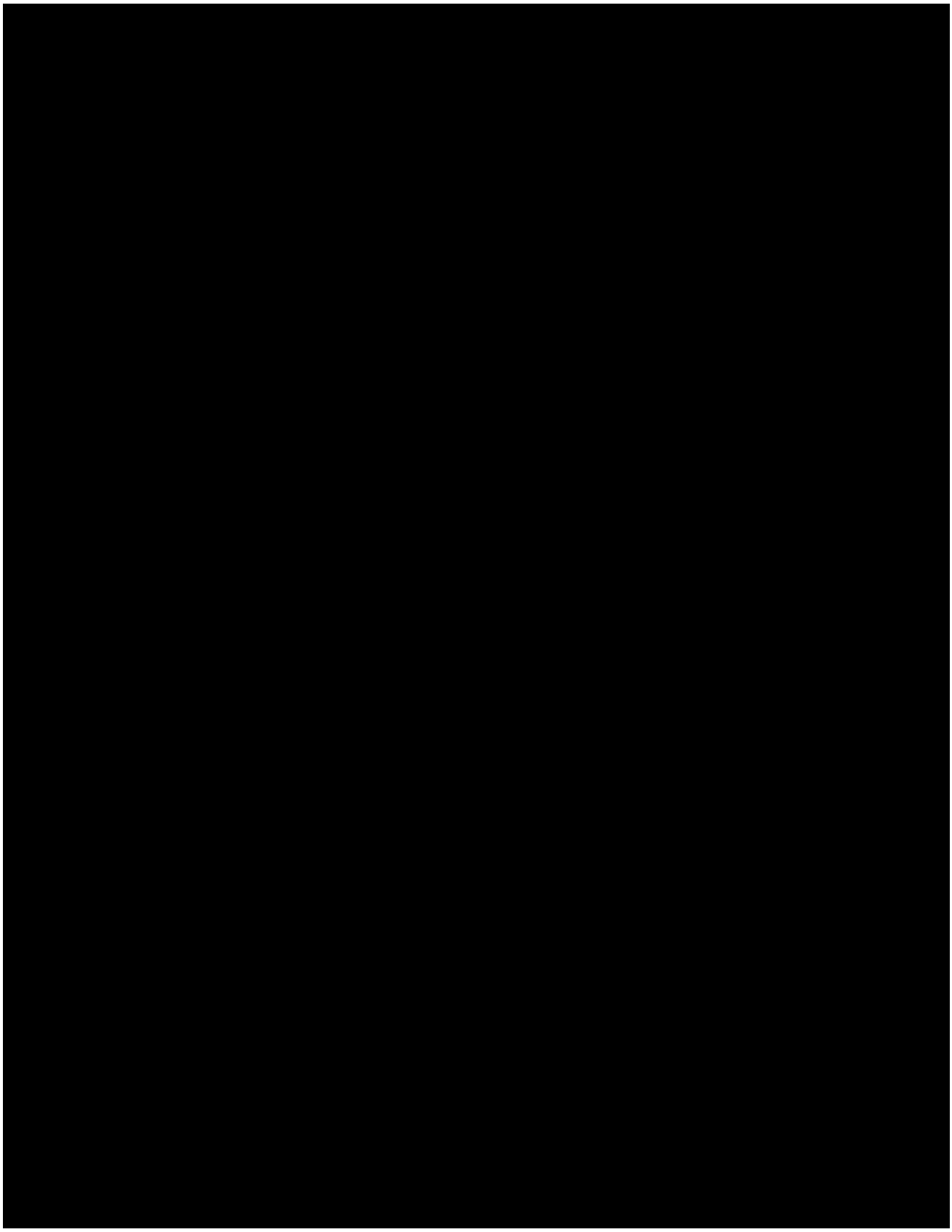
[redacted]











7.8 EXTENT OF EXPOSURE

Extent of exposure will be summarised for the TS in terms of treatment duration, from date of first intake to date of last intake of IMP, ignoring any IMP interruptions. Treatment duration [days] will be calculated as

$$Treatment\ duration\ [days] = Date\ of\ last\ IMP\ intake - Date\ of\ 1st\ IMP\ intake + 1.$$

Treatment duration will additionally be presented in categories showing the number and percentage of participants with treatment duration ≥ 1 day, ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 42 days. Additionally, for the BI 1569912 treatment groups, the total dose received will be summarised, calculated from the number of days with IMP taken (i.e. excluding interruptions) and the actual dose per intake as:

$$Total\ dose\ [mg] = \#\ days\ with\ IMP\ taken * actual\ dose\ [mg]$$

IMP interruption data will further be summarised as number of participants with interruptions, total number of interruptions per participant (0, 1, 2, > 2), and reason for interruption (related AE [each PT], unrelated AE [each PT], other). The total number of interruption days per treatment group will also be presented.

Date and time of first and last trial drug administration, IMP interruptions and reasons, calculated treatment duration and total dose will be listed.

7.9 SAFETY ANALYSIS

All safety analyses will be performed on the TS. Analysis will be performed as defined in CTP Section 7.2.6.

7.9.1 Adverse Events

AEs will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version in use at Boehringer Ingelheim at the time of (interim) database lock.

The analyses of AEs will be descriptive in nature (see [ref. 9.10], [ref. 9.11]). All analyses of AEs will be based on the number of participants with AEs and NOT on the number of AEs.

CTP Section 7.2.6:

All treated trial participants will be included in the safety analysis and summarised by the actual trial medication received at randomisation. In general, safety analyses will be descriptive in nature and will be based on Boehringer Ingelheim standards. No hypothesis testing is planned.

The analysis of AEs will apply the concept of treatment-emergent AEs (TEAEs). All AEs occurring between first IMP intake and last IMP intake + REP will be considered treatment-emergent. Note that with this definition, TEAEs are all AEs that occur on-treatment, when using the on-treatment definition provided in Section 6.1.

All AEs occurring before first IMP intake will be assigned to 'screening' and all AEs occurring after last IMP intake + REP will be assigned to 'follow-up'. For AEs that start before first IMP intake and deteriorate between first IMP intake and last IMP intake + REP, the deterioration will also be considered 'treatment-emergent'. For details on the treatment definition and REP, see Section 6.1.

If not otherwise specified, only TEAEs will be included in the AE summaries. In the patient listing of all AEs, non-TEAEs will also be included..

AEs related to hepatic injury (potential severe drug induced liver injury (DILI)) are considered protocol-specified AEs of special interest (AESIs) (see CTP Section 5.2.6.1.4), and are classified as such by the investigator in the eCRF.

For summaries by SOC and PT, the SOC will be sorted by default alphabetically, PTs will be sorted by decreasing frequency (within SOC) in the total column.

An overall summary of AEs will be presented for on-treatment AEs and will be repeated for on-treatment AEs and AEs during follow-up combined.

The frequency of participants with AEs will be summarised by treatment, primary SOC and PT. Separate tables will be provided for participants with:

- Any AE
- Investigator defined drug-related AEs
- Severe AEs
- AESIs
- Serious AEs
- AEs leading to treatment discontinuation

The summary for any AE will be repeated for on-treatment AEs and AEs during follow-up combined.

Tables will include TEAEs only, with the exception of AEs leading to treatment discontinuation, which will include all respective AEs regardless of occurrence relative to IMP end.

According to ICH E3 [ref. 9.8], in addition to deaths and serious AEs, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or interruptions [as recorded on the study medication interruption page]). These will also be summarised in an frequency table by SOC and PT.

For disclosure of AE data on ClinicalTrials.gov, additionally the frequency of participants with non-serious AEs occurring in at least 5% (on PT level) of the participants in at least one treatment arm in the TS will be summarised by treatment, primary SOC and PT. There will also be a summary on all-cause mortality.

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 PT) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of participants with drug-related serious AEs will be summarised by treatment, primary SOC and PT.

7.9.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on Boehringer Ingelheim standards [ref. 9.12]. All summaries will include data from baseline and the on-treatment analysis phase. Safety laboratory parameters to be assessed are listed in CTP Table 5.3.4:1.

Data will be received from a central laboratory; the respective reference ranges will be provided in the investigator site file.

CTP Section 7.2.6: *Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of trial participants with abnormal values or clinically relevant abnormal values.*

Descriptive statistics of laboratory values over time and for the difference from baseline will be provided (based on selected values within analysis time windows as specified in Section 6.7.). In these summaries, also the last value in follow-up as well as the change from baseline to last value in follow-up will be presented.

Frequency tables of shifts from baseline to last value on treatment, worst value on treatment and last value in follow-up will be presented. Worst value will be defined and analysed separately for worst low and worst high values (where applicable, with respect to the respective reference range).

Number and percentage of participants with possibly clinically significant abnormalities (low/high) will be presented per lab parameter.

Clinically relevant findings in laboratory data will be reported as baseline conditions (prior to first administration of trial drug) or as AEs (after first administration of trial drug) if judged clinically relevant by the investigator, and will be analysed as such.

Quantitative analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range, see [ref 9.12]. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

7.9.3 Vital signs

Descriptive statistics of vital signs (systolic and diastolic blood pressure, pulse rate and weight) over time and for the difference from baseline will be provided (based on selected values within analysis time windows as specified in Section 6.7). All summaries will include data from baseline and the on treatment analysis phase. Additionally, the last value in follow-up as well as the change from baseline to last value in follow-up will be presented, if applicable.

The mean change from baseline in systolic and diastolic blood pressure, and in pulse rate per time point and dose group will be displayed in a bar chart, including whiskers for the SD.

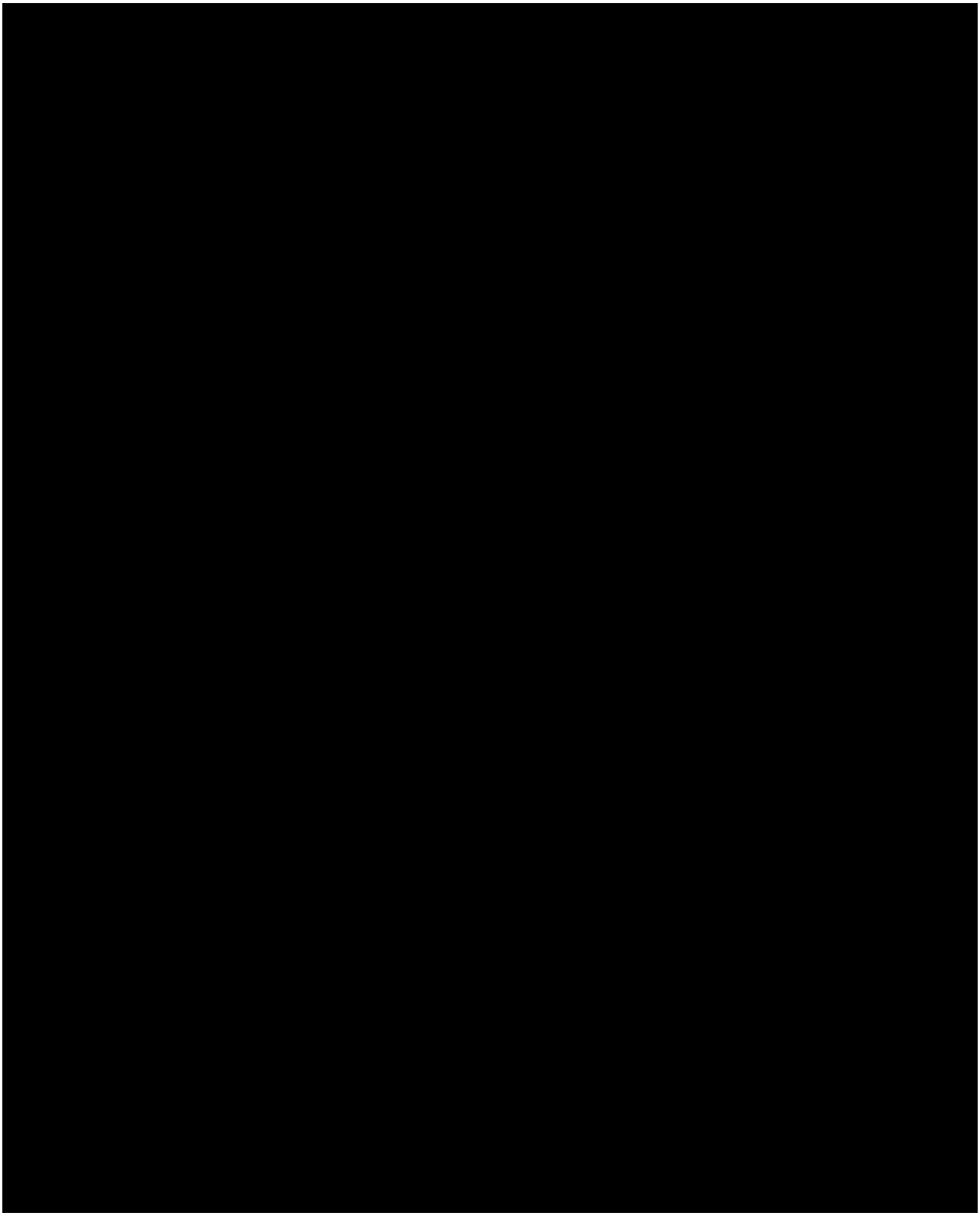
Furthermore, mean and SEM for the change from baseline per time point and dose group will be presented graphically for systolic and diastolic blood pressure, as well as pulse rate. The figures will be restricted to data assessed at baseline and the on treatment analysis phase.

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

7.9.4 ECG

All ECG summaries will include data from baseline and the on treatment analysis phase.

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.



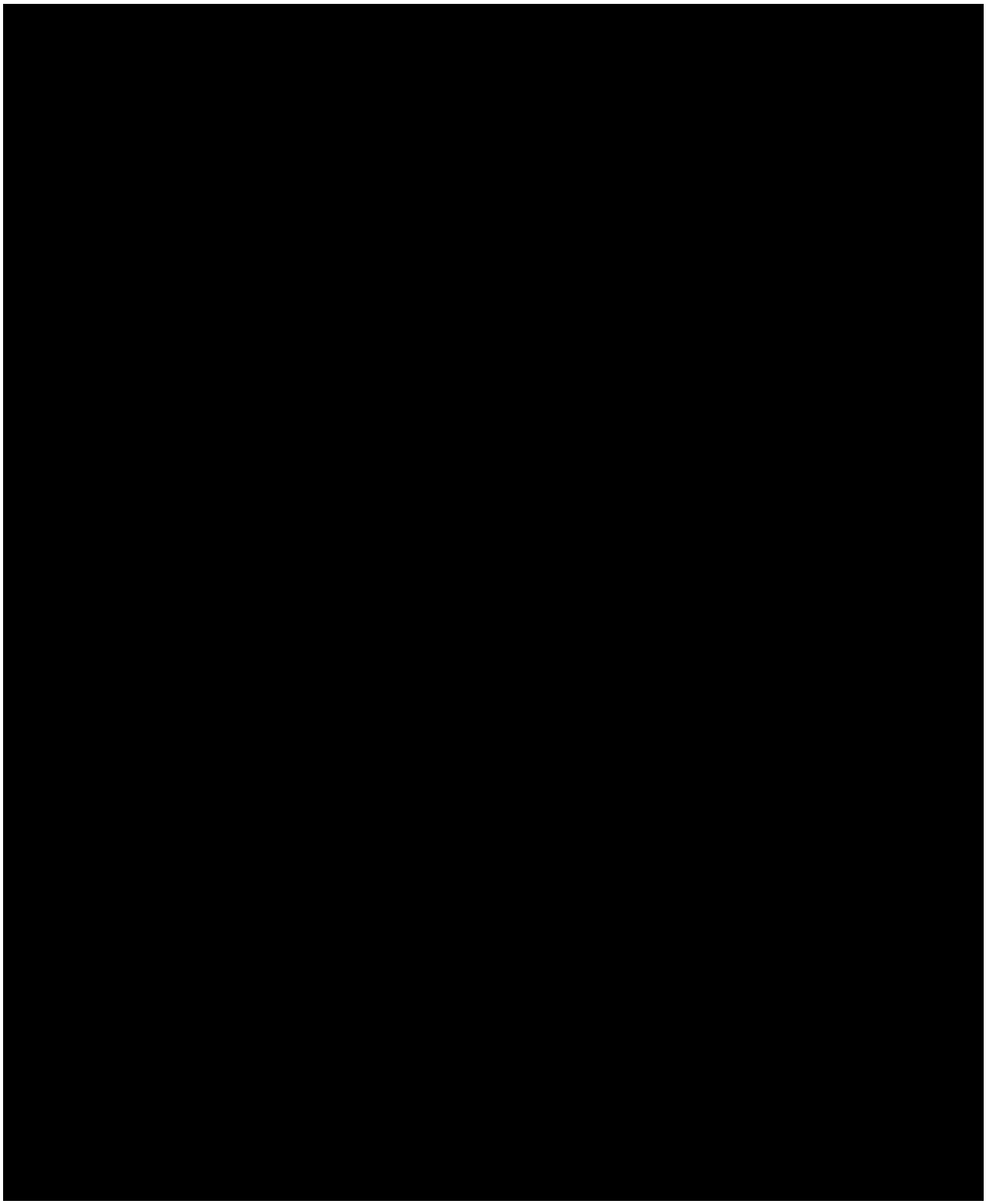
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

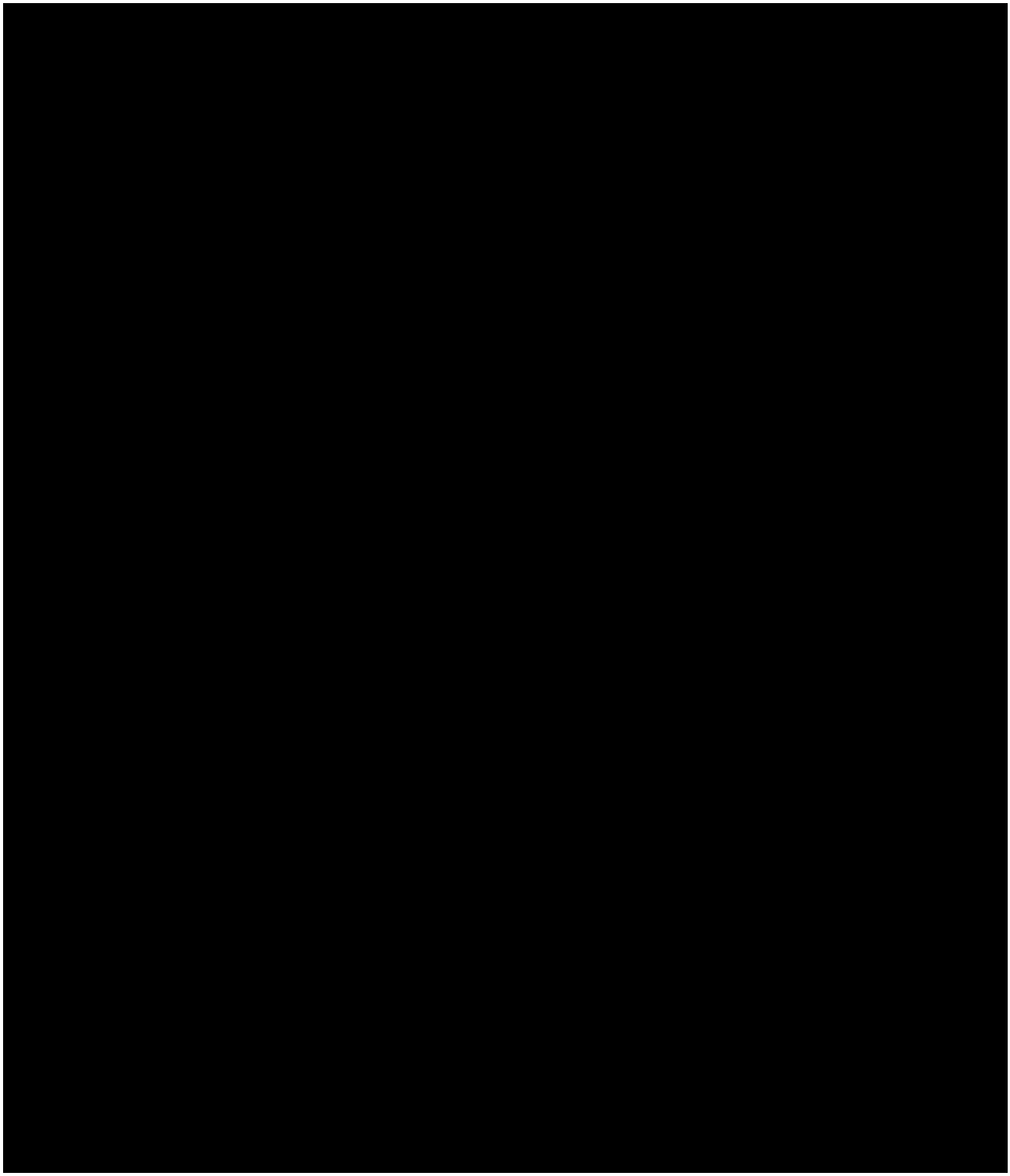
The treatment information will be released to unblind the trial database after the last participant has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

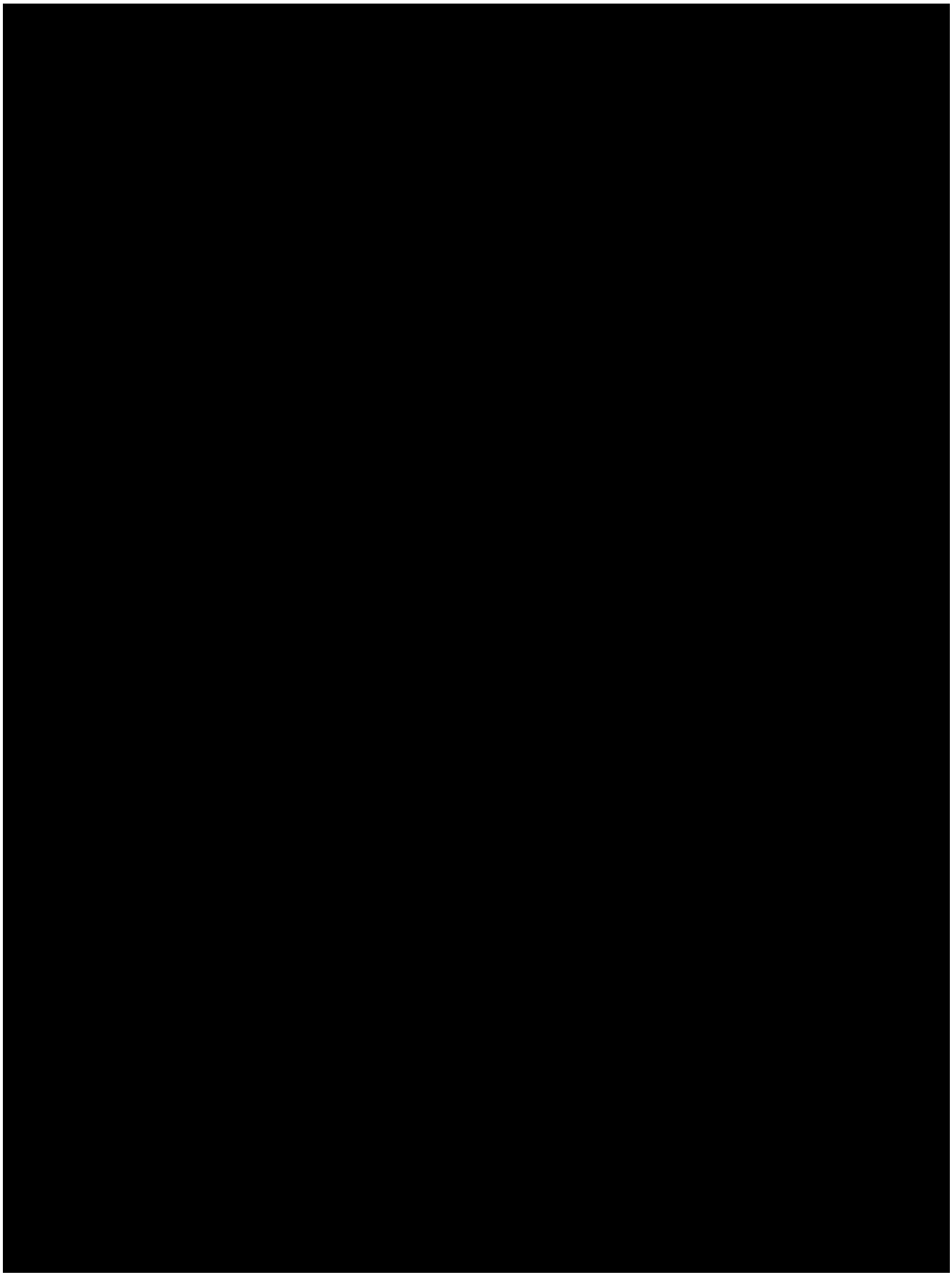
9. REFERENCES

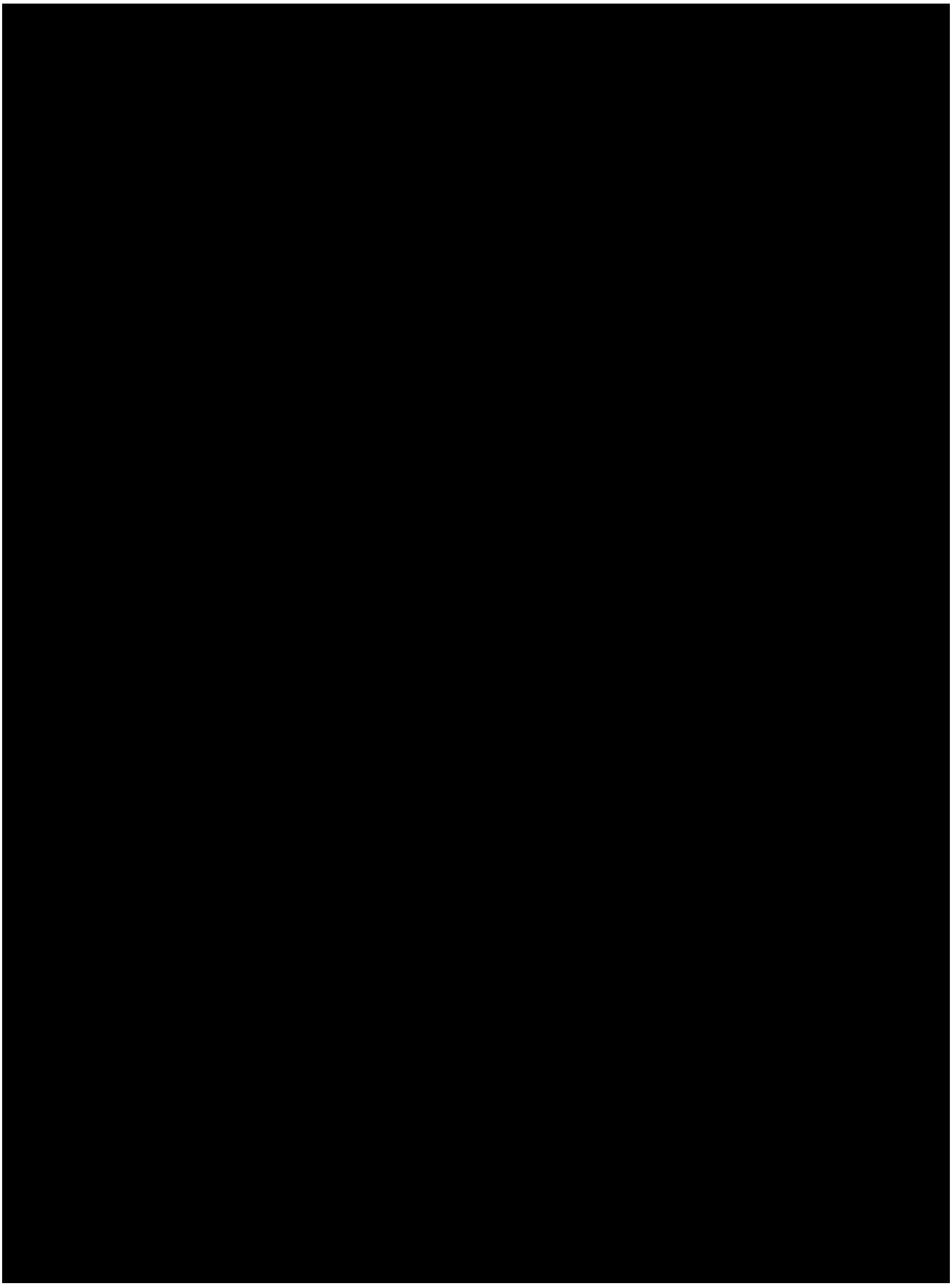
9.1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
9.2	*EMEA/CHMP/ICH/436221/2017:* "ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials", current version
[redacted]	
9.8	*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.
[redacted]	

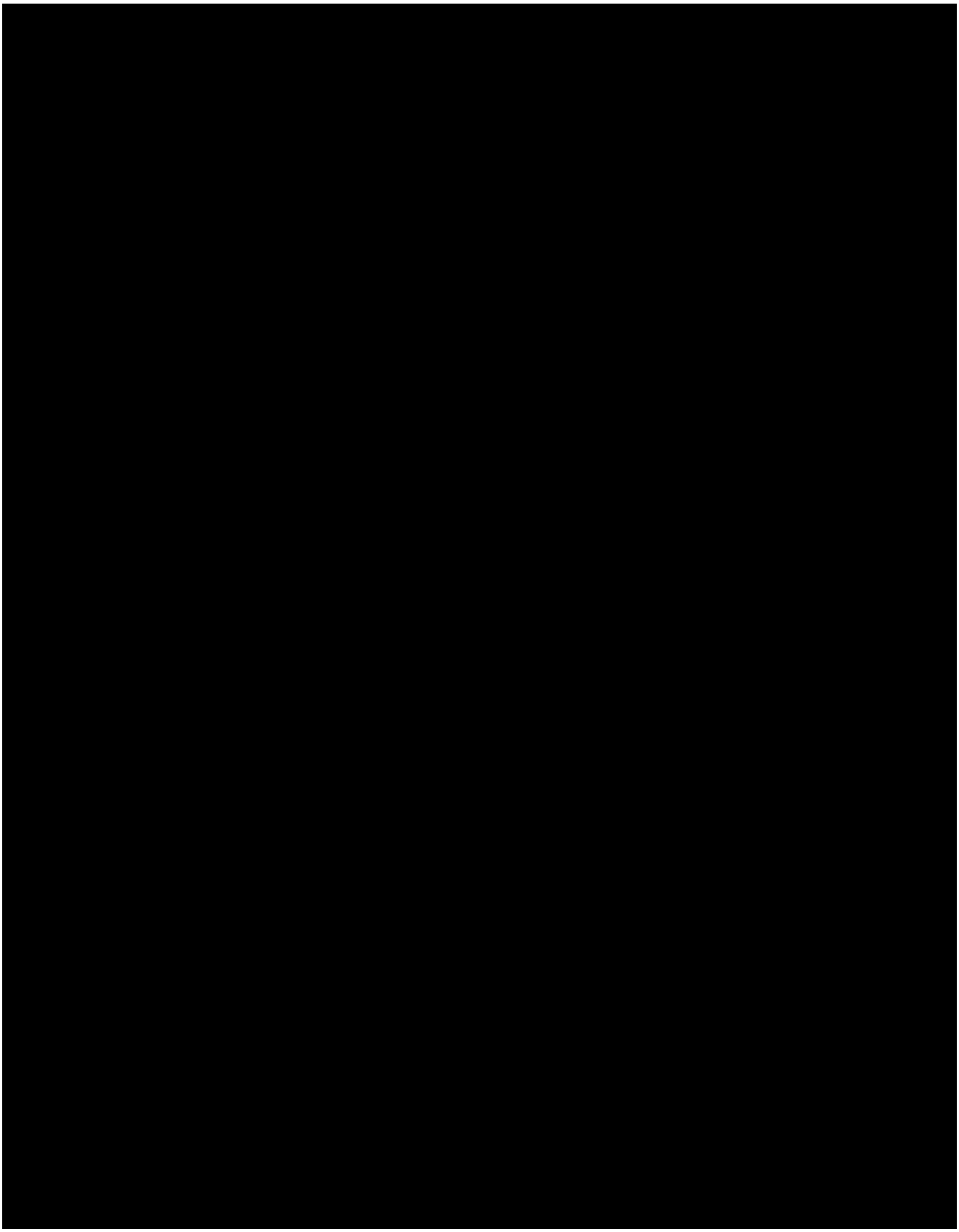
9.14	[redacted]
	[redacted]
9.17	Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat; 2006; 16(5); 639-656.
9.18	Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-389.
	[redacted]
	[redacted]
	[redacted]

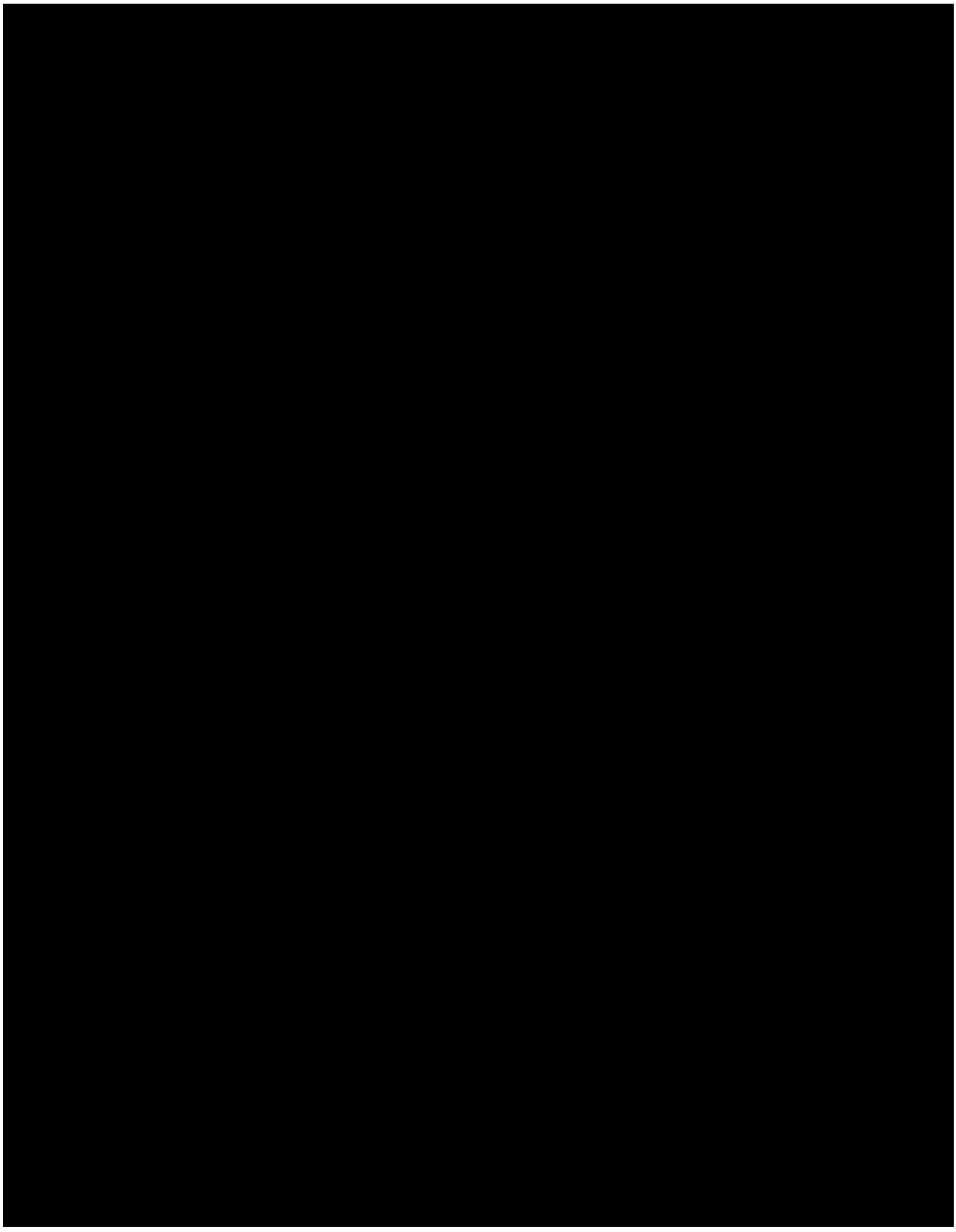


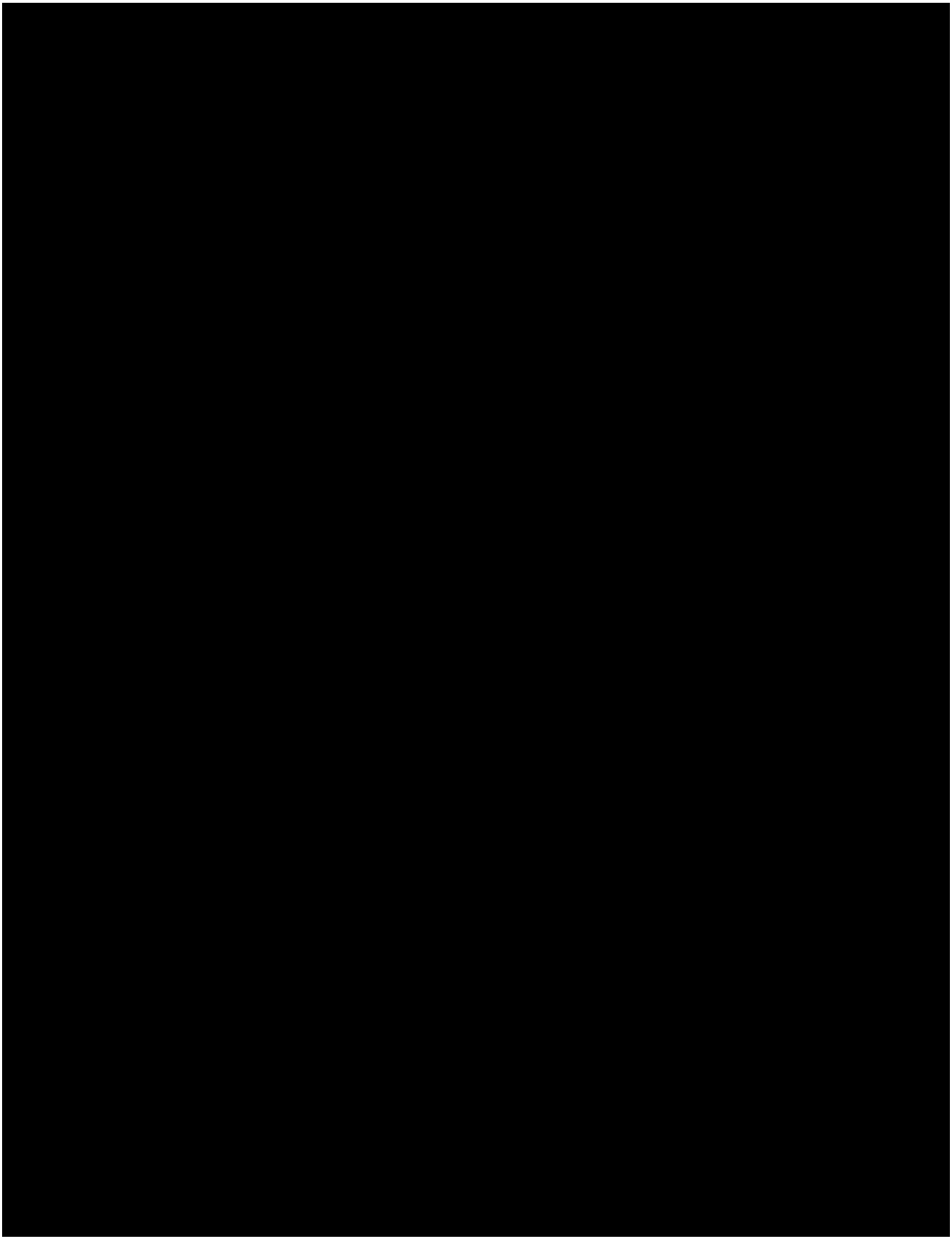












11. HISTORY TABLE

Table 18: History Table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**10-JUN-2025**		NA	Initial version of TSAP