PROTOCOL TITLE:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety, and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type.

Protocol:	15-AVP-786-301-Amendment 3	**IND:** 124099
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 16 May 2016
Drug:	AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM; INN: deudextromethorphan]/ quinidine sulfate [Q])	**Version:** 4.0

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Protocol Amendment 3 (Version 4.0)

Summary of Changes

Section No.	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of approval, Version 4.0, Amendment 3. Updated Medical Monitor and contact information.
Study Synopsis	Study Population	Clarified that the study centers will be in North America.
	Assessments and Visits	Included an additional visit at Day 15 (Visit 2.1).
	Response Measures	Revised the primary measure to Cohen-Mansfield Agitation Inventory (CMAI) and moved Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI) to secondary measures. Specified that the CMAI, NPI, mADCS-CGIC-Agitation, and CGIS-Agitation scales must be administered by the same rater. Added the Epworth Sleepiness Scale (ESS) as a safety assessment.
	Efficacy Analyses	Revised the wording on primary efficacy endpoint to reflect CMAI instead of Agitation/Aggression domain of the NPI. Included the Agitation/Aggression domain of the NPI in the secondary analyses.
Figure 1	Study Schematic	Included an additional visit at Day 15 (Visit 2.1).
Table 1		• Added Visit 2.1 (Day 15, Week 2) with the following assessment at this visit: vital signs, ECG, AEs, prior and concomitant: medications, nondrug therapies, and nonpharmacological interventions for agitation, CMAI, NPI-Agitation/Aggression domain, S-STS, drug administration, and review and return of unused medication and diary card. • Clarified that information on nondrug therapies will be collected at all visits and also included data collection on concomitant nonpharmacological interventions for agitation. • Added safety laboratory procedures at Day 22 (Visit 3) and Day 64 (Visit 5) and HbA1c test at the Screening Visit and Visit 6. • Added ESS at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6). • Specified that the screening period may be extended after discussion with and approval by the medical monitor. • Clarified that the following scales MUST be administered by the same rater: CMAI, NPI, mADCS-CGIC-Agitation, and mCGIS-Agitation. • Added that the study medication can be administered at home at Visit 2 and Visit 2.1 if the visit will occur within 2 hours of dosing.

Section No.	Section Title	Description
3	Study Design	Revised number of visits to 8 scheduled clinic visits with the new visit occurring on Day 15 (Visit 2.1). Clarified that the study centers will be in North America. Specified that Screening *will* occur within 4 weeks prior to randomization.
[redacted]		
5.1.6	Study Medication Administration	Specified that, for Visits 2 (Day 8) and 2.1 (Day 15), patients/caregivers should be advised to take the morning dose within 2 hours of the clinic appointment and note the time of dosing.
5.4	Patient Compliance	Specified that patients should bring their unused medication and Diary Card on Visit 2.1 (Day 15).
5.5.1	[redacted]	[redacted]
5.5.4	Nondrug Therapies	Clarified that information on nondrug therapies will be collected.
5.5.5	Nonpharmacological Interventions for the Treatment of Agitation	Added that information will be collected on any nonpharmacological interventions that were used for agitation prior to enrollment or used concomitantly during the study.
6.1	Efficacy	Included that whenever possible, each patient and caregiver should have the rating scales administered by the same raters throughout the study, for consistency of ratings and that the following scales MUST be administered by the same rater at each visit: CMAI, NPI, mADCS-CGIC-Agitation and CGIS-Agitation.
6.1.1	Cohen-Mansfield Agitation Inventory (CMAI)	Revised to indicate that the CMAI is the primary efficacy measure. Clarified that the long-form version will be used. Added CMAI assessment at Day 15 (Visit 2.1). Clarified that the scale MUST be administered by the same rater at all applicable visits.
6.1.2	Neuropsychiatric Inventory (NPI)	Added NPI-Agitation/Aggression domain assessment at Day 15 (Visit 2.1). Clarified that the scale MUST be administered by the same rater at all applicable visits.
6.1.3	Clinical Global Impression of Severity of Illness-Agitation (CGIS-Agitation)	Clarified that the scale MUST be administered by the same rater at all applicable visits.

Section No.	Section Title	Description
6.1.5	Modified Alzheimer's Disease Cooperative Study –Clinical Global Impression of Change Rating (mADCS-CGIC Agitation)	Clarified that the scale MUST be administered by the same rater at all applicable visits.
6.3.2	Physical and Neurological Examinations	Clarified the assessments involved in physical and neurological examinations.
6.3.3	Vital Signs	Included the assessment of orthostatic blood pressure and heart rate.
6.3.4	Clinical Laboratory Tests	Added safety laboratory procedures at Day 22 (Visit 3) and Day 64 (Visit 5) and HbA1c test at the Screening Visit and Visit 6.
6.3.7	Sheehan Suicidality Tracking Scale (S-STS)	Added S-STS assessment at Day 15 (Visit 2.1).
6.3.10	Epworth Sleepiness Scale (ESS)	Added this scale as a safety assessment to be performed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).
6.4	Schedule of Evaluations and Procedures	Revised the assessments to match the changes made in Table 1 and rearranged the order of procedures. Added patient/caregiver instruction at the Baseline Visit, Visit 2 (Day 8) and Visit 2.1(Day 15).
8.3.1	Study Endpoints	Revised the primary endpoint to reflect CMAI instead of Agitation/Aggression domain of the NPI. Revised the secondary endpoints to include Agitation/Aggression domain of NPI and moved CMAI to the primary endpoint.
8.3.2	Primary Efficacy Analyses	Revised to reflect the CMAI instead of NPI Agitation/Aggression domain. Revised to state that an appropriate measure will be included to control the overall type I error and will be specified in the SAP.
8.3.3	Secondary Efficacy Analyses	Updated to match changes to study endpoints.
10	References	Added references related to the CMAI [redacted]) and the ESS [redacted]).
11	Appendices	[redacted]
Overall		Formatting and minor wording modification throughout the document.

Protocol Amendment 2 (Version 3.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 3.0, Amendment 2. Updated Medical Monitor and contact information.
Study Synopsis	Dose Regimen, Stage 2 Secondary Measures and Efficacy Analyses	Described the criteria and the definition for responders and non-responders for patients who received placebo in Stage 1. [redacted] Separated CGIC evaluation for Overall Clinical Status (ADCS-CGIC-Overall) from the evaluation for agitation syndrome (mADCS-CGIC-Agitation). Removed the EQ-5D-5L scale.
Table 1		• Specified that ECG should be performed in triplicate at Screening • Added CMAI assessment at Screening, Baseline, Visits 2, 3, 4, 5, and 6 • Separated the ADCS-CGIC to ADCS-CGIC-Overall and mADCS-CGIC-Agitation, both of which are assessed only at Visits 4 and 6 with baseline evaluations at the Baseline visit • Revised the NPI assessment at Visit 2 to only the assessment of Agitation/Aggression domain • Deleted the following assessments at Visits 3 and 5, ZBI, PGIC, ADCS-CGIC-Overall, and mADCS-CGIC-Agitation • Deleted the EQ-5D-5L at all visits • Added weight assessment at visit 6
3	Study Design	[redacted]
4.1	Inclusion Criteria	[redacted]
4.2	Exclusion Criteria	[redacted]
5.3.1	Randomization	Provided details on the randomization plan for Stage 2. Specified that patients who receive placebo and who drop out early in Stage 1 will also be assigned a re-randomization treatment.
5.5	[redacted]	[redacted]

Section Number	Section Title	Description
		[redacted].
5.5.1	[redacted]	[redacted]
5.5.3	[redacted]	[redacted]
6.1.1	NPI	Revised the assessment of the NPI to only Agitation/Aggression domain at Visit 2. Revised the NPI recall period to 2 weeks for all the visits.
6.1.2 (new)	CMAI	Added background on the CMAI and frequency of assessment. [redacted]
6.1.3	CGIS-Agitation	Removed the CGIS assessment of overall clinical status. The CGIS will be used to only assess severity of Agitation.
6.1.4	ADCS-CGIC-Overall	Separated and clarified the terminology for the scale that assesses the impression of change in overall clinical status (ADCS-CGIC-Overall). Revised the frequency of assessment to only Visits 4 and 6, with a baseline evaluation at the Baseline visit.
6.1.5	mADCS-CGIC-Agitation	Separated and clarified the terminology for the scale that assesses the impression of change in agitation (mADCS-CGIC-Agitation). Revised the frequency of assessment to only Visits 4 and 6, with a baseline evaluation at the Baseline visit.
6.1.6	ZBI	Added a description of the scoring of ZBI and removed assessment of ZBI at Visits 3 and 5.
6.1.7	PGIC	Removed assessment of PGIC at Visits 3 and 5.
6.1.11 (old)	EQ-5D-5L	Deleted the section on EQ-5D-5L as it will not be assessed at any visit.
6.3.3	Vital Signs	Clarified that vital signs should be performed after 5 minutes of resting.
6.3.6	Electrocardiograms	Specified that ECGs will be performed in triplicate at Screening
6.4.1	Description of Study Procedures	Revised the assessments to match the changes made in the Schedule of Events and Procedures (Table 1).
8.3.1	Study Endpoints	[redacted]
8.3.3	Secondary Efficacy Analyses	Deleted the detailed description of the gate keeping procedure used to analyze secondary endpoints, as the procedure will be described appropriately in the Statistical Analysis Plan (SAP).
10	References	Added 2 references related to the CMAI: [redacted]

Section Number	Section Title	Description
11	Appendices	[redacted]
Overall		Formatting and minor wording modification throughout the document.

Protocol Amendment 1 (Version 2.0)

Summary of Changes

Section Number	Section Title	Description
Title Page	Title page	The date, version number, and amendment number were changed to reflect date of finalization, Version 2.0, Amendment 1.
Study Synopsis and 8.3	Secondary Measures and Efficacy Analyses	Clarified wording to specify that the secondary measure is the Caregiver Distress score of the NPI Agitation/Aggression domain.
Table 1	Schedule of Evaluations and Visits	Renumbered the footnotes and deleted footnote 6 in Version 1.0 that specified that only inclusion/exclusion criteria from the protocol eligibility form need to be reviewed at baseline. Revised footnote 10 and 11 of current version to specify that the EQ-5D-5L, DEMQOL, and ADAS-COG should be performed by patients with an MMSE score of ≥ 10 'at baseline' instead of 'at that visit'. Added footnote (14) that thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) should be performed at the Screening Visit.
4.2	Exclusion Criteria	[redacted]
5.1.6	Study Medication Administration	Clarified that study medication should be administered to the patient by the caregiver, family member, nursing home staff, or self-administered with supervision and that the time the patient takes each dose of medication should be recorded in the diary card.
6.1.3	Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change Rating (ADCS-CGIC)	Clarified that at Day 22 (Visit 3) the ADCS-CGIC will be completed to assess change from the Baseline visit (Day 1) and at Day 64 (Visit 5) it will be completed to assess change from Day 43 (Visit 4) and change from the Baseline visit (Day 1).
6.1.5	Patient Global Impression of Change (PGIC)	Deleted the statement on the reference point from which the change in PGIC will be assessed for each visit.
6.1.6	Dementia Quality of Life (DEMQOL)	Clarified that the DEMQOL is a 28-item questionnaire and should be used for patients with MMSE ≥10 at the 'Baseline visit'.
6.1.7	Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)	Revised to specify that ADAS-cog will be assessed for patients with an MMSE score of ≥ 10 at the Baseline visit instead of a score of ≥ 10 at that visit.
6.1.11	EuroQol 5-Dimension 5-level (EQ-5D-5L)	Revised to specify that the patient version will be rated only by patients with an MMSE score of ≥10 at the Baseline visit instead of a score of ≥10 at that visit.

Section Number	Section Title	Description
6.3.1.3	Reporting	Clarified that a death occurring during the study, or which comes to the attention of the investigator within '30 days' (instead of 4 weeks) after stopping the treatment whether considered treatment-related or not, must be reported to the sponsor.
6.3.4	Clinical Laboratory Tests	Added leucocyte esterase and nitrates in urinalysis Added thyroid function tests (TSH, and reflex T3 and T4 tests if TSH is abnormal) at Screening visit only.
6.3.7	Sheehan Suicidality Tracking Scale (S-STS)	Added that 'any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to the MM'.
Overall		Formatting and minor wording modification throughout the document.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alzheimer's Association
AE	Adverse event
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCS	Alzheimer's Disease Cooperative Study
ADCS-CGIC-Overall	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Overall Clinical Status
ADWG	Agitation Definition Work Group
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUC	Area under the concentration-by-time curve
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
Cit AD	Citalopram study for Agitation in Alzheimer's disease
CGIC	Clinical Global Impression of Change
CGIS-Agitation	Clinical Global Impression of Severity of Illness scale for Agitation
CK	Creatine kinase
CMAI	Cohen-Mansfield Agitation Inventory
CNS	Central nervous system
CRO	Contract research organization
CSDD	Cornell Scale for Depression in Dementia
[redacted]	
d6-DM	Deuterated (d6)-dextromethorphan hydrobromide
DEMQOL	Dementia Quality of Life
DM	Dextromethorphan hydrobromide
DMP	Data management plan
DSMB	Data and Safety Monitoring Board
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders
ECDEU	Early Clinical Drug Evaluation Unit
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EP	European Pharmacopeia

Abbreviation	Definition
ESS	Epworth Sleepiness Scale
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMHR	General Medical Health Rating
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IP	Investigational product
IPA	International Psychogeriatric Association
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
mADCS-CGIC-Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MM	Medical Monitor
MMRM	Mixed effects model repeated measures
MMSE	Mini-Mental State Examination
NF	National Formulary
NIA	National Institute on Aging
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory - Nursing Home version
OTC	Over–the-counter
PGIC	Patient Global Impression of Change
pH	Potential hydrogen
PK	Pharmacokinetics
PR	The P-R interval from an ECG tracing
PVC	Premature ventricular contraction
Q	Quinidine sulfate
QRS	The Q-R-S complex from an ECG tracing
QT	QT interval from an ECG tracing
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia's formula

Abbreviation	Definition
RBC	Red blood cell
RUD	Resource Utilization in Dementia
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SPCD	Sequential Parallel Comparison Design
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TUG	Timed Up and Go
USP	United States Pharmacopoeia
WBC	White blood cell
ZBI	Zarit Burden Interview

PROTOCOL AGREEMENT

Protocol Title:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety, and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type.

Protocol Number: 15-AVP-786-301 (Amendment 3, 16 May 2016)

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The signatures of the principal investigator and representative of the sponsor below constitute their approval of this protocol and further provide the necessary assurances that:

1. This study will be conducted according to Good Clinical Practice (GCP) and to all stipulations, as specified in both clinical and administrative sections of the protocol including the Declaration of Helsinki.

2. The conduct and results of this study will be kept confidential, and the electronic case report forms (eCRFs) and other pertinent data will become the property of Avanir Pharmaceuticals.

3. The protocol contains all necessary information required to conduct the study, as outlined in the protocol, and that the study will not be initiated without the approval of an appropriate Institutional Review Board/Ethics Committee (IRB/EC).

4. All participants in this study will provide written informed consent in accordance with the requirements specified in the Code of Federal Regulations (21 CFR Parts 50, 56, 312) and/or the Declaration of Helsinki. All participants will also be informed that their medical records will be kept confidential except for review by Avanir or its representatives, the U.S. Food and Drug Administration (FDA), or other regulatory agencies if applicable.

Principal Investigator Signature	Date
Principal Investigator Name:_____	
Avanir Representative Signature	Date
Avanir Representative: [redacted]	

STUDY SYNOPSIS

Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study to assess the efficacy, safety, and tolerability of AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q]) for the treatment of agitation in patients with dementia of the Alzheimer's type.

Study Objectives

The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo, for the treatment of agitation in patients with dementia of the Alzheimer's type.

Study Population

Number of Patients: Approximately 380 patients will be enrolled at approximately 60 centers in North America.

Condition/Disease: Patients with agitation secondary to dementia of the Alzheimer's type. The diagnosis of probable Alzheimer's disease will be based on the '2011 Diagnostic Guidelines for Alzheimer's Disease' issued by the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups.[1] Diagnosis of agitation will be based on the provisional consensus definition of agitation in patients with cognitive disorders developed by the International Psychogeriatric Association (IPA) Agitation Definition Work Group.[2]

Key Inclusion Criteria: Patients with clinically significant, moderate/severe agitation at the time of screening and for at least 2 weeks prior to randomization, that interferes with daily routine and for which a prescription medication is indicated in the opinion of the investigator. A Clinical Global Impression of Severity of Illness scale for Agitation (CGIS-Agitation) score of ≥ 4 (moderately ill) at screening and baseline is required for study participation. Eligible patients must have a reliable caregiver who is able and willing to comply with study procedures, including not administering any prohibited medications during the course of the study.

Key Exclusion Criteria: Patients with dementia predominantly of the non-Alzheimer's type (e.g., vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia) and patients with symptoms of agitation that are not secondary to Alzheimer's disease (e.g., secondary to pain, other psychiatric disorder or delirium) are not eligible.

A complete list of inclusion/exclusion criteria is presented in Section 4 of the study protocol.

Study Design

Structure: This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, SPCD study comprising 2 stages. A schematic of the study design is presented in Figure 1.

Duration: Patients will be enrolled in the study for approximately 16 weeks; with up to 4-week screening period and 12-week treatment period. The treatment period is divided equally into 2 stages of 6 weeks each, Stage 1 and Stage 2.

Study Treatment: The investigational product is AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM; INN:deudextromethorphan]/quinidine sulfate [Q]). Two doses of AVP-786 will be evaluated; d6-DM 28 mg/Q 4.9 mg and d6-DM 18 mg/Q 4.9 mg, hereafter referred to as AVP-786-28/4.9 and AVP-786-18/4.9, respectively.

Control: Placebo capsules of identical appearance to study medication will be used as control.

Randomization/Stratification: Eligible patients will be randomized into the study in a [redacted] (active:active:placebo) ratio to receive either AVP-786-28/4.9 capsules, AVP-786-18/4.9 capsules, or matching placebo capsules in Stage 1. The randomization will be stratified by the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain score (≤ 6 vs. > 6), risk assessment for falls (normal/mild vs. moderate/severe), and concomitant use of antipsychotic medications (yes vs. no).

Dose Regimen: Eligible patients will be randomly assigned at the Baseline visit to receive AVP-786 or matching placebo capsules. Study medication will be administered orally twice daily (BID, 1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart) throughout the study.

Stage 1

- Patients randomized to receive AVP-786-28/4.9 will start with AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of the study. From Day 8, patients will receive AVP-786-18/4.9 BID for 14 days. From Day 22, patients will receive AVP-786-28/4.9 BID for the remaining 3-week duration of Stage 1.
- Patients randomized to receive AVP-786-18/4.9 will start with AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of the study. From Day 8, patients will receive AVP-786-18/4.9 BID for the remaining 5-week duration of Stage 1.
- Patients randomized to receive placebo will be dosed with placebo BID during Stage 1.

Stage 2:

Patients who complete Stage 1 are eligible to participate in Stage 2 of the study. In Stage 2, patients will be assigned to study treatment as follows:

- Patients who received AVP-786 in Stage 1 will continue to receive the same dose of AVP-786 BID (either AVP-786-18/4.9 or AVP-786-28/4.9) for the entire 6-week duration of Stage 2.
- Patients who received placebo in Stage 1 will be further stratified into two sub-groups ("responders" and "non-responders") on Visit 4 (Day 43) based on their treatment response. Patients will be considered "responders" if their CGIS-Agitation score is ≤ 3 at Visit 4 (Day 43) and their NPI Agitation/Aggression domain score has decreased by ≥ 25% from baseline. Patients who do not meet these criteria will be considered "non-responders". Patients within each placebo sub-group will be re-randomized in a [redacted] (active:active:placebo) ratio to receive either AVP-786-18/4.9, AVP-786-28/4.9 capsules, or matching placebo capsules.
    - Patients who are re-randomized to placebo will continue to receive placebo BID for the entire 6-week duration of Stage 2.

- Patients who are re-randomized to AVP-786-28/4.9 will receive AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of Stage 2 (Days 43-49). From Day 50, patients will receive AVP-786-18/4.9 BID for 14 days (Days 50-63). From Day 64, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of the study.
- Patients who are re-randomized to AVP-786-18/4.9 will receive AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of Stage 2 (Days 43-49). From Day 50, patients will receive AVP-786-18/4.9 BID for the remaining 5 weeks of the study.

Assessments and Visits

Patients will attend clinic visits at Screening, Baseline (Day 1), and on Days 8 (Week 1), 15 (Week 2), 22 (Week 3), 43 (Week 6), 64 (Week 9), and 85 (Week 12). Safety follow-up phone calls will be made on Days 29 (Week 4) and 71 (Week 10). Study procedures will be performed at each visit as outlined in the Schedule of Evaluations and Visits (Table 1).

Response Measures

Efficacy

Primary measure: Primary efficacy will be assessed using the Cohen-Mansfield Agitation Inventory (CMAI).

Secondary measures: Secondary efficacy measures include: Agitation/Aggression domain of the NPI, modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change-Agitation (mADCS-CGIC-Agitation), NPI-Agitation/Aggression domain Caregiver Distress score, NPI-Aberrant Motor Behavior domain, Zarit Burden Interview (ZBI), NPI-Irritability/Lability domain, Patient Global Impression of Change (PGIC, rated by caregiver), Dementia Quality of Life (DEMQOL), Cornell Scale for Depression in Dementia (CSDD), Resource Utilization in Dementia (RUD), total NPI, ADCS-CGIC-Overall, CGIS-Agitation, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), and General Medical Health Rating (GMHR).

For consistency of rating, assessments should be performed, whenever possible, by the same rater throughout the study. The following scales MUST be administered by the same rater at each visit: CMAI, NPI, mADCS-CGIC-Agitation, and CGIS-Agitation.

Pharmacokinetics

Plasma concentrations of d6-DM, its metabolites, and Q will be measured.

Safety and Tolerability

Safety and tolerability of AVP-786 will be assessed by reported adverse events (AEs), physical and neurological examinations, vital signs, clinical laboratory assessments, resting 12-lead electrocardiograms (ECGs), Sheehan Suicidality Tracking Scale (S-STS), Mini Mental State Examination (MMSE), Timed Up and Go (TUG) test, and the Epworth Sleepiness Scale (ESS).

Pregnancy tests will be conducted for females of childbearing potential.

General Statistical Methods and Types of Analyses

Analysis Populations

Three analysis populations will be used; modified intent-to-treat (mITT), intent-to-treat (ITT), and safety. The mITT population includes all patients randomized in the study who had at least one post-baseline efficacy assessment, and will be used for all analyses of efficacy. Patients in the mITT population will be included in the treatment group to which they were randomized regardless of treatment received. The ITT population includes all randomized patients in the study, and will be used for exploratory efficacy analyses. The safety population includes all patients who received study treatment, and will be used for all analyses of safety. Patients will be included in the treatment group based on the actual treatment received.

Efficacy Analyses

The primary efficacy analysis will be based on the SPCD method. The primary efficacy endpoint of the study is the change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) in the composite CMAI scores. A weighted test statistics combining treatment effects from Stage 1 and 2[3] will be used. The treatment effect in each stage will be estimated by using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data. Data from Stage 1 placebo non-responders who are re-randomized into Stage 2 will be used to estimate the Stage 2 treatment effect. Appropriate procedures to control type I error will be implemented and the details will be provided in the Statistical Analysis Plan (SAP).

Secondary efficacy endpoints include change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) for the following efficacy measures: mADCS-CGIC-Agitation, NPI-Agitation/Aggression domain score and Caregiver Distress score, NPI-Aberrant Motor Behavior domain, ZBI, NPI-Irritability/Lability domain, PGIC, DEMQOL, CSDD, RUD, total NPI, CGIS-Agitation, ADCS-CGIC-Overall, ADAS-cog; and change from Baseline to Week 12 for GMHR.

Safety Analyses

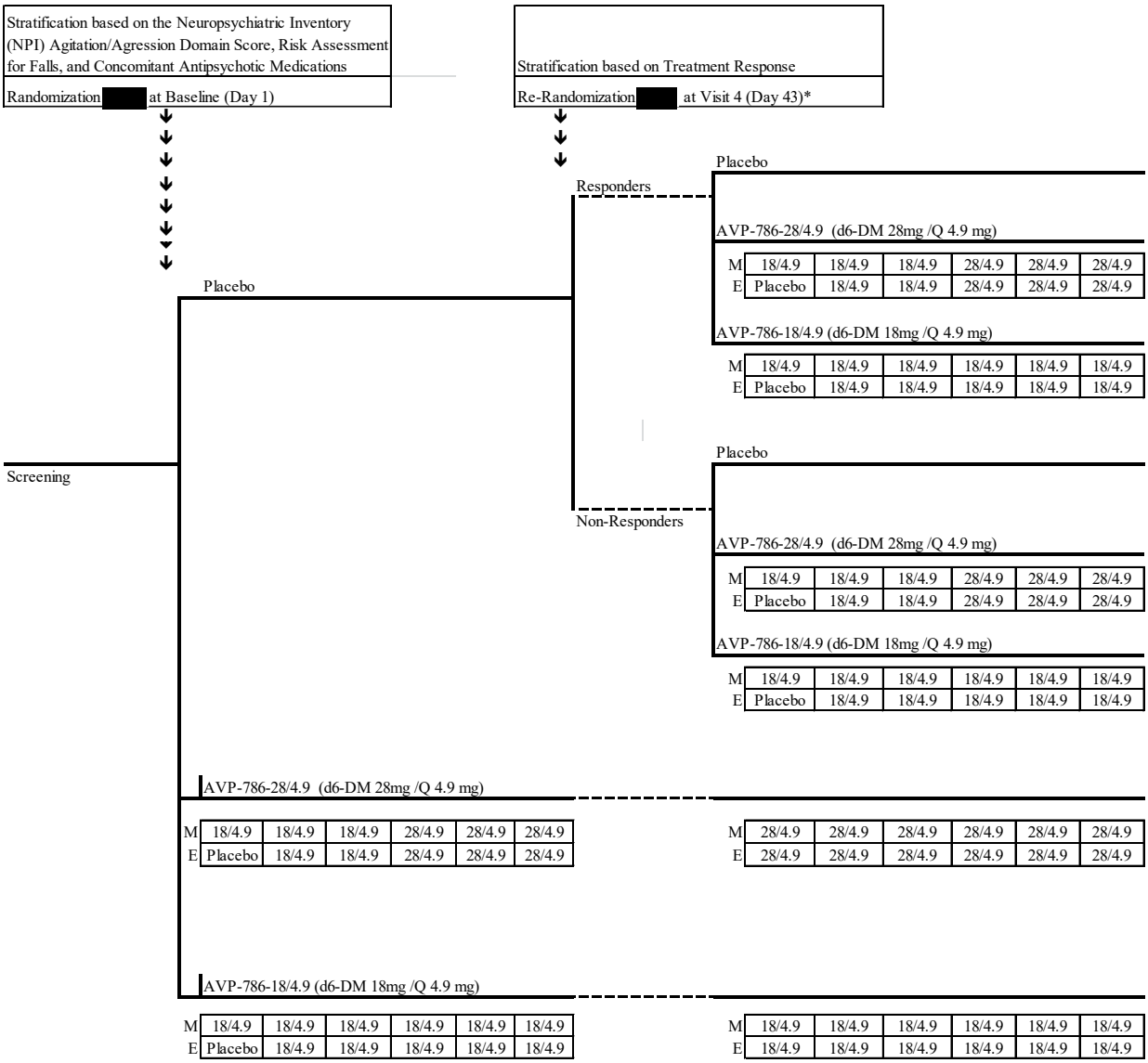
Safety measures will be summarized by Stage 1, Stage 2, and the 2 stages combined.

Sample Size Calculation

Power calculations were performed assuming a bivariate normal distribution for the primary efficacy endpoint with AVP-786-28/4.9 (high dose) versus placebo. [redacted] To control the

overall type I error rate at [redacted] level, the null hypothesis about the low dose AVP-786-18/4.9 will be tested only if the null hypothesis about the high dose is rejected.

Figure 1 Study Schematic



Period	Screening	Stage 1					
Visit	Screening	Baseline	Visit 2	Visit 2.1	Visit 3	Phone	
Day	-28	1	8		22	29	
Week	Week -4	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6

Stage 2					
Visit 4*			Visit 5	Phone	Visit 6
43			64	71	85
week 7	Week 8	Week 9	Week 10	Week 11	Week 12

Study medication (active or placebo) will be administered as capsules; 1 in the morning and 1 in the evening, approximately 12 hours apart.
M: Morning Dose (in mg d6-DM/mg Q)
E: Evening Dose (in mg d6-DM/mg Q)
*: Visit 4 (Day 43) stratification for the placebo arm is based on treatment response criteria followed by Re-Randomization [redacted].

Table 1 Schedule of Evaluations and Visits

Procedure	Visit:	Screening[1]	Baseline		Visit 2[1]	Visit 2.1[1]	Visit 3[1]	Phone Call[1,2]	Visit 4[1]		Visit 5[1]	Phone Call[1,2]	Visit 6[1] /ET[3,4]
	Study Day:	Day -28 to -1	Day 1		Day 8	Day 15	Day 22	Day 29	Day 43		Day 64	Day 71	Day 85
	End of Study Week:	Week -4 to -1			Week 1	Week 2	Week 3	Week 4	Week 6		Week 9	Week 10	Week 12
Sign informed consent forms		X											
Medical history		X											
Review of eligibility[5]		X	X										
Randomization			X										
Physical and neurological examination		X							X				X
Vital signs and weight		X	X[6]		X	X	X		X		X		X[6]
ADCS-CGIC-Overall			X[7]						X				X
CGIS-Agitation		X	X						X				X
mADCS-CGIC-Agitation			X[8]						X				X
Risk assessment for falls (worksheet and TUG test)		X							X[9]				X[9]
ECG		X[10]	X[11]	X[11]		X	X		X[11]	X[11]	X		X
AEs			X		X	X	X	X	X		X	X	X
Prior and concomitant: medications, nondrug therapies, and nonpharmacological interventions for agitation		X	X		X	X	X	X	X		X	X	X
MMSE		X	X						X				X
GMHR		X											X
CMAI		X	X		X	X	X		X		X		X
NPI		X[12]	X		X[12]	X[12]	X		X		X		X
CSDD		X							X				X

Procedure	Visit:	Screening[1]	Baseline		Visit 2[1]	Visit 2.1[1]	Visit 3[1]	Phone Call[1,2]	Visit 4[1]		Visit 5[1]	Phone Call[1,2]	Visit 6[1] /ET[3,4]
	Study Day:	Day -28 to -1	Day 1		Day 8	Day 15	Day 22	Day 29	Day 43		Day 64	Day 71	Day 85
	End of Study Week:	Week -4 to -1			Week 1	Week 2	Week 3	Week 4	Week 6		Week 9	Week 10	Week 12
ZBI			X						X				X
DEMQOL[13]			X						X				X
ADAS-cog[14]			X						X				X
PGIC[15]									X				X
RUD			X						X				X
ESS			X						X				X
S-STS		X	X		X	X	X		X		X		X
Administer morning dose of study medication in clinic				X	X[16]	X[16]	X			X	X		X
Chemistry, hematology, and urinalysis		X[17]					X			X	X		X[17]
Urine pregnancy test[18]		X	X							X			X
PK blood sample										X			X
[redacted]			X										
Dispense study drug and diary card			X				X			X	X		
Review and return unused study medication and diary card					X[16]	X[16]	X		X		X		X

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ADCS-CGIC-Overall = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Overall Clinical Status; AE = adverse event; CGIS-Agitation = Clinical Global Impression of Severity of Illness scale for Agitation; CMAI = Cohen-Mansfield Agitation Inventory; CSDD = The Cornell Scale for Depression in Dementia; DEMQOL = Dementia Quality of Life scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ET = early termination; GMHR = General Medical Health Rating; mADCS-CGIC-Agitation = modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PGIC = Patient Global Impression of Change rated by the caregiver; PK = pharmacokinetics; RUD = Resource Utilization in Dementia; S-STS = Sheehan Suicidality Tracking Scale; TUG = Timed Up and Go; ZBI = Zarit Burden Interview

Note: Whenever possible, each patient and caregiver should have the rating scales administered by the same raters throughout the study, for consistency of ratings. The following scales MUST be administered by the same rater at each visit: CMAI, NPI, mADCS-CGIC-Agitation, and CGIS-Agitation.

1 Study visits have a +/- 3-day window except Screening, Visit 2, and phone calls. Screening, Visit 2, and phone calls have a +3-day window. The screening period may be extended after discussion with and approval by the medical monitor.

2 Phone call should be made to patient/caregiver to collect adverse events and query on concomitant medication use

3 Early termination visit for patients who withdraw prior to study completion

4 Patients who terminate early from the study or who do not roll over to the extension study (Study 15-AVP-786-303) will receive a safety follow-up phone call 30 days after the last dose of study medication

5 For each patient, a protocol eligibility form will be completed

6 Weight should be measured only at the Baseline Visit and Visit 6

7 The ADCS-CGIC-Overall baseline evaluation worksheet should be completed to record baseline information for assessing change at Visits 4 and 6

8 The mADCS-CGIC-Agitation baseline evaluation worksheet should be completed to record baseline information for assessing change at Visits 4 and 6

9 Only the TUG test should be performed for risk assessment of falls at Visits 4 and 6

10 ECG should be performed in triplicate at the Screening visit

11 ECG to be performed pre-dose and post-dose

12 Only the Agitation/Aggression domain of the NPI should be performed at the Screening Visit,Visit 2, and Visit 2.1

13 The proxy version is to be rated by the caregiver. The non-proxy version is to be rated only by patients with an MMSE score of ≥ 10 at baseline

14 ADAS-cog is to be rated only by patients with an MMSE score of ≥ 10 at baseline

15 PGIC is to be rated by the caregiver

16 The morning dose of study medication can be administered at home if the visit will occur within 2 hours of dosing; the time of dosing should be noted by the patient/caregiver. The blister card and diary card should be returned to the patient/caregiver after reviewing for compliance.

17 Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) should be performed at the Screening Visit. Glycosylated hemoglobin (HbA1c) test should be performed at the Screening Visit and Visit 6.

18 Urine pregnancy test to be performed for females of child bearing potential only

1 BACKGROUND AND CLINICAL RATIONALE

[redacted]

1.1 [redacted]

[redacted]

[redacted]

1.2 [redacted]

[redacted]

2 STUDY OBJECTIVES

The objectives of the study are to evaluate the efficacy, safety, and tolerability of AVP-786 compared to placebo, for the treatment of agitation in patients with dementia of the Alzheimer's type.

3 STUDY DESIGN

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, SPCD study of 12-week treatment duration. The treatment period is divided equally into 2 stages of 6 weeks each, Stage 1 and Stage 2.

Sequence	Screening	Stage 1	Stage 2
Study Day	Day -28 to -1	Day 1 to 42	Day 43 to 85

There will be 8 scheduled clinic visits including a screening visit, and 2 safety follow-up phone visits in this study. Patients will attend clinic visits at Screening, Baseline (Day 1), and on Days 8 (Visit 2/Week 1), 15 (Visit 2.1/Week 2), 22 (Visit 3/Week 3), 43 (Visit 4/Week 6), 64 (Visit 5/Week 9), and 85 (Visit 6/Week 12). Safety follow-up phone calls will be made on Days 29 (Week 4) and 71 (Week 10). A schematic of the study design is depicted in Figure 1.

Approximately 380 patients will be enrolled at approximately 60 centers in North America.

Eligible patients will be randomly assigned at the Baseline visit to receive AVP-786 or matching placebo. Study medication will be administered orally twice daily from Day 1 through Day 85. Patients (or caregivers) will self-administer study medication on all study days except on the clinic-visit days when patients will be administered their morning dose of study medication at the clinic in the presence of site personnel, regardless of the time of day. Screening will occur within 4 weeks prior to randomization.

Stage 1

Following screening procedures for assessment of inclusion and exclusion criteria, eligible patients will be randomized into the study in a [redacted] (active:active:placebo) ratio to receive either AVP-786-28/4.9 capsules, AVP-786-18/4.9 capsules, or matching placebo capsules. The randomization will be stratified by the NPI Agitation/Aggression domain score (≤ 6 vs. > 6), risk assessment for falls (normal/mild vs. moderate/severe), and concomitant use of antipsychotic medications (yes vs. no). Study medication (active or placebo) will be administered orally BID (1 capsule in the morning and 1 capsule in the evening approximately 12 hours apart) throughout the treatment period.

- Patients randomized to receive AVP-786-28/4.9 will start with AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of the study. From Day 8, patients will receive AVP-786-18/4.9 BID for 14 days. From Day 22, patients will receive AVP-786-28/4.9 BID for the remaining 3-week duration of Stage 1.
- Patients randomized to receive AVP-786-18/4.9 will start with AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of the study. From Day 8, patients will receive AVP-786-18/4.9 BID for the remaining 5-week duration of Stage 1.
- Patients randomized to receive placebo will be dosed with placebo BID during Stage 1.

Stage 2:

Patients who complete Stage 1 are eligible to participate in the 6-week Stage 2 of the study. In Stage 2, patients will be assigned to study treatment as follows:

- Patients who received AVP-786 in Stage 1 will continue to receive the same dose of AVP-786 BID (either AVP-786-28/4.9 or AVP-786-18/4.9) for the entire 6-week duration of Stage 2.
- Patients who received placebo in Stage 1 will be further stratified into two sub-groups ("responders" and "non-responders") on Visit 4 (Day 43) based on their treatment response. Patients will be considered "responders" if [redacted] will be considered "non-responders". Patients within each placebo sub-group will be re-randomized in a [redacted] (active:active:placebo) ratio to receive either AVP-786-28/4.9 capsules, AVP-786-18/4.9 capsules, or matching placebo capsules.
    - Patients who are re-randomized to placebo will continue to receive placebo BID for the entire 6-week duration of Stage 2.
    - Patients who are re-randomized to AVP-786-28/4.9 will receive AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of Stage 2 (Days 43-49). From Day 50, patients will receive AVP-786-18/4.9 BID for 14 days (Days 50-63). From Day 64, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of the study.
    - Patients who are re-randomized to AVP-786-18/4.9 will receive AVP-786-18/4.9 once a day in the morning and placebo in the evening for the first 7 days of Stage 2 (Days 43-49). From Day 50, patients will receive AVP-786-18/4.9 BID for the remaining 5 weeks of the study.

4 STUDY POPULATION

Patients enrolled in this study must have a diagnosis of probable AD and must present with clinically meaningful, moderate/severe agitation secondary to AD.

The diagnosis of probable AD will be based on the '2011 Diagnostic Guidelines for Alzheimer's Disease' issued by the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups.[1] These new criteria were developed based on the review of the NINCDS–ADRDA criteria.[22] Neither AD nor agitation should be explainable by delirium, substance use and/or major psychiatric disorders.

The provisional consensus definition of agitation in patients with cognitive disorders developed by the Agitation Definition Work Group (ADWG) from the International Psychogeriatric Association (IPA)[2], will be used for selecting study patients. This proposed definition is limited to patients with cognitive impairment and requires: (a) evidence of emotional distress; (b) one of 3 observable types of behaviors-excessive motor activity, verbal aggression, or physical aggression; (c) that the behavior causes excess disability; and (d) that the behaviors cannot be solely attributable to a suboptimal care environment or other disorder such as a psychiatric illness, a medical illness, or effects of a substance.

Eligible patients must have agitation (persistent or frequently recurrent) at the time of study screening and for at least 2 weeks prior to randomization and the agitation symptoms must be severe enough such that they interfere with daily routine and cause distress to the patient and caregiver for which a prescription medication is deemed indicated, in the opinion of the treating physician.

Agitation will further be assessed using the CGIS-Agitation scale (0-7). A score of ≥ 4 (moderately ill) at screening and baseline are required for study participation.

Eligible patients are to have otherwise acceptable and stable general health as required by the study protocol, and documented by medical history, physical examination, electrocardiogram (ECG), and clinical laboratory examinations.

Eligible patients must have a caregiver who is able and willing to comply with all required study procedures, ensuring that the patient attends all study visits and takes the study medication as instructed. Caregivers will also be instructed to keep a study diary, to report any changes in patient's status, including adverse events, standard of care setting (e.g., becoming a resident in an assisted living facility), and to provide their impression and assessment regarding the investigational treatment. In order to qualify as a reliable informant (i.e., caregiver) capable of assessing changes in the patient's condition during this study, the individual must spend a minimum of 2 hours per day for 4 days per week with the study patient.

4.1 Inclusion Criteria

1. Males and females 50 to 90 years of age, inclusive at the time of informed consent.

2. Diagnosis of probable AD according to the 2011 NIA-AA working groups criteria. Either out-patients or residents of an assisted-living facility or a skilled nursing home.

3. The patient has clinically significant, moderate/severe agitation at the time of screening and for at least 2 weeks prior to randomization, that interferes with daily routine and for which a prescription medication is indicated, in the opinion of the investigator.
4. The diagnosis of agitation must meet the IPA provisional definition of agitation.
5. CGIS-Agitation score is ≥ 4 (moderately ill) at Screening and Baseline.
6. MMSE score is between 6 and 26 (inclusive) at Screening and Baseline.
7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

15. [redacted]

16. Caregiver must be willing and able to comply with study procedures, including not administering any prohibited medications during the course of the study.

17. [redacted]

4.2 Exclusion Criteria

1. Caregiver is unwilling or unable, in the opinion of the investigator, to comply with study instructions.

2. Patient has dementia predominantly of non-Alzheimer's type (e.g., vascular dementia, frontotemporal dementia, Parkinson's disease, substance-induced dementia).

3. [redacted]

4. Patients with myasthenia gravis [redacted]

5. [redacted]

   a. [redacted]

   b. [redacted]

6. [redacted].

7. [redacted]

8. [redacted]

9. [redacted]

10. [redacted]

11. Patients with co-existent clinically significant or unstable systemic diseases that could confound the interpretation of the safety results of the study (e.g., malignancy [except skin basal-cell carcinoma or untreated prostate cancer], poorly controlled diabetes, poorly controlled hypertension, unstable pulmonary, renal or hepatic disease, unstable ischemic cardiac disease, dilated cardiomyopathy, or unstable valvular heart disease). [redacted]
12. [redacted]
13. [redacted]
14. [redacted]
15. [redacted]
16. [redacted]

4.3 Patient Withdrawal From the Study

Patients and caregivers will be advised verbally and in the written ICF that they have the right to withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. The investigator or sponsor may discontinue a patient from the study in the event of an intercurrent illness, adverse event, other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation, non-compliance, protocol violation, or other administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Regardless of the circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the caregiver return all unused investigational product (IP), and follow-up with the patient regarding any unresolved adverse events.

[redacted]

Patients who withdraw prior to study completion will be asked to return to the clinic to complete the Visit 6 (end of study) assessments.

If the patient withdraws from the study, and consent is withdrawn by the caregiver and/or patient's representative for disclosure of future information, no further evaluations should be performed, and no

additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Patients who withdraw from the study will not be replaced.

5 STUDY TREATMENTS

5.1 Treatments Administered

5.1.1 Description of Study Medications

Clinical study medication will be provided as hard, printed, [redacted], gelatin capsules [redacted]. Each capsule of the study medication contains 1 of the following:

- 28 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-28/4.9
- 18 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-18/4.9
- AVP-786 placebo

Drug supplies will be provided to the site in double-blind, individual, pre-labeled blister cards.

All medication used in this study will be prepared, packaged, and labeled in accordance with Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

5.1.2 Composition of AVP-786

The qualitative and quantitative compositions of the 2 doses of the IP and the placebo are listed in Table 2.

Table 2 Composition of Investigational Product

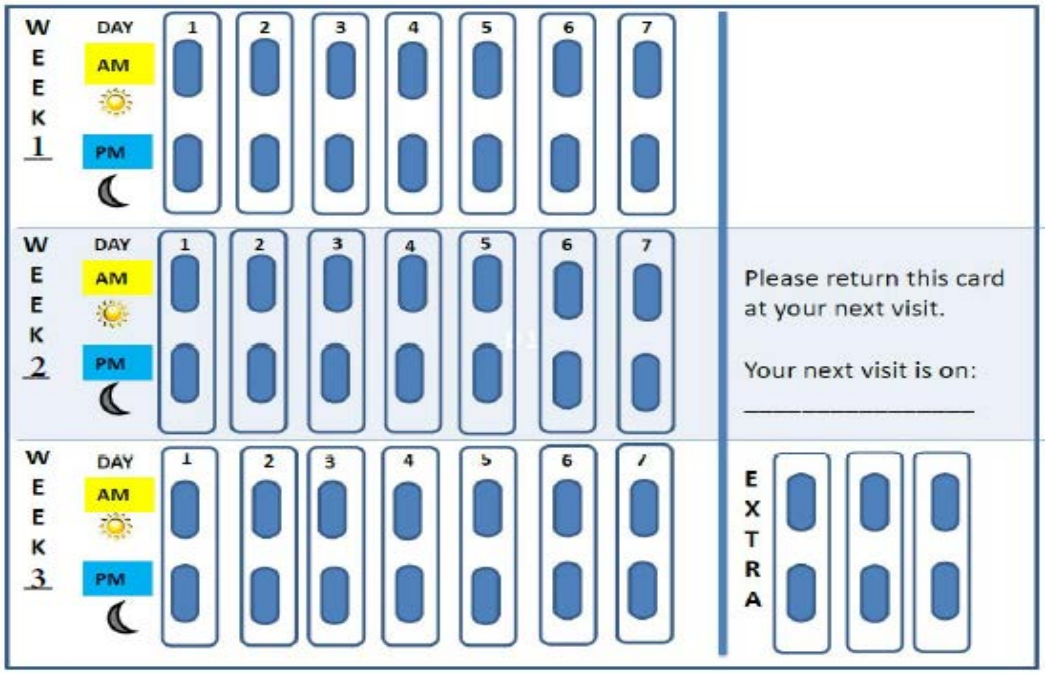
Ingredient (amounts in mg)	AVP-786-28/4.9	AVP-786-18/4.9	AVP-786 Placebo
d6-Dextromethorphan hydrobromide	28.00	18.00	0
Quinidine sulfate USP, EP	4.90	4.90	0
Croscarmellose sodium NF	[redacted]	[redacted]	[redacted]
Microcrystalline cellulose NF			
Colloidal silicone dioxide NF			
Magnesium stearate NF			
Total			
[redacted] **capsules (average weight)**			
Total			

EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary

5.1.3 Packaging

The investigators will be supplied with pre-labeled, individually pre-packaged and tamper-proof sealed blister cards. Each panel of the blister card (1 week of study medication) consists of 2 rows of blister strips, one row for the morning dose and one row for the evening dose (Figure 2). Each blister card will contain 3 panels, providing sufficient study medication for 3 weeks of treatment and an additional 3 days of supply (total of 48 capsules).

Figure 2 Sample Configuration of Investigational Product Blister Card



5.1.4 Labeling

All labels will contain protocol number, product name, blister card number, an investigational drug warning, and dosage instructions to take 1 capsule in the morning and 1 capsule in the evening, storage conditions, and company name. The blister card label will consist of 2 panels, with 1 detachable panel that will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the card label to record Patient Number, the Visit Week, and Dispensing Date. All investigational product labels comply with all applicable federal and local regulations.

5.1.5 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with label requirements in a secure place and kept at room temperature; 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F-86°F).

5.1.6 Study Medication Administration

All patients will receive study medication according to the blister card numbers assigned by an interactive web response system (IWRS) randomization scheme. Designated staff at each site will dispense study medication. Study medication should be administered to the patient by the caregiver, family member, nursing home staff, or self-administered with supervision, except on the applicable clinic visit days when patients will be administered their dose of study medication at the clinic in the presence of site personnel, regardless of the time of day. For Visits 2 (Day 8) and 2.1 (Day 15), the morning dose of study medication can be administered at home if the visit will occur within 2 hours of dosing; the time of dosing should be noted by the patient/caregiver. Patients and caregivers will be instructed that the patient should take the study medication orally with water approximately every 12 hours ± 4 hours (morning and evening). The time the patient takes each dose of medication should be recorded in the diary card. Patient's missed doses will be noted in the electronic case report form (eCRF).

All study medication will be supplied and administered in a double-blind manner throughout the entire duration of the study.

5.2 Accountability of Study Supplies

5.2.1 Receipt of Supplies

The investigator is responsible for maintaining an inventory of each shipment of IP received and comparing it with the accompanying Drug Accountability Report/Material Shipping Form. The investigator will verify the accuracy of the information on the form, sign and date it, and return the form to the sponsor or its representative. All IP supplied is for use only in this study and should not be used for any other purpose. All blister card material ID numbers will also be recorded and tracked at the site using the Drug Accountability Log.

5.2.2 Record of Dispensing

Accurate recording of all IP dispensing for individual patients will be made in the appropriate section of the patient's eCRF. This eCRF will contain the following information: (i) patient number to whom the drug was dispensed; (ii) the date(s) and quantity of the drug dispensed to the patient; and (iii) the blister card material ID number assigned to the patient via IWRS.

Additionally, the detachable panel of the two-panel label on each blister card will be removed and affixed to the study medication Dispensing Log page at the time of dispensing. Space is provided on both panels of the blister card label to record patient number, the visit week and dispensing date.

5.2.3 Unused Supplies

At the end of the study, all unused investigational supplies must be inventoried on the Drug Accountability Log and returned to the sponsor or its representative, along with a completed and signed Drug Accountability Report/Material Shipping Form. If any study medication is lost or damaged, it should be indicated on the form.

5.3 Methods of Assigning Patients to Treatment Groups

5.3.1 Randomization

Upon entry into the study (after ICF is signed at screening), all patients will be assigned a [redacted] patient number. [redacted]. This [redacted] number is the main identifier for patients.

Stage 1

Eligible patients will be randomized to receive AVP-786-28/4.9 capsules, AVP-786-18/4.9 capsules, or matching placebo capsules in a [redacted] ratio on Day 1 (Baseline, Stage 1) in a double-blind manner according to a randomization scheme devised by Avanir or its representative and managed within an IWRS. The randomization will be stratified by NPI Agitation/Aggression domain score (≤ 6 vs. > 6), risk assessment for falls (normal/mild vs. moderate/severe), and concomitant use of antipsychotic medications (yes vs. no). Blocked randomization is used to ensure treatment balance in each stratum.

Stage 2

Re-randomization will occur for patients who were assigned to placebo in Stage 1. The patient number will not be re-assigned; it will remain the same in both stages of the study.

- Patients who receive placebo in Stage 1 will be further stratified into two sub-groups ("responders" and "non-responders") based on their treatment responses. Patients will be considered "responders" if [redacted] Patients who do not meet [redacted] will be considered "non-responders". Patients within each placebo sub-group will be re-randomized in a [redacted] (active:active:placebo) ratio to receive either AVP-786-18/4.9, AVP-786-28/4.9 capsules, or matching placebo capsules.
- Patients who receive placebo and who drop out early in Stage 1 will also be assigned a re-randomization treatment in the same manner as the other placebo patients. Their "responders" and "non-responders" status will be based on their treatment responses using measurements at their early termination visit.
- Patients who receive AVP-786 in Stage 1 will not be re-randomized and will continue to receive the same dose of AVP-786 BID (either AVP-786-18/4.9 or AVP-786-28/4.9) for the entire 6-week duration of Stage 2.

5.3.2 Blinding/Masking

Blinding will be maintained by providing capsules of the 2 doses of AVP-786 and placebo that are identical in appearance. The sponsor, patients, caregivers, investigators, or other study personnel will not be aware of a patient's treatment assignment. In the event that it becomes medically necessary to identify which treatment a patient has received, the blind can be broken. In that event, the investigator is to contact Avanir's medical monitor or representative to request the unmasking of a patient. The IWRS manager is not required to be blinded and he or she will have access to the study medication list and the randomization code.

5.4 Patient Compliance

Patients and caregivers will be instructed to bring any unused study medication and empty blister cards to the clinic on Days 8, 15, 22, 43, 64, and 85 (Visits 2 – 6). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses (compliance range 80-120%). Caregivers will be provided with diary cards and will be instructed to record daily the number of capsules taken and the time of administration. Diary cards will be reviewed for compliance and collected on Days 22, 43, 64, and 85 (Visits 3 – 6), or at the time of early study discontinuation. Patients should bring their Diary Card on Day 8 (Visit 2) and Day 15 (Visit 2.1) for compliance review; the Diary Card will be returned to the patient and collected at the next visit.

5.5 [redacted]

[redacted]

5.5.1 [redacted]

[redacted]

[redacted]

5.5.2 Rescue Medication for the Symptoms of Agitation

Patients will be allowed to receive oral lorazepam as rescue medication for the short-term treatment of symptoms of agitation if deemed necessary by the investigator. Lorazepam will be administered in a dose up to 1.5 mg/day and not to exceed 3 days in a 7-day period. Caregivers must record concomitant use of lorazepam in the diary and must be reminded of the potential increase in the risk of falling by benzodiazepines.

5.5.3 [redacted]

[redacted]

5.5.4 Nondrug Therapies

Information on any prior and concomitant nondrug therapies will be recorded.

5.5.5 Nonpharmacological Interventions for the Treatment of Agitation

Information on any nonpharmacological interventions for the treatment of agitation that were used prior to enrollment or used concomitantly during the study will be recorded

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Efficacy

Samples of all the scales and questionnaires to be used during the study are attached as Appendices. Whenever possible, each patient and caregiver should have the rating scales administered by the same raters throughout the study, for consistency of ratings. The following scales MUST be administered by the same rater at each visit: CMAI, NPI, mADCS-CGIC-Agitation, and CGIS-Agitation.

6.1.1 Cohen-Mansfield Agitation Inventory (CMAI)

The CMAI will be used as the primary efficacy measure in this study. The CMAI (Appendix 2) is used to assess the frequency of manifestations of agitated behaviors in elderly persons. It consists of 29 agitated behaviors [redacted]. Each of the 29 items is rated on a 7-point scale of frequency (1 = never, 2 = less than once a week but still occurring, 3 = once or twice a week, 4 = several times a week, 5 = once or twice a day, 6 = several times a day, 7 = several times an hour). The ratings are based on the 2 weeks preceding assessment of CMAI.

The CMAI (long-form version, Appendix 2) will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Day 8 (Visit 2), Day 15 (Visit 2.1), Day 22 (Visit 3), Day 43 (Visit 4), Day 64 (Visit 5), and Day 85 (Visit 6). The CMAI must be administered by the same rater at each visit.

6.1.2 Neuropsychiatric Inventory (NPI)

The NPI [redacted] is a validated clinical instrument for evaluating psychopathology in a variety of disease settings, including dementia. The NPI is a retrospective caregiver-informant interview covering 12 neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavioral disorders, and appetite/eating disorders. The scripted NPI interview includes a compound screening question for each symptom domain, followed by a list of interrogatives about domain-specific behaviors that is administered when a positive response to a screening question is elicited. Neuropsychiatric manifestations within a domain are collectively rated by the caregiver in terms of both frequency (1 to 4) and severity (1 to 3), yielding a composite symptom domain score (frequency x severity). Frequency and severity rating scales have defined anchor points to enhance the reliability of caregiver responses. Caregiver distress is rated for each positive neuropsychiatric symptom domain on a scale anchored by scores of 0 (not distressing at all) to 5 (extremely distressing). The NPI will be administered to the patient's caregiver at Baseline (Day 1), Day 22 (Visit 3), Day 43 (Visit 4), Day 64 (Visit 5), and Day 85 (Visit 6). The Agitation/Aggression

domain of the NPI will be administered to the patient's caregiver at Screening (Day -28 to Day -1),Day 8 (Visit 2) and Day 15 (Visit 2.1). The NPI must be administered by the same rater at each visit.

The NPI domains are generally evaluated for behaviors within the preceding 4 weeks but can be modified according to the needs of the study. In this study, the recall period will be 2 weeks for all the visits

The NPI nursing-home version (NPI-NH) will be used for patients from in-patient or assisted living facilities. The questions in the NPI-NH were rephrased for professional caregivers who may not know the patients prior to the onset of illness; however, the overall instrument domains and scoring is identical to the NPI except for the caregiver distress section which is replaced with occupational disruptiveness in the NPI-NH version.

The Agitation/Aggression domain in the NPI will be assessed as part of the total NPI as described above and the composite score obtained for this category will be recorded separately at Baseline (Day 1), Day 22 (Visit 3), Day 43 (Visit 4), Day 64 (Visit 5), and Day 85 (Visit 6).

6.1.3 Clinical Global Impression of Severity of Illness-Agitation (CGIS-Agitation)

The CGIS (Appendix 4) is an observer-rated scale that measures illness severity and is one of the most widely used brief assessment tools in psychiatry research.

The Early Clinical Drug Evaluation Unit (ECDEU) version of the CGIS is the most widely used format of this validated tool, and asks that the clinician rate the patient relative to their past experience with other patients with the same diagnosis, with or without collateral information. The CGIS has proved to be a robust measure of efficacy in many clinical drug trials[26–30] and is easy and quick to administer, provided that the clinician knows the patient well.[31]

Reliability and validity of CGI have been tested in multiple studies, including patients with dementia, schizophrenia and affective disorders. Overall, CGI showed high correlation (r: ~90%) with other assessment instruments and it has also shown positive significant relationships and concurrent validity with other clinician's rating. In addition, the scale has good sensitivity to change over time.[32–34]

The CGIS is a 7-point (1-7) scale (1 = normal, not at all ill; 7 = among the most extremely ill patients) and assesses severity of agitation in this study. The CGIS-Agitation will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6). The CGIS-Agitation must be administered by the same rater at each visit.

6.1.4 Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change Rating (ADCS-CGIC-Overall)

The intent of the ADCS version of the CGIC (Appendix 5) (herein referred to as ADCS-CGIC-Overall), is to provide a means to reliably assess change from a baseline level of global function within the timeframe of a clinical trial. Unlike a targeted symptom scale, the ADCS-CGIC-Overall takes into account a patient's overall function in the cognitive, behavioral and functional activity domains. Relying

on information gathered through a semi-structured interview of the patient and caregiver, the ADCS-CGIC-Overall focuses on clinician's observations of change in the patient's cognitive, functional, and behavioral performance since the beginning of a trial. Once the baseline level of severity is established, the change score at the follow-up visits is based on information gathered from the patient and caregiver interviews. The ADCS-CGIC-Overall is rated as: marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, or marked worsening.

The baseline ADCS-CGIC-Overall evaluation will be conducted at the Baseline (Day 1) visit. The ADCS-CGIC-Overall will be assessed at Day 43 (Visit 4) and Day 85 (Visit 6) for change in Overall Clinical Status. At Day 43 (Visit 4), change from the Baseline visit (Day 1) will be assessed. At Day 85 (Visit 6), change from Day 43 (Visit 4) and change from the Baseline visit (Day 1) will be assessed.

6.1.5 Modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change Rating (mADCS-CGIC-Agitation)

The standard ADCS-CGIC instrument was modified to better assess aspects relevant to studying agitation in AD (mADCS-CGIC-Agitation). The mADCS-CGIC-Agitation (Appendix 6) contains questions related to agitation and an assessment of the Clinician's Impression of Change focused specifically on agitation. It was originally designed for the Citalopram study for Agitation in Alzheimer's disease (CitAD)[35,36] and utilizes a semi-structured interview of both patient and caregiver to determine a baseline level of severity for agitation. Subsequent evaluations assess for change from baseline and also utilize the semi-structured agitation interview of both patient and caregiver.

The baseline mADCS-CGIC-Agitation evaluation will be conducted at the Baseline (Day 1) visit. The mADCS-CGIC-Agitation will be assessed at Day 43 (Visit 4) and Day 85 (Visit 6) for change in agitation syndrome. At Day 43 (Visit 4), change from the Baseline visit (Day 1) will be assessed. At Day 85 (Visit 6), change from Day 43 (Visit 4) and change from the Baseline visit (Day 1) will be assessed. The mADCS-CGIC-Agitation must be administered by the same rater at each visit.

6.1.6 Zarit Burden Interview (ZBI)

The ZBI (Appendix 7) is a 22-item scale used to assess the impact of patient's disabilities on the caregiver's life. It is designed to reflect the burden experienced by caregivers of dementia patients and can either be completed by the caregiver or administered as an interview.[37] It is the most commonly used scale for measuring burden in caregivers' of patients with dementia and also other illnesses.[38] The ZBI has been shown to have high internal-reliability with an estimated Cronbach's alpha at 0.88 and 0.91, and test-retest reliability at 0.71. Validity has been estimated by correlating the total score with a single global rating of burden (r = 0.71).[39] For each item of the scale, the caregiver has to indicate how often they felt that way (never, rarely, sometimes, quite frequently, or nearly always). The score ranges from 0 to 88 and is determined by adding the numbered responses of the individual items. Higher scores indicate greater caregiver distress.

The ZBI will be assessed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.1.7 Patient Global Impression of Change (PGIC)

The PGIC (Appendix 8) is a 7-point (1-7) scale used to assess treatment response, and it is rated as: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.[31]

The PGIC will be assessed and rated by the patient's caregiver at Day 43 (Visit 4) and Day 85 (Visit 6) and will focus on the patient's agitation.

6.1.8 Dementia Quality of Life (DEMQOL)

The DEMQOL (Appendix 9) is a scale used to evaluate health related quality of life in patients with dementia and their caregivers.[40] There are 2 versions of the DEMQOL, a 28-item version (rated by patient) and a 31-item version (DEMQOL-proxy, rated by caregiver). Both the 28-item and 31-item version are recommended to be used for evaluating patients (and their caregivers) with mild to moderate dementia (MMSE ≥10). For patients with severe dementia, only the DEMQOL-proxy (administered to caregiver) is used.

The DEMQOL-proxy (and DEMQOL for patients with MMSE ≥10 at the Baseline visit) will be assessed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.1.9 Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-cog)

The ADAS (Appendix 10) was designed to evaluate the cognitive and non-cognitive behavioral dysfunction characteristics of patients with AD.[41] The cognitive sub-scale (ADAS-cog) consists of 11 subsets related to memory, praxis, and language. The ADAS-cog takes about 30 to 45 minutes to complete.

The ADAS-cog will be assessed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6) for patients with an MMSE score of ≥ 10 at the Baseline visit.

6.1.10 Cornell Scale for Depression in Dementia (CSDD)

The CSDD (Appendix 11) was specifically developed to assess signs and symptoms of major depression in patients with dementia.[42] Because some of these patients may give unreliable reports, the CSDD uses a comprehensive interviewing approach that derives information from the patient and the caregiver. Information is elicited through two semi-structured interviews; an interview with a caregiver and an interview with the patient. The interviews focus on depressive symptoms and signs occurring during the week preceding the assessment. The CSDD takes approximately 20 minutes to administer.

Each item is rated for severity on a scale of 0-2 (0 = absent, 1 = mild or intermittent, 2 = severe). The item scores are added. Scores above 10 indicate a probable major depression, scores above 18 indicate a

definite major depression, and scores below 6 as a rule are associated with absence of significant depressive symptoms.

The CSDD will be assessed at Screening (Day -28 to Day -1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.1.11 Resource Utilization in Dementia (RUD)

The RUD (Appendix 12) is used to calculate healthcare costs associated with dementia.[43] It evaluates dementia patients' utilization of formal and informal healthcare resources, including hospitalizations and doctor visits, living assistance, and time spent by non-professional caregivers. Within the context of clinical trials, the RUD is often used to determine the cost effectiveness of new pharmaceutical treatments.[44]

The RUD is administered as a semi-structured interview with the patient's primary caregiver, and contains 2 sections; one focusing on caregiver impact (loss of work and leisure time incurred by caregiver) and the other focusing on the patient's use of healthcare resources. The total healthcare costs associated with the patient's dementia can be estimated by multiplying the number of units used (e.g., hours of caregiver time, visits to doctors, nights in accommodation) by the corresponding unit price vector.

The RUD will be assessed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.1.12 General Medical Health Rating (GMHR)

The GMHR (Appendix 13) is a global clinical rating for medical health, designed to quantify in a single number (1 to 4) the severity of general co-morbidity in a patient with dementia.[45] A rating of 1 = poor, 2 = fair, 3 = good and 4 = excellent to very good.

The GMHR will be assessed at Screening (Day -28 to Day -1) and Day 85 (Visit 6).

6.2 Pharmacokinetics (PK)

At Day 43 (Visit 4) and Day 85 (Visit 6), patients will have a blood sample collected between 0 to 3 hours after the morning dose of study medication for analysis of plasma levels of d6-DM, d6-DM metabolites and Q. The time when the patient was administered the dose of study medication and the time of the blood draw will be recorded on the eCRF. Plasma samples will be separated by centrifugation and then frozen at -20° C until assayed at the analytical unit.

6.3 Safety

6.3.1 Adverse Events

6.3.1.1 Definitions

An adverse event (AE) is any untoward medical occurrence or unintended change (including physical, psychological, or behavioral) from the time ICF is signed, including inter-current illness, which occurs during the course of a clinical trial after treatment has started, whether considered related to treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Changes associated with normal growth and development that do not vary in frequency or magnitude from that ordinarily anticipated clinically are not AEs (e.g., onset of menstruation occurring at a physiologically appropriate time).

Clinical AEs should be described by diagnosis and not by symptoms when possible (e.g., cold, seasonal allergies, instead of "runny nose").

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than known therapeutic doses. It must be reported irrespective of outcome even if toxic effects were not observed.

AEs will be graded on a 3-point scale and reported in detail as indicated on the eCRF:

Mild: easily tolerated, causing minimal discomfort and not interfering with normal everyday activities

Moderate: sufficiently discomforting to interfere with normal everyday activities

Severe: incapacitating and/or preventing normal everyday activities

The relationship of each AE to study medication should be determined by the investigator using the following explanations:

Not related: the event is clearly related to other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

Unlikely related: the event is most likely produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient; and does not follow a known response pattern to the study medication

Possibly related: the event follows a reasonable temporal sequence from the time of drug administration; and/or follows a known response pattern to the study medication; but could have been produced by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

Related: the event follows a reasonable temporal sequence from the time of drug administration; and follows a known response pattern to the study medication;

and cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient

6.3.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening experience (one that places the patient, in the view of the initial reporter, at immediate risk of death from the AE as it occurred, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
3. Persistent or significant disability/incapacity (disability is a substantial disruption of a person's ability to conduct normal life functions)
4. In-patient hospitalization or prolongation of hospitalization
5. Congenital anomaly/birth defect

Important medical events that may not result in death, or be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in the definition.

The terms "cancer" and "overdose" are not considered to be SAEs, but if a patient experiences cancer or overdose, they are still reportable as AEs.

Pregnancy is not considered to be an AE or an SAE, unless a complication occurs that meets the requirements for an AE or SAE, but must be reported on a pregnancy report form. Women who are pregnant or likely to become pregnant are excluded from this study. In the event a patient becomes pregnant during the study, study medication must be discontinued, a pregnancy report form must be completed to capture potential drug exposure during pregnancy, and the pregnancy must be reported within 24 hours of notice. Any pregnant patient must be followed until the outcome of her pregnancy is known (i.e., normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). The pregnancy (i.e., the mother and the fetus) must be followed up through delivery with regard to outcome.

A pregnancy report form must also be completed in the event that a female partner of a male patient becomes pregnant within 30 days after his last dose of study medication or study completion, whichever is greater.

The term 'severe' is a measure of intensity; thus a severe AE is not necessarily serious. For example, nausea of several hours duration may be rated as severe, but may not be clinically serious.

6.3.1.3 Reporting

Caregivers will be queried regarding AEs at each clinic visit after the screening visit (Baseline [Day 1], Days 8, 15, 22, 43, 64, and 85 [Visits 2-6]) and at safety follow-up phone calls at Days 29 and 71. The investigator will assess and record all reported AEs. Any AE newly reported after receiving the last dose of study medication will be followed up until 30 days.

A death occurring during the study, or which comes to the attention of the investigator within 30 days after stopping the treatment whether considered treatment-related or not, must be reported to the sponsor.

For all SAEs, including an abnormal laboratory test value, the investigator should consult with Avanir's MM or designated representative as needed and report any SAE by fax/email form no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to test drug, action taken regarding test drug, treatment required, and outcome to date. These details must be recorded on the clinical study AE form that is provided. This form should be transmitted by fax and the details given by telephone to the contact numbers below.

SAE reporting by FAX or e-mail correspondence
FAX: [redacted]
E-mail: [redacted]

SAE hotline (24-hour/7 days a week)
Phone: [redacted]

Such preliminary reports will be followed by detailed descriptions later, which may include copies of hospital case reports, autopsy reports, and other related documents when requested.

The Institutional Review Board/Ethics Committee (IRB/EC) will be notified of such an event in writing as soon as is practical in compliance with federal and local regulations.

6.3.1.4 Procedures to be followed in the Event of Abnormal Test Values

Any patients with clinically significant abnormal laboratory test results may be required by the MM to have a repeat test 1 week later or earlier, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry.

6.3.2 Physical and Neurological Examinations

Physical and neurological examinations will be performed at Screening (Day -28 to Day -1), Day 43 (Visit 4), and Day 85 (Visit 6). The physical examination will include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems. The neurological examination will include assessments of mental status, cranial nerves, motor system, reflexes, coordination, gait and station, and sensory system. The physical and neurological examinations should be performed by the same person each time, whenever possible.

Physical and neurological examination abnormalities determined by the investigator to be clinically significant at Screening should be recorded as medical history.

Any clinically significant changes in physical and neurological examination findings from the screening examination should be recorded as AEs.

6.3.3 Vital Signs

Orthostatic blood pressure (BP) and heart rate (HR) measurements will be performed at all clinic visits. Supine BP and HR will be measured after a patient has rested for at least 5 minutes in the supine position. Each measurement will be taken twice in the same position and recorded. After the measurement of supine BP and HR, the patient will stand still for up to 3 minutes and a single measurement of standing BP and HR will be recorded within these 3 minutes of standing.

Respiratory rate (breaths/minute) and body temperature (ºF) will be assessed at all clinic visits. Weight will be recorded at Baseline (Day 1) and Day 85 (Visit 6).

6.3.4 Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at Screening (Day -28 to Day -1), Day 22 (Visit 3), Day 43 (Visit 4), Day 64 (Visit 5), and Day 85 (Visit 6):

- Blood chemistry (calcium, magnesium, phosphorus, glucose, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen [BUN], serum creatinine, uric acid, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT], alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT], creatine kinase [CK], gamma-glutamyl transferase [GGT], triglycerides, total protein, and total cholesterol)
- Hematology (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count, neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, platelet count, and morphology)
- Urinalysis (pH, specific gravity, protein, glucose, ketones, blood, leucocyte esterase, nitrates, and microscopic appearance)
- Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) at Screening visit only
- Glycosylated hemoglobin (HbA1c) test at the Screening visit and Visit 6 only

Any patients with clinically significant abnormal laboratory test results may be required by the MM to have a repeat test 1 week later or earlier, if medically indicated. Clinically significant laboratory abnormalities may be a basis for exclusion from study entry.

6.3.5 Pregnancy Tests

Urine pregnancy tests are to be performed for females of childbearing potential at Screening (Day -28 to Day -1), Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

All female patients of childbearing potential should be instructed to use appropriate birth control methods for up to 4 weeks following the last dose of study medication.

6.3.6 Electrocardiograms

A resting 12-lead ECG will be performed at all clinic visits except on Day 8 (Visit 2). At Screening, ECG will be performed in triplicate. At Baseline (Day 1) and Day 43 (Visit 4), two ECGs will be performed; one prior to study medication dosing and one 2-3 hours after dosing. ECG equipment will be provided by the central reader. ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute) QRS complex and PR and QTc intervals (milliseconds). Results will be provided by the central reader to the investigators within 24 hours. ECG data will be transferred automatically from the central reader into the eCRF monthly. ECG abnormalities present at Screening will be recorded as medical history. Any changes from the ECG status at Screening Visit that are deemed to be clinically significant by the investigator should be captured as AEs. Any clinically significant abnormal ECG should be discussed with the study MM and, if necessary be repeated within a 1-week period.

6.3.7 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS (Appendix 14) is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors.[46] Each item of the S-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderate; 3 = very; and 4 = extremely). The Sheehan-STS can be analyzed as individual item scores, suicidal ideation subscale score, suicidal behavior subscale score, or total score. For the screening visit, the timeframe for the items on the scale will be 'in the past 6 months' and for all other visits it will be 'since last visit'.

The S-STS will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Day 8 (Visit 2), Day 15 (Visit 2.1), Day 22 (Visit 3), Day 43 (Visit 4), Day 64 (Visit 5), and Day 85 (Visit 6). Any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to the MM.

6.3.8 Mini-Mental State Examination (MMSE)

The MMSE (Appendix 15) is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used in medicine to screen for dementia. It is also used to estimate the severity of cognitive impairment at a specific time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The MMSE scale comprises 11 questions or simple tasks concerning orientation, memory, attention, and language to evaluate the patient's cognitive state.[47] It requires only 5 to 10 minutes for a trained rater to administer it.

The MMSE will be assessed at Screening (Day -28 to Day -1), Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.3.9 Timed Up and Go (TUG) Test

The TUG test (Appendix 16) measures the time (in seconds) taken for an individual to stand up from a standard armchair, walk 3 meters, turn, walk back to the chair and sit down. It is a commonly used scale for measuring functional mobility and risk of falls.[48,49]

The TUG test will be performed at Screening (Day -28 to Day -1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.3.10 Epworth Sleepiness Scale (ESS)

The ESS (Appendix 17) is an 8-item questionnaire that is used to measure sleepiness by rating the probability of falling asleep on 8 different situations that most people engage in during the day.[50] The questions are rated on a 4 point scale (0 to 3) where 0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, and 3 = high chance of dozing. A total score of 0 to 9 is considered to be normal.

The ESS will be assessed at Baseline (Day 1), Day 43 (Visit 4), and Day 85 (Visit 6).

6.4 Schedule of Evaluations and Procedures

A schedule of evaluations and procedures for both Stage 1 and Stage 2 is provided in Table 1.

6.4.1 Description of Study Procedures

At each visit throughout the study, site staff will be required to enter information into the IWRS regarding patient data and pre-defined study assessment results. Further instructions will be provided in the IWRS Site Manual.

6.4.1.1 Screening Visit (Days -28 to -1, + 3-day window)

The following procedures will be performed at Screening (within 28 days prior to Day 1). The screening period may be extended after discussion with and approval by the MM. In the event that a patient is rescreened for enrollment, new informed consent and/or assent documents must be signed, new patient number assigned and all screening procedures repeated.

1. The investigator will provide the patients, authorized representatives and/or their caregivers with informed consent and/or assent documents and will explain the rationale for the study, providing ample time for participants, authorized representatives, and/or caregivers to ask questions.

2. Medical history, including patient demographics, any prior and concomitant medications (including OTC, vitamins, and supplements), nondrug therapies, and any nonpharmacological interventions for the treatment of agitation will be reviewed and recorded.
3. Review inclusion/exclusion criteria (eligibility form).
4. Vital signs will be measured and recorded.
5. Physical and neurological examination will be performed.
6. Risk assessment for falls will be performed (worksheet and TUG test).
7. A resting 12-lead ECG will be performed in triplicate.
8. A blood and urine specimen will be collected for safety laboratory assessments.
9. A urine pregnancy test will be performed for females of childbearing potential only.
10. The following assessments will be completed:

    - MMSE; a score between 6 and 26 (inclusive) is required for study entry
    - CMAI
    - NPI Agitation/Aggression domain
    - CGIS-Agitation; a score of ≥ 4 is required for study entry
    - S-STS
    - CSDD; a score of <10 is required for study entry
    - GMHR

Following screening procedures for assessment of inclusion and exclusion criteria, the site will complete a protocol eligibility form and submit to the MM for approval. Patients deemed eligible by the PI and the MM will be randomized into the study. Patients who have ECG or laboratory test results outside of the reference normal range that the investigator considers to be clinically significant, and may put the patient at a higher risk for study participation, will not be enrolled.

6.4.1.2 Baseline Visit (Day 1)

The Baseline visit (Day 1) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. Inclusion/exclusion criteria will be reviewed.

2. Caregivers will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements) nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.
3. Vital signs and weight will be measured and recorded.
4. A resting 12-lead ECG will be performed (twice this visit - pre and 2-3 hours post dose).
5. A blood specimen will be collected [redacted].
6. A urine pregnancy test will be performed for females of childbearing potential only.
7. The following assessments will be completed:
    - MMSE
    - CMAI
    - NPI
    - CGIS-Agitation
    - Baseline mADCS-CGIC-Agitation
    - ADAS-cog (only for patients with an MMSE score of ≥ 10 at baseline)
    - DEMQOL-proxy (and DEMQOL for patients with an MMSE score of ≥ 10 at baseline)
    - S-STS
    - ZBI
    - RUD
    - Baseline ADCS-CGIC-Overall
    - ESS

Patients will be randomized once it is determined that they satisfy all of the inclusion and none of the exclusion criteria (on the basis of the screening and baseline assessments described above) and will be assigned with a study medication kit number via IWRS.

Study Medication Dosing:

The first dose of study medication will be administered from the AM strip of blister card at the clinic regardless of the time of day.

After Dosing:

1. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
2. The caregiver will be queried regarding AEs.
3. Patient Diary Card and sufficient study medication for a 3-week treatment period will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 7 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication and patient's Diary Card at each study visit. For the next scheduled visit (Visit 2), caregivers will be advised to administer the morning dose of study medication to the patient within 2 hours of the clinic appointment and note the time of dosing.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.4.1.3 Visit 2 (Day 8 + 3-day window)

Visit 2 (Day 8) should occur in the morning within 2 hours of taking the AM dose. The morning dose of study medication can be administered at home if the visit will occur within 2 hours of dosing; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.
2. Vital signs will be measured and recorded.
3. The following assessments will be completed:
    - CMAI
    - NPI Agitation/Aggression domain
    - S-STS

4. Unused study medication will be accounted for compliance and the blister card returned to the patient.

5. Patient's Diary Card will be reviewed for compliance and returned to the patient

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 7 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication and patient's Diary Card at each study visit. For the next scheduled visit (Visit 2.1), caregivers will be advised to administer the morning dose of study medication to the patient within 2 hours of the clinic appointment and note the time of dosing.

Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.4.1.4 Visit 2.1 (Day 15 ± 3-day window)

Visit 2.1 (Day 15) should occur in the morning within 2 hours of taking the AM dose. The morning dose of study medication can be administered at home if the visit will occur within 2 hours of dosing; the time of dosing should be noted by the patient/caregiver.

The following procedures will be performed:

1. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.

2. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.

3. Vital signs will be measured and recorded.

4. The following assessments will be completed:

    - CMAI
    - NPI Agitation/Aggression domain
    - S-STS

5. Unused study medication will be accounted for compliance and the blister card returned to the patient.

6. Patient's Diary Card will be reviewed for compliance and returned to the patient.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 7 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication and patient's Diary Card at each study visit. Caregivers will be queried at the end of each visit to be certain they understand what is required of them.

6.4.1.5 Visit 3 (Day 22 ± 3-day window)

Visit 3 (Day 22) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.

2. Vital signs will be measured and recorded.

3. Returned, unused study medication will be accounted for compliance.

4. Patient's Diary Card will be collected and reviewed for compliance.

5. The following assessments will be completed:

    - CMAI
    - NPI
    - S-STS

Study Medication Dosing:

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. A blood and urine specimen will be collected within 3 hours for safety laboratory assessments.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. Patient Diary Card and sufficient study medication for a 3-week treatment period will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 21 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.6 Visit 4 (Day 43 ± 3-day window)

Visit 4 (Day 43) should occur in the morning. The following procedures will be performed

Before Dosing (End of Stage 1):

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.
2. Vital signs will be measured and recorded.
3. Physical and neurological examination will be performed.
4. A resting 12-lead ECG will be performed (twice this visit - pre and 2-3 hours post dose)
5. Patient's Diary Card will be collected and reviewed for compliance.
6. Returned, unused study medication will be accounted for compliance.
7. The following assessments will be completed:
    - CMAI
    - NPI
    - CGIS-Agitation

- mADCS-CGIC-Agitation
- ADCS-CGIC-Overall

Beginning of Stage 2

Patients will be re-randomized after the procedures above have been completed. A new study medication kit number will be assigned via IWRS. The patient number will remain the same.

Study Medication Dosing:

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. A blood specimen will be collected within 3 hours after the morning dose of study medication for PK analysis and for safety laboratory assessments.
2. A urine sample will be collected for urinalysis.
3. Urinary pregnancy test will be performed in women of childbearing potential.
4. The following assessments will be completed:
    - MMSE
    - ADAS-cog (only for patients with an MMSE score of ≥ 10 at baseline)
    - CSDD
    - DEMQOL-proxy (and DEMQOL for patients with an MMSE score of ≥ 10 at baseline)
    - S-STS
    - TUG
    - ZBI
    - RUD
    - PGIC
    - ESS
5. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
6. A new patient's Diary Card will be dispensed.
7. Sufficient study medication for a 3-week treatment period will be dispensed.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 21 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.7 Visit 5 (Day 64 ± 3-day window)

Visit 5 (Day 64) should occur in the morning. The following procedures will be performed.

Before Dosing:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.
2. Vital signs will be measured and recorded.
3. Returned, unused study medication will be accounted for compliance.
4. Patient's Diary Card will be collected and reviewed for compliance.
5. The following assessments will be completed:
    - CMAI
    - NPI
    - S-STS

Study Medication Dosing:

Study medication will be administered from the AM strip of the newly dispensed blister card at the clinic regardless of the time of day.

After Dosing:

1. A blood and urine specimen will be collected within 3 hours for safety laboratory assessments.
2. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
3. Patient Diary Card and sufficient study medication will be dispensed for a 3-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient the study medication twice-daily (1 capsule of study medication from the top row [AM] of blister card in the morning and 1 capsule of study medication from the bottom row [PM] of the blister card in the evening, approximately every 12 hours ± 4 hours) for 21 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the patient's Diary Card. They will also be instructed to consult with the study site prior to taking any non-study medications. These requirements will be reviewed in person. Caregivers will also be instructed to bring to the clinic any unused study medication at each study visit. Caregivers will be queried at the end of each visit to be certain that they understand what is required of them.

6.4.1.8 Visit 6 (Day 85 ± 3-day window) / Early Termination

Visit 6 (Day 85) should occur in the morning. Patients who withdraw prior to study completion are required to complete study procedures as listed in Visit 6 within 48 hours of the last dose of study medication. There is no specific time frame for the 12-lead ECG, and sample blood/urine specimen collection (safety labs and PK samples) for early termination patients.

The last dose of study medication will be administered to the patient at the clinic regardless of the time of day, from the blister card brought in by the patient.

The following procedures will be performed after dosing:

1. The caregiver will be queried regarding AEs, concomitant medication use (including OTC, vitamins, and supplements), nondrug therapies, and concomitant nonpharmacological interventions for the treatment of agitation.
2. Returned, unused study medication will be accounted for compliance.
3. Patient's Diary Card will be collected and reviewed.
4. Vital signs and weight will be measured and recorded.
5. Physical and neurological examination will be performed.
6. The following assessments will be completed:

- MMSE
- CMAI
- NPI
- CGIS-Agitation
- mADCS-CGIC-Agitation
- ADAS-cog (only for patients with an MMSE score of ≥ 10 at baseline)
- CSDD
- DEMQOL-proxy (and DEMQOL for patients with an MMSE score of ≥ 10 at baseline)
- S-STS
- TUG
- GMHR
- ZBI
- RUD
- ADCS-CGIC-Overall
- PGIC
- ESS

7. A resting 12-lead ECG will be performed between 2 and 3 hours (± 15 minutes) after taking the morning dose of study medication.
8. A blood specimen will be collected within 3 hours after the morning dose of study medication for PK analysis and for safety laboratory assessments.
9. A urine sample will be collected for urinalysis.
10. Urinary pregnancy test will be performed in women of childbearing potential.

Any previously reported and not yet resolved AE, and any newly reported AE at the time of this visit will be followed-up for up to 30 days after the last dose of study medication.

6.4.1.9 Follow-up Phone Call (Days 29 and 71, + 3-day window)

Patient's caregiver will receive a safety follow-up phone call on Days 29 and 71. Caregiver will be queried on adverse events, concomitant medication use, nondrug therapies, and nonpharmacological interventions for agitation, since the last visit. Patients who terminate early from the study or who do not roll over to the extension study (Study 15-AVP-786-303) will receive a safety follow-up phone call 30 days after the last dose of study medication.

7 DATA MANAGEMENT

7.1 Data Collection

The sponsor or designated representative (e.g., CRO) will perform the data management activities in accordance with the data management plan (DMP). The DMP will outline the systems and procedures to be used in the study.

Clinical study data will be reported (captured) by study site personnel on eCRFs. An eCRF must be completed for every patient enrolled in the study. The eCRF data will be entered by trained study-site personnel and then reviewed for completeness and accuracy and electronically signed by the investigator or authorized designee. All study-site personnel must use a password-protected user account to enter, review, or correct study data. Electronic signature procedures shall comply with the CFR Title 21 Part 11. Passwords will be strictly confidential.

All eCRF data will be exported from the electronic data capture (EDC) system and transferred to the sponsor or representative. The sponsor or representative will also receive electronic transfers of non-eCRF data such as laboratory data from the central laboratory, ECG data from the central ECG reader, as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the sponsor or representative and documented in the DMP or vendor data transfer requirements document as appropriate.

The clinical monitoring staff will perform source data verification (SDV) of the data recorded in the EDC system with source documents at the clinical study sites according to the data management plan and clinical monitoring plan. The data will be subjected to consistency and validation checks within the EDC system with supplemental data reviews performed outside of the EDC system.

Medical history and adverse events will be coded using a current version of Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications using a current version of the WHO Drug Dictionary. The sponsor or representative will perform a medical safety review of the coding.

Completed eCRF images with a date- and time-stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the investigator's site and at the sponsor's site.

8 STATISTICAL METHODS

8.1 Analysis Populations

Three analysis populations will be used, modified intent-to-treat (mITT), intent-to-treat (ITT), and safety.

- mITT: The mITT population includes all patients randomized in the study who had at least one post-baseline efficacy assessment. The mITT population will be used for all analyses of efficacy. Patients will be included in the treatment group to which they were randomized regardless of treatment received.
- ITT: The ITT population includes all randomized patients in the study. The ITT population will be used for exploratory efficacy analyses.
- Safety: The safety population includes all patients who received study treatment. The safety population will be used for all analyses of safety. Patients will be included in the treatment group based on the actual treatment received.

8.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the ITT and mITT populations using descriptive statistics.

8.3 Efficacy Analysis

The efficacy measures are assessed in each of the two stages of the trial. For the primary efficacy analysis, as well as for all other efficacy analyses, the SPCD method will be used to combine data from Stage 1 and 2. Data from Stage 1 placebo non-responders who are re-randomized into Stage 2 will be used to estimate Stage 2 treatment effect.

8.3.1 Study Endpoints

Primary efficacy endpoint:

The primary efficacy endpoint is the change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) in the composite CMAI scores.

Secondary efficacy endpoints:

The secondary efficacy endpoints are the change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) in the following measures:

- mADCS-CGIC-Agitation
- NPI – Agitation/Aggression domain score and Caregiver Distress score

- NPI - Aberrant Motor Behavior domain
- ZBI
- NPI - Irritability/Lability domain
- Total NPI
- CGIS-Agitation
- ADCS-CGIC-Overall
- PGIC
- DEMQOL
- CSDD
- ADAS-cog
- RUD
- GMHR (change from Baseline to Week 12 (Day 85)

8.3.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) in the composite CMAI scores. The primary efficacy analysis will be based on SPCD method using a weighted test statistics combining treatment effects from Stage 1 and 2.[3] Data from Stage 1 placebo non-responders who are re-randomized into Stage 2 will be used to estimate Stage 2 treatment effect.

For the primary efficacy endpoint, the null hypothesis is that there is no treatment effect in Stage 1 and Stage 2 and it will be tested against the alternative that there is a treatment effect in at least one of the 2 stages. The treatment effect in each stage will be estimated by using a likelihood-based linear mixed effects model repeated measures (MMRM) on observed data. The model will include fixed effects for treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction and baseline covariates which include baseline value and other randomization stratification factors. An unstructured covariance model will be used. Analyses with missing values imputed by last observation carried forward (LOCF) and Multiple Imputation (MI) may be performed as sensitivity analyses.

The 2 primary comparisons are AVP-786-28/4.9 vs. placebo and AVP-786-18/4.9 vs. placebo. An appropriate multiple comparison procedure will be used to control the overall type I error at 2-sided $\alpha = 0.05$.

8.3.3 Secondary Efficacy Analyses

Secondary efficacy endpoints include change from Baseline to Week 6 (Day 43, Stage 1) and from Week 6 to Week 12 (Day 85, Stage 2) for the following efficacy measures: mADCS-CGIC-Agitation,

NPI Agitation/Aggression domain score and Caregiver Distress score, NPI-Aberrant Motor Behavior domain score, ZBI, NPI-Irritability/Lability domain score, PGIC, DEMQOL, CSDD, RUD, total NPI, CGIS-Agitation, ADCS-CGIC-Overall, ADAS-cog; and change from Baseline to Week 12 for GMHR.

Treatment comparison tests using similar SPCD method as the primary efficacy analysis will be performed. A proper multiple comparison procedure, e.g, gate keeping procedure, will be used to control overall type I error at 2-sided $\alpha = 0.05$ for treatment comparisons (high dose vs. placebo, low dose vs. placebo) and the secondary endpoints tested. The testing procedure will be pre-specified in the statistical analysis plan (SAP) before un-blinding the study. [redacted] Detailed analyses will be described in the SAP.

8.4 PK/PD Analysis

Plasma concentrations of d6-DM, its metabolites, and Q will be measured and results will be summarized descriptively overall [redacted]. Plasma concentration results will be used to assess the PK properties of d6-DM and its metabolites. Additional PK/PD correlations may also be performed. Additional details will be described in the SAP.

8.5 [redacted]

[redacted]

8.6 Safety Analysis

Safety will be assessed by the following measurements: AEs, physical and neurological examination, vital signs, urine pregnancy test, clinical laboratory assessments, resting 12-lead ECG, S-STS, MMSE, TUG test, and ESS. All safety measures will be summarized by Stage 1, Stage 2, and the 2 stages combined.

Safety analyses will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment.

8.6.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, non-fatal SAEs, AEs, AEs resulting in study discontinuation, and treatment-emergent AEs (TEAE). TEAEs are those AEs that occur after the first dose of study medication up until 30 days after last dose.

8.6.2 Vital Signs and ECGs

Summary statistics of absolute values and percentage change from baseline for BP (diastolic and systolic), heart rate, respiratory rate, and ECG parameters will be provided. All values outside a pre-defined normal range will be highlighted in the individual patient data listings.

8.6.3 Clinical Laboratory Values

Laboratory parameters will be summarized via descriptive statistics and via shifts in results in respect to normal ranges between Screening and end of treatment as increased, decreased, or no change.

8.6.4 Data and Safety Monitoring Board

The sponsor will appoint a Data and Safety Monitoring Board (DSMB) for the periodic review of available study data.

The DSMB is an independent group of experts that advises the sponsor and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and (2) make recommendations to the sponsor concerning the continuation, modification, or termination of the study.

The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

The DSMB is responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking, and voting procedures prior to initiating any data review. The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it.

8.6.5 Interim Analysis

Interim analysis may be performed and will be pre-specified in the SAP.

8.7 Sample Size Calculations

Power calculations were performed assuming a bivariate normal distribution for the primary efficacy endpoint with AVP-786-28/4.9 (high dose) versus placebo. [redacted]

[redacted] To control the overall type I error rate at [redacted] level, the null hypothesis about the low dose AVP-786-18/4.9 will be tested only if the null hypothesis about the high dose is rejected.

9 ADMINISTRATIVE PROCEDURES

9.1 Institutional Review Board/Ethics Committee Approval

Institutional Review Boards/Ethics Committees (IRBs/ECs) must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB/EC approval for the protocol and the signed ICF must be obtained and transmitted to Avanir Pharmaceuticals or representative before the study can be initiated. The IRB/EC must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with local laws and according to National and State/Provincial laws (Appendix 18, Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 19.

9.2 Informed Consent Form

The ICF will follow the principles outlined in the current version of the Declaration of Helsinki. For each patient found to be eligible for the study, informed consent will be obtained from the patient (if the patient is capable in the judgment of the investigator to provide informed consent) or the authorized representative. For patients that are not capable of providing informed consent, but are capable of providing assent, the patient will be asked to provide assent. If the patient is not capable of providing assent, the investigator will document the reasons why and maintain that documentation with the other informed consent documents. The patient's caregiver will also be asked to provide informed consent as they will be providing data on themselves and the patient, as well as, being responsible for ensuring compliance from the patient between study visits.

The patients and/or patient's authorized representative and the caregiver will be properly informed of the purpose of the study. The patients and/or patient's authorized representative and the caregiver will be alerted to any anticipated AE that may be encountered with the study medication. A signed ICF will be obtained from all patients and/or patient's authorized representative and the caregiver prior to patient entry into this study. Patients and/or patient's authorized representative and the caregiver will be provided with a copy of their signed ICF.

9.3 Patient's Diary Card

The patient's Diary Card will be reviewed by clinical study personnel at all study treatment visits for confirmation of medication dosage and any rescue medication received. The study personnel are responsible for (i) ensuring that patients and/or caregivers are properly collecting data and recording it into the diaries; and (ii) transcribing the diary recordings into the eCRF. The diary will be collected at all study visits after baseline except Visit 2 (Day 8) and Visit 2.1 (Day 15), wherein the diary will be reviewed and returned to the patient. The originals of all diaries will be maintained at the site as source documents.

9.4 Electronic Case Report Forms

For each patient enrolled who has given informed consent, an eCRF must be completed and electronically signed by the investigator to certify that the data within each eCRF are complete and correct. This also applies to those patients who fail to complete the study. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to document the outcome.

Any site personnel delegated responsibility for data entry, query resolution, or eCRF approval must complete training prior to accessing the eCRF. The electronic data capture (EDC) vendor will provide user-specific access to the live (production) eCRF once training completion has been confirmed and the account has been approved by the sponsor. Changes to the data once it has been initially saved will be tracked via audit trail and will require a reason for the change. The audit trail will also include who made the change and a date/time stamp.

The eCRFs will be reviewed by the study monitor at the study site. Errors detected by subsequent in-house data review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

All investigators will be provided with copies of the eCRFs for their site on a CD-ROM at the end of the study.

9.5 Quality Assurance

9.5.1 Documentation

For each process, evaluation, or test that generates study data but is not described in the protocol or eCRF, a written description of the data generation procedures shall be retained in the quality assurance section of the study files. In the case of routine clinical diagnostic procedures, only a copy of the relevant certification document is required.

9.5.2 Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative and the caregiver for study procedures and for the release of medical records to the sponsor, FDA, other regulatory authorities, and the IRB/EC. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that

documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

9.6 Record Retention

To enable evaluations and/or audits from regulatory authorities or Avanir, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator is unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Avanir should be prospectively notified. The study records must be transferred to a designee acceptable by Avanir, such as another investigator, another institution, or to Avanir. The investigator must obtain Avanir's written permission before disposing of any records, even if retention requirements have been met.

9.7 Source Data

The documents that will form the source data for the clinical study (e.g., patient charts, laboratory reports) must be defined and documented in the in-house study master file prior to the start of the study. Data on the eCRFs which will be checked against source data during monitoring visits must also be defined and documented in the in-house study master file including the percentage of each of the source data to be verified and the percentage of patients' eCRFs to be monitored.

9.8 Data Handling

Data collected on the eCRFs will be entered into EDC system by trained site staff. Any queries arising from data entry will be checked with the investigator and changes approved.

9.9 Laboratory Procedures

Each individual site laboratory will collect hematology and chemistry blood samples and urine samples at Screening (Day -28 to Day -1), and Visits 3-6 (Day 22, Day 43, Day 64, and Day 85) for safety analysis. Instructions for specimen evaluation and transport to a central laboratory will be provided at the time of study initiation. Blood samples will also be taken [redacted] at Baseline (Day 1) and for

PK analysis on Visits 4 and 6 (Day 43 and Day 85). Instructions for shipping the laboratory samples for evaluation by central facilities will be provided.

9.10 Guidelines for Good Clinical Practice

Standards for GCP must be adhered to for all study-based procedures.

9.11 Conditions for Amending the Protocol

Protocol modification to ongoing studies which could potentially adversely affect the safety of patients or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of patients treated, or patient selection criteria must be made only after appropriate consultation between an appropriate representative of Avanir and the investigator.

Protocol modifications must be prepared by a representative of Avanir or the investigator, and reviewed and approved by Avanir.

All protocol modifications must be reviewed and approved by the appropriate IRB/EC in accordance with local requirements, before the revised edition can be implemented. Modifications which eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB/EC.

9.12 Conditions for Terminating the Study

Both Avanir and the principal investigator reserve the right to terminate the study at the site at any time. Should this be necessary, the procedures to effect study termination will be arranged after review and consultation by both parties. In terminating the study, Avanir and the investigator will assure that adequate consideration is given to the protection of the patient's interests.

9.13 Confidentiality of Study Documents and Patient Records

The investigator must assure that the patient's anonymity will be maintained. On eCRFs or other documents submitted to Avanir, patients should not be identified by their names but by an identification code.

The investigator should keep a separate log of patient's codes, names, and addresses. Documents not for submission to Avanir, for example, patients' signed ICFs, should be maintained by the investigator in strict confidence.

9.14 Reports

At the completion of the study, the investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study as described in the Code of Federal Regulations (CFR) Title 21, Part 312.64.

9.15 Publications

It is anticipated that a report of this study will be published in the scientific literature by the sponsor. The investigator will not seek to arrange for publication of any of the information or results from the study in any scientific journal, or other publication or by way of lecture without Avanir's prior review and written consent.

9.16 Audits/Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel or designee(s) from Avanir or to health authority inspectors after appropriate notification. The verification of the eCRF data may be by direct inspection of source documents (where permitted by law) or through an interview exchange.

The inspector from the regulatory authority will be especially interested in the following items:

- Visits from the sponsor's representatives
- IRB/EC approval(s)
- Study medication accountability
- Study protocol and amendments
- ICFs of the patient (if capable of providing ICF, according to the investigator) or patient's authorized representatives and caregivers
- Assent of the patients (if capable of providing assent, according to the investigator)
- Medical records supportive of eCRF data
- Reports to the IRB/EC and the sponsor
- Record retention

The sponsor will be available to help investigators prepare for an inspection.

10 REFERENCES

[redacted]

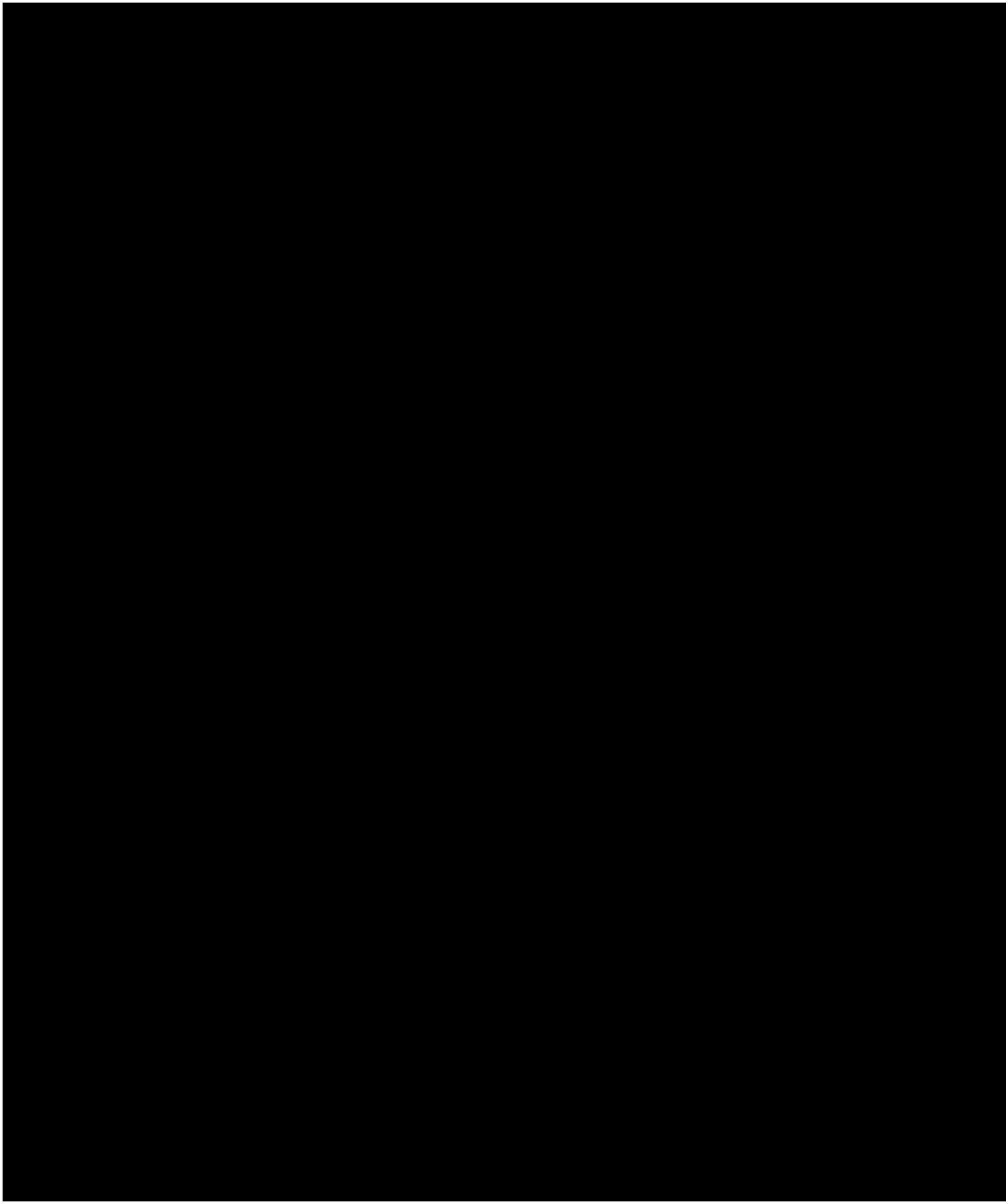
[redacted]

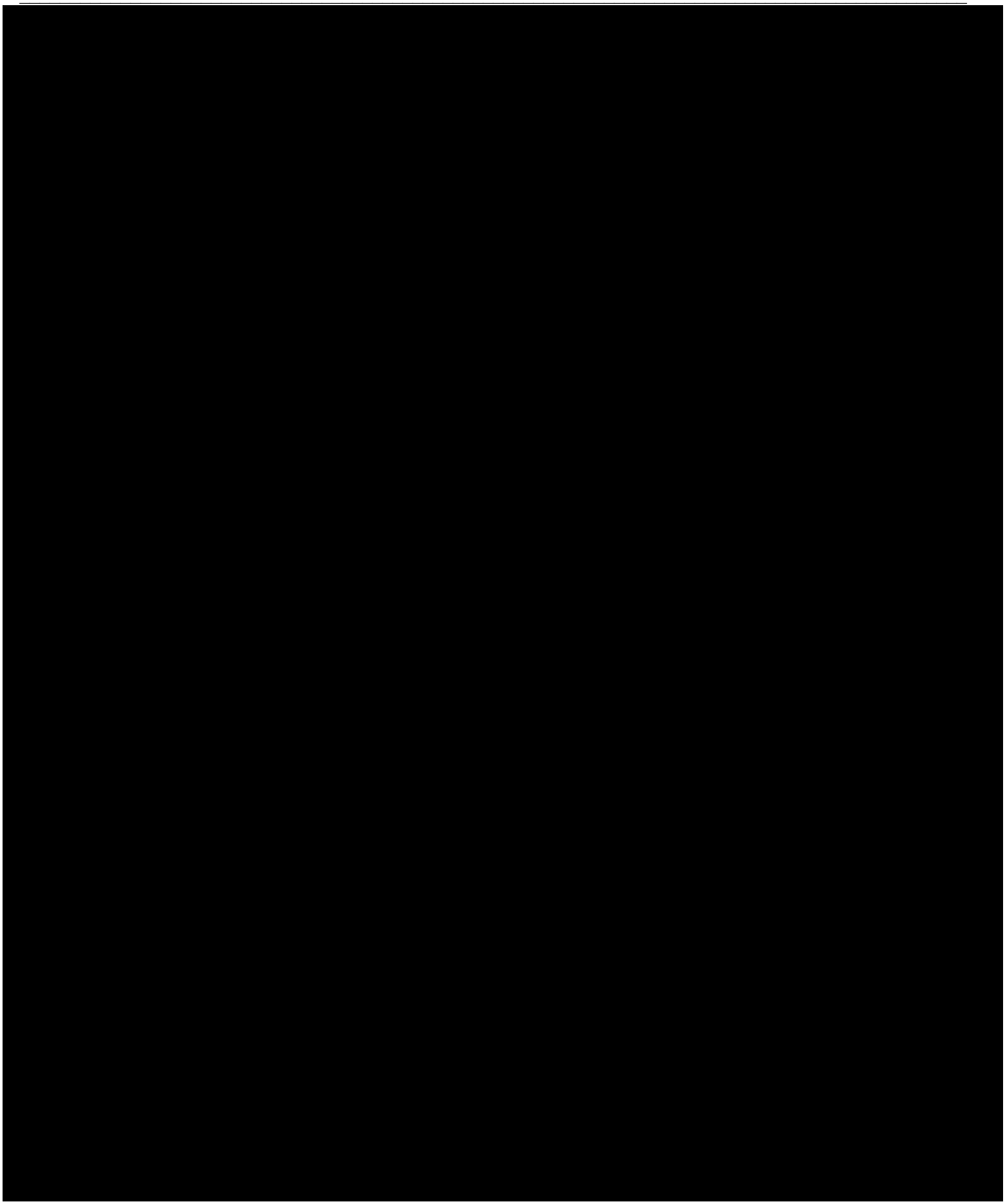
[redacted]

11 APPENDICES

[redacted]

[redacted] [redacted]





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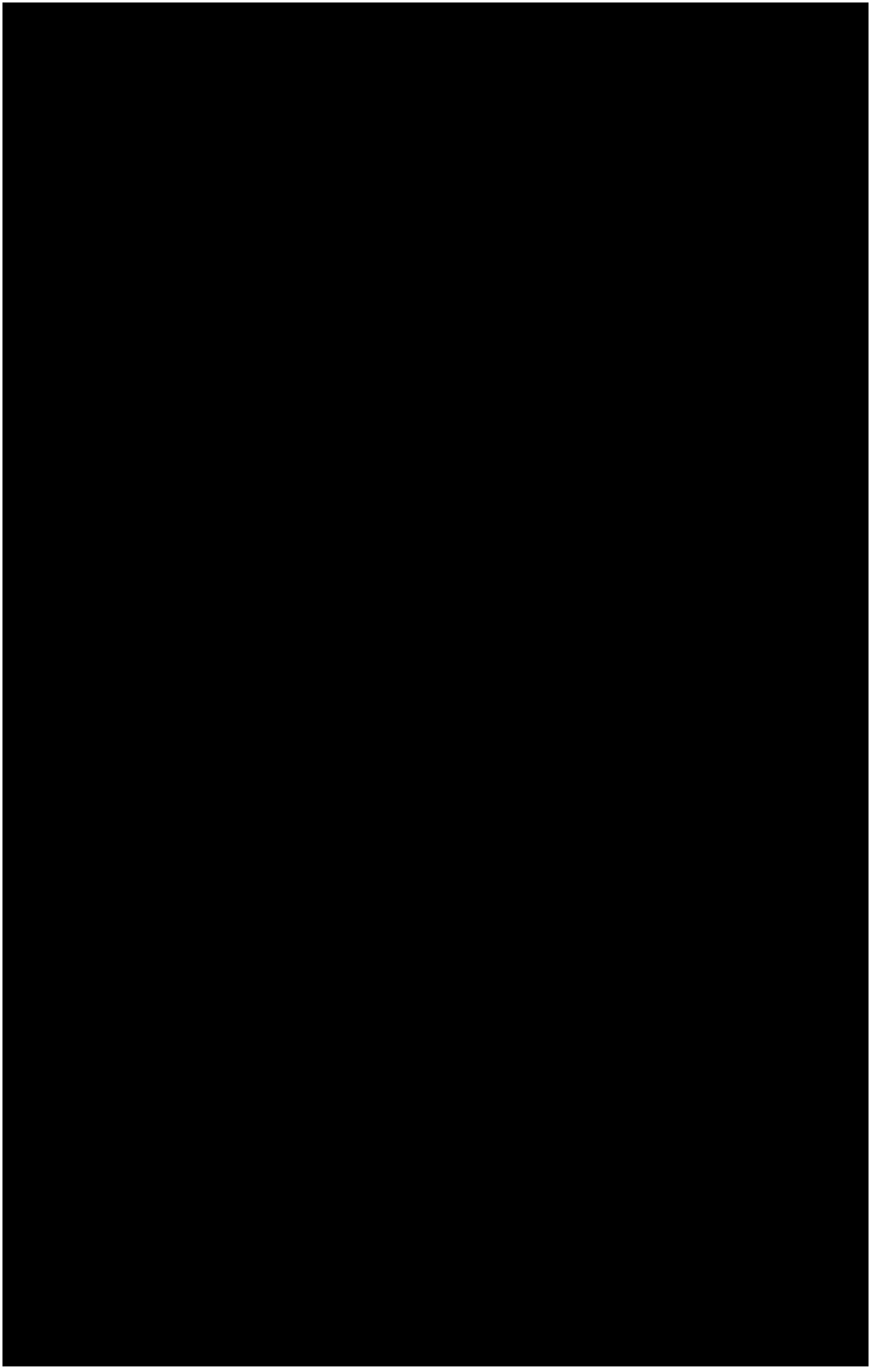

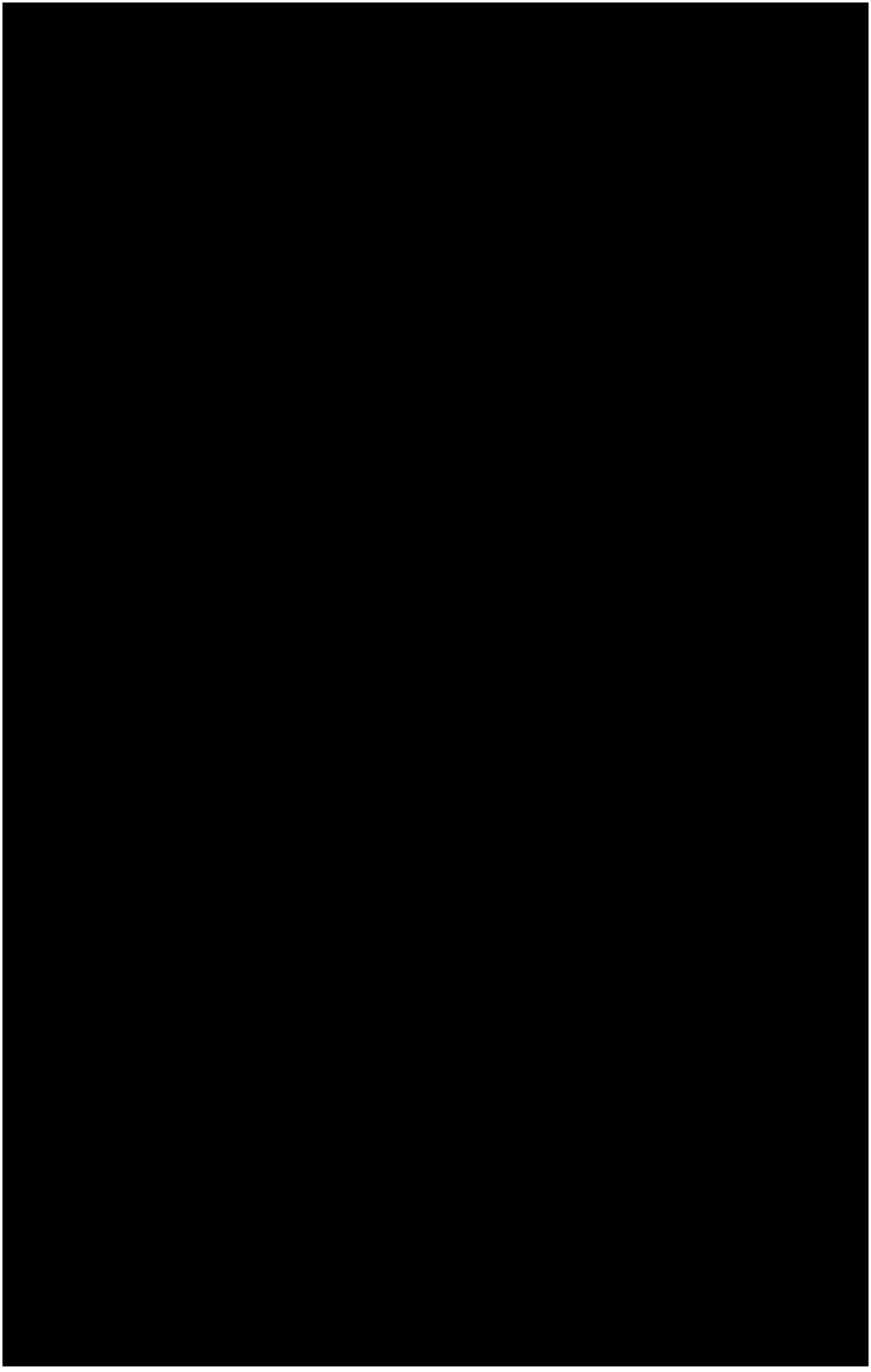

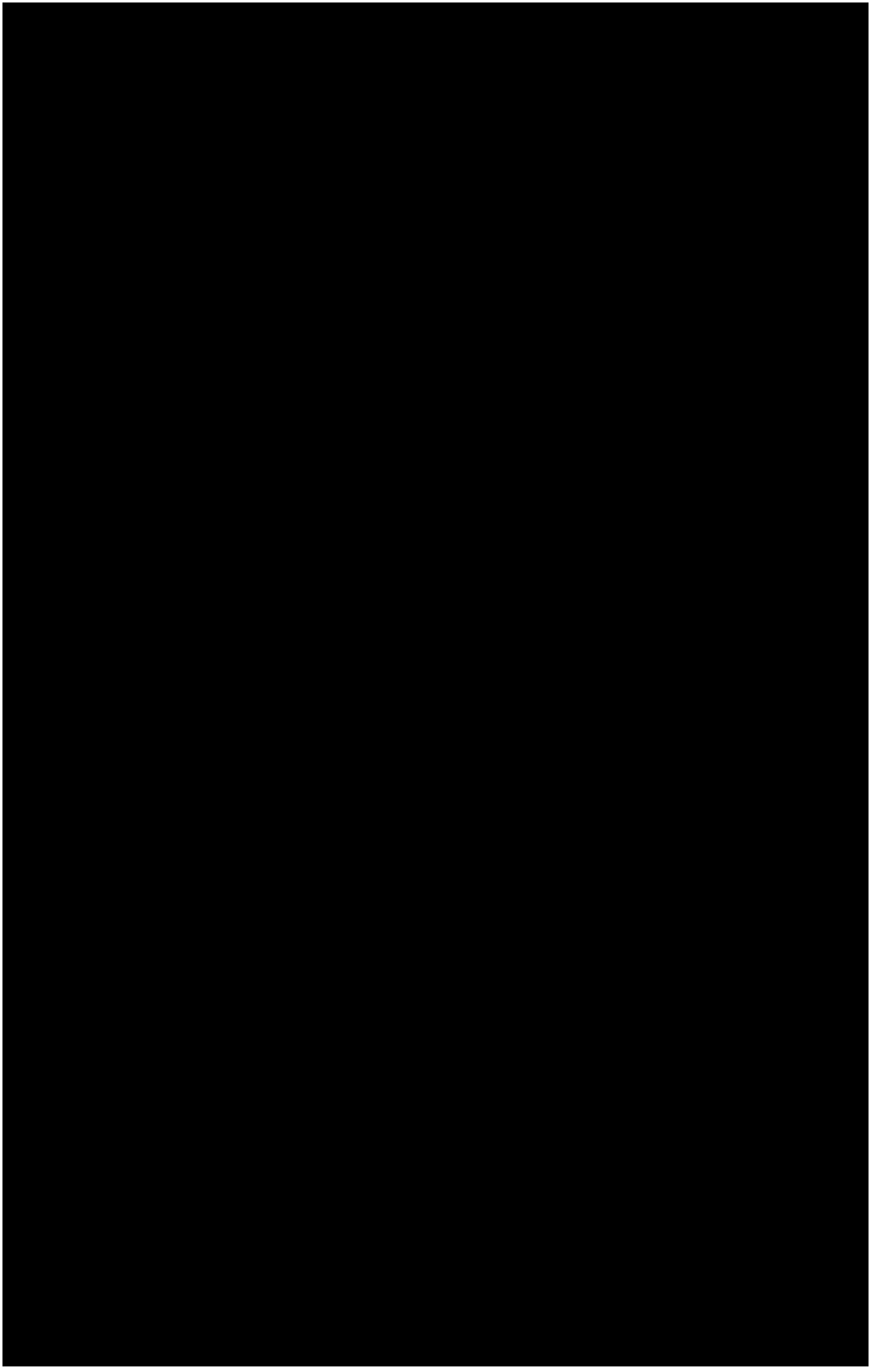

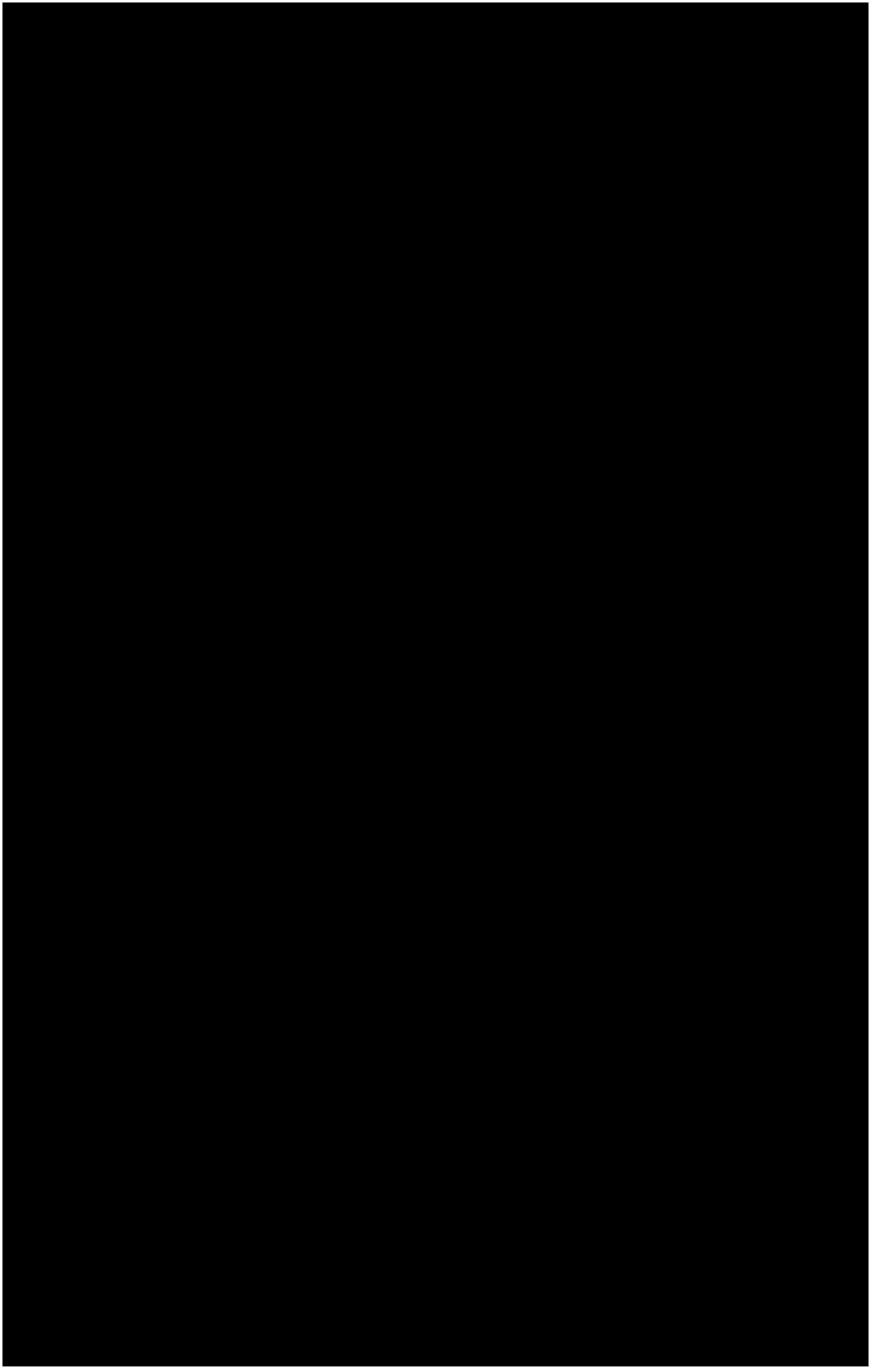

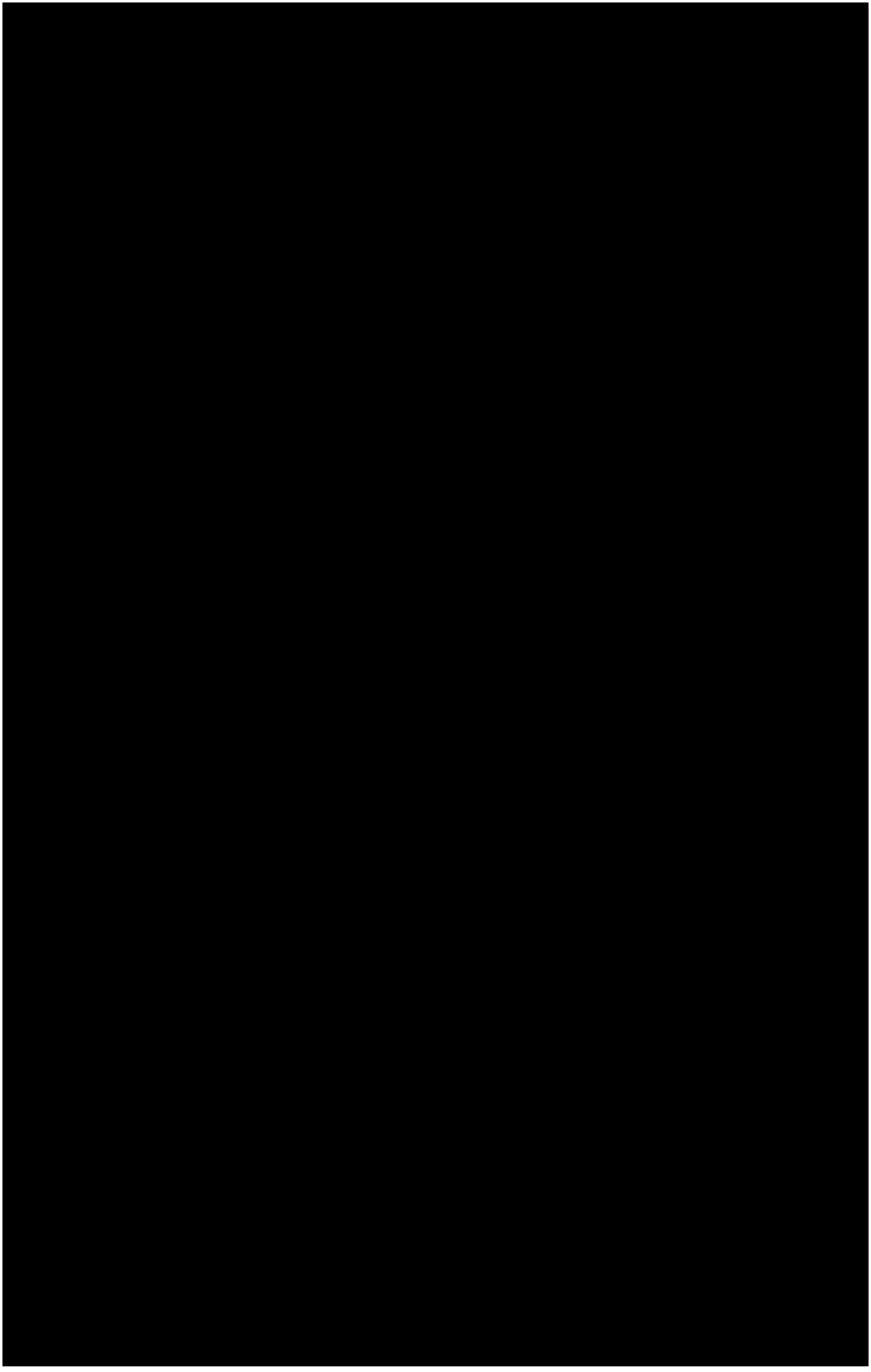

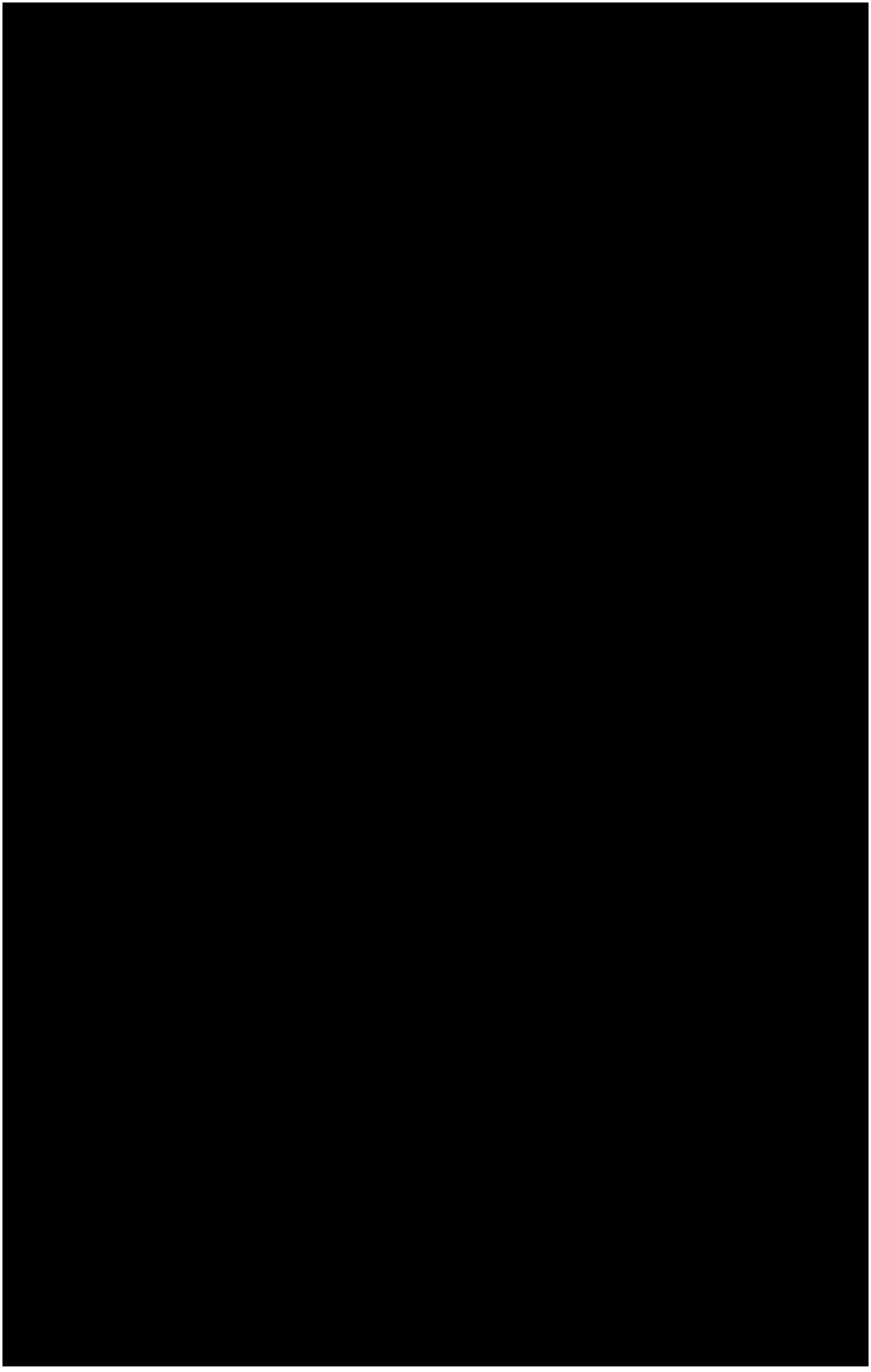

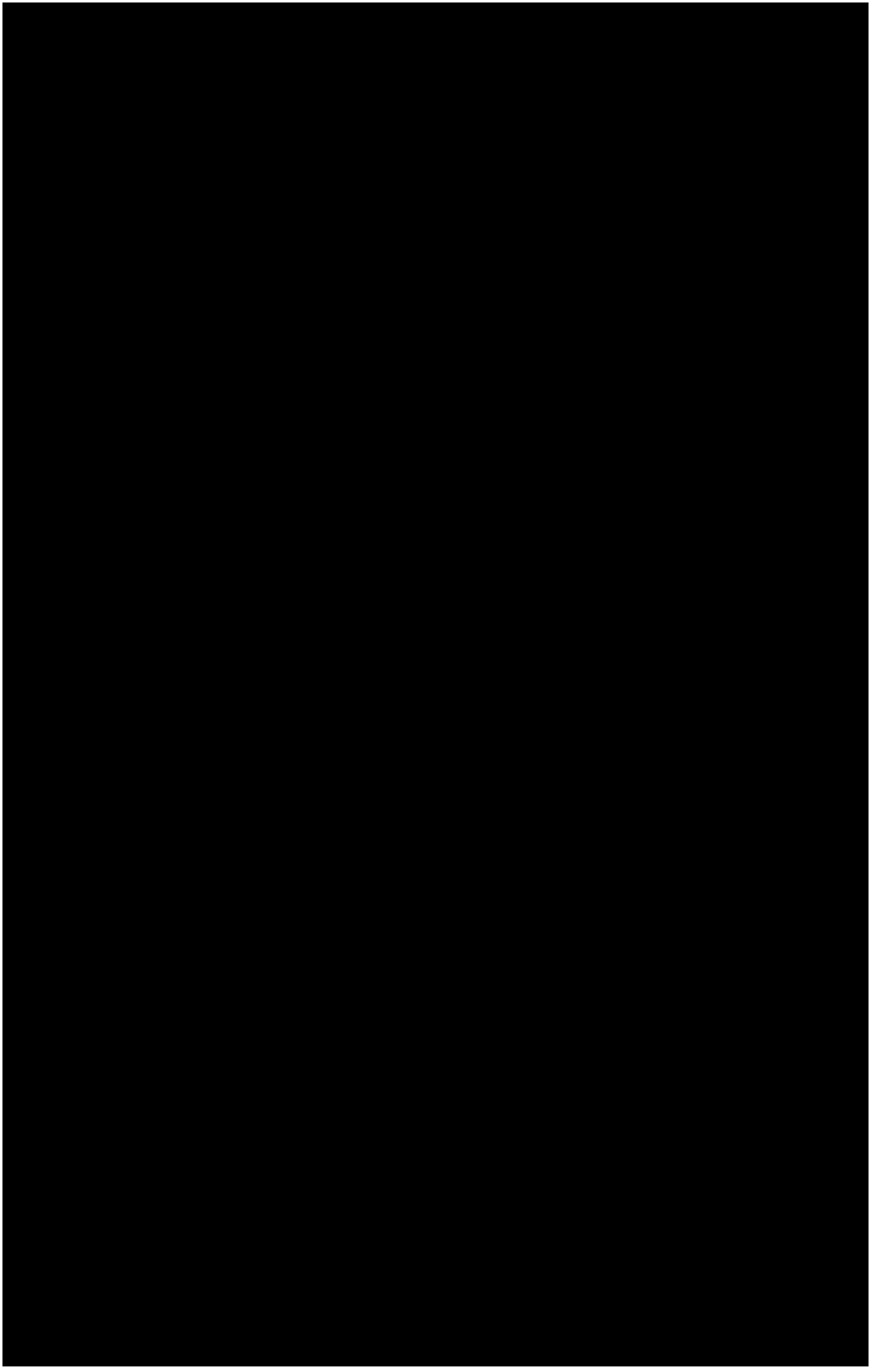

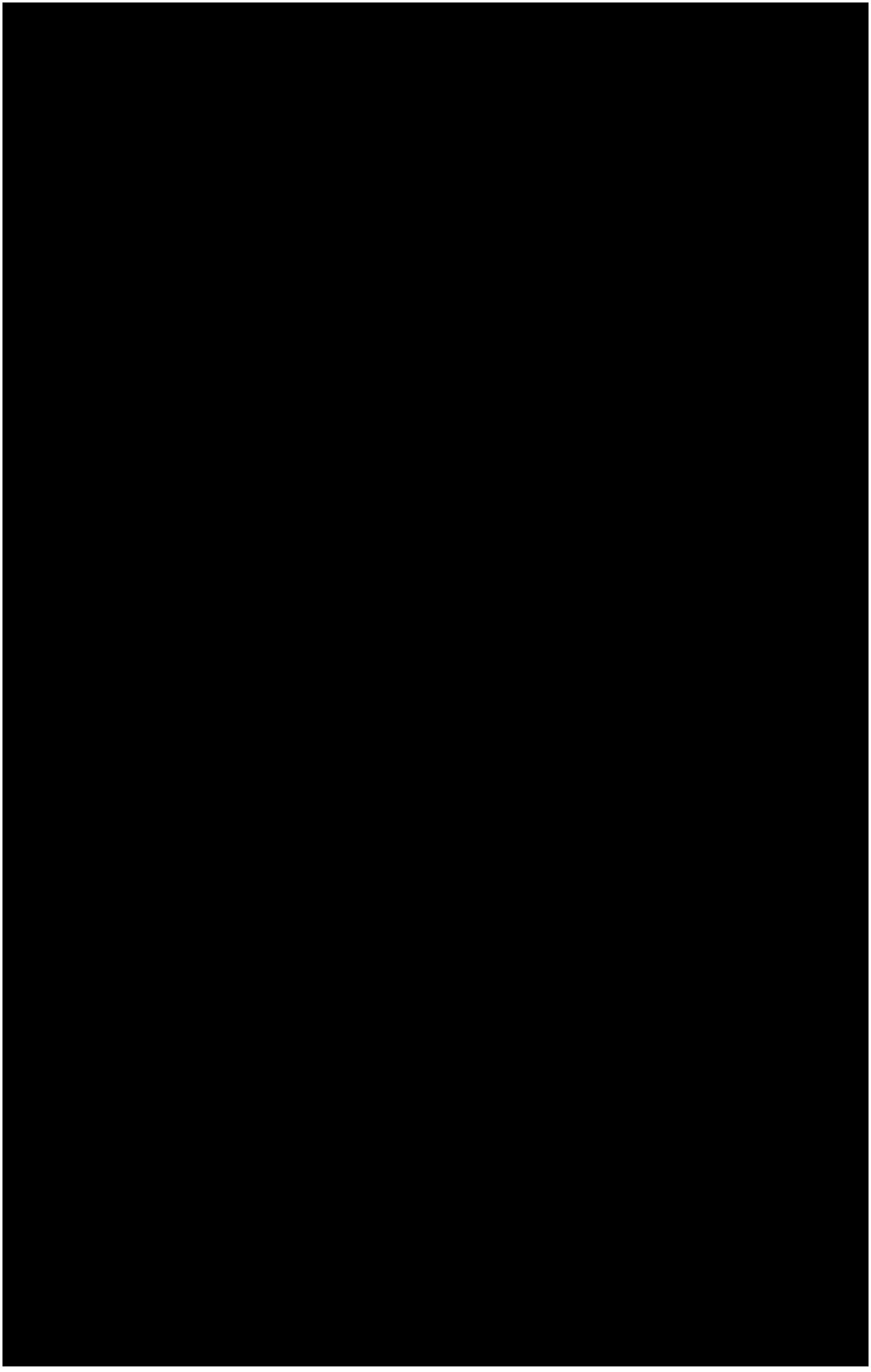

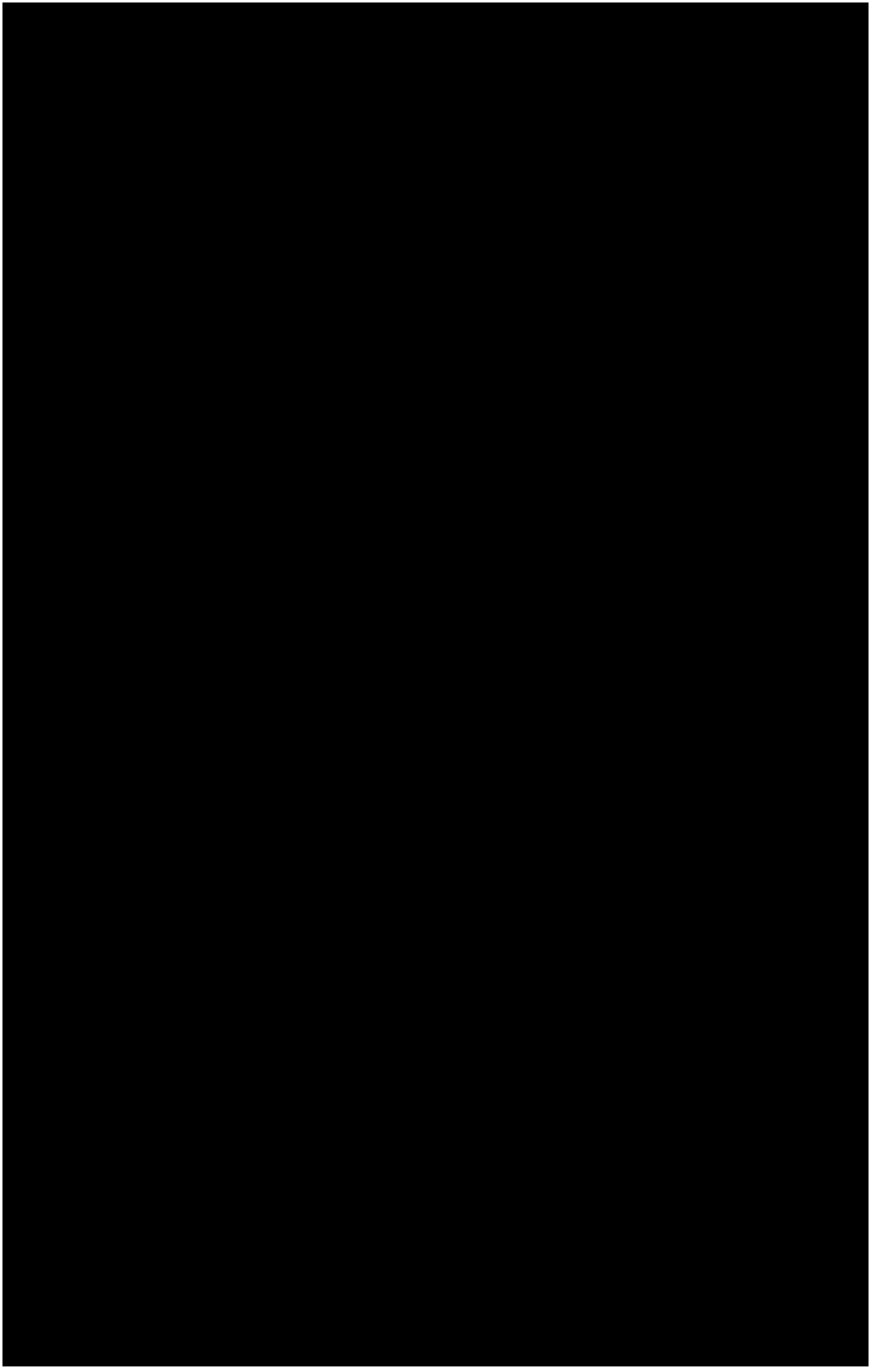

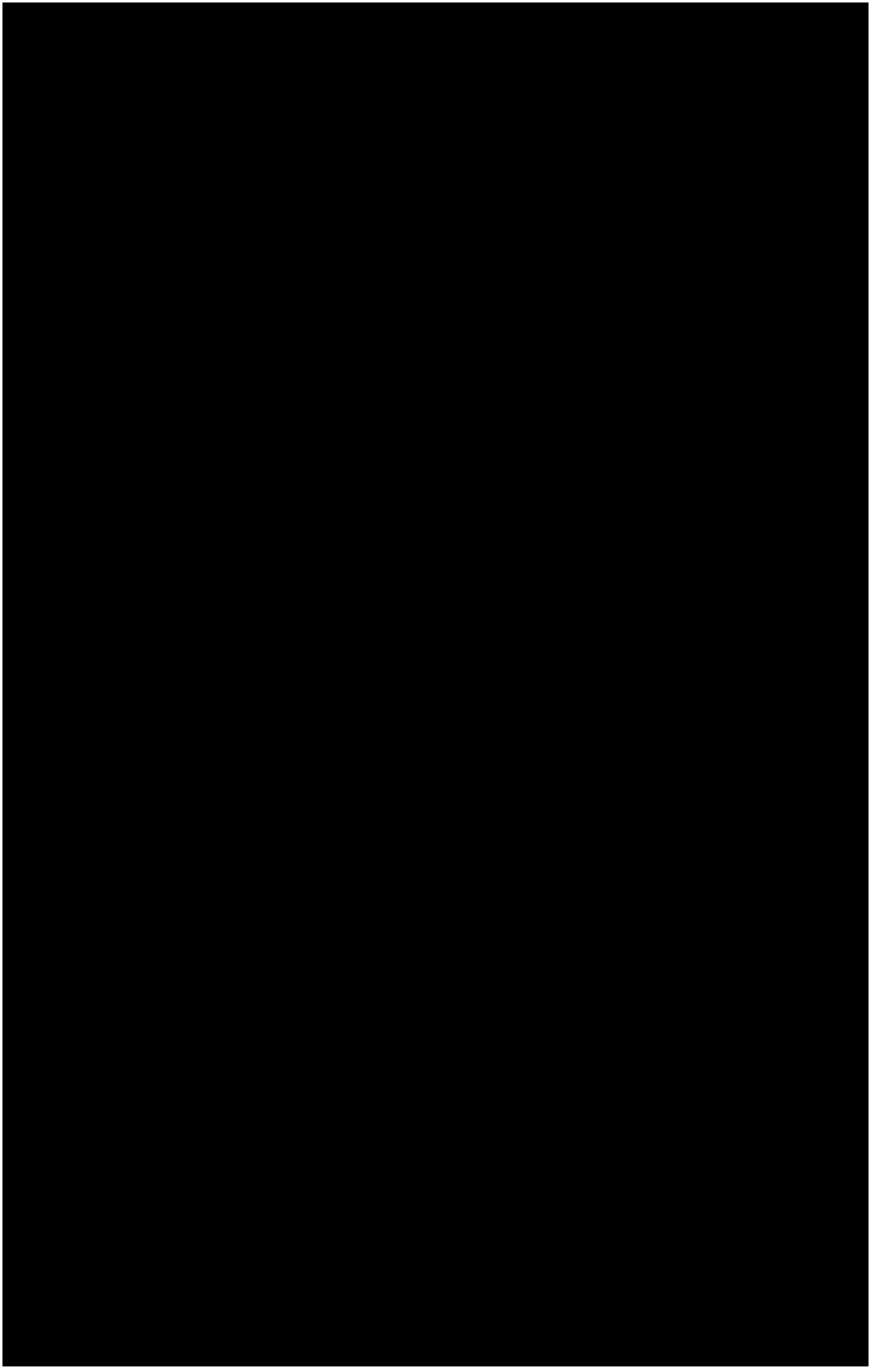

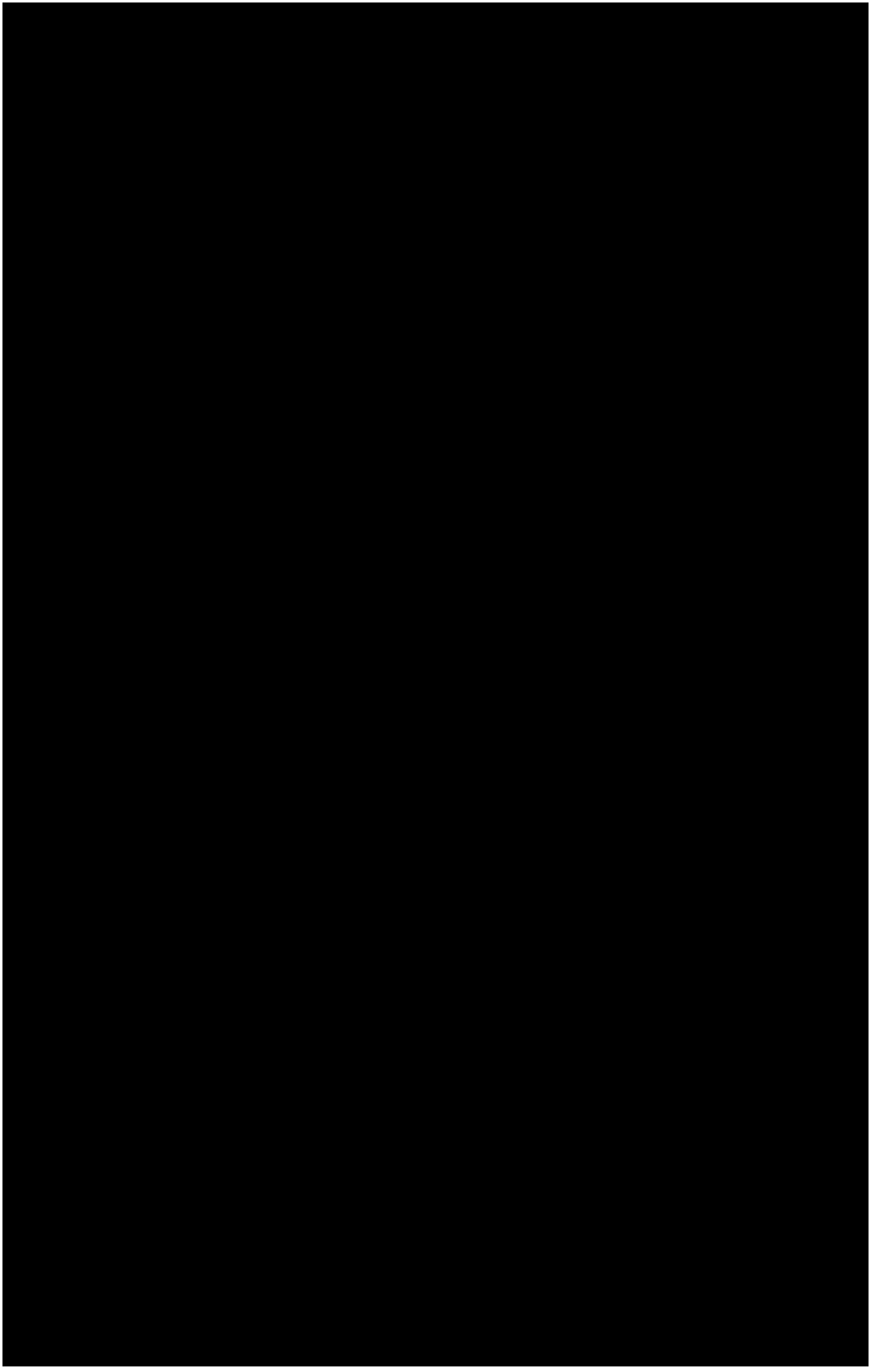

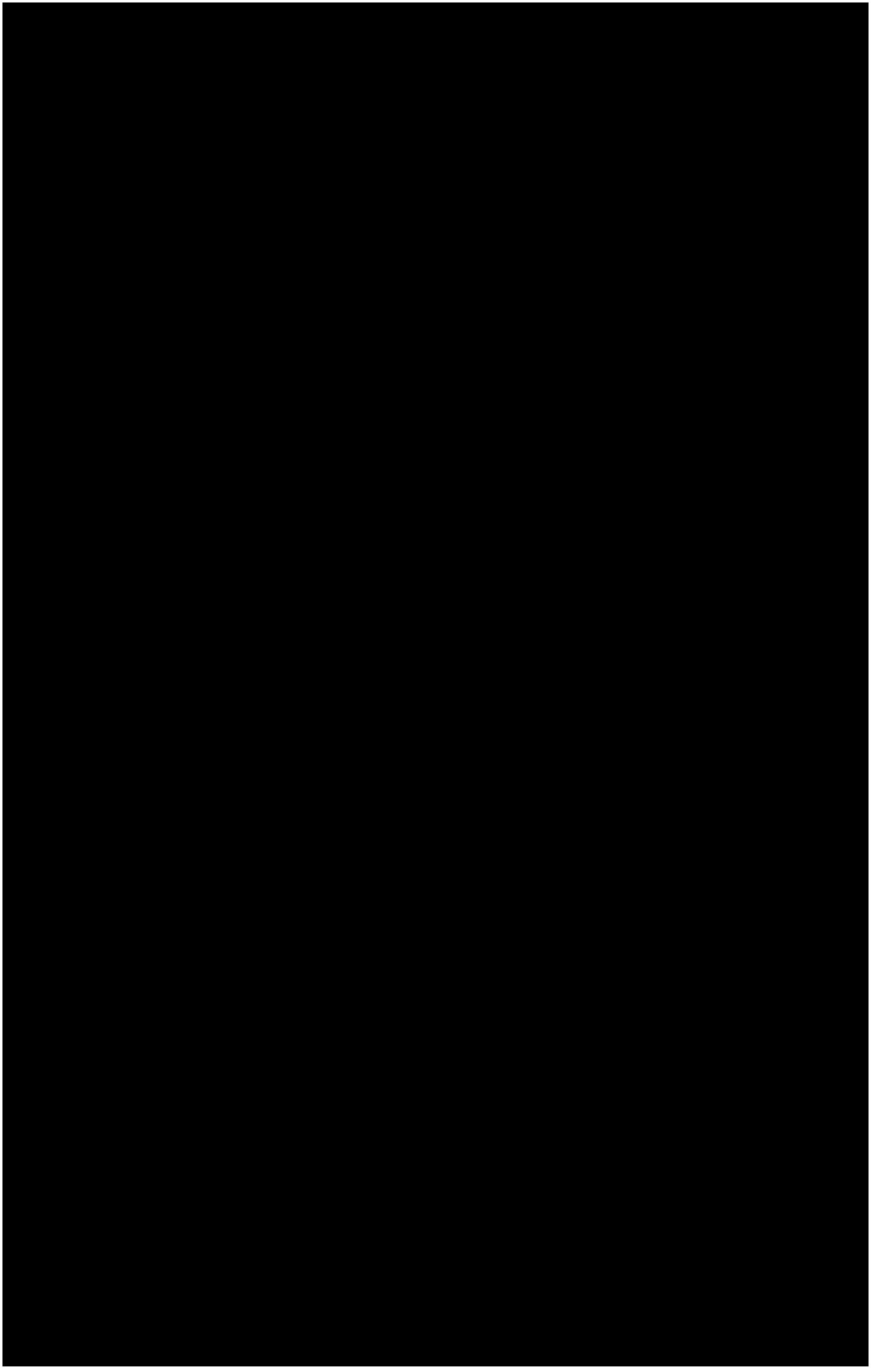

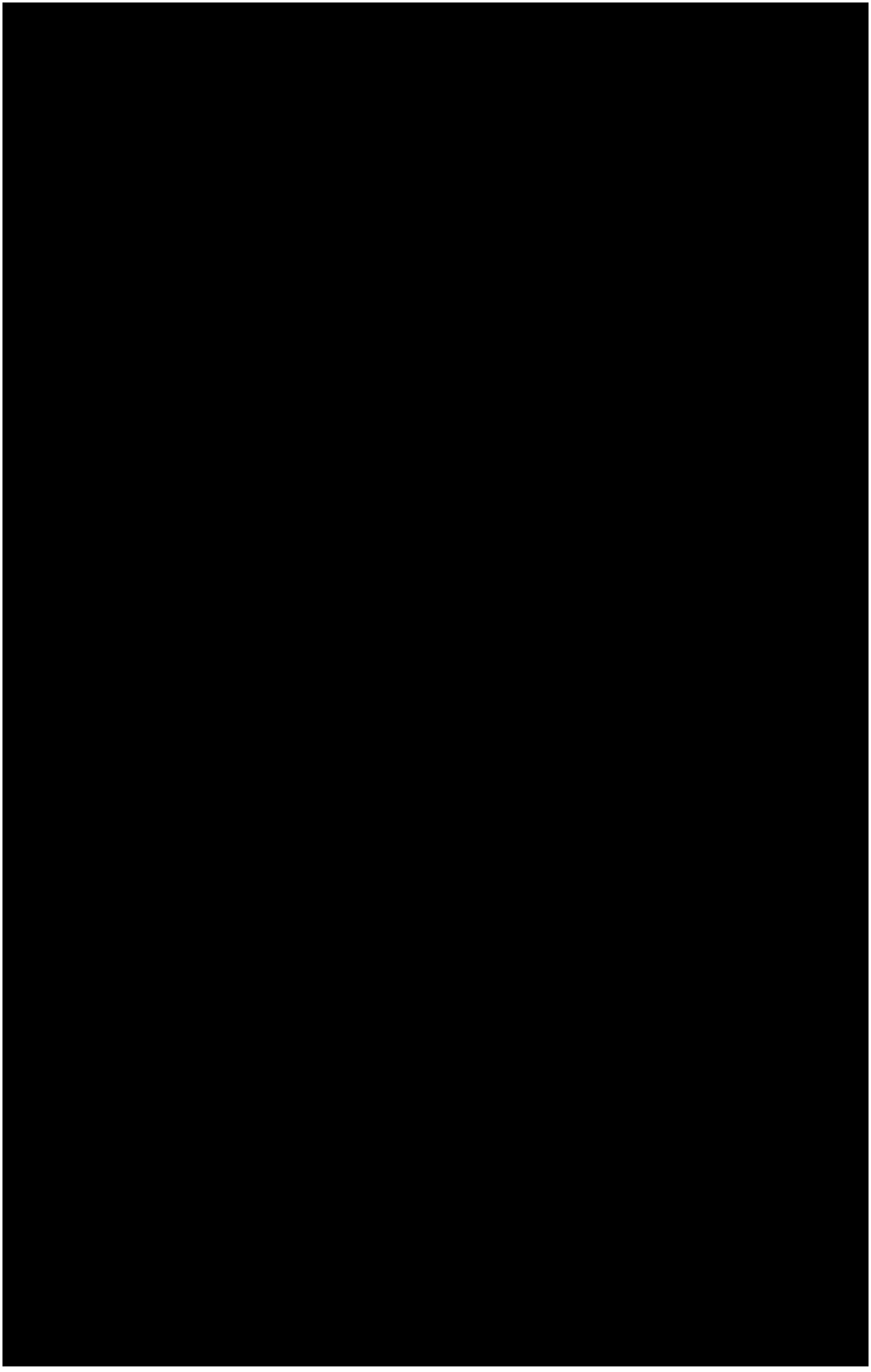

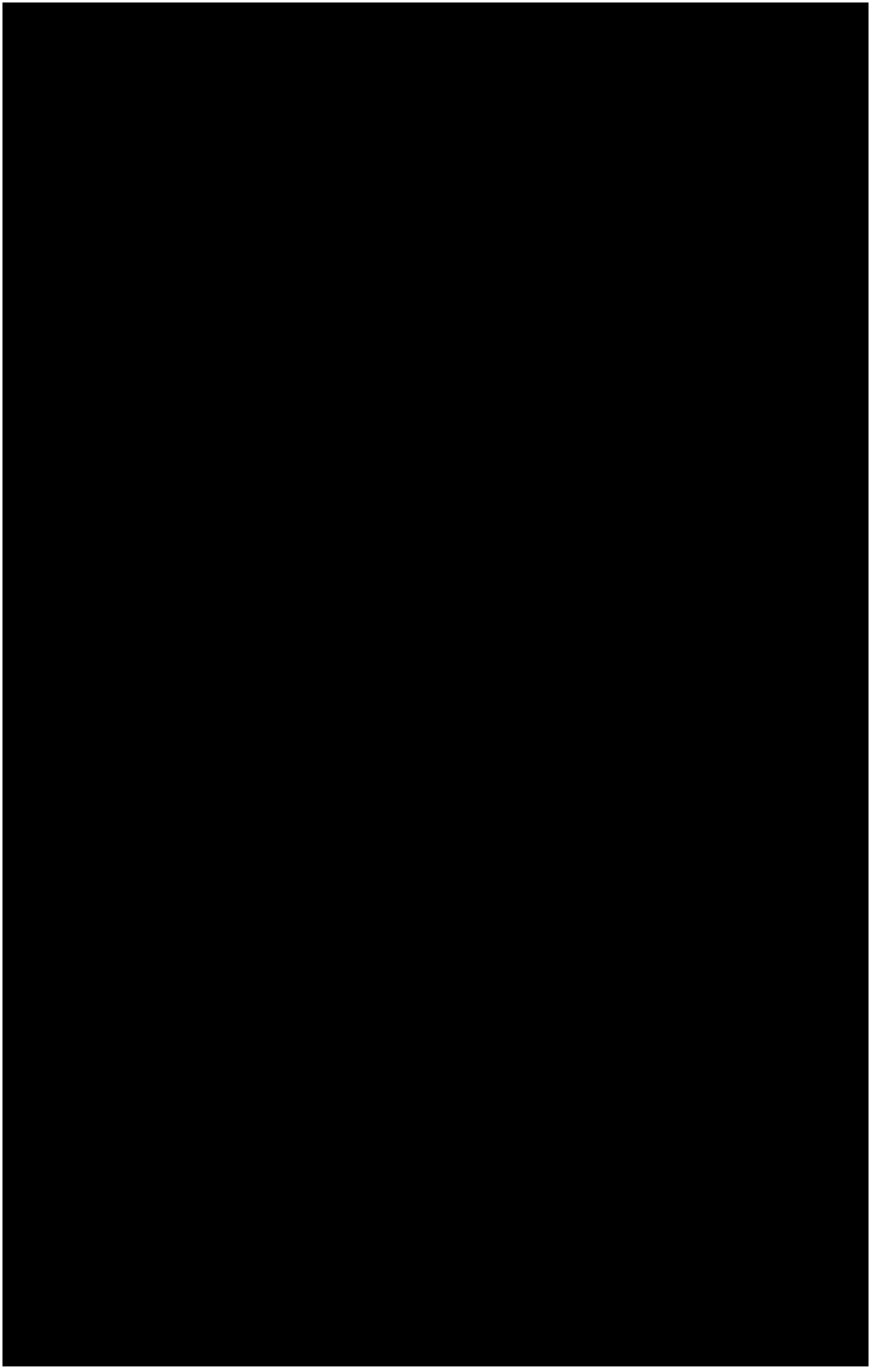

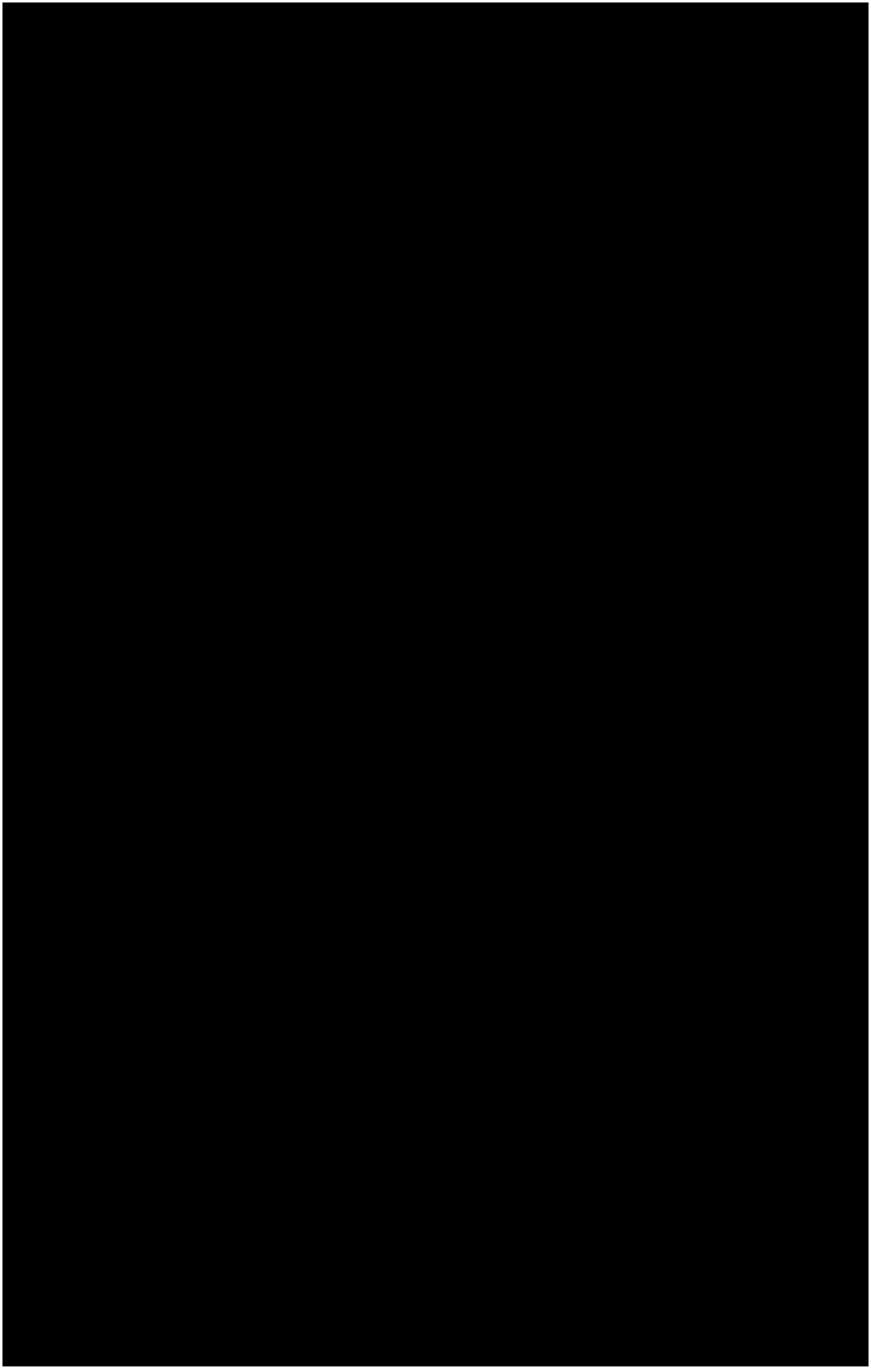

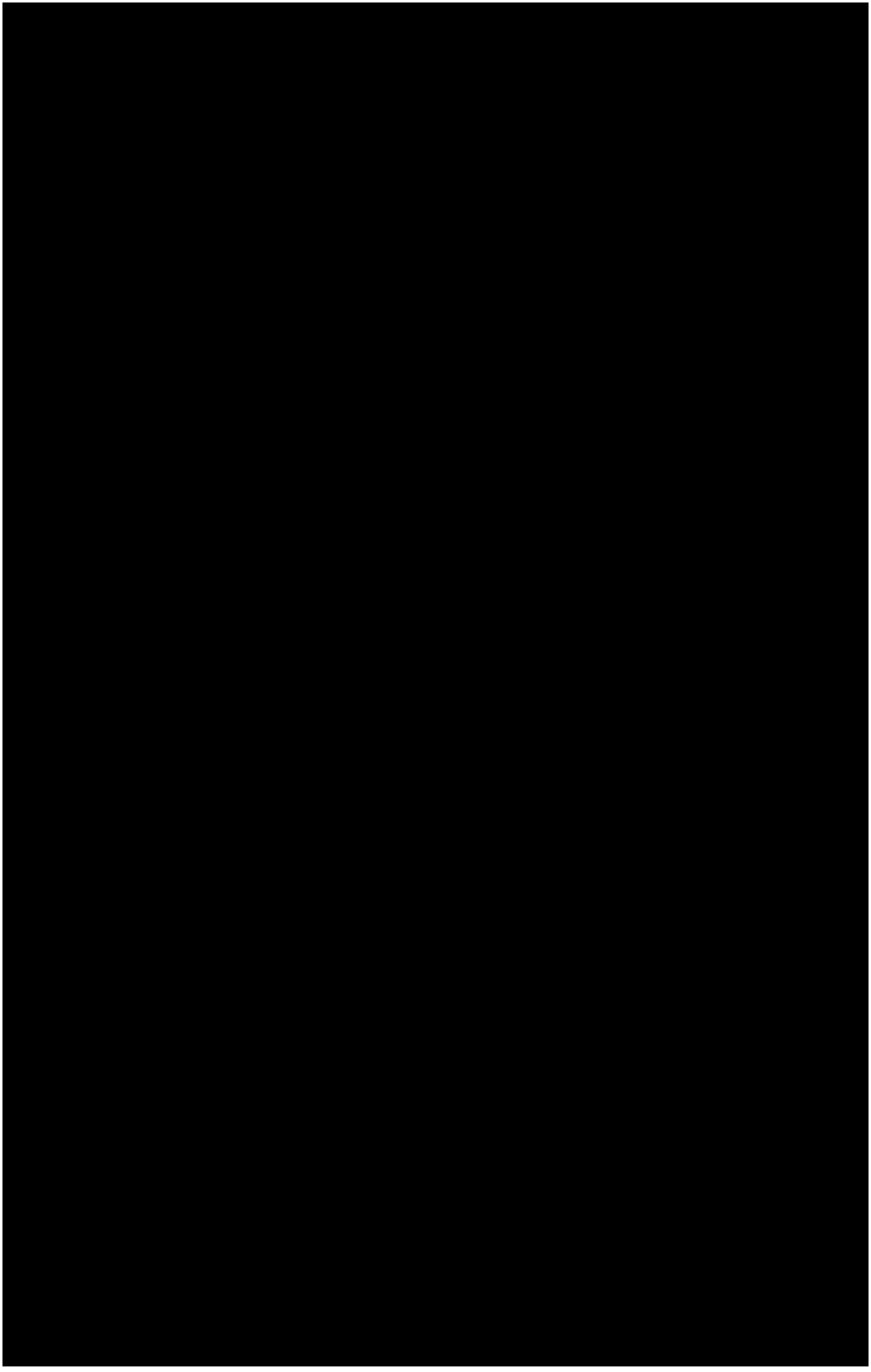

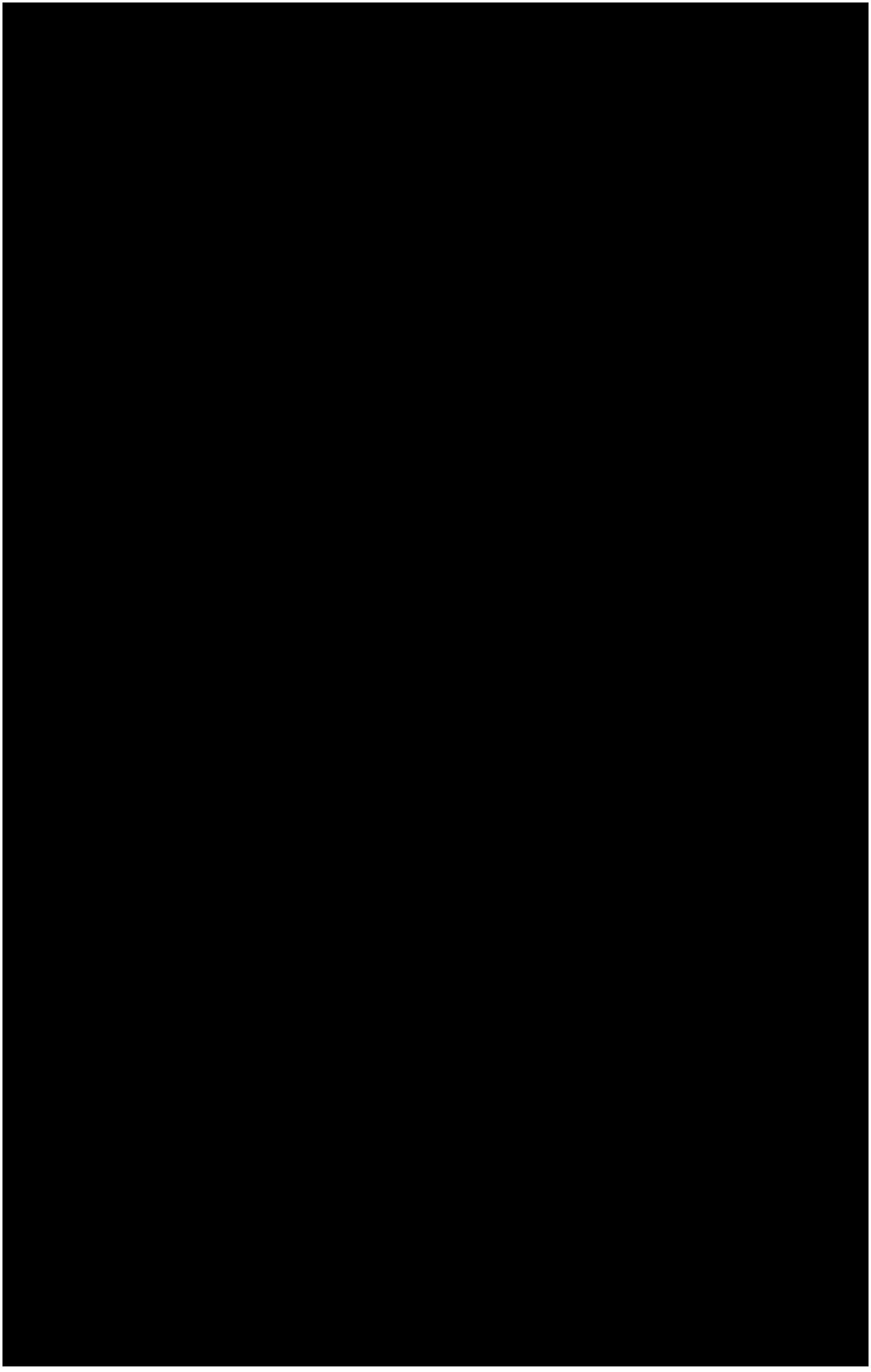

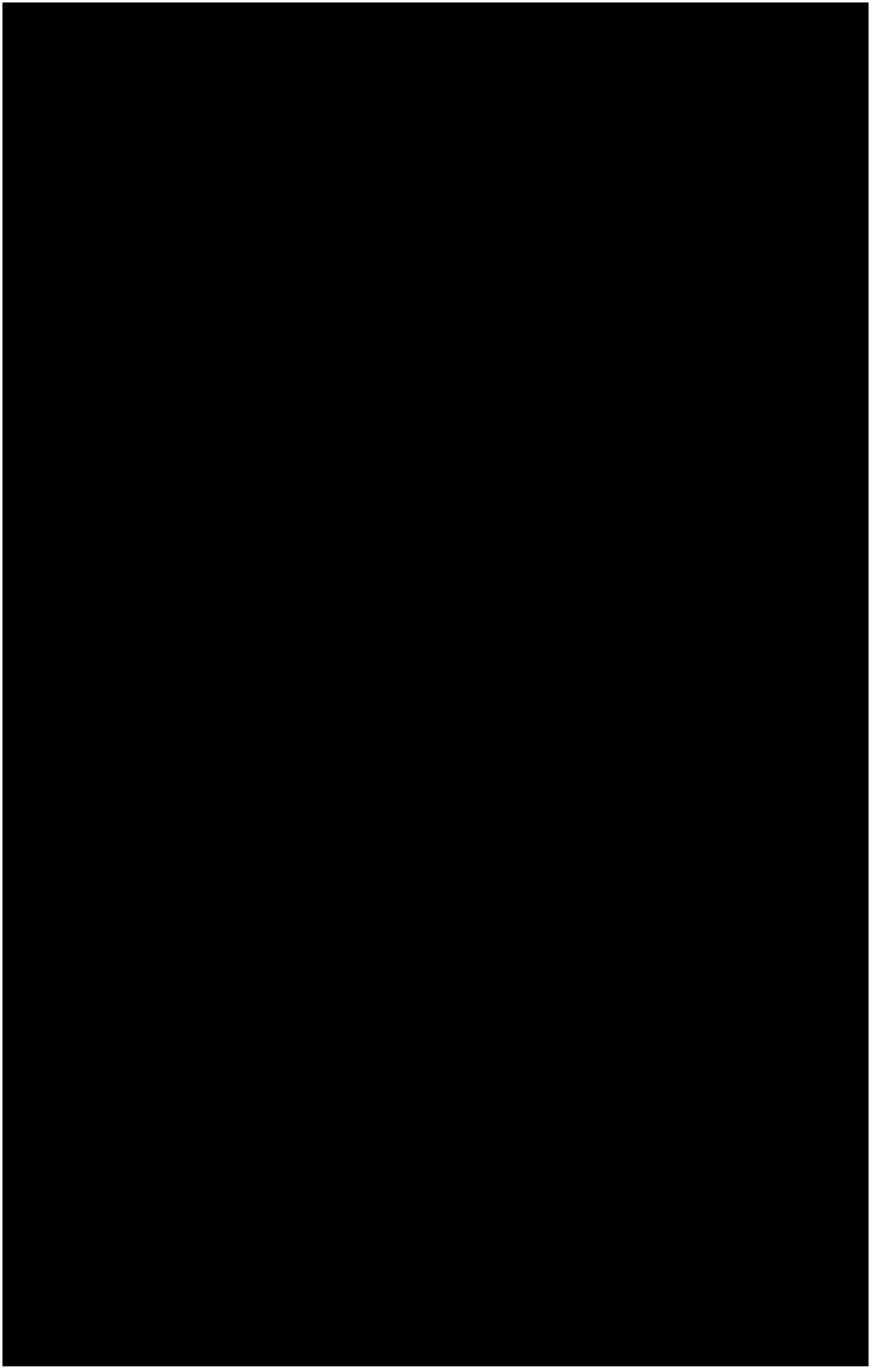

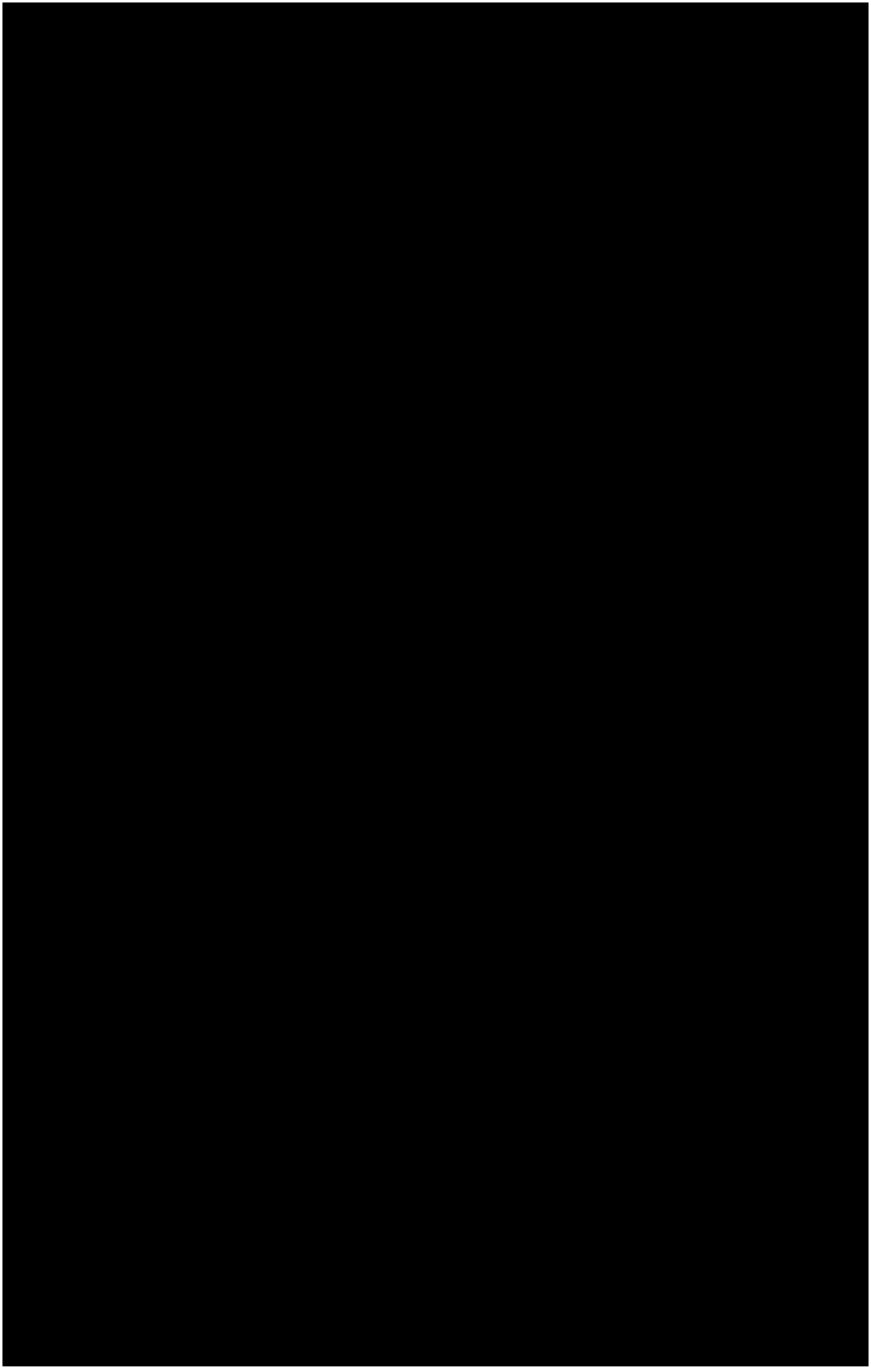

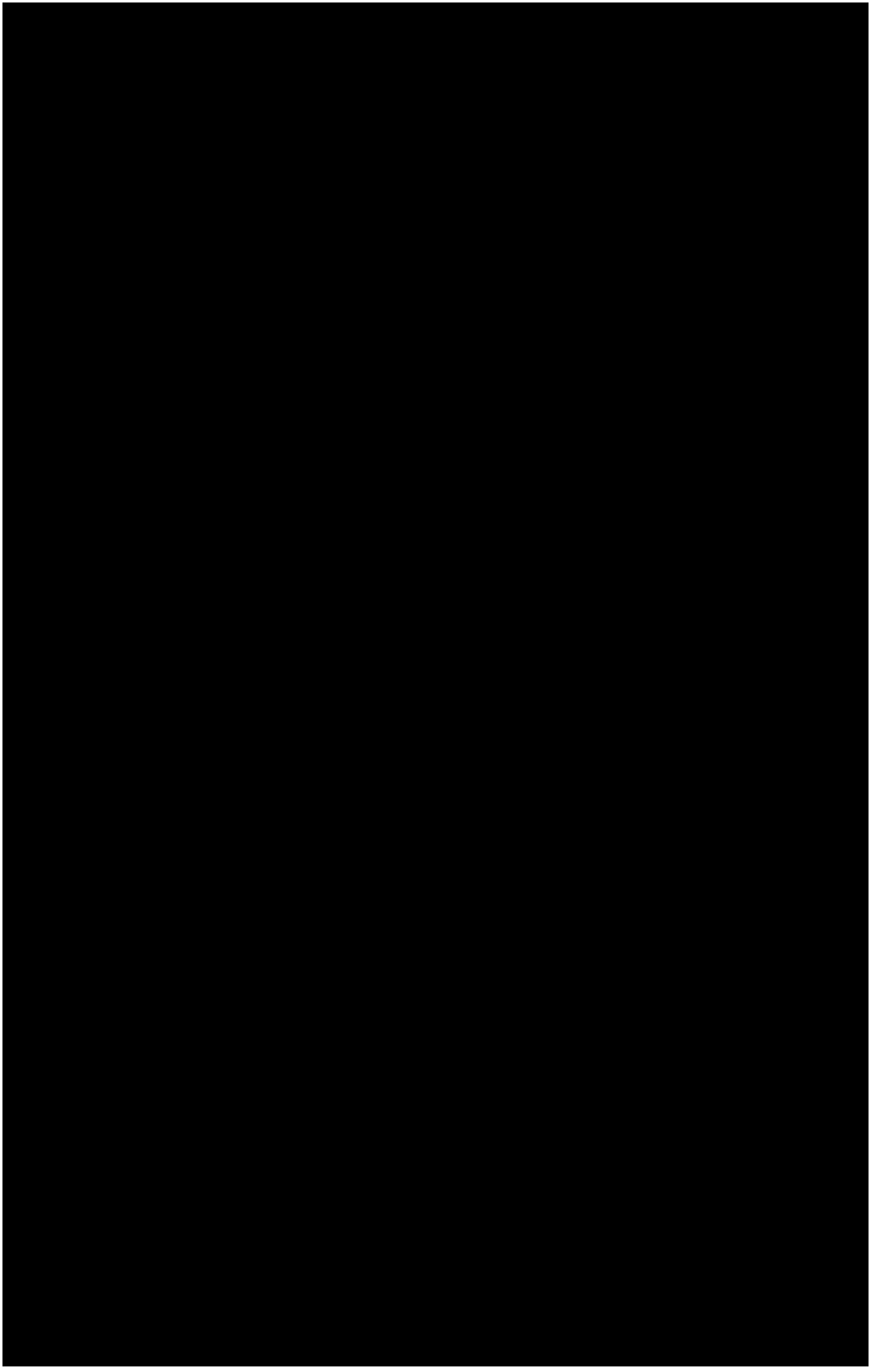

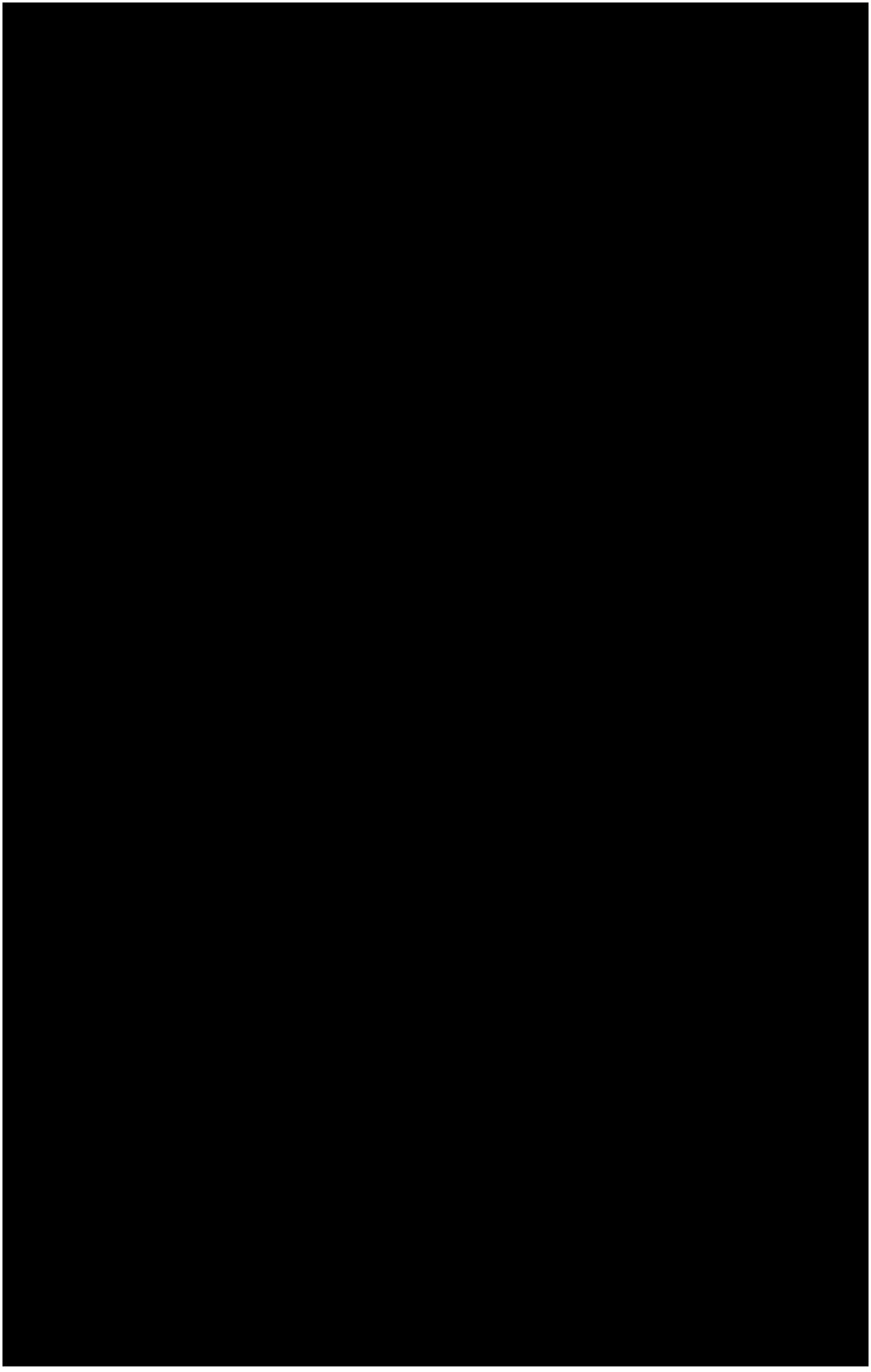

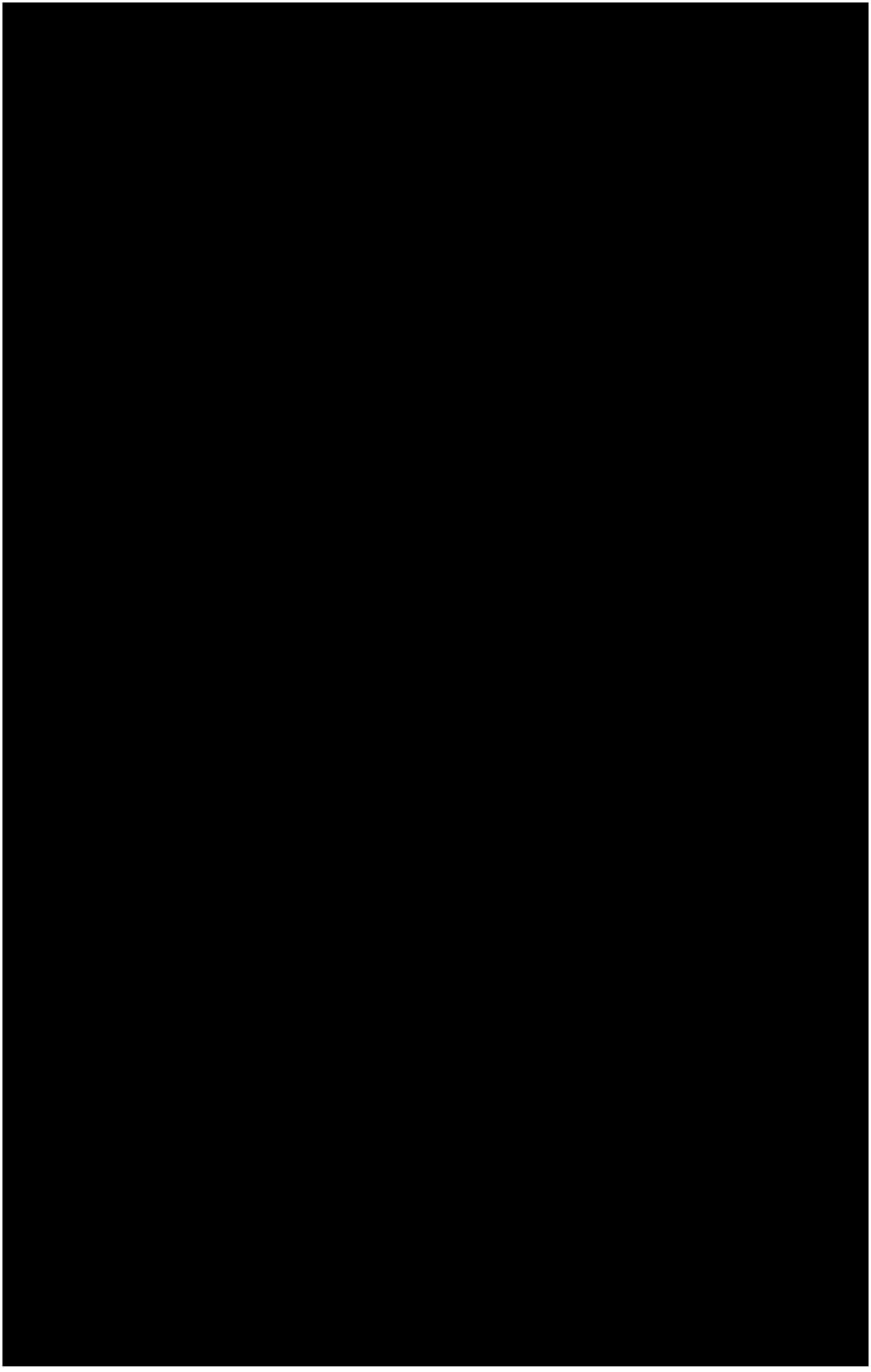

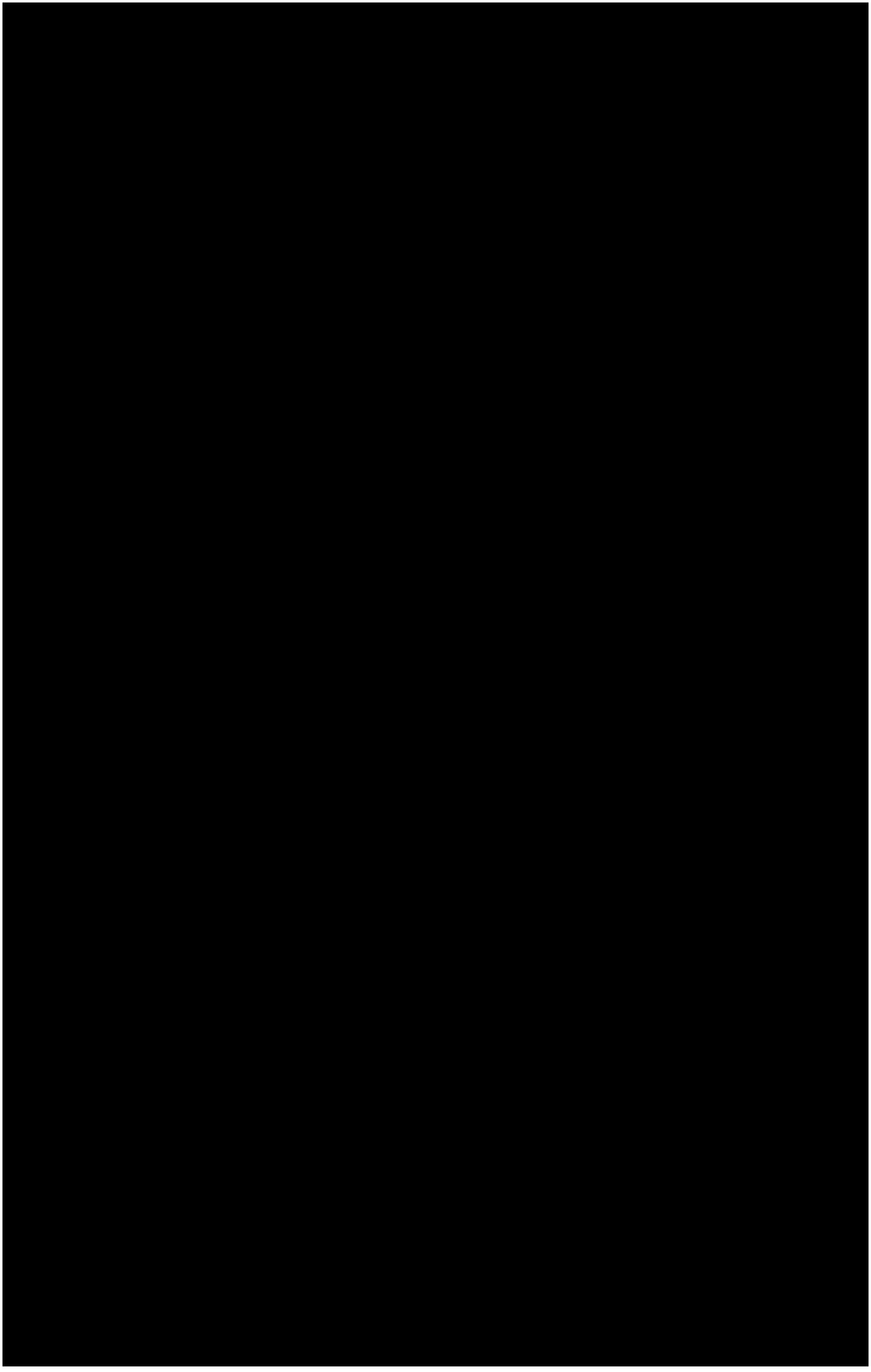

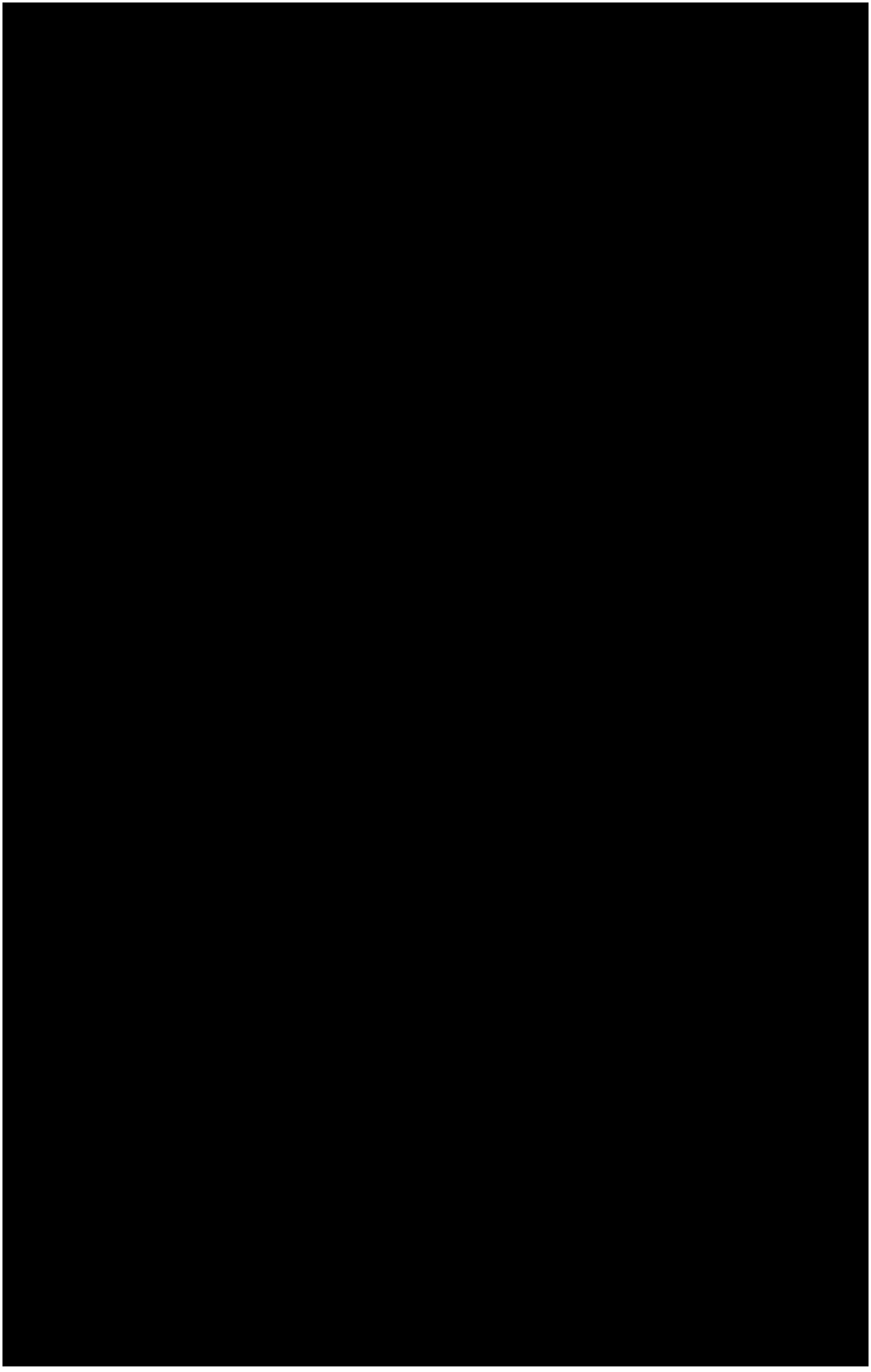

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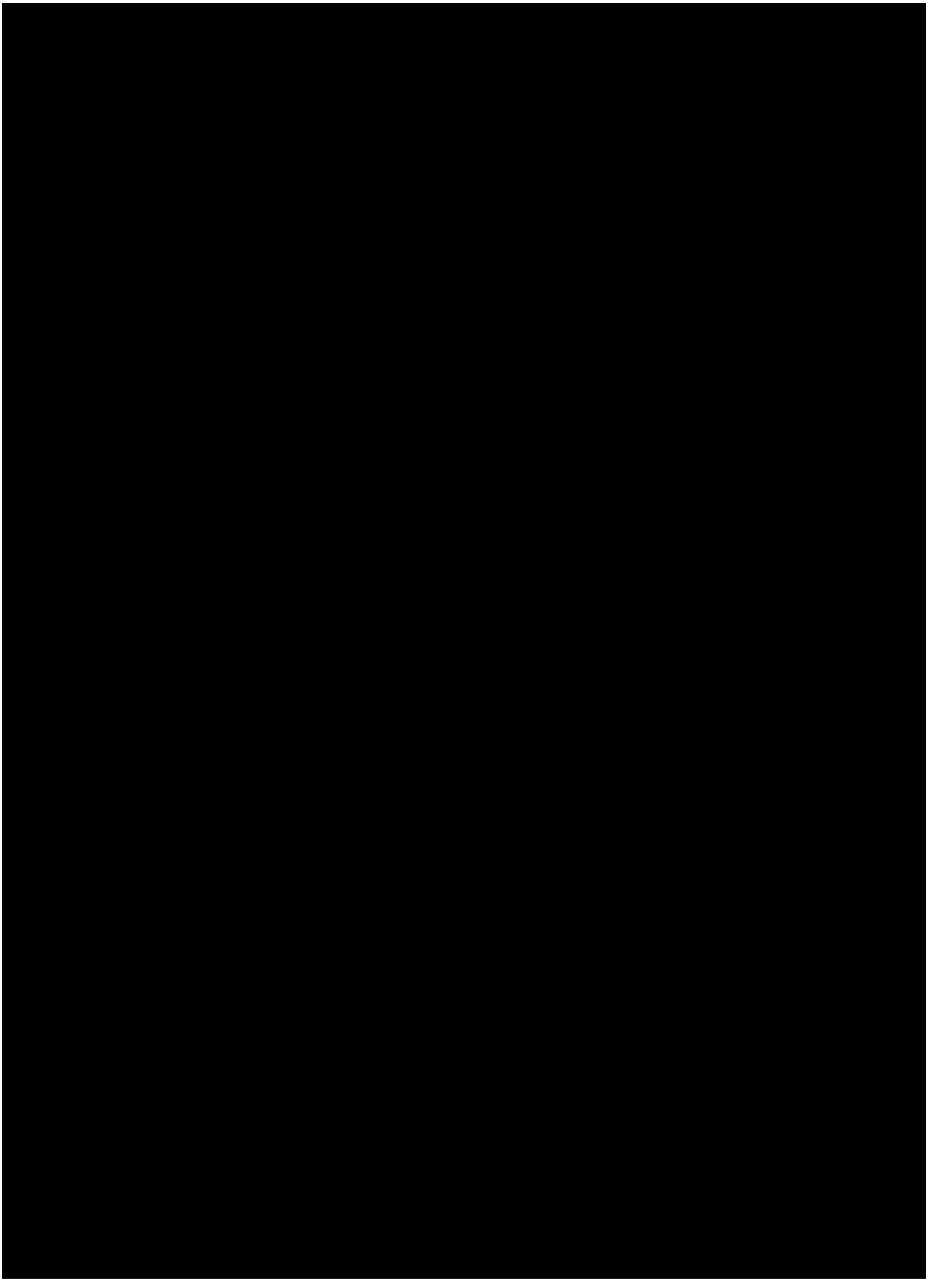

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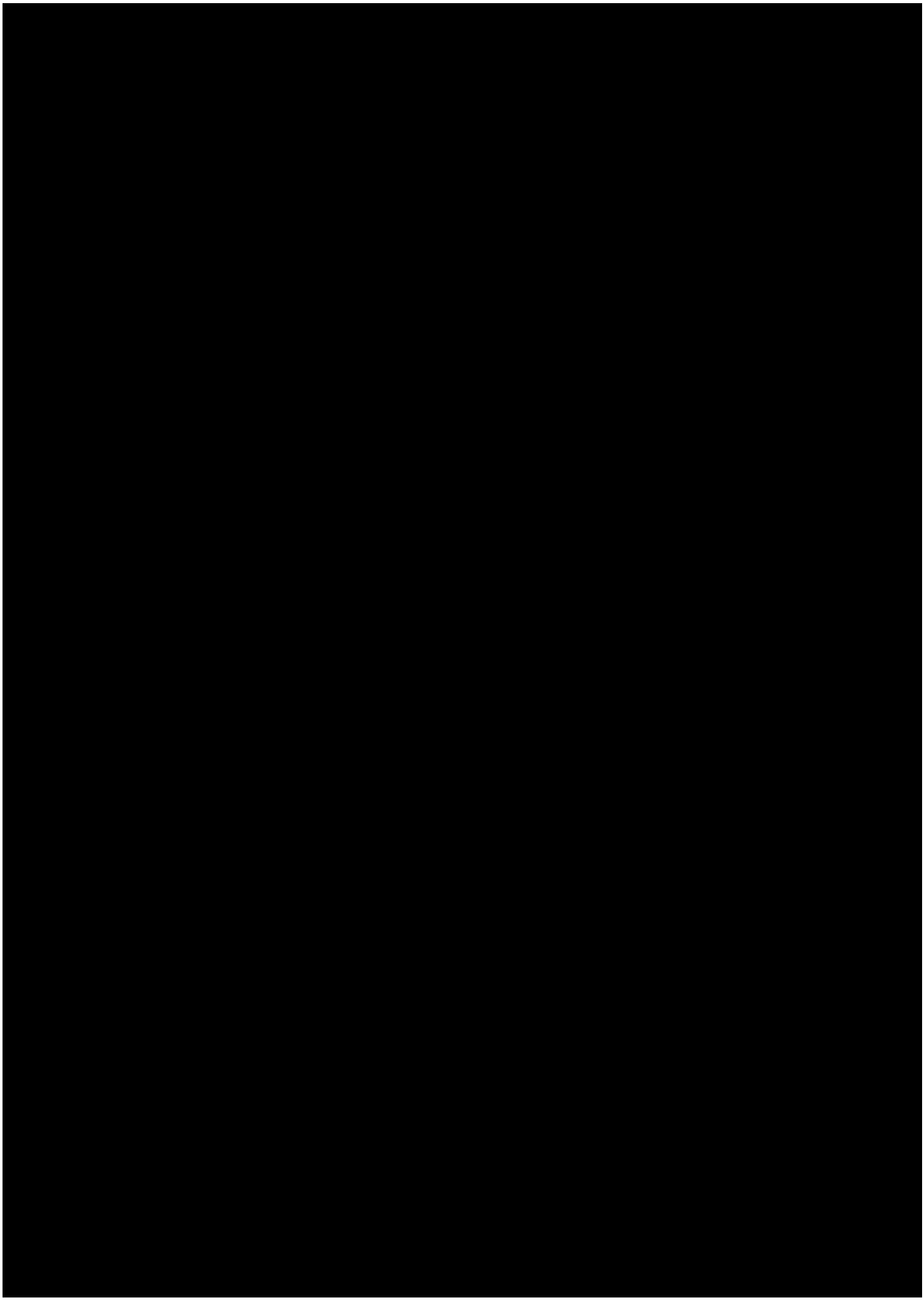

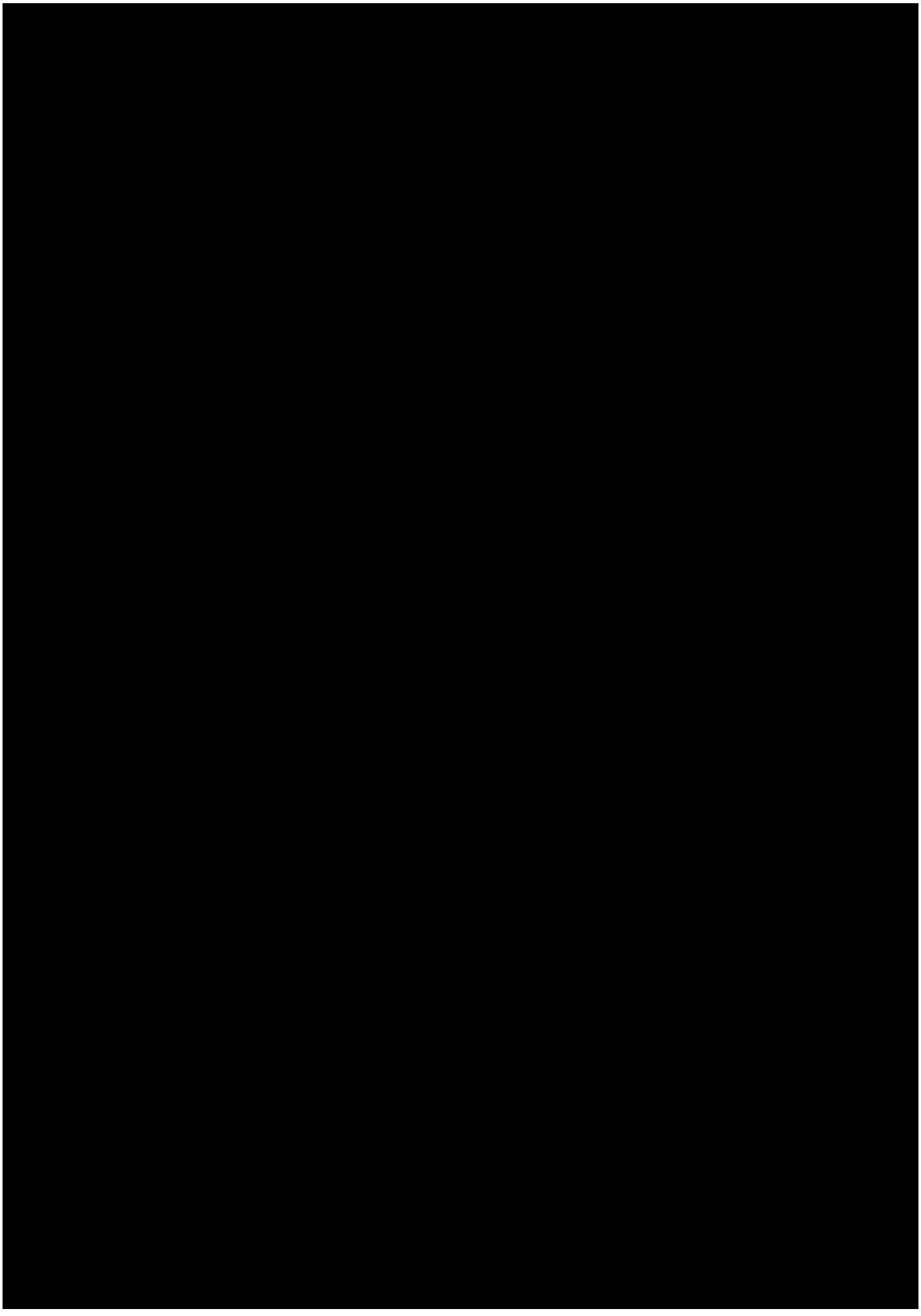

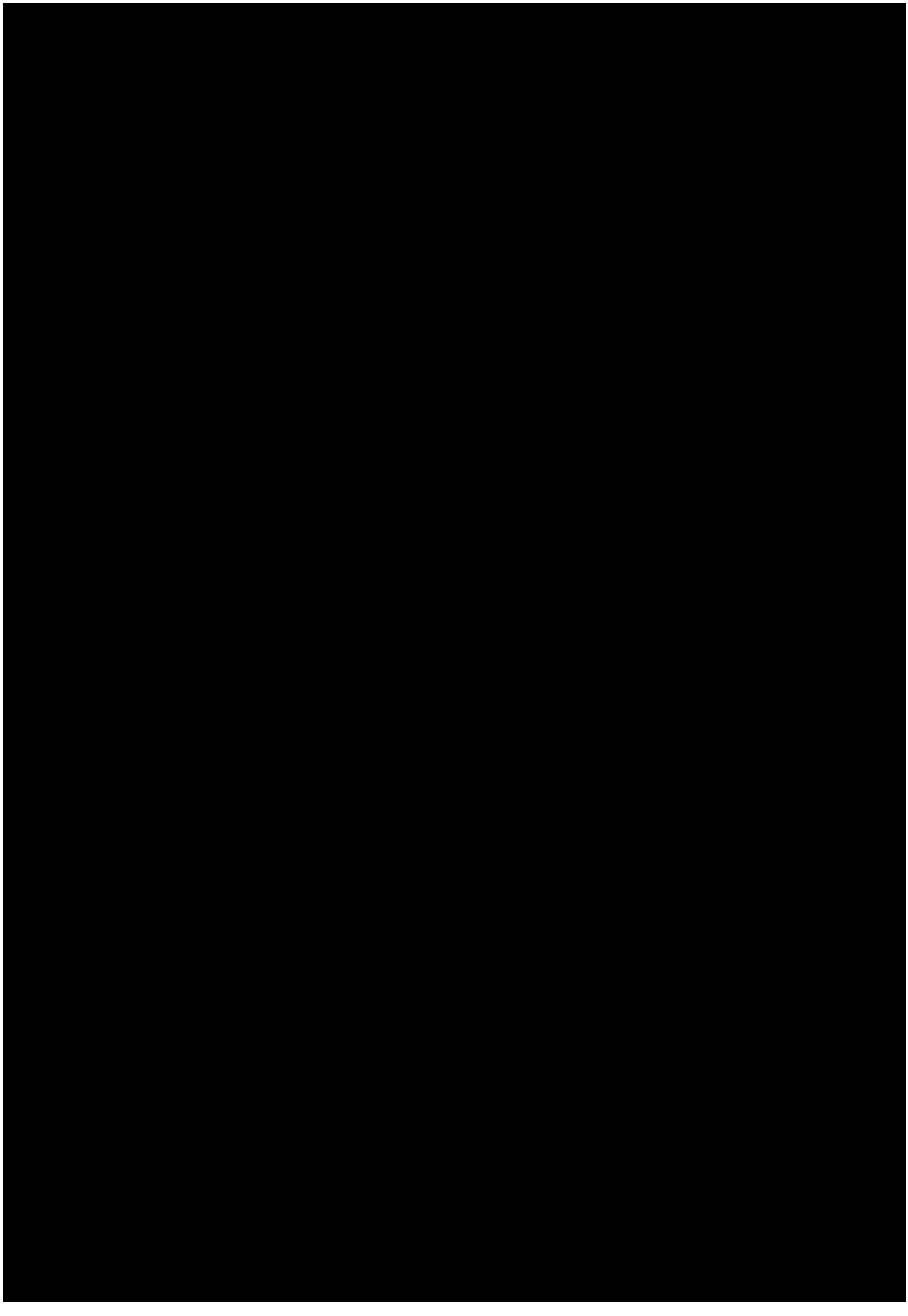

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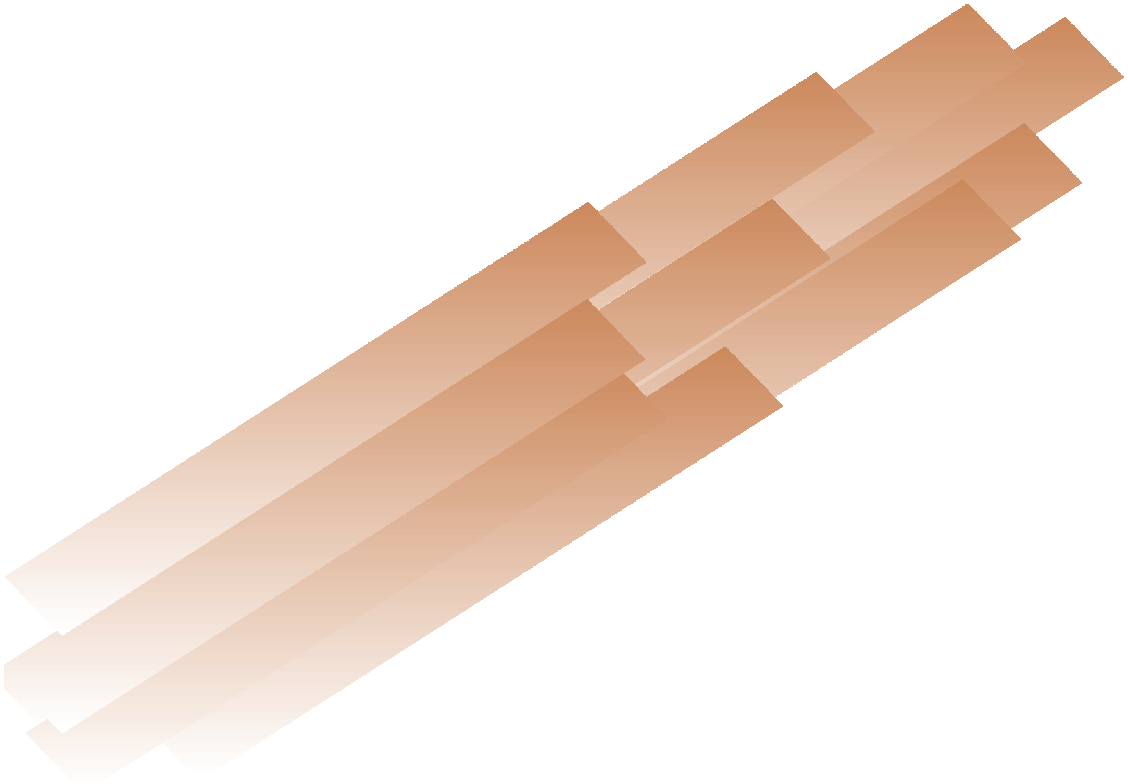
Appendix 18: Investigator Responsibilities

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance



ICH
April 1996

Guidance for Industry

E6 Good Clinical Practice: Consolidated Guidance

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication,
Training, and Manufacturers Assistance (HFM-40)
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448,
http://www.fda.gov/cber/guidelines.htm
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 1996
ICH

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented

deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded,

the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

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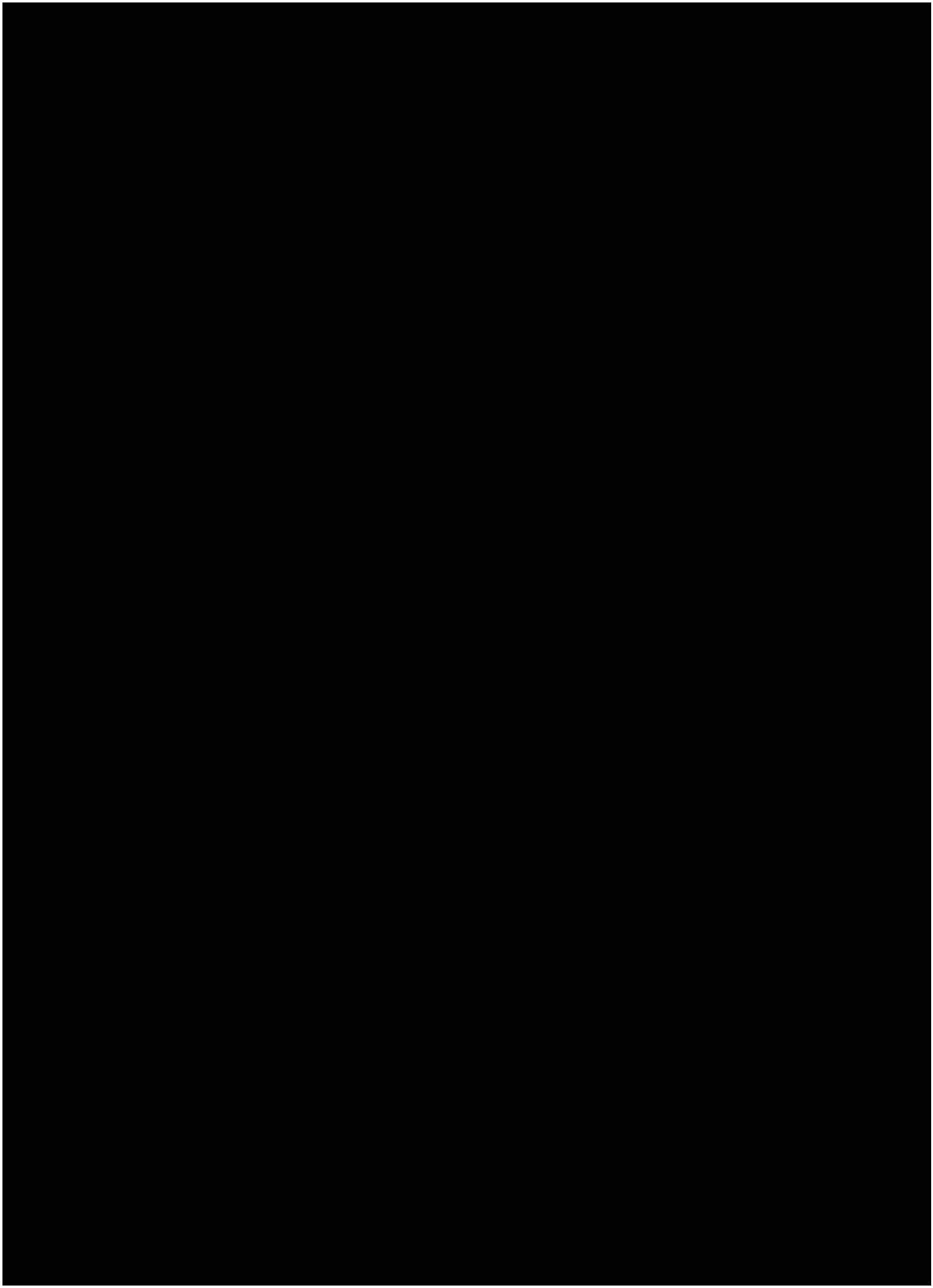

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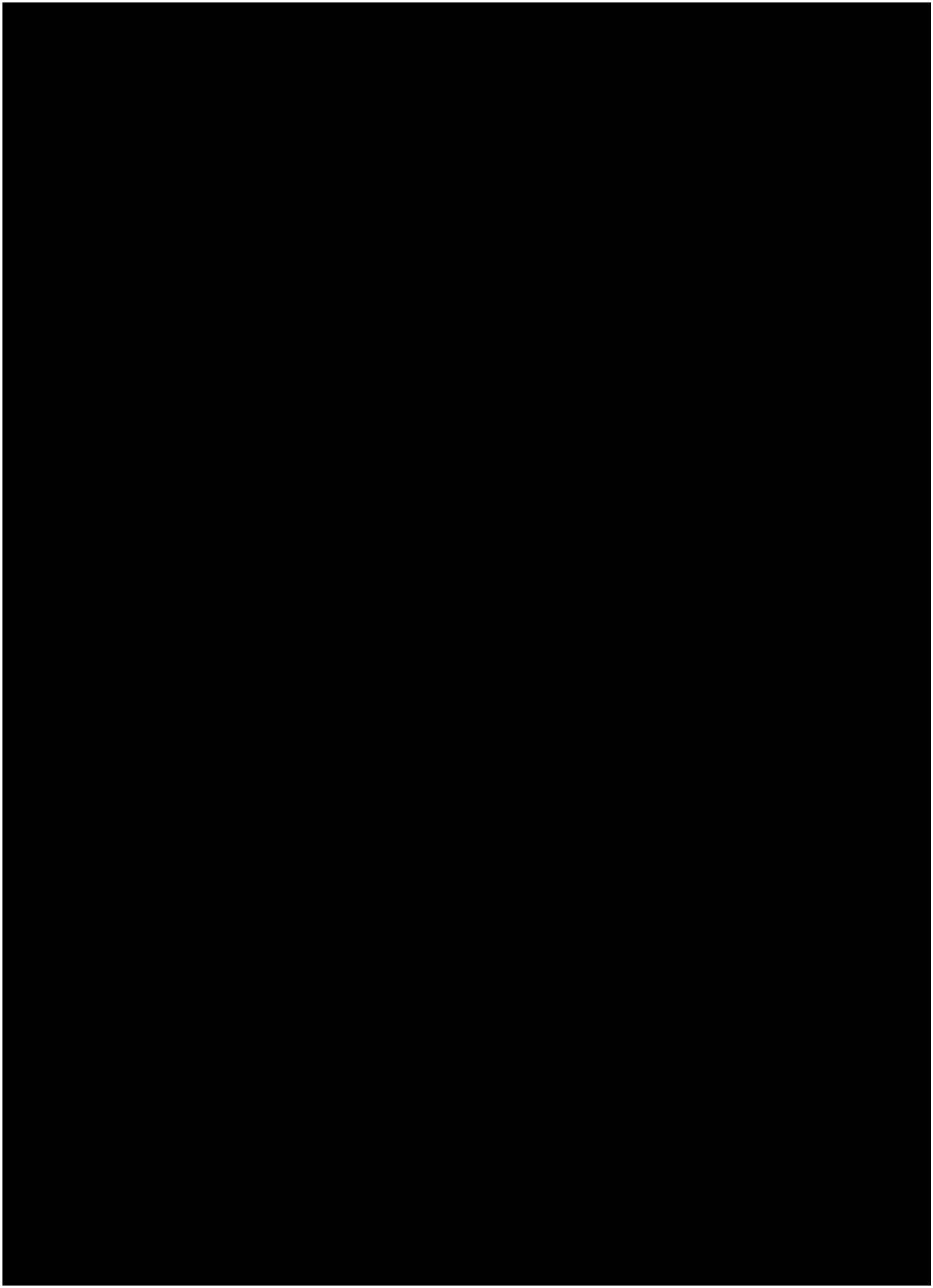

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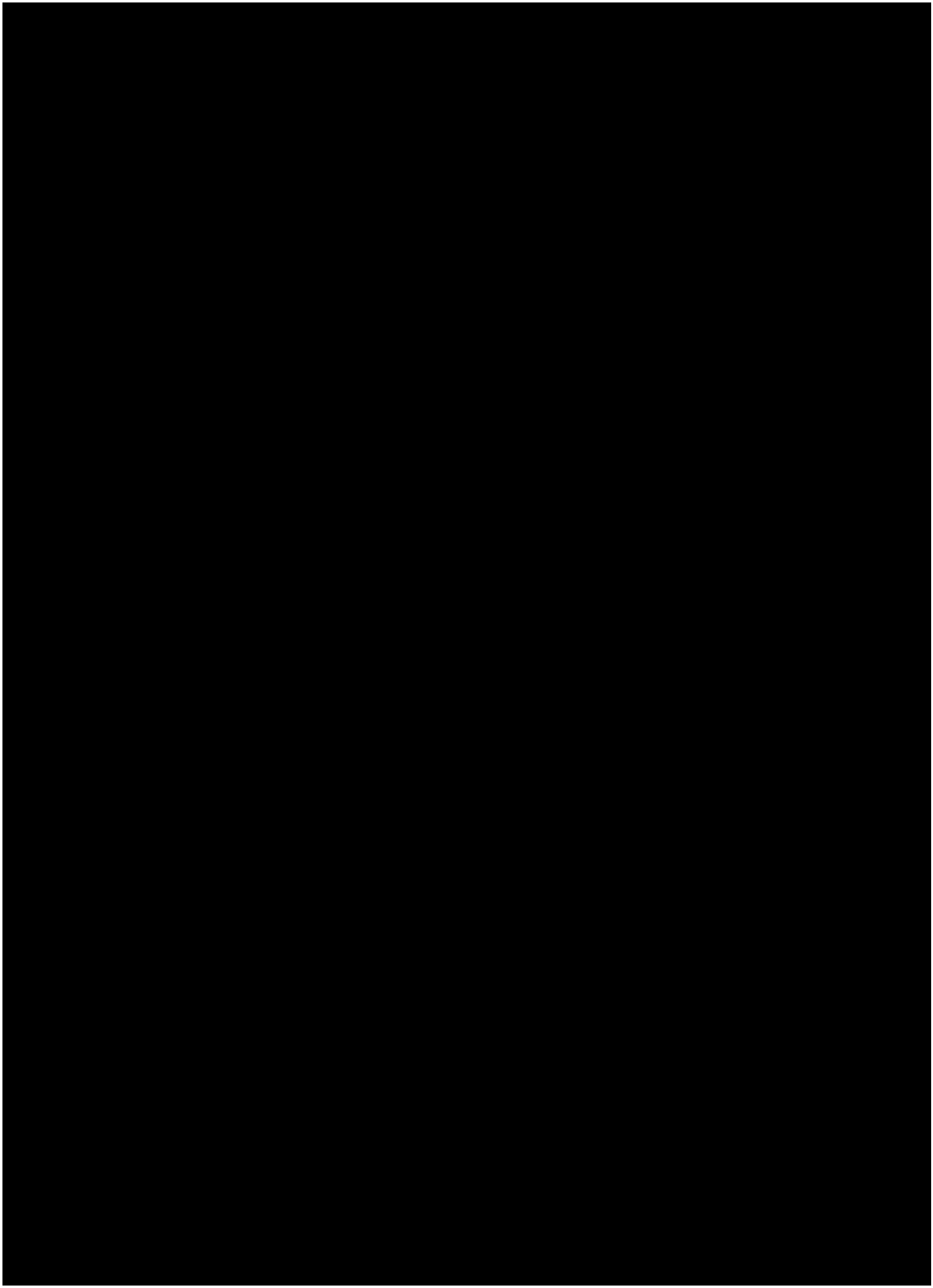

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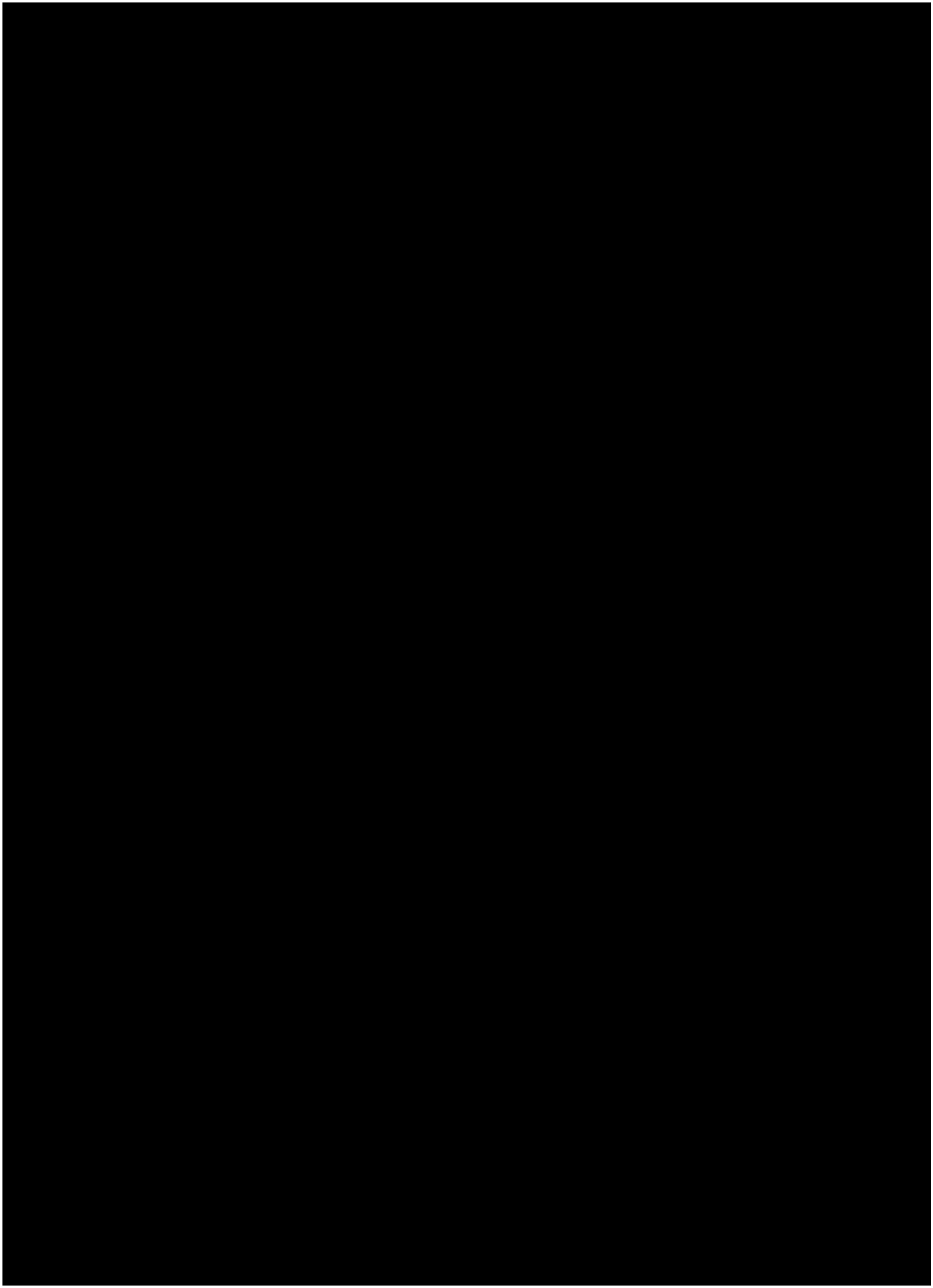

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