Official Title:	A Phase 3, multicenter, randomized, double-blind, placebo-controlled 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
NCT Number:	NCT02442778
Document Date:	Protocol Version 5.0: 28 February 2017

PROTOCOL TITLE:

A Phase 3, multicenter, randomized, double-blind, placebo-controlled 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-786-302-Amendment 4	**IND:**124099
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 28 February 2017
Drug:	AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM; INN:deudextromethorphan]/ quinidine sulfate [Q])	**Version:** 5.0

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Protocol Amendment 2 (Version 3.0)

Summary of Changes

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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
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
CYP	Cytochrome P450
d6-DM	Deuterated (d6)-dextromethorphan hydrobromide (or free base form)
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
EC	Ethics Committee
ECDEU	Early Clinical Drug Evaluation Unit
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EP	European Pharmacopeia
ESS	Epworth Sleepiness Scale

Abbreviation	Definition
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
MS	Multiple Sclerosis
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 (or free base form)
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
TCA	Tricyclic antidepressant
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 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-786-302 (Amendment 4, 28 February 2017)

This document is a confidential communication of Avanir Pharmaceuticals. The recipient agrees that no unpublished information contained within this document or protocol will be disclosed or published without prior consent and written approval from Avanir. An exception to this agreement may be made for the purposes of ethical or regulatory review, in which case this document may be disclosed to an Ethics Review Board or any authorized representative of a national authority as required by regulation.

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 Name: [redacted], MD	

STUDY SYNOPSIS

Title: A Phase 3, multicenter, randomized, double-blind, placebo-controlled 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 470 patients will be enrolled at approximately 75 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 study.

Duration: Patients will be enrolled in the study for approximately 16 weeks; with up to 4-week screening period and 12-week treatment period.

Study Treatment: The investigational product is AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM; INN:deudextromethorphan]/quinidine sulfate [Q]). Three doses of AVP-786 will

be used in the study, d6-DM 18 mg/Q 4.9 mg, d6-DM 28 mg/Q 4.9 mg and d6-DM 42.63 mg/Q 4.9 mg, hereafter referred to as AVP-786-18/4.9, AVP-786-28/4.9, and AVP-786-42.63/4.9, 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 to either AVP-786-28/4.9, AVP-786-42.63/4.9, or placebo group. 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.

Patients randomized to the AVP-786-28/4.9 group 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 9 weeks of the study. If deemed necessary by the investigator, a one-time downward dose adjustment to AVP-786-18/4.9 will be allowed after Visit 3 up to and including Visit 4 (ie, Day 23 to Day 43), and the patient will remain on the lower dose of study medication for the remaining study duration. Patients requiring a dose-adjustment between study visits will need to have an unscheduled visit to perform safety assessments.

Patients randomized to the AVP-786-42.63/4.9 group will start with AVP-786-28/4.9 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-786-28/4.9 BID for 14 days. From Day 22, patients will receive AVP-786-42.63/4.9 BID for the remaining 9 weeks of the study. If deemed necessary by the investigator, a one-time downward dose adjustment to AVP-786-28/4.9 will be allowed after Visit 3 up to and including Visit 4 (ie, Day 23 to Day 43), and the patient will remain on the lower dose of study medication for the remaining study duration. Patients requiring a dose-adjustment between study visits will need to have an unscheduled visit to perform safety assessments.

Patients will have at least a [redacted] chance of receiving AVP-786 at some point during 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). Patients who terminate early will receive daily phone calls for 5 consecutive days following the early termination (ET) visit to query on their overall well-being and will be asked to return for an in-clinic Follow-up visit 30 days after last dose of study medication for selected safety and efficacy assessments. 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 (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 endpoint is the change from Baseline to Week 12 (Day 85) in the composite CMAI scores. The primary treatment comparisons (AVP-786-42.63/4.9 vs. placebo and AVP-786-28/4.9 vs. placebo) will be performed by using a linear mixed effects model repeated measures (MMRM) with comparisons being made between the patients treated with AVP-786 and patients treated with concurrent placebo. 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 factors as appropriate. An unstructured covariance model will be used.

A gate-keeping procedure will be used to control the overall type I error at 2-sided $\alpha = 0.05$ for the 2 primary treatment comparisons (AVP-786-42.63/4.9 vs. placebo and AVP-786-28/4.9 vs. placebo). Specifically, the comparison between AVP-786-42.63/4.9 vs. placebo will be performed first at the significance level of 0.05. If the comparison is statistically significant, the comparison between AVP-786-28/4.9 vs. placebo will be performed at the same significance level.

Secondary efficacy endpoints include change from Baseline to Week 12 (Day 85) 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, ADCS-CGIC-Overall, CGIS-Agitation, ADAS-cog, and GMHR.

Safety Analyses

Safety measures will be summarized by treatment group.

Sample Size Calculation

Power calculation was performed assuming a normal distribution for the primary efficacy endpoint. [redacted]

The study protocol is amended to include another dose arm (AVP-786-42.63/4.9) with 140 patients in the treatment arm, when approximately 100 patients have already been enrolled (50 AVP-786 28/4.9 and 50 placebo) in the study. To maintain an approximate [redacted] chance for an incoming patient to receive active drug, the sample size for the placebo treatment group is amended to 190. Overall, the total sample size of 470 patients will include 140 patients for AVP-786 28/4.9 and AVP-786 42.63/4.9 groups each and 190 patients in the placebo group. This sample size will provide approximately [redacted] power to detect a treatment effect size of [redacted] between AVP-786 42.63/4.9 and concurrent placebo treatment group.

Table 1 Schedule of Evaluations and Visits

Procedure	Visit: / Study Day: / End of Study Week:	Screening[1] Day -28 to -1 Week -4 to -1	Baseline Day 1	Visit 2[1] Day 8 Week 1	Visit 2.1[1] Day 15 Week 2	Visit 3[1,19] Day 22 Week 3	Phone Call[1,2,19] Day 29 Week 4	Visit 4[1,19] Day 43 Week 6	Visit 5[1] Day 64 Week 9	Phone Call[1,2] Day 71 Week 10	Visit 6[1,4]/ET[3] Day 85 Week 12	Follow-up Visit[3] 30-days Postdose
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	X
Risk assessment for falls (worksheet and TUG test)		X						X[9]			X[9]	
ECG		X[10]	X[11]		X	X		X	X		X	
AEs			X	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	X
MMSE		X	X					X			X	
GMHR		X									X	
CMAI		X	X	X	X	X		X	X		X	X
NPI		X[12]	X	X[12]	X[12]	X		X	X		X	
CSDD		X						X			X	
ZBI			X					X			X	

Procedure	Visit:	Screening[1]	Baseline	Visit 2[1]	Visit 2.1[1]	Visit 3[1,19]	Phone Call[1,2,19]	Visit 4[1,19]	Visit 5[1]	Phone Call[1,2]	Visit 6[1,4] /ET[3]	Follow-up Visit[3]
	Study Day:	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 64	Day 71	Day 85	30-days Postdose
	End of Study Week:	Week -4 to -1		Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 10	Week 12	
DEMQOL[13]			X					X			X	
ADAS-cog[14]			X					X			X	
PGIC[15]								X			X	
RUD			X					X			X	
ESS[14]			X					X			X	
S-STS		X	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; 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 (excludes follow-up phone calls for ET patients) 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 usage

3 Early termination visit for patients who withdraw prior to study completion. Patients who terminate early from the study will receive daily phone calls for 5 consecutive days

Procedure	Visit:	Screening[1]	Baseline	Visit 2[1]	Visit 2.1[1]	Visit 3[1,19]	Phone Call[1,2,19]	Visit 4[1,19]	Visit 5[1]	Phone Call[1,2]	Visit 6[1,4] /ET[3]	Follow-up Visit[3]
	Study Day:	Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 64	Day 71	Day 85	30-days Postdose
	End of Study Week:	Week -4 to -1		Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 10	Week 12	

following the ET visit to query on their overall well-being and an in-clinic Follow-up visit 30 days after last dose of study medication for selected safety and efficacy assessments.

4 Patients 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 $\geq$ 10 at baseline

14 ADAS-cog and ESS are to be rated only by patients with an MMSE score of $\geq$ 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 brought to the clinic and 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

19 A one-time downward dose adjustment is allowed after Visit 3 (Week 3) up to and including Visit 4 (Week 6), ie Day 23 to Day 43. Patient will need to return to the clinic for an unscheduled visit for safety assessments

1 BACKGROUND AND CLINICAL RATIONALE

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease eventually leading to death. An estimated 5.4 million Americans have Alzheimer's disease, this number has doubled since 1980 and is expected to be as high as 16 million by 2050.[3] Among US adults over age 65, prevalence estimates of dementia range from 5% to 15%, with AD being the most common type of dementia.[4–6]

Agitation is widely recognized as a common and important clinical feature of AD and other forms of dementia.[7] Although readily recognized by clinicians and caregivers, a consensus definition of agitation in dementia was only recently developed by the International Psychogeriatric Association (IPA) Agitation Definition Working Group (ADWG) with the following criteria: "1) occurring in patients with a cognitive impairment or dementia syndrome; 2) exhibiting behavior consistent with emotional distress; 3) manifesting excessive motor activity, verbal or physical aggression; and 4) evidencing behaviors that cause excess disability impairing relationships and/or daily activities and are not solely attributable to another disorder (psychiatric, medical, or substance-related)".[2] Agitation and/or aggression are estimated to affect up to approximately 80% of patients with dementia[8,9] with an increase in prevalence as the disease progresses.

Agitation in patients with dementia is associated with increased functional disability,[10] worse quality of life,[11] earlier institutionalization,[12] increased caregiver burden,[10] increased healthcare costs,[13] shorter time to severe dementia,[14] and accelerated mortality.[14] For these reasons, agitation and aggression are the neuropsychiatric symptoms most likely to require pharmacological intervention in Alzheimer's patients.[7] However, there are currently no FDA-approved pharmacological treatments for agitation in AD, and clinicians ultimately resort to off-label use of antipsychotics, sedatives/hypnotics, anxiolytics, and antidepressants in an attempt to control symptoms.[15] Unfortunately, these treatments have limited utility given a modest efficacy that is offset by relatively poor adherence, safety, and tolerability.[7,16,17] Thus a critical need exists to develop a safe and effective pharmacological intervention for the treatment of agitation in dementia. Such a treatment could profoundly impact patient care, reduce caregiver burden, and potentially improve overall disease prognosis.

1.1 Rationale for Studying AVP-786 for Treatment of Agitation in Dementia

AVP-786 is a combination product of deuterated (d6)-dextromethorphan hydrobromide (d6-DM), the central nervous system (CNS)-active component, and quinidine sulfate (Q), used as an inhibitor of d6-DM metabolism via the cytochrome P450 (CYP) liver isoenzyme 2D6 (CYP2D6). AVP-786 is being developed by Avanir Pharmaceuticals Inc. (Avanir) for the treatment of neurological and psychiatric disorders.

The hypothesis that AVP-786 can provide clinical benefit for agitation in patients with AD is based on the demonstrated receptor pharmacology of d6-DM and the efficacy and safety results of a Phase 2 clinical

study of AVP-923 (dextromethorphan/quinidine combination) for the treatment of agitation in AD (Study 12-AVR-131).

d6-DM binds to receptors responsible for modulation of glutamate, monoamine, sigma-1, and nicotinic cholinergic pathways that may be key to CNS therapeutics. Pharmacology studies conducted by Avanir with d6-DM have demonstrated that deuteration does not alter the basic pharmacology of DM. Pharmacokinetic (PK) and drug metabolism studies indicate that d6-DM is metabolized by the same metabolic pathways as DM, but that deuteration results in a decreased rate of metabolism by CYP2D6.

The recently completed Phase 2 Study 12-AVR-131 met the primary efficacy endpoint and showed clear improvement of agitation in patients receiving AVP-923 compared with placebo. Study 12-AVR-131 was a 10-week, randomized, double-blind, placebo-controlled, 2-stage, sequential parallel comparison design (SPCD) study to assess the efficacy, safety, and tolerability of AVP-923 for the treatment of symptoms of agitation in 220 patients with AD. Patients who received AVP-923 had significantly reduced agitation compared to patients who received placebo ($p<0.001$) as measured by the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI). The majority of the secondary endpoints studied (e.g., NPI-total, NPI-Agitation/Aggression domain Caregiver Distress, Clinical Global Impression of Change [CGIC]-Agitation, Clinical Global Impression of Severity [CGIS]-Agitation and Patient Global Impression of Change [PGIC]) were also statistically significant. Both clinician and patient/caregiver impressions of change corroborated the clinical meaningfulness of improvements observed in agitation. Numerically favorable response in cognition as measured by the Mini Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) were observed but neither achieved statistical significance.

Studies conducted by Avanir have shown that d6-deuterium modification of DM reduced the rate of CYP2D6 metabolism such that combination with a significantly lower dose of quinidine (< 50% of the amount of Q contained in AVP-923) was sufficient for bioequivalence of d6-DM to DM in AVP-786 and AVP-923, respectively (Studies 12-AVR-132, 13-AVR-134, 14-AVP-786-101, and 14-AVP-786-102). The lower amount of Q in AVP-786 may reduce interactions with other CYP2D6 substrates, limit Q levels even in the presence of CYP3A4 inhibitors, and reduce the effects on cardiac repolarization and QTc interval.

The receptor pharmacology of d6-DM and the robust clinical effect observed in Study 12-AVR-131 suggest AVP-786 may have a benefit in agitation, while the significantly lower dose of Q in AVP-786 may lead to improvement in the safety profile compared with AVP-923. Combined, the potential efficacy and safety of AVP-786 warrant further clinical investigation. The current study (Study 15-AVP-302) is designed to evaluate the efficacy, safety, and tolerability of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer’s type.

1.2 Rationale for the Study Design

The randomized, placebo-controlled, double-blind design reduces sources of bias that are inherent in less well-controlled designs. The safety assessments used are standard in clinical research and are generally

recognized as reliable, accurate, and relevant. The rating scales used to assess efficacy are well-established instruments that are widely used in clinical studies of AD.

1.3 Rationale for AVP-786 Dose

The planned doses of AVP-786 for this study initially were 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. The AVP-786-28/4.9 dose is achieved by gradual titration schedule starting with AVP-786-18/4.9. The study protocol is amended to include an additional treatment arm with a dose of d6-DM 42.63 mg/Q 4.9 mg (AVP-786-42.63/4.9) achieved by gradual titration with AVP-786-28/4.9 using the same titration regimen.

[redacted]

1.4 Rationale for the Duration of Dosing

A drug being developed for treatment of a chronic condition needs to show maintenance of effect. A 12-week treatment duration is generally considered by experts and regulators as a reasonable time frame to assess acute and chronic effects and safety of a compound for chronic use. To ensure tolerability, patients allocated to the study treatment (AVP-786) will gradually be exposed to the assigned dose; beginning with once-daily dosing of a dose lower than the assigned dose for one week, followed by twice-daily dosing of the same dose for 2 weeks, and then twice-daily dosing of the assigned dose (AVP-786-28/4.9) for the remaining study duration. [redacted]

Thus, patients assigned to AVP-786-28/4.9 will receive AVP-786-18/4.9 once daily for one week, followed by AVP-786-18/4.9 twice daily for 2 weeks and then AVP-786-28/4.9 for the remaining study duration, with a provision for a one-time down titration to AVP-786-18/4.9, whereas patients assigned to AVP-786-42.63/4.9 will receive AVP-786-28/4.9 once daily for one week, followed by AVP-786-28/4.9 twice daily for 2 weeks and then AVP-786-42.63/4.9 for the remaining study duration, with a provision for a one-time down titration to AVP-786-28/4.9 during the study.

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 study of 12-week treatment duration.

Approximately 470 patients will be enrolled at approximately 75 centers in North America. There will be 8 scheduled clinic visits including a screening visit, and 2 safety follow-up phone calls 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). Patients who terminate early will receive daily phone calls for 5 consecutive days following the ET visit to query on their overall well-being and will be asked to return for an in-clinic Follow-up visit 30 days after last dose of study medication for selected safety and efficacy assessments. Patients 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. 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).

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 applicable 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.

Following screening procedures for assessment of inclusion and exclusion criteria, eligible patients will be randomized into the study to either the AVP-786-28/4.9, AVP-786-42.63/4.9, or placebo group. 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 the AVP-786-28/4/9 group 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 9 weeks of the study. If deemed necessary by the investigator, a one-time downward dose adjustment to AVP-786-18/4.9 will be allowed after Visit 3 up to and including Visit 4 (ie, Day 23 to Day 43), and the patient will remain on the lower dose of study medication for the remaining study duration. Patients requiring a dose-adjustment between study visits will need to have an unscheduled visit to perform safety assessments.

Patients randomized to the AVP-786-42.63/4.9 group will start with AVP-786-28/4.9 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-786-28/4.9 BID for 14 days. From Day 22, patients will receive AVP-786-42.63/4.9 BID for the remaining 9 weeks of the study. If deemed necessary by the investigator, a one-time downward dose adjustment to AVP-786-28/4.9 will be allowed after Visit 3 up to and including Visit 4 (ie, Day 23 to Day

43), and the patient will remain on the lower dose of study medication for the remaining study duration. Patients requiring a dose-adjustment between study visits will need to have an unscheduled visit to perform safety assessments.

Patients will have at least a [redacted] chance of receiving AVP-786 at some point during 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.[18] 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 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]

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 terminate early will be asked to return to the clinic to complete the Visit 6 assessments and an in-clinic Follow-up visit, 30 days after last dose of study medication for selected safety and efficacy assessments. In addition, daily phone calls for 5 consecutive days following ET visit will be made for these patients to assess their overall well-being.

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:

- 42.63 mg of d6-DM and 4.9 mg of Q (USP, EP): AVP-786-42.63/4.9
- 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 3 doses of the IP and the placebo are listed in Table 2.

Table 2 Composition of Investigational Product

Ingredient (amounts in mg)	AVP-786-42.63/4.9	AVP-786-28/4.9	AVP-786-18/4.9	AVP-786 Placebo
Deudextromethorphan hydrobromide	42.63 (33)	28.00 (21.67)	18.00 (13.93)	0
Quinidine sulfate USP, EP	4.9 (4.26)	4.90 (4.26)	4.90 (4.26)	0
Croscarmellose sodium NF	X	X	X	X
Microcrystalline cellulose NF	X	X	X	X
Colloidal silicone dioxide NF	X	X	X	X
Magnesium stearate NF	X	X	X	X
[redacted] **capsules**	X	X	X	X

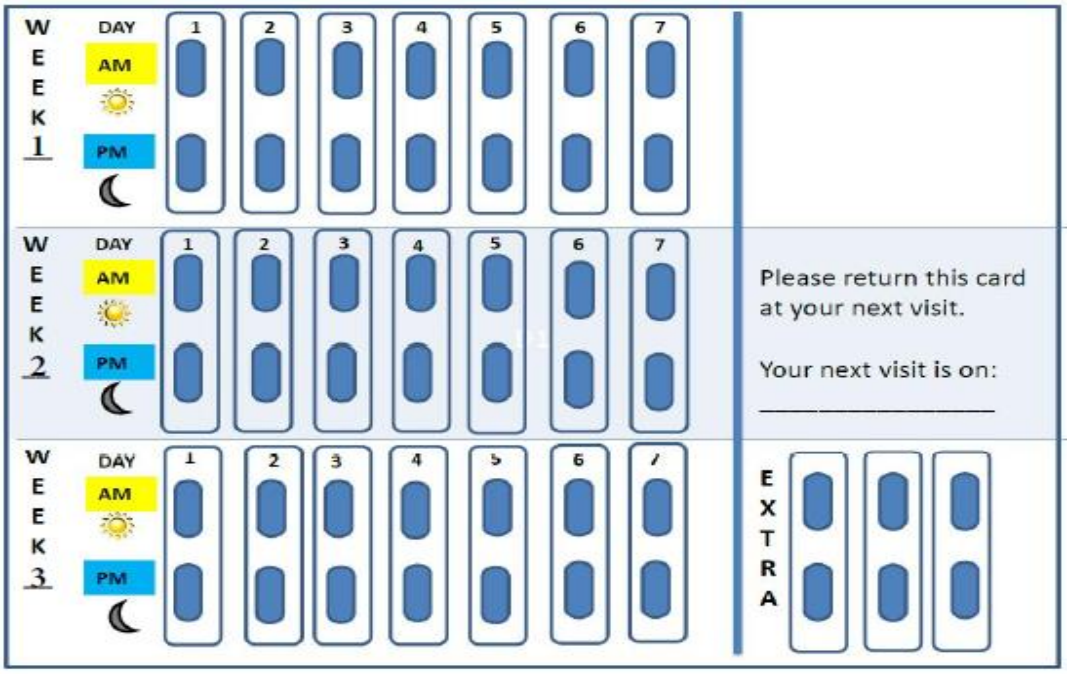
EP = European Pharmacopoeia; USP = United States Pharmacopoeia; NF = National Formulary

* Free base equivalent indicated in parenthesis

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 1). 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 1 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 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. 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. For Visits 2 (Day 8) and 2.1 (Day 15), caregivers should be advised that the patient should take the morning dose of study medication within 2 hours of the clinic appointment. 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) the initials and 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.

Eligible patients will be randomized to receive either AVP-786-28/4.9, AVP-786-42.63/4.9, or placebo on Day 1 (Baseline) according to a randomization scheme devised by Avanir or its representative and managed within an IWRS. 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). Blocked randomization is used to ensure treatment balance in each stratum. Patients will have at least a [redacted] chance of receiving AVP 786 at some point during the study.

5.3.2 Blinding/Masking

Blinding will be maintained by providing capsules 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 containers 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 Concomitant Medications and Nondrug Therapies

Patients may not take any of the disallowed medications listed in Appendix 1 during the study [redacted] prior to the start of dosing on Day 1. At each visit, caregivers will be queried as to whether or not the patient has taken any concomitant medications and, if so, the investigator

will record the medications taken and the reasons for their use. Caregivers will be instructed to record concomitant use of rescue medication [redacted] in the diary.

[redacted]

[redacted]

For patients who terminate early, the conditions of use for allowed concomitant medications and nondrug therapies or prohibited medications do not apply between the ET visit and the Follow-up visit. Any use of medications during this period will be at the discretion of the investigator. Patients should allow at least 14 days after stopping study medication before starting an MAOI.

5.5.1 [redacted]

[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]

[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 [redacted] is used to assess the frequency of manifestations of agitated behaviors in elderly persons. [redacted] Each of the [redacted] 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, [redacted] 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), and Follow-up visit (for ET patients). 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 [redacted] 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[22–26] and is easy and quick to administer, provided that the clinician knows the patient well.[27]

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.[28–30]

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 [redacted] (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 [redacted] 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)[31,32] 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), Day 85 (Visit 6) and Follow-up visit (for ET patients) 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. At the Follow-up visit (for ET patients), change from Day 85 (Visit 6) 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 [redacted] 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.[33] It is the most commonly used scale for measuring burden in caregivers' of patients with dementia and also other illnesses.[34] 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 ($r = 0.71$).[35] 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 [redacted] 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.[27]

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 [redacted] is a scale used to evaluate health related quality of life in patients with dementia and their caregivers.[36] 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 [redacted] was designed to evaluate the cognitive and non-cognitive behavioral dysfunction characteristics of patients with AD.[37] 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 [redacted] was specifically developed to assess signs and symptoms of major depression in patients with dementia.[38] 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 [redacted] is used to calculate healthcare costs associated with dementia.[39] It evaluates dementia patients' utilization of formal and informal healthcare resources, including hospitalizations and doctor visits, living assistance, and time spent by nonprofessional caregivers. Within the context of clinical trials, the RUD is often used to determine the cost effectiveness of new pharmaceutical treatments.[40]

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 [redacted] 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.[41] 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 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, 85 [Visit 2-6], Follow-up visit [for ET patients]), 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 and up until 30 days after receiving the last dose of study medication will be followed.

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] or [redacted]
E-mail [redacted]

SAE hotline (24-hour/7 days a week)
Phone: [redacted] or [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), 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 [redacted] is a prospective scale that assesses treatment-emergent suicidal thoughts and behaviors.[42] 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), Day 85 (Visit 6), and Follow-up visit (for ET patients). 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 [redacted] 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.[43] 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 [redacted] 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.[44,45]

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 [redacted] 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.[46] 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) for patients with an MMSE score of ≥ 10 at the Baseline visit.

6.4 Schedule of Evaluations and Procedures

A schedule of evaluations and procedures 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).

[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 (only for patients with an MMSE score of ≥ 10 at baseline)

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 study 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 study 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 study 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 study 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:

1. 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.
2. Vital signs will be measured and recorded.
3. Physical and neurological examination will be performed.
4. Patient's Diary Card will be collected and reviewed for compliance.
5. Returned, unused study medication will be accounted for compliance.
6. The following assessments will be completed:
    - CMAI
    - NPI
    - CGIS-Agitation
    - mADCS-CGIC-Agitation
    - ADCS-CGIC-Overall

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. A urine pregnancy test will be performed for females of childbearing potential only.
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 (only for patients with an MMSE score of ≥ 10 at baseline)
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. 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 study 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 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 study 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 patients who terminate early.

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 (only for patients with an MMSE score of ≥ 10 at baseline)

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 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. The caregiver will be queried on the overall well-being of the patient.

6.4.1.10 Follow-up Visit and Phone Calls for ET Patients

The Follow-up visit is for patients who terminate early and should occur 30 days after last dose of study medication (± 3-day window).

The following procedures will be performed at the visit:

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. The following assessments will be completed:
    - CMAI
    - mADCS-CGIC-Agitation
    - S-STS

The follow-up phone calls for patients who terminate early should be made for 5 consecutive days following the ET visit. The caregiver will be queried on the overall well-being of the patient.

6.4.1.11 Unscheduled Visit

Patients may be required to return to the clinic for an unscheduled visit between Visit 3 (Day 22) and Visit 5 (Day 64) for safety assessments, if the investigator determines that dose adjustment is necessary. A one-time downward dose adjustment will be allowed after Visit 3 up to and including Visit 4 (ie, Day 23 to Day 43), at the discretion of the investigator.

The safety assessments to be performed at the unscheduled visit will be based on the clinical judgment of the investigator.

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

8.3.1 Study Endpoints

Primary efficacy endpoint:

The primary efficacy endpoint is the change from Baseline to Week 12 (Day 85) in the composite CMAI scores.

Secondary efficacy endpoints:

The secondary efficacy endpoints are the change from Baseline to Week 12 (Day 85) 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
- GMHR
- ADAS-cog
- RUD

8.3.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline to Day 85 (Week 12) in the composite CMAI scores.

For the primary efficacy analysis, the null hypothesis is that there is no treatment effect between AVP-786-42.63/4.9 and placebo during the study and it will be tested against the alternative that there is a treatment effect. Similar hypotheses apply to the comparison of the AVP-786-28/4.9 vs. placebo. The treatment effect will be estimated by using a linear mixed effects model repeated measures (MMRM) with comparisons being made between the patients treated with AVP-786 and the patients treated with concurrent placebo. 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 factors as appropriate. 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.

A gate-keeping procedure will be used to control the overall type I error at 2-sided $\alpha = 0.05$ for the 2 primary treatment comparisons (AVP-786-42.63/4.9 vs. placebo and AVP-786-28/4.9 vs. placebo). Specifically, the comparison between AVP-786-42.63/4.9 vs. placebo will be performed first at the significance level of 0.05. If the comparison is statistically significant, the comparison between AVP-786-28/4.9 vs. placebo will be performed at the same significance level.

8.3.3 Secondary Efficacy Analyses

Secondary efficacy endpoints include change from Baseline to Week 12 (Day 85) 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 GMHR.

Treatment comparison tests using similar MMRM method as the primary efficacy analysis will be performed when appropriate. 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 the secondary endpoints tested. The testing procedure will be pre-specified in the statistical analysis plan (SAP) before un-blinding the study.

8.4 PK/PD Analysis

Plasma concentrations of d6-DM, its metabolites, and Q will be measured and results will be summarized descriptively [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.

[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.

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 prespecified in the SAP.

8.7 Sample Size Calculations

Power calculation was performed assuming a normal distribution for the primary efficacy endpoint. [redacted]

The study protocol is amended to include another dose arm (AVP-786-42.63/4.9) with 140 patients in the treatment arm, when approximately 100 patients have already been enrolled (50 AVP-786 28/4.9 and 50 placebo) in the study. To maintain an approximate [redacted] chance for an incoming patient to receive active drug, the sample size for the placebo treatment group is amended to 190. Overall, the total sample size of 470 patients will include 140 patients for AVP-786 28/4.9 and AVP-786 42.63/4.9 groups each and 190 patients in the placebo group. This sample size will provide approximately [redacted] power to detect a treatment effect size of [redacted] between AVP-786 42.63/4.9 and concurrent placebo treatment group.

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 (see, 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 and dated 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 call 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] 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

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11 APPENDICES

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Appendix 18: Investigator Responsibilities

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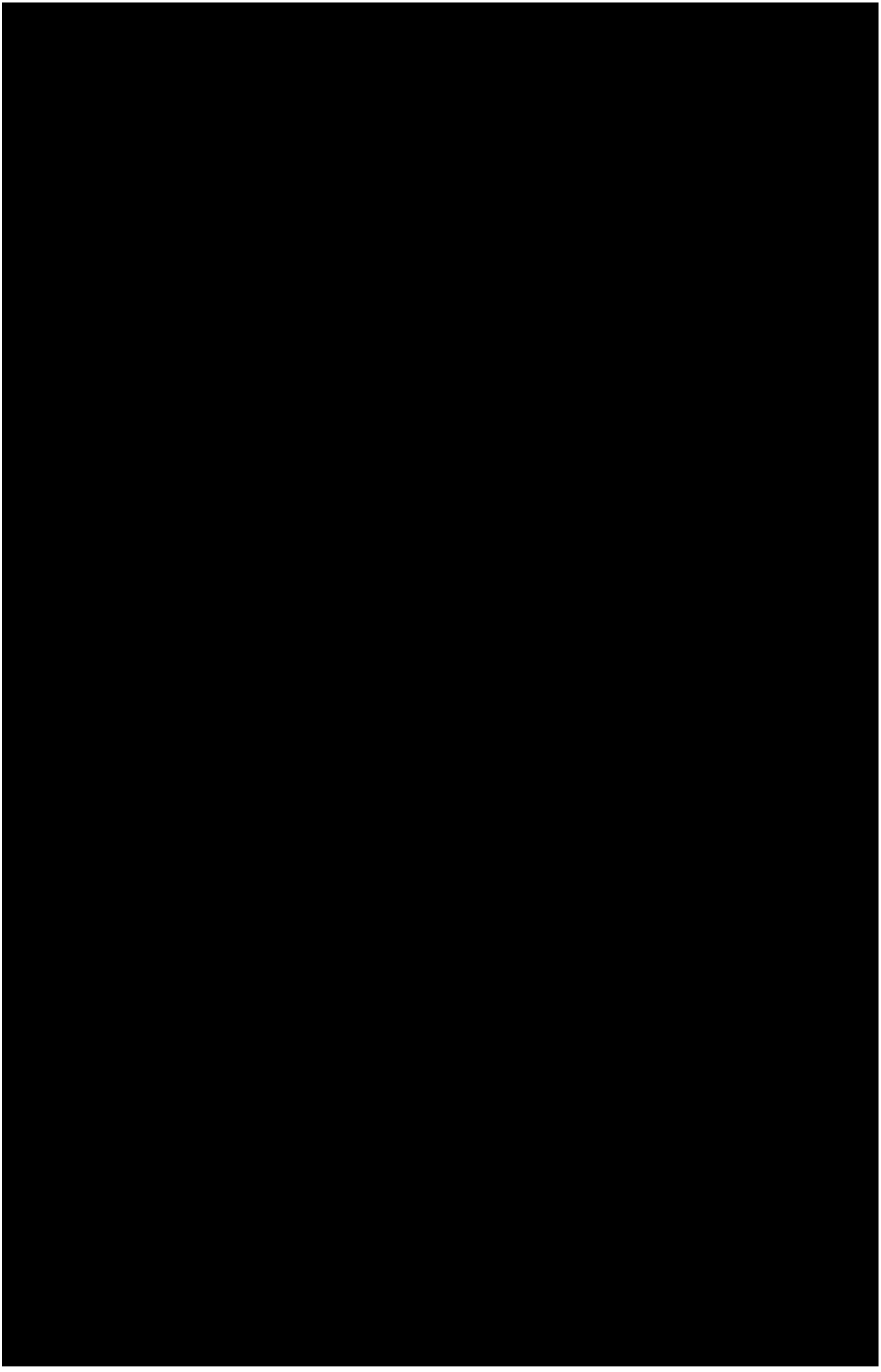

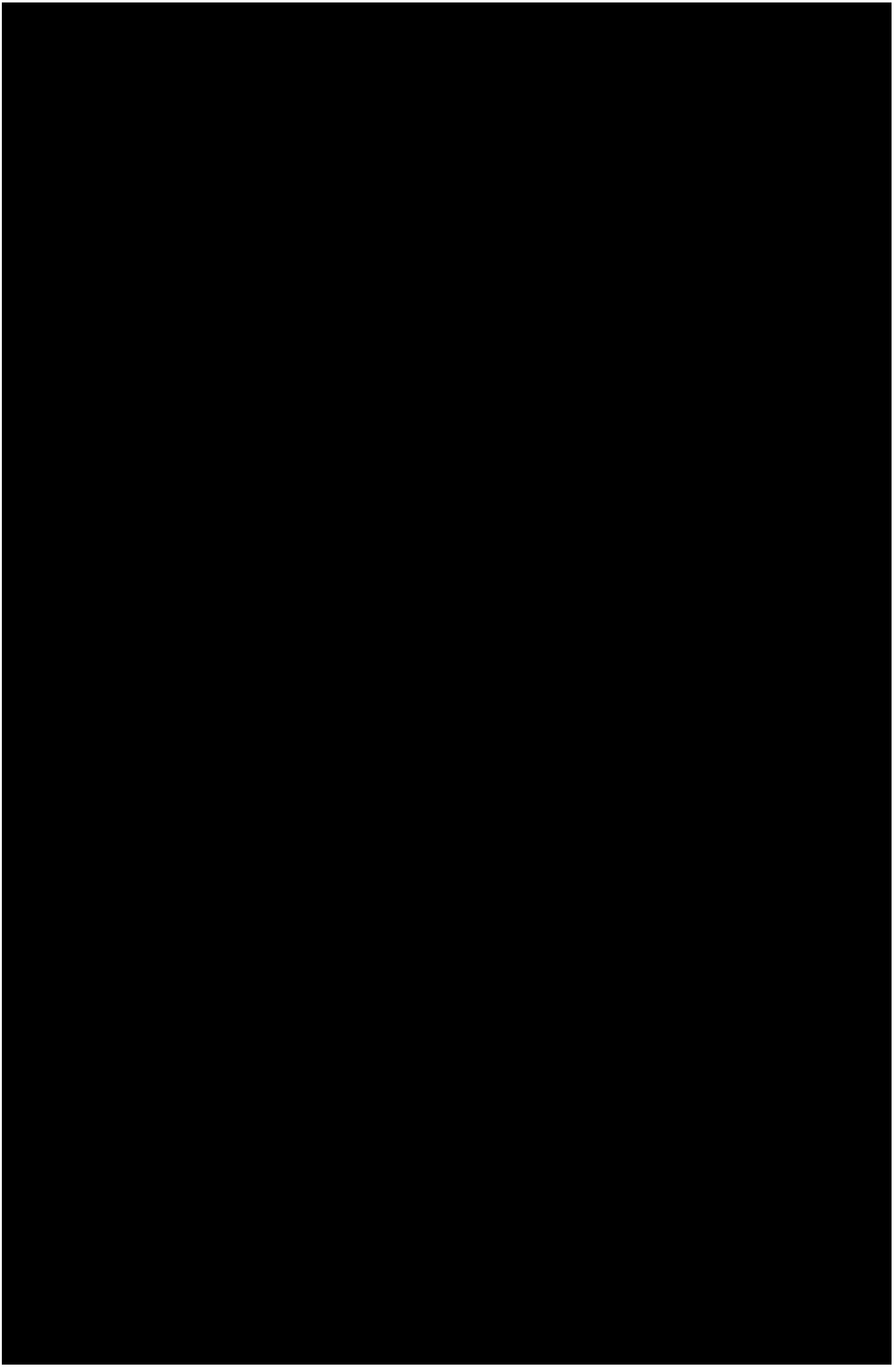

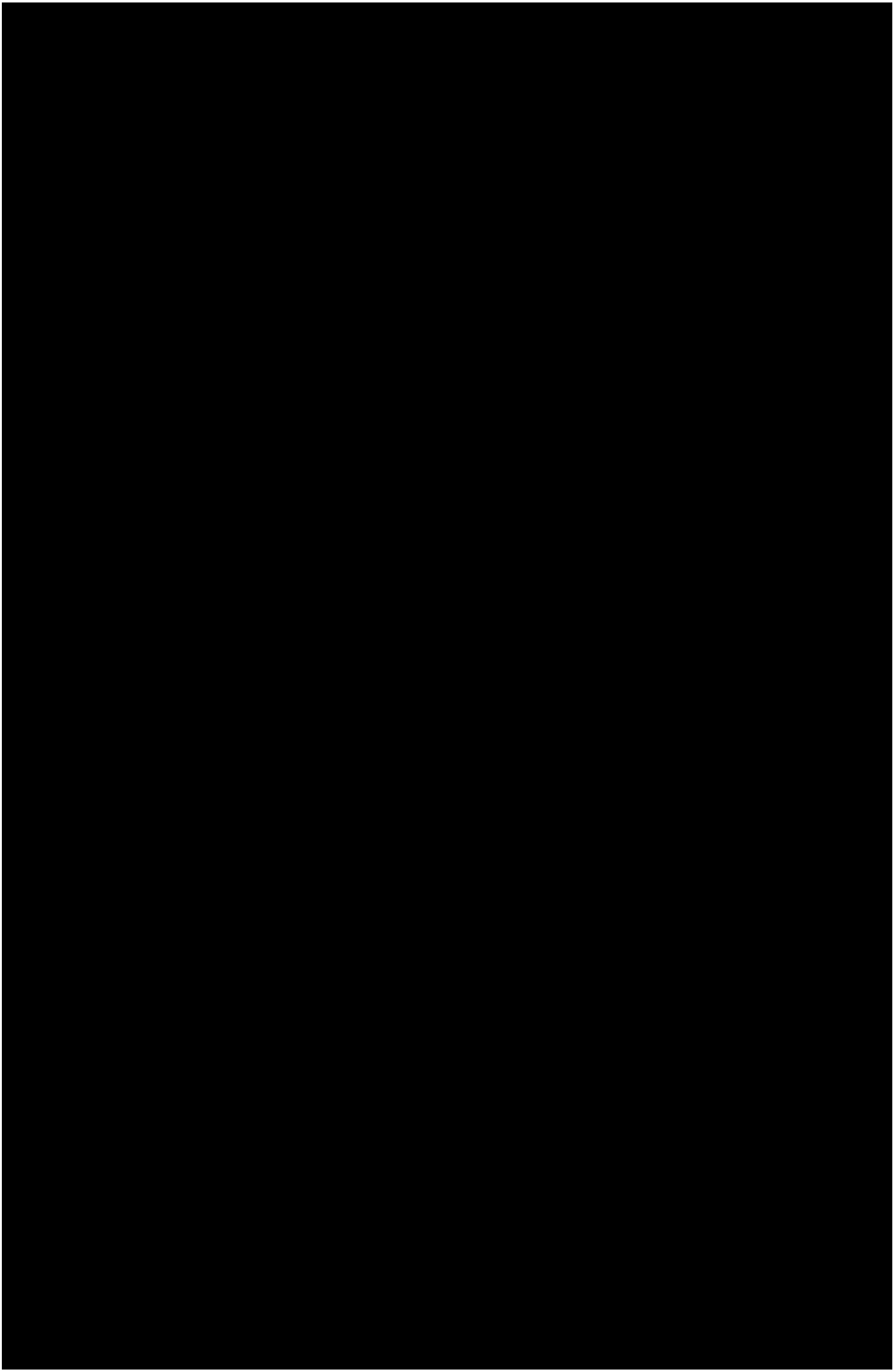

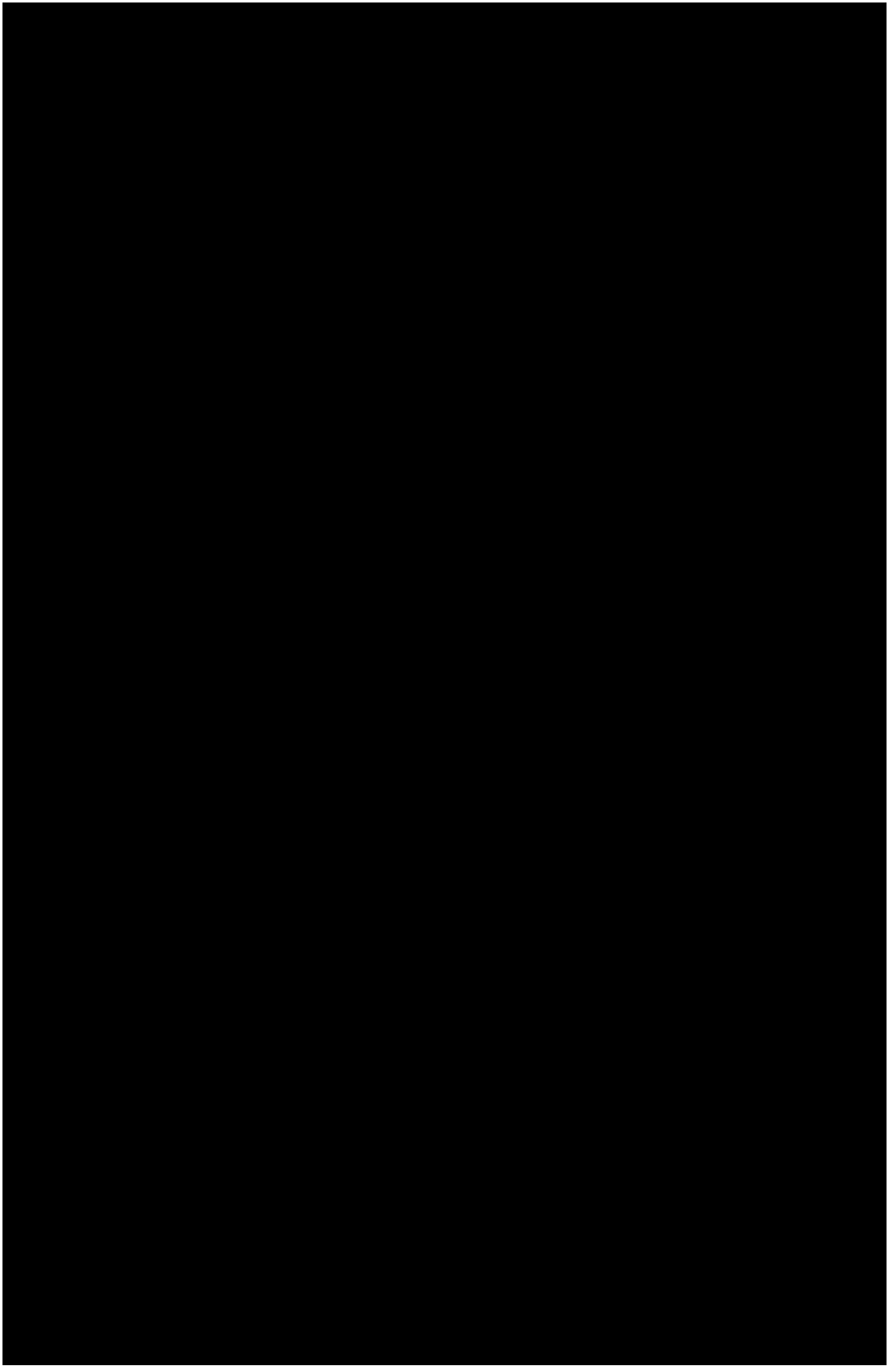

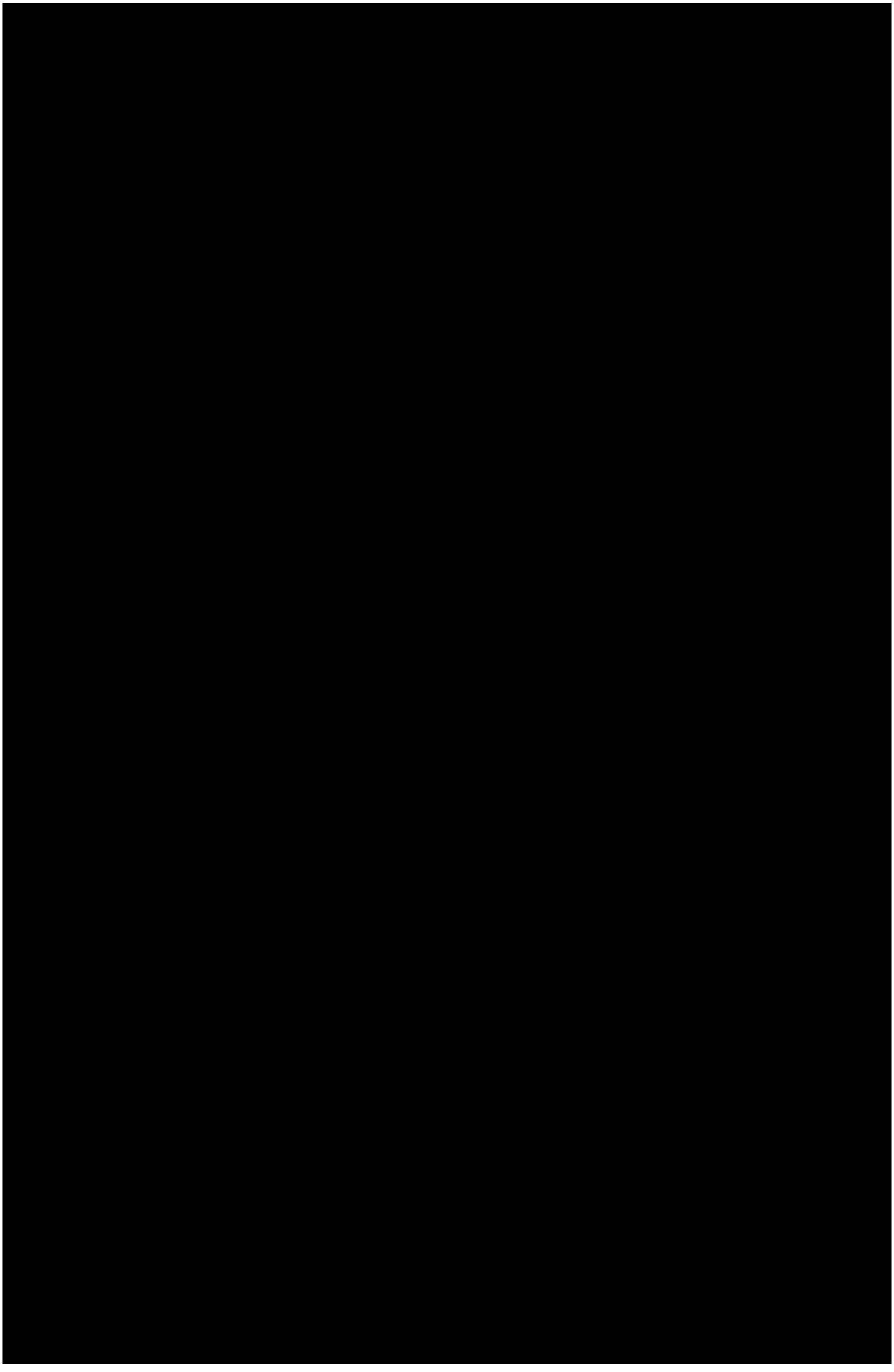

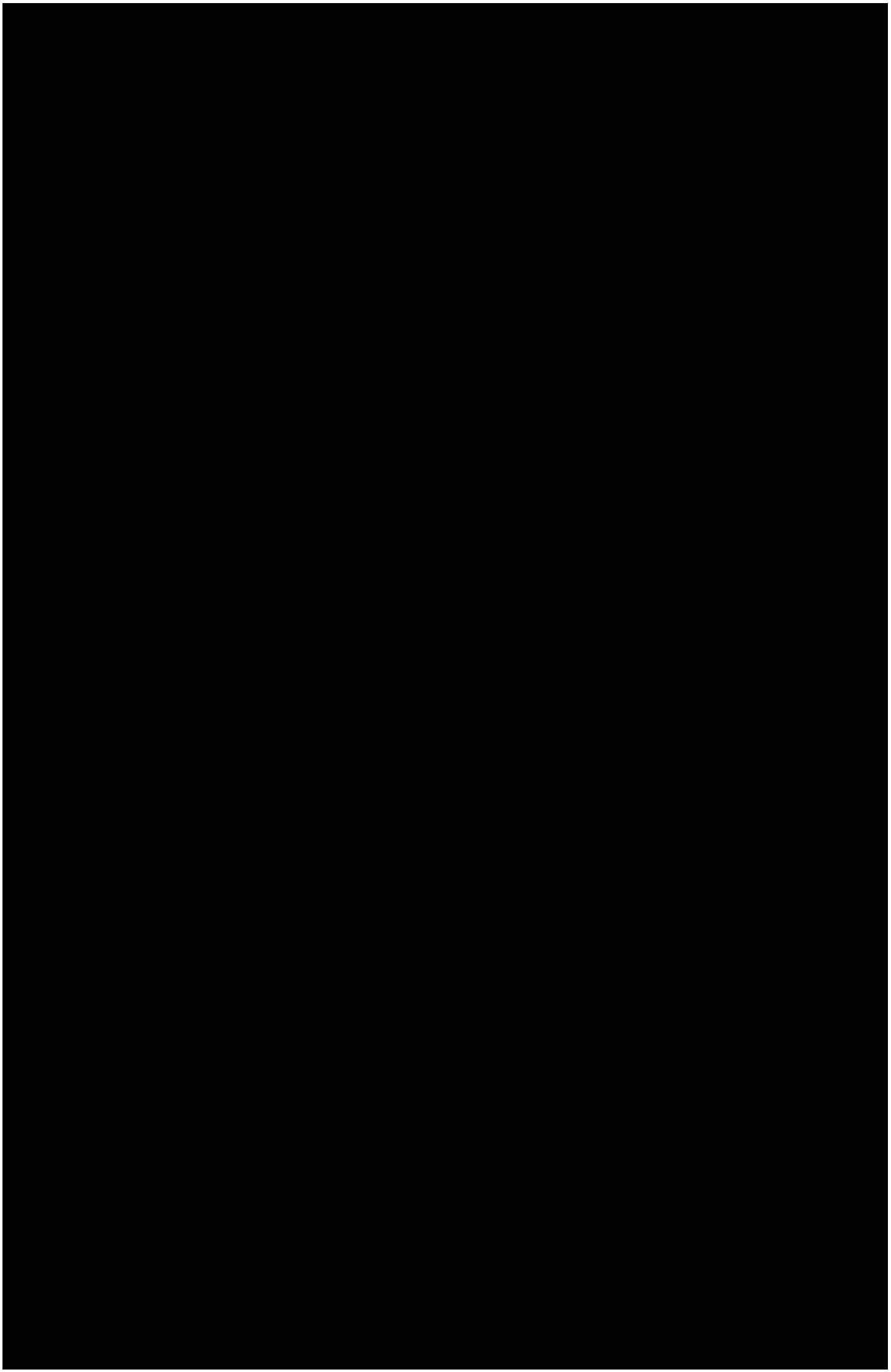

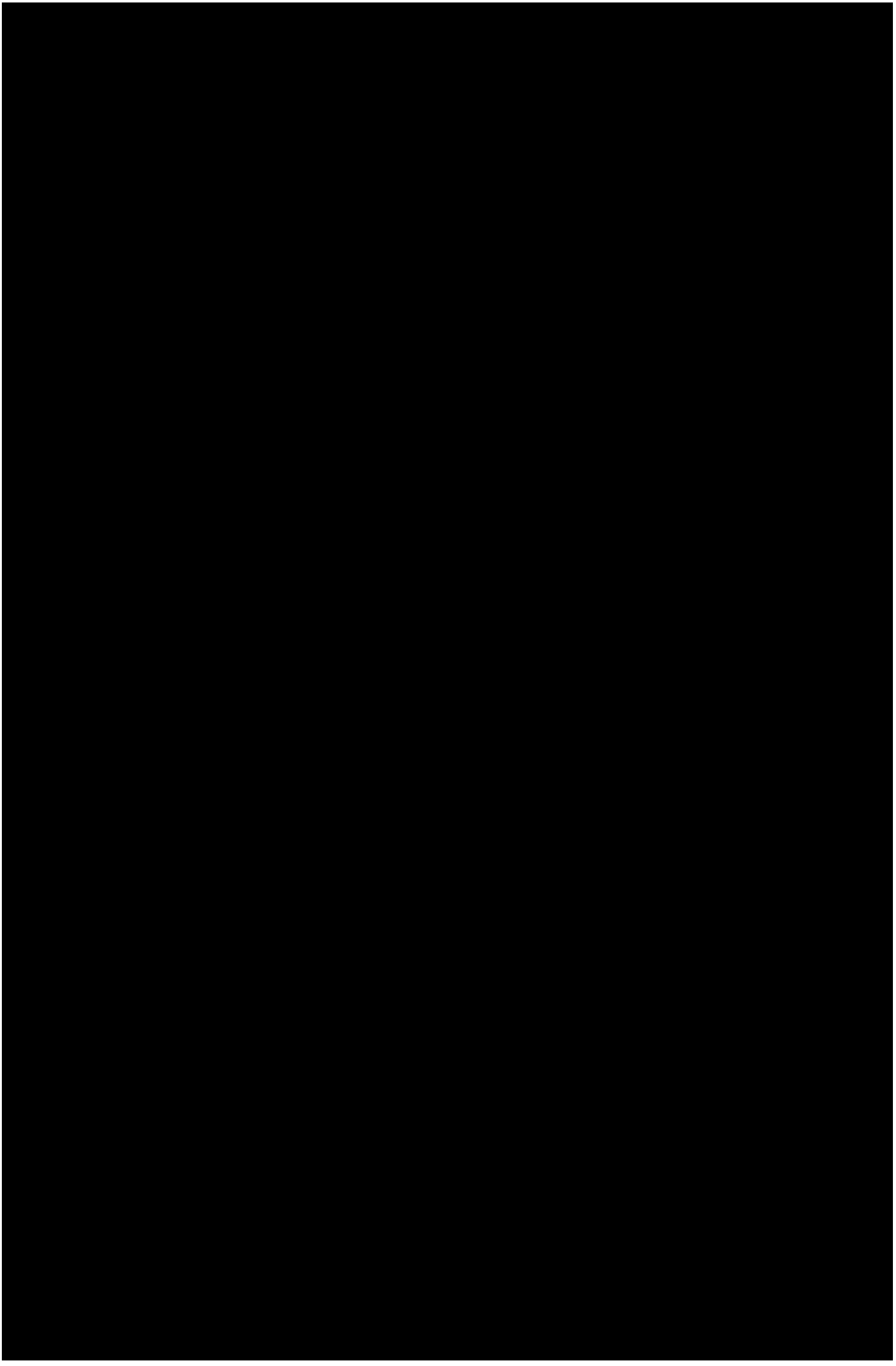

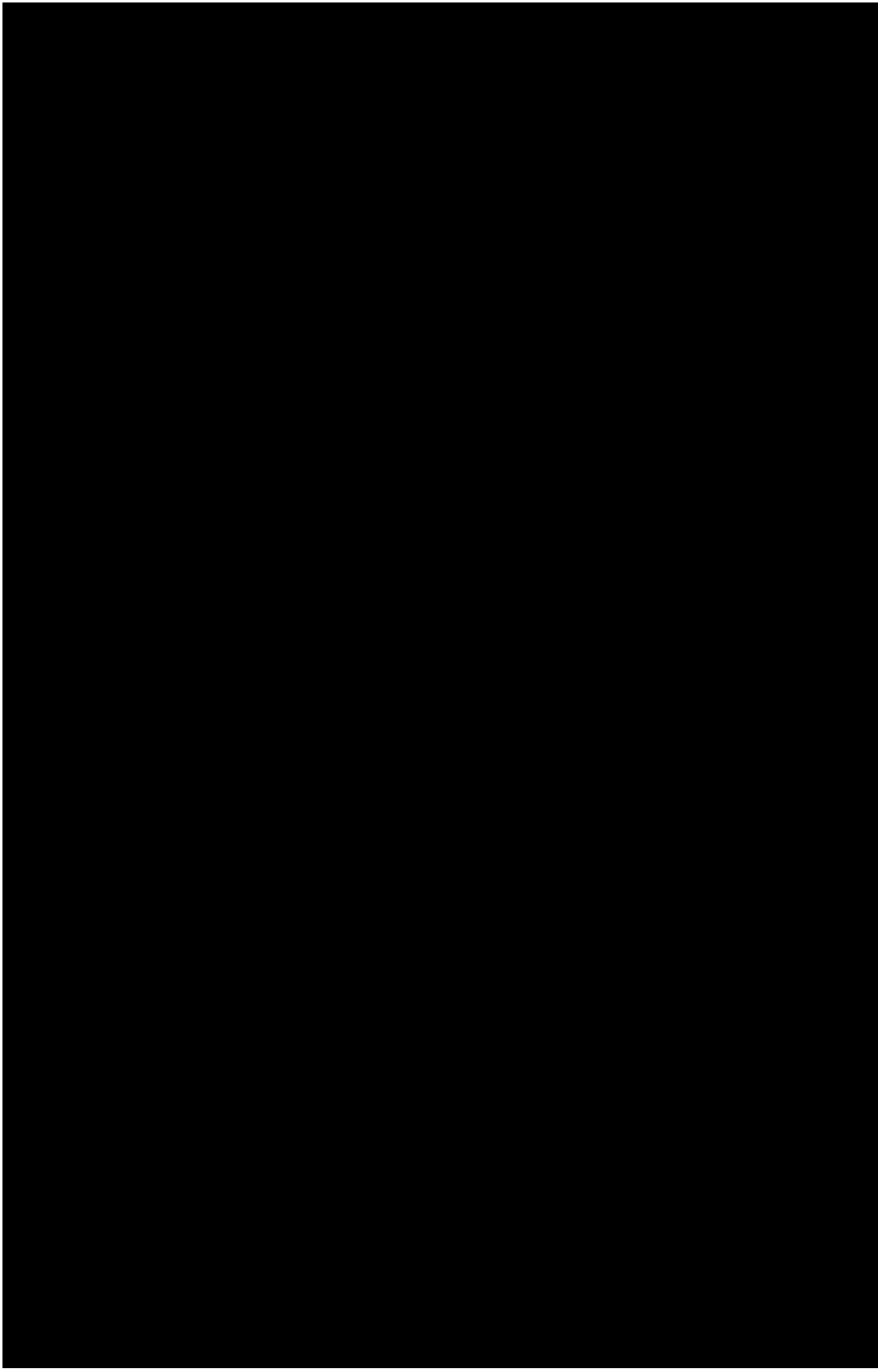

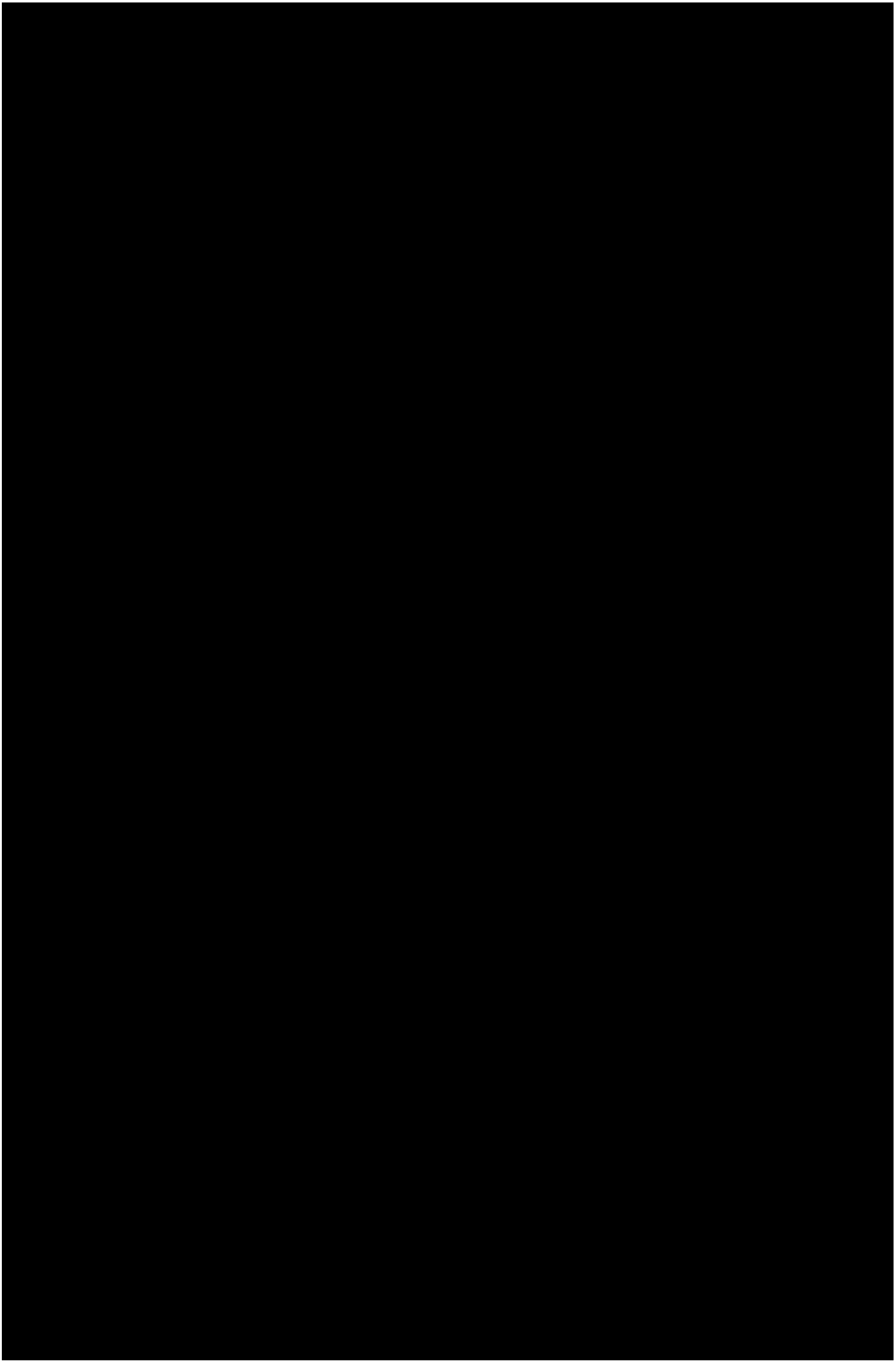

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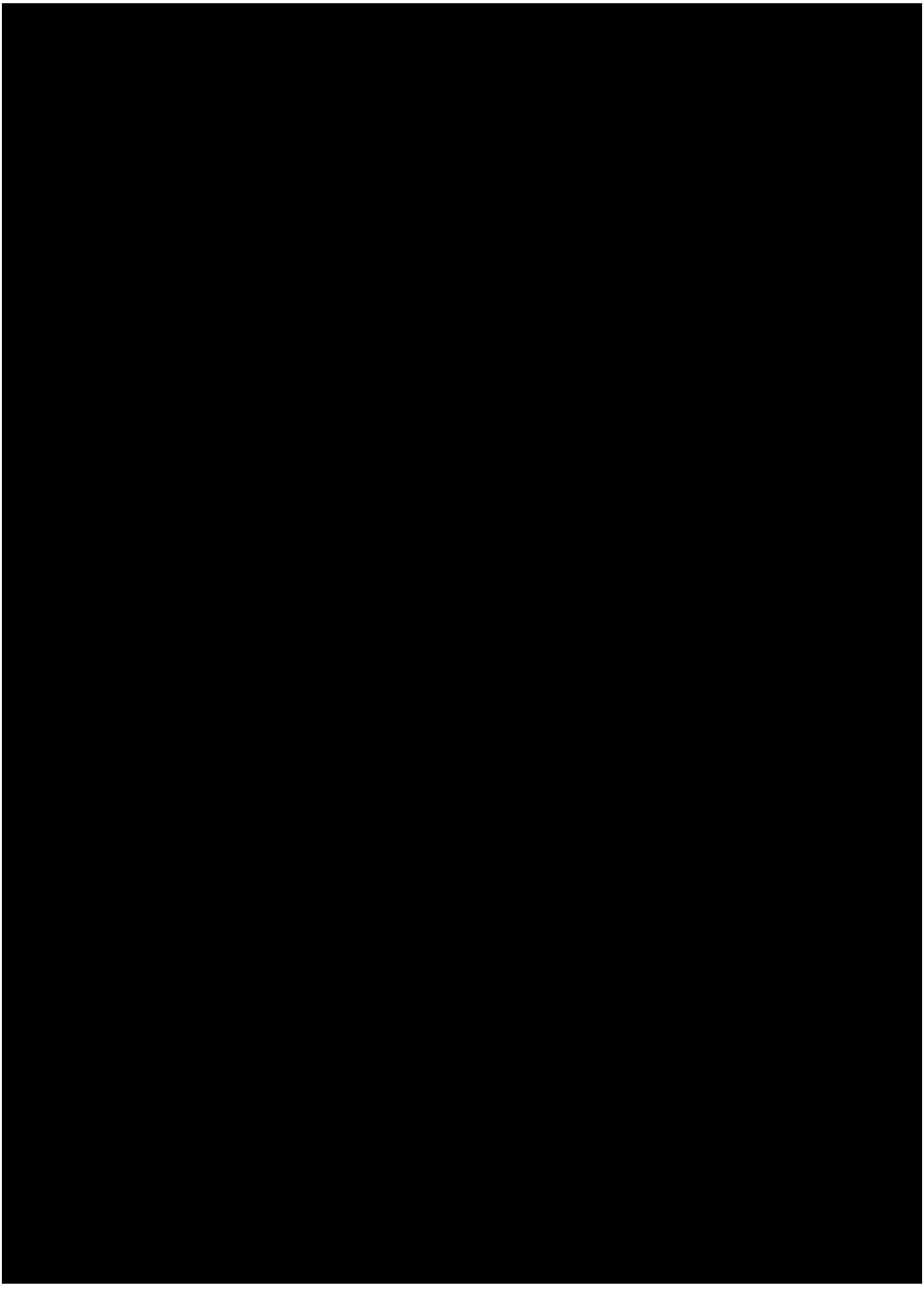

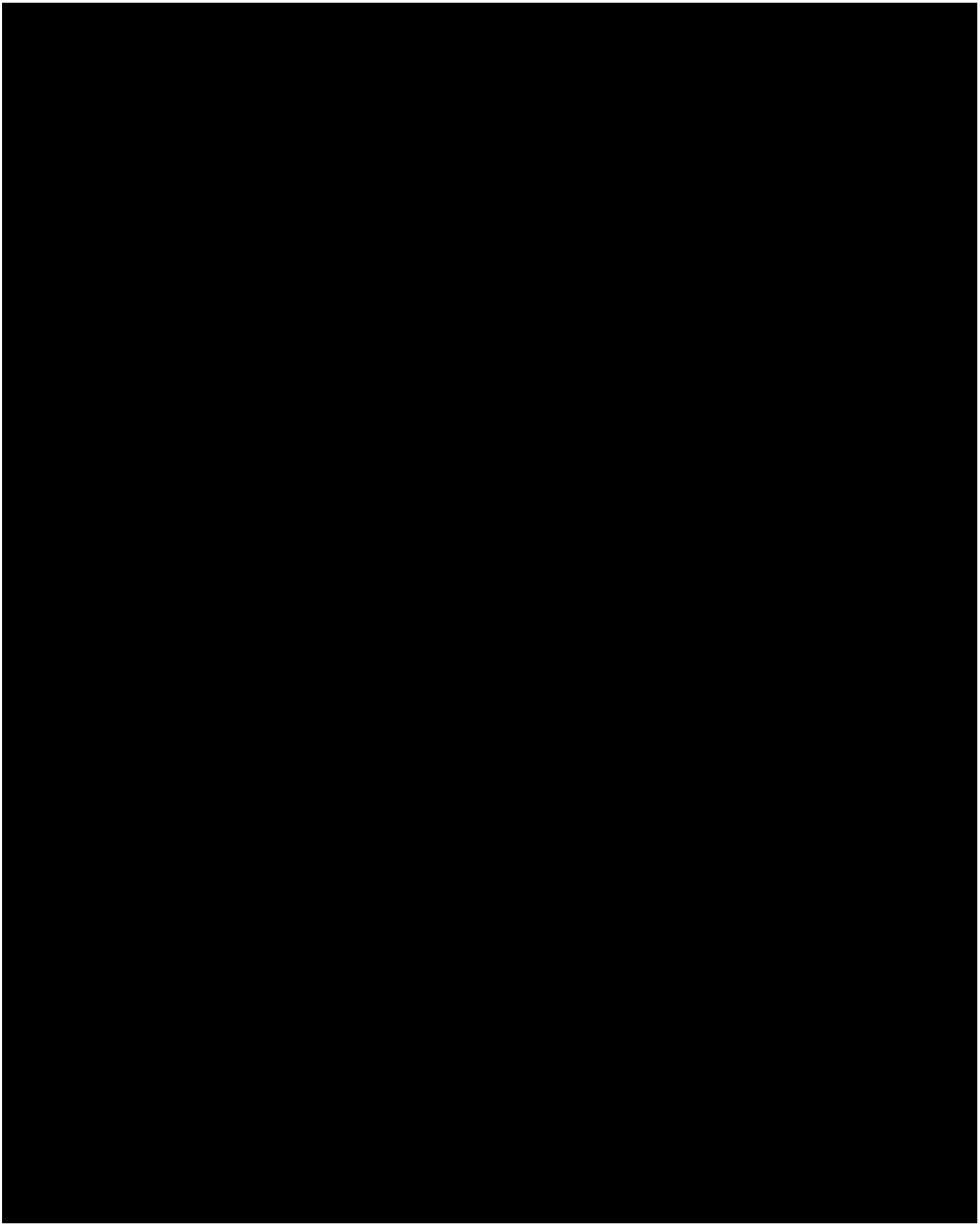

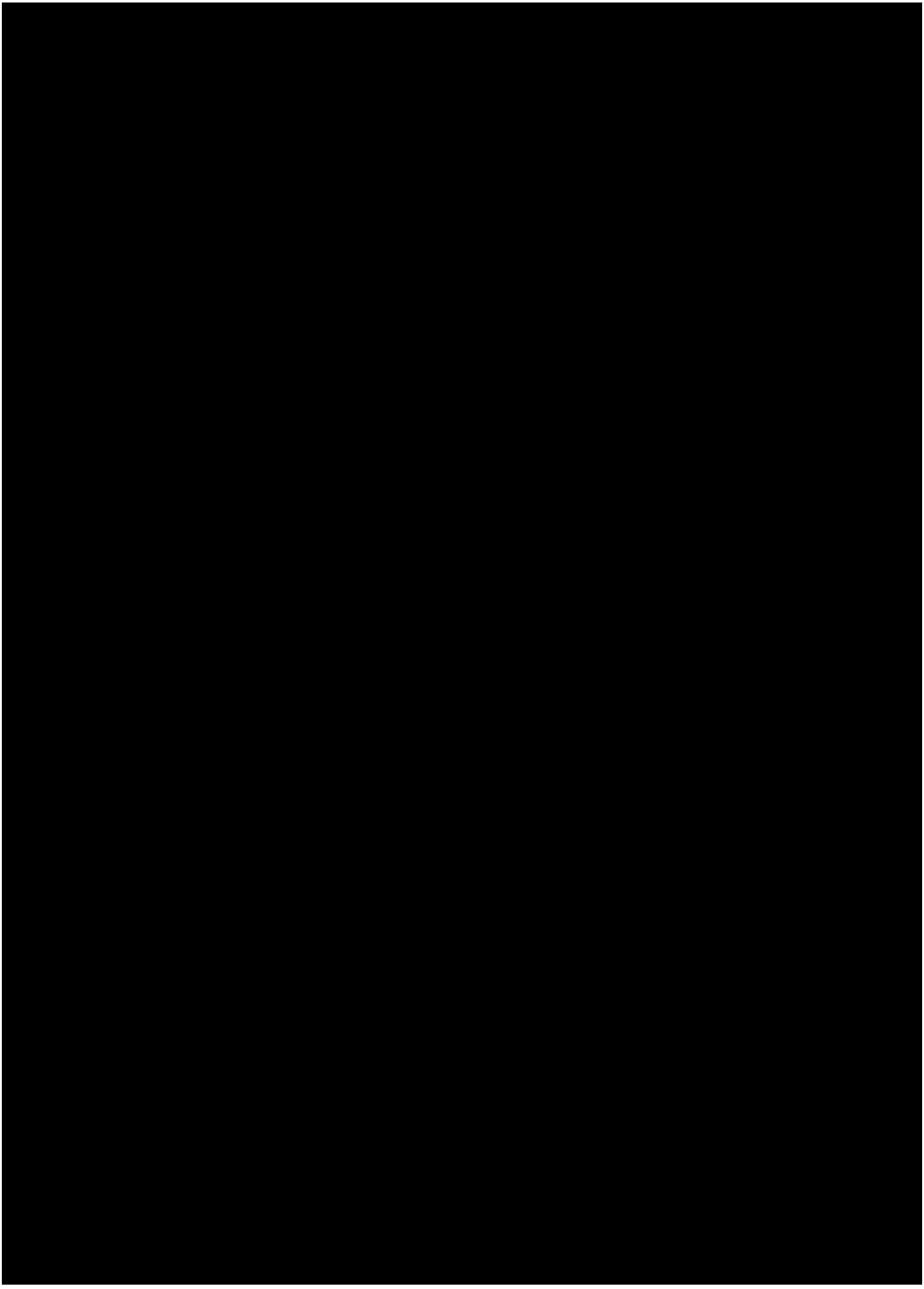

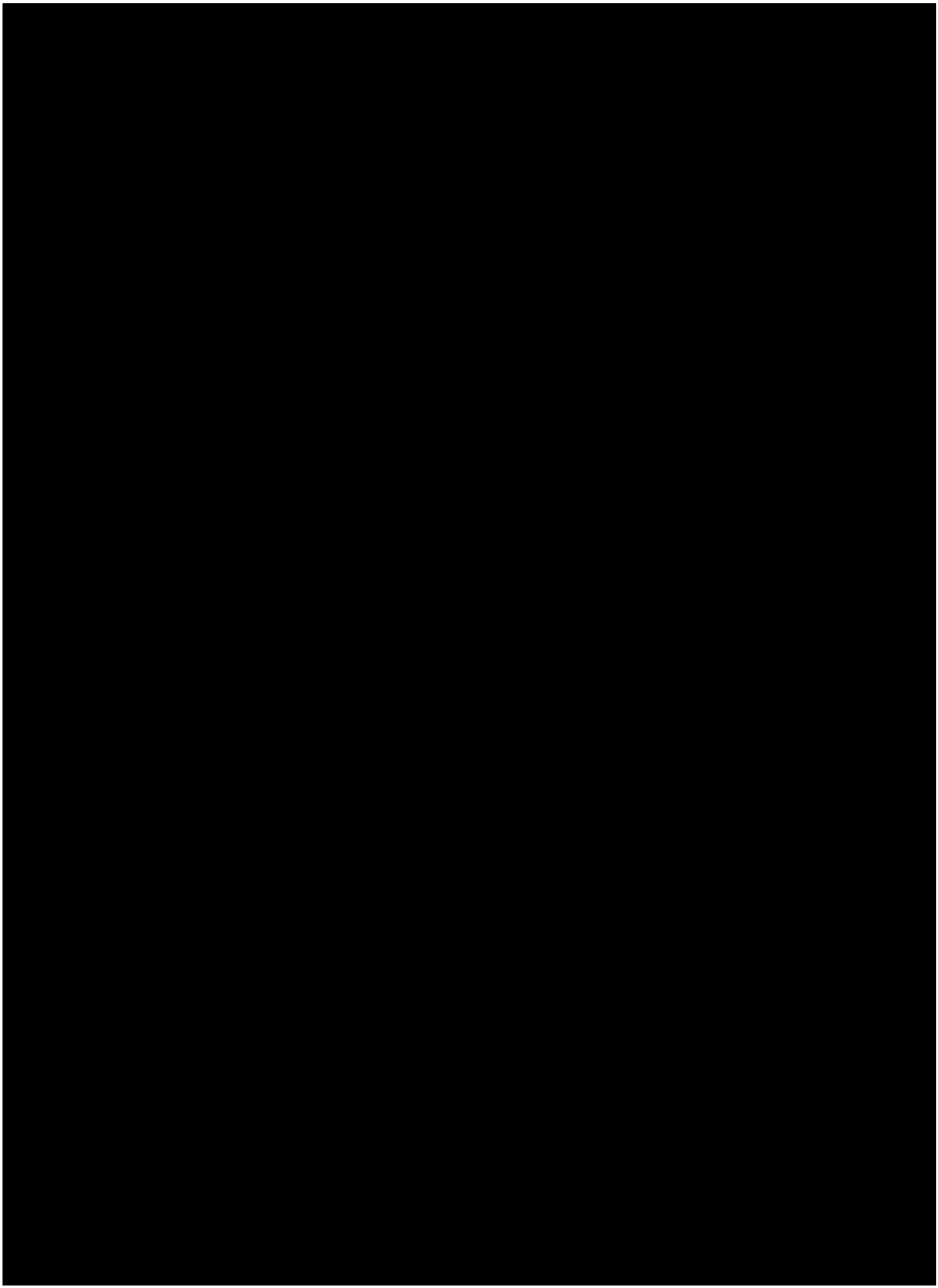

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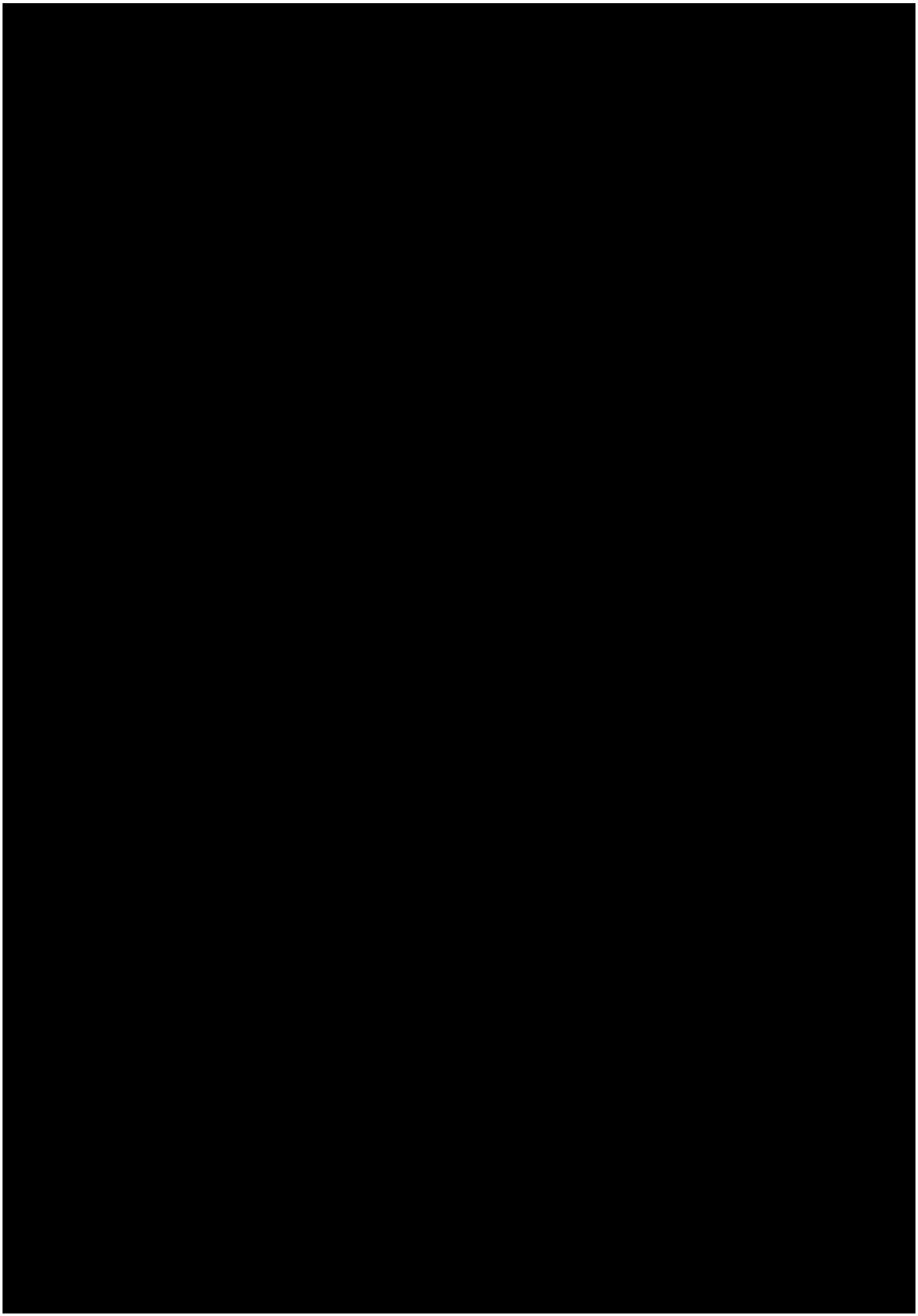

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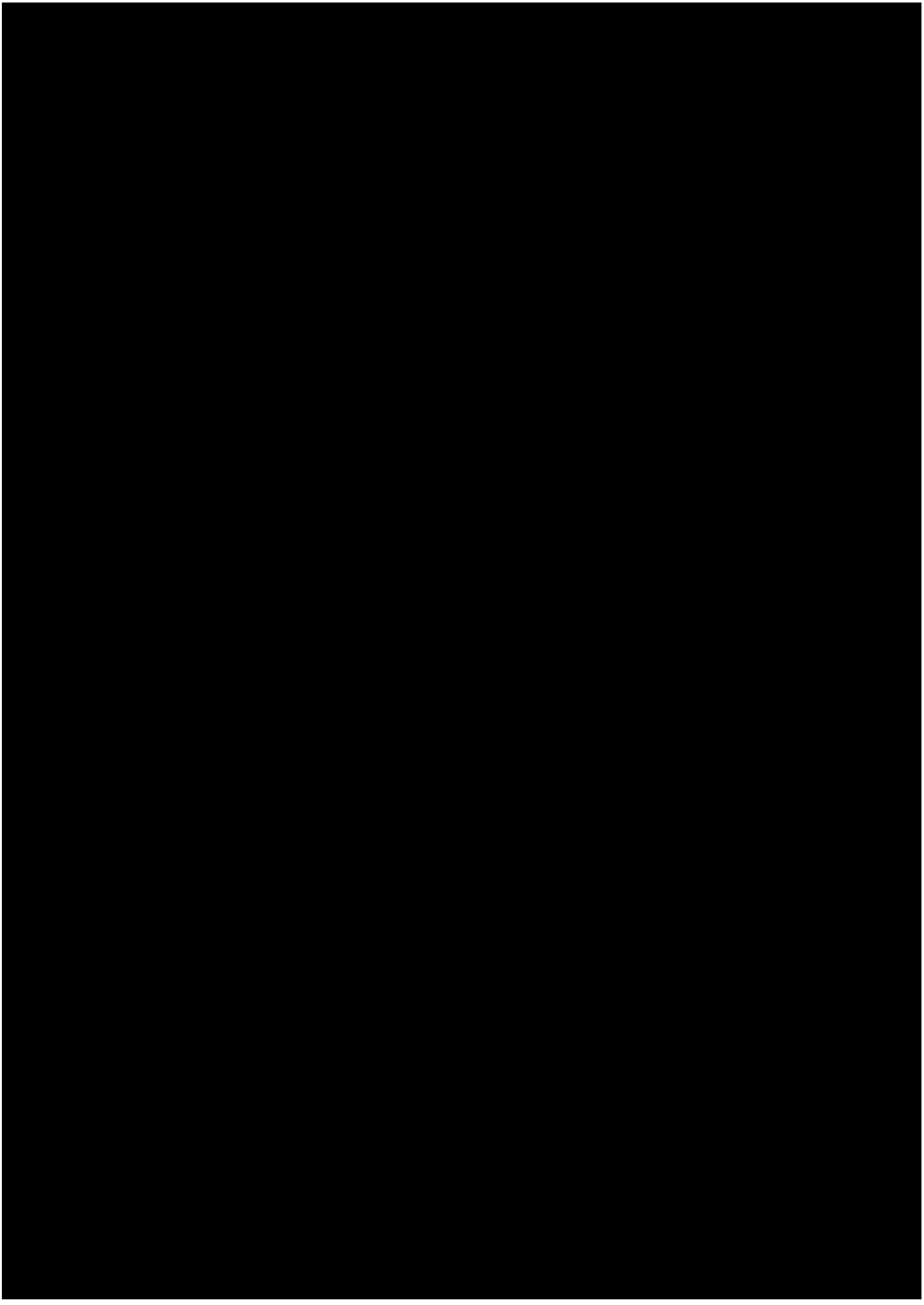

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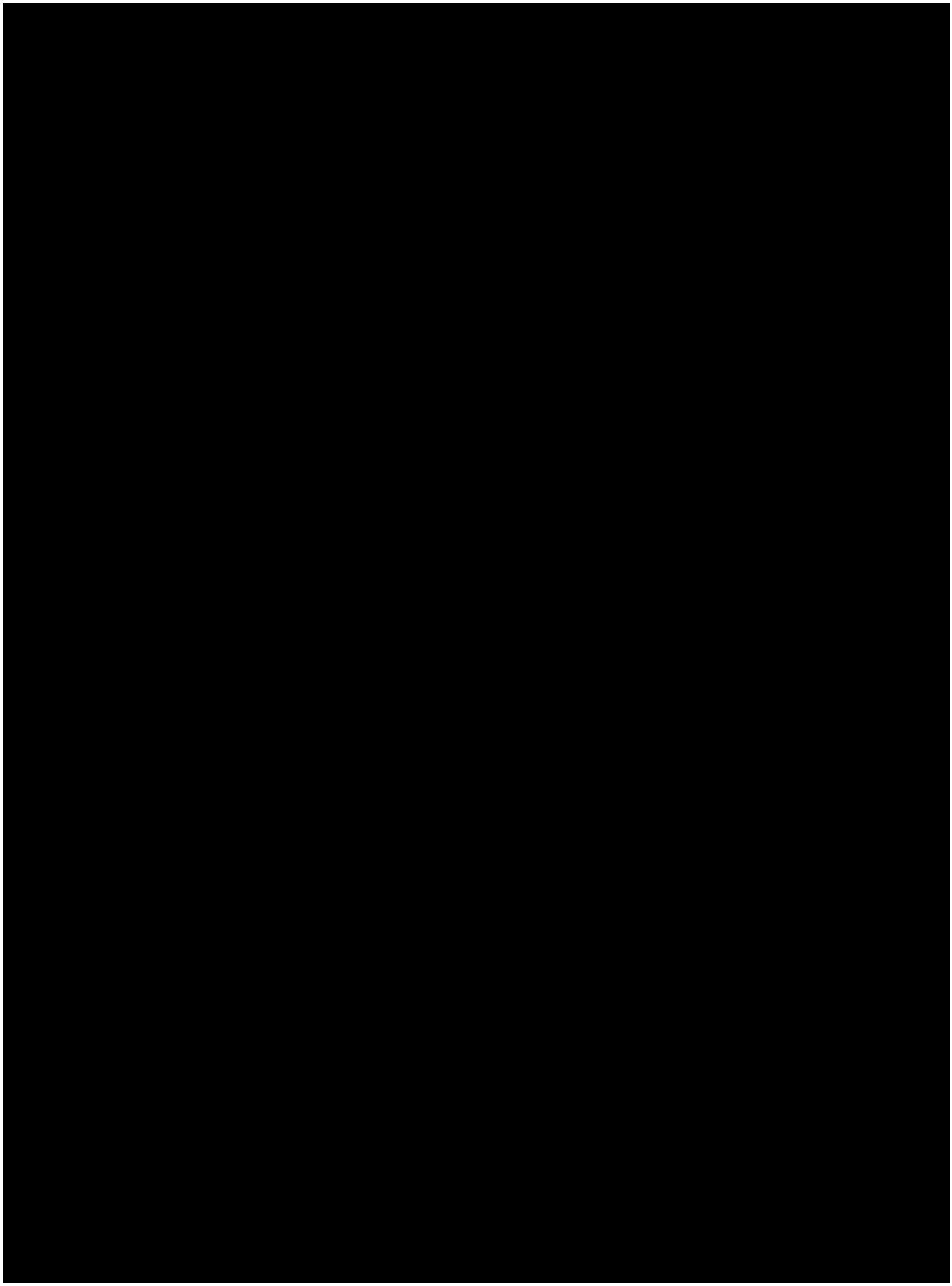

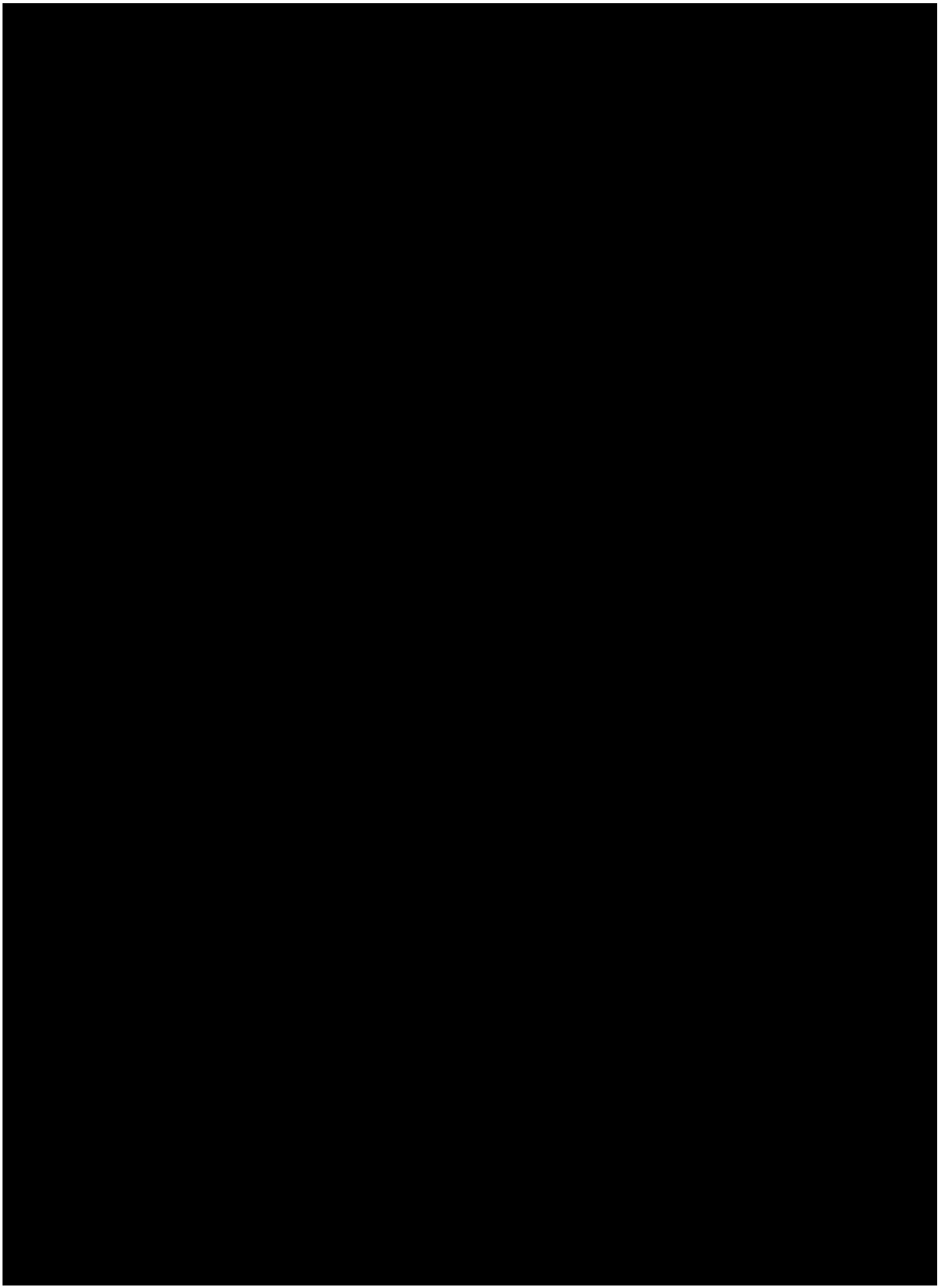

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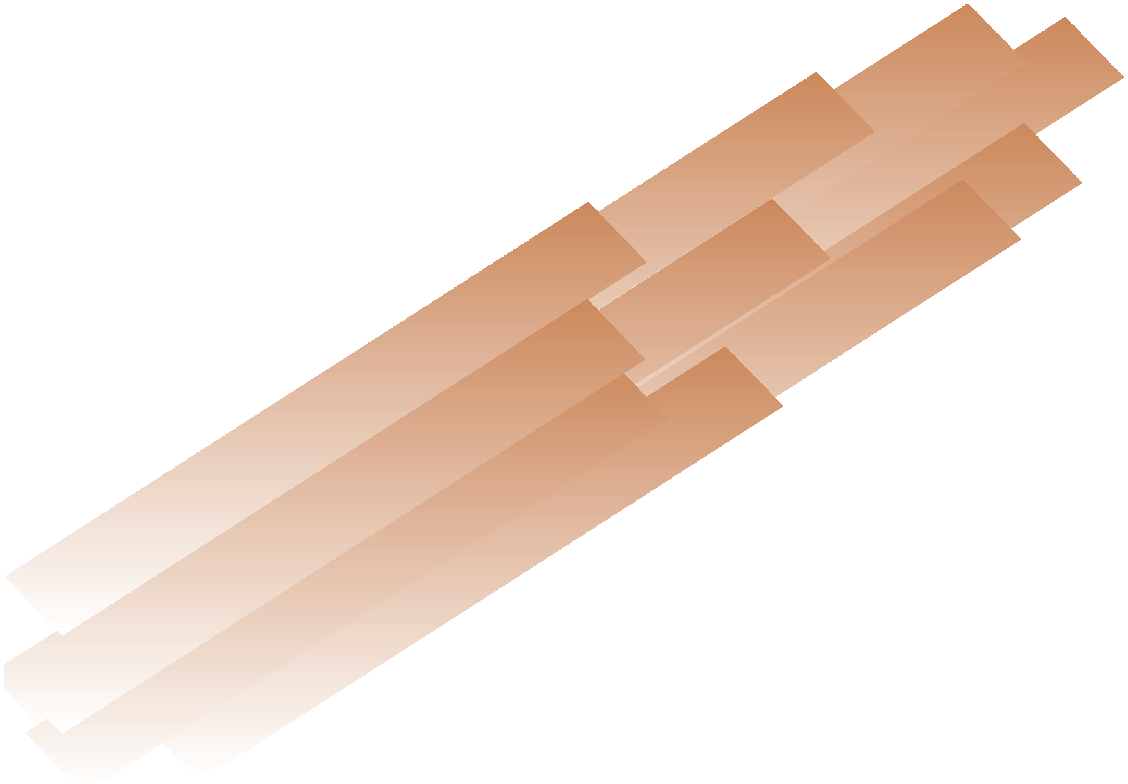
Appendix 18: Investigator Responsibilities

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.

[redacted]