TRIAL STATISTICAL ANALYSIS PLAN

Global ID_Version:	**228892_1168295_1.0**
BI Trial No.:	1434-0004
Title:	A multicenter, randomized double-blind, parallel group, placebo-controlled study to assess the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics profile of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Investigational Product(s):	BI 764198
Responsible trial statistician(s):	[redacted] **Telephone:**
Date of statistical analysis plan:	20 NOV 2024
Version:	1.0

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2. LIST OF ABBREVIATIONS

See Medicine Glossary:

Term	Definition / description
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHR	Aryl Hydrocarbon Receptor
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Plasma Concentration Curve
AUC0-∞	Area under the Plasma Concentration Curve from 0 to ∞
AUCt1-t2	Area under the Plasma Concentration Curve from t1 to t2
AUCt1-t2,ss	Area under the Plasma Concentration Curve from t1 to t2 at steady state
BI	Boehringer Ingelheim
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
Cmax	Maximum Plasma Concentration
Cmax,ss	Maximum Plasma Concentration at steady state
Cpre,ss	Pre-dose Plasma Concentration at steady state
CS	Corticosteroid
ECG	Electrocardiogram
ECGPCS	Electrocardiogram Pharmacokinetic Concentration Analysis Set
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
ES	Entered Set
ESKD	End Stage Kidney Disease
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
FUP1	Follow-up Visit #1
GCP	Good Clinical Practice
gCV	Geometric Coefficient of Variation
GGT	Gamma-Glutamyl Transferase
gMean	Geometric Mean
HA	Health Authority
[redacted]	
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IgA	Immunoglobulin A
IRT	Interactive Response Technology
[redacted]	
MedDRA	Medical Dictionary for Drug Regulatory Activities
Ms	Milliseconds
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per Protocol Analysis Set
QT	Time between start of the Q-wave and end of the T-wave in an electrocardiogram
QTc QT	interval corrected for heart rate
QTcF QT	interval corrected for heart rate using the method of Fridericia

RPM	Report Planning Meeting
SAE	Serious Adverse Event
SGLT2	Sodium-Glucose Cotransporter-2
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TS	Treated set
TSAP	Trial Statistical Analysis Plan
TPE	Total Protein Excretion
TRPC6	Transient Receptor Potential Cation subfamily C Member 6
[redacted]	
ULN	Upper Level of Normal
UPCR	Urine Protein-Creatinine Ratio

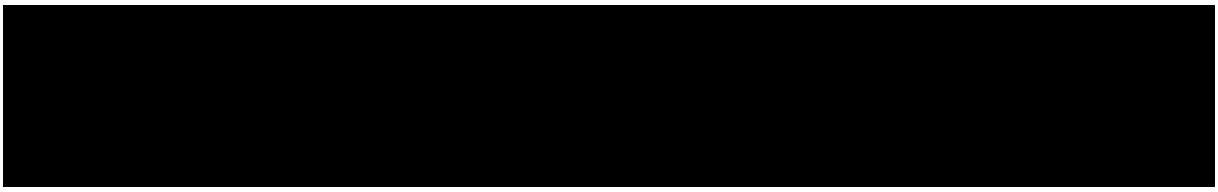
3. INTRODUCTION

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 the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP) version 5.0 (Dated 08Jan24), including any Protocol Amendment(s). In particular, this TSAP is based on the planned analysis specification as written in CTP Section 7.2. 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 (or later) will be used for statistical analyses. R version 4.0.2 (or later) with "DoseFinding" package [R15-2001] will be used for analysis based on MCP-Mod.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY



2) Two additional analysis sets were added to the list of Analysis Sets.

   - The Per Protocol Analysis Set (PPS), consisting of all patients who were randomized and completed treatment with evaluable measurements of primary endpoint at both baseline and end of treatment visits within the residual period (5 days), has been included in the set of Analysis Sets analyzed in the trial. The PPS is the analysis set used in the Sensitivity analysis.

   - The Electrocardiogram Pharmacokinetic Concentration Analysis Set (ECGPCS) has also been added. This patient set includes all subjects from the Treated Set who provided at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analysis e.g. concentration-QT plots. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values were used) will be made no later than at the Report Planning Meeting (RPM) before database lock.

3) The CTP stated, as part of the primary analysis, that an ANOVA model, for the proteinuria (24-hr urine protein-creatinine ratio (UPCR)) change from baseline at week 12 (and other endpoints, as applicable), would be used to see the difference(s) across arms. However, an ANCOVA model with use of corticosteroid (CS) at randomization and baseline 24-hr UPCR, as covariates will be utilized instead. This

change was performed to align with the protocol study design that stratifies by CS use at randomization to ensure even distribution of patients taking CS across treatment groups, and to further control for any potential confounding effects related to CS use. Therefore, ensuring a more robust analysis.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

Primary endpoint will be used as described in, the CTP, Section 5.1.1: The primary endpoint is patients achieving at least 25% reduction in UPCR from 24-hour urine (24-hr UPCR) relative to baseline after 12 weeks of treatment. The baseline UPCR will be from the average of two 24-hour urine samples collected before Visit 2.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

This section is not applicable as there are no key secondary endpoints specified in the CTP.

5.2.2 Secondary endpoint(s)

Secondary endpoint(s) will be used as described in the CTP, Section 2.1.3 and assessments described in CTP, Section 5.1.1.

The secondary endpoints are:

Secondary endpoints are listed in CTP Section 2.1.3 and will be assessed, as follows:

- Change in 24-hr UPCR relative to visit 3 at week 12: the samples will be from the 24-hour
  urine samples collected at visits 3 and 12.
- Change in 24-hr UPCR relative to baseline at week 13: the samples will be the 24-hour urine samples collected at baseline and week 13.
- Change in 24-hour urinary protein excretion relative to baseline at week 12.
- The following pharmacokinetic parameters of BI 764198 will be determined, if feasible:
  - Steady state trough concentration $C_{pre,ss}$ on week 4 and week 12

For details on efficacy assessments and definition of baseline, see CTP Section 5.1.1.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Refer to Section 4 of the CTP for details.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Patients with important PDs that could potentially impact the evaluation of the primary endpoint(s) will be excluded from PPS, if applicable.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. Important PDs will be reviewed at Clinical Quality Monitoring Process (CQMP) conducted periodically during the trial.

6.3 INTERCURRENT EVENTS

An intercurrent event (ICE) is defined as an event of early discontinuation, lost to follow-up, or death.

The strategies for handling intercurrent events in this trial are as follows:

- Hypothetical estimand: assuming all subjects remained adherent to the assigned trial medication and the study protocol. This strategy will include all data collected until time of an ICE.

- Treatment policy estimand: using all available data including data collected after an ICE.

6.4 SUBJECT SETS ANALYSED

Subject sets will be used, as defined in the CTP Section 7.2.1.

The following analysis sets will be defined for statistical analyses:

- Entered Set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analysis of patient disposition.
- Randomized Set (RS): This patient set includes all patients who signed the informed consent form and were also randomised, regardless whether the patient was treated with trial medication or not.
- Treated Set (TS): This patient set includes all patients who received at least one dose of trial medication. The TS is used for safety and treatment exposure.
- Full Analysis Set (FAS): This patient set includes all patients who were randomized and treated with evaluable measurements of 24-hr UPCR at baseline and at least one 24-hr UPCR measurement after the first dose. The FAS is the main analysis set for the analysis of efficacy.
- Per Protocol (PPS): All patients who were randomized and completed treatment with evaluable measurements of primary endpoint at both baseline and end of treatment visits within the residual period (5 days). The PPS is the analysis set used in the Sensitivity analysis.
- Pharmacokinetic Analysis Set (PKS): This patient set includes all patients in the TS who provide at least one PK endpoint that was not excluded due to protocol violation relevant to the evaluation of PK or due to PK non-evaluability.
- ECG Pharmacokinetic Concentration Set (ECGPCS): This patient set includes all subjects from the TS who provided at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analysis e.g. concentration-QT plots. For placebo subjects, the plasma concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values were used) will be made no later than at the RPM before database lock.

If a patient receives incorrect medication for the entire treatment period, efficacy will be analysed as randomized and safety will be analysed as treated. If a patient receives incorrect medication for part of the treatment period, the primary analysis of the primary efficacy endpoint will be performed on the randomized set following the intention-to-treat principle. Such cases will be discussed in the RPM, if needed.

Table 6.4: 1 Subject sets analysed

	Subject sets						
Class of analysis	ES	RS	TS	FAS	PPS	PKS	ECGPCS
Efficacy				X	X		
Safety & treatment exposure			X				
Demographic & baseline		X					
Disposition	X						
Pharmacokinetic						X	
Exposure-Response							X

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No missing data will be imputed in the UPCR, [redacted], and urinary protein excretion analyses. Handling of missing PK data will be performed according to the relevant Corporate Procedure.

Missing or incomplete AE dates will be imputed according to BI standards (4). With respect to safety evaluations, it is not planned to impute missing values.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The trial consists of a screening period, treatment period, and a follow-up period. Following

the screening period, patients will be randomized (prior to visit 2) to one of the four treatment arms. The treatment period is followed by a 30-day follow-up period which consists of 2 follow-up visits. The 2nd follow-up visit which is also the EoS visit will be completed by telephone except for the eye exams.

For the endpoints collected from 24-hr urine samples, the baseline value will be the average of two (if available) 24-hour urine samples collected before visit 2 (prior to the first treatment).

Baseline for other endpoints will be defined as last available measurement (or sample) prior to first dose..

There will not be any time windows considered or visits calculated.

7. PLANNED ANALYSIS

[redacted]

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

For end-of-text tables, the set of summary statistics for non-PK parameters is:

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

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

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

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actually missing values. Percentages will be based on all subjects, in the respective subject set, whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic parameters collected and to be presented include, but are not limited to, the following:

- Sex (Male, Female)
- Race and ethnicity (as defined in the eCRF)
- Race (Asian/ non-Asian)
- Age [years]
- Age (< Median [years], =>Median [years])
- Height [cm] at baseline
- Weight [kg] (continuous) at baseline
- Body mass index (BMI) [kg/m^2] (defined as weight [kg]/(height [cm]/100)^2) at baseline
- eGFR [mL/min/1/1.73m^2] at screening: <=45, >45 mL/min/1/1.73m^2]
- eGFR [mL/min/1/1.73m^2] at baseline
- UPCR from 24-hour Urine [g/g] at baseline (Baseline UPCR is the average of two, 24-hour urine samples collected before Visit 2)
- UPCR from 24−hour Urine: <3.5[g/g] , => 3.5[g/g]
- Serum Albumin (Screening Visit): <30 [g/L], =>30 [g/L]
- FSGS history: <6 [months], 6 [months] to <2 [years] and => 2 [years]
- SGLT2 Inhibitors Use at baseline (Yes, No)
- Corticosteroid Use at randomization (Yes, No)
- Presence of Monogenic Disease (TRPC6) (Yes, No)

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be summarized descriptively. The frequency [N (%)] of patients with different concomitant diseases (baseline conditions) will be presented. The concomitant medications taken at baseline and those taken while on treatment will be coded using the World Health Organization (WHO) Drug coding dictionary. These will then be summarized by ATC class 3 and preferred term and listed by patient with each medication taken.

Concomitant non-Drug Therapies will also be summarized descriptively.

7.3 TREATMENT COMPLIANCE

Neither pill counts nor compliance percentages are collected in this trial. However, information is obtained regarding patients who were treatment non-compliant. A by-patient listing for non-compliance will be provided.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Primary analysis of the primary endpoint(s)

This is an exploratory trial. No confirmatory testing is performed and hence neither null nor alternative hypotheses are defined. Nominal p-values may be presented. The FAS will be used for the analysis of the primary endpoint.

An exploratory analysis for the primary endpoint, in terms of proportion of patients achieving at least 25% UPCR reduction relative to baseline at week 12 (patients missing the week 12, 24-hr UPCR will be counted as non-responders) will be conducted by providing 95% confidence intervals from each treatment group, via logistic regression utilizing corticosteroid use at randomization (variable CORTIC) and baseline 24-hr UPCR, as covariates. The baseline UPCR will be from the average of two 24-hour urine samples collected before visit 2 (before the first dose). Graphical representations of change in 24-hour UPCR from baseline will also be presented.

The primary estimand of interest is the treatment effect, assuming all subjects remained adherent to the assigned trial medication, and the study protocol using a hypothetical approach, i.e., study drug is taken as directed. This analysis will include all data collected until time of an ICE. For primary analysis, UPCR measurements after ICE will not be included. ICE and the strategies for handling intercurrent events are defined in the CTP section 7.2.2 and section 6.3, above, as follows:

An intercurrent event (ICE) is defined as an event of,

- Early discontinuation,
- Lost to follow-up, or
- Death.

The strategies for handling intercurrent events in this trial are as follows:

(1) Hypothetical estimand: assuming all subjects remained adherent to the assigned trial medication and the study protocol. This strategy will include all data collected until time of an ICE.

(2) Treatment policy estimand: using all available data including data collected after an ICE.

For this analysis only the Hypothetical estimand will be considered.

In addition, an analysis of covariance (ANCOVA) model (for the UPCR change from baseline at week 12) will be used to see differences across arms, with corticosteroid use at randomization and baseline 24-hr UPCR, as covariates. Dose-response relationship based on reduction in log of UPCR may be explored using a graphical approach.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

All secondary endpoints in CTP, Section 2.1.3 will be analysed by using descriptive statistics and figures.

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The extent of exposure is calculated as drug stop date minus drug start date plus one day and treatment interruptions are not taken into account in the calculation.

Extent of exposure will be summarised using descriptive statistics (e.g. frequency, mean, SD, Min, median, and Max) in days

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, by treatment group. Placebo patients will be pooled in a single group.

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 analysis of adverse events will be based on the concept of treatment emergent adverse events. AEs occurring from the start of treatment until stop of treatment + residual effect period (REP = 5 days) will be considered on-treatment. AEs occurring prior to the start of treatment will be assigned to ‘screening’. AEs occurring after the REP will be assigned to ‘post-treatment’.

An overall summary of adverse events will be presented for each study treatment for all treated subjects. This will show the number and percent of patients with any AE, any investigator defined drug-related AE, AEs leading to the discontinuation of study medication, and serious AEs (including reason for serious (death, life-threatening, disability/permanent damage, required or prolonged hospitalization, congenital abnormality/birth defect and other medically important).

The AEs will be coded using the Medical Dictionary for Regulatory Agencies (MedDRA) coding dictionary. The frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term. A patient with multiple on-treatment occurrences of the same preferred term meeting the criteria for inclusion in the table will be counted only once in these tabulations. Separate tables will be provided for patients with any AE, adverse events leading to discontinuation and serious adverse events. Additional table will present the frequency of patients with AEs by worst severity (mild, moderate, severe). When no events meet the criteria for inclusion in one of these four tables, the table will be shown as indicating no events of that type have occurred.

The system organ classes will be sorted according to the standard sort order specified by EMEA, preferred terms will be sorted by descending overall frequency (within system organ class).The following adverse events of special interest (AESI) have been defined in the protocol. Please refer to section 5.2.6.1.4 Adverse events of special interest in the CTP.

Ocular Safety Assessments

Eye exams including the evaluation of cataract by slit lamp will be performed by an ophthalmologist or an optometrist in both eyes to evaluate the presence or absence of lens disorders and cataract during the screening period. Eye assessments will be performed according to the Eye Examination Worksheet provided by the sponsor. The individual ophthalmological values for all treated subjects will be presented via by-patient listing.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). The number and percent of patients with abnormalities on treatment as identified by being outside the reference ranges for each laboratory parameter collected will be presented. The patients with possibly abnormalities/clinically significant abnormalities will be identified within the on-treatment period by study treatment.

Laboratory values will be summarized as frequencies of patients with abnormal values with patient individual listings.

A graphical summary highlighting potential cases of Hy's Law within each treatment group will be presented. The maximum on-treatment values of total bilirubin and ALT will be plotted each on a scale as multiples of the upper limit of normal. The figure will show areas that meet the criteria of cholestasis (total bilirubin > 2x ULN), Temple's corollary (ALT > 3 x ULN) and Hy's Law as the combination of these two factors. A similar figure using maximum AST values in place of ALT will be constructed. An accompanying listing will show by sample date and study day the full course of the total bilirubin, direct bilirubin, ALT, AST and alkaline phosphatase values for patients whose total bilirubin are > 2xULN or AST or ALT values > 3 x ULN at any time during the study. The listing will indicate where the value meets the criteria, either falling in the cholestasis range, that for Temple's corollary or where the combination meets that for Hy's Law itself.

Laboratory data at unscheduled visits will be summarized in the listing: summary table for descriptive statistics will only include laboratory data from the scheduled visits.

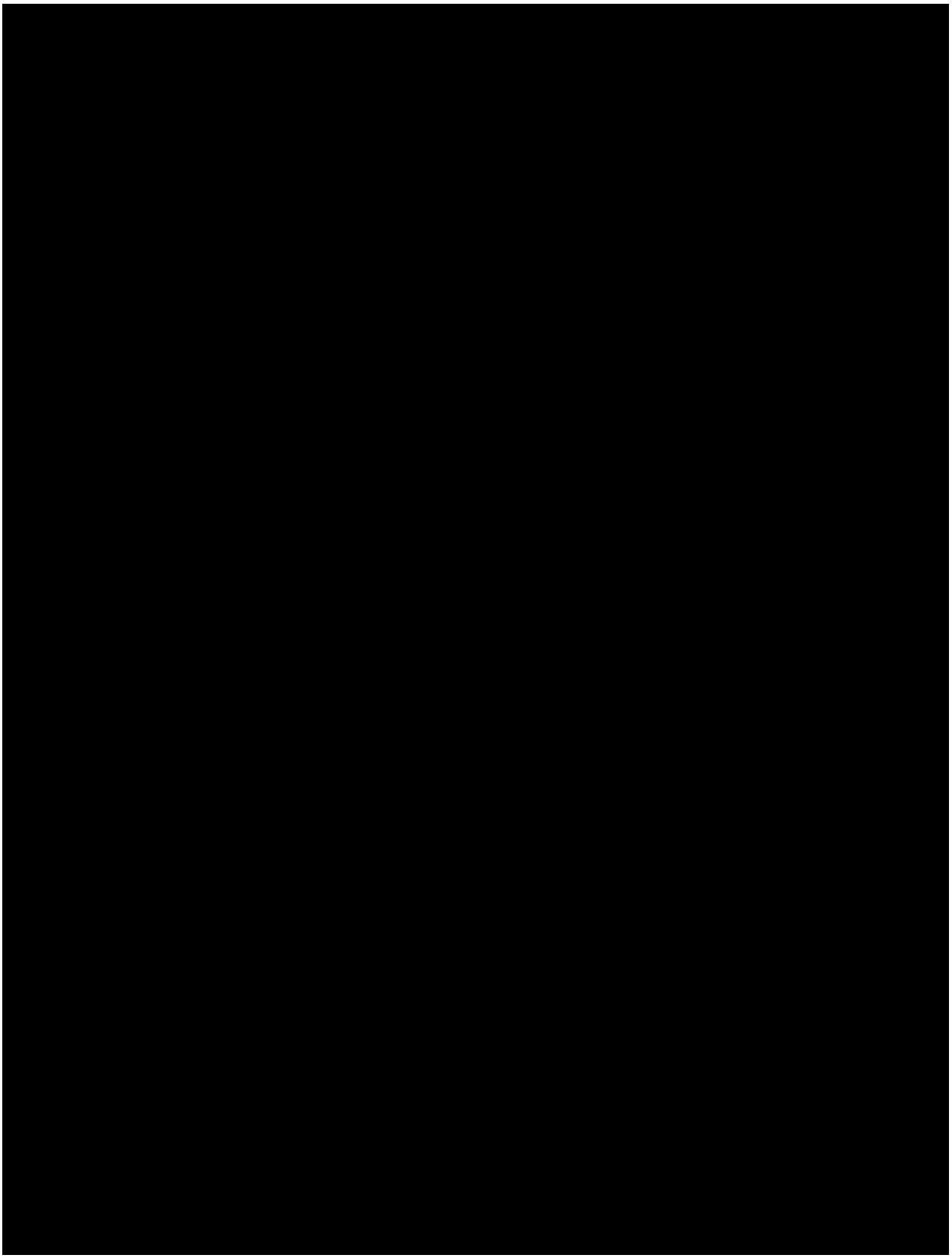
7.8.3 Vital signs

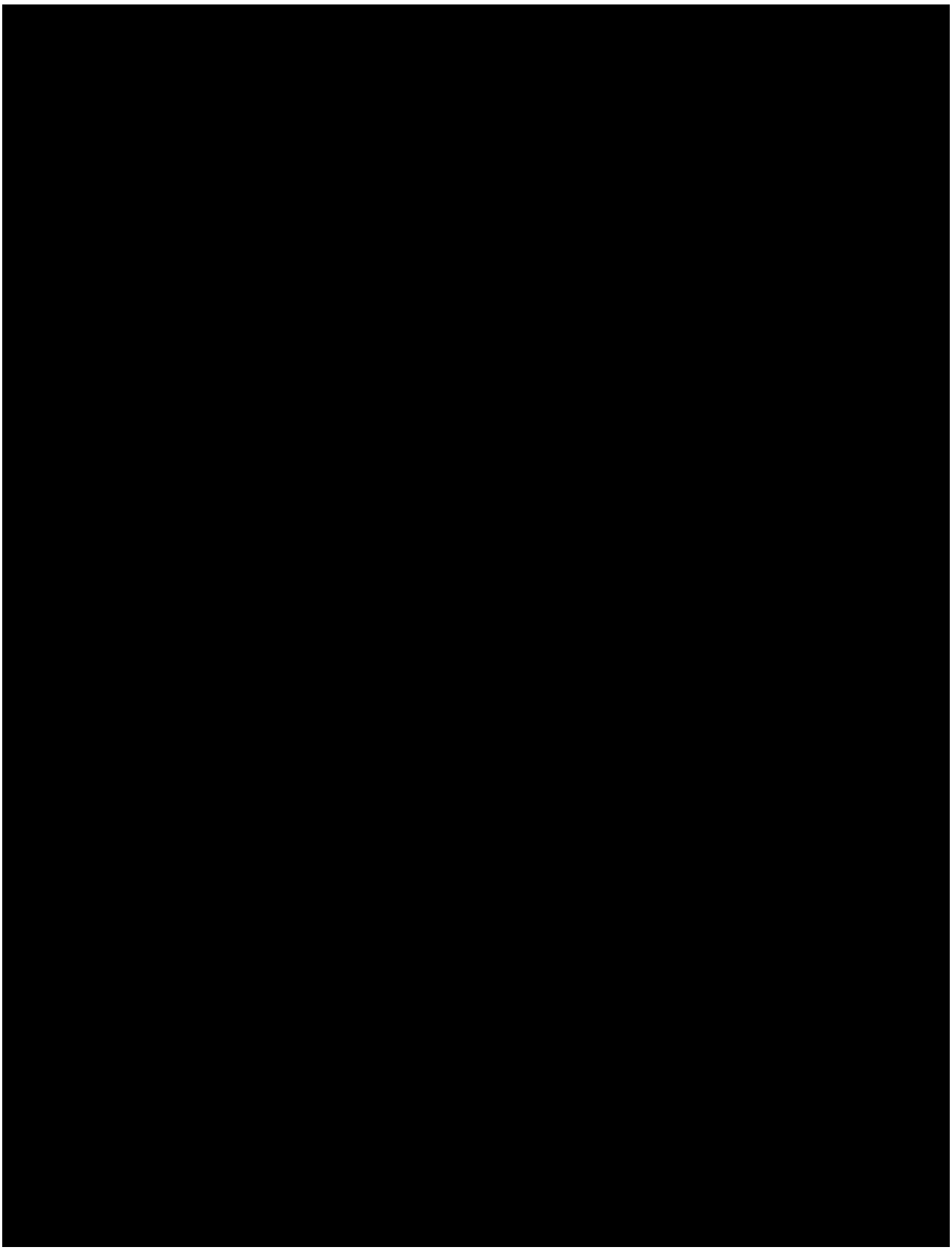
Only descriptive statistics are planned for this section of the report. Vital signs observed at screening, baseline, during the course of the study and at the end-of-study evaluation will be assessed with regards to possible changes compared to findings before start of treatment. The analyses of vital signs (blood pressure, pulse rate, and body weight) will be descriptive in nature.

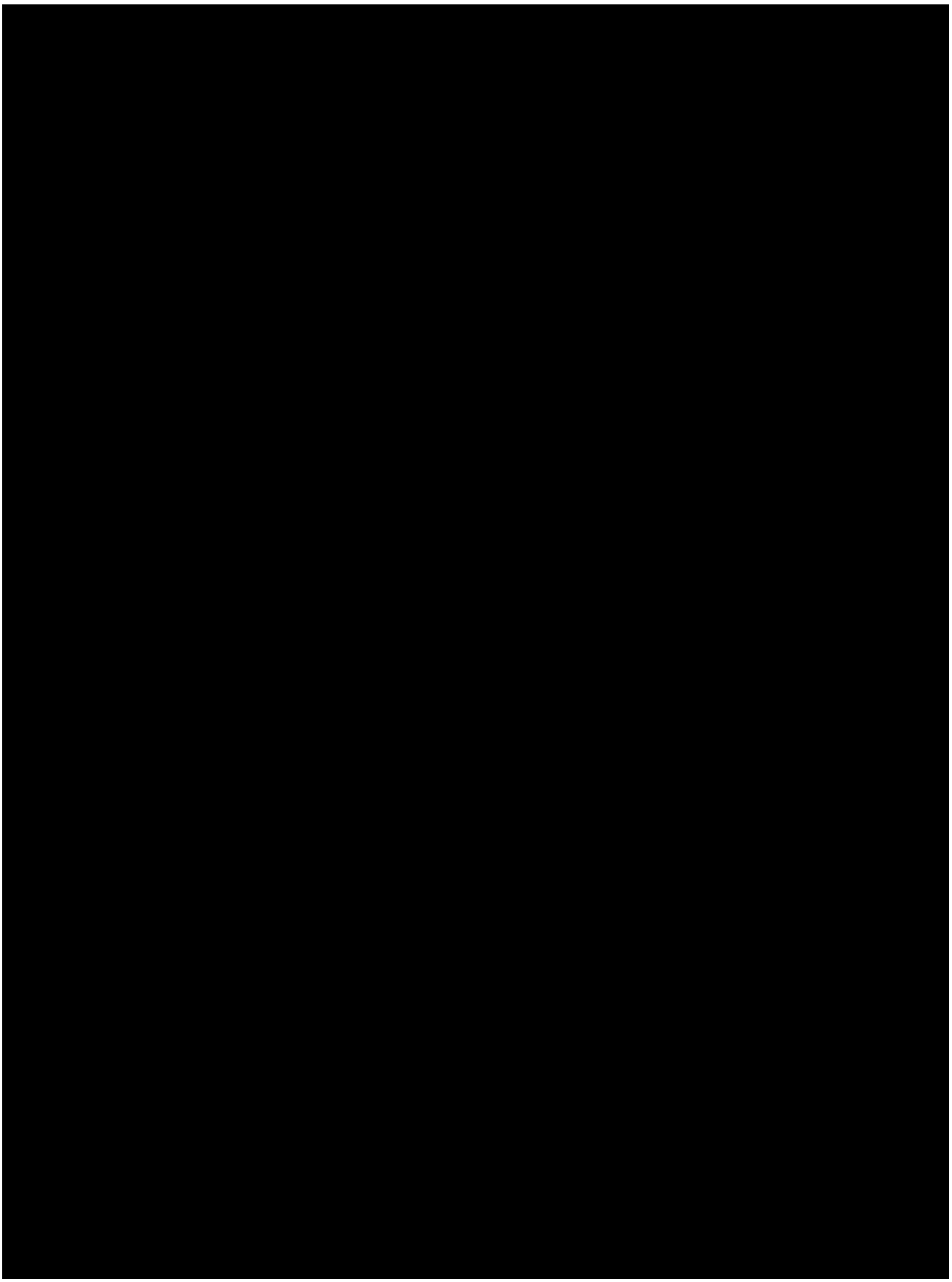
7.8.4 ECG

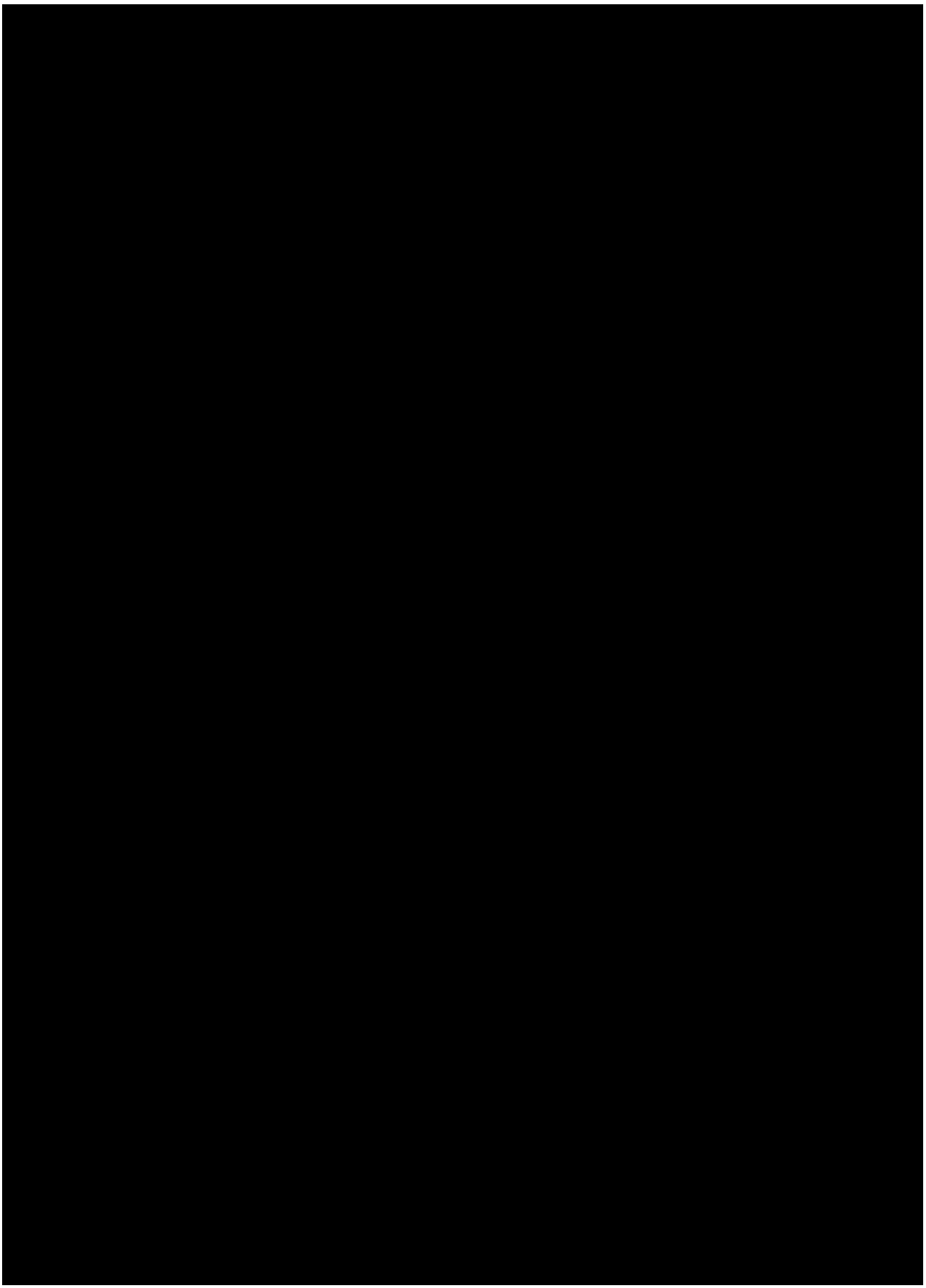
The analyses of ECG quantitative endpoints will be descriptive in nature. Abnormal ECG recordings will be noted, and clinically relevant abnormal findings will be reported as AEs by

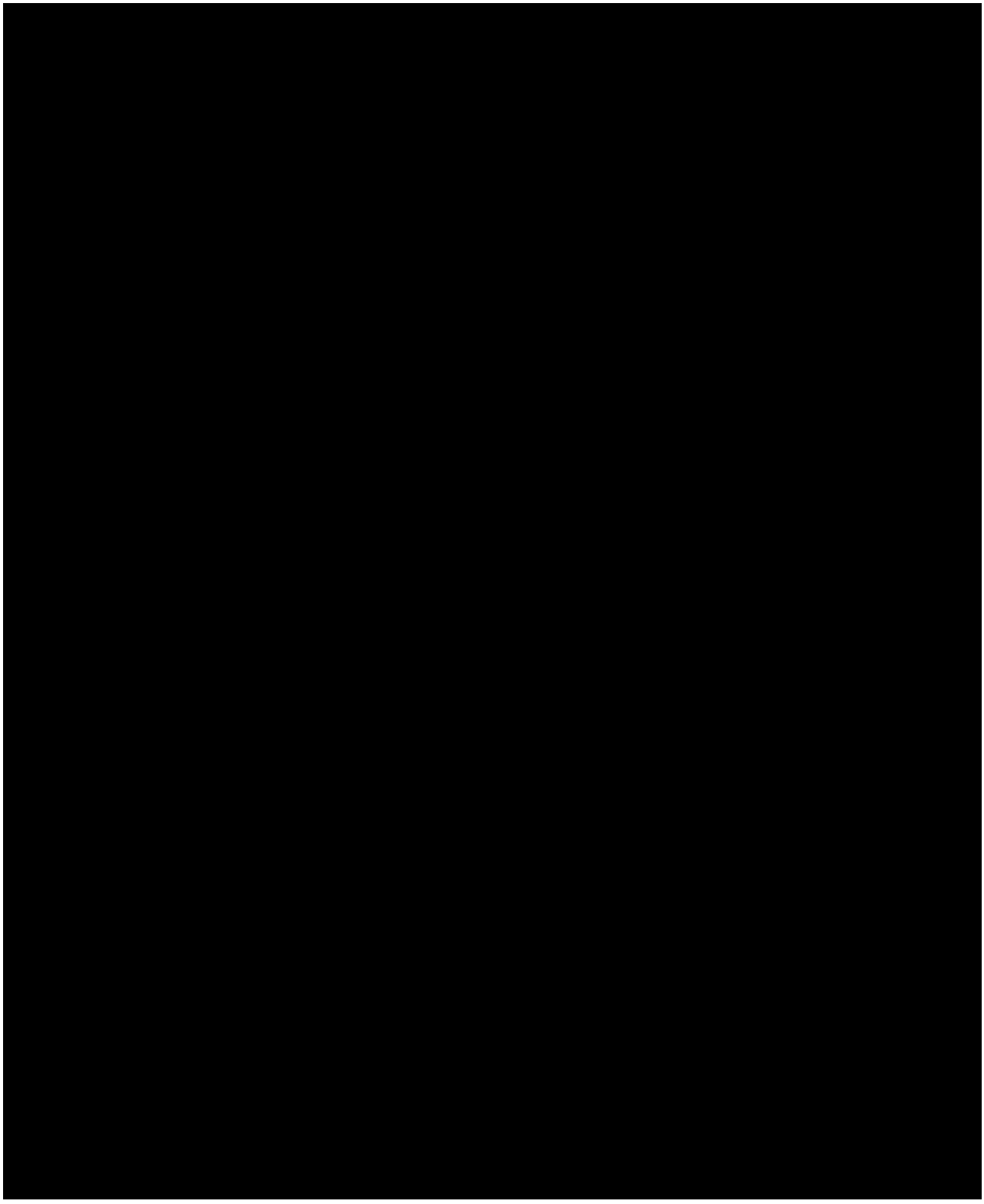
the investigator. Presentations of the individual ECG parameter values for HR, PR, QRS, QT and QTcF for all treated subjects will be available as listings for review. ECG recordings at unscheduled visits will be summarized in the listings and summary tables.









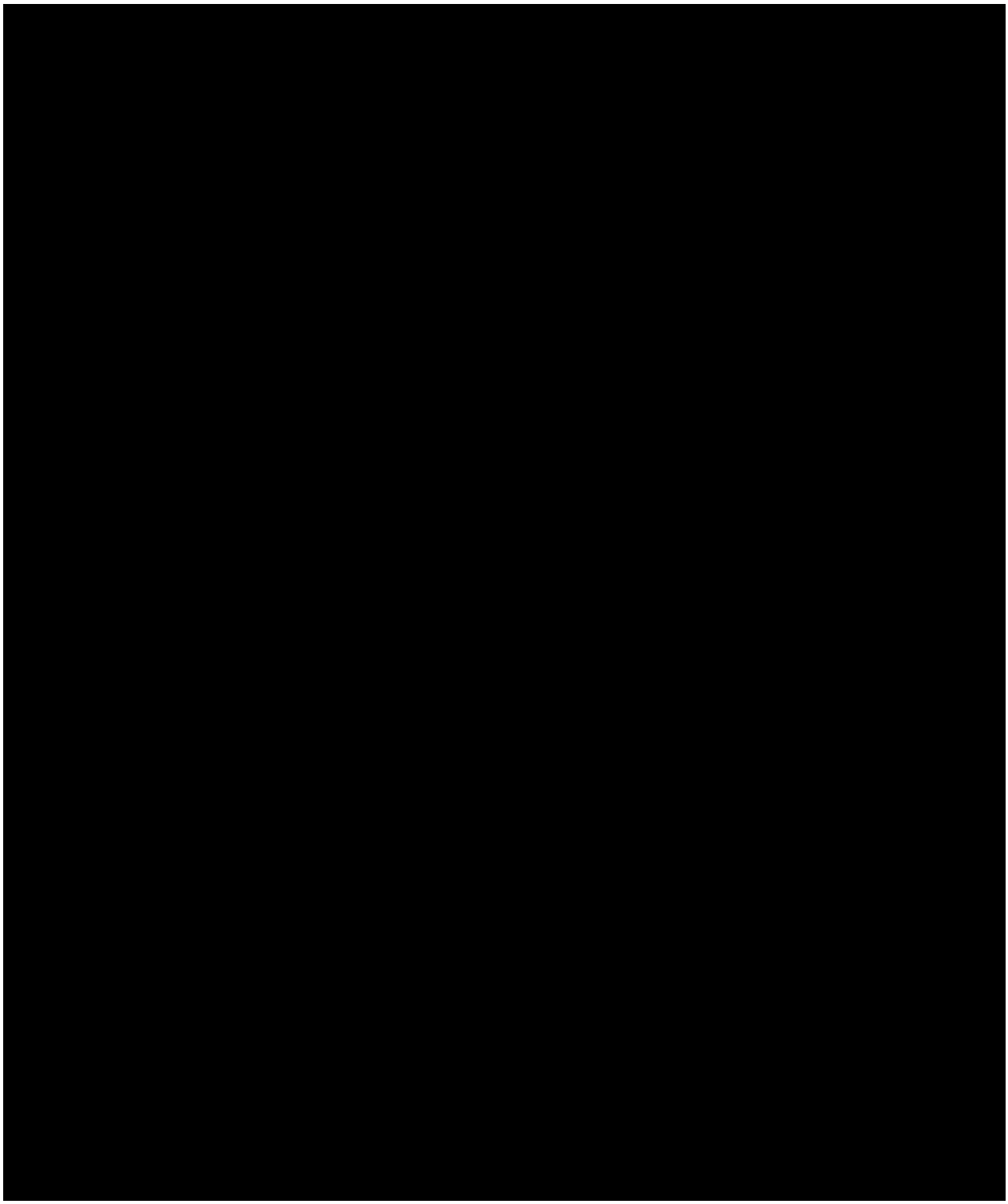


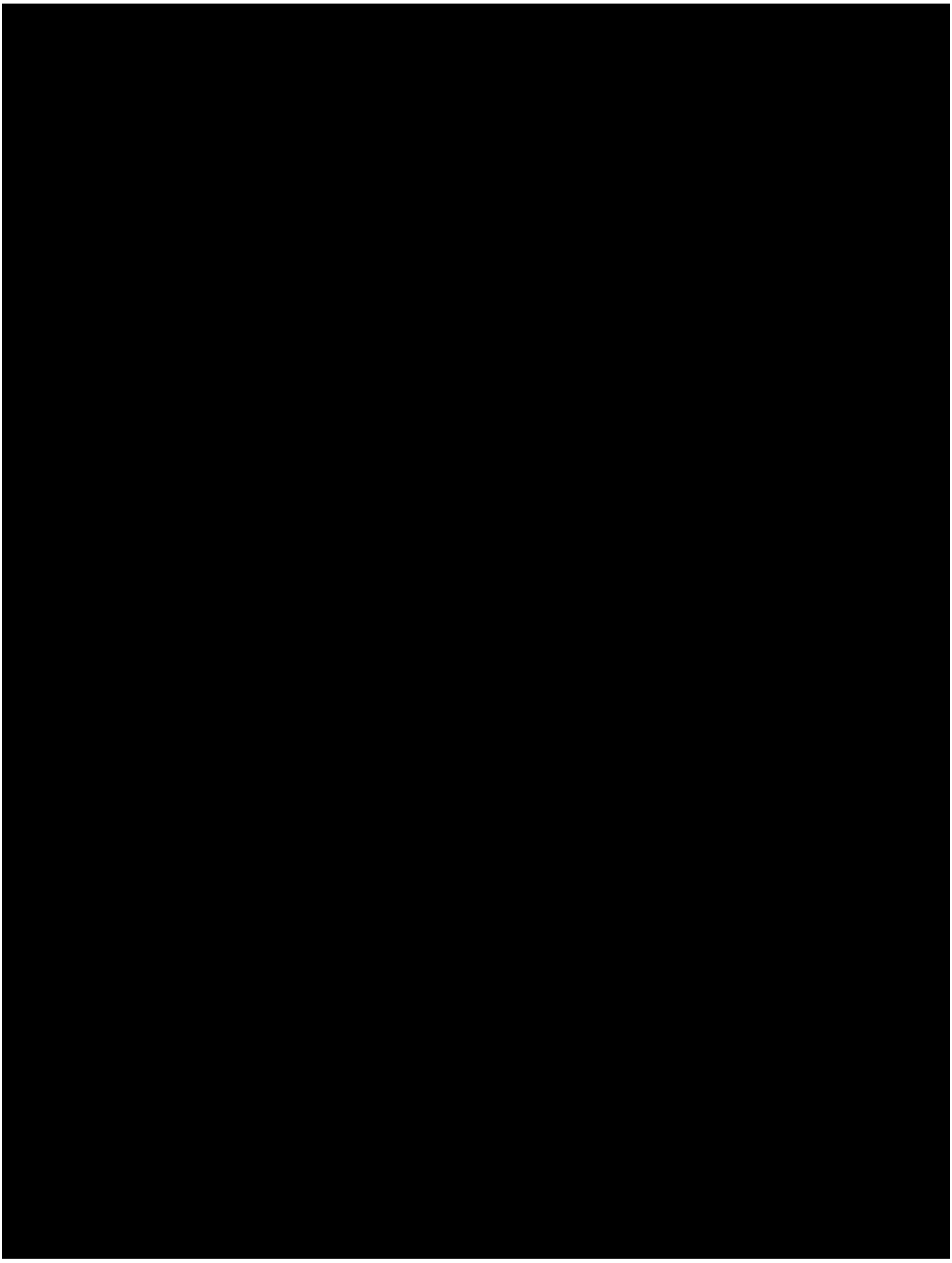
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

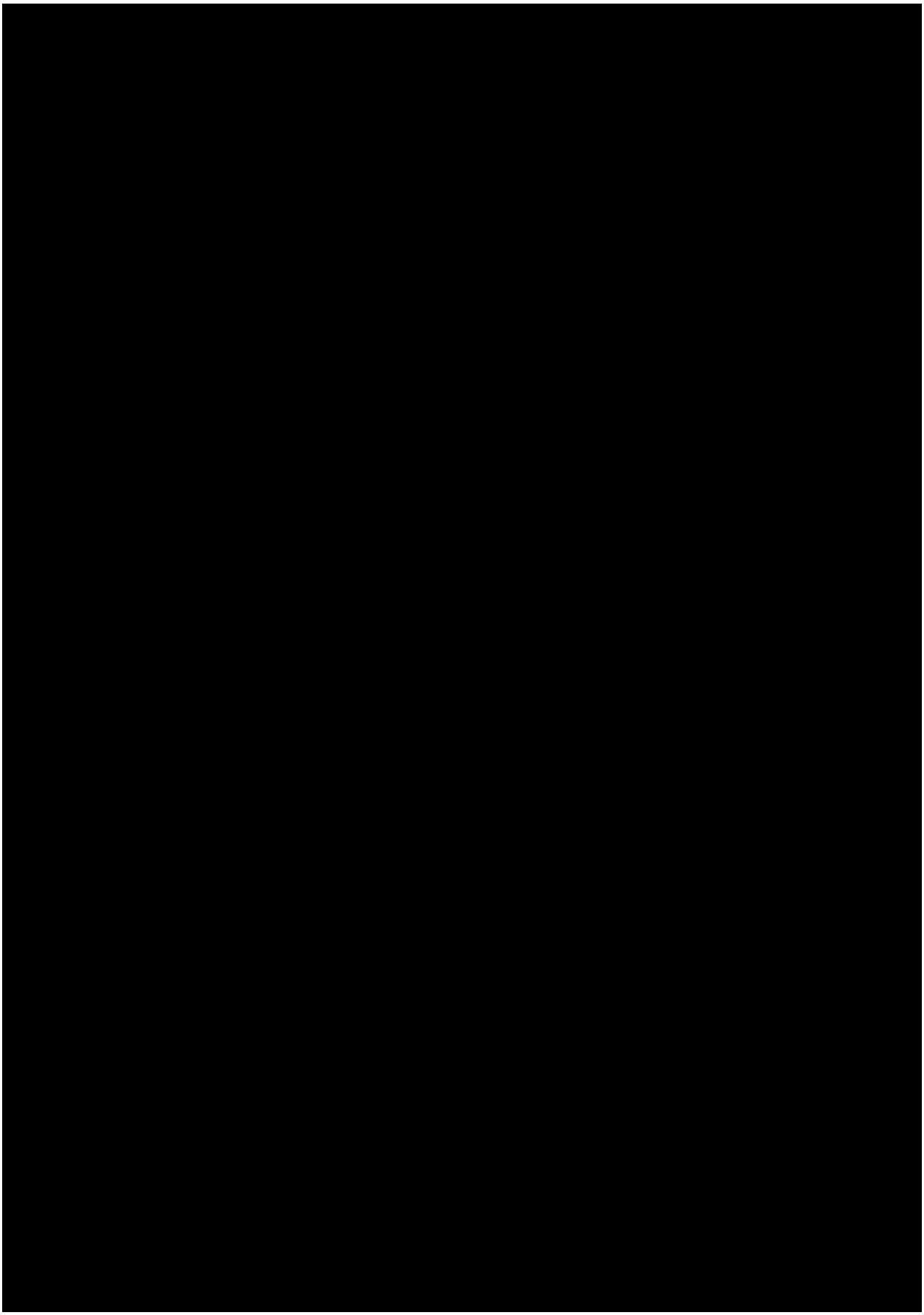
Timing of unblinding / receiving access to the treatment information (including rationale) is described in CTP Section 4.1.5.

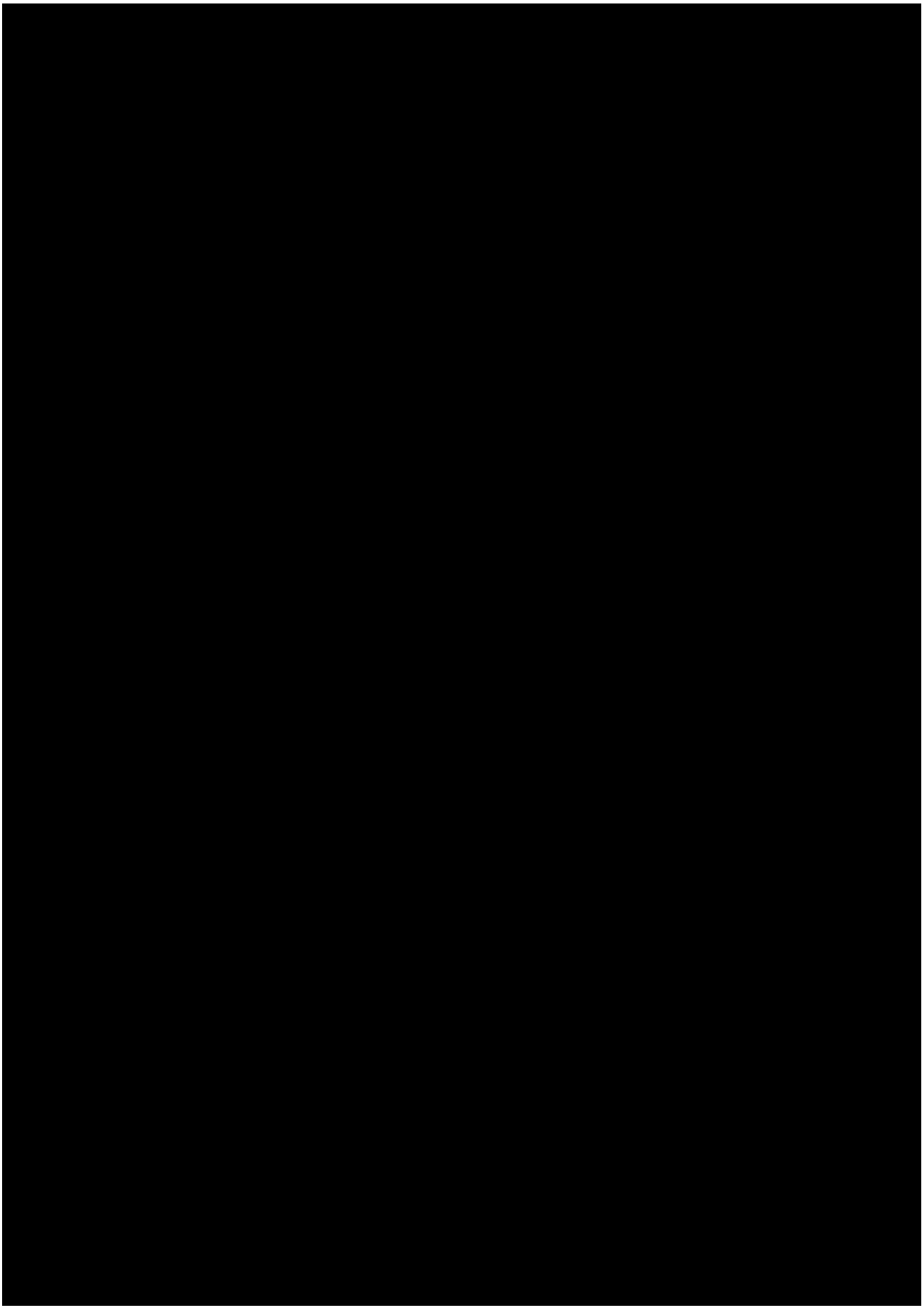
9. REFERENCES

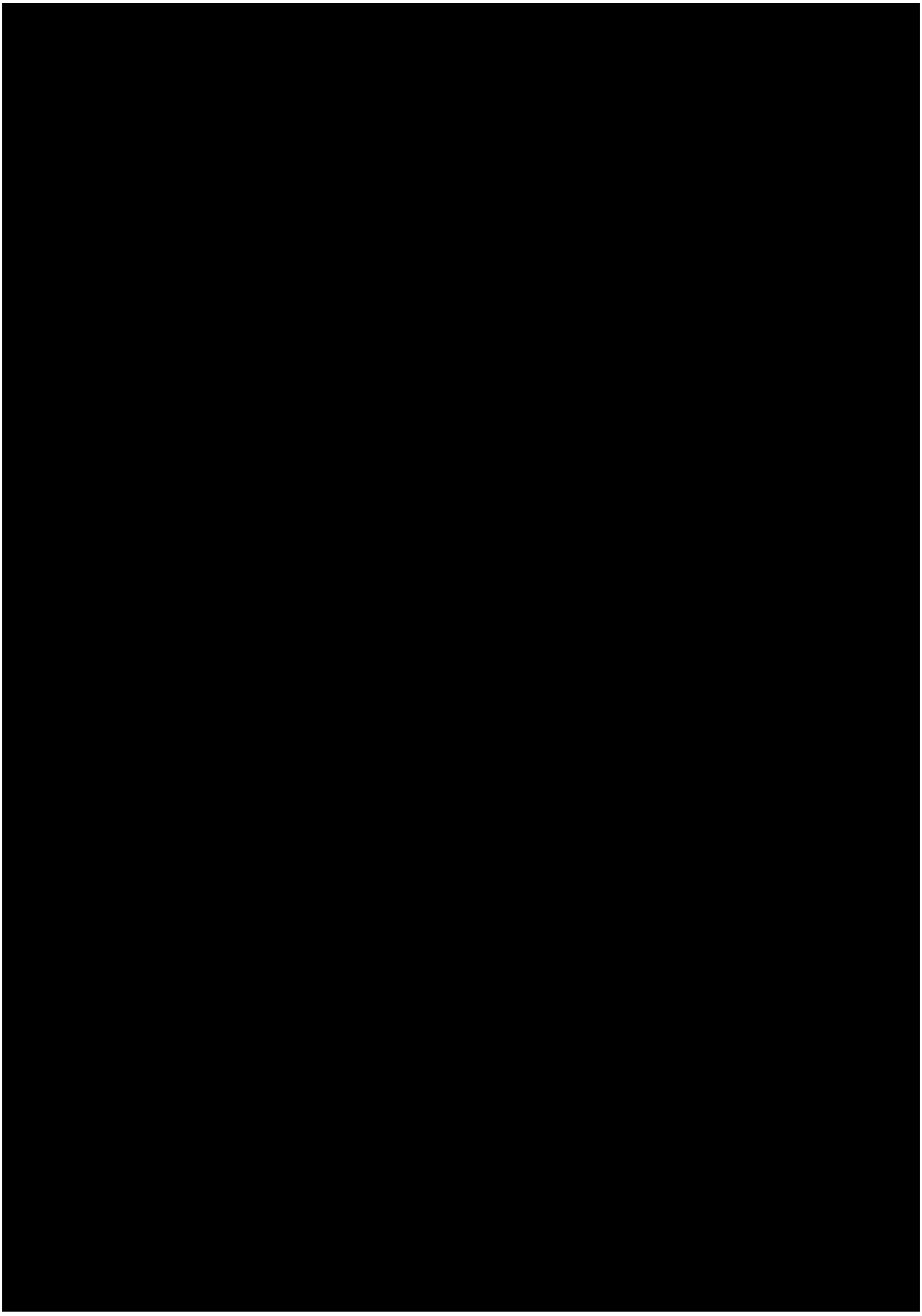
1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version
[redacted]	
6	Firth, D. 1993. “Bias Reduction of Maximum Likelihood Estimates.” *Biometrika* 80 - 1: 27–38.
R10-1424	Pinheiro JC, Bornkamp, B, Bretz F: Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. Journal of Biopharmaceutical Statistics 2006; 16: 639-656.
R15-4293	Pinheiro JC, Bornkamp, B, Glimm, E, and Bretz, F: Model-based dose-finding under model uncertainty using general parametric models. Statistics in Medicine 2014; 33(10); 1646–1661.

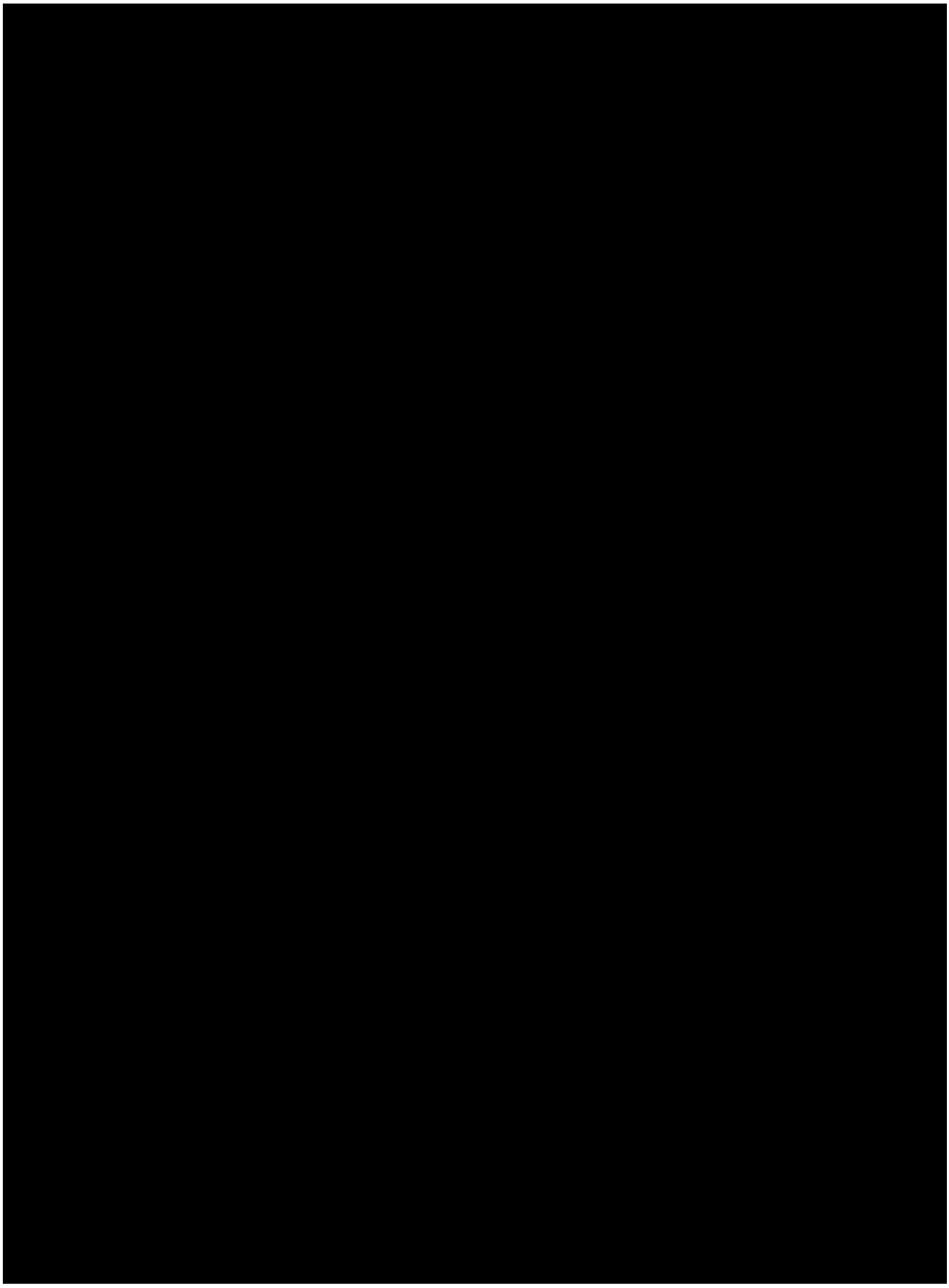


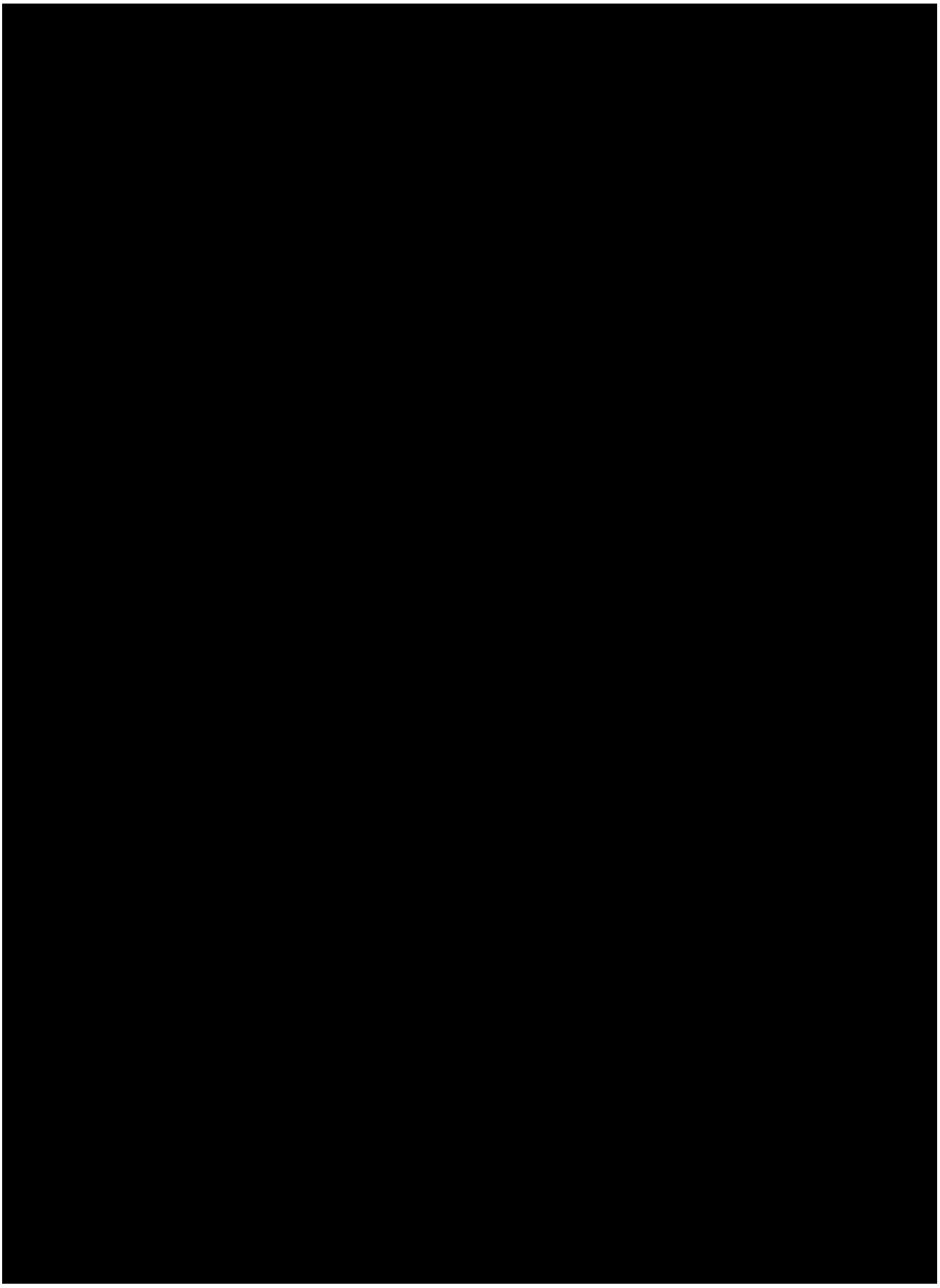


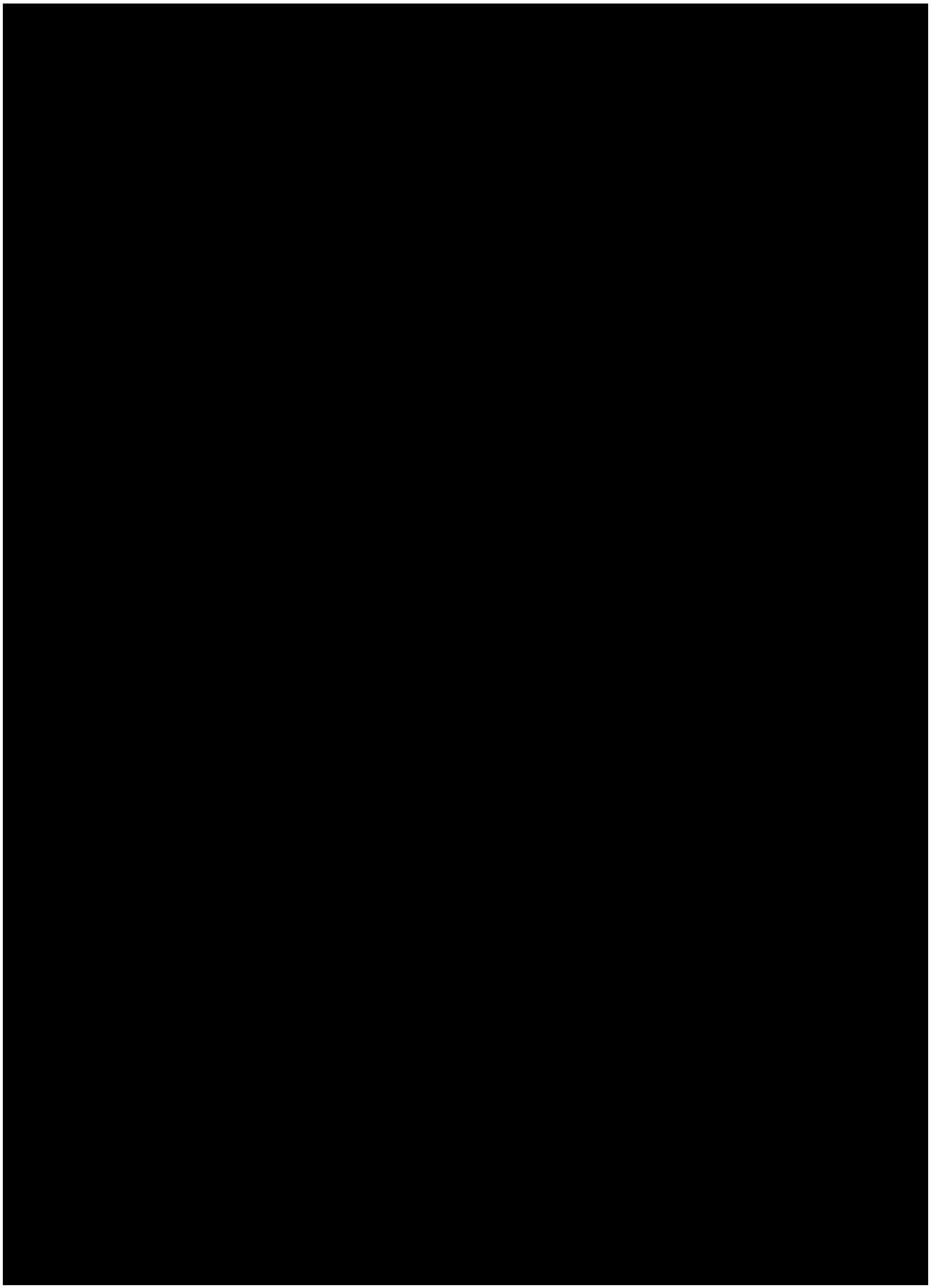


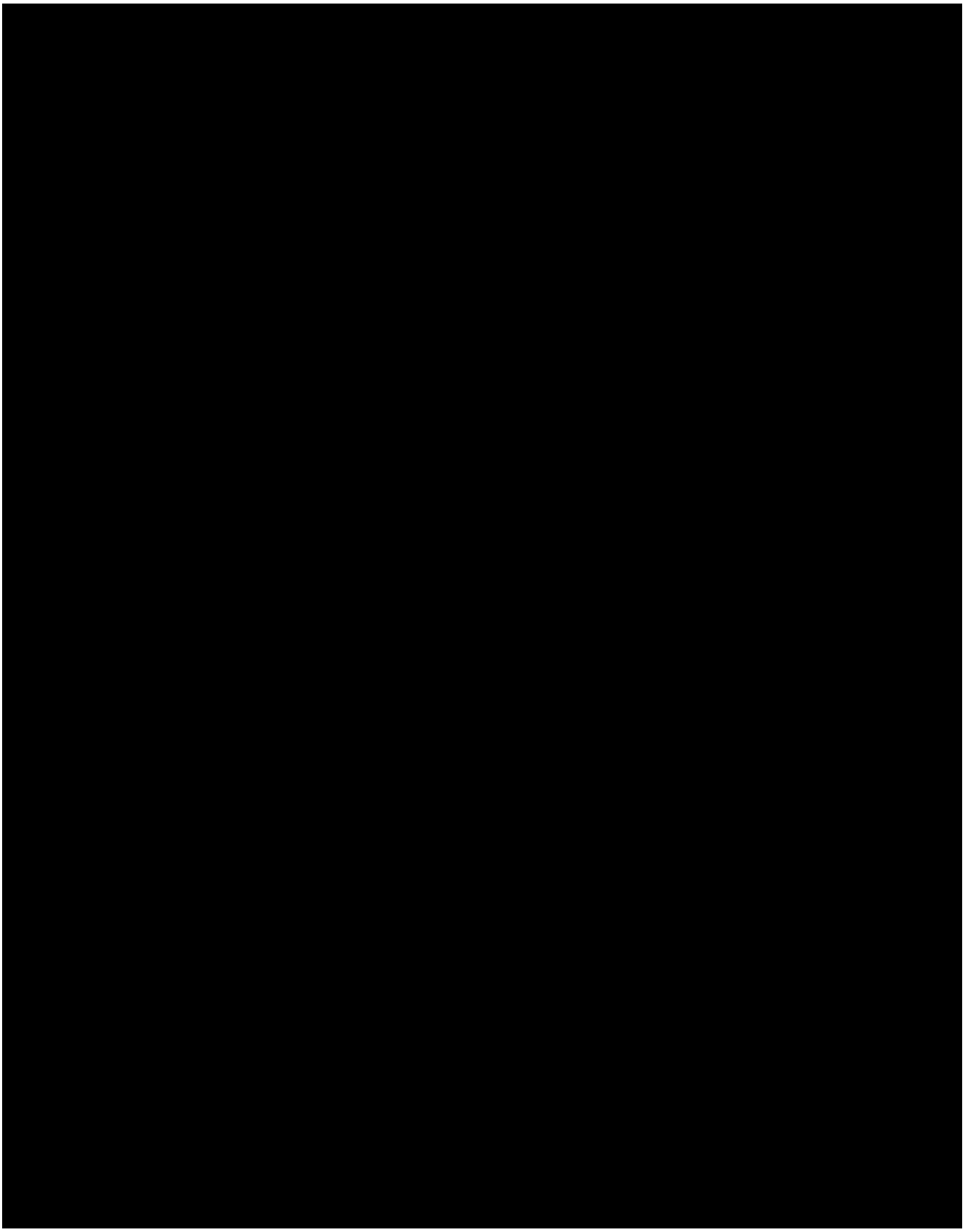


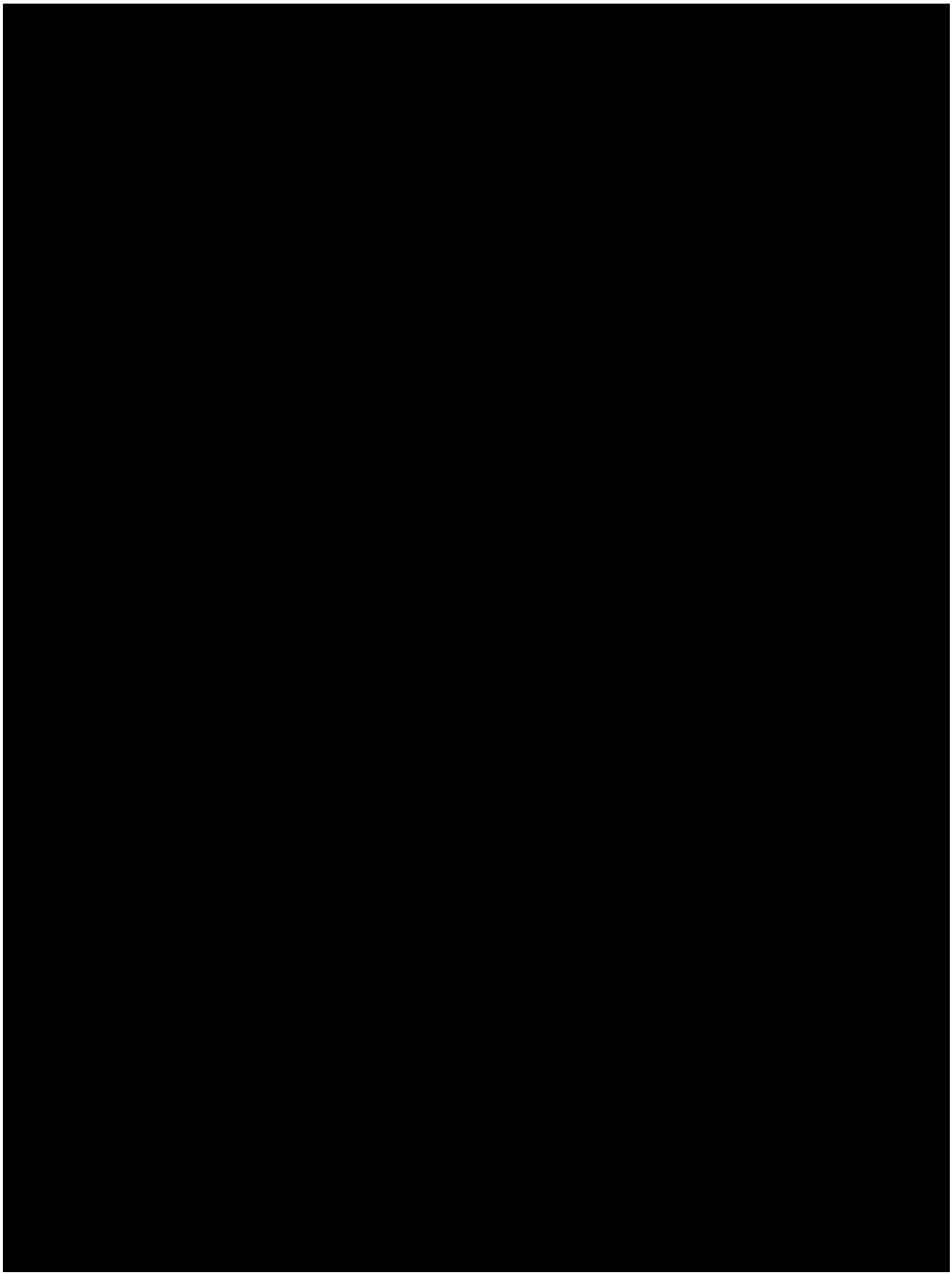


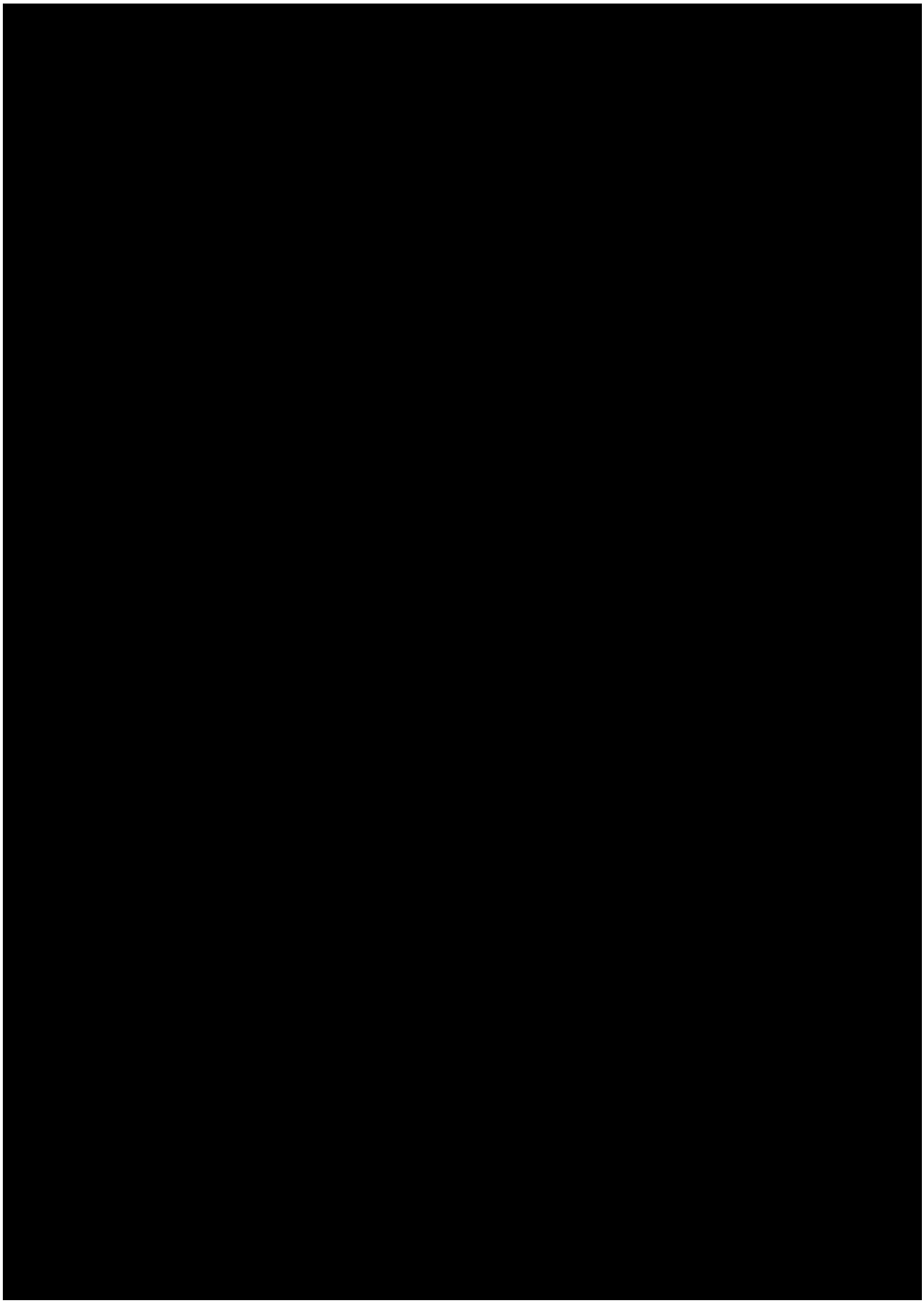


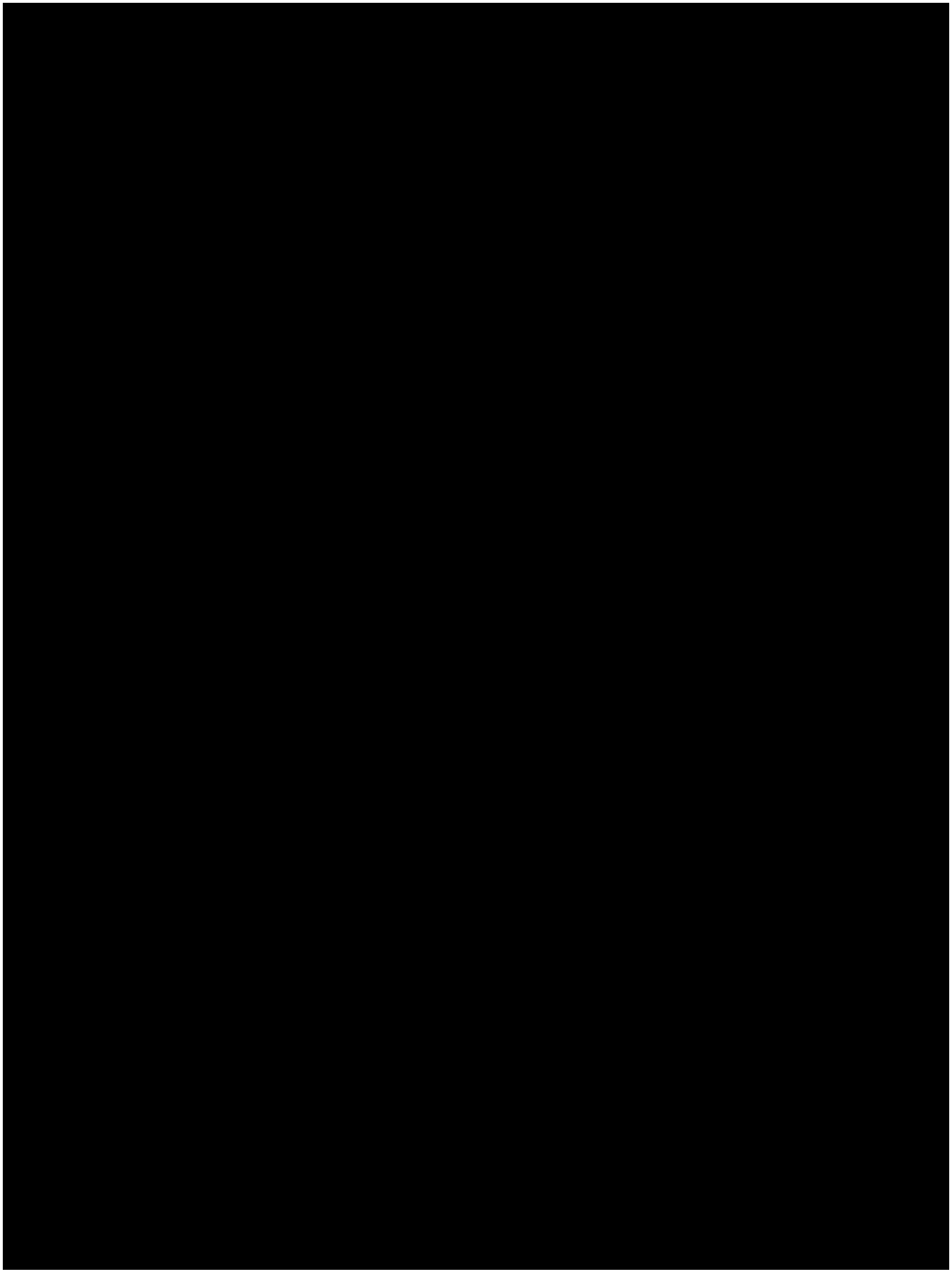


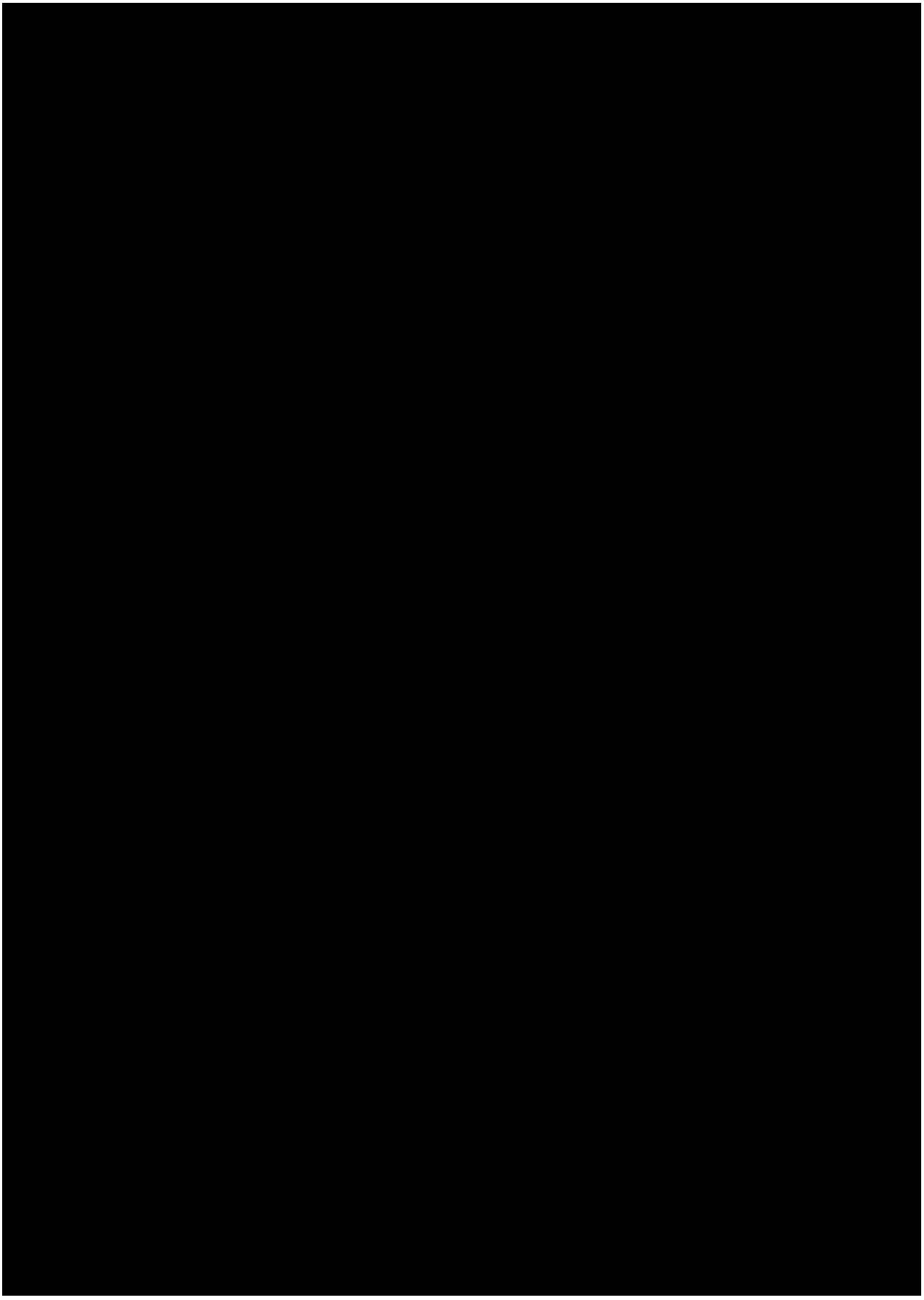


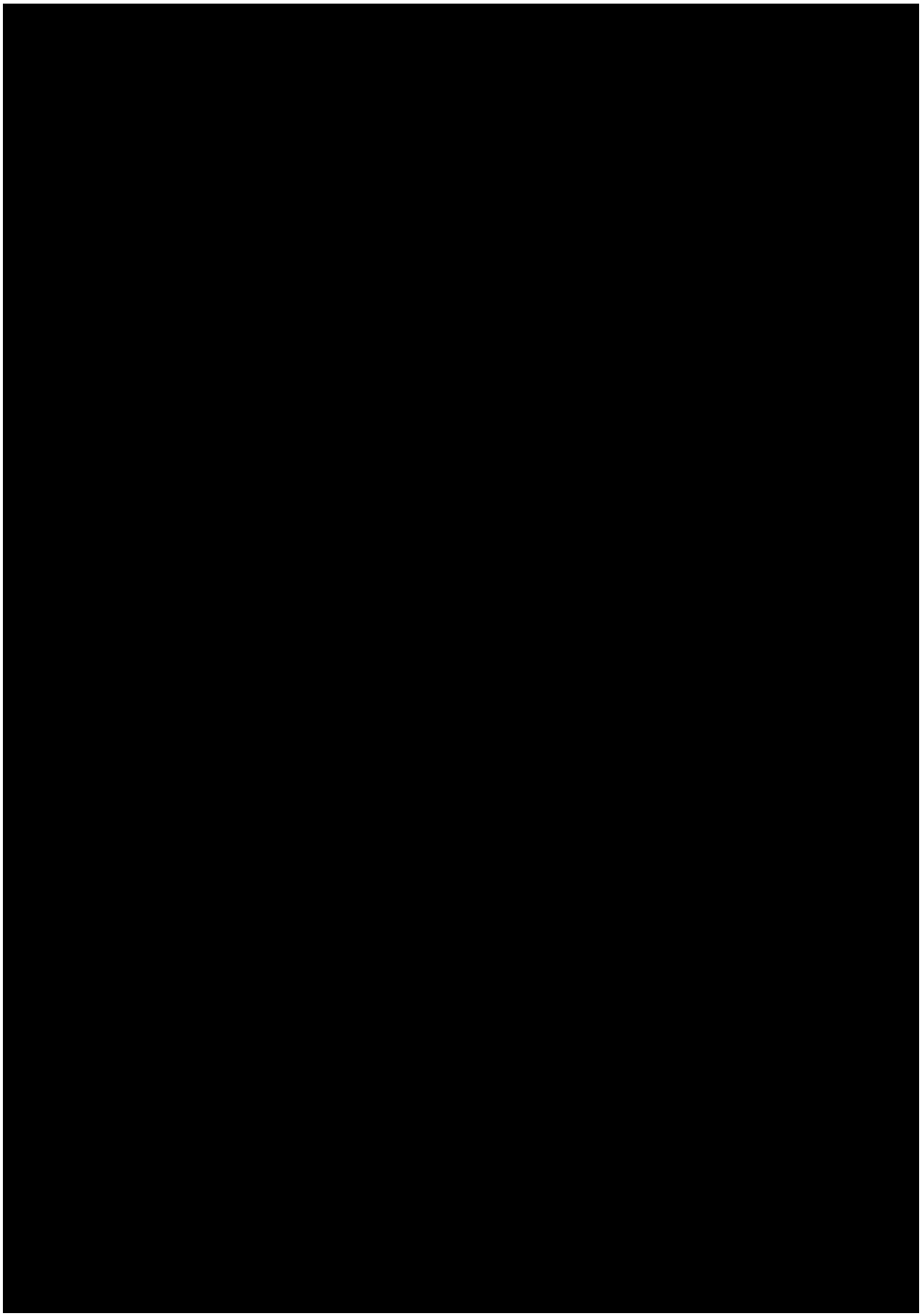












11. HISTORY TABLE

Table 11: 1 History Table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	20-NOV-24	[redacted]	None	This is the original final TSAP