TRIAL STATISTICAL ANALYSIS PLAN

c44703258-02

BI Trial No.:	1346-0011
Title:	A phase III randomized, double-blind, placebo-controlled, parallel group trial to examine the efficacy and safety of iclepertin once daily over 26 week treatment period in patients with schizophrenia (CONNEX-1)
Investigational Product(s):	Iclepertin
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	25 Oct 2024
Version:	2

1. TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

[redacted]

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	Analysis of Covariance
BARS	Barns Akathisia Rating Scale
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CIAS	Cognitive Impairment Associated with Schizophrenia
C-SSRS	Columbia Suicidality Severity Rating Scale
CTP	Clinical Trial Protocol
EQ-5D VAS	EQ-5D Visual Analogue Scale
EQ-5D-5L	EuroQol-5-Dimension-5-Level
HCRU	Health Care Resource Utilization
ICE	Intercurrent Event
iPD	Important Protocol Deviation
J2R	Jump to Reference
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-effects Model for Repeated Measures
PANSS	Positive and Negative Syndrome Scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRECIS	Patient Reported Experience of Cognitive Impairment in Schizophrenia
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAS	Simpson Angus Scale

Term	Definition / description
SCoRS	Schizophrenia Cognition Rating Scale
SCQ	Schizophrenia Caregiver Questionnaire
SDS	Sheehan Disability Score
SPGI-C	Study Partner Impression of Change
SPGI-S	Study Partner Global Impression of Severity
ToL	Tower of London
VRFCAT	Virtual Reality Functional Capacity Assessment Tool

3. INTRODUCTION

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

This 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.

SAS® Version 9.4 will be used for all analyses if not otherwise specified. Pheonix WinNonlin™ Version 8.1 will be used for pharmacokinetic (PK) analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

For the further endpoint of change from screening Visit 1a in PRECIS individual items and domain scores at Week 24, only the PRECIS domain scores will be analyzed, and the PRECIS individual items will not be analyzed.

Definition of baseline for the assessments of efficacy, PANSS and C-SSRS will include assessments up to but no later than the day of the first administration of study medication.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is

- Change from baseline in MCCB overall composite T-score at Week 26.

MCCB assessments are planned to be performed at screening (Visit 1), baseline (Visit 2), Week 12 (Visit 6), and Week 26 (Visit 11/EOT) or any early end of treatment visit.

Any post-baseline MCCB assessments performed within 28 days of the previous assessment will be considered invalid because of potential practice effects and will be excluded prior to any subsequent data handling and therefore from the planned analyses (5).

The MCCB overall composite T-score will be derived from seven domain scores from a total of ten tests (see CTP Table 5.1: 1). A larger MCCB overall composite T-score indicates better cognition.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

The key secondary endpoints are:

- Change from baseline in Schizophrenia Cognitive Rating Scale (SCoRS) interviewer total score at Week 26

- Change from baseline in Virtual Reality Functional Capacity Assessment Tool (VRFCAT) adjusted total time T-score at Week 26.

A lower rating in SCoRS reflects a lesser degree of impairment. A higher T-score in VRFCAT indicates a better functional outcome.

The endpoints will be used as defined in CTP Section 5.

5.2.2 Secondary endpoint(s)

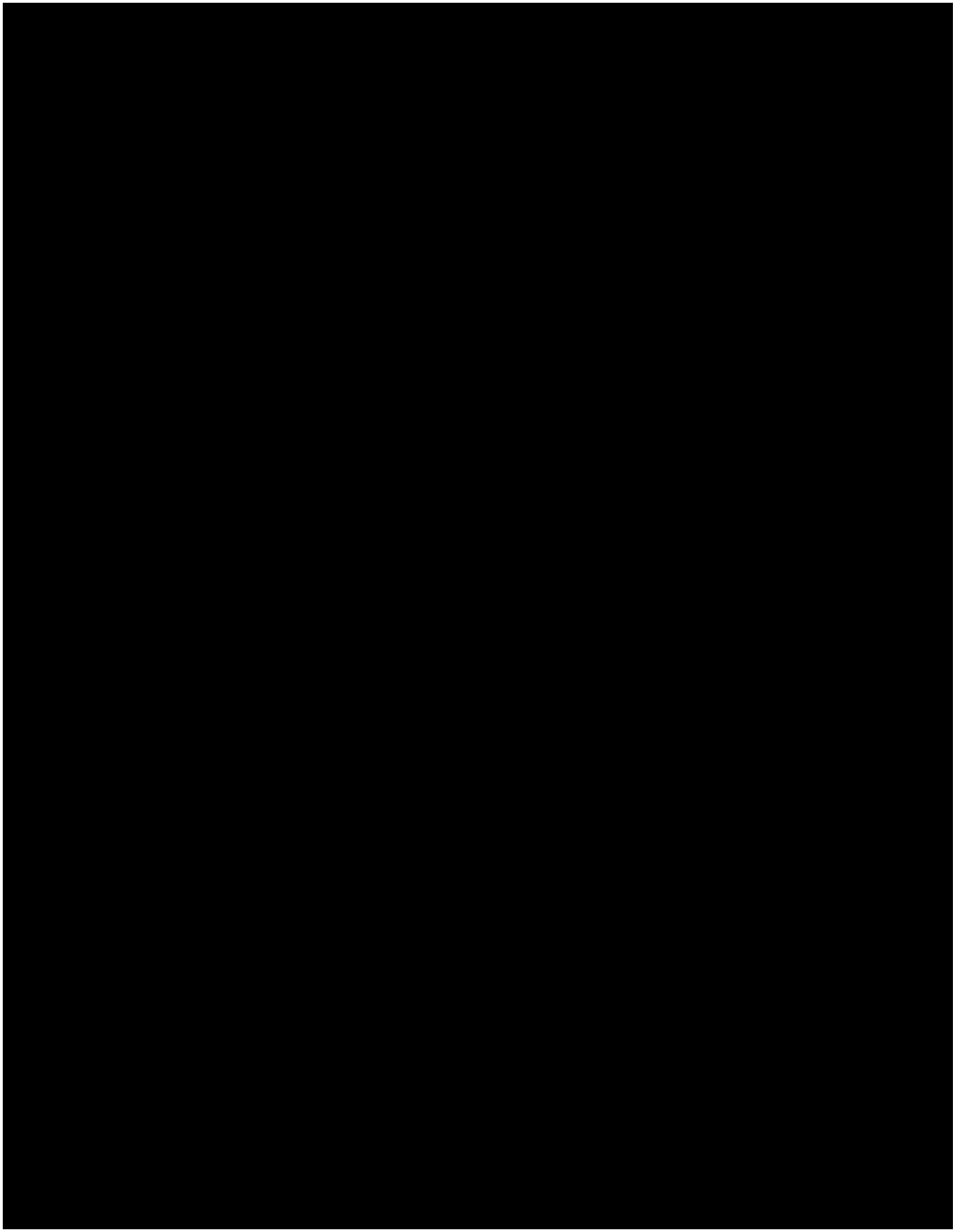
The other secondary endpoints are:

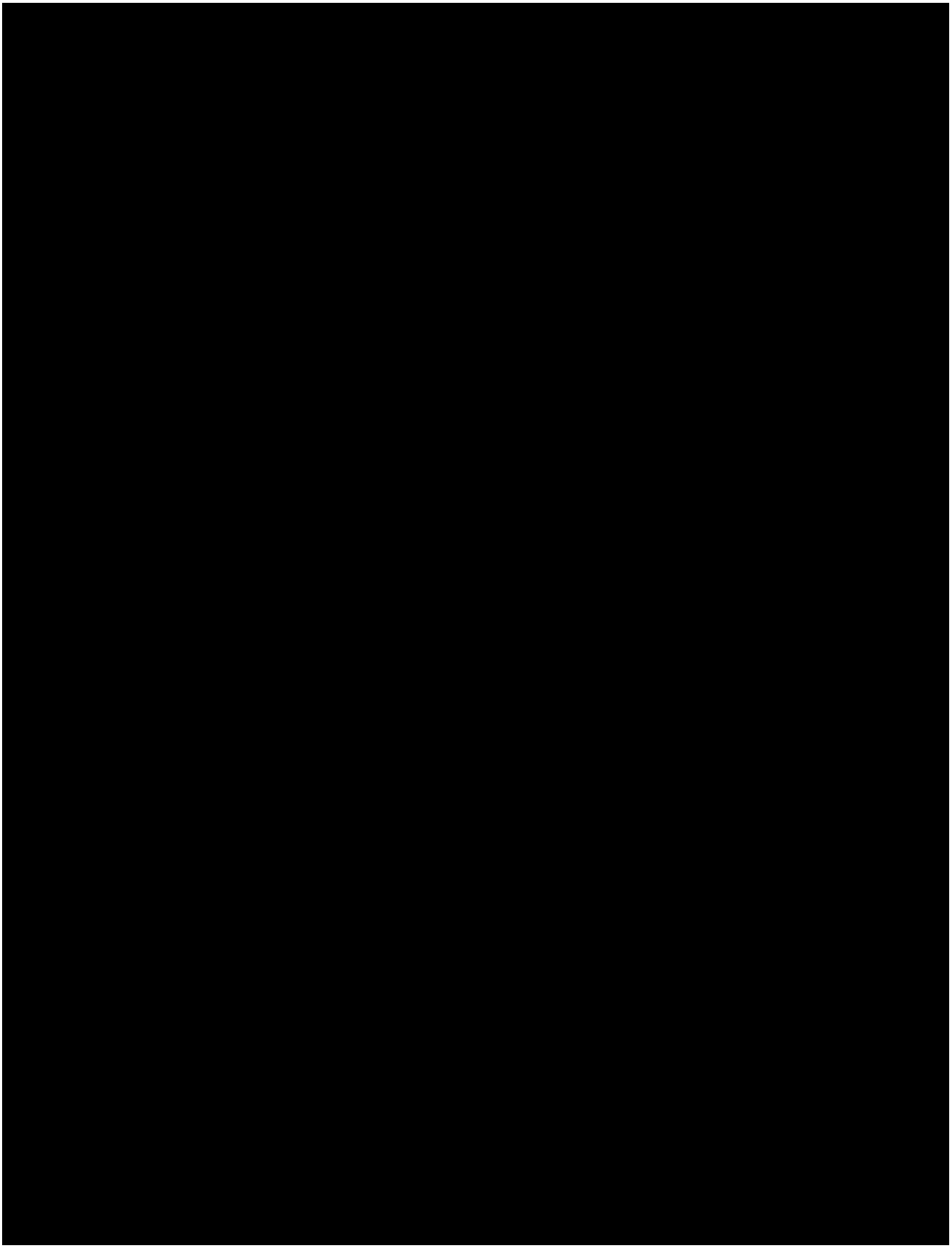
- Change from baseline in the T-score of the number of correct responses on Tower of London (ToL) at Week 26

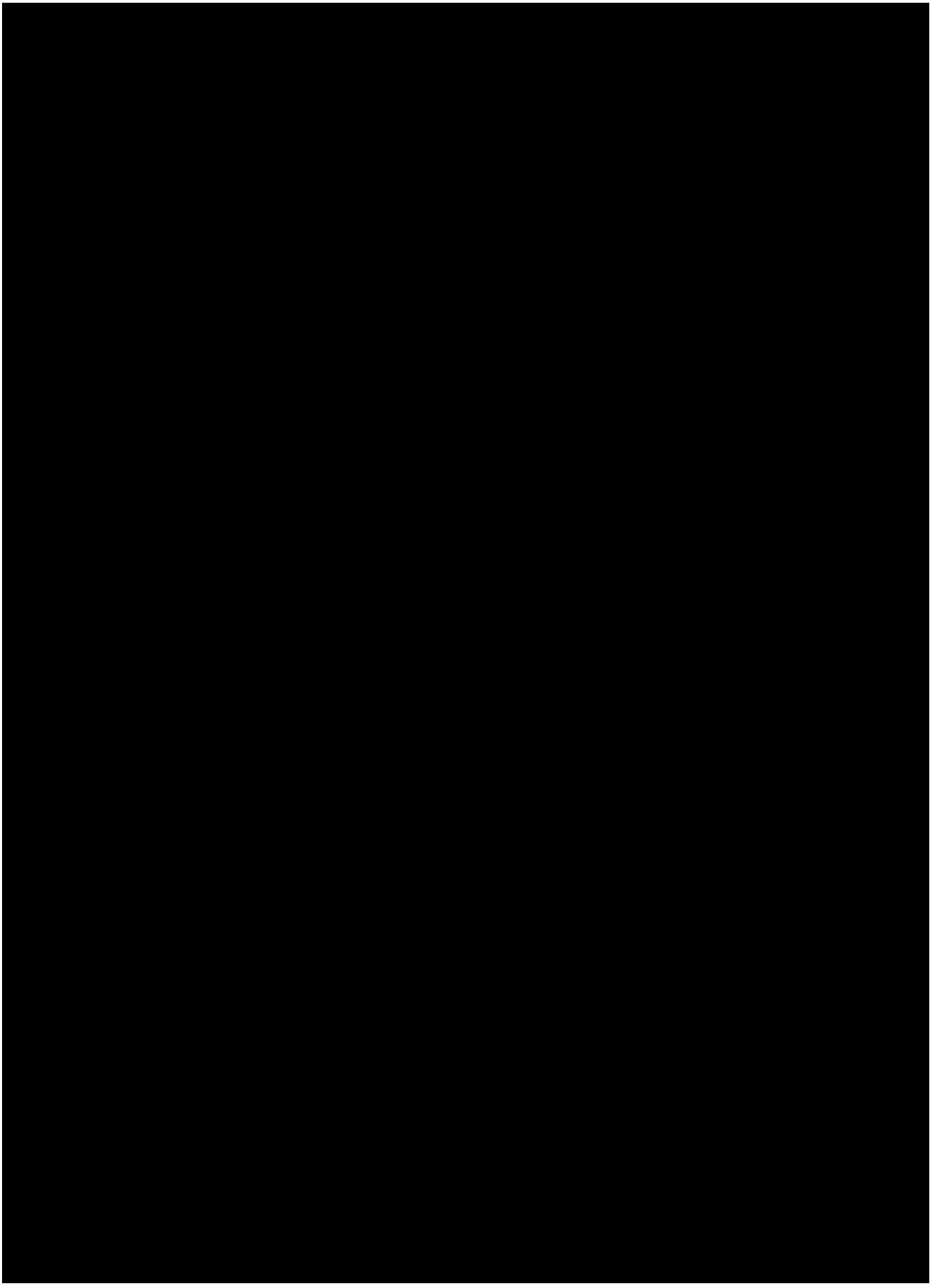
- Change from screening Visit 1a in Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) total score at Week 24

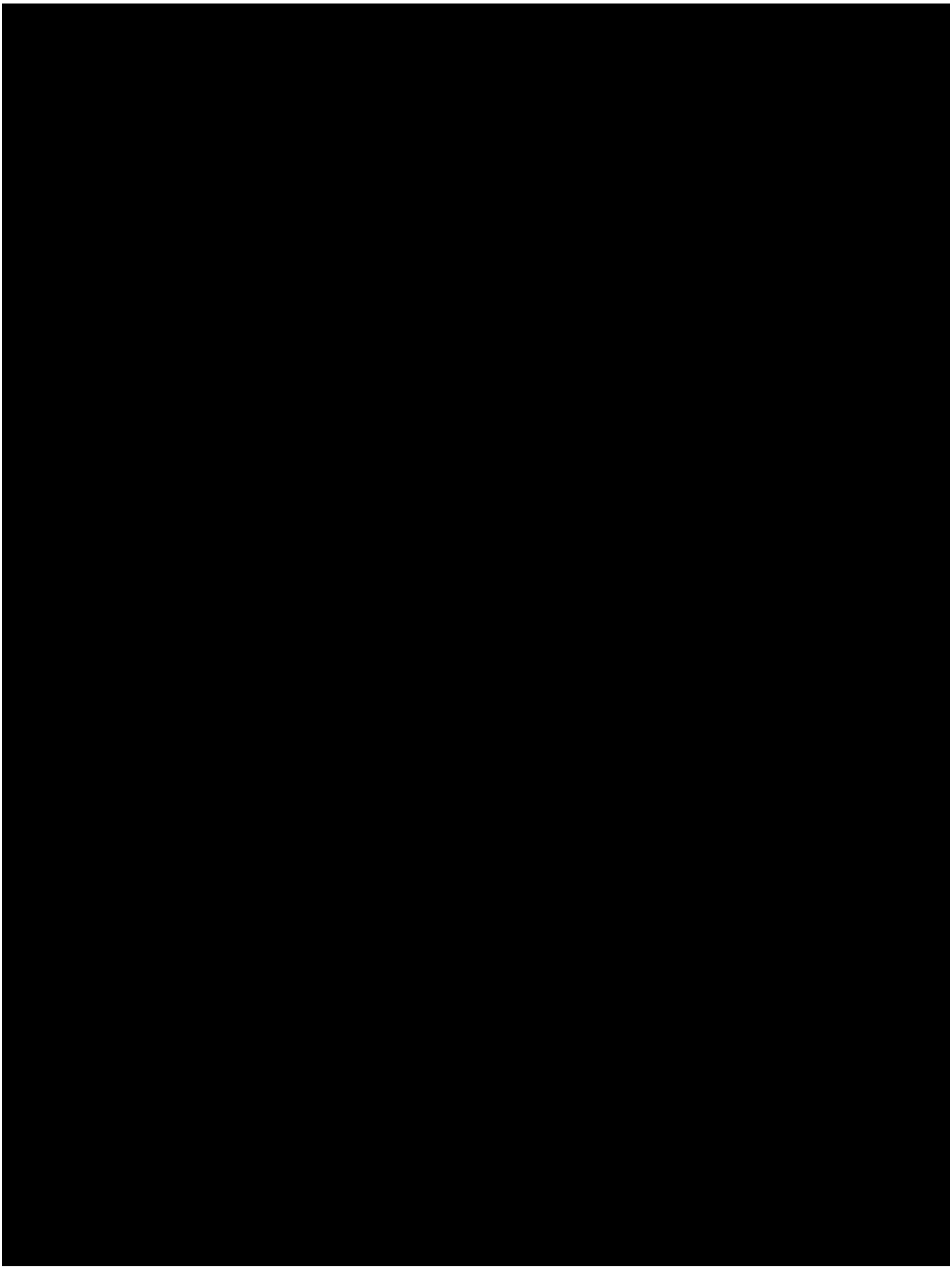
A higher T-score in ToL indicates a better outcome. A lower score in PRECIS corresponds to a better patient experience.

The endpoints will be used as defined in CTP Section 5.









6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, select of doses, see CTP Section 4.

Table 6.1: 1 lists the two treatment groups in this study. Table 6.1: 2 defines the analysing treatment period for safety analyses. For this study, the residual effect period (REP) is defined as 12 days after the last dose of trial medication.

Table 6.1: 1 Treatment descriptions

Long Name	Short Name
Placebo	Placebo
Iclepertin 10 mg QD	Iclepertin 10 mg

Table 6.1: 2 Analysing treatment periods (same for all treatment groups)

Analysing Treatment Period	Start Date	End Date
Screening period	Date of informed consent	Date of the first treatment administration – 1 day
On-treatment period	Date of the first treatment administration	Date of the last treatment administration + REP
Post-treatment period	Date of the last treatment administration + REP + 1 day	Date of the last per protocol visit

REP is the residual effect period which is defined as 12 days after the last dose of trial treatment.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analyses is described in the iPD specification document and stored in the Trial Master File (TMF) in the electronic Document Management System (eDMS).

6.3 INTERCURRENT EVENTS

Definition and technical specification of protocol defined intercurrent events (ICEs) are listed in Table 6.3: 1. In general, when handled under the hypothetical approach, data collected during the off-treatment period of an ICE will be considered irrelevant to the estimand and excluded from the analysis. While off-treatment data will be excluded, the patient will still be considered as on-treatment (hypothetically) from an analysis perspective by the statistical models, and during any imputations.

For an ICE of temporary treatment discontinuation or interruptions, the off-treatment period spans from the last treatment administration prior to the interruption + REP to the restart of

the study medication. For an ICE of early permanent treatment discontinuation, the off-treatment period starts from the last treatment administration + REP. Figure 6.3: 1 illustrates the on-/off-treatment status after each type of ICEs. When there is more than one ICE of early permanent treatment discontinuation, any treatment policy ICE take precedence in data and analysis handling over any hypothetical ICE.

ICEs of change in concomitant therapies and other ICEs will always be considered as part of the treatment policy in the primary and all supplementary estimands. ICEs of this category will not affect the on-/off- treatment status which is only determined by changes in the study medication. These ICEs will be listed and summarized descriptively but will not be explicitly accounted for in the inferential analysis of efficacy.

Table 6.3: 1 Definition and technical specification of intercurrent events

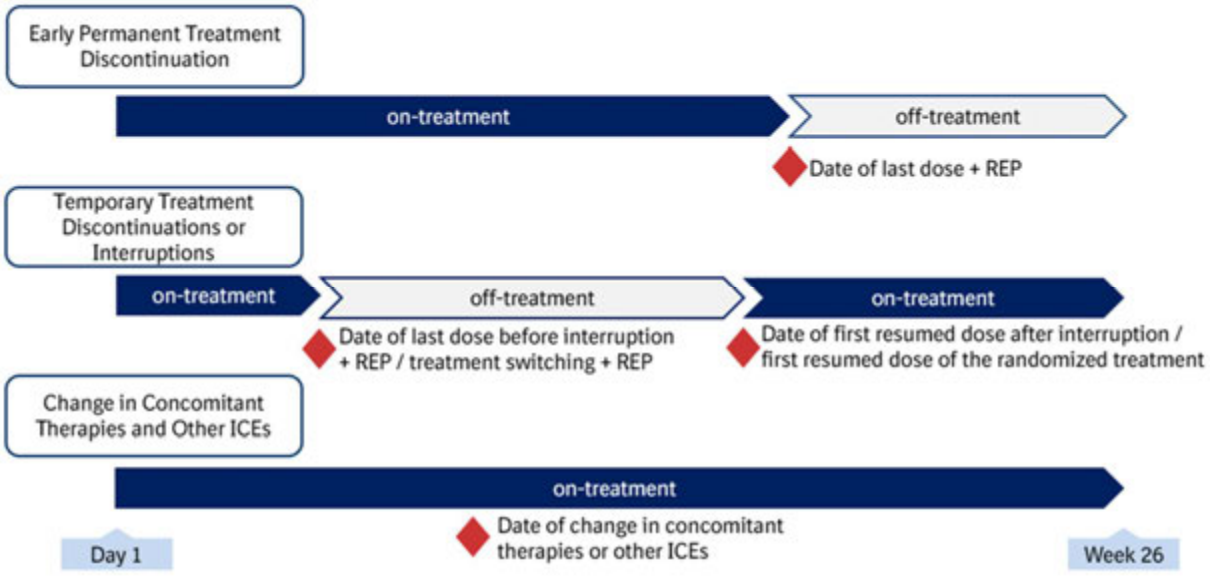
Type of Intercurrent Event	**Definition and Documentary Sources**	**Handling under the Primary Estimand**
Temporary Treatment Discontinuations or Interruptions		
Exacerbation or acute episode of schizophrenia resulting in interruption of treatment	Identified from data collected in the Temporary Trial Treatment Discontinuation and Adverse Event pages of the CRF: - Temporary discontinuation of trial treatment reported with reason being "Adverse Event", and - AE category reported as "Schizophrenia Relapse" or MedDRA preferred term coded as "Schizophrenia"	Treatment policy
Temporary treatment discontinuation or interruption due to other reasons	Identified from data collected in the Temporary Discontinuation page of the CRF.	Hypothetical – only data collected from the end of REP after the interruption, to end of the interruption will be subject to exclusion from the analysis
Temporary treatment-switch due to dispensation error	Identified from the dispensation records. Temporary treatment-switch will be handled as temporary interruptions in the same way for both directions (iclepertin to placebo or placebo to iclepertin)	Hypothetical – only data collected from the end of REP after the treatment switch, to end of the treatment switch will be subject to exclusion from the analysis
Early Permanent Treatment Discontinuation		

Exacerbation or acute episode of schizophrenia resulting in early termination of treatment	Identified from data collected in the Adverse Event page of the CRF: - "Drug Withdrawn" reported in the Action Taken with Study Treatment field, and - Category reported as "Schizophrenia Relapse" or MedDRA preferred term coded as "Schizophrenia"	Treatment policy
Investigator assessed drug-related adverse events which lead to early termination of study medication	Identified from data collected in the Adverse Event page of the CRF: - "Drug Withdrawn" reported in the Action Taken with Study Treatment field, and - "Yes" reported in the Relationship to Study Treatment field	Treatment policy
Protocol-defined drug withdrawal due to treatment – haemoglobin decrease	Identified from data collected in the End of Treatment and Adverse Event pages of the CRF and laboratory data: - Subject who did not complete the planned treatment period as reported in the End of Treatment page with reason being "Adverse Event", and - AE indicating haemoglobin decrease with action taken being "Drug Withdrawn"	Treatment policy
Protocol-defined drug withdrawal due to treatment – CYP3A4 inhibitors or CYP3A4 sensitive drugs with NTI	Identified from data collected in the End of Treatment page of the CRF: - Subject who did not complete the planned treatment period as reported in the End of Treatment page with "Protocol Deviation" as the reason, and - Use of CYP3A4 inhibitors or CYP3A4 sensitive drugs with NTI specified as the detailed reason of discontinuation	Treatment policy
Early termination of study	Identified from data collected in the End of Treatment page of the CRF:	Hypothetical

medication due to other AEs	- Subject who did not complete the planned treatment period as reported in the End of Treatment page with reason being "Adverse Event" and not otherwise covered by any of the ICEs above.	
Early termination of study medication due to perceived lack of efficacy	Identified from data collected in the End of Treatment page of the CRF: - Subject who did not complete the planned treatment period as reported in the End of Treatment page with reason being "Perceived Lack of Efficacy".	Hypothetical
Early termination of study medication due to other reasons	Identified from data collected in the End of Treatment page of the CRF: - Subject who did not complete the planned treatment period as reported in the End of Treatment page for reasons not covered by any of the ICEs above.	Hypothetical
Change in Concomitant Therapies and Other ICEs		
Change in background medication	Identified from data collected in the Concomitant Medications page of the CRF: - Start of a new or stop of an on-going antipsychotic, benzodiazepines (or derivatives), anticholinergics, antiepileptics, or antidepressants during the on-treatment period, or - Change of dosage or dosing frequencies of an on-going antipsychotic, benzodiazepines (or derivatives), anticholinergics, antiepileptics, or antidepressants during the on-treatment period See Table 10.7: 1 for definitions of antipsychotics, benzodiazepines (or derivatives), anticholinergics, antiepileptics, and antidepressants.	Treatment policy
Change in psychotherapy	Identified from data collected in the Psychotherapy page of the CRF:	Treatment policy

	- Change in frequency, setting or session of a psychotherapy during the on-treatment period	
Change in other non-pharmacological therapy	Identified from data collected in the Concomitant Non-Drug Therapies page of the CRF: - Start of a new non-drug therapy or stop of an on-going non-drug therapy during the on-treatment period	Treatment policy
Change in study partner in the assessment of functional capacity, e.g. SCoRS	Identified from data collected in the Study Partner Informed Consent page of the CRF and date/time of SCoRS assessments: - Any new study partner informed consent signed between the baseline SCoRS assessment and the SCoRS assessment being considered	Treatment policy – relevant only to endpoints from the SCoRS assessment

Figure 6.3: 1 On-/off-treatment status of the study medication for efficacy analysis after ICEs



6.4 SUBJECT SETS ANALYSED

The following patient analysis sets are defined:

- Screened Set (SS): includes all patients who signed informed consent and were screened for the trial with at least one screening procedure done at Visits 1 or 1a.

- Randomised Set (RS): includes all patients who signed informed consent and were randomised into the trial, regardless of whether a patient was treated with trial medication. Patients randomized in error and discontinued from the study before the start of trial medication will be excluded from the RS. Patients in RS will be analysed under the randomized trial medication. The RS will be used for efficacy analyses as well as demographics and baseline characteristics.

- Treated Set (TS): includes all patients who signed informed consent and were treated with at least one dose of the trial medication. Patients in TS will be analysed under the actual trial medication received at randomisation. The TS will be used for safety analyses.

- PK parameter analysis Set (PKS): includes all treated patients who have at least one evaluable PK plasma concentration measurement.

- Ocular sub-study Set (EYE): includes all treated patients who consented to participate in the ocular sub-study (including late/retrospective consent to the ocular sub-study) and had evaluable ophthalmologic measurements. The Ocular sub-study Set will be used for safety analyses, demographics, baseline characteristics and ophthalmologic endpoint analyses of the ocular sub-study.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates will be imputed according to BI standards (1). Missing data and outliers of PK data will be handled according to (2).

If not specified otherwise, missing data will not be imputed and will remain missing. Potential outliers will be reported and analysed as observed.

Handling and derivation of total/domain/subscale scores for the assessment scales in case of missing individual item scores are specified below:

MCCB

Handling of missing data in MCCB tests will follow the MCCB Manual (available in the ISF). See Section 10.1 for detailed descriptions and imputation rules.

SCoRS

For the 20-item SCoRS assessment, if six or more of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the SCoRS total score for that subject at that visit is missing. If five or less of the 20 items have missing response, which includes the response of "N/A", for a subject at a visit, then the item with missing response will be imputed first with the average of the non-missing item values for the subject at the visit, and then SCoRS total score for the subject at the visit will be derived as the sum of the non-missing item values and the imputed item values.

PANSS

PANSS total and subscale scores will be calculated as sums of their constituting item scores. If ≤20% of the items are missing in the calculation of the total or subscale scores, the missing items will be temporarily imputed with the mean of the non-missing item scores. The total or subscale score will then be calculated as the sum of the non-missing and imputed item scores.

For calculation of PANSS total score and the subscale scores, the maximum numbers of missing items allowed are:

PANSS total score:	6 out of 30
Positive Symptom:	1 out of 7
Negative Symptom:	1 out of 7
General Psychopathology:	3 out of 16
Marder Positive Factor:	1 out of 8
Marder Disorganized Thought Factor:	1 out of 7
Marder Negative Factor:	1 out of 7
Marder Uncontrolled Hostility/Excitement Factor:	0 out of 4
Marder Anxiety/Depression Factor:	0 out of 4

If more than the maximum allowed number of items are missing, the score will not be calculated.

PRECIS

PRECIS total score and domain scores will be calculated as averages of their constituting non-missing items. Table 6.6:1 lists the minimum number of non-missing items required for

calculation of PRECIS total score and domain scores. If fewer items than the minimum requirement are non-missing, the corresponding total score or domain score will not be calculated and will be treated as missing.

Table 6.6: 1 PRECIS minimum non-missing items required for total/domain score calculation

		Minimum required non-missing items
		PRECIS (28-item version)
Domain	Memory	3 out of 6
	Communication	3 out of 4
	Self-Control	3 out of 3
	Executive Function	4 out of 4
	Attention	3 out of 6
	Sharp Thinking	3 out of 3
PRECIS total score		19 out of 26

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, baseline values are the measurements taken prior to the first administration of trial medication. For assessments of efficacy, PANSS and C-SSRS, baseline will be defined as the last available assessment performed at or before randomization (Visit 2), and no later than the day of the first administration of study medication. Assessments done at Visit 1 or Visit 1a can be used as baseline if Visit 2 assessment is not planned, not available, or invalid.

For MCCB, only the assessment performed at randomization (Visit 2), and no later than the day of the first administration of study medication will be used as the baseline. If no valid assessment is available at Visit 2 then baseline value will be missing; assessments performed at Visits 1 and 1a will not be used as baseline.

Tables in this section define the analysis visits and windows which will be used for the analyses of efficacy and safety endpoints. Actual study day will be calculated starting with the date of first administration of trial treatment as Day 1. Unscheduled assessments will be mapped to the analysis visits together with the scheduled assessments.

Inclusion of an assessment into mapping consideration will depend on its on-/off-treatment status and per specific estimand (i.e., off-treatment data will be included into mapping consideration only when the associated ICE is handled under the treatment policy approach). If more than one assessment falls into the same analysis visit window, the assessment performed closest to the planned day will be selected for analyses. In case of a tie, the later assessment will be used.

Table 6.7: 1 Analysis visit windows for MCCB, VRFCAT, SCoRS, and PANSS

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 6	Week 12	85	2 – 126
Visit 11	Week 26	183	≥127

Table 6.7: 2 Analysis visit windows for PRECIS, EQ-5D-5L (patient)

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 7	Week 15	106	2 – 126
Visit 10	Week 24	169	≥127

Table 6.7: 3 Analysis visit windows for Tower of London, SDS, EQ-5D-5L (caregiver), SPGI-S, SCQ

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 10 (for SDS only)	Week 24	169	≥2
Visit 11 (for Tower of London, EQ-5D-5L (caregiver), SPGI-S, and SCQ)	Week 26	183	≥2

Table 6.7: 4 Analysis visit windows for CGI-S

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 6	Week 12	85	2 – 126
Visit 10	Week 24	169	127 – 175
Visit 11	Week 26	183	≥176

Table 6.7: 5 Analysis visit windows for PGI-S

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 10	Week 24	169	2 – 175
Visit 11	Week 26	183	≥176

Table 6.7: 6 Analysis visit windows for SAS/BARS/AIMS

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 4	Week 6	43	2 – 74
Visit 7	Week 15	106	75 – 137
Visit 10	Week 24	169	138 – 175
Visit 11	Week 26	183	≥176

Table 6.7: 7 Analysis visit windows for clinical laboratory evaluations (on-treatment period)

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 2	Week 0 (post-baseline)	1	2 – 35
Visit 4	Week 6	43	36 – 77
Visit 6	Week 12	85	78 – 119
Visit 8	Week 18	127	120 – 140
Visit 9	Week 21	148	141 – 161
Visit 10	Week 24	169	162 – 175
Visit 11	Week 26	183	≥176

All post-baseline actual day windows will be curtained at the end of residual period if earlier than the specified upper bound in the table.

Table 6.7: 8 Analysis visit windows for weight and vital signs (on-treatment period)

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		1	≤1
Visit 2	Week 0 (post-baseline)	1	2 – 56
Visit 5	Week 9	64	57 – 119
Visit 8	Week 18	127	120– 175
Visit 11	Week 26	183	≥176

All post-baseline actual day windows will be curtained at the end of residual period if earlier than the specified upper bound in the table.

Table 6.7: 9 Analysis visit windows for Ophthalmological variables

Analysis Visit	Nominal Week	Planned Day	Actual Day Window
Baseline		-7	≤1
Visit 10	Week 24	169	≥2

Note that for placebo patients who rolled over to the extension study, any ophthalmological assessments incidentally performed after the first administration of iclepertin in the extension study will not be included in the safety analysis.

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / Standard Deviation (STD) / 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 STDs 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.

Tabulations of frequencies for categorical data include all possible categories (even if there is no count in a category) and display the number of observations in a category as well as the percentage (%) relative to the number of subjects in the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). Percentages are rounded to one decimal place, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are rounded to the nearest integer. The category missing will be displayed only if there are actually missing values.

If a table presents only categorical data, "[N (%)]" is displayed in the column header only.

Abbreviations (e.g. Wors.) or acronyms (e.g. PD) will not be displayed in tables and subject data listings without any explanation. They will be either spelled out or explained in footnotes.

If applicable, days will be converted to weeks, months or years as follows:

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded similarly as AEs based on the most current MedDRA version. A summary of concomitant diseases will be provided by treatment group, system organ class (SOC), and preferred term (PT).

Concomitant therapies (CTs) will be coded according to WHO DD and classified by the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be

used to categorise 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. CTs will be summarised in two groups: CNS-active and non-CNS-active concomitant medications.

Summaries will also be provided for the following CTs of special interest: antipsychotics, benzodiazepines, anticholinergics, antiepileptics, and antidepressants, as defined in Table 10.7: 1.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. See Section 5.4 for definitions of treatment compliance. In addition, descriptive statistics of treatment adherence based on the AiCure data, as defined in Section 5.4, will also be reported.

7.4 PRIMARY ENDPOINT ANALYSIS

7.4.1 Primary analysis

In the primary analysis under the primary estimand, intercurrent events will be addressed using a strategy that differs depending upon the nature of the intercurrent event. For details please refer to Section 6.3 above (or Section 7 of the CTP). This primary analysis of the primary efficacy endpoint will be performed on the Randomized Set. With regard to the stratification factor, subjects will be analyzed according to the screening MCCB overall composite T-score stratum to which they correctly belong. Missing data resulting from the strategy (including both actual missing outcomes and excluded outcomes) will be handled using a mixed-effects model for repeated measures (MMRM) under the assumption of missing at random.

The primary endpoint is the change from baseline to Week 26 in overall composite T-score of the MCCB.

The primary analysis will be a restricted maximum likelihood (REML) based approach using a mixed-effects model for repeated measurements (MMRM) comparing the change from baseline in MCCB overall composite T-score at Week 26 between iclepertin 10 mg QD and placebo. The MMRM will includes the fixed categorical effects of treatment at each visit, a fixed categorical effect of the stratification factor using the screening MCCB overall composite T-score, and a fixed effect for the continuous covariate of baseline (i.e. baseline MCCB overall composite T-score) at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-subject dependencies.

The statistical model will be as follows:

$$y_{ijkm} = \beta_j S_i + \tau_{jk} + \varphi_m + e_{ij},$$

where

$$\left(e_{i1}., \ldots, e_{ij}\right)' \sim N_J(\mathbf{0}, \Sigma),$$

and

y_{ijkm} = response variable for subject i in stratum m at visit j randomized to treatment k
S_i = the baseline MCCB overall composite T-score of subject $i, i = 1, 2, \ldots$
β_j = coefficient of baseline effect at visit $j, j = 1, \ldots, J$
τ_{jk} = the effect of treatment k at vist $j, k = 1, 2$
φ_m = the effect of screening MCCB overall composite T-score stratum m for $m = 1, 2,$ and $\varphi_1 \equiv 0$ for stratum 1 of T-score < 30
e_{ij} = the random error associated with jth visit of the ith subject.
Σ = a $J \times J$ unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means, following the testing strategy described in CTP Section 7.1. The primary treatment comparison will be the contrast between iclepertin 10 mg QD and placebo at Week 26. Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

Example SAS code for the primary analysis of MMRM is provided in Section 10.2.1. In the event of non-convergence, methods described in Section 10.2.2 will be attempted to overcome the issue.

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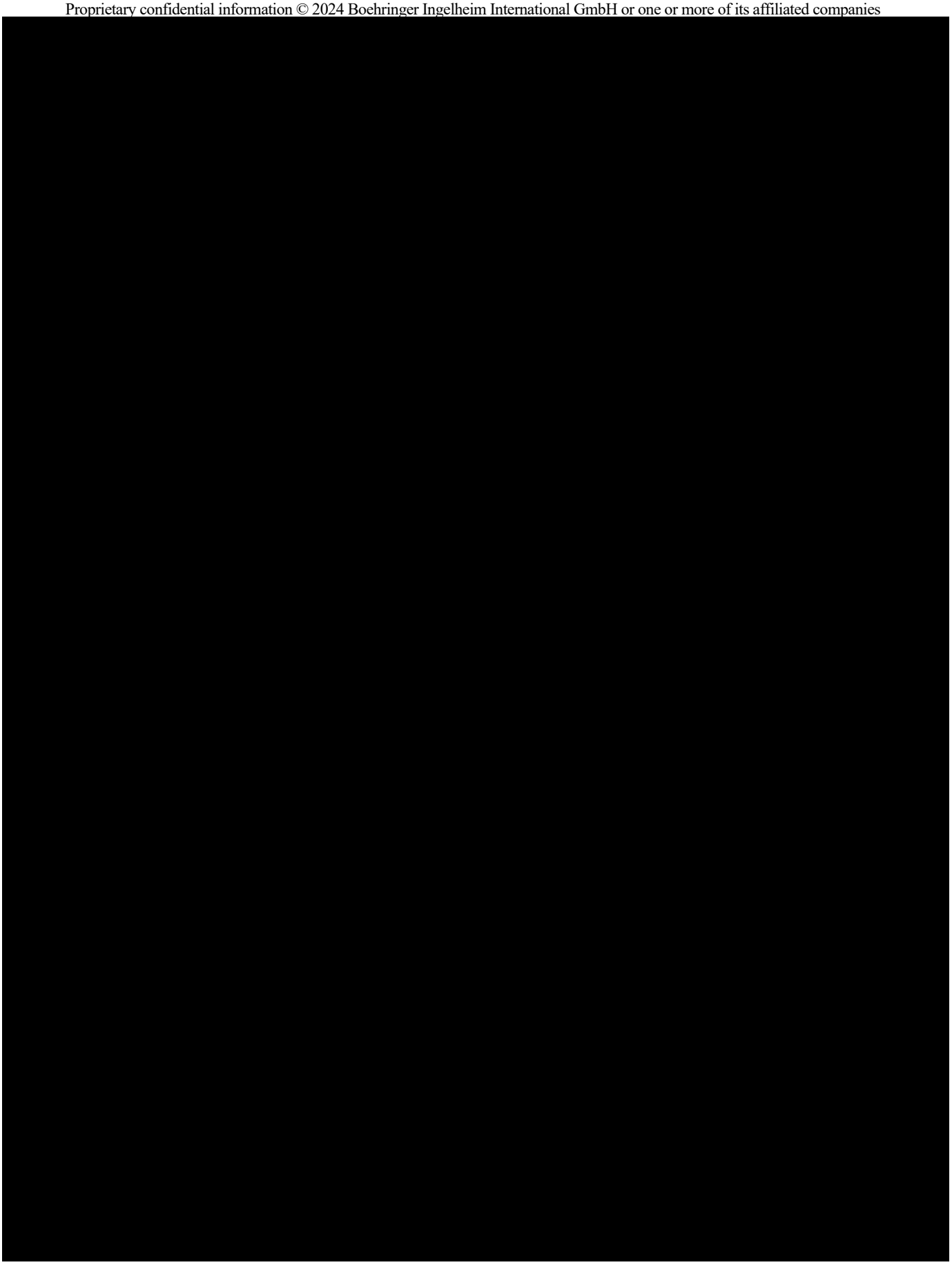

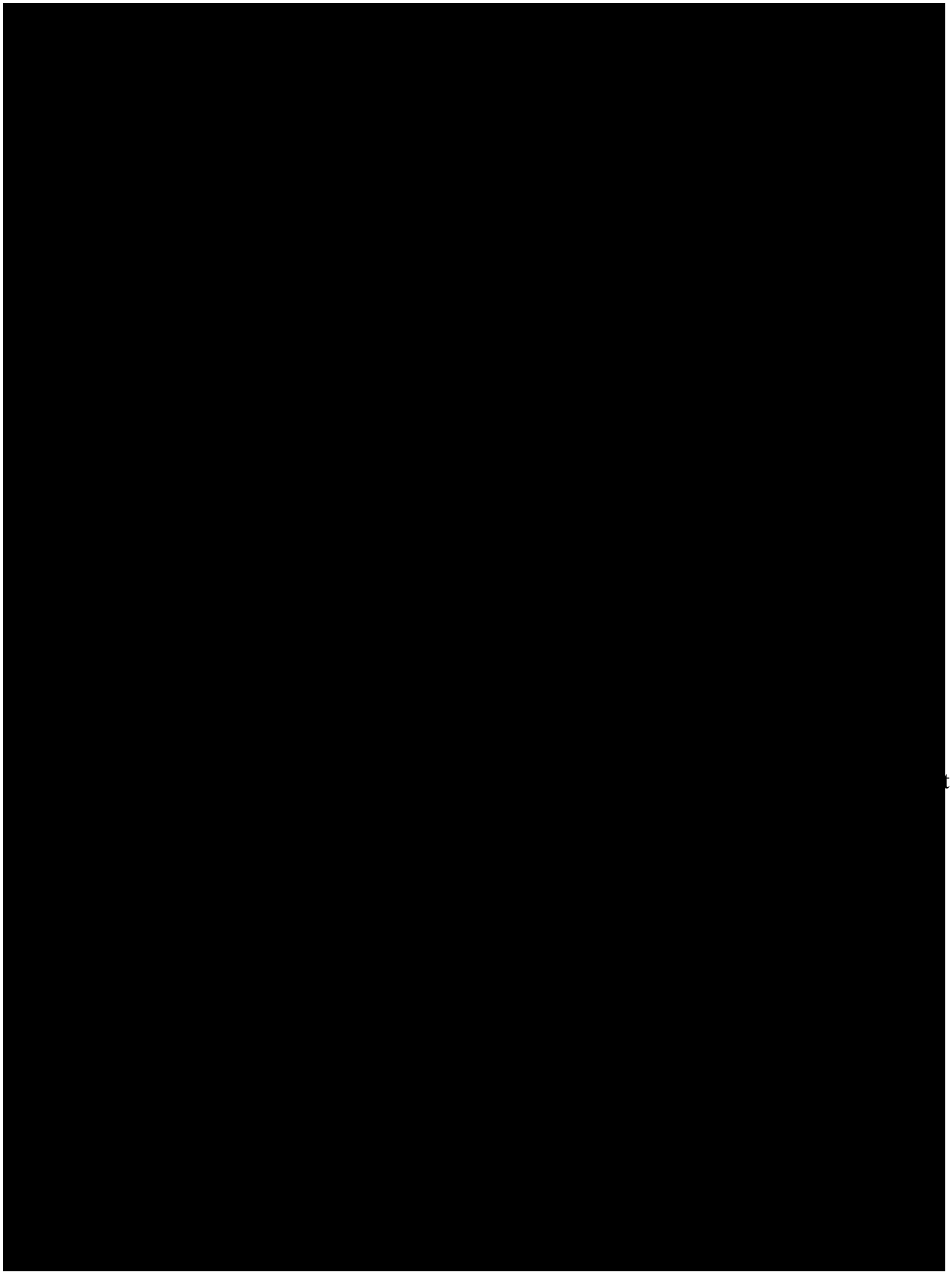

7.5 SECONDARY ENDPOINT ANALYSIS

7.5.1 Key secondary endpoint analysis

7.5.1.1 Primary analysis

For the two key secondary efficacy endpoints of change from baseline at Week 26 in SCoRS interviewer total score and VRFCAT adjusted total time T-score, the same strategy for handling the intercurrent events in the primary analysis under the primary estimand will be applied.

The primary analysis will be a restricted maximum likelihood (REML) based approach using the same primary analysis model of MMRM specified in Section 7.4.1, but with the baseline covariate replaced by the baseline of the corresponding key secondary endpoint.

[redacted]

7.5.2 (Other) Secondary endpoint analysis

For the secondary efficacy endpoints of change from screening to Week 24 in PRECIS total score and change from baseline to Week 26 in Tower of London number of correct responses T-score, the same strategy for handling the intercurrent events in the primary analysis under the primary estimand will be applied.

For change from screening to Week 24 in PRECIS total score, the primary analysis will be a restricted maximum likelihood (REML) based approach using the same primary analysis model of MMRM specified in Section 7.4.1, but with the baseline covariate replaced by the screening PRECIS total score. The same subgroup analyses as planned for the primary efficacy endpoint in Section 7.4.3 will also be conducted for PRECIS total score.

For change from baseline to Week 26 in the T-score of number of correct responses on Tower of London, an analysis of covariance (ANCOVA) model including treatment, stratification factor of screening MCCB overall composite T-score (<30, ≥30), and baseline number of correct responses on Tower of London T-score will be fitted to the data.

[redacted]

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarized for the treated set using descriptive statistics for days on treatment as well as frequency and percentage of subjects in the following categories: <42, 42 - <84, 84 - <126, 126 - <168, 168 - <179, 179 - <190, ≥190.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set and other subject sets as appropriate.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI guideline (3). AEs will be coded with the most current version of MedDRA®.

For further details on summarization of AE data, please refer to (1, 3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between the date of the first administration of trial treatment till the date of the last administration of trial treatment + residual effect period will be assigned to the on-treatment period. All AEs occurring before the first administration of trial treatment will be assigned to 'screening' and all AEs occurring after the residual effect period will be assigned to 'follow-up'. For details on the treatment definition, 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 and / or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample; and / or
- marked peak aminotransferase (ALT and / or AST) elevations ≥ 10 fold ULN.

See CTP Section 5.2.6.1.

Other significant AEs

User-defined AE category	**MedDRA preferred terms**	
Drug abuse, dependence, withdrawal and substance-related disorders, including diversion	Accidental death	Intentional overdose
	Drug abuse	Muscle rigidity
	Accidental overdose	Nasal necrosis
	Accidental poisoning	Nasal septum perforation
	Dependence	Nasal septum ulceration
	Drug abuser	Needle track marks
	Product administered at inappropriate site	Neonatal complications of substance abuse
	Drug dependence	Overdose
	Drug detoxification	Poisoning
	Drug dependence antepartum	Poisoning deliberate
	Drug dependence, postpartum	Substance dependence
	Drug diversion	Prescription form tampering
	Drug tolerance	Product tampering
	Drug tolerance increased	Product used for unknown indication
	Toxicity to various agents	Rebound effect
	Drug use disorder	Seizure
	Drug use disorder antepartum	Status epilepticus
	Drug use disorder, postpartum	Substance abuse
	Drug withdrawal convulsions	Substance abuser
	Drug withdrawal headache	Substance use
	Drug withdrawal syndrome	Substance use disorder
	Drug withdrawal syndrome neonatal	Substance-induced mood disorder
	Generalised tonic-clonic seizure	Substance-induced psychotic disorder
	Hangover	Treatment noncompliance
	Intentional product misuse	Withdrawal syndrome
Euphoria-related adverse events	Dizziness	Feeling drunk
	Euphoric mood	Feeling of relaxation
	Feeling abnormal	Inappropriate affect
CNS depressant effects	Depressed level of consciousness	Sedation
	Fatigue	Sluggishness
	Hypersomnia	Somnolence
	Lethargy	Stupor
	Loss of consciousness	
Stimulation and anxiety-related adverse events	Agitation	Morbid thoughts
	Anxiety	Nervousness
	Anxiety disorder	Panic attack
	Anticipatory anxiety	Panic disorder
	Energy increased	Panic reaction
	Fear	Psychogenic tremor

	Fear of death	Psychomotor hyperactivity
	Feeling jittery	Restlessness
	Generalised anxiety disorder	Tension
	Hypervigilance	
Perceptual disturbances / psychotomimetic effects	Abnormal dreams	Hypoaesthesia
	Acute psychosis	Ideas of reference
	Aggression	Illogical thinking
	Alice in wonderland syndrome	Illusion
	Altered state of consciousness	Incoherent
	Altered visual depth perception	Indifference
	Anger	Jamais vu
	Communication disorder	Loose associations
	Confusional state	Magical thinking
	Consciousness fluctuating	Nightmare
	Déjà vu	Paranoia
	Delirium	Paroxysmal perceptual alteration
	Delusion	Psychotic behaviour
	Delusion of grandeur	Psychotic disorder
	Delusion of reference	Psychotic symptom
	Delusion of replacement	Reactive psychosis
	Delusional perception	Rebound psychosis
	Derailment	Sensory disturbance
	Disinhibition	Sensory level abnormal
	Disorientation	Slow speech
	Dysarthria	Somatic delusion
	Flight of ideas	Somatic hallucination
	Formication	Staring
	Hallucination	Suspiciousness
	Hallucination, auditory	Tangentiality
	Hallucination, gustatory	Thinking abnormal
	Hallucination, olfactory	Thought blocking
	Hallucination, synaesthetic	Thought broadcasting
	Hallucination, tactile	Thought insertion
	Hallucination, visual	Thought withdrawal
	Hallucinations, mixed	Transient psychosis
	Hostility	
Dissociation	Daydreaming	Hypogeusia
	Depersonalisation/derealisation disorder	Metamorphopsia
	Derealisation	Ocular discomfort
	Diplopia	Oral dysaesthesia
	Dissociation	Oral hyperaesthesia

	Dissociative disorder	Pain threshold decreased
	Dissociative identity disorder	Paraesthesia
	Dysaesthesia	Paraesthesia oral
	Dysaesthesia pharynx	Pharyngeal hypoaesthesia
	Dysgeusia	Pharyngeal paraesthesia
	Dysmetropsia	Photophobia
	Feeling cold	Photopsia
	Feeling hot	Synaesthesia
	Feeling of body temperature change	Time perception altered
	Flashback	Tinnitus
	Hyperacusis	Vision blurred
	Hyperaesthesia	Visual impairment
	Hypersensitivity	
Mood disorders and disturbances	Abnormal behaviour	Depressive delusion
	Affect lability	Depressive symptom
	Affective disorder	Disturbance in social behaviour
	Anhedonia	Emotional disorder
	Antisocial behaviour	Emotional distress
	Apathy	Feeling of despair
	Asocial behaviour	Flat affect
	Attention-seeking behaviour	Hypomania
	Belligerence	Impatience
	Blunted affect	Impulse-control disorder
	Compulsive cheek biting	Impulsive behaviour
	Compulsive handwashing	Irritability
	Compulsive hoarding	Mania
	Compulsive lip biting	Mood altered
	Compulsive sexual behaviour	Mood swings
	Compulsive shopping	Parasomnia
	Obsessive-compulsive symptom	Personality change
	Compulsions	Sleep talking
	Confusional arousal	Sleep terror
	Depressed mood	Sleep-related eating disorder
	Depression	Somnambulism
Mental and cognitive impairment	Amnesia	Impaired driving ability
	Amnestic disorder	Impaired reasoning
	Anterograde amnesia	Judgement impaired
	Balance disorder	Memory impairment
	Bradyphrenia	Mental disability
	Change in sustained attention	Mental disorder
	Cognitive disorder	Mental impairment
	Confabulation	Mental status changes

	Coordination abnormal	Paramnesia
	Distractibility	Psychomotor retardation
	Disturbance in attention	Psychomotor skills impaired
	Dyslogia	Retrograde amnesia
	Executive dysfunction	Transient global amnesia

According to ICH E3, in addition to deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will include:

1. Any adverse events that led to an intervention, such as withdrawal of drug treatment.

2. Marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator during medical quality review at TOM.

AEs suggestive of abuse potential or related to CNS depressant effects

In support of an evaluation of human abuse potential, user-defined AE categories (UDAEC) are defined in Table 7.8.1: 1 for AEs suggestive of abuse potential and AEs related to CNS depressant effects.

Table 7.8.1: 1 MedDRA preferred terms for user-defined AE categories of AEs suggestive of abuse potential or related to CNS depressant effects

Other UDAECs are defined as follow:

Ocular events
The grouping of "ocular events" includes all MedDRA preferred terms under the SOC of "eye disorder" regardless of primary or secondary SOC.

Anaemia
Anaemia will be analyzed by BI customized medical query (BIcMQ) of Decreased haemoglobin and anaemia (incl. non-haematological causes), as defined in Table 7.8.1: 2

In addition, Standardised MedDRA Query (SMQ) of Haematopoietic cytopenias will be analyzed.

Table 7.8.1: 2 MedDRA preferred terms for BIcMQ of Decreased haemoglobin and anaemia (incl. non-haematological causes)

User-defined AE category	**MedDRA preferred terms**	
Decreased haemoglobin and anaemia (incl. non-haematological causes)	Anaemia	Haemoglobin abnormal
	Anaemia Heinz body	Haemoglobin decreased
	Anaemia folate deficiency	Haemolytic anaemia
	Anaemia macrocytic	Haemolytic anaemia enzyme specific
	Anaemia megaloblastic	Haemolytic icteroanaemia
	Anaemia of chronic disease	Hyperchromic anaemia
	Anaemia of malignant disease	Hypochromic anaemia

	Anaemia postoperative	Hypoplastic anaemia
	Anaemia splenic	Iron deficiency anaemia
	Anaemia vitamin B12 deficiency	Leukoerythroblastic anaemia
	Anaemia vitamin B6 deficiency	Macrocytosis
	Anaemic hypoxia	Melanaemia
	Anaemic retinopathy	Microangiopathic haemolytic anaemia
	Aplasia pure red cell	Microcytic anaemia
	Aplastic anaemia	Nephrogenic anaemia
	Autoimmune anaemia	Normochromic anaemia
	Autoimmune aplastic anaemia	Normochromic normocytic anaemia
	Autoimmune haemolytic anaemia	Normocytic anaemia
	Blood loss anaemia	Pernicious anaemia
	Cardiac haemolytic anaemia	Proerythroblast count abnormal
	Cold type haemolytic anaemia	Proerythroblast count decreased
	Coombs negative haemolytic anaemia	Protein deficiency anaemia
	Coombs positive haemolytic anaemia	Radiation anaemia
	Copper deficiency anaemia	Red blood cell abnormality
	Deficiency anaemia	Red blood cell count abnormal
	Dilutional anaemia	Red blood cell count decreased
	Erythroblast count abnormal	Reticulocyte count abnormal
	Erythroblast count decreased	Reticulocyte count decreased
	Erythroid dysplasia	Reticulocyte percentage decreased
	Erythroid maturation arrest	Reticulocytopenia
	Erythropenia	Scorbutic anaemia
	Erythropoiesis abnormal	Sideroblastic anaemia
	Erythropoietin deficiency anaemia	Spherocytic anaemia
	Haematocrit abnormal	Spur cell anaemia
	Haematocrit decreased	Warm autoimmune haemolytic anaemia

Drowsiness

Drowsiness will be analyzed by a customized query defined in Table 7.8.1: 3.

Table 7.8.1: 3 MedDRA preferred terms for user-defined AE category of Drowsiness

User-defined AE category	**MedDRA preferred terms**	**Scope**
Drowsiness	Depressed level of consciousness	Narrow

	Post-injection delirium sedation syndrome	Narrow
	Radiation somnolence syndrome	Narrow
	Sedation	Narrow
	Altered state of consciousness	Broad
	Brain fog	Broad
	Concussion	Broad
	Consciousness fluctuating	Broad
	Intracranial hypotension	Broad
	Lethargy	Broad
	Obstructive sleep apnoea syndrome	Broad
	Orexin deficiency	Broad
	Pickwickian syndrome	Broad
	Post concussion syndrome	Broad
	Presyncope	Broad
	Sedation complication	Broad
	Sleep-related hypoventilation	Broad
	Shift work disorder	Broad
	Sleep apnoea syndrome	Broad

Sleep disorder

Sleep disorder related AE search terms are based upon the FDA Medical Queries (FMQs) of Insomnia (broad) and Somnolence (broad). Refer to Table 7.8.1: 4 for a list of MedDRA preferred terms in each of the groupings.

Table 7.8.1: 4 MedDRA preferred terms for user-defined AE categories of sleep disorder AEs

User-defined AE category	**MedDRA preferred terms**	
FMQ Insomnia (broad)	Advanced sleep phase	Primary insomnia
	Behavioural induced insufficient sleep syndrome	Psychophysiologic insomnia
	Circadian rhythm sleep disorder	Shift work disorder
	Delayed sleep phase	Sleep disorder due to general medical condition, insomnia type
	Dyssomnia	Sleep disorder due to general medical condition, mixed type
	Early morning awakening	Terminal insomnia
	Fatal familial insomnia	Dysfunctions associated with sleep stages or arousal from sleep
	Hyposomnia	Dyssomnia NOS
	Initial insomnia	Jet lag
	Insomnia	Microsleep
	Insomnia exacerbated	Sleep deficit
	Insomnia NEC	Sleep disorder
	Insomnia related to another mental condition	Sleep disorder due to a general medical condition
	Irregular sleep phase	Sleep disorder NOS
	Irregular sleep wake rhythm disorder	Sleep disorder therapy

	Middle insomnia	Sleep inertia
	Non-24-hour sleep-wake disorder	Sleep study abnormal
	Poor quality sleep	
FMQ Somnolence (broad)	Central nervous system depression NOS	Sedation aggravated
	Consciousness fluctuating	Somnolence
	Depressed level of consciousness	Somnolence neonatal
	Hypersomnia	Stupor
	Infant sedation	Altered state of consciousness
	Lethargy	Fatigue
	Neonatal oversedation	Fatigue aggravated
	Primary hypersomnia	Prostration
	Sedation	Sluggishness

An overall summary of adverse events will be presented, including frequency of schizophrenia relapse.The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). The SOCs will be sorted by default in descending frequency and PTs will be sorted in descending frequency within an SOC in the iclepertin arm. Separate tables will be provided for patients with

- Related AEs
- Serious AEs
- Serious related AEs
- AESIs
- Other significant AEs
- AEs leading to death
- AE leading to discontinuation of trial medication
- AEs occurred with incidence in the preferred term >2%
- AEs suggestive of abuse potential or related to CNS depressant effects
- AEs in user-defined AE categories
- AEs occurred during the follow-up period.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will follow BI standards (4).

Descriptive statistics for laboratory values will be displayed using the converted values in standard unit for data analyzed by the central laboratory. Shift tables of change in laboratory measurements between baseline and minimum, maximum or last value on treatment will be presented.

7.8.3 Vital signs

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

7.8.4 ECG

Clinically relevant abnormal ECG findings will be reported and analysed as AEs.

7.9 OTHER ANALYSES

Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses
A population PK analysis for iclepertin may be performed. Data of this study may be pooled with data of other iclepertin trials. Population PK and PK/PD analyses will be subject to a separate analysis plan(s) and report(s), and will not be part of the CTR.

Ophthalmologic variables
Each ophthalmologic variable is measured for both the right eye and the left eye. For continuous variables, summary statistics including mean, median, standard deviation, minimum, maximum will be presented for the change from baseline measurements.

For categorical variables, shift tables will be presented for the categorical changes from baseline.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

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

9. REFERENCES

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2.	*BI-KMED-TMCP-HTG-0025:* "How to Guide: Standards and Processes for Analyses Performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, KMED.
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4.	*BI-KMED-BDS-HTG-0042*: "How to Guide: Handling, Display and Analysis of Laboratory Data", current version, KMED
5.	Keefe et al. (2017) Placebo Response and Practice Effects in Schizophrenia Cognition Trial. JAMA Psychiatry 74(8):807-814. [R19-3822]
6.	Carpenter, J. and Kenward, M. (2013) Multiple Imputation and its Application, 1st ed. Wiley, New York. [R22-0188]
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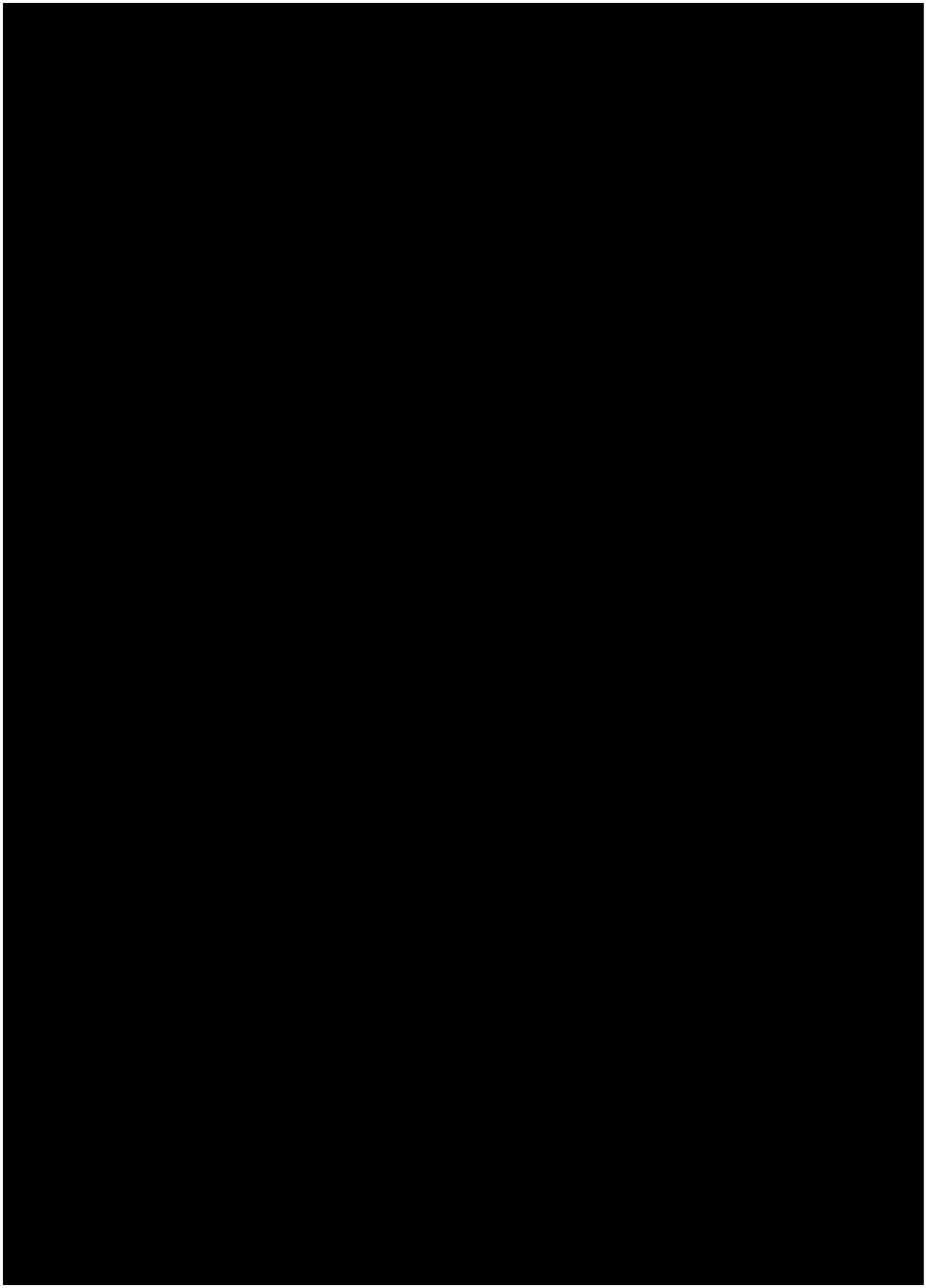
8.	Guizzaro, et al (2021) The Use of a Variable Representing Compliance Improves Accuracy of Estimation of the Effect of Treatment Allocation Regardless of Discontinuation in Trials with Incomplete Follow-up. Statistics in Biopharmaceutical Research, 13(1):119-127. [R23-1510]
9.	Little, R. J. & Rubin, D. B. (2002). Statistical Analysis with Missing Data (2nd ed). New York: John Wiley & Sons. [R12-2094]
10.	Bell, J. (2022). Implementation of the treatment policy strategy for continuous longitudinal endpoints: a comparison of estimation methods. PSI Conf, Gothenburg. [R23-0137]



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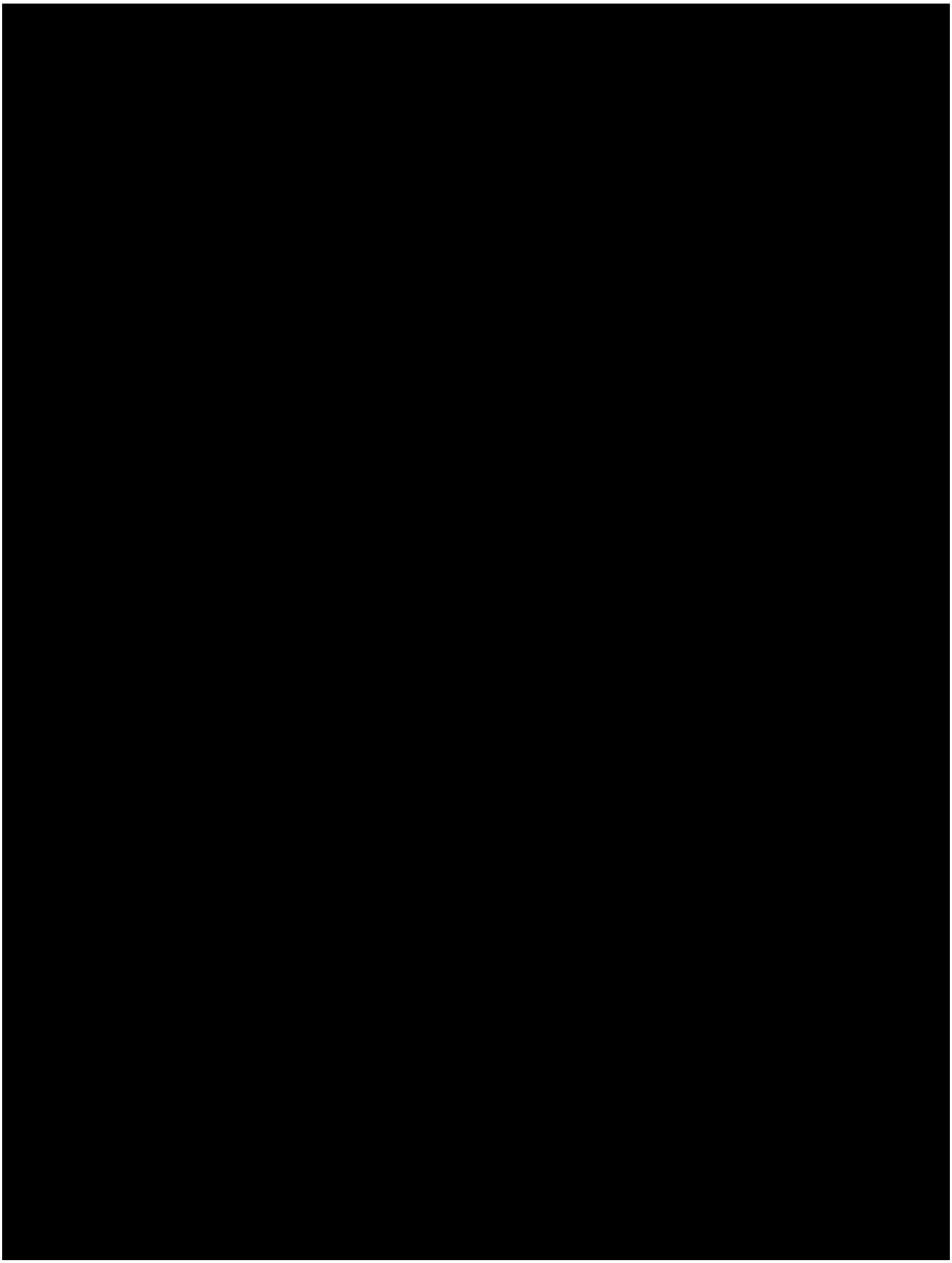

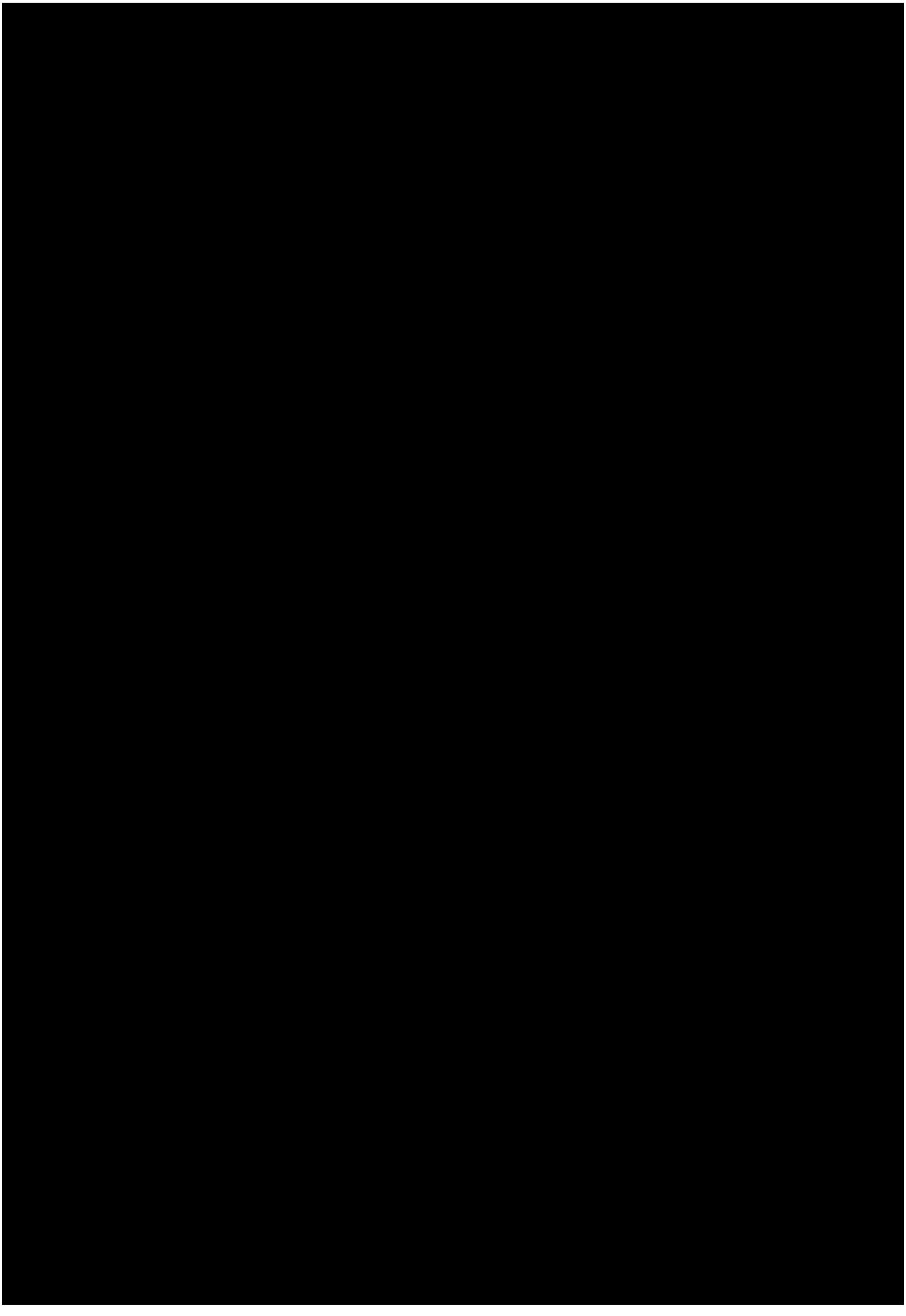

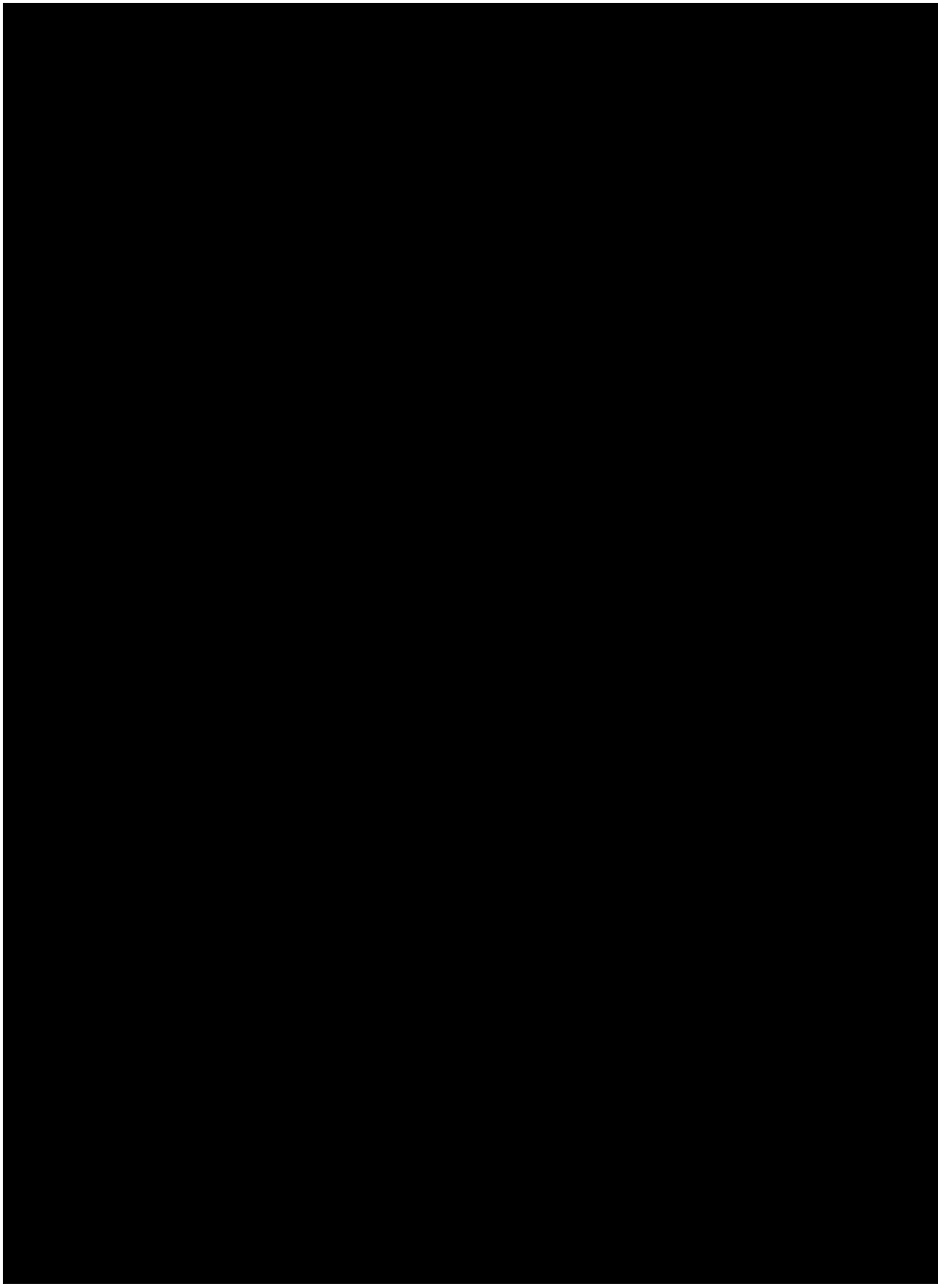

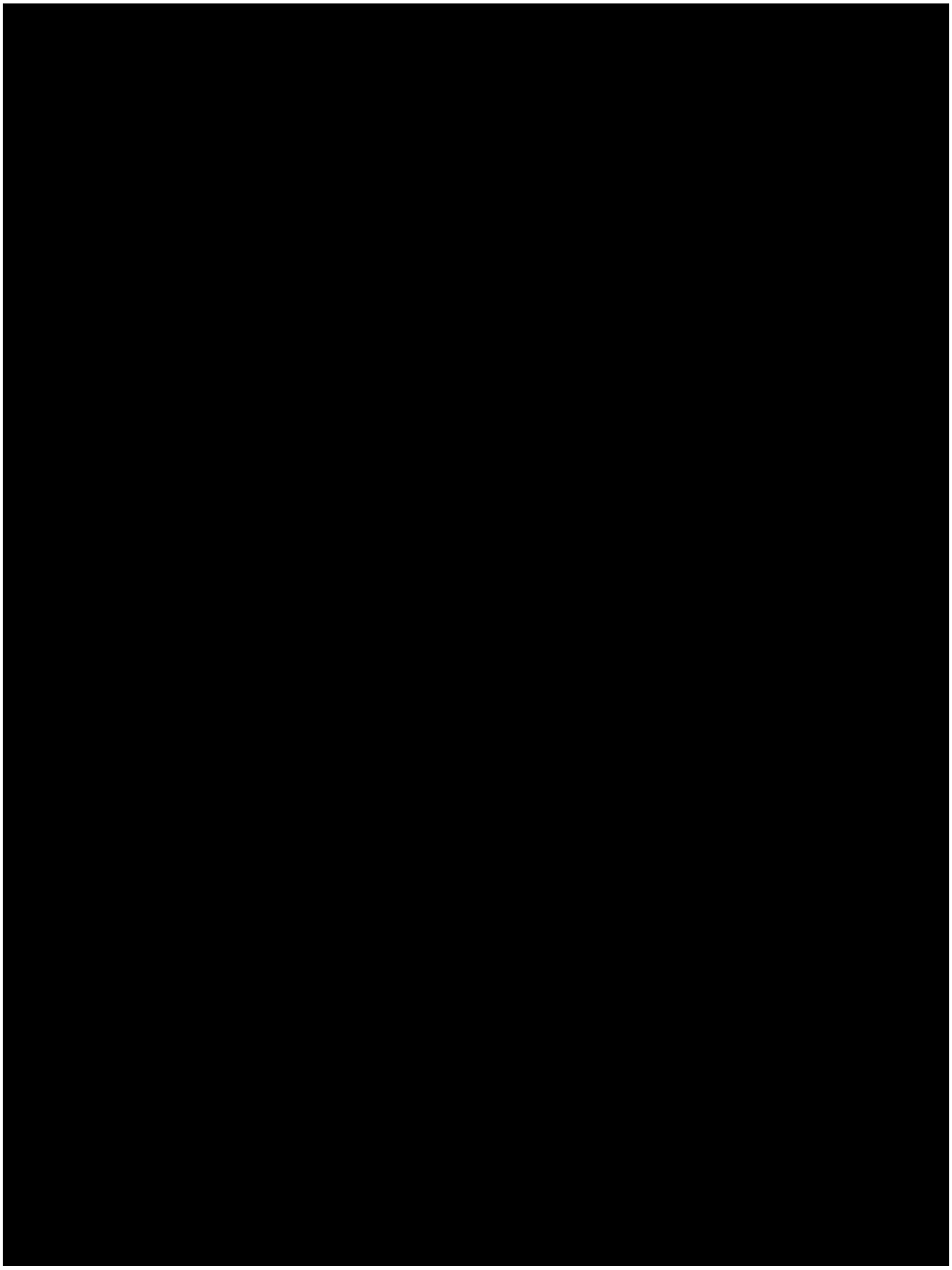

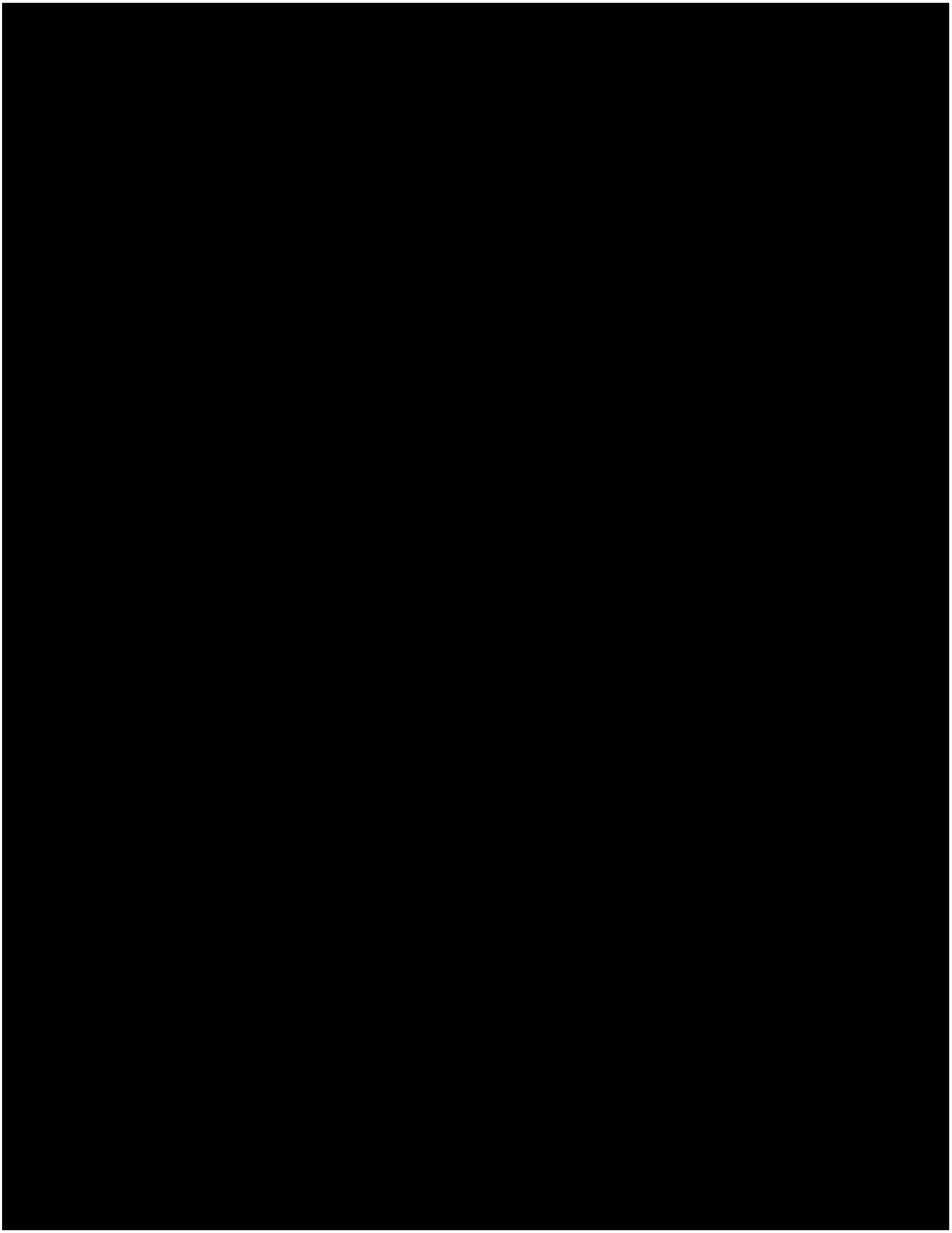

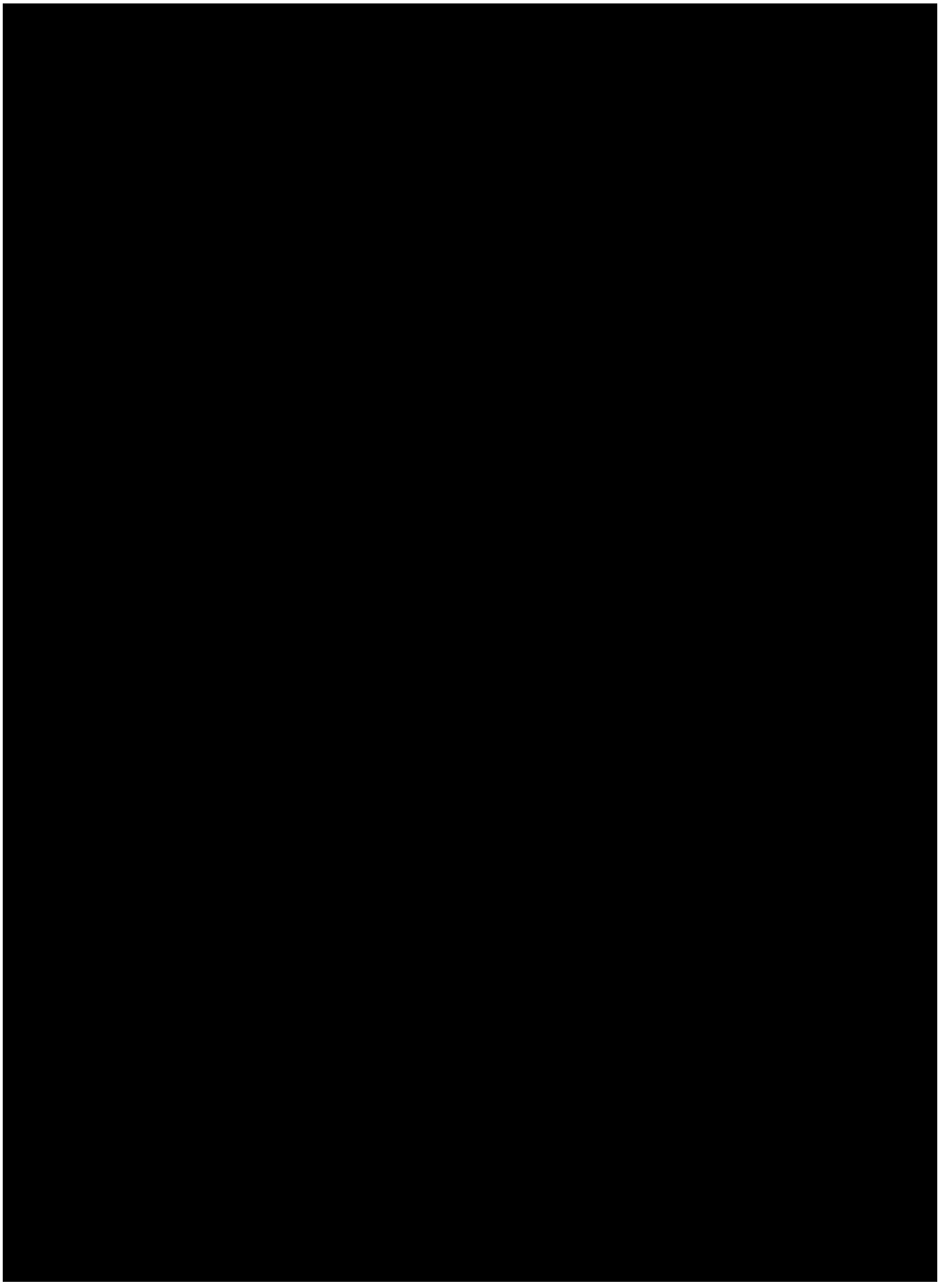

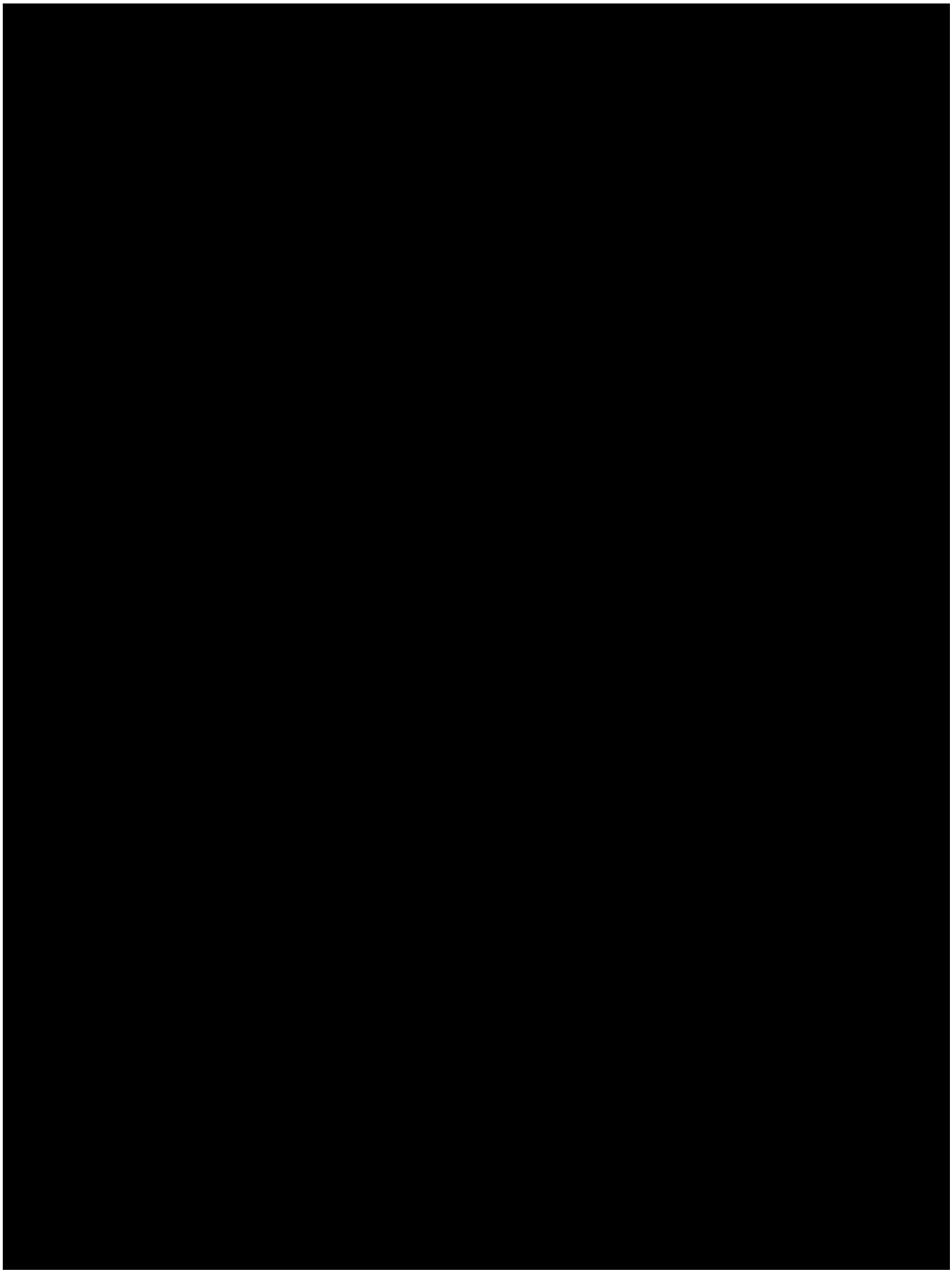

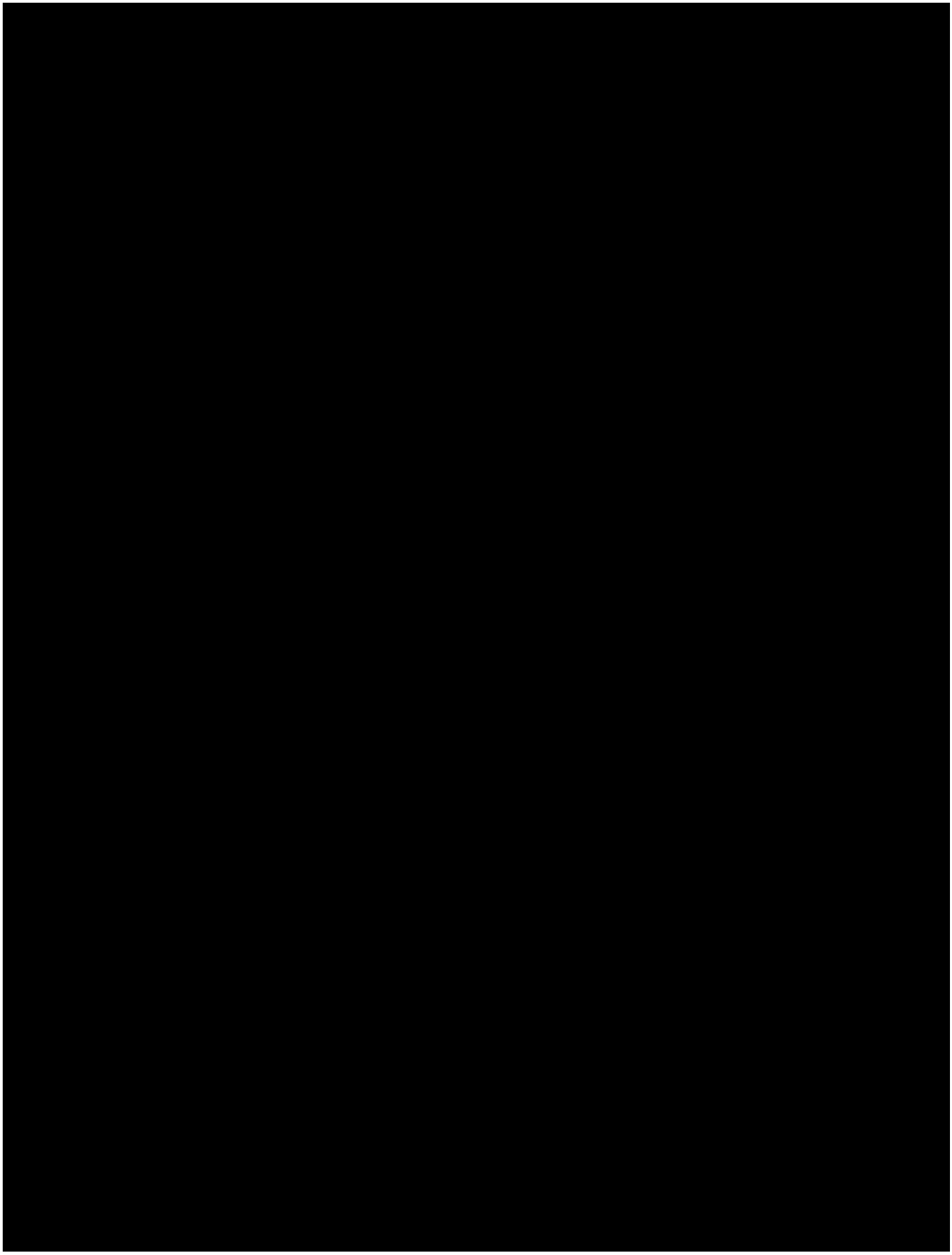

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
2	**25-OCT-24**	[redacted]	Table 7.8.1: 2	This table was updated to fix a truncation issue in the previous version.