TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	c42619468-01
BI Trial No.:	1402-0011
Title:	A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants.
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	[redacted] [redacted] Phone: [redacted]
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criteria
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
CGI-S	Clinical Global Impression Severity Scale
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CNS	Central Nervous System
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Concomitant therapies
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBLM	Database Lock Meeting
DDI	Drug Drug Interaction
DV	Dataset Domain for Protocol Deviations
EC50	Half maximal effective concentration
ECG	Electrocardiogram
[redacted]	[redacted]
eCOA	electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
ED	Effective Dose
EDMS	Electronic Document Management System

Term	Definition / description
[redacted]	[redacted]
EoStudy / EoS	End of Study
eEOT	Early End of Treatment
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	[redacted]
FU / FUP	Follow Up
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Council on Harmonization
iPD	Important Protocol Deviation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LLT	Lower Level Term
LPLT	Last Patient Last Treatment
LS	Least Square
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at random
MCPMod	Multiple comparisons procedure and modeling
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
MMRM	Mixed effects model for repeated measures
MQRM	Medical Quality Review Meeting
OAA	Overall [redacted] adherence
[redacted]	[redacted]
PD	Protocol deviation
PK	Pharmacokinetics
[redacted]	[redacted]

Term	Definition / description
PoC	Proof of concept
PPS	Per Protocol Set
PT	Preferred Term
QD	quaque die (once a day)
[redacted]	[redacted]
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RPM	Report Planning Meeting
RUN	Data Ready to be Unblinded and/or Final Trial Closure Notification
SAE	Serious Adverse Event
SCID-5	Structured Clinical Interview for DSM-5 Clinical Trials
SD	Standard deviation
[redacted]	[redacted]
SMDDS	Symptoms of Major Depressive Disorder Scale
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SS	Screened Set
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
t.i.d.	ter in die (3 times a day)
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TOM	Trial Oversight Meeting
TS	Treated Set
TSAP	Trial statistical analysis plan
UDAEC	User-defined AE categories
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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

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

The main analyses of this TSAP will be conducted under the estimand concept. To quote ICH E9 R1, “An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared.” So, an estimand is a way for the clinical trial protocol to address how intercurrent events will be handled. According to ICH E9 R1, intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. In other words, intercurrent events are occurrences after randomization that involve a change in treatment regimen.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In this TSAP the following are the changes to the statistical methods described in the CTP (including amendments).

- The full analysis set will comprise of all randomized participants who received at least one dose of trial medication during the trial, and have a baseline and at least one evaluable post-baseline measurement for the primary endpoint. The requirement to have a baseline and at least one evaluable post-baseline measurement for the primary endpoint was added to help ensure that this patient set was as complete as possible with respect to the analysis of the primary endpoint.
- [redacted]
- Missing data for the binary secondary endpoint, MADRS response at week 6, will be handled using multiple imputation. Under the assumption of missing at random, multiple imputation would produce unbiased treatment effect estimates for this endpoint (3,4).
- The categorical baseline value of MADRS (<=19/>19) will not be used in statistical models as the continuous baseline value is already included and the size of the lower group contains only about 3% of total patients.
- Subgroup analyses on mild/moderate/severe categories of MADRS baseline values will be collapsed into absent/mild/moderate (combined) versus severe as there are hardly any values for ‘mild’ collected.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Change from baseline in Montgomery–Asberg Depression Rating Scale (MADRS) total score at Week 6 is the primary efficacy endpoint. See CTP Section 5.2.1 for details.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There is no key secondary endpoint in this trial.

5.2.2 Secondary endpoint(s)

The secondary efficacy endpoints are:

- Response defined as ≥ 50% MADRS reduction from baseline at Week 6.
- Change from baseline in State-Trait Anxiety Inventory (STAI) State and Trait version scores at Week 6.
- Change from baseline in Clinical Global Impression Severity Scale (CGI-S) score at Week 6.
- Change from baseline in Symptoms of Major Depressive Disorder Scale (SMDDS) total score at Week 6.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For details on the treatment regimen, assignment of treatment groups, and the selection of doses, refer to CTP Section 4. Below in Table 1 are the description of the short and long names of the treatments in this trial. The definitions of the study phases for the analysis periods are in Table 2.

Table 1 Treatment descriptions

Long Name	Short Name
Placebo matching BI 1358894 and placebo matching quetiapine	Placebo
BI 1358894 5 mg qd	BI 5 mg
BI 1358894 25 mg qd	BI 25 mg
BI 1358894 75 mg qd	BI 75 mg
BI 1358894 125 mg qd	BI 125 mg
Quetiapine 300 / 150 mg	Quetiapine

Table 2 Study analysis phases

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

The defined treatment phases are the same for all treatment groups.

[redacted]

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the data base (i.e., randomized patients). Consistency check listings (i.e., identification of violations of time windows) and a list of CTP deviations will be provided to be discussed at the Report Planning Meeting (RPM)/Database Lock Meeting (DBLM)/Medical Quality Review Meeting (MQRM). At these meetings, it will be decided whether a discrepant data value can be used in analyses and/or whether it must be queried in the clinical database. Each CTP deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the current BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (5).

Generally, a protocol deviation is considered as an iPD if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. If any iPDs are identified, they are to be summarized into categories and will be captured in the RPM/DBLM/MQRM minutes via an accompanying DV domain specifications Excel spreadsheet (6). If the data presents additional iPDs (e.g., based on monitor visits to the sites), then the DV domain specifications will be supplemented accordingly at TOMs or RPMs or through team review of the manual PD log.

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

6.3 INTERCURRENT EVENTS

Primary estimand approach

The primary analysis of the primary endpoint will use a hypothetical estimand, which focuses on the treatment effect assuming all patients remained adherent to the assigned trial medication and the trial protocol. Endpoint data collected after any of the intercurrent events will be excluded from these analyses.

Supplementary estimand approach

A supplementary analysis of the primary endpoint will use a treatment policy estimand, i.e., effectiveness/intention to treat. For patients who die during the trial, MADRS scores do not exist (rather than just being unmeasured), so that a treatment policy approach to death is not

possible. An intercurrent event of death will be handled utilising a hypothetical approach that assumes that the patient was still alive but hence stopped taking trial medication.

The rules for handling intercurrent events during the trial are summarized in Table 3.

Table 3 Handling Rules for Intercurrent Events

ICE	Primary Estimand	Supplementary Estimand
Treatment discontinuation (regardless of reason)	Hypothetical	Treatment policy
Prohibited medication use	Hypothetical	Treatment policy
Change in antidepressant background/ adjunctive therapy	Hypothetical	Treatment policy
Death	Hypothetical	Not applicable

Further details on these estimand approaches are discussed in Section 7.4.1 and Section 7.4.5

In addition, the number of patients reporting each type of intercurrent event will be summarized by treatment group.

6.4 PATIENT SETS ANALYSED

The following analysis sets are defined for this trial:

- Screened Set (SS): consists of all patients who signed informed consent.
- Treated Set (TS): consists of all patients that have been randomized and that received at least one administration of study drug. The TS will be the main analysis set for the evaluation of safety. Patients are analysed according to the actual received treatment.
- Full analysis set (FAS): consists of all patients in TS that have a baseline and at least one evaluable post-baseline measurement for the primary endpoint. This is the main analysis set for the evaluation of efficacy data.
- Per protocol set (PPS): consists of all patients in FAS without any important protocol deviations that impact efficacy assessments. This is a subset of FAS, for patients with adequate protocol compliance.
- [redacted]

The endpoints included in each analysis set are described in Table 4.

Table 4 Patient sets analysed

	Patient Set				
Class of analyses	TS	SS	FAS	PPS	[redacted]
Primary and secondary endpoints, compliance, adherence			X	X*	
Further endpoints [redacted]			X		
Disposition		X			
[redacted]					X
Safety variables and iPDs	X				
Demographics, baseline variables, exposure	X				

* If the percentage of patients in FAS with iPD that lead to the exclusion from the PPS is > 10%, then sensitivity analysis of the primary and secondary efficacy endpoints using PPS may be conducted.

Note that the number of patients with available data for an endpoint may differ. For details, refer to Section 6.6.

[redacted]

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing data will not be explicitly imputed and will remain missing except for the binary efficacy endpoints. For the continuous efficacy endpoints that are assessed over time, a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will be used, which will ensure that missing data are handled implicitly via a missing at random assumption (MAR) by the statistical model. For the binary efficacy endpoints, multiple imputation will be used, which will ensure that missing data are also handled via the MAR assumption.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (7).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last non-missing value recorded prior to first drug administration and is typically collected at visit 2 (day 1). If visit 2 data is missing, visit 1 data will be used (if available). [redacted]

Planned and actual test days are included in the analysis data sets and are calculated relative to the beginning of treatment as indicated in

Table 6 below.

For efficacy measurements, only one observation per time window will be selected for statistical analysis – the closest one to the planned day in the corresponding time window. If there are two observations which have the same difference in days to the planned day, or if there are two observations on the same day, the first value will be selected. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window. Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data. Repeated and unscheduled efficacy measurements will be assigned to the nominal visits according to the time windows described in

Table 6.

For safety measurements, data collected at all visits will be used. For repeated and unscheduled safety measurements for the same visit on treatment, the worst of these will be

selected for analysis. In the case for which there is no standard reference direction for the safety parameter, the average of all values for the same visit will be used for analysis.

Table 6 Planned study days and analysis time windows

Planned visit	Relative to treatment start	
	Planned test day	Analysis time windows
2	1	Up to Day 1
3	8	Day 2 – Day 13
4	15	Day 14 – Day 20
5	22	Day 21 – Day 27
6	29	Day 28 – Day 34
7	36	Day 35 – Day 41
8 / EOT	43 for completed patients	Day 42 – treatment stop date (stopdt) + 7 days
eEOT	N/A (for early discontinued patients)	Date of the last administration of trial medication + 7 days (for early discontinued patients). The number of days will be assigned to the visit. Thus, if days to eEOT is 35, it will be mapped to Visit 7. For those who discontinue treatment early but continue with the collection of efficacy data, those data points will be mapped to the later visits as per the above visit window. Hence, if this same patient collects MADRS at Day 36, it will be mapped to Visit 7.
End of Trial	stopdt + 28 days	(stopdt + 8 days) to study end

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

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

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (9).

The individual values of all patients will be listed, sorted by dose group, patient number and visit. AE listings will be sorted by assigned treatment (see Section 7.8.1 for details). The listings will be contained in an Appendix of the CTR.

For End-Of-Text tables, the set of summary statistics is: N / Mean / Standard Deviation (SD) / Min / Median/ Max. For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles are preferred to mean, standard deviation, minimum and maximum. In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places than the raw data. Minima and Maxima are presented to the same number of decimal places as the raw data.

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

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

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

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

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases (i.e., baseline conditions) will be coded similarly as AEs using the most recent version of MedDRA. A summary of concomitant diseases will be provided by

treatment group, System Organ Class (SOC) and Preferred Term (PT). Concomitant diseases which are present at start of the study will be descriptively summarized by treatment.

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

Concomitant therapies (CTs) are coded according to WHO Drug Dictionary. CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorize CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level-three category will be counted more than once and footnote will clarify this possible multiple counting in tables. The most current WHO Drug Dictionary version will be used.

7.3 TREATMENT COMPLIANCE

7.3.1 Compliance

Only descriptive statistics are planned for this section of the report. Treatment compliance is the percentage of tablets that were correctly taken by a patient, and is calculated at Weeks 1, 2, 4, and 6 (EOT) as follows, based on the CTP's flow chart:

$$\text{Treatment compliance (\%)} = \frac{Number\ of\ doses\ actually\ taken}{Number\ of\ doses\ which\ should\ have\ been\ take\ as\ directed\ by\ investigator} * 100$$

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

For completers: if a patient's observed treatment compliance rates are 80%, 81%, 82%, 83% at Weeks 1, 2, 4, and 6, then the cumulative treatment compliance percent = (.8*1 + .81*1 + .82*2 + .83*2)/6*100 = 81.83%.

For early discontinued patient: if a patient's observed treatment compliance rates are 80% at Week 1, 81% at Week 2, 82% at Week 4, 50% at eEOT, then the cumulative treatment compliance rate = (0.80*1 + 0.81*1 + 0.82*2 + 0.5*((eEOT date – drug start date + 1)/7 – 4))/((eEOT date – drug start date + 1)/7) * 100% = 74.3% if the quantity (eEOT date – drug start date + 1) is assumed to be 36 days.

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

Treatment compliance will be summarised overall and by visit for the FAS using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of

patients with the following overall compliance categories will also be presented overall and by visit:

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

[redacted]

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

The primary endpoint is the change from baseline to Week 6 in MADRS total score. Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication and is typically recorded at Visit 2. If data from Visit 2 are missing, the value recorded at Visit 1 will be considered the baseline value. The investigator reported MADRS total scores will be used for the primary analysis.

Total scores as delivered by the vendor will be re-calculated and in case of discrepancies, the re-calculated scores will be used for analysis.

The primary analysis of the primary endpoint will use a hypothetical estimand. The hypothetical approach focuses on the treatment effect assuming all patients remained adherent to the assigned trial medication and the trial protocol, i.e., took study drug as directed. The primary analysis of the primary endpoint will include all data collected while on treatment, which is defined as the time from the date of the first dose of trial medication until the date of the last dose of trial medication plus 7 days (3 times the estimated elimination half-life). Any data collected after any intercurrent event listed in Table 3 will be censored and not included in the primary analysis. Data from participants assigned to the quetiapine arm will not be included in the primary analysis.

The Multiple Comparison Procedures and Modeling (MCPMod) approach (10, 11) is implemented in two main stages: (1) trial design stage; (2) trial analysis stage. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations are provided in the CTP Sections 7.2.2 and 7.5. The procedures for the trial analysis stage are specified below. FAS is used for the primary analysis of the primary efficacy endpoint.

MMRM analysis
The change from baseline in MADRS total score at Week 6 for each dose group as well as the corresponding variance-covariance matrix will be estimated by an MMRM model including the fixed categorical effects of treatment at each visit, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score at each visit. Visit will be treated as a repeated measure with an unstructured covariance matrix used to estimate within patient error variability. 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 (LS) means using a two-sided $\alpha = 0.1$ (two-sided 90% confidence intervals (CIs)). Analyses will be implemented using SAS 9.4 PROC MIXED.

More specifically, the change in MADRS total score from baseline at Visits 3, 4, 6, and 8 (Weeks 1, 2, 4, and 6) will be evaluated using an MMRM accounting for the following sources of variation: ‘concomitant psychotherapy use’, ‘treatment*visit’ interaction, and ‘baseline MADRS total score*visit’ interaction as fixed effects, and visit as a repeated measure within each patient. The methods described in Section 10.1.1 will be utilized to resolve model non-convergence.

The following SAS code will be used to run the MMRM model, with some modifications if necessary:

```
PROC MIXED DATA=indata cl method=reml;
        CLASS visit trt(REF='placebo') ptno conPTuse;
        MODEL aval = conPTuse visit*trt base*visit / ddfm=kr s;
        REPEATED visit / subject= ptno type=un r rcorr;
        LSMEANS visit*trt / pdiff=all om cl alpha=0.10 slice=visit;
RUN;
```

Results of the MMRM (N, LS means, standard errors, and 90% CIs per dose group) will be presented in tables and displayed graphically.

Descriptive summaries for observed values and change from baseline in MADRS total score at Weeks 1, 2, 4 and 6 will be presented by treatment arm, including the quetiapine arm. The frequency and proportion of participants reporting each response category for each MADRS item at baseline and up to Week 6 will also be displayed.

MCPMod Analysis

The adjusted mean estimates of the change from baseline at Week 6 for each dose and their estimated variance-covariance matrix from the MMRM model will be used in the trial analysis stage. Then, the multiple pair-wise comparison procedure will be implemented using the optimal contrast tests which control the family-wise type I error rate at one-sided $\alpha = 0.10$.

The basic shape of each of the models to be tested must be predefined in the trial analysis stage. The following candidate models were selected based on healthy volunteer data to cover a plausible and diverse range of dose response patterns for the trial medication.

- Emax1: 50% of the maximum effect is achieved at 25 mg; corresponding to the assumed true ED50 = 25 mg.
- Emax2: 70% of the maximum effect is achieved at 5 mg; corresponding to a drug effect achieved mainly with low doses, ED50 = 2.14 mg.
- Sigmax: 50% of the maximum effect is achieved at 25 mg, and
- 90% of the maximum effect is achieved at 75 mg; corresponding to a more flexible model of the assumed true ED50 = 25 mg.
- Exponential: 5% of the maximum effect is achieved at 25 mg; corresponding to a drug effect achieved mainly at higher doses.
- Linear: No parameter assumptions required. Corresponding dose response is linear.

For the MCPMod test, the optimal contrasts corresponding to the candidate models are calculated as in the trial design stage (using the R-function optContr using weights proportional to the sample size of each dose group) and are shown in Table 7 below. These contrasts will be updated using the expected model means from the candidate set and the

estimated variance-covariance matrix from the data. The final contrasts will be presented in the CTR.

Table 7 Optimal contrast coefficients

	Optimal Contrast Coefficients for Dose				
Model	**0**	**5mg**	**25mg**	**75mg**	**125mg**
Linear	-0.643	-0.161	-0.073	0.146	0.731
Emax1	-0.772	-0.119	0.084	0.235	0.572
Emax2	-0.867	0.076	0.178	0.201	0.413
Sigmax	-0.731	-0.188	0.055	0.266	0.597
Exponential	-0.545	-0.150	-0.127	0.007	0.815

Proof of concept is established if at least one dose-response model is statistically significant, i.e., the null hypothesis of a flat dose-response curve for change from baseline in MADRS total score at Week 6 is rejected, indicating a benefit of at least one BI 1358894 dose over placebo.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using the model averaging method.

The selected dose-response model(s) is re-fitted to the data without any parameter assumptions to generate a set of new estimates of the model parameters from the data. The final dose-response model is obtained via the weighted model averaging of the significant models (p-value<0.10) based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). The weights for each significant model (M_k) are given by,

$$w(M_k) = \frac{exp(-0.5 * AIC(M_k))}{\sum_{i=1}^{K} exp(-0.5 * AIC(M_i))}$$

where AIC(M_k) is the AIC for model M_k.

[redacted] Test statistics and p-values will also be displayed for different dose-response models. Figures and tables will be displayed for the MCPMod modeling.

The following displays are planned:

- Table of the contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value
- For the average model, figure of the dose-response curve
- For all significant model shapes, figures of the dose-response curve plus 90% confidence band (of the predicted shape)

The MCPMod trial analysis will be implemented by calling an R function/package within SAS. Please see Section 10.1.2 for the R code to implement the MCPMod analysis.

[redacted]

7.4.3 Supplementary analysis

An additional analysis of the primary endpoint will repeat the primary analysis methodology (MMRM/MCPMod) specified in Section 7.4.1, but under a treatment policy estimand, i.e., effectiveness/intention to treat. This estimand approach will use all available MADRS data, including data collected after any intercurrent event listed in Table 3. As discussed in Section 6.3, an intercurrent event of death will be handled using a hypothetical approach.

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoints were specified in the protocol.

7.5.2 Secondary objective analysis

Data from participants assigned to the quetiapine arm will not be included in the analysis models for the secondary endpoints.

7.5.2.1 MADRS response

Response is defined as ≥ 50% reduction in MADRS total score from baseline to a specific post-baseline visit (Visit X), where percent reduction from baseline at Visit X is calculated as:

$$\%\ reduction = \frac{(MADRS\ total\ score\ at\ baseline - MADRS\ total\ score\ at\ Visit\ X)}{MADRS\ total\ score\ at\ baseline} * 100$$

The proportions of participants achieving response for each analysis visit up to Week 6 (Visit 8/EOT) will be summarized as the frequency and percentage of participants in each treatment arm.

To handle missing data when analyzing MADRS response, multiple imputation and logistic regression modeling will be used. Specifically, missing data will first be multiply imputed using fully conditional specification methods (12, 13). Specifically, a regression model will first be used for imputation, including baseline MADRS total score and MADRS total score at each post-baseline timepoint by treatment, to fill in missing values for MADRS total score for all timepoints. These filled-in values will serve as starting values for the next step, which is to use the regression method to complete the imputation in each dataset. This process will be repeated to create 100 imputed datasets where for each one, a binary variable for response up to week 6 will be created using the imputed values of MADRS total score at baseline and up to week 6. The seed to be used for the multiple imputation step is '14020011'.

MADRS response up to week 6 will be analyzed in each imputed dataset using a logistic regression model, including the fixed categorical effects of treatment and baseline MDD severity. The results will then be combined using Rubin's rule to obtain pooled estimates of the population odds ratio (OR), and associated confidence intervals and p-values, for each active treatment arm versus placebo. Response at week 6 is the defined secondary endpoint but the other analysis visits will be displayed as well.

Please see Section 10.1.4 for SAS code to implement the multiple imputation procedure described above.

7.5.2.2 Other secondary endpoints

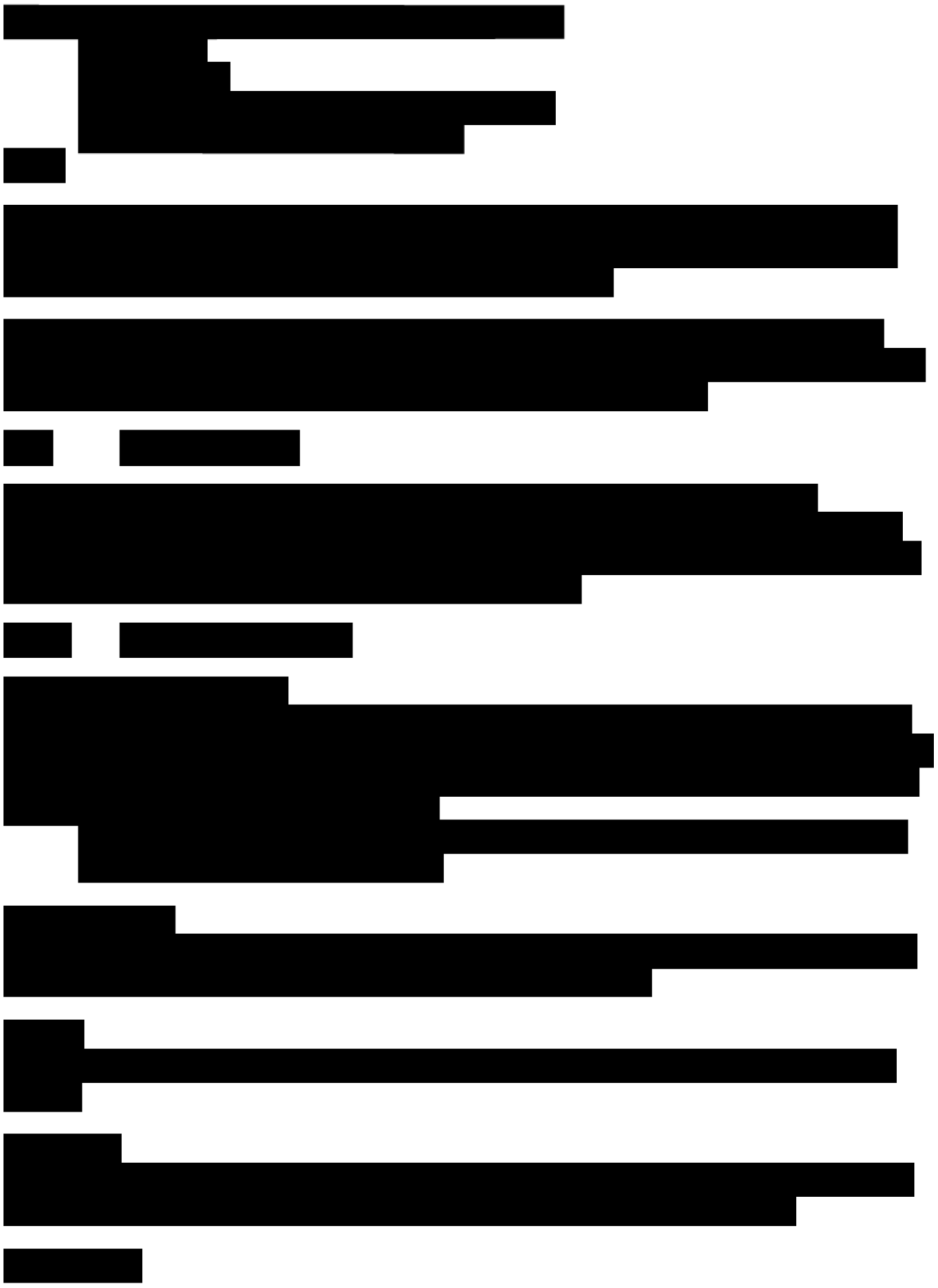
For changes from baseline at Week 6 in (i) STAI State and Trait version scores, (ii) CGI-S score, and (iii) SMDDS total score, an MMRM model like that described for the primary endpoint analysis in Section 7.4.1 (replacing the fixed continuous effect of baseline MADRS total score at each visit with baseline value of the specified score at each visit) will be used to obtain the adjusted change from baseline at Week 6 for each of the BI active arms versus placebo.

Descriptive statistics for observed and change from baseline values at Week 6 will be presented by treatment arm, including the quetiapine arm. For STAI State and Trait Anxiety, CGI-S, and SMDDS, the frequency and proportion of participants reporting each response category at baseline and at Week 6 will also be displayed.

[redacted]

[redacted]

[redacted]



7.7 EXTENT OF EXPOSURE

Extent of exposure will be calculated as the difference between last intake of study drug and the first administration of the study drug, plus one day. Descriptive statistics will be provided for number of days of exposure for each treatment arm. Also, cumulative exposure of number and percentage (N, %) of patients will also be displayed as "< 1 week", "1 to < 2 weeks", "2 to <3 weeks", "3 to <4 weeks", "4 to <5 weeks", "5 to <6 weeks", "6 weeks" or ">6 weeks".

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS. Adverse events (AEs) will be coded based on the most current version of MedDRA. Analyses will be performed as defined in CTP Section 7.2.5.

7.8.1 Adverse Events

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 guideline (14).

For further details on summarisation of AE data, please refer to (7, 14).

The analysis of AEs will be based on the concept of treatment emergent adverse events. Thus, all AEs occurring between the date of the first administration of trial treatment through the date of the last administration of trial treatment + residual effect period, a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. AEs that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. Adverse event data will be summarized by treatment taken at the onset of the event. AEs that occur before first drug intake will be assigned to ‘screening’, and adverse events that occur within 28 days after the residual effect period will be assigned to ‘follow-up’ (for listings only).

For details on the treatment definitions, see Section 6.1.

Adverse events of special interest (AESIs)

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST 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.

Refer to CTP Section 5.3.6.1.4 for details.

Other significant AE (according to ICH E3)

According to ICH E3 (15), AEs classified as "other significant" needs to be reported and will include those non-serious and non-significant AEs with

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

AE summaries

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

- drug-related AEs
- serious AEs
- serious related AEs
- AESIs
- other significant AEs (according to ICH E3)
- AEs leading to death
- AEs leading to discontinuation of trial medication
- AEs occurred with incidence in the preferred term >2%
- AEs occurred with incidence in the preferred term >5%
- AEs occurred during the follow-up period
- Extrapyramidal AEs (AEs in the 'extrapyramidal syndrome' SMQ and all of its sub-SMQs (akathisia, dyskinesia, dystonia, and Parkinson-like events)).

AEs suggestive of abuse potential

In support of an evaluation of human abuse potential, user-defined AE categories (UDAEC) are defined in Section 10.2. In addition, frequency of patients with AEs suggestive of abuse potential will be summarized by treatment, UDAEC, and PT. A listing of the AEs and a listing of patients with >100% compliance or unreturned medication kits will also be provided.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (16). Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings. Study visits will be presented by the Visit labels in Table 6.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. In case of multiple measurements including unscheduled visits, the value for the vital sign measurement will be the average of all the measurements for the corresponding visit.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. 12-lead ECG-findings before first intake of trial drug will be considered as baseline condition, or as

AEs (during the trial) if judged clinically relevant by the investigator and will be analyzed as such. No quantitative analysis of these ECG data will be prepared. For ECG-related AEs, all qualitative findings will be listed per patient.

7.8.5 C-SSRS

Suicidality, as measured by the C-SSRS, will be assessed descriptively as follows.

The number and percentage of patients that respond "yes" to each question on the 'Baseline/Screening' and 'Since Last Visit' versions of the C-SSRS will be summarized. For 'Baseline/Screening' separate tables will be presented for 'lifetime' data and 'past 3 months/ past 12 months' data. In addition, the number and percentage of patients with a transition of their suicidal ideation score (0-5) at baseline to their worst score while on treatment will also be provided.

[redacted]

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be released for analysis according to the details specified in the logistics plan.

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study (EoS)/Follow-up (FU) 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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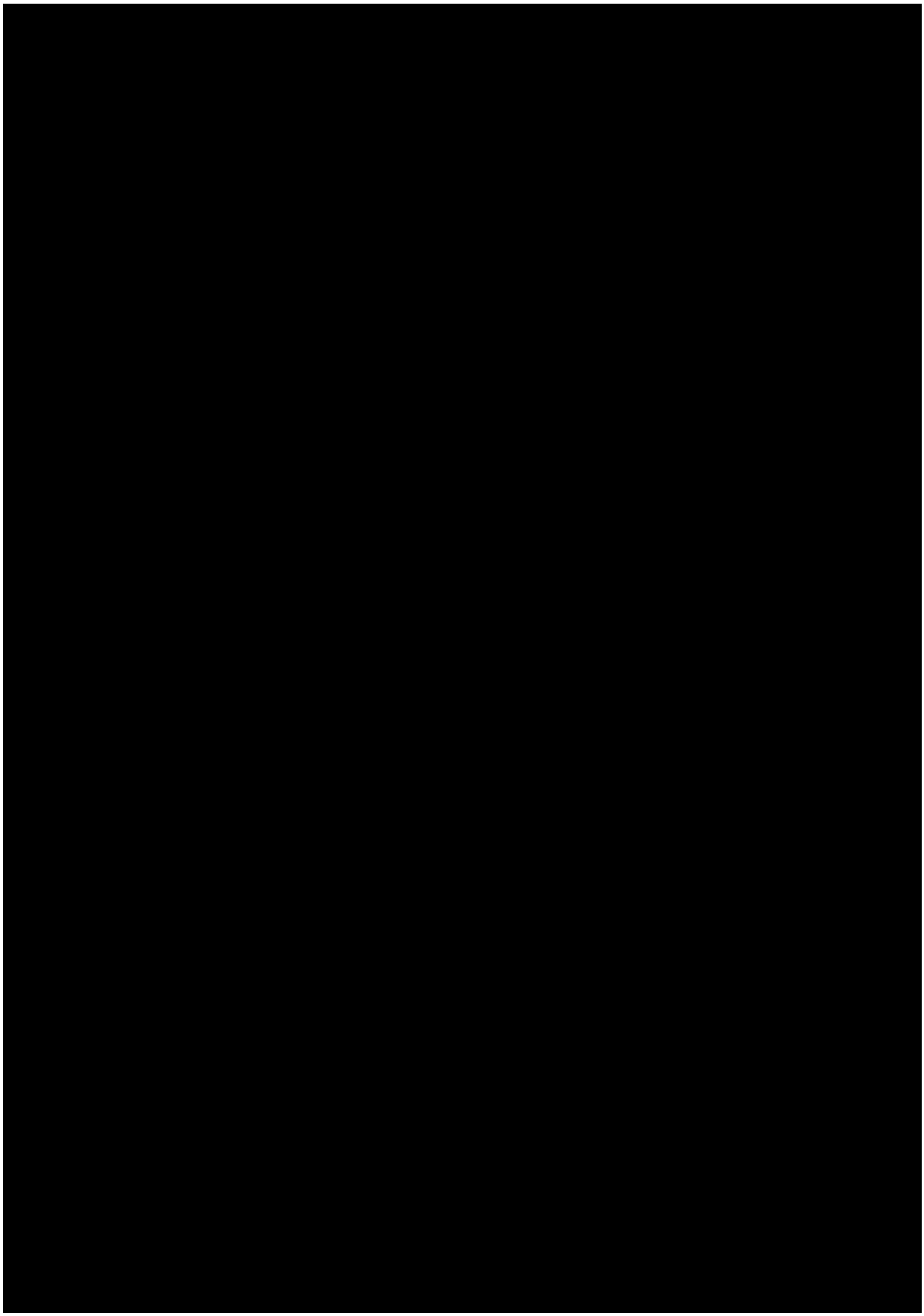

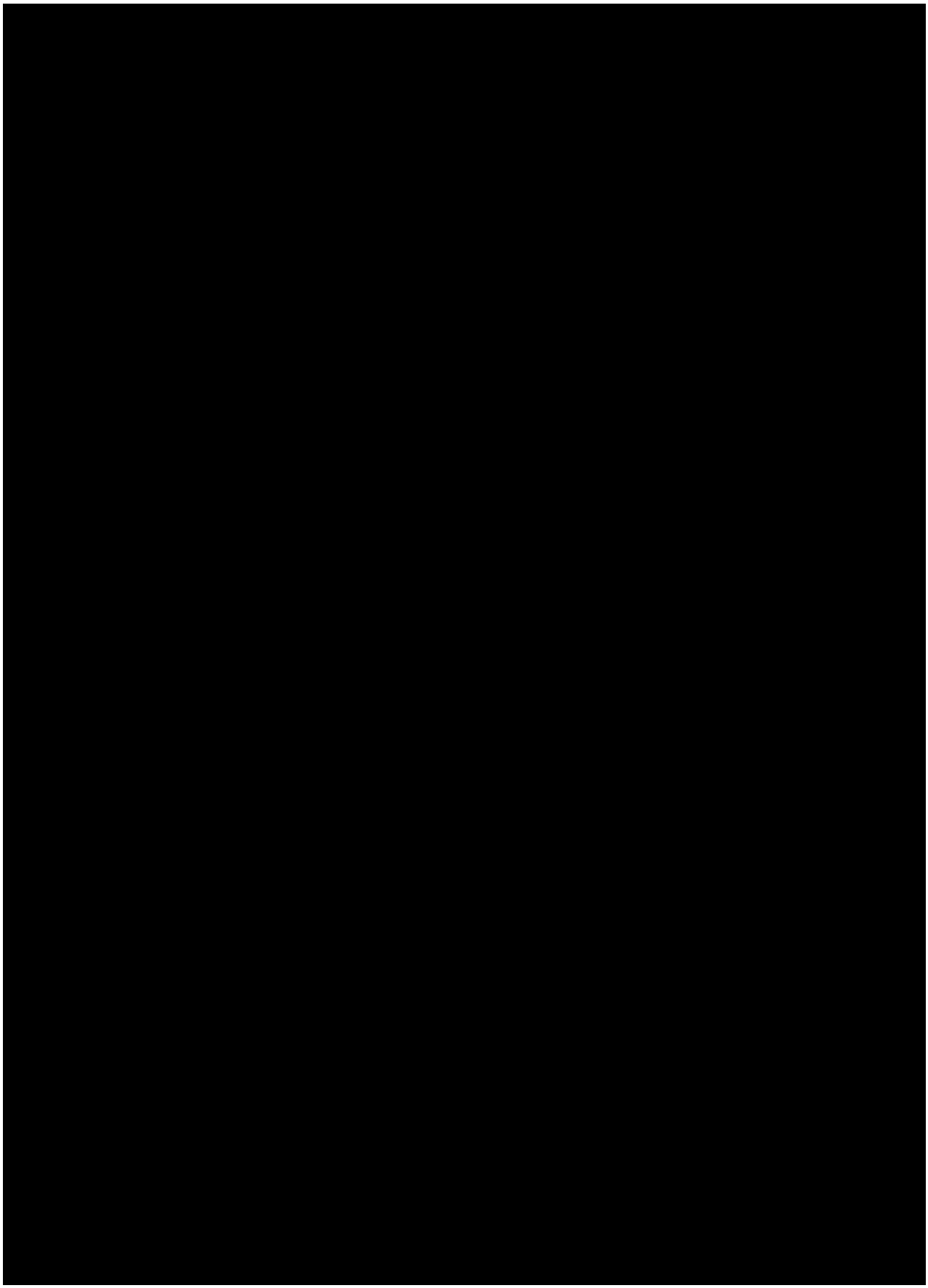

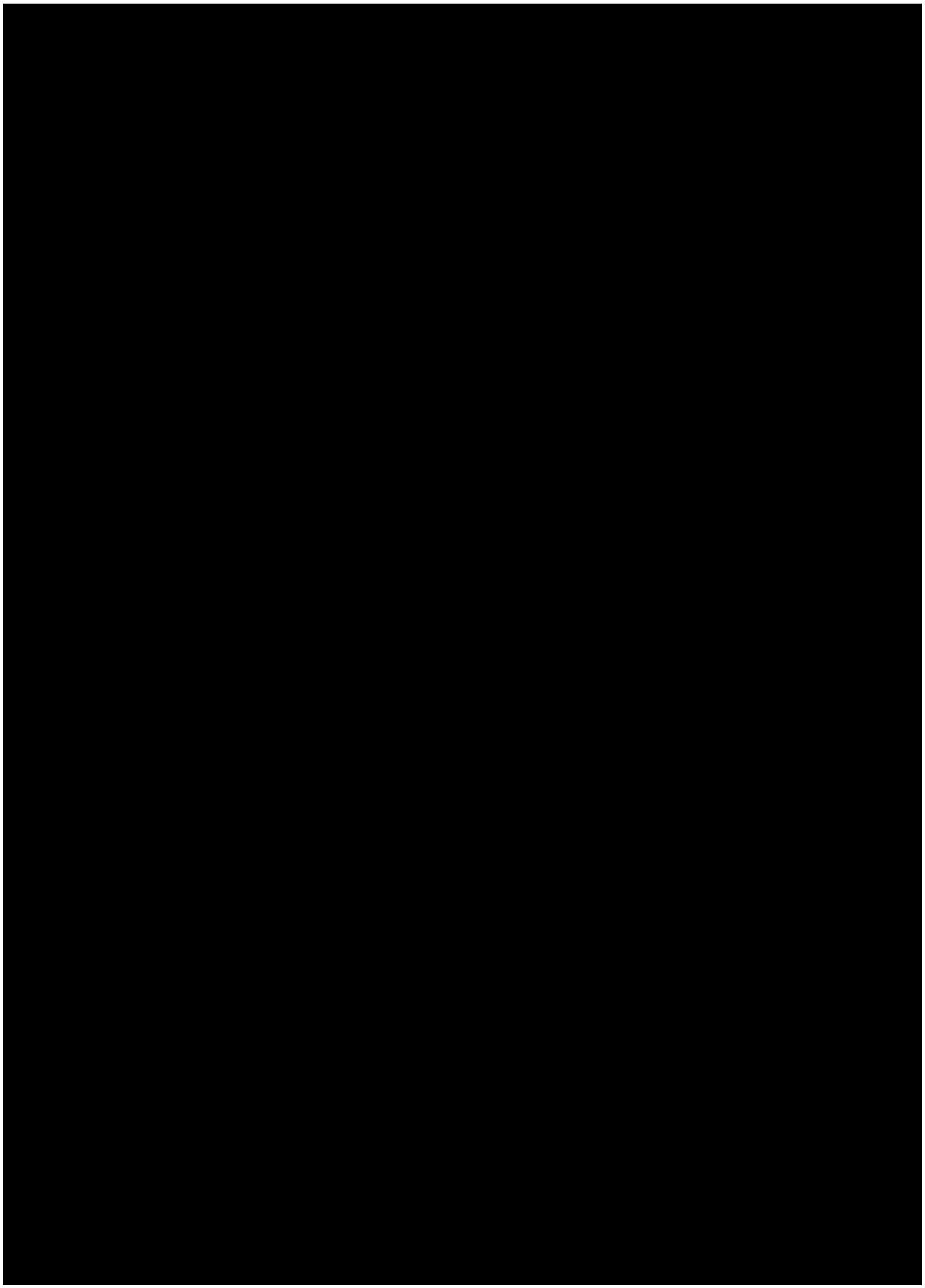

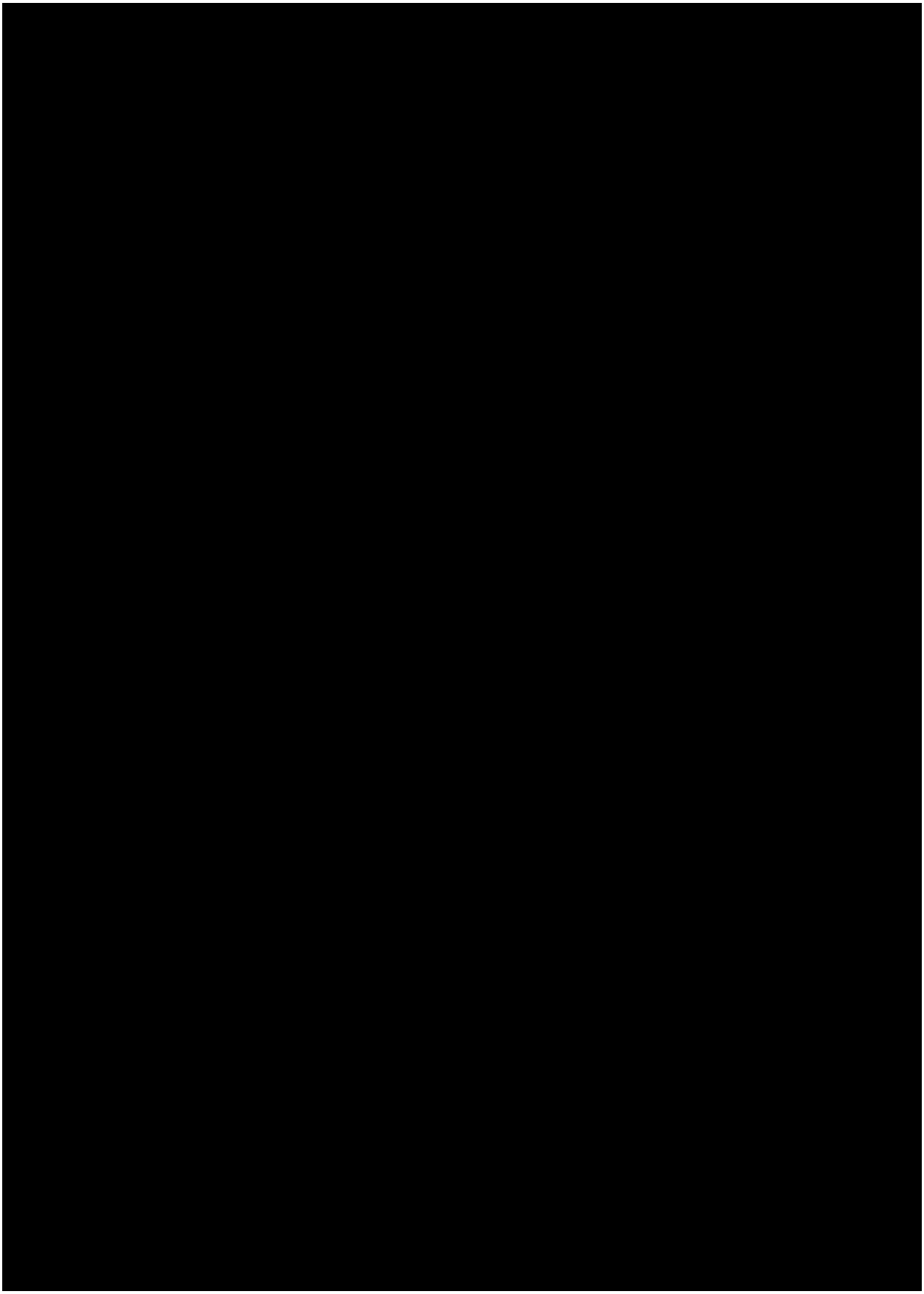

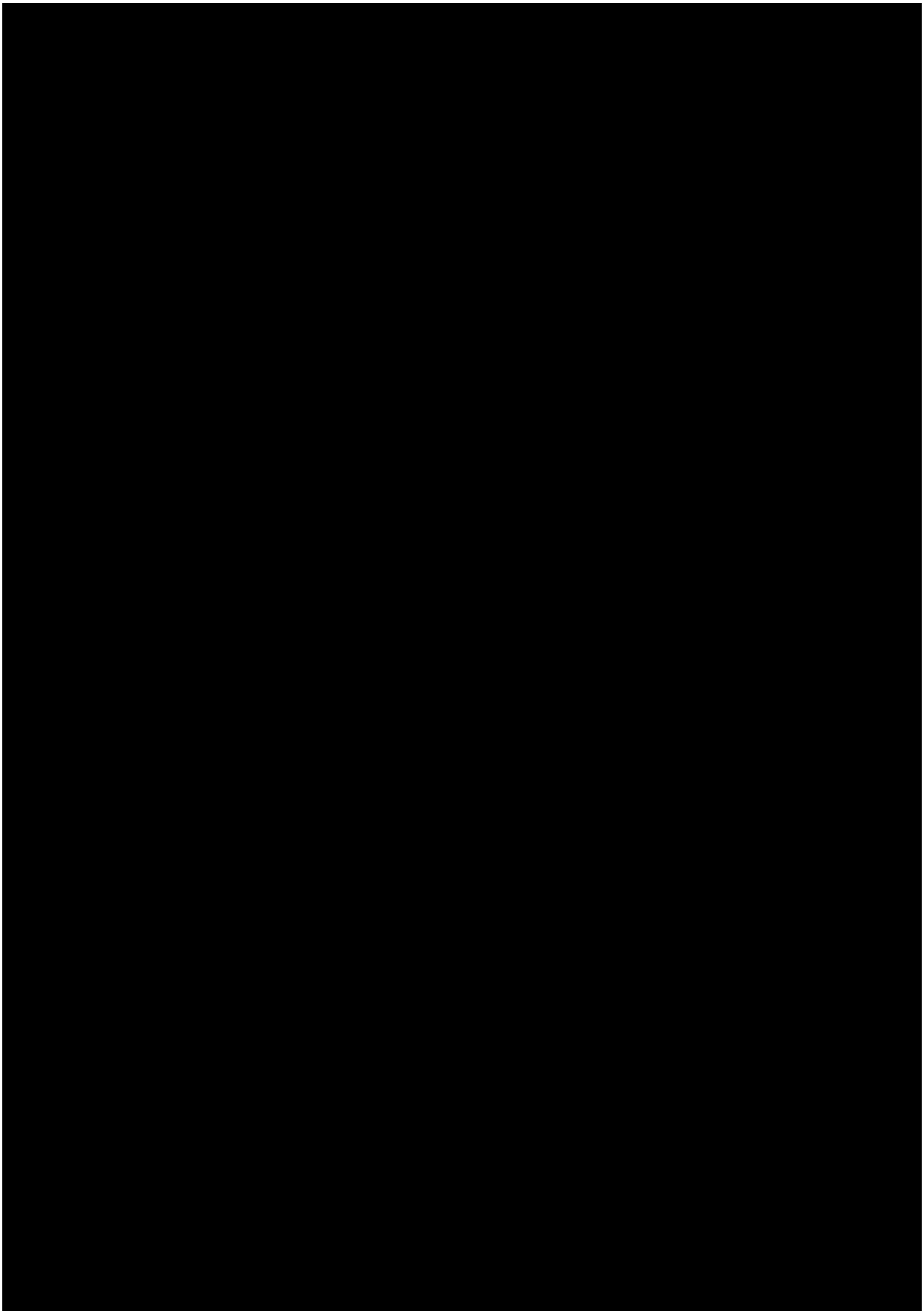

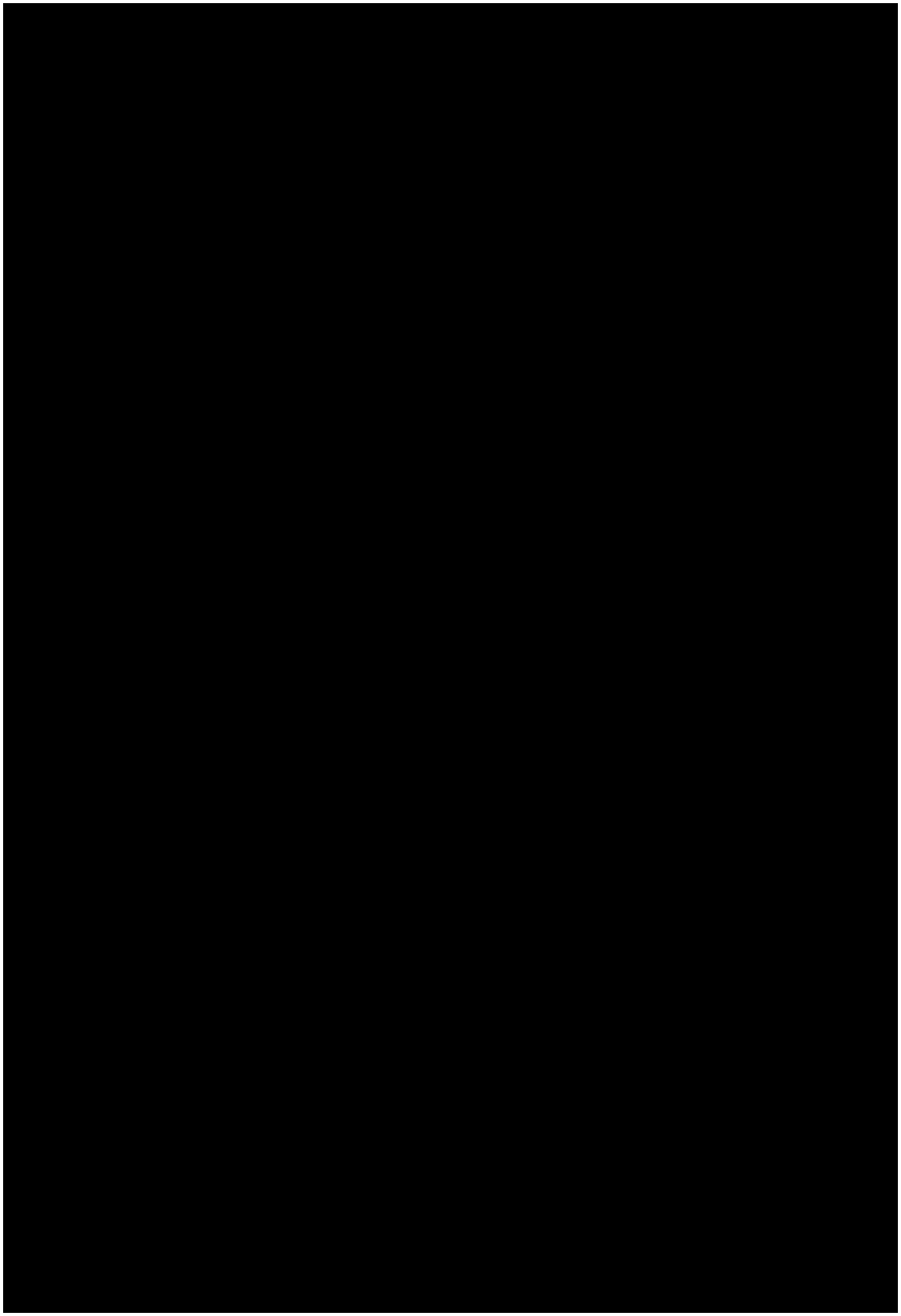

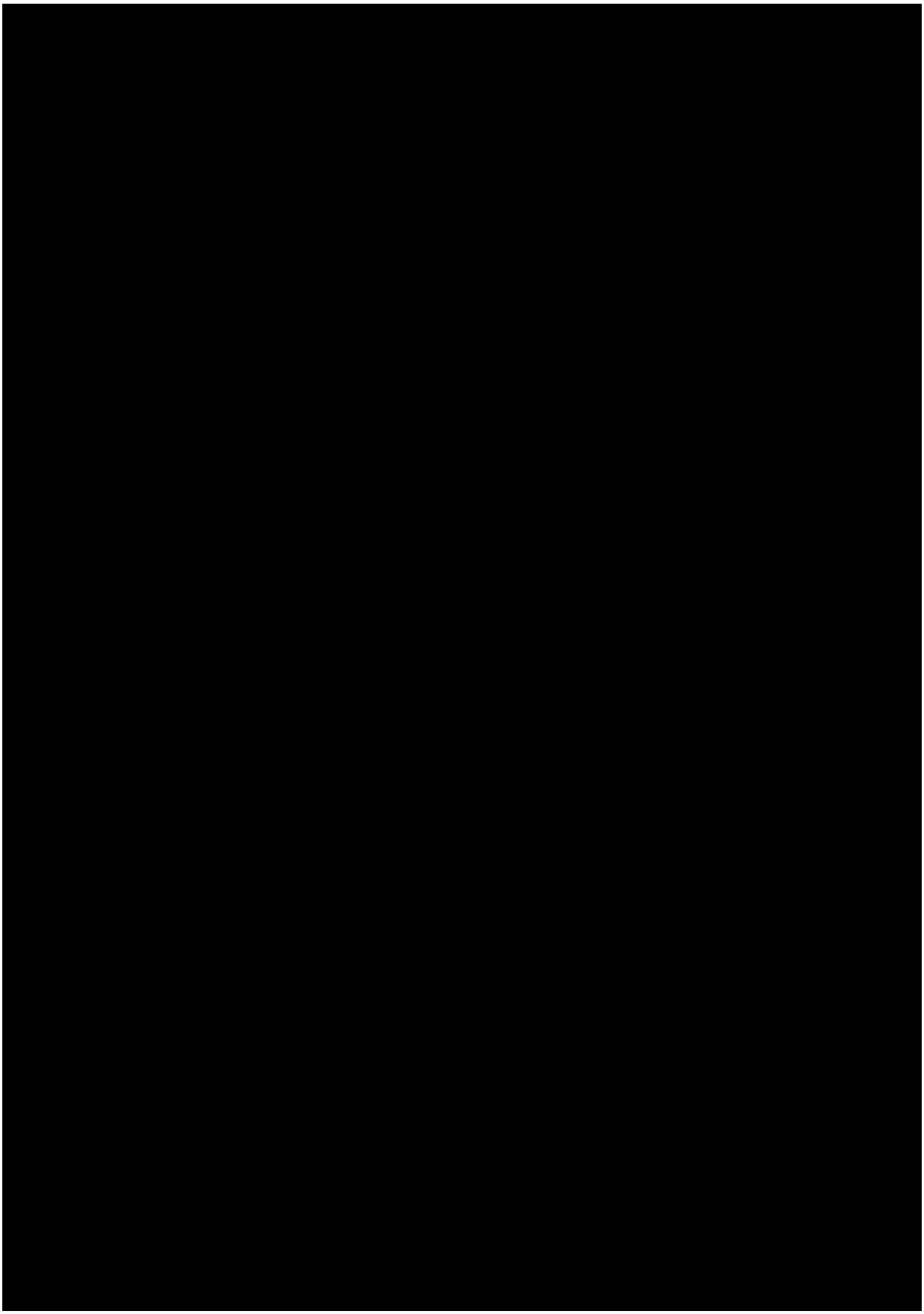

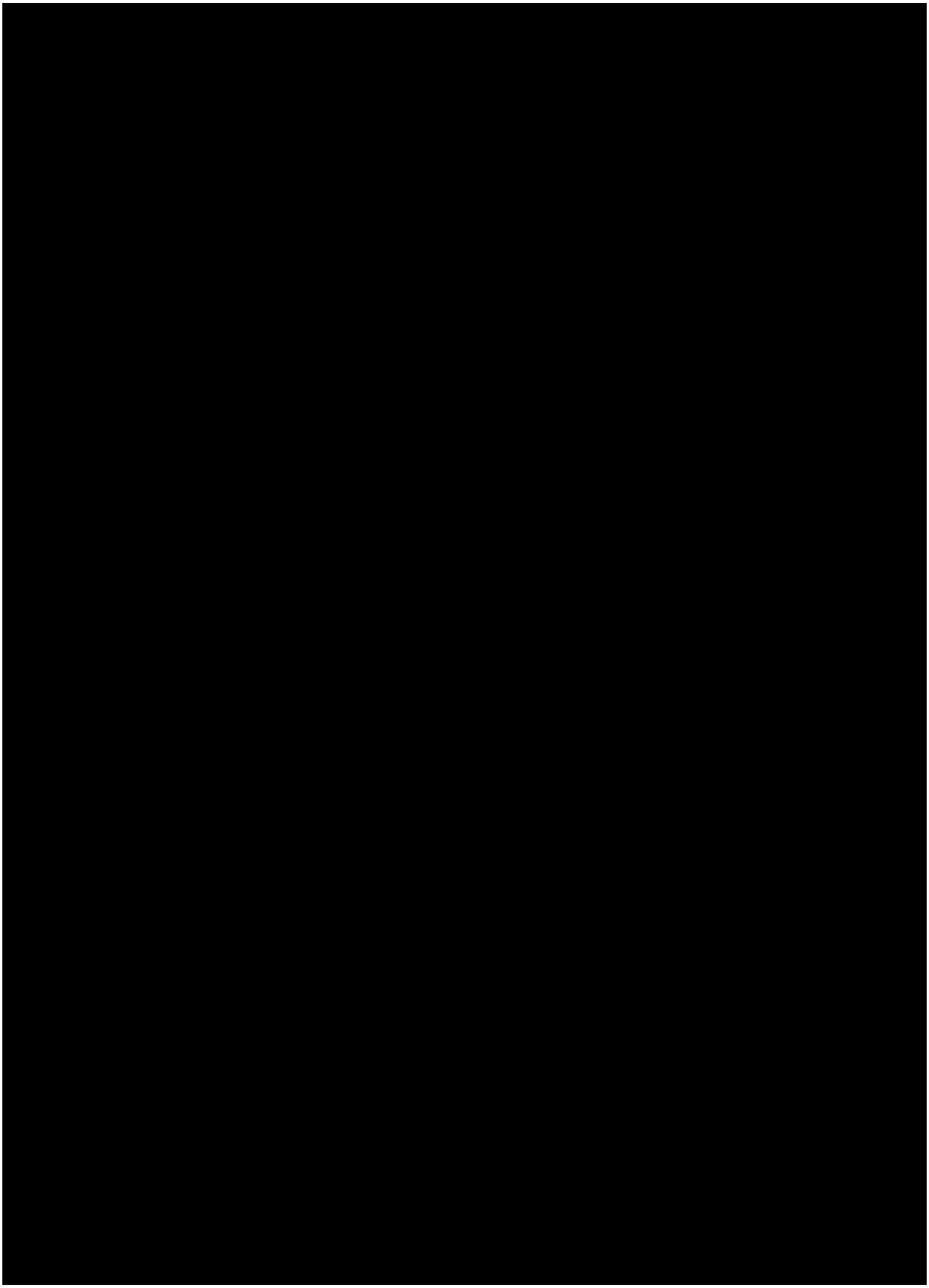

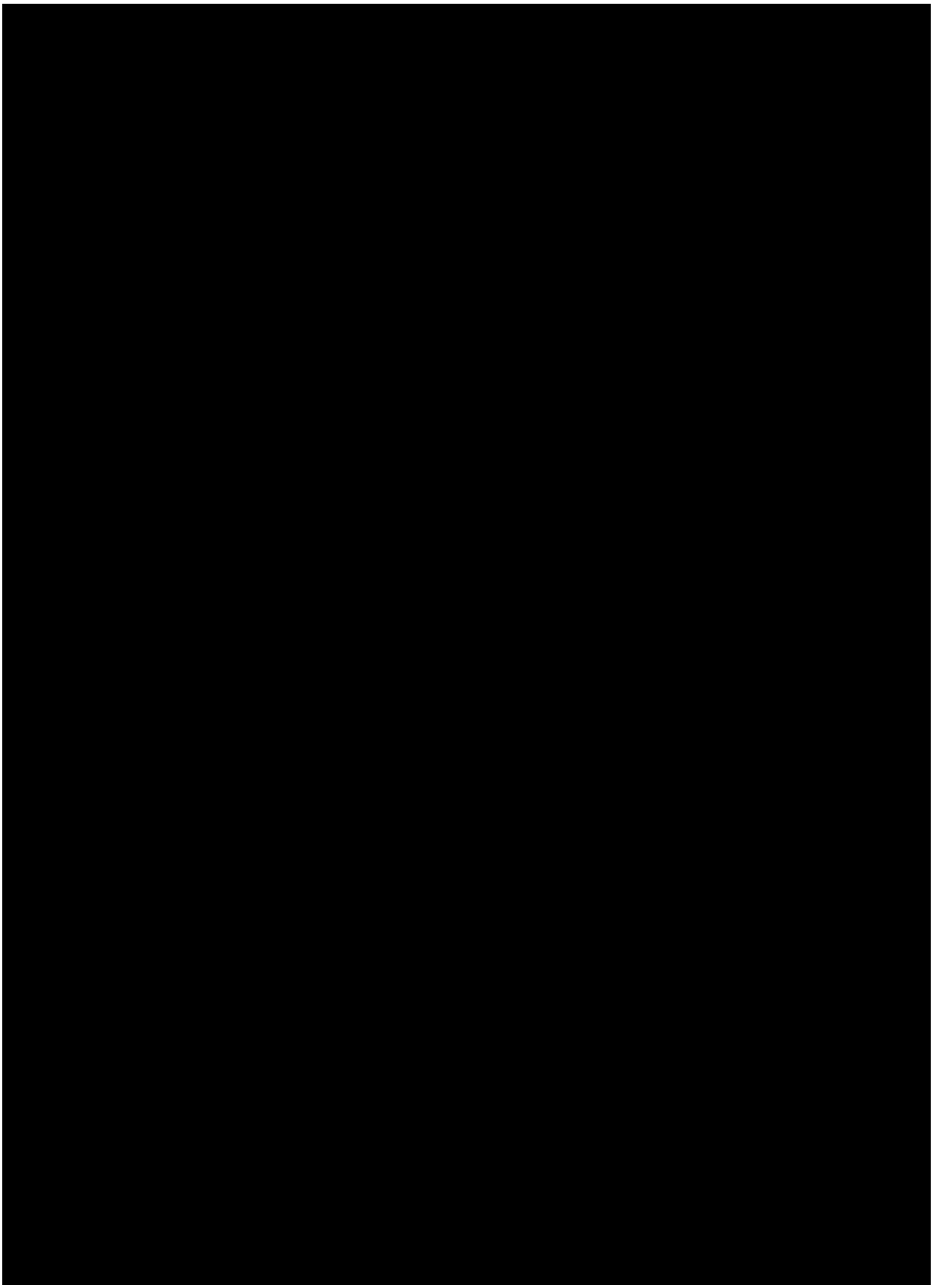

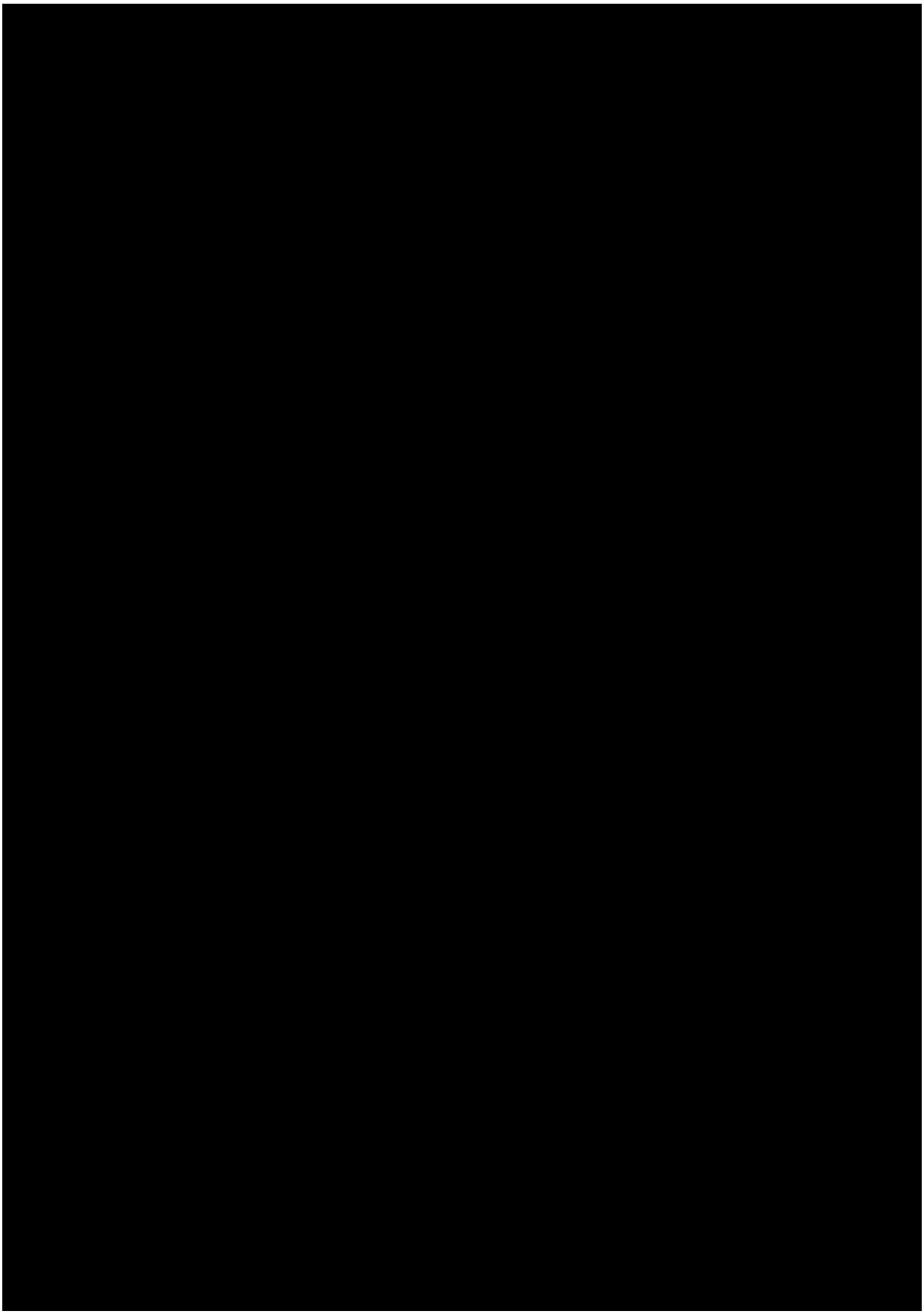

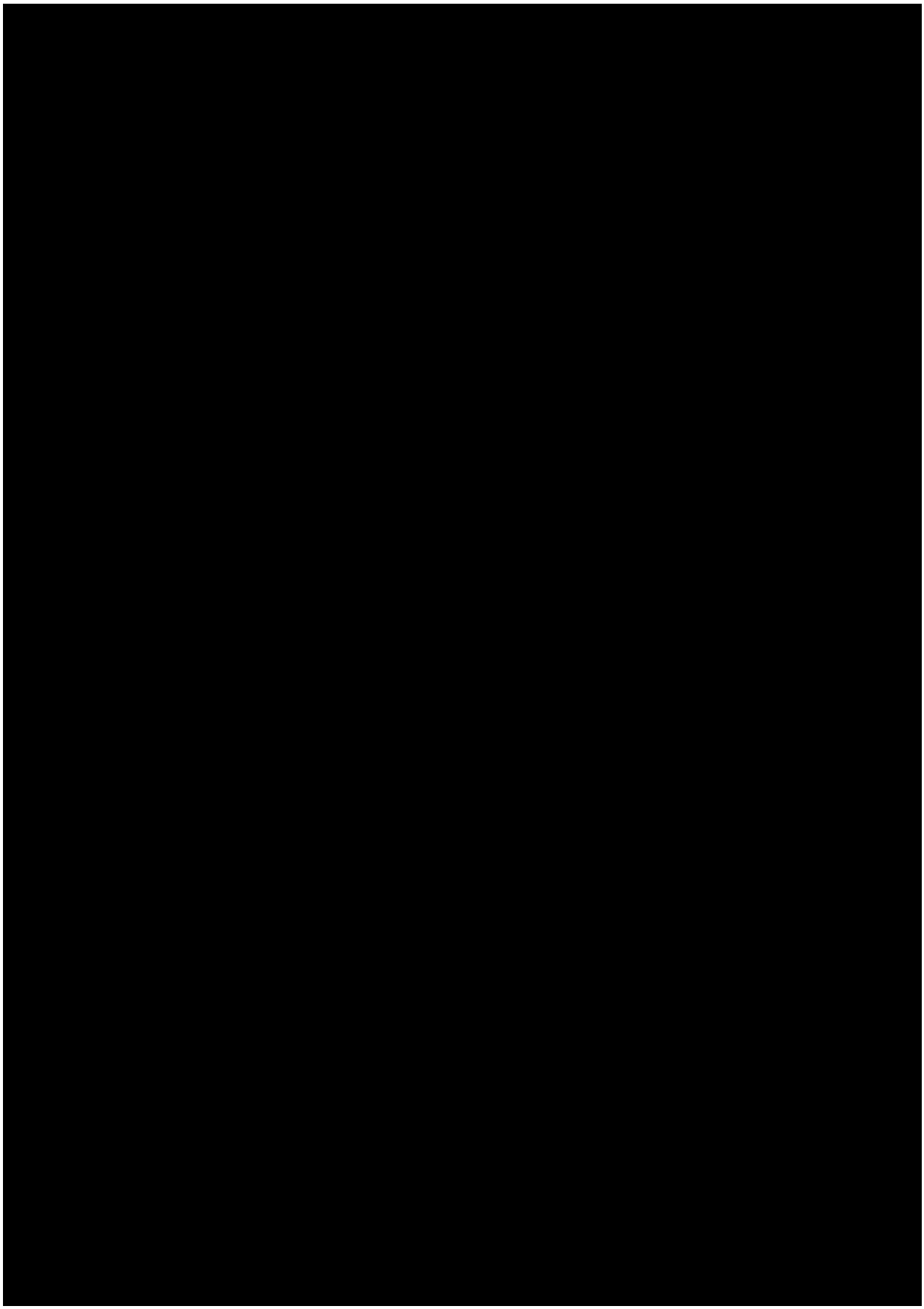

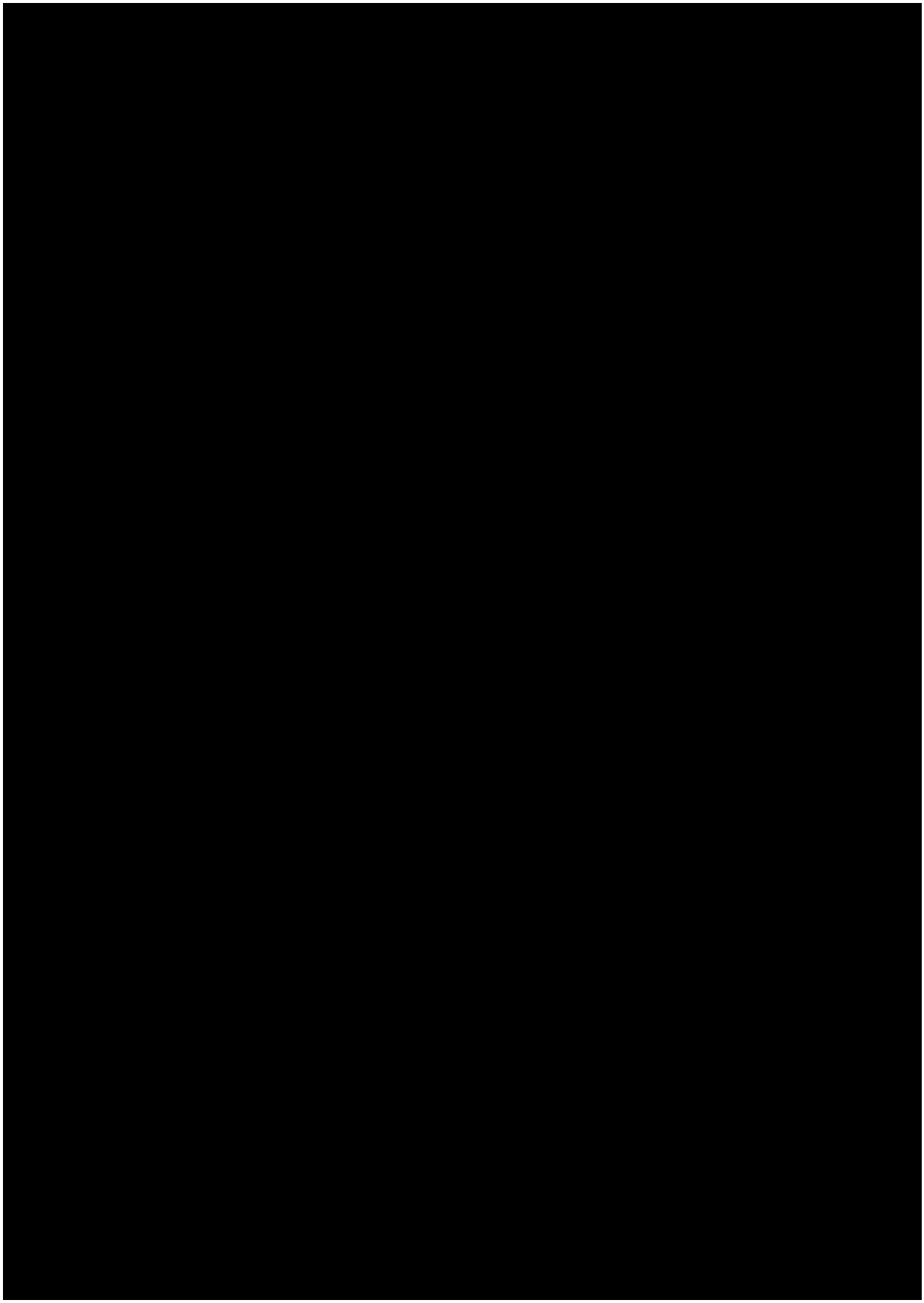

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11 HISTORY TABLE

Table 8 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**18-DEC-23**	[redacted]	None	This is the final TSAP