TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_144276_1.0**
BI Trial No.:	1346-0014
Title:	An open label, single arm, extension trial to examine long-term safety of Iclepertin once daily in patients with schizophrenia who have completed previous Iclepertin Phase III trials (CONNEX-X)
Investigational Product:	Iclepertin (BI 425809)
Responsible trial statistician:	[redacted] Phone: [redacted]
Date of statistical analysis plan:	18 FEB 2025
Version:	1.0
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2. LIST OF ABBREVIATIONS

See Medicine Glossary:

http://glossary

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
[redacted]	
ATC	Anatomical, Therapeutic, Chemical
[redacted]	
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customised Medical Query
CGI-S	Clinical Global Impressions - Severity
CNS	Central nervous system
[redacted]	
CT	Concomitant therapy
CTP	Clinical Trial Protocol
ECG	Electrocardiogram
EOT	End of treatment
[redacted]	
FMQ	FDA Medical Query
Hb	Haemoglobin
IA	Interim analysis
ICH	International Conference on Harmonisation
iPD	Important protocol deviation
[redacted]	
PT	Preferred term
QD	Once daily
REP	Residual effect period

Term	Definition / description
SAE	Serious adverse event
[redacted]	
SOC	System organ class
TEAE	Treatment emergent adverse event
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UDAEC	User-defined adverse event category
[redacted]	

3. INTRODUCTION

As per ICH E9 (1) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of 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.

SAS® Version 9.4 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following further safety endpoints are defined:

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) throughout the extension study.

5.2 SECONDARY ENDPOINTS

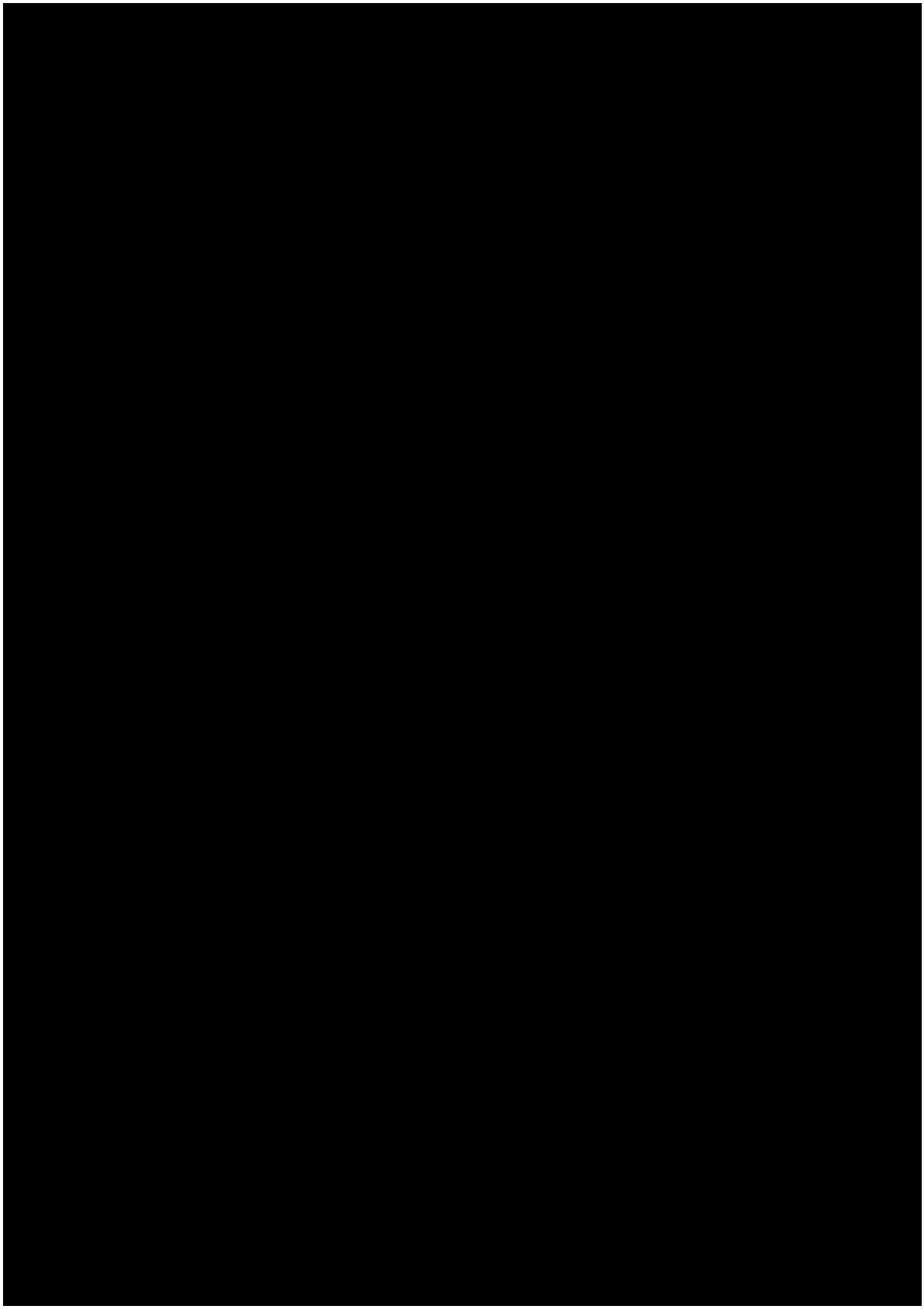
5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

The secondary endpoints are:

- Change from baseline in haemoglobin (Hb) to end of treatment (EOT)
- Change from baseline in Clinical Global Impressions – Severity (CGI-S) to EOT



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

All patients will receive Iclepertin 10 mg once daily (QD) for 52 weeks. For additional information on the treatment and drug assignment, see CTP Section 4.

Table 6.1: 1 lists the treatment group in this study and Table 6.1: 2 defines the analysing treatment periods 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**
Iclepertin 10 mg QD	Iclepertin 10 mg

Table 6.1: 2 Analysing treatment periods

Analysing Treatment Period	**Start Date**	**End Date**
On-treatment period	Date of the first treatment administration	Date of the last treatment administration + REP
Safety follow-up 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 important Protocol Deviations (iPD) in analyses is described in the iPD specification document and stored in the Trial Master File in the electronic Document Management System.

6.3 INTERCURRENT EVENTS

Not applicable.

6.4 PATIENT SETS ANALYSED

The following patient analysis sets are defined:

- Entered set: Includes all patients who signed informed consent and entered the trial, regardless of whether a patient was treated with trial medication.

- Treated set (TS): Includes all patients who signed informed consent and were treated with at least one dose of the trial medication. The TS will be used for all efficacy and safety analyses.

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

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to Boehringer Ingelheim (BI) standards (2).

[redacted]

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

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

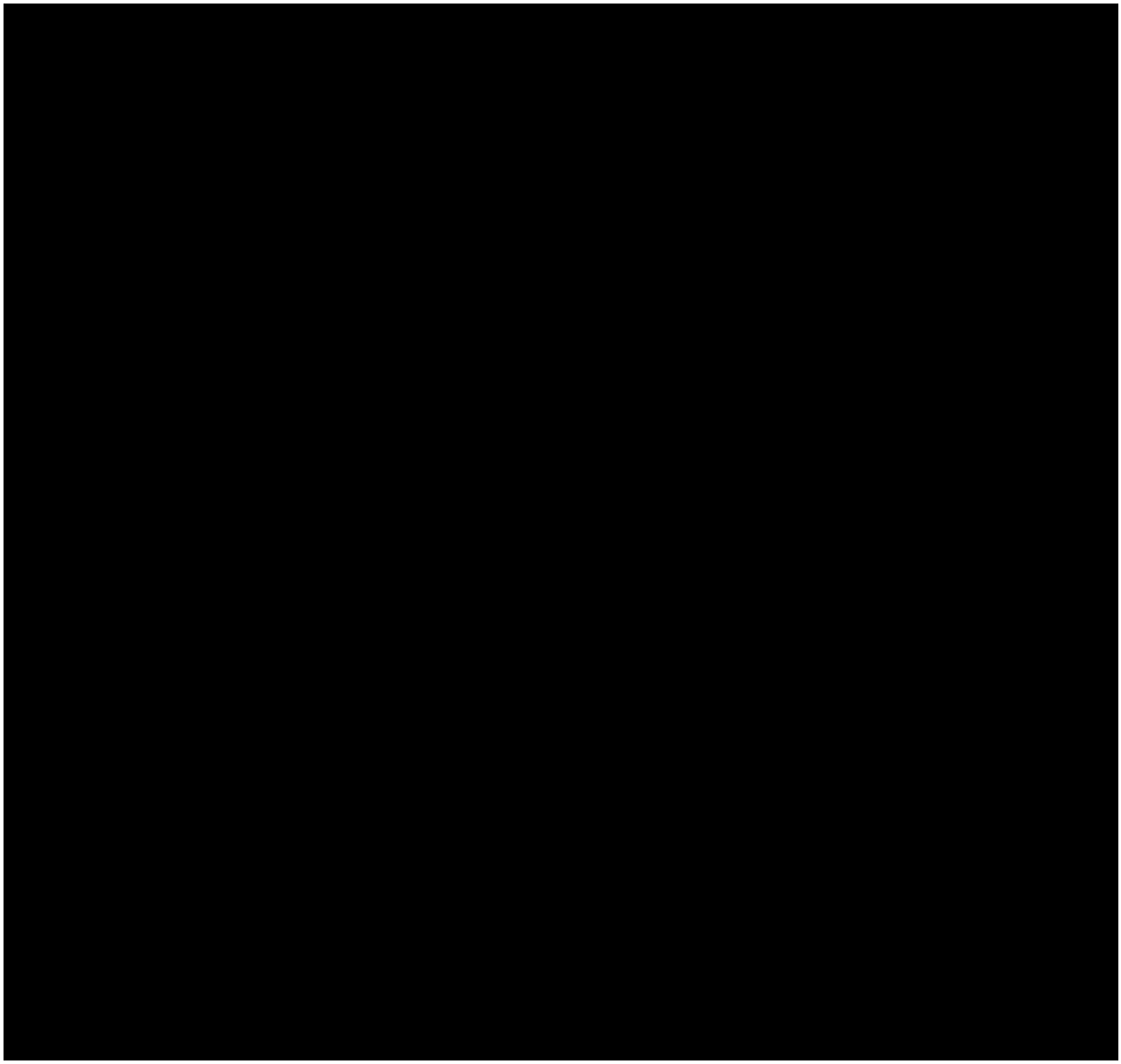
In general, baseline values are the last measurement (including measurements in the parent trial) taken prior to or on the day of first administration of trial medication in this extension trial. Specifically for Hb, baseline will be the last on-treatment (including REP) value prior to first administration of trial medication in this extension trial.

Tables 6.7: 1, 6.7: 2, 6.7: 3, 6.7: 4, 6.7: 5, 6.7: 6 and 6.7: 7 define the analysis visits and time windows which will be used for the analyses of safety and efficacy endpoints. Actual study day will be calculated starting with the date of first administration of trial treatment in the extension trial as Day 1. Unscheduled assessments will be mapped to the analysis visits together with the scheduled assessments.

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 CGI-S

Analysis Visit	**Nominal Visit**	**Planned Day**	**Actual Day Window**
Baseline		1	Last measurement in parent trial – Day 1
Week 21	Visit 6	147	2 – 266
Week 52	EOT	365	≥267



[redacted]

Table 6.7: 6 Analysis visit windows for clinical laboratory evaluations (on-treatment period)

Analysis Visit	**Nominal Visit**	**Planned Day**	**Actual Day Window**
Baseline		1	Last measurement in parent trial – Day 1
Week 4	Visit 2	28	2 – 48
Week 8	Visit 3	56	49 – 76
Week 12	Visit 4	84	77 – 104
Week 16	Visit 5	112	105 – 174
Week 26	Visit 7	182	175 – 216
Week 32	Visit 9	224	217 – 258
Week 38	Visit 11	266	259 – 300
Week 44	Visit 13	308	301 – 357
Week 52	EOT	365	≥358

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

Table 6.7: 7 Analysis visit windows for weight and vital signs (on-treatment period)

Analysis Visit	**Nominal Visit**	**Planned Day**	**Actual Day Window**
Baseline		1	Last measurement in parent trial – Day 1
Week 4	Visit 2	28	2 – 48
Week 8	Visit 3	56	49 – 76
Week 12	Visit 4	84	77 – 104
Week 16	Visit 5	112	105 – 140
Week 21	Visit 6	147	141 – 174
Week 26	Visit 7	182	175 – 216
Week 32	Visit 9	224	217 – 258
Week 38	Visit 11	266	259 – 300
Week 44	Visit 13	308	301 – 357
Week 52	EOT	365	≥358

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

Other data including follow-up visits will not be mapped to analysis visits and instead will be analysed according to the planned visit name.

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places 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 will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to all patients in the respective patient set whether they have non-missing values or not.

The precision for percentages should be one decimal point, unless the denominator is smaller than 100, in which case percentages are given in integer numbers. 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 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.

7.2.1 Concomitant diseases

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

7.2.2 Concomitant therapies

Concomitant therapies (CTs) will be coded according to WHO DD and classified by the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level (ATC3) 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, patients receiving CTs with more than one possible ATC3 category will be counted more than once.

Summaries will be provided for CTs of special interest such as antipsychotics, benzodiazepines, anticholinergics, antiepileptics and antidepressants, as defined in Table 10.1:1.

In addition, CTs will be summarised in two groups: central nervous system (CNS)-active and non-CNS-active concomitant medications. Summaries will be presented for therapies which are ongoing at baseline and those which started during the on-treatment period, by ATC3 and preferred name.

Concomitant non-drug therapies, including psychotherapies, will be coded according to MedDRA. A summary will be provided of therapies ongoing at baseline or which started during the on-treatment period by PT.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. See Section 5.4.2 for definitions of treatment compliance.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary endpoint is a safety endpoint. Further details on the analysis are in Section 7.8.1.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

Not applicable.

7.5.2 Secondary objective analysis

The change from baseline in Hb is a safety endpoint and the analysis is described further in Section 7.8.2.

The change from baseline in CGI-S will be analysed descriptively with summary statistics over time for the TS.

[redacted]

7.7 EXTENT OF EXPOSURE

Extent of exposure will be summarised for the TS using descriptive statistics for total time (days, weeks) on treatment as well as frequency and percentage of patients in the following categories: <56, 56 - <112, 112 - <182, 182 - <224, 224 - <266, 266 - <308, 308 - <365, >=365 days.

The frequency and percentage of patients with temporary treatment discontinuations will be summarized along with descriptive statistics for the total duration (days) of all temporary treatment discontinuations.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

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 patients with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI standards (3). AEs will be coded with the most current version of MedDRA.

The analysis of AEs will be based on the concept of TEAEs. That means that all AEs occurring between the start of treatment in the extension trial and the end of the REP as well as AEs that start before first drug intake in the extension trial and deteriorate under treatment during the extension trial will be assigned to the on-treatment period. All AEs occurring after

the residual effect period will be assigned to the safety follow-up period. For details on the treatment definition, see Section 6.1.

AESIs are potential severe DILI as defined in CTP Section 5.2.6.1.5. Other significant AEs, according to ICH E3 (5), include:

- Any non-serious AE which led to an action taken with study drug (e.g. discontinuation).
- Marked haematological and other lab abnormalities and any AE which led to significant additional concomitant therapy, other than those reported as serious.

An overall summary of AEs will be presented, including the frequency of schizophrenia relapse as defined in CTP Section 5.2.5. The frequency of patients with AEs will be summarised by primary SOC and PT. The SOCs will be sorted by default in descending frequency and PTs will be sorted in descending frequency within SOC. Separate tables will be provided for patients with drug-related AEs, SAEs, drug-related SAEs, AEs leading to death, AEs leading to treatment discontinuation, AESIs, other significant AEs and AEs occurring in the safety follow-up period.

AEs suggestive of abuse potential or related to CNS depressant effects will be identified by user-defined AE categories (UDAEC) defined in Table 10.2: 1 and will be summarised by UDAEC and PT.

Other UDAEC are defined as follows and will be summarised by UDAEC and PT:

- Ocular events: Includes all PTs under the Eye disorder SOC, regardless of primary or secondary SOC.
- Anaemia: BI customised Medical Query (BIcMQ) of Decreased haemoglobin and anaemia (incl. non-haematological causes) as defined in Table 10.2: 2.
- Haematopoietic cytopenias: Standardised MedDRA Query.
- Drowsiness: BIcMQ as defined in Table 10.2: 3.
- Sleep disorder: FDA Medical Queries (FMQs) of Insomnia (broad) and Somnolence (broad) as defined in Table 10.2: 4.

7.8.2 Laboratory data

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

Laboratory data from the central laboratory will be converted to standard units. Values over time including change from baseline and ratio to baseline will be summarised with descriptive statistics. Shift tables of laboratory values relative to reference ranges between baseline and minimum, maximum or last value on treatment will be presented.

Hb is a laboratory parameter of special interest and is linked to secondary and further endpoints. Descriptive statistics for the change from baseline over time will be provided along with other laboratory parameters. [redacted]

The number and percentage of patients with possibly clinically significant abnormalities and those with elevated liver enzymes will also be summarised.

7.8.3 Vital signs

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

7.8.4 ECG

Abnormal findings will be reported as AEs during the trial if judged clinically relevant by the investigator.

Frequency tables will be provided for the categorical ECG data. These will also include morphological findings that might be attributable to Iclepertin. A morphological finding observed on treatment that was not reported at baseline will be categorized as a ‘new onset’ of this finding.

Listings will be provided for morphological findings and quantitative data, where notable findings will also be flagged.

7.9 OTHER ANALYSIS

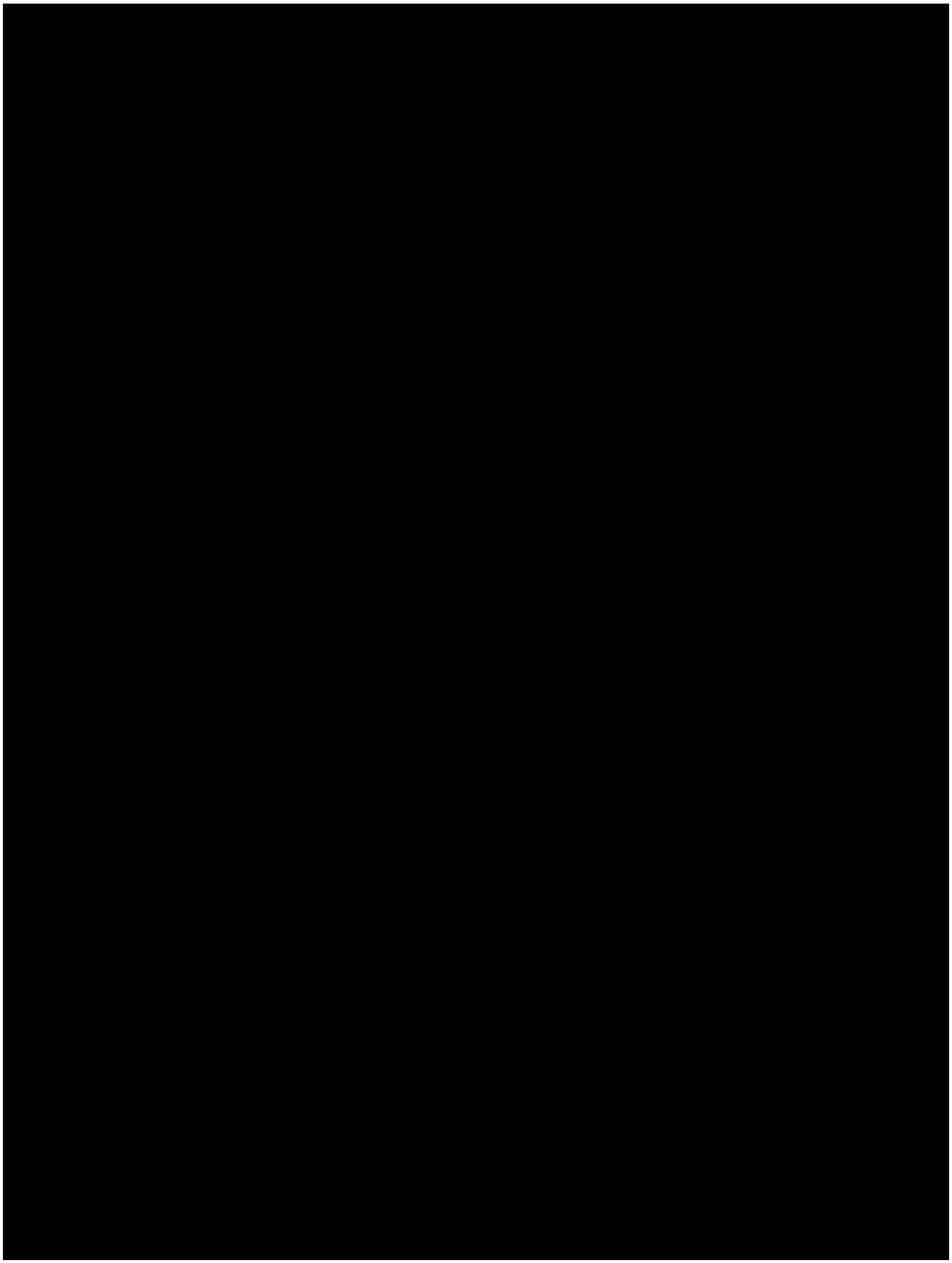
[redacted]

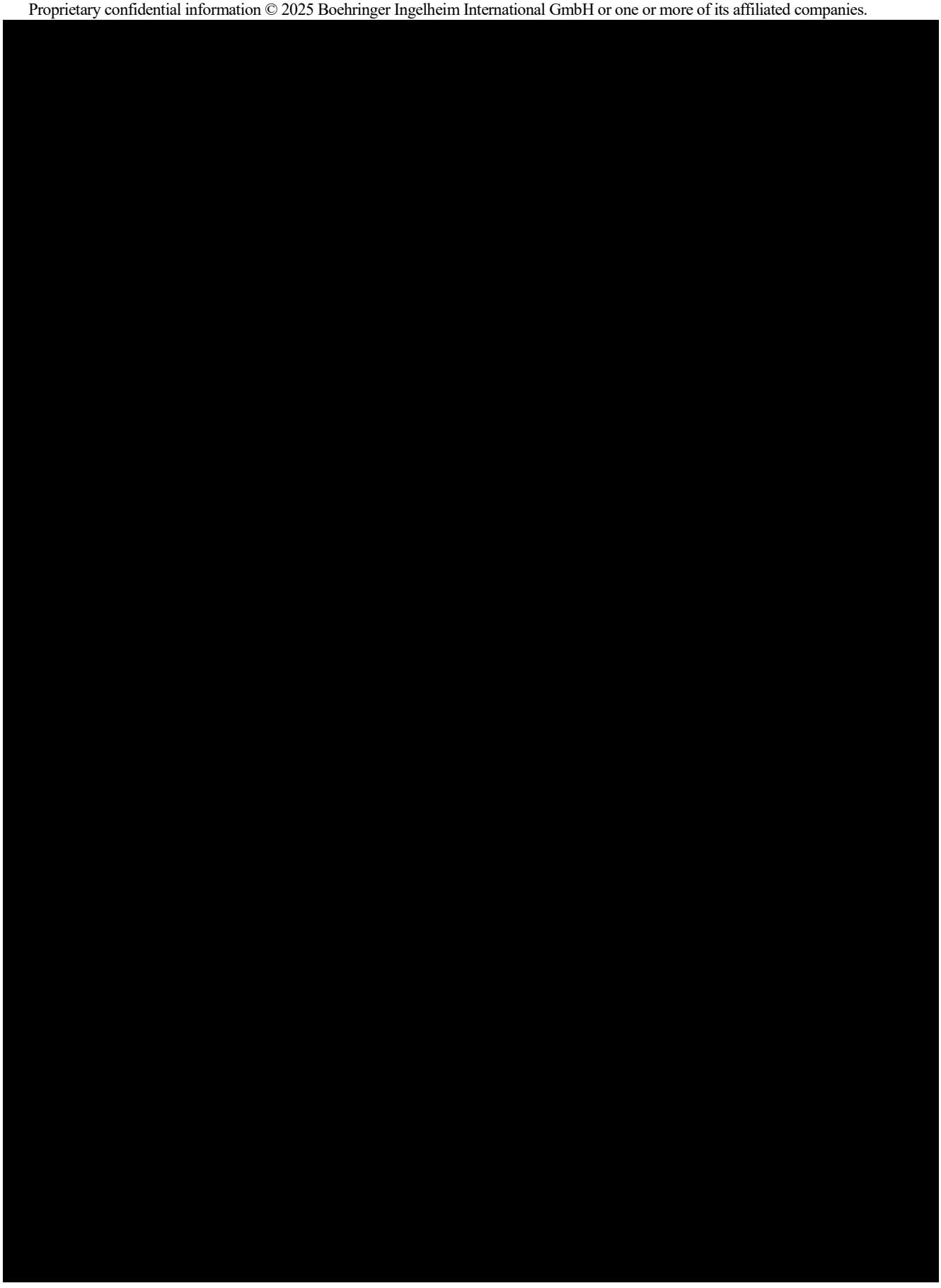
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

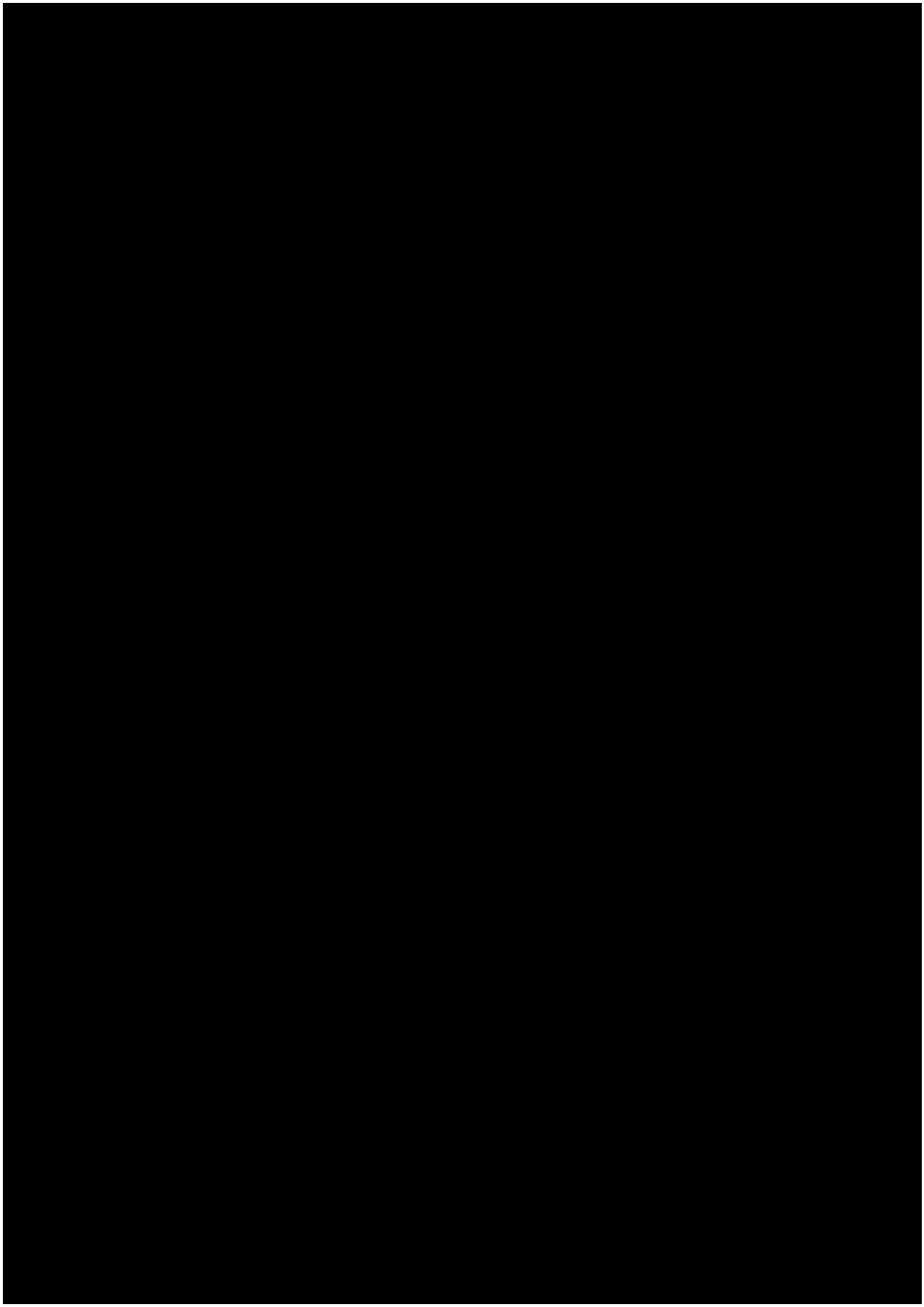
The treatment information will be loaded into the trial database at trial initiation.

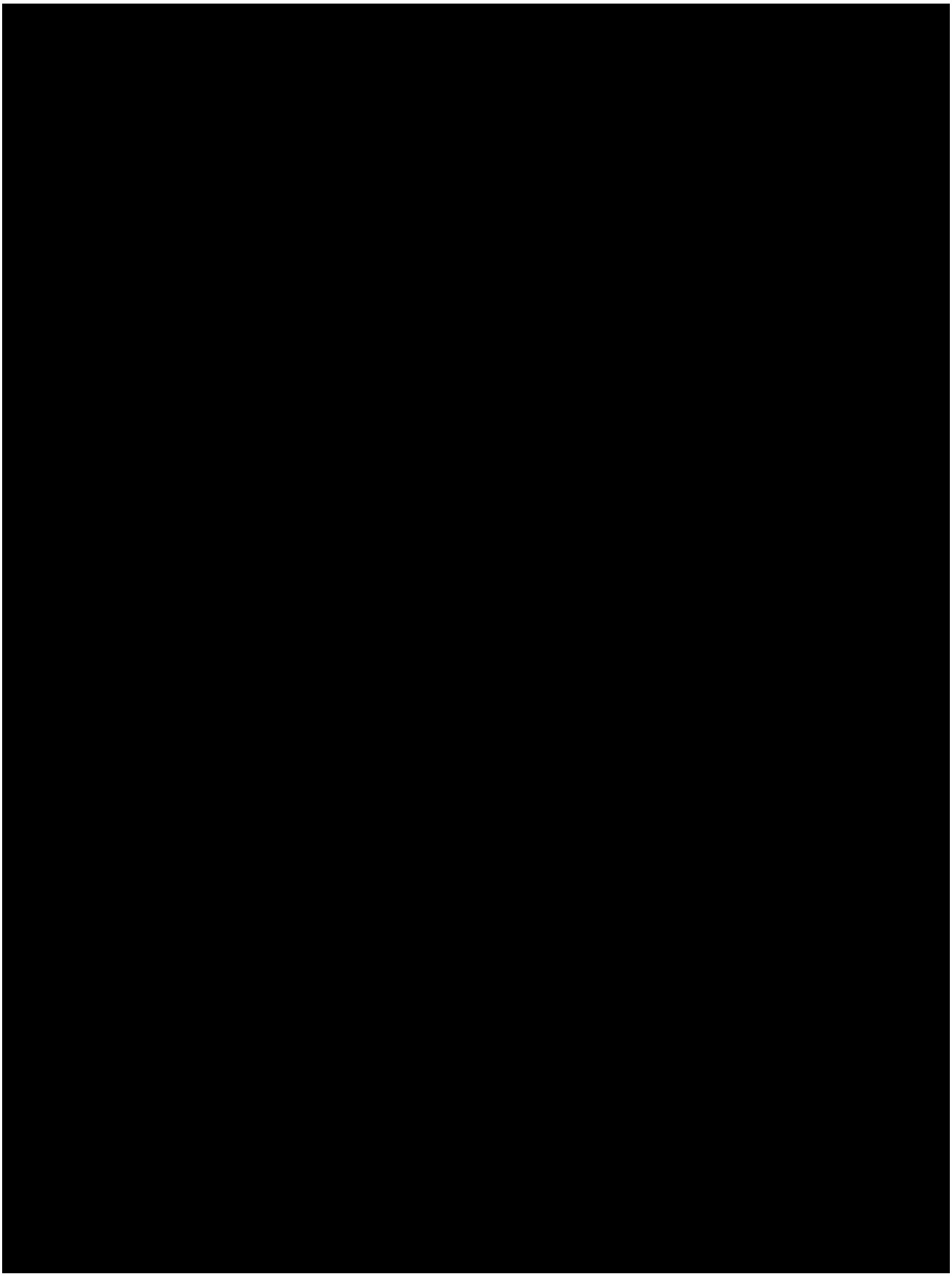
9. REFERENCES

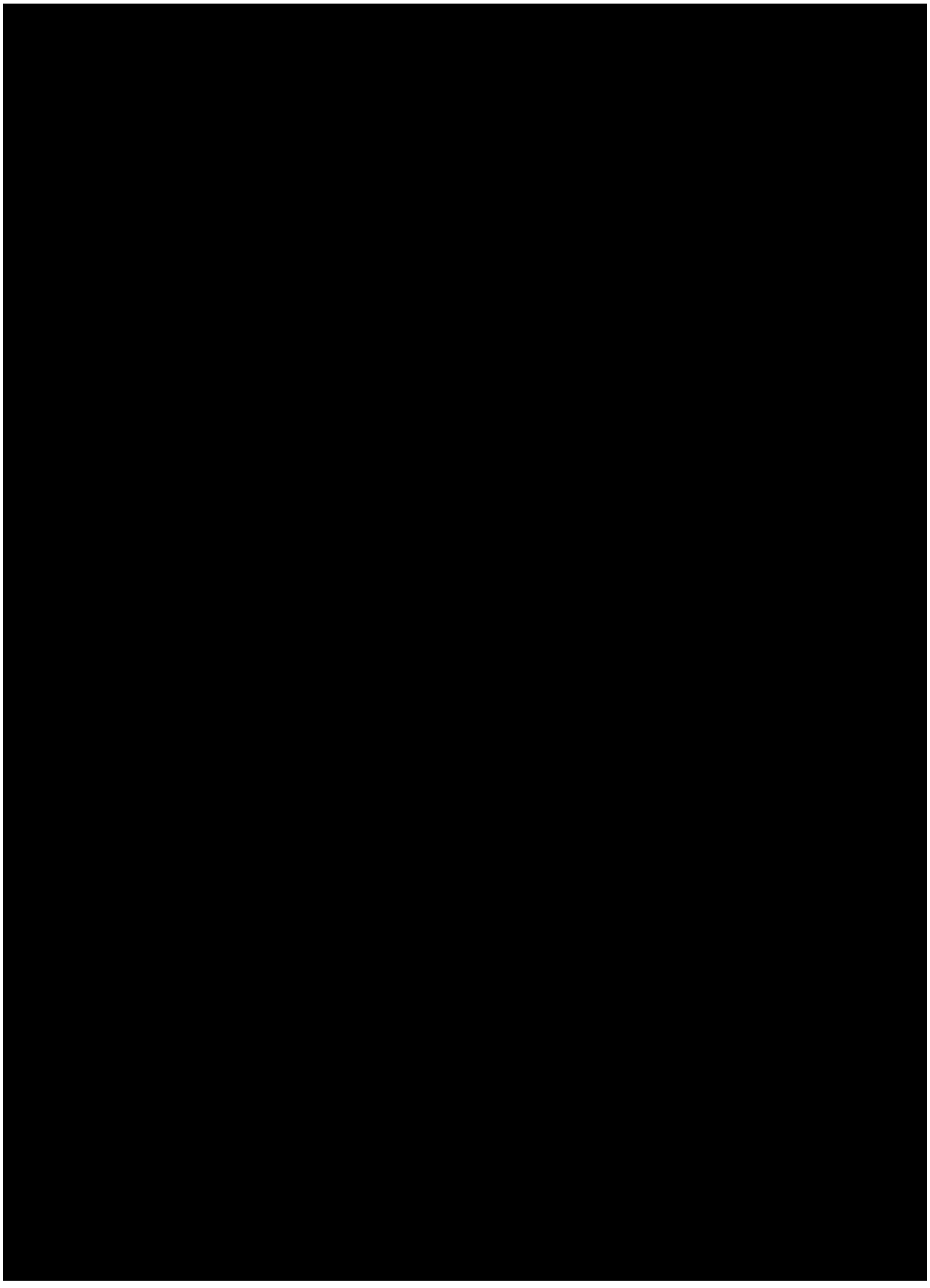
1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-HTG-0035*: "How to Guide: Handling of Missing and Incomplete AE dates", current version, KMED
3.	*BI-KMED-BDS-HTG-0041*: "How to Guide: Analysis and Presentation of AE Data from Clinical Trials", current version, KMED
4.	*BI-KMED-BDS-HTG-0042*: "How to Guide: Handling, Display and Analysis of Laboratory Data", current version, KMED
5.	*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.

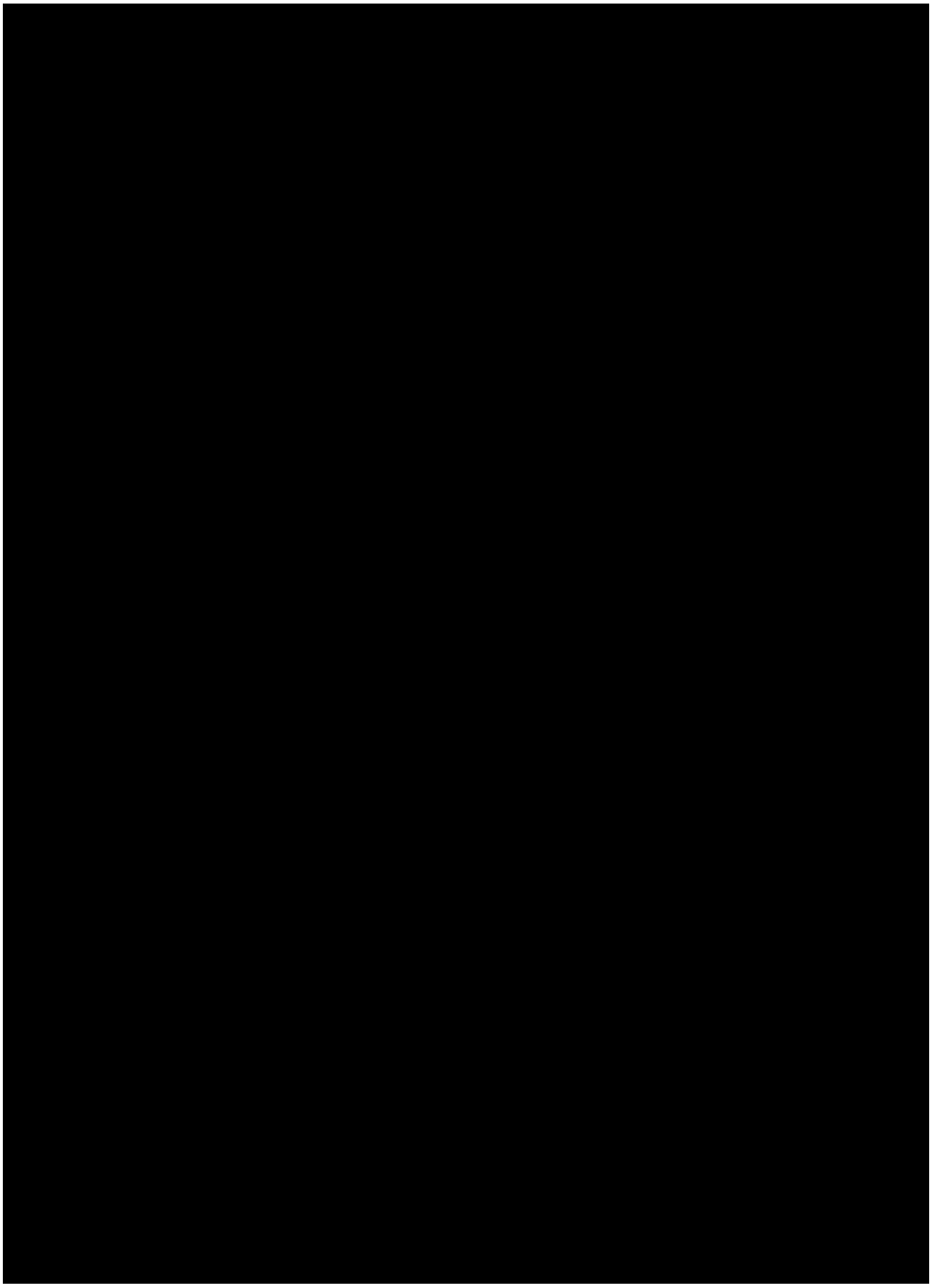


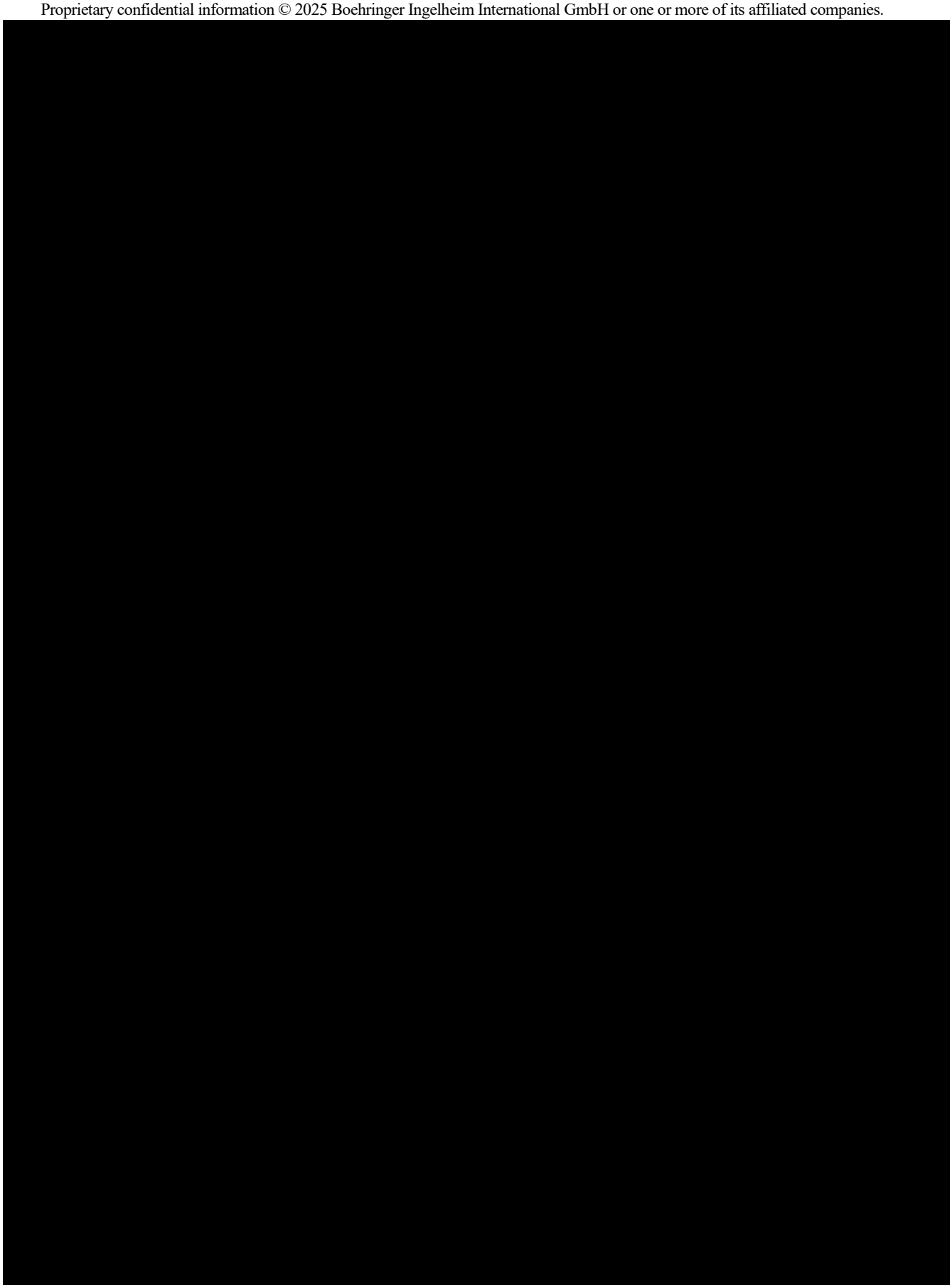


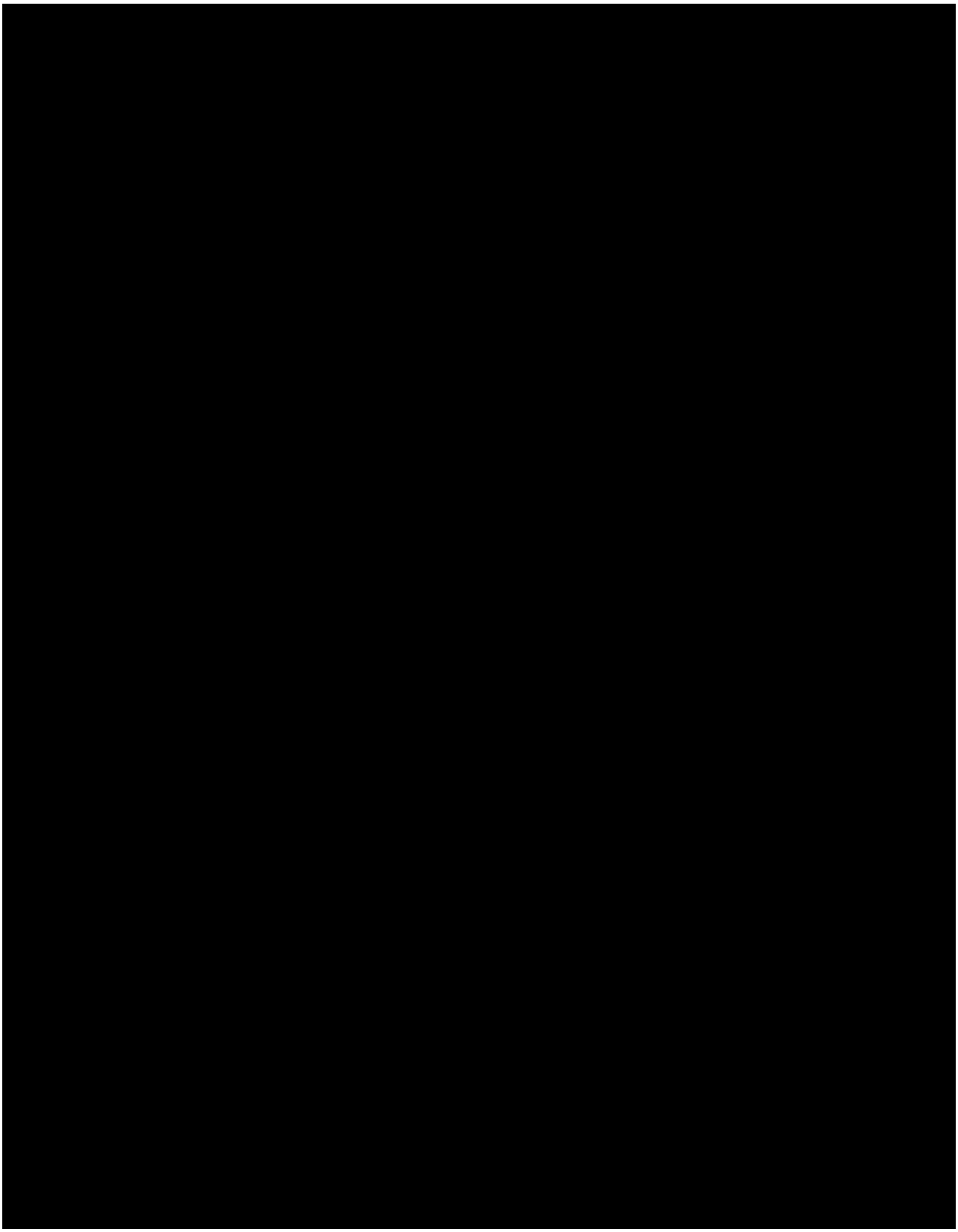












11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	18-FEB-2025	[redacted]	None	This is the final TSAP