PROTOCOL TITLE:
A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Cross-over Study to Assess the Safety, Tolerability, and Efficacy of AVP-786 for the Treatment of Disinhibition in Patients with Neurodegenerative Disorders

Protocol:	15-AVP-786-203	**IND:**124, 099
Sponsor:	Avanir Pharmaceuticals, Inc.	**Date:** 1 September 2015
Drug:	AVP-786 (deuterated [d6]-dextromethorphan hydrobromide [d6-DM]/quinidine sulfate [Q])	**Version:** 1.0

Medical Monitor: [redacted]
Phone: [redacted] **Fax**: [redacted]
Avanir Pharmaceuticals, Inc.
30 Enterprise, Suite 400
Aliso Viejo, California 92656

Study Monitor: [redacted]
Phone: [redacted] **Fax**: [redacted]
Avanir Pharmaceuticals, Inc.
30 Enterprise, Suite 400
Aliso Viejo, California 92656

AVANIR PHARMACEUTICALS, INC.
30 Enterprise, Suite 400
Aliso Viejo, California 92656
Phone: (949) 389-6700 Fax: (949) 643-6800
24-hour Emergency Phone Number: 949-525-8658

NCT Number: NCT02534038
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AD	Alzheimer's Disease
ALT/SGPT	Alanine aminotransferase/serum glutamic-pyruvic transaminase
ANCOVA	Analysis of covariance
AST/SGOT	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
beta-hCG	Beta subunit of human chorionic gonadotropin
BID	twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
BvFTD	behavioral variant of frontotemporal dementia
CBD	corticobasal degeneration
CD-ROM	Compact disc read-only-memory
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity of Illness
CK	Creatine kinase
CNS	Central nervous system
CNS-LS	Center for Neurologic Study-Lability Scale
CRO	Contract research organization
CSDD	Cornell Scale for Depression in Dementia
CYP	Cytochrome P450
DLB	dementia with Lewy bodies
DM	Dextromethorphan
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EP	European Pharmacopeia
FBI	Frontal Behavioral Inventory
FDA	US Food and Drug Administration
[redacted]	
FRsBe	Frontal-Subcortical Behavior Scale
FTD	frontotemporal dementia
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation

Abbreviation	Definition
IP	Investigational product
IRB	Institutional Review Board
IRI	Interpersonal Reactivity Index
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MAOI	Monoamine oxidase inhibitor
mCGIC	Modified Clinical Global Impression of Change
mCGIS	Modified Clinical Global Impression of Severity of Illness
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MM	Medical Monitor
MMSE	Mini-Mental State Examination
NDD	Neurodegenerative Disorder
NF	National Formulary
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory - Nursing Home version
OTC	Over–the-counter
PBA	pseudobulbar affect
PGIC	Patient Global Impression of Change
pH	Potential Hydrogen
PK	Pharmacokinetics
PR	The P-R interval from an ECG tracing
PSP	progressive supranuclear palsy
Q	Quinidine
QoL	Quality of Life
QoR	Quality of Relationships
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
RBC	Red blood cell
SAE	Serious adverse event
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
S-STS	Sheehan Suicidality Tracking Scale
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
USP	United States Pharmacopoeia
WBC	White blood cell

PROTOCOL AGREEMENT

Protocol Title:

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Cross-over Study to Assess the Safety, Tolerability and Efficacy of AVP-786 for the Treatment of Disinhibition in Patients with Neurodegenerative Disorders

Protocol Number: 15-AVP-786-203

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

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

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

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

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]	

STUDY SYNOPSIS

Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Cross-over Study to Assess the Safety, Tolerability, and Efficacy of AVP-786 for the Treatment of Disinhibition in Patients with Neurodegenerative Disorders

Study Objectives

The objectives of the study are to evaluate the safety, tolerability, and efficacy of AVP-786 compared to placebo, for the treatment of disinhibition in patients with Neurodegenerative Disorders (NDD) including frontotemporal dementia, Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, vascular cognitive disorders, or Huntington's disease.

Study Population

Number of Patients: Approximately 12 patients will be enrolled at 2 centers; approximately 6 patients at each center.

Condition/Disease: Disinhibition syndrome in patients with a diagnosis of a NDD including frontotemporal dementia, Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, vascular cognitive disorders, or Huntington's disease. The definition of disinhibition syndrome will be based on the disinhibition criteria developed to identify patients with the behavioral variant of frontotemporal dementia (BvFTD)[1] which includes descriptions of disinhibited behavior in three general areas: socially inappropriate behavior, loss of manners and decorum, and impulsive, rash, and careless actions.

Key Inclusion Criteria:

- Patients with a documented diagnosis of a NDD with a duration of at least 3 months prior to Baseline;
- Patients with behaviors from 2 of the 3 categories of disinhibited behavior from the definition of the behavioral variant of frontotemporal dementia;[1]
- [redacted]
- A score of ≥ 4 on the 3 core disinhibition questions of the Frontal Behavioral Inventory (FBI) at the Screening and Baseline visits;
- Availability of a caregiver known to the patient and 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.

Key Exclusion Criteria:

- Patients with symptoms of disinhibition that are not secondary to NDD (e.g., substance use, traumatic brain injury [TBI]);
- [redacted]

- [redacted]
- [redacted]

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

Study Design

Design: This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, cross-over study. A schematic of the study design is presented in Figure 1.

Duration: The study duration is approximately 22 weeks with up to 4 weeks of screening, 14 weeks of treatment and 4 weeks of safety follow-up.

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

Control: AVP-786 Placebo capsules of identical appearance and excipients to study medication will be used as control.

Randomization: Eligible patients will be randomized into this 2x2 crossover study in a [redacted] ratio at the Baseline visit to receive either treatment sequence 1 AB (period 1: A, period 2: B) or treatment sequence 2 BA (period 1: B, period 2: A), where A is AVP-786 and B is placebo.

Dose Regimen: 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.

Period 1

- Patient randomized to treatment sequence 1 AB will start with AVP-786-[redacted] 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-[redacted] BID for 14 days. From Day 22, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of period 1.
- Patients randomized to treatment sequence 2 BA will be dosed with placebo BID during period 1

A 2-week washout period will follow period 1 (Days 44 to 56). For the washout period, suffient supply of placebo will be dispensed in a single-blind manner to patient/caregiver to ensure continuity and study medication compliance.

Period 2:

Patients who complete period 1 and the 2-week wash-out period are eligible to participate in period 2 of the study. In Period 2, patients will be assigned to study treatment as follows:

- Patients who received AVP-786 in period 1 (treatment sequence 1 AB) will receive placebo BID for the entire 6-week duration of period 2.

- Patients who received placebo in period 1 (treatment sequence 2 BA) will start with AVP-786-[redacted] once a day in the morning and placebo in the evening for the first 7 days of period 2. From Day 64, patients will receive AVP-786-[redacted] BID for 14 days. From Day 78, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of period 2.

Assessments and Visits

The study includes a total of 9 scheduled clinic visits and 1 safety follow-up phone call. Patients will attend clinic visits at Screening (Day -28 to -1), in period 1: on Day 1 (Baseline), Day 8 (Week 1), Day 22 (Week 3), Day 43 (Week 6), and in period 2: on Day 57 (Week 8), Day 64 (Week 9), Day 78 (Week 11), and Day 99 (Week 14). A safety follow-up phone call will be made 30 days after the last clinic visit (Day 129). 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 Disinhibition domain of the Neuropsychiatric Inventory (NPI)

Secondary measures: Secondary efficacy measures include total NPI, NPI total caregiver distress score, NPI Disinhibition domain caregiver distress, Frontal Behavioral Inventory (FBI) total score, FBI disinhibition core questions score (questions 15, 16, and 17), Modified Clinical Global Impression of Severity of Illness (mCGIS), Modified Clinical Global Impression of Change (mCGIC), Patient Global Impression of Change (PGIC), Quality of Life (QoL), Quality of Relationships (QoR), Interpersonal Reactivity Index (IRI), Center for Neurologic Study-Lability Scale (CNS-LS), Mini Mental State Examination (MMSE), Cornell Scale for Depression in Dementia (CSDD), Stroop color and word task

[redacted]

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), and Sheehan Suicidality Tracking Scale (S-STS).

Pregnancy tests will be conducted for females of childbearing potential.

General Statistical Methods and Types of Analyses

Analysis Populations

Two analysis populations will be used, modified intent-to-treat (mITT), and safety. The mITT population includes all patients randomized in the study who have at least one post-baseline efficacy assessment, and

will be used for all analyses of efficacy. The safety population includes all patients who received study treatment, and will be used for all analyses of safety. Patients in the safety population will be summarized based on their actual study treatment received.

Efficacy Analyses

The primary efficacy endpoint of the study is the change from Baseline to Week 6 in each study period in the Disinhibition domain of the NPI. Treatment group comparison will be performed using an analysis of covariance (ANCOVA) model. The model includes fixed effects of treatment, period, treatment sequence, and covariate of baseline value. A point estimate of the treatment difference and the corresponding 95% confidence intervals will be provided. Secondary efficacy endpoints will be analyzed similarly. Summaries of [redacted] and [redacted] results will be provided.

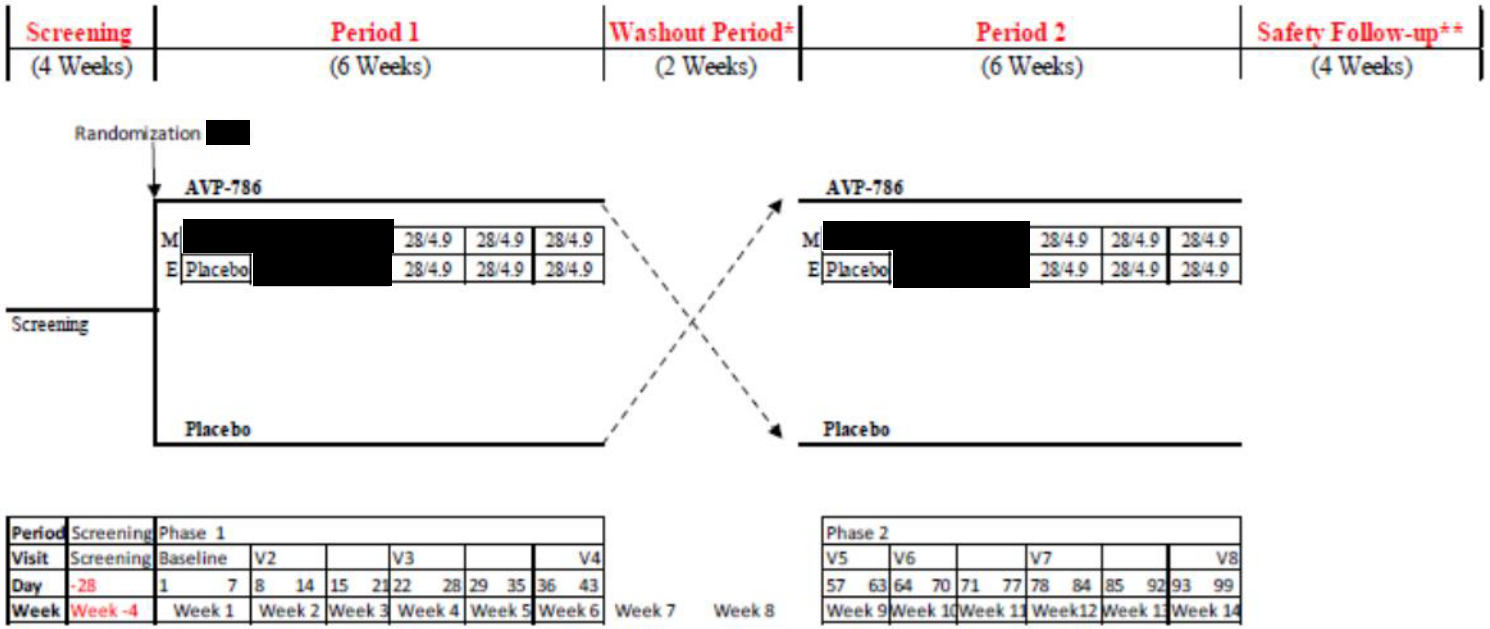
Safety Analyses

Safety analyses will consist of data summaries for biological parameters and AEs. Safety analyses will be tabulated by treatment group across the 2 periods.

Sample Size Calculation

This is a proof-of-concept (POC) study and as such, no data is available on which to base power calculations. Based on prior clinical studies, randomizing approximately 12 patients is a reasonable number to assess POC.

Figure 1 Study Schematic



Study medication (active or placebo) will be administered as capsules; 1 in the morning and 1 in the evening, approximately 12 hours apart.

M: Morning Dose (in mg d6-DM/mg Q)

E: Evening Dose (in mg d6-DM/mg Q)

* A sufficient supply of placebo will be provided for the washout period in a single-blind manner to ensure continuity and patient compliance

** A safety follow-up phone call will be made 30 days after last study dose (Day 129)

Table 1 Schedule of Evaluations and Visits

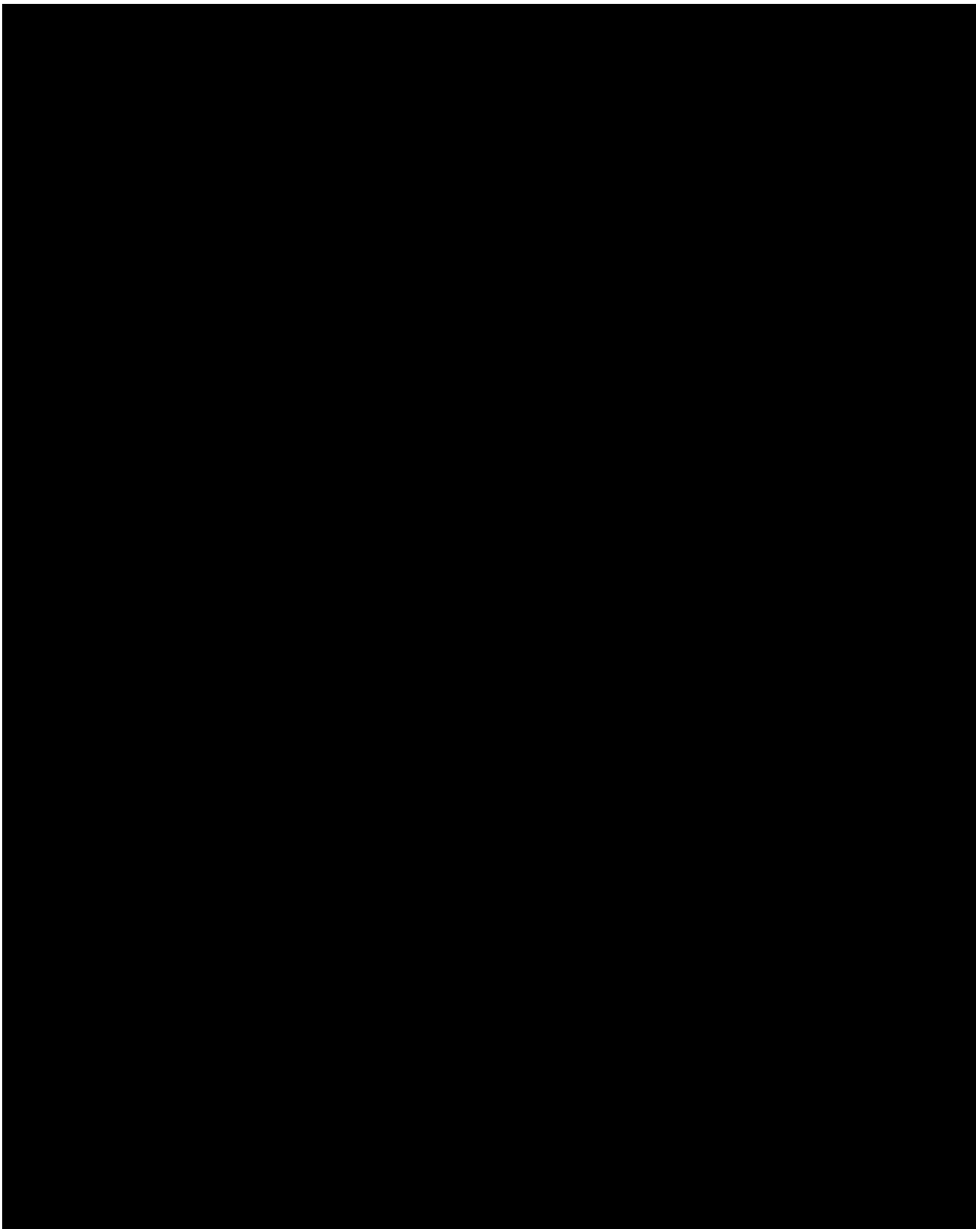
		Period 1					Washout Period	Period 2			
Procedure	**Visit:**	**Screening**	**Baseline[4]**	**Visit 2[3]**	**Visit 3[4]**	**Visit 4[4]**		**Visit 5[4]**	**Visit 6[3]**	**Visit 7[4]**	**Visit 8[4]/ET[5]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 22**	**Day 43**		**Day 57**	**Day 64**	**Day 78**	**Day 99**
	End of Study Week:	**Week -4 to -1**		**Week 1**	**Week 3**	**Week 6**		**Week 8**	**Week 9**	**Week 11**	**Week 14**
Informed consent		X									
Medical history		X									
Risk assessment for falls (worksheet)		X									
Review of prior and concomitant medications		X	X	X	X	X		X	X	X	X
Inclusion and exclusion criteria		X	X								
Randomization			X								
Physical and neurological examination		X				X		X			X
Vital signs and weight[6]		X	X	X	X	X		X	X	X	X
Hematology, chemistry, and urinalysis		X[7]				X		X			X
Urine pregnancy test[8]		X	X			X		X			X
PK blood sample						X					X
Resting 12-lead ECG		X[9]	X[10]	X	X	X[10]		X[10]	X	X	X[10]
Review of adverse events[11]			X	X	X	X		X	X	X	X[11]
[redacted]		X				X[2]					X[2]
[redacted]			X[12]			X[2,12]					X[2,12]
FBI		X	X	X	X	X		X	X	X	X
NPI		X	X	X[1]	X[1]	X		X	X[1]	X[1]	X
mCGIS			X					X			
mCGIC					X	X				X	X
PGIC					X	X				X	X
QoL			X			X		X			X
QoR			X			X		X			X
CNS-LS			X			X		X			X
MMSE			X			X		X			X

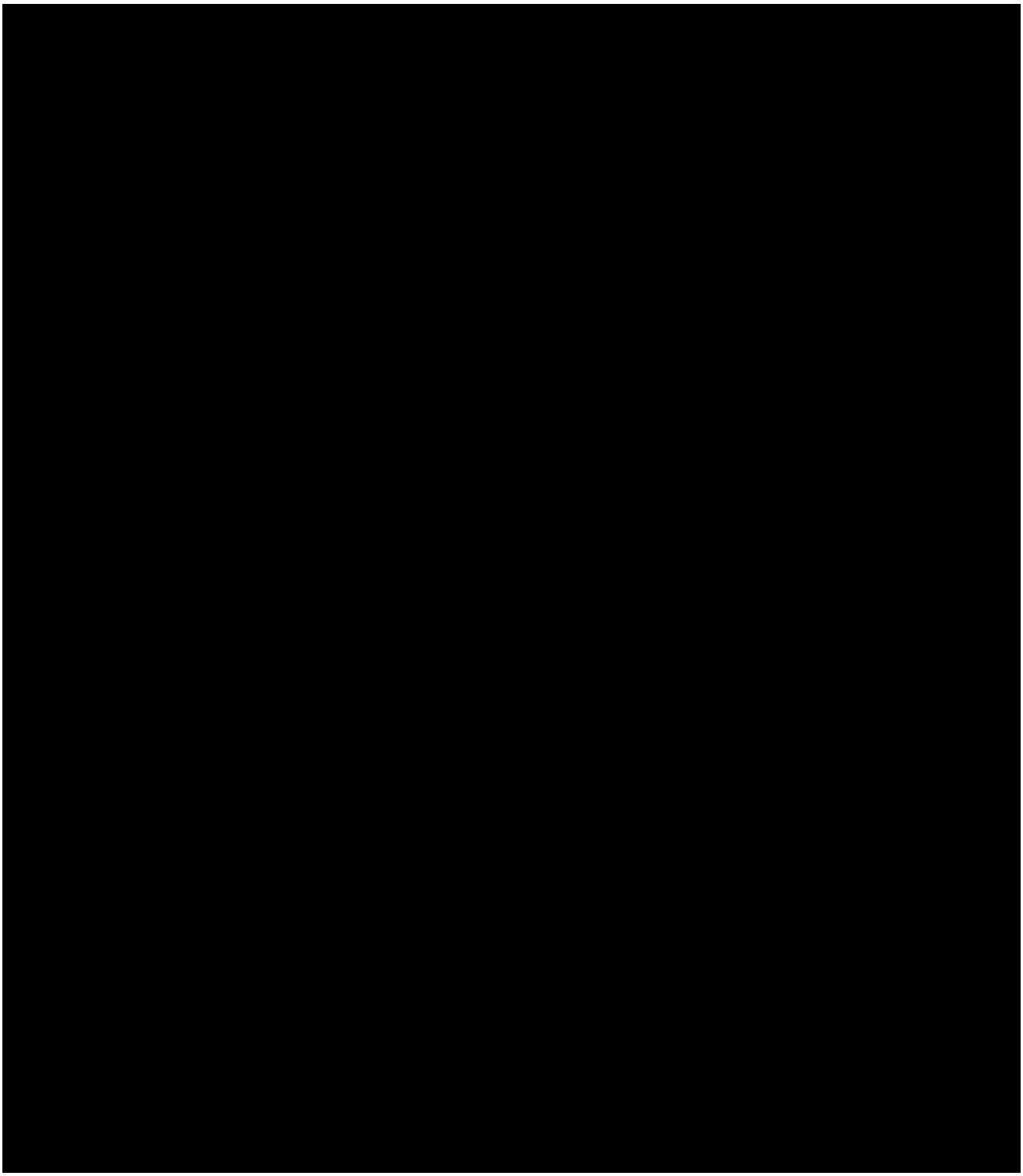
			Period 1				Washout Period	Period 2			
	Visit:	**Screening**	**Baseline[4]**	**Visit 2[3]**	**Visit 3[4]**	**Visit 4[4]**		**Visit 5[4]**	**Visit 6[3]**	**Visit 7[4]**	**Visit 8[4]/ET[5]**
	Study Day:	**Day -28 to -1**	**Day 1**	**Day 8**	**Day 22**	**Day 43**		**Day 57**	**Day 64**	**Day 78**	**Day 99**
Procedure	**End of Study Week:**	**Week -4 to -1**		**Week 1**	**Week 3**	**Week 6**		**Week 8**	**Week 9**	**Week 11**	**Week 14**
CSDD		X				X		X			X
Stroop color and word task			X[12]			X[12]		X			X[12]
IRI			X			X		X			X
S-STS		X	X	X	X	X		X	X	X	X
Administer first dose of study medication in clinic			X					X			
Administer last dose of study medication in clinic						X					X
Dispense study medication and diary card			X	X	X	X[13]		X	X	X	
Review and return unused study medication and diary card				X	X	X		X	X	X	X

CNS-LS = Center for Neurologic Study-Lability Scale; CSDD = Cornell Scale for Depression in Dementia; ECG = electrocardiogram; [redacted] FBI = Frontal Behavioral Inventory; [redacted]; IRI = interpersonal Reactivity Index; mCGIC = Modified Clinical Global Impression of Change; mCGIS = Modified Clinical Global Impression of Severity of Illness; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; QoL = Quality of Life; QoR = Quality of Relationships; S-STS = Sheehan Suicidality Tracking Scale

1 Perform NPI Disinhibition domain only
2 [redacted] and [redacted] scan should be completed within 7 days of Visit 4 and within 7 days of Visit 8.
3 Visit 2 and Visit 6 have a +3 days window
4 All study visits have a +/- 3 days window (except Visit 2 and Visit 6)
5 Early Termination visit for patients who withdraw prior to study completion
6 Weight should be measured at the baseline visit only
7 Thyroid function tests (TSH, and reflex T3 and T4 if TSH is abnormal) should be performed at the Screening Visit
8 Urinary beta-hCG test will be performed for females of childbearing potential only
9 ECG will be performed in triplicate at Screening
10 ECG will be performed pre-dose and post-dose
11 A safety follow-up call must be made 30 days after the last clinic visit (on Day 129) to review adverse events
12 Stroop color and word task should be performed in conjunction with [redacted]
13 Sufficient supply of placebo will be dispensed to all patients (single-blind) for the washout period, for continuity and medication compliance purposes.

1 BACKGROUND AND CLINICAL RATIONALE





2 STUDY OBJECTIVES

The objectives of the study are to evaluate the safety, tolerability, and efficacy of AVP-786 compared to placebo, for the treatment of disinhibition in patients with NDD including frontotemporal dementia, Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, vascular cognitive disorders, or Huntington's disease.

3 STUDY DESIGN

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, cross-over design study. The study duration is approximately 22 weeks and consists of a 4-week screening period, 2 treatment periods of 6-week duration each (period 1 and period 2), a 2-week washout period between the treatment periods, and a 4-week safety follow-up period following period 2.

Sequence	Screening	Period 1	Washout Period	Period 2	Follow-up Phone call
Study Day	Day -28 to -1	Day 1 to 43	Day 44-56	Day 57 to 99	Day 129

Approximately 12 patients will be enrolled at 2 centers, with approximately 6 patients at each center.

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 43 during period 1 and Day 57 through Day 99 during period 2. The first and last dose of study medication will be administered in the clinic on Day 1 (Baseline visit) and Day 99 (Visit 8), respectively. Patients (or caregivers) will self-administer study medication on all other study days. Screening must occur within 4 weeks prior to randomization.

Period 1

Following screening procedures for assessment of inclusion and exclusion criteria, eligible patients will be randomized into this 2x2 crossover study in a [redacted] ratio to receive either treatment sequence 1 AB (period 1: A, period 2: B) or treatment sequence 2 BA (period 1: B, period 2: A), where A is AVP-786 and B is placebo. 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.

- Patient randomized to treatment sequence 1 AB will start with AVP-786-[redacted] 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-[redacted] BID for 14 days. From Day 22, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of period 1.
- Patients randomized to treatment sequence 2 BA will be dosed with placebo BID during period 1.

A 2-week washout period will follow period 1 (Days 44 to 56). For the washout period, suffient supply of placebo will be dispensed in a single-blind manner to patient/caregiver to ensure continuity and study medication compliance.

Period 2:

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

- Patients who received AVP-786 in period 1 (treatment sequence 1 AB) will receive placebo BID for the entire 6-week duration of period 2.
- Patients who received placebo in period 1 (treatment sequence 2 BA) will start with AVP-786-[redacted] once a day in the morning and placebo in the evening for the first 7 days of period 2. From Day 64, patients will receive AVP-786-[redacted] BID for 14 days. From Day 78, patients will receive AVP-786-28/4.9 BID for the remaining 3 weeks of period 2.

Patients who complete period 2 will have a safety follow-up phone call on Day 129, 30 days after the last clinic visit.

All study medication including AVP-786-[redacted], AVP-786-28/4.9, and placebo capsules are of identical appearance in order to maintain the integrity of the blind.

4 STUDY POPULATION

Patients enrolled in this study must have a diagnosis of a NDD including frontotemporal dementia, Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies, vascular cognitive disorders, or Huntington's disease.

Patients must exhibit disinhibition syndrome of sufficient severity to warrant treatment and to exhibit a reduction in severity if the intervention is successful. The definition of disinhibition syndrome used is based on the criteria developed to identify patients with the behavioral variant of frontotemporal dementia[1] which includes descriptions of disinhibited behavior in three general areas: socially inappropriate behavior, loss of manners and decorum, and impulsive, rash, and careless action, and have been shown to have good intra rater reliability.[35]

Eligible patients must have a caregiver that 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 caregiver for this study, the individual should spend time with the patient at least 2 hours per day on 4 separate days per week.

4.1 Inclusion Criteria

1. Males and females 50 to 90 years of age, inclusive.
2. Documented diagnosis of a Neurodegenerative Disorder including frontotemporal dementia, Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy bodies (DBL), vascular cognitive disorders, or Huntington's disease, at least 3 months prior to Baseline.
3. The patient has behavior from 2 of the 3 categories below of disinhibited behavior from the definition of the behavioral variant of frontotemporal dementia
    - Socially inappropriate behavior: Examples of behaviors that violate social norms include inappropriately approaching, touching or kissing strangers, verbal or physical aggression, public nudity or urination, inappropriate sexual acts and criminal behavior (such as theft or shoplifting).
    - Loss of manners or decorum: Examples include inappropriate laughter, cursing or loudness, offensive jokes or opinions, or crude or sexually explicit remarks. Patients may also display a general lack of etiquette (e.g. failing to wait in line, eating with mouth open), loss of respect for interpersonal space and a lack of response to social cues (e.g. patient will continue talking despite other's attempts to end a conversation). Some patients with FTD exhibit poor hygiene or grooming (e.g. wearing malodorous, stained, torn or inappropriate clothing) or impolite physical behaviors (e.g. flatulence, scratching or fondling private parts, picking teeth, belching or spitting).

- Impulsive, rash or careless actions: These include reckless driving, new-onset gambling, stealing (usually food or 'shiny' objects), buying or selling objects without regard for consequences, or indiscriminate sharing of personal information (e.g. credit card information, social security number).

4. [redacted]
5. The behavioral changes are not due to a pre-existing major psychiatric disorder (e.g., schizophrenia, bipolar disease, etc.) and are not due to the direct effect of systemic illness, drug action, or substance use.
6. A score of ≥ 4 on the 3 core disinhibition questions of the Frontal Behavioral Inventory (FBI) at Screening and Baseline.
7. The patient has stable cardiac, pulmonary, hepatic, and renal function.
8. [redacted]
9. If female of childbearing age, must have been practicing a medically-acceptable method of birth control for at least 1 month prior to randomization and continue with the same method during the entire study duration (oral contraceptive tablets, hormonal implant device, hormone patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, or abstinence) or be surgically sterile or post-menopausal. All male patients must follow the same methods of birth control with partners of childbearing potential during the entire study duration.
10. [redacted]
11. [redacted]
12. [redacted]

13. [redacted]
14.
15.

16. Availability of a caregiver known to the patient and who is able and willing to comply with study procedures, including not administering any prohibited medications during the course of the study and ensuring that the patient attends all study visits.
17. Caregiver must provide a signed informed consent form (ICF) after the nature and risks of study participation have been fully explained.
18. Patients must have at least eight years of education and should have previously (in pre-AD condition) been capable of reading, writing, and communicating effectively with others in English.

4.2 Exclusion Criteria

1. Caregiver is unwilling or unable, in the opinion of the investigator, to comply with study instructions.
2. Patients with symptoms of disinhibition that is <u>not</u> secondary to NDD (e.g., substance use, systemic illness, or TBI).
3. [redacted]
4.
5.
6. Patients with myasthenia gravis.
7. [redacted]
8.
9. 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). Certain other non-metastatic cancer may be allowed. Each case to be evaluated individually with the Medical Monitor (MM).

10. [redacted]
11.
12.
13.
14.
15.
16.
17.
18.

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. In any 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.

In addition, patients who present a QTc interval (QTcF) >500 msec (unless due to ventricular pacing) or a QTc interval change from the screening ECG of >60 msec at any time after randomization, will be withdrawn from the study. The QTc values will be assessed for clinical significance and recorded.

Patients who withdraw prior to study completion will be asked to return to the clinic to complete the Visit 8 (end of study) assessments.

If the patient withdraws from the study, and consent is withdrawn by the caregiver and/or patient's representative for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

5 STUDY TREATMENTS

5.1 Treatments Administered

5.1.1 Description of Study Medications

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

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

Drug supplies will be provided to the site in double-blind, individual, pre-labeled containers as described below.

- Day 1 (Baseline): Bundle consisting of one AM bottle with 10 capsules and one PM bottle with 10 capsules.
- Day 8 (Visit 2): Bundle consisting of one AM bottle with 17 capsules and one PM bottle with 17 capsules.
- Day 22 (Visit 3): Bundle consisting of one AM bottle with 24 capsules and one PM bottle with 24 capsules.

Sufficient supply of AVP-786 placebo will be provided to the site to dispense to the patients in a single-blind manner on Day 43 (Visit 4), for the 2-week washout period.

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

[redacted]

Table 2 Composition of Investigational Product

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

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

5.1.3 Packaging

Clinical study medication (capsules) will be packaged into 50cc HDPE bottles with matching child resistant closure/cap. Bottles will contain 10 capsules, 17 capsules, and or 24 capsules each. Capsules will be configured as provided to the clinical research center in bottles labeled with a code specific to each drug product and strength and clearly marked as AM or PM bottles. Bottles with the same code, one AM bottle and one PM bottle, will be bundled together and clearly identified with the specific code, storage condition, protocol number and an investigational drug warning. The unblinded site pharmacist will assign individual bundle kit for each patient based on the randomized Medication List.

5.1.4 Labeling

The bottle label will consist of 2 panels, with 1 detachable panel that will be removed and affixed to the study medication Dispensing Log page at time of dispensing. Space will be provided on both panels of the label to record Patient Number, the Visit Week, and Dispensing Date. The bottle label will consist of 1 panel, containing protocol number, product name, randomized Med ID Code, investigational drug warning, dosage instructions, AM or PM, company name and address, and AM or PM clearly marked. 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 to 86°F).

5.1.6 Study Medication Administration

An unmasked site pharmacist will dispense study medication using the randomized Medication List.

Period 1: At Baseline (Day 1), Visit 2 (Day 8), and Visit 3 (Day 22), study medication will be dispensed and administered as follows:

- Day 1 (Baseline): Patients will be dispensed a 1-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 10 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 7 days.
- Day 8 (Visit 2): Patients will be dispensed a 2-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 17 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 14 days.
- Day 22 (Visit 3): Patients will be dispensed a 3-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 24 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 21 days.

Washout period: At Day 43 (Visit 4), study medication will be dispensed as follow:

- Patients will be dispensed a 2-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 17 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 14 days.

Period 2: At Day 57 (Visit 5), Day 64 (Visit 6), and Day 78 (Visit 7), study medication will be dispensed and administered as follows:

- Day 57 (Visit 5): Patients will be dispensed a 1-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 10 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 7 days.
- Day 64 (Visit 6): Patients will be dispensed a 2-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 17 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 14 days.
- Day 78 (Visit 7): Patients will be dispensed a 3-week medication kit containing one AM bottle and one PM bottle. Each bottle will contain 24 capsules. Patients will be administered 1 capsule from the AM bottle in the morning and 1 capsule from the PM bottle in the evening, approximately 12 hours apart for 21 days.

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 study medication 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 study medication supplied is for use only in this study and should not be used for any other purpose. All randomized Med 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 study medication 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.

Additionally, the detachable panel of the two-panel label on each blister card will be removed and affixed to the study medication Subject Drug 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 study medication 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

For this 2x2 cross over study, patients will be randomized in a [redacted] ratio within investigation site into 2 treatment sequence: AB or BA, where A = AVP-786 and B = Placebo. [redacted]

Eligible patients will be randomized at the Baseline visit to receive either treatment sequence AB or BA in a double-blind manner according to a randomization scheme devised by Avanir or its representative.

5.3.2 Blinding/Masking

Blinding will be maintained by providing capsules of the 2 doses of AVP-786 and placebo that are identical in appearance. The sponsor, patients, caregivers, investigator, 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 unblinding of a patient.

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, 22, 43, 57, 64, 78, and 99 (Visits 2 to 8). For this study, compliance will be defined as when a patient takes at least 80% of their scheduled doses. 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 collected on Days 8, 22, 43, 57, 64, 78, and 99 (Visits 2 to 8), or at the time of early study discontinuation.

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.

6.1.1 Neuropsychiatric Inventory (NPI)

The NPI [redacted] is a validated clinical instrument for evaluating psychopathology in a variety of disease settings, including dementia.[29] 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 behaviors, sleep and nighttime behavioral disturbances, 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 (0 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 Screening (Day -28 to -1), Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

The Disinhibition domain only of the NPI will be administered to the patient's caregiver at Day 8 (Visit 2), Day 22 (Visit 3), Day 64 (Visit 6), and Day 78 (Visit 7).

The NPI domains are evaluated for behaviors within the past 4 weeks. However, it also depends on the visit intervals from Baseline. The longest or maximum interval is within the past 4 weeks, as the NPI was validated based on this interval. Therefore, for Visits 2 and 6 the evaluation will be within the past 1 week, for Visit 5 the evaluation will be within the past 2 weeks, for Visits 3 and 7 will be within the past 3 weeks and for Visits 4 and 8 will be within the past 4 weeks.

6.1.2 Frontal Behavioral Inventory (FBI)

The FBI is a 24-item questionnaire that is often used to assess frontal lobe dementia [redacted].[30] It includes questions on inappropriateness, excessive jocularity, and poor judgment and impulsivity. Each item is measured on a 4-point scale (rated as 0 = none, 1 = mild, occasional, 2 = moderate, 3 = severe, most of the time) and is dependent on the caregiver's response.

When interview of the potential study patient confirms that the individual has disinhibited behavior, then the disinhibition will be scored by using the 3 core disinhibition questions of the FBI (Questions 15, 16 and 17). These generally parallel the behavioral variant of frontotemporal dementia (BvFTD) criteria and

include questions on inappropriateness, excessive jocularity, and poor judgment and impulsivity.[1] Each question is scored 0-3 and a minimum score of 4 (out of 9 possible) is required for study entry.

The FBI will be administered to the patient's caregiver at all clinic visits; Screening (day -28 to -1), Day 1 (Baseline), Day 8 (Visit 2), Day 22 (Visit 3), Day 43 (Visit 4), Day 57 (Visit 5), Day 64 (Visit 6), Day 78 (Visit 7), and Day 99 (Visit 8).

6.1.3 Modified Clinical Global Impression of Severity of Illness (mCGIS)

The CGIS 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 Program (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[36–40] and is easy and quick to administer, provided that the clinician knows the patient well.[41]

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.[42–44]

The CGIS is a 7-point (1-7) scale (1 = normal, not at all ill; 7 = among the most extremely ill patients) and is assessed for overall clinical status. The CGIS used in this protocol is modified to also assess severity of disinhibition on a 7-point scale (1 = normal, not at all disinhibited; 7 = among the most extremely disinhibited patients) (mCGIS, [redacted]). The mCGIS will be assessed at Day 1 (Baseline) and Day 57 (Visit 5).

6.1.4 Modified Clinical Global Impression of Change Rating (mCGIC)

The CGIC is a 7-point scale that requires the clinician to rate the change of the patient's condition at the time of assessment, relative to the clinician's past experience with the patient's condition at admission. The CGIC used in this protocol is modified to also assess severity of disinhibition on a 7-point scale (mCGIC, [redacted]). Considering total clinical experience, a patient is assessed for change of disinhibition symptoms and overall clinical status as 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; or 7 = Very much worse.

The mCGIC will be administered at Day 22 (Visit 3), Day 43 (Visit 4), Day 78 (Visit 7), and Day 99 (Visit 8). At Day 22 (Visit 3) and Day 43 (Visit 4), the mCGIC will be completed to assess change from the Baseline visit (Day 1). At Day 78 (Visit 7) and Day 99 (Visit 8), the mCGIC will be completed to assess change from Day 57 (Visit 5).

6.1.5 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: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; or 7 = Very much worse.[41]

The PGIC will be administered at Day 22 (Visit 3), Day 43 (Visit 4), Day 78 (Visit 7), and Day 99 (Visit 8) and will focus on the patient's disinhibition symptoms.

6.1.6 Quality of Life (QoL)

The QoL scale [redacted] is a 10-cm visual analog scale used to assess quality of life. Visual analog scales have been widely used in pain assessment[45] and their psychometric properties have been established. This scale has been used previously in patients with PBA treated with AVP-923.[46]

The QoL scale will be used to assess the impact of disinhibition on the global subjective well-being of the patient. It will be administered at Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.7 Quality of Relationships (QoR)

The QoR scale [redacted] is a 10-cm visual analog scale used to assess quality of relationships of the patient. Like the QoL, the QoR scale has been used previously in patients with PBA treated with AVP-923.[46]

The QoR will be used to assess the impact of disinhibition on the relationships of the patient. It will be administered at Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.8 Interpersonal Reactivity Index (IRI)

The IRI [redacted] is a 28-item questionnaire that measures empathy defined as reactions of one individual to the observed experiences of another.[47] It consists of 4 subscales; perspective taking, fantasy, empathic concern and personal distress. Each subscale is made up of 7 different items that are answered on a 5-point Likert scale ranging from 'does not describe me well' to 'describes me very well'.

The IRI will be administered at Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.9 Center for Neurologic Study-Lability Scale (CNS-LS)

The CNS-LS [redacted] is a 7-item questionnaire designed to be completed by the patient or patient's caregiver that provides a quantitative measure of the perceived frequency of pseudobulbar affect (PBA) episodes. It is composed of 2 subscales measuring labile laughter (4 items) and labile crying (3 items). The CNS-LS requires approximately 5 minutes to be completed.

The CNS-LS will be administered at Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.10 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.[48] It requires only 5 to 10 minutes for a trained rater to administer it.

The MMSE will be administered at Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.11 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.[49] 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 administered at Screening (Day -28 to Day -1), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

6.1.12 Stroop Color and Word Task with [redacted]

The Stroop color and word task is a standard measure that is useful for measuring cognitive flexibility and processing speed. A sample of the Stroop task to be performed in this study is provided in [redacted]. [redacted] In this task, subjects are asked to identify the color in which words are written. The color can be the same as the word (so-called congruent trial) or the color of the word can be different (so-called incongruent trial). If the color and the word do not match (i.e. for incongruent trials, for example the word "blue" shown in red color), cognitive interference occurs which involves activation of a functional network in the prefrontal cortex[50].

The Stroop task probes semantic interference, which means that naming the ink color of incongruent stimuli is slower than for neutral or congruent stimuli. On the other hand semantic facilitation explains the finding that naming the ink of congruent stimuli is faster (e.g. when the ink color and the word match).

Both semantic interference and facilitation disappear when the task consists of reading the word instead of naming the color. This fact has been sometimes called Stroop asynchrony, and has been explained by a reduced automatization when naming colors compared to reading words.

For patients with compromised executive functioning, the Stroop color interference task is an important tool to map the functioning of the prefrontal cortex. [redacted]

The Stroop task with the [redacted] will be performed at Day 1 (Baseline), Day 43 (Visit 4), and Day 99 (Visit 8). The Stroop task alone (without [redacted]) will be performed at Day 57 (Visit 5).

[redacted] In addition, the 3 summary scores of the Stroop (based on the number of items completed on each of the three stimulus conditions) and the Stroop interference score will be used to assess the patient's cognitive flexibility and reaction to cognitive stress at baseline and compare performance between the placebo and active drug stages of the study.

[redacted]

6.2 Pharmacokinetics (PK)

At Visit 4 (Day 43) and Visit 8 (Day 99), 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 visit after the Screening visit (Day 1 [Baseline], Days 8, 22, 43, 57, 64, 78, and 99 [Visits 2-8]). A phone call will be made on Day 129 (± 3-days) to review any newly reported AE after receiving and up to 30 days after the last dose of study medication.

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 must inform Avanir's MM by telephone no later than 24 hours after becoming aware of the event. Subsequently, the SAE must be assessed for the following details: seriousness of event, start date, stop date, intensity, frequency, relationship to test drug, action taken regarding test drug, treatment required, and outcome to date. These details must be recorded on the clinical study AE form that is provided. This form should be transmitted by fax and the details given by telephone to the contact numbers below.

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

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

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

The Institutional Review Board (IRB) 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), Day 57 (Visit 5), and Day 99 (Visit 8), and include assessments of head, eyes, ears, nose, throat, lymph nodes, skin, extremities, respiratory, gastrointestinal, musculoskeletal, cardiovascular, and nervous systems.

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

Vital signs, systolic and diastolic blood pressure (BP; mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute) and body temperature (ºF) should be recorded at all clinic visits.

6.3.4 Clinical Laboratory Tests

The following clinical laboratory assessments are to be performed at Screening (Day -28 to Day -1), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8):

- 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

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 Test

A urine pregnancy test will be performed on females of childbearing potential at Screening (Day -28 to Day -1), Baseline (Day 1), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8).

All female patients of childbearing potential should be instructed to use appropriate birth control methods until 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. At Screening (day 28 to -1), ECG will be performed in triplicate. At Day 1 (Baseline), Day 43 (Visit 4), Day 57 (Visit 5), and Day 99 (Visit 8), two ECGs will be performed; one prior to study medication dosing and one 2-3 hours after dosing.

ECG data will be recorded at the study center and will include general findings, heart rate (beats/minute) the Q-R-S complex from an ECG tracing (QRS) and the P-R interval from an ECG tracing (PR) and QTc intervals (milliseconds). ECG abnormalities present at Screening will be recorded as medical history. Any changes from the ECG status at screening that are deemed to be clinically significant by the

investigator will be captured as AEs. Any clinically significant abnormal ECG should be discussed with the 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.[56] Each item of the S-STS is scored on a 5-point Likert scale (0 = not at all; 1 = a little; 2 = moderately; 3 = very; and 4 = extremely). The S-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 -1), Day 1 (Baseline), Day 8 (visit 2), Day 22 (Visit 3), Day 43 (Visit 4), Day 57 (Visit 5), Day 64 (Visit 6), Day 78 (Visit 7), and Day 99 (Visit 8). Any change in the S-STS score indicating the presence of suicidality should be evaluated by the investigator and reported to the MM.

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

6.4.1.1 Screening Visit (Days -28 to -1)

The following procedures will be performed at Screening (within 28 days prior to Day 1).

1. The investigator will provide the patients, authorized representative 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, and any prior and concomitant medications use (including OTC medications, vitamins, and supplements) will be reviewed and recorded.
3. Review inclusion/exclusion criteria.
4. Physical and neurological examination findings and vital signs measurements (including BP, heart rate, respiratory rate, and body temperature) will be recorded.
5. Risk assessment for falls will be performed.
6. A blood and urine specimen will be collected for safety laboratory assessments.
7. A urine pregnancy test will be performed for females of childbearing potential only.
8. Resting 12-lead ECG will be performed in triplicate.
9. [redacted]

10. The following tests will be completed:

    - NPI
    - FBI
    - CSDD
    - S-STS

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 with study participation, will not be enrolled.

6.4.1.2 Baseline Visit (Day 1)

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

Before dosing:

1. Inclusion/exclusion criteria will be reviewed.
2. Vital signs and weight will be measured and recorded.
3. Caregivers will be queried regarding patient's AEs and concomitant medication use (including OTC, vitamins, and supplements).
4. A urine pregnancy test will be performed for females of childbearing potential only.
5. The following tests will be completed:

    - NPI
    - FBI
    - CGIS
    - QoL
    - QoR
    - CNS-LS
    - MMSE
    - Stroop color and word task with [redacted]
    - IRI
    - S-STS

6. A resting 12-lead ECG will be performed (twice this visit - pre and post dose).

Patients will be randomized once it is determined that they satisfy all of the inclusion and exclusion criteria (on the basis of the screening and baseline assessments described above) and will be assigned with a study medication kit number.

Study Medication Dosing:

The first dose of study medication will be administered from the AM-label bottle at the clinic regardless of the time of day.

After Dosing:

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. The caregiver will be queried regarding AEs.
9. Patient's diary card and sufficient study medication will be dispensed for a 1-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient 1 capsule of study medication from the 10-count, AM-label bottle in the morning and 1 capsule of study medication from the 10-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours, for 7 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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 they understand what is required of them.

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

Caregiver is advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be measured and recorded.
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. The following tests will be completed:
    - NPI –Disinhibition domain only
    - FBI

- S-STS

4. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
5. Patient's diary card will be collected and reviewed for compliance.
6. Returned, unused study medication will be accounted for compliance.
7. Patient diary card and sufficient study medication for a 2-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 from the 17-count, AM-label bottle in the morning and 1 capsule from the 17-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures including how to complete the Patient's diary card. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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.

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

Caregiver is advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be measured and recorded.
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. The following tests will be completed:

    - NPI –Disinhibition domain only
    - CGIC
    - PGIC
    - FBI
    - S-STS

4. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC medications, vitamins, and supplements).

5. Patient's diary card will be collected and reviewed for compliance.
6. Returned, unused study medication will be accounted for compliance.
7. 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 from the 24-count, AM-label bottle in the morning and 1 capsule from the 24-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours) for 21 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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.

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

Visit 4 (Day 43) should occur in the morning. The last dose of study medication will be administered at the clinic after the required procedures are performed.

The following procedures will be performed:

1. Physical and neurological examination findings and vital signs measurements (including BP, heart rate, respiratory rate, and body temperature) will be recorded.
2. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC, vitamins, and supplements).
3. A blood specimen will be collected within 3 hours after the morning dose of study medication for PK analysis and for safety laboratory assessments
4. A urine sample will be collected for urinalysis.
5. A urine pregnancy test will be performed for females of childbearing potential only.
6. A resting 12-lead ECG will be performed (twice this visit - pre and post dose).
7. [redacted]
8. The following tests will be completed:
    - NPI
    - FBI
    - CGIC

- PGIC
- QoL
- QoR
- CNS-LS
- MMSE
- CSDD
- Stroop color and word task with [redacted]
- IRI
- S-STS

9. The patient's diary card will be collected and reviewed for compliance.
10. Returned, unused study medication will be accounted for compliance.
11. Patient diary card and sufficient study medication for a 2-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 from the 17-count, AM-label bottle in the morning and 1 capsule from the 17-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours) for 14 days. Caregivers will also be instructed to bring to the clinic any unused study medication. 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 5 (Day 57 ± 3-day window)

Visit 5 (day 57) should occur in the morning. The following procedures will be performed:

Before Dosing:

1. Physical and neurological examination findings and vital signs measurements (including BP, heart rate, respiratory rate, and body temperature) will be recorded.
2. Caregivers will be queried regarding patient's AEs and concomitant medication use (including OTC, vitamins, and supplements).
3. A blood and urine specimen will be collected for safety laboratory assessments.
4. A urine pregnancy test will be performed for females of childbearing potential only.
5. The following tests will be completed:

- NPI
- FBI

- CGIS
- QoL
- QoR
- CNS-LS
- MMSE
- CSDD
- Stroop color and word task
- IRI
- S-STS

6. A resting 12-lead ECG will be performed (twice this visit - pre and post dose).

Study Medication Dosing:

The first dose of study medication will be administered from the AM-label bottle at the clinic regardless of the time of day.

After Dosing:

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. The caregiver will be queried regarding AEs.
9. Returned, unused study medication will be accounted for compliance.
10. Patient's diary card and sufficient study medication will be dispensed for a 1-week treatment period.

Patient/Caregiver Instruction

Caregivers will be instructed to administer to the patient 1 capsule of study medication from the 10-count AM-label bottle in the morning and 1 capsule of study medication from the 10-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours, for 7 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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 they understand what is required of them.

6.4.1.7 Visit 6 (Day 64 + 3-day window)

Caregiver is advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be measured and recorded.
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. The following tests will be completed:
    - NPI –Disinhibition domain only
    - FBI
    - S-STS
4. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC medications, vitamins, and supplements).
5. Patient's diary card will be collected and reviewed for compliance.
6. Returned, unused study medication will be accounted for compliance.
7. Patient diary card and sufficient study medication for a 2-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 from the 17-count, AM-label bottle in the morning and 1 capsule from the 17-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours) for 14 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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 7 (Day 78 ± 3-day window

Caregiver is advised to administer to the patient the morning dose of study medication within 2 hours prior to the clinic appointment.

The following procedures will be performed:

1. Vital signs will be measured and recorded.

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. The following tests will be completed:

    - NPI –Disinhibition domain only
    - CGIC
    - PGIC
    - FBI
    - S-STS

4. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC medications, vitamins, and supplements).

5. Patient's diary card will be collected and reviewed for compliance.

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

7. 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 from the 24-count, AM-label bottle in the morning and 1 capsule from the 24-count, PM-label bottle in the evening, approximately every 12 hours ± 4 hours) for 21 days.

The investigator and/or clinical coordinator will give patients and caregivers detailed instructions regarding study procedures. They will also be instructed to consult with the study site prior to the patient taking any non-study medications. These requirements will be reviewed in person, and written instructions will be provided to the patient and their caregiver. 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.

6.4.1.9 Visit 8 (Day 99 ± 3-day window) / Early Termination

Visit 8 (Day 99) should occur in the morning. Patients who withdraw prior to study completion are required to complete study procedures as listed in Visit 8 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 sample) for early termination patients.

The last dose of study medication will be administered to the patient from the AM-label bottle at the clinic regardless of the time of day.

The following procedures will be performed:

1. Physical and neurological examination findings and vital signs measurements (including BP, heart rate, respiratory rate, and body temperature) will be recorded.

2. The caregiver will be queried regarding patient's AEs and concomitant medication use (including OTC, vitamins, and supplements).
3. A blood specimen will be collected within 3 hours after the morning dose of study medication for PK analysis and for safety laboratory assessments
4. A urine sample will be collected for urinalysis.
5. A urine pregnancy test will be performed on females of childbearing potential only.
6. A resting 12-lead ECG will be performed (twice this visit - pre and post dose).
7. [redacted]
8. The following tests will be completed:
    - NPI
    - FBI
    - CGIC
    - PGIC
    - QoL
    - QoR
    - CNS-LS
    - MMSE
    - CSDD
    - Stroop color and word task with [redacted]
    - IRI
    - S-STS
9. The patient's diary card will be collected and reviewed for compliance.
10. Returned, unused study medication will be accounted for compliance.

6.4.1.10 Safety Follow-up Call (Day 129 ± 3-day window)

A phone call will be made on Day 129 (± 3-days) to review any newly reported AE after receiving and up to 30 days after the last dose of study medication.

7 DATA MANAGEMENT

7.1 Data Collection

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

Clinical study data will be reported (captured) by study site personnel on eCRFs. An eCRF must be completed for every subject 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 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 archived with backup at the sponsor's site.

8 STATISTICAL METHODS

8.1 Analysis Populations

Two analysis populations will be used, modified intent-to-treat (mITT), 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. The safety population includes all patients who received study treatment, and will be used for all analyses of safety. Patients in the safety population will be summarized based on their actual study treatment received.

8.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics.

8.3 Efficacy Analysis

8.3.1 Study Endpoints

Primary Endpoint:

The primary efficacy endpoint is the change from Baseline to Week 6 for each study period, in the Disinhibition domain of the NPI.

Secondary Efficacy Endpoints:

Change from Baseline (raw value for mCGIC and PGIC) for the following:

- Total NPI score
- NPI Total Caregiver Distress
- NPI Disinhibition domain Caregiver Distress
- FBI Total score
- FBI Disinhibition core questions score (questions 15, 16, and 17)
- mCGIC
- PGIC
- QoL
- QoR
- IRI
- CNS-LS

- MMSE
- CSDD
- Stroop color and word task

8.3.2 Primary and Secondary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline to Week 6 for each study period, in the Disinhibition domain of the NPI. Treatment group comparison will be performed using an analysis of covariance (ANCOVA) model. The model includes fixed effects of treatment, period, treatment sequence, and covariate of baseline value. A point estimate of the treatment difference and the corresponding 95% confidence intervals will be provided. Missing value will be imputed by the last observation carry forward (LOCF).

Secondary efficacy endpoints will be analyzed similarly as the primary efficacy end points. Summaries of [redacted] and [redacted] results will be provided.

8.4 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, and S-STS.

Safety analyses will consist of data summaries for AEs, biological parameters and S-STS. Safety analyses will be tabulated by treatment groups across the 2 periods.

Adverse Events

AEs will be coded using the MedDRA. The percentages of patients experiencing 1 or more AEs will be summarized by treatment, system organ class (SOC), deaths, nonfatal 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.

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.

Clinical Laboratory Values

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

8.5 Sample Size Calculations

This is a proof-of-concept (POC) study and, as such, no data is available on which to base power calculations. Based on prior clinical studies, randomizing approximately 12 patients is a reasonable number to assess POC.

9 ADMINISTRATIVE PROCEDURES

9.1 Institutional Review Board Approval

Institutional Review Boards must meet the guidelines set out by the FDA and conform to local laws and customs where appropriate. Written IRB 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 must be informed of and approve all protocol amendments. The investigator will ensure that this study is conducted in full conformance with the laws and regulations of the US (see, Appendix 15, Investigator Responsibilities). The complete text of the World Medical Association Declaration of Helsinki is given in Appendix 16.

9.2 Informed Consent Form

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

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

9.3 Patient's Diary Card

The patient's diary card will be reviewed by clinical study personnel at all study treatment visits for confirmation of medication dosage and any rescue medication received. The study personnel are responsible for (i) ensuring that patients and/or caregivers are properly collecting data and recording it into the diaries; and (ii) transcribing the diary recordings into the eCRF. The diary will be collected at all study visits after Baseline. 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 a username 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.

The investigator 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. The study monitor will also verify that assent was obtained for patients not capable of providing informed consent or that documentation is provided by the investigator explaining why the patient was unable to provide assent. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

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

9.6 Record Retention

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

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

9.7 Source Data

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

9.8 Data Handling

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

9.9 Laboratory Procedures

Site laboratory will collect hematology and chemistry blood samples and urine samples for analysis. Blood samples will be collected for PK analysis at Visit 4 (Day 43) and Visit 8 (Day 99). Instructions for shipping the laboratory samples for evaluation 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 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.

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.

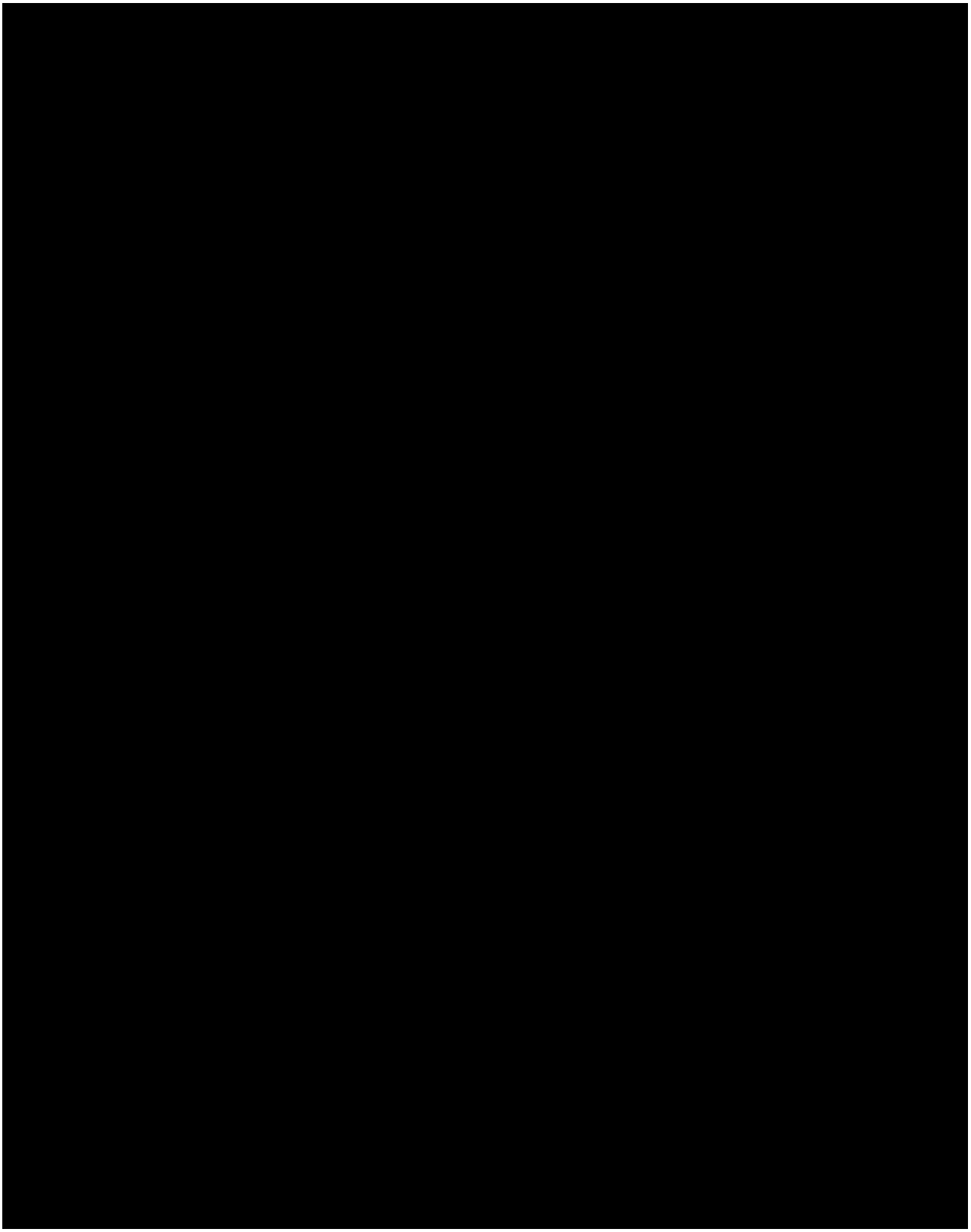
The inspector from the regulatory authority will be especially interested in the following items:

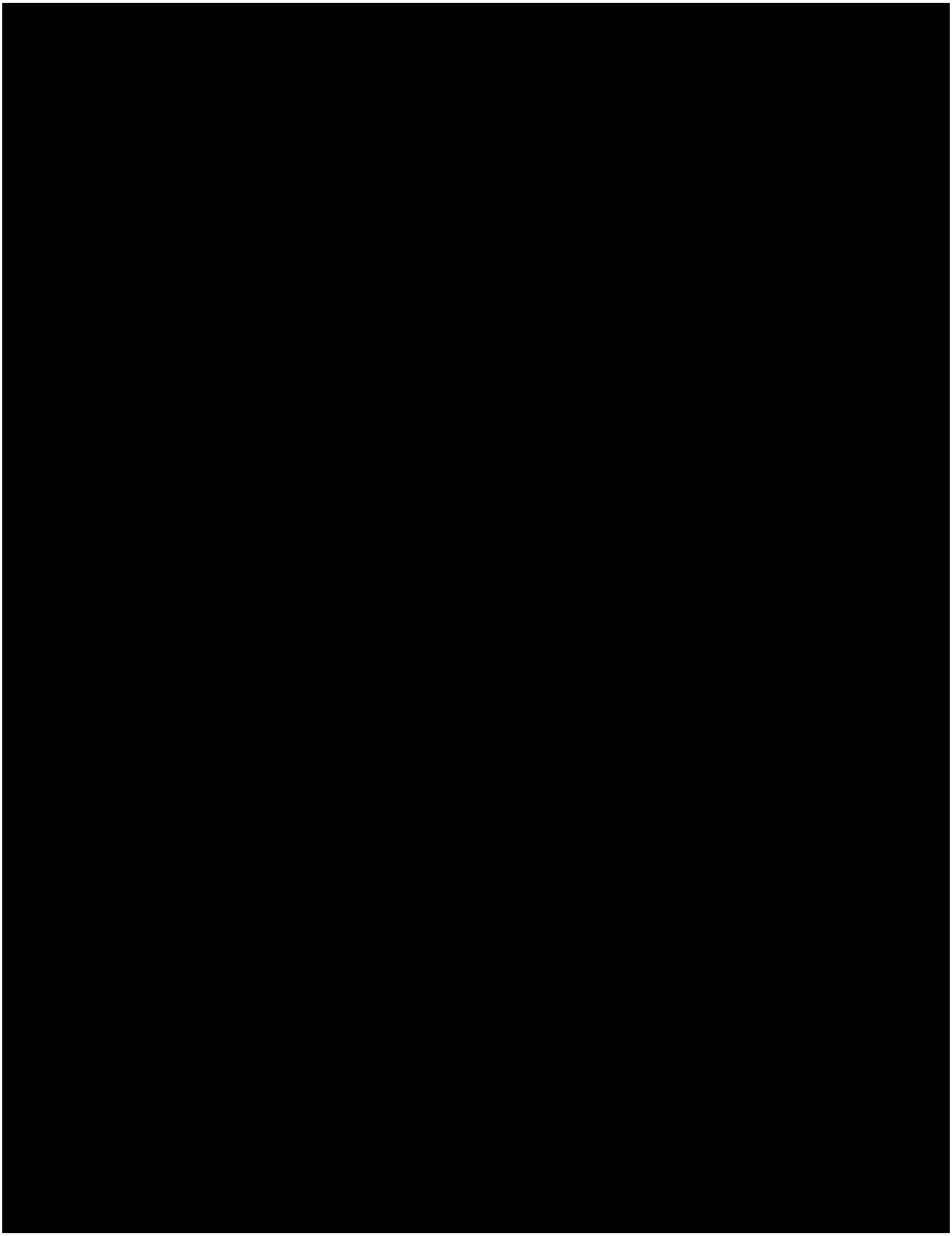
- Visits from the sponsor's representatives

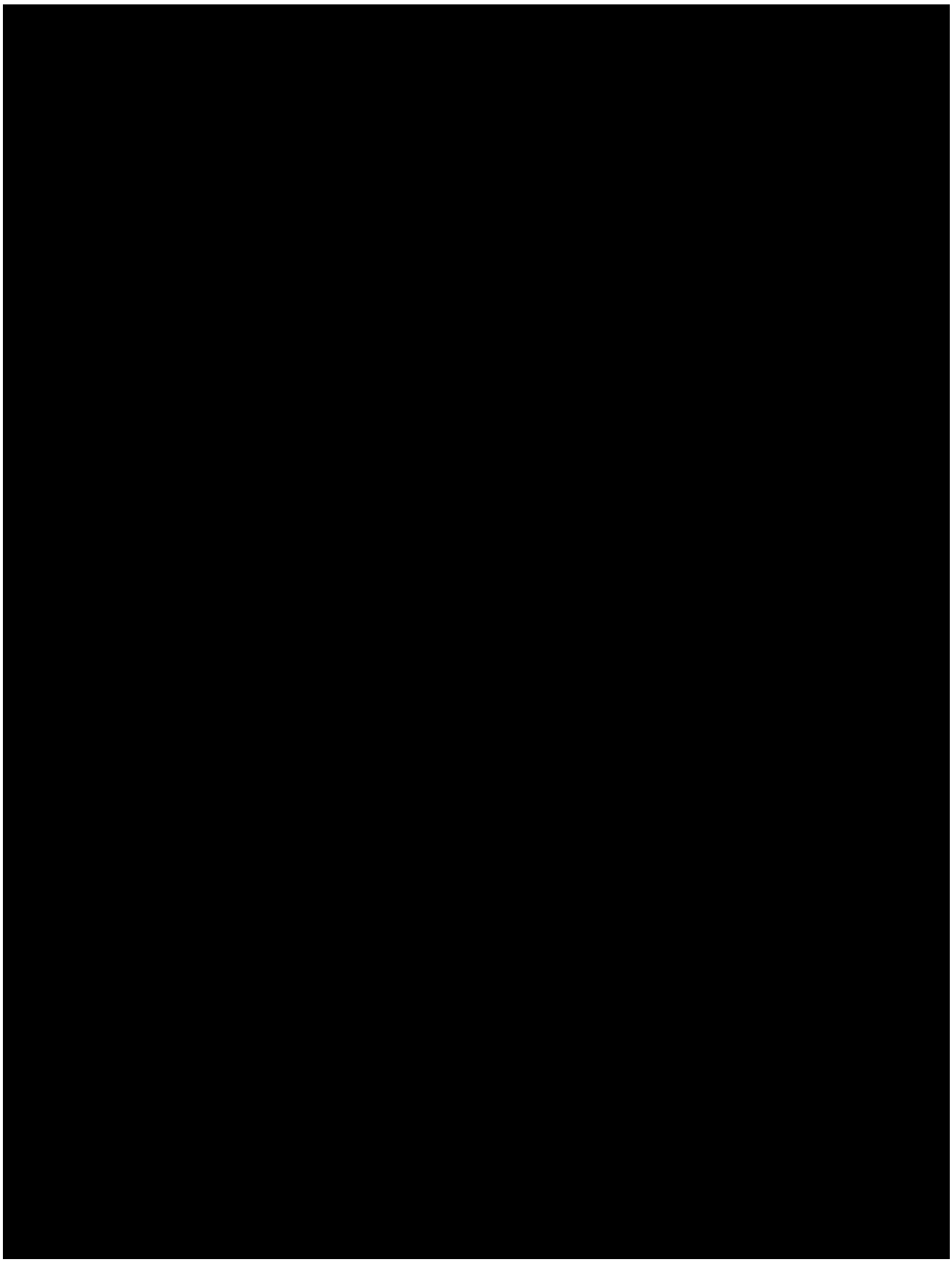
- IRB approval(s)
- Study medication accountability
- Study protocol and amendments
- ICFs of the patient (if capable of providing ICF, according to the investigator) or patient's authorized representatives and caregivers
- Assent of the patients (if capable of providing assent, according to the investigator)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

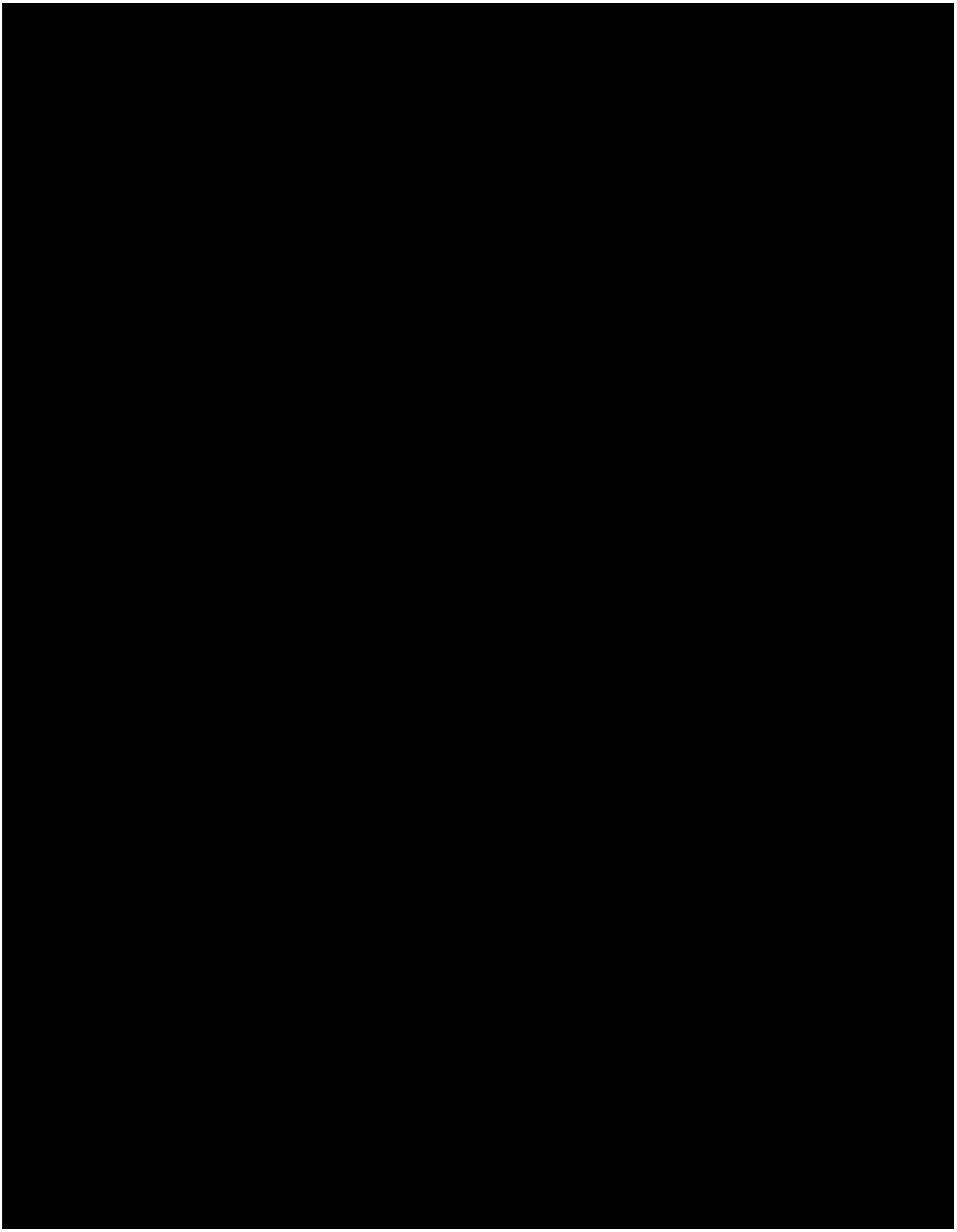
The sponsor will be available to help investigators prepare for an inspection.

10 REFERENCES





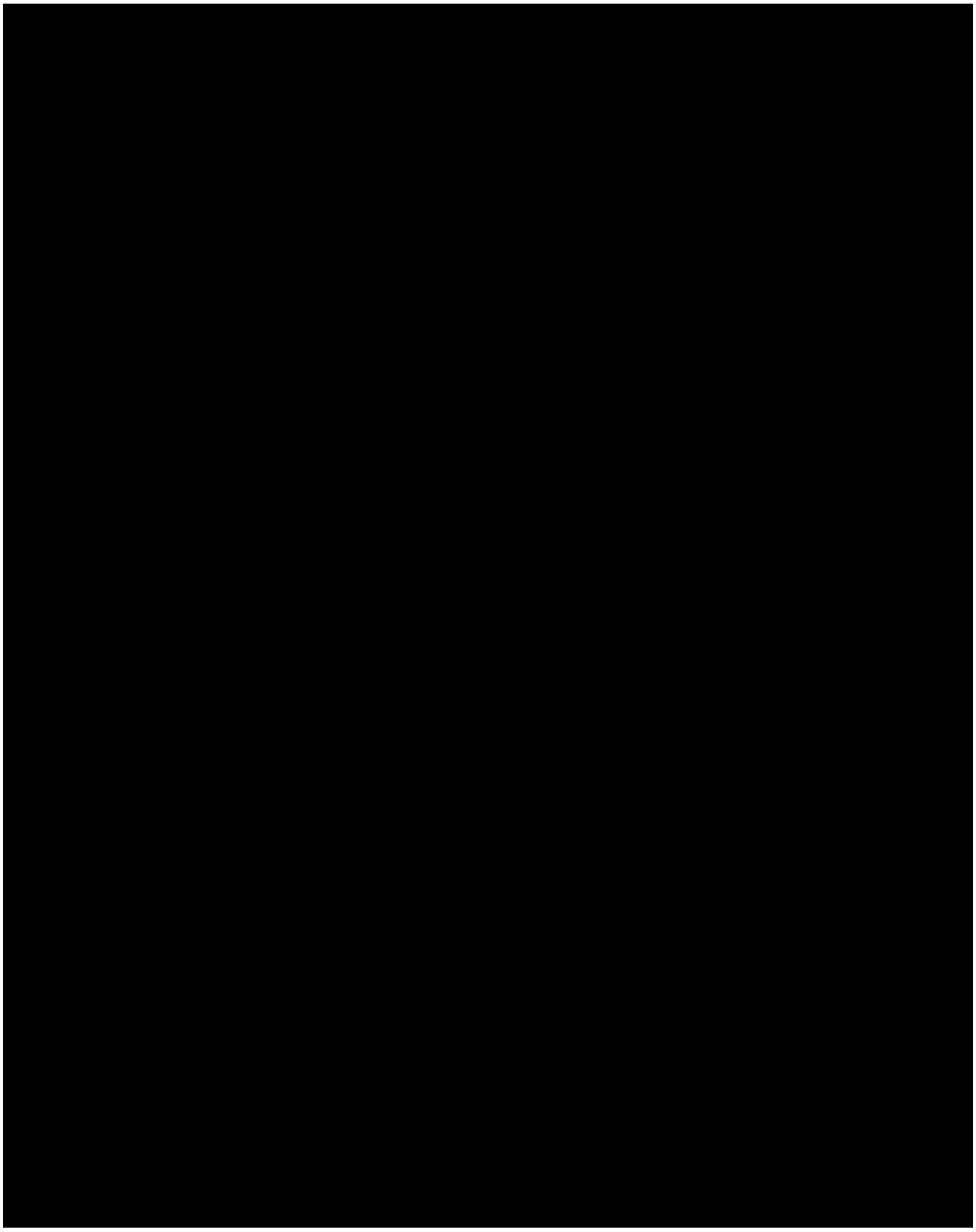


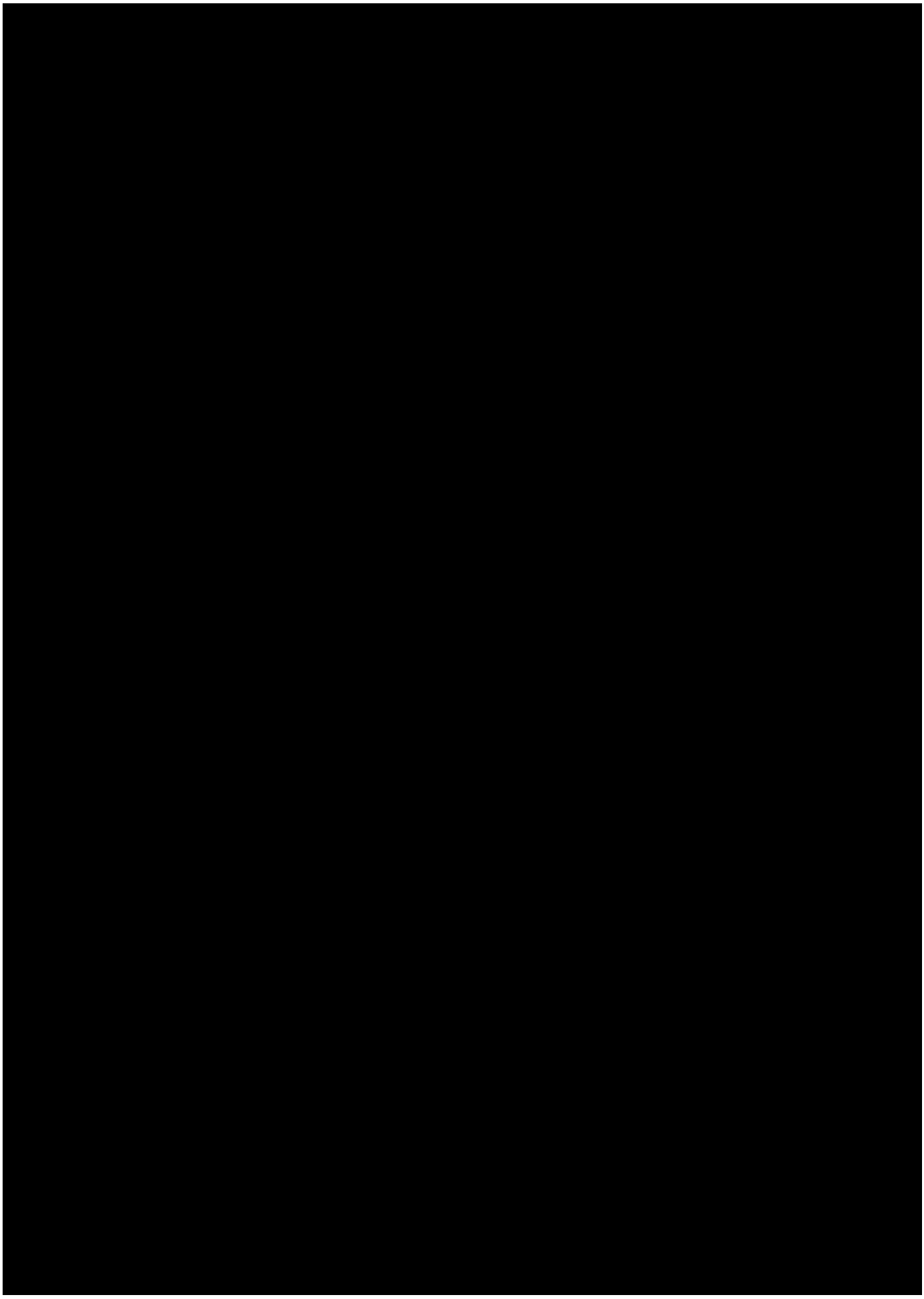


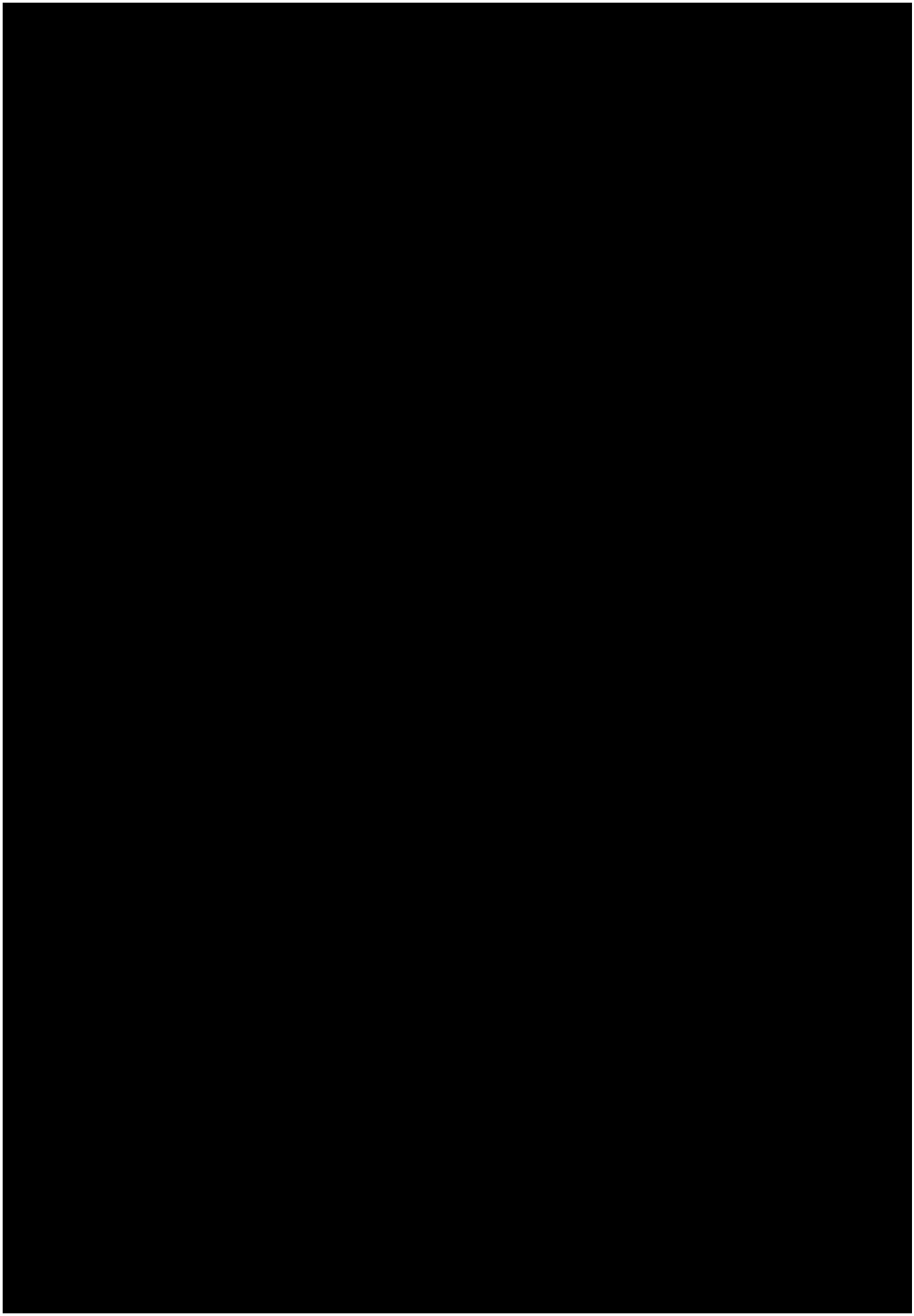
11 APPENDICES

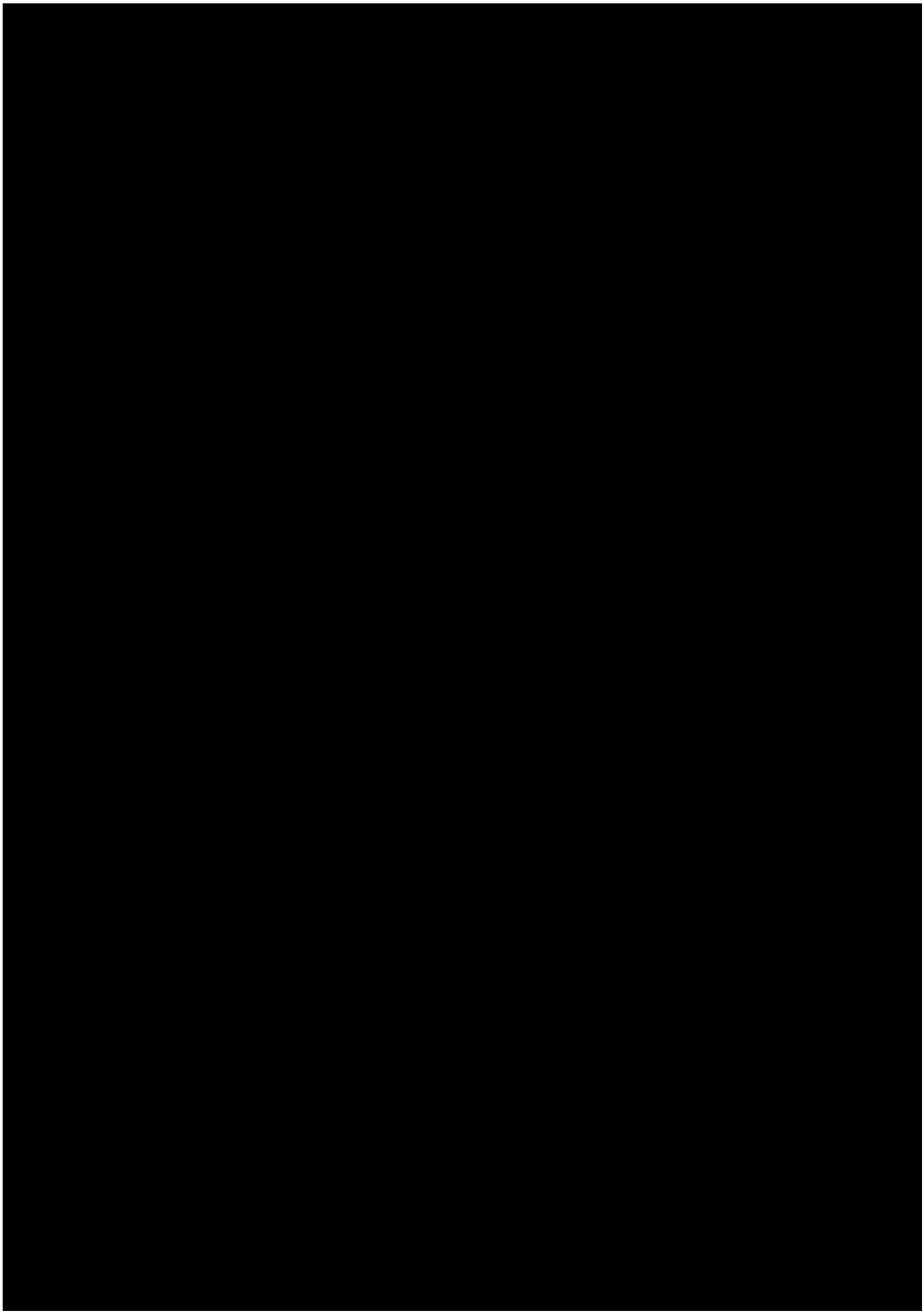
Appendix 15: Investigator Responsibilities

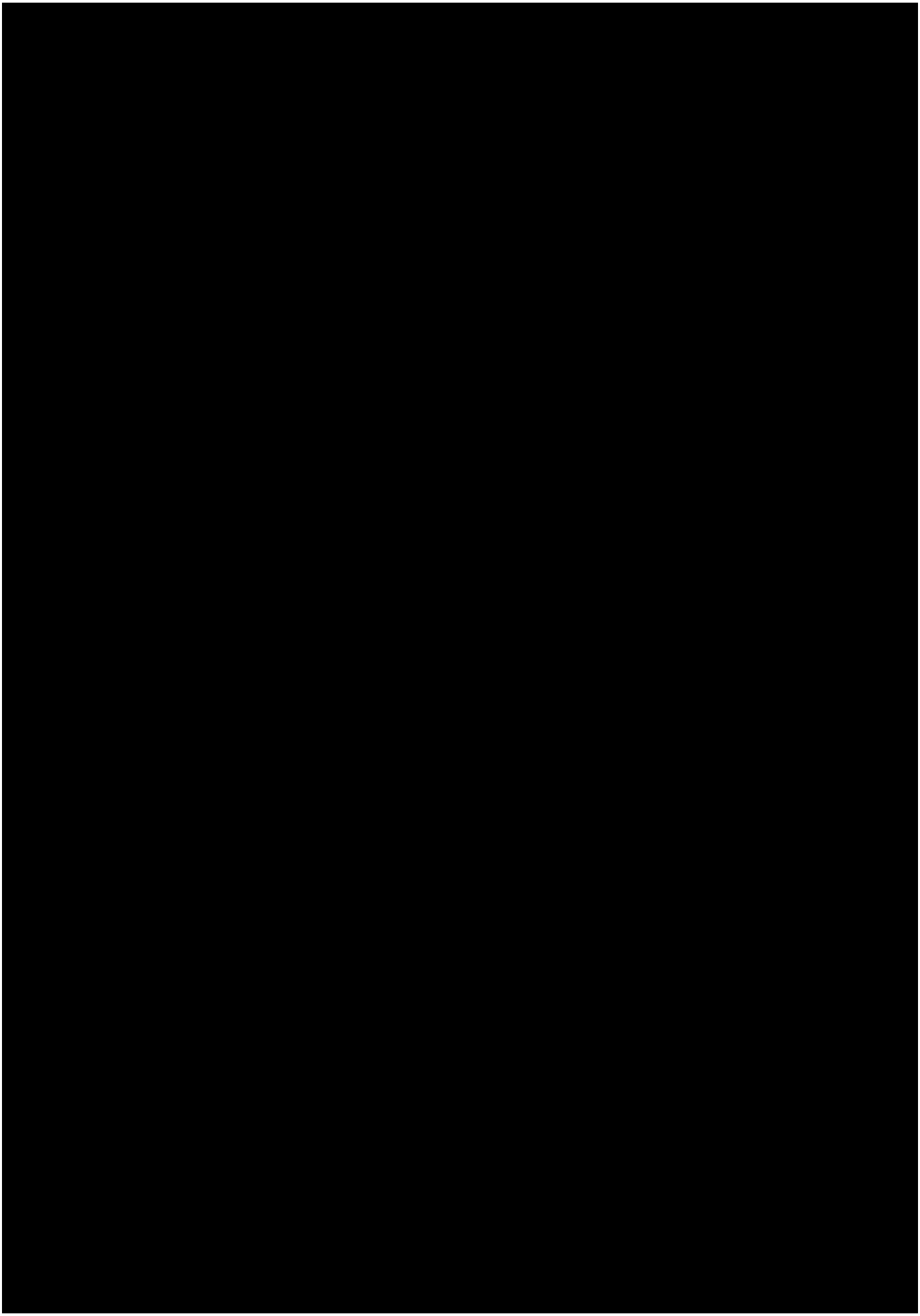
Appendix 16: World Medical Association Declaration of Helsinki

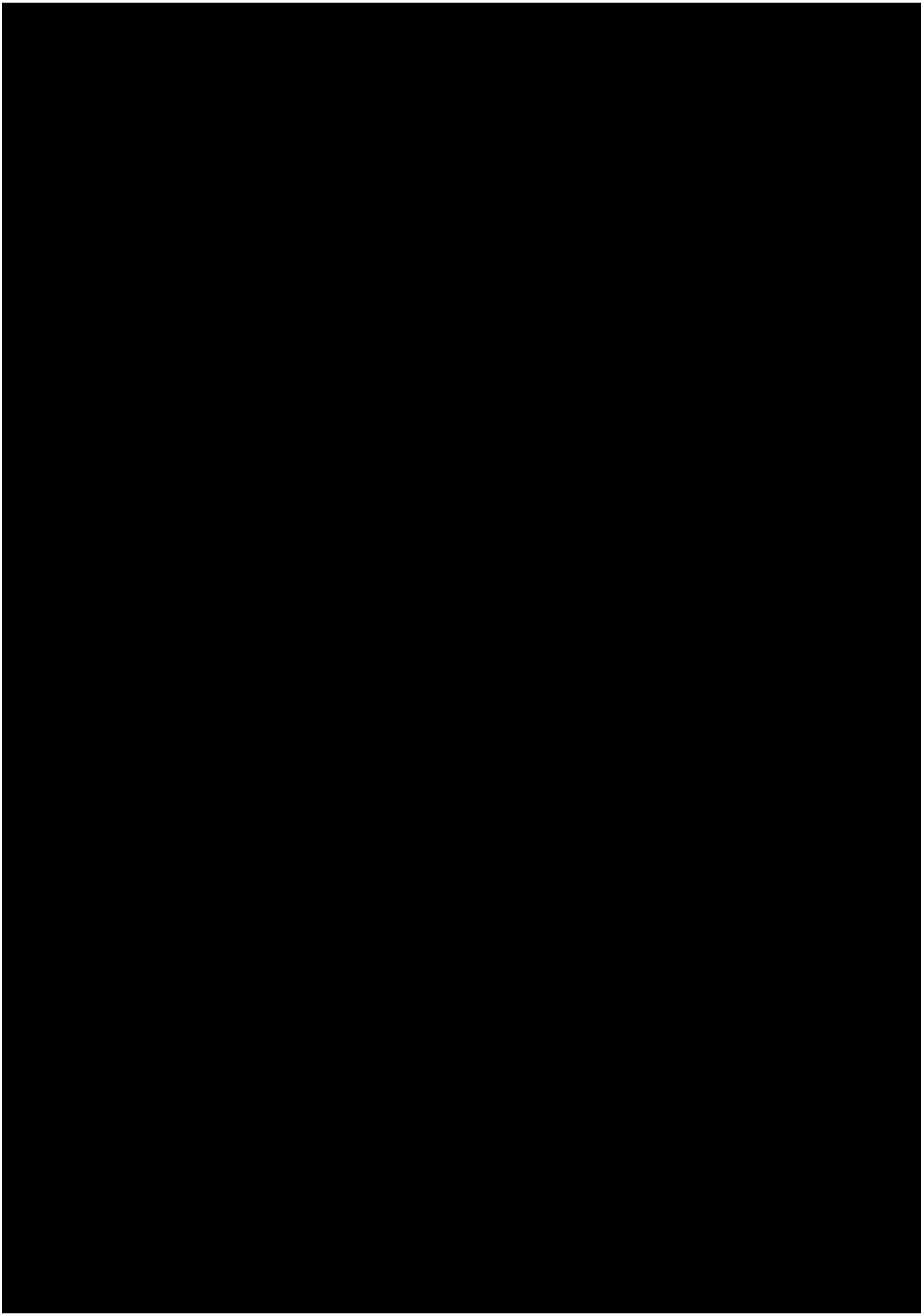


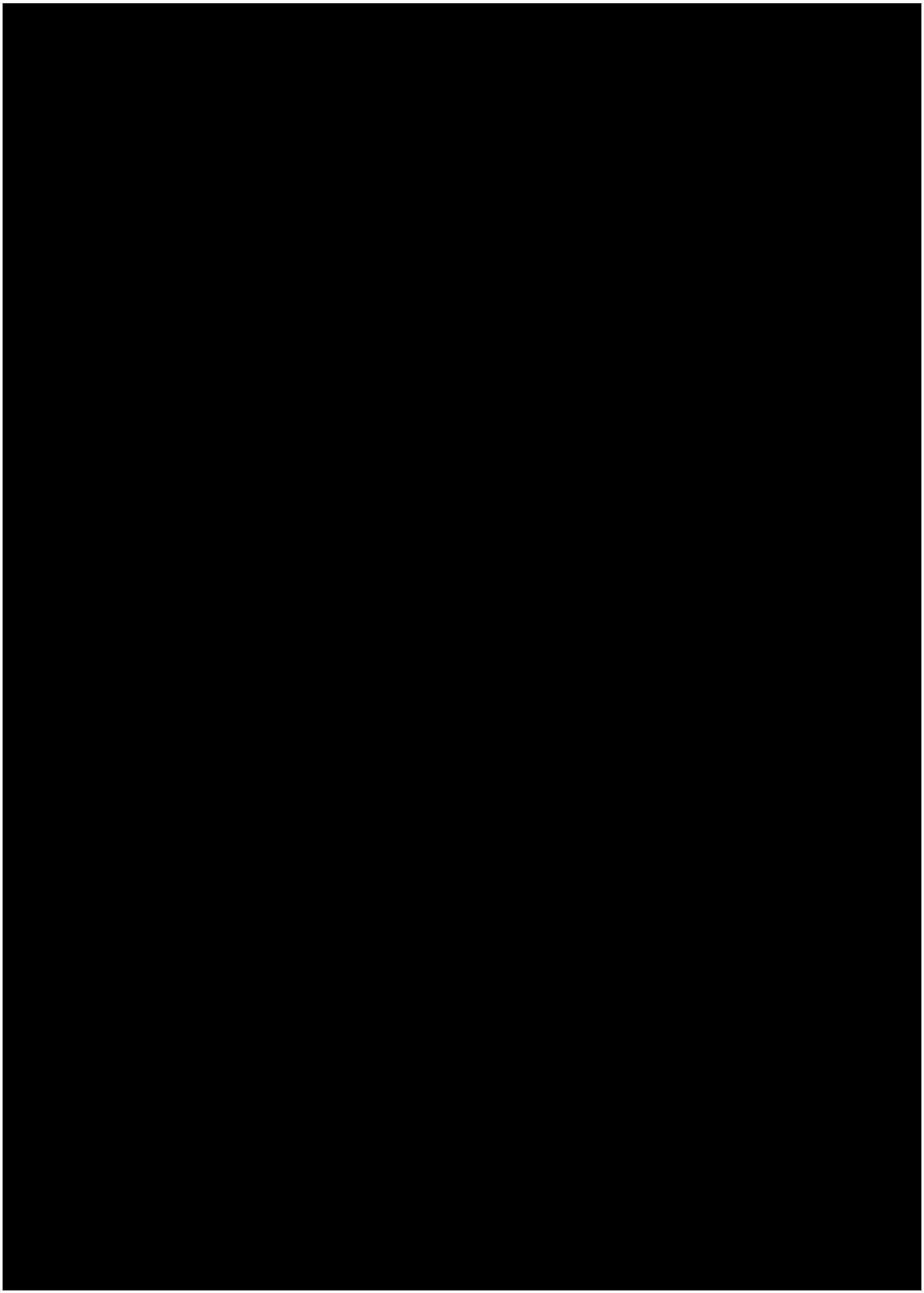


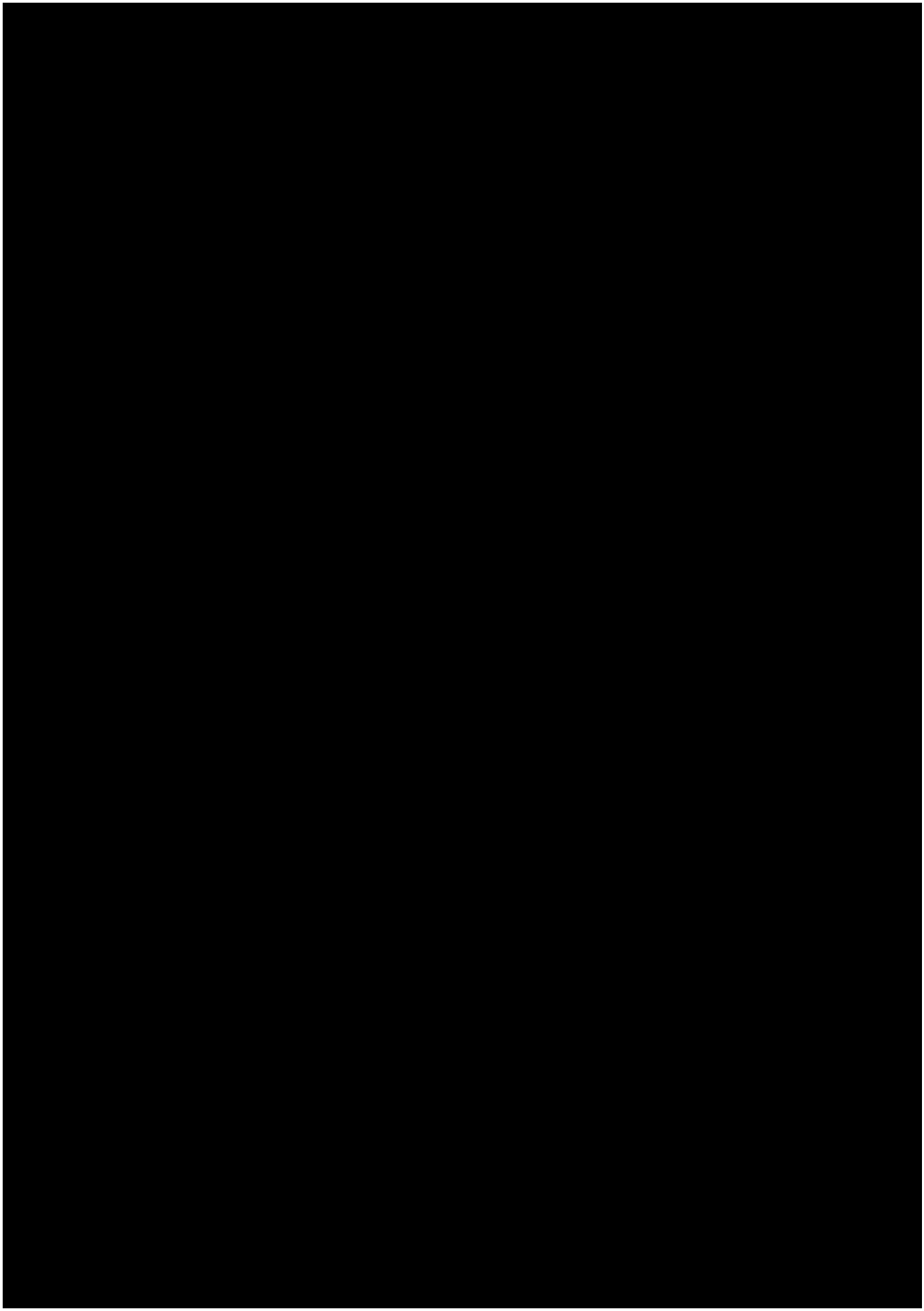


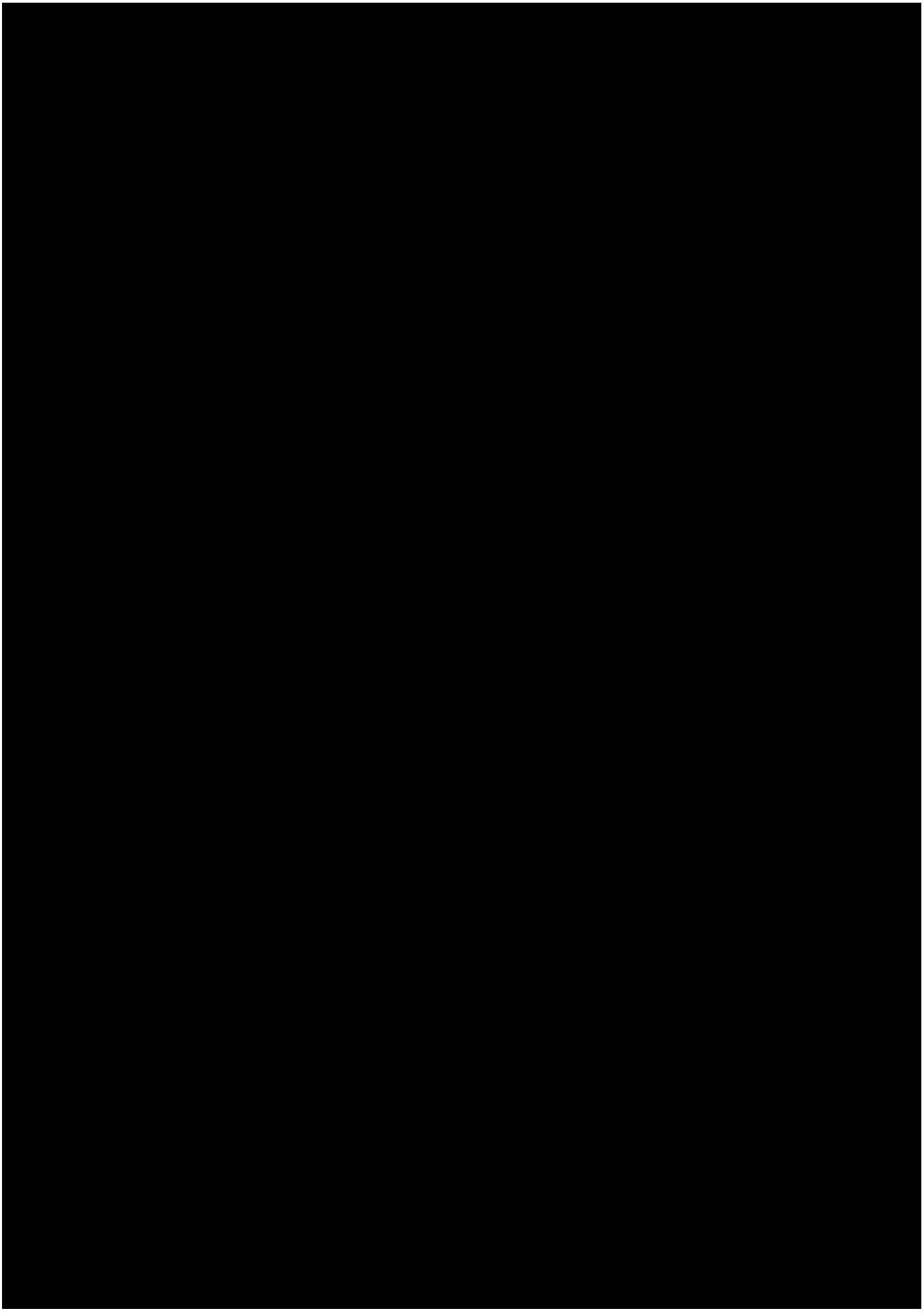


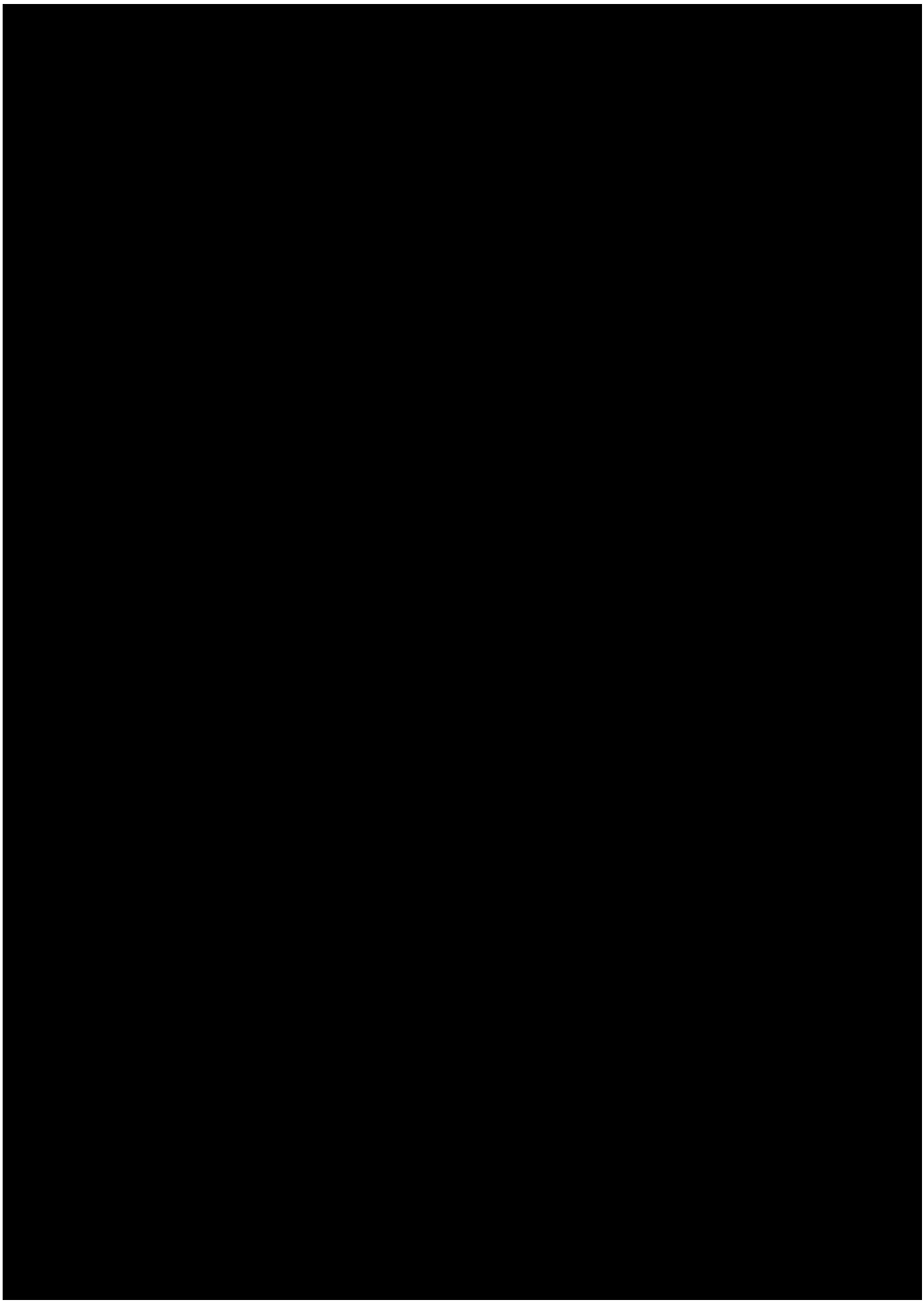


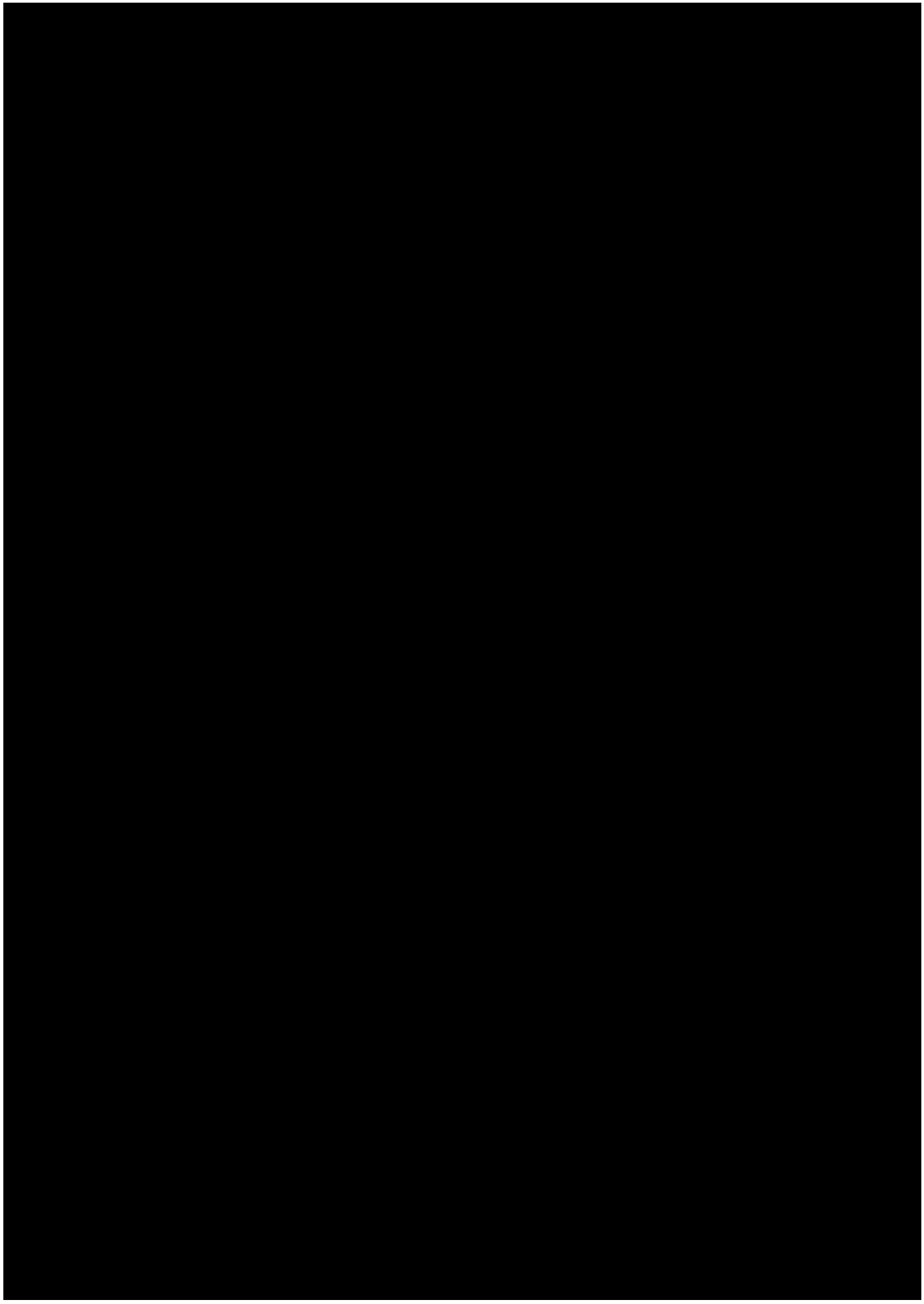


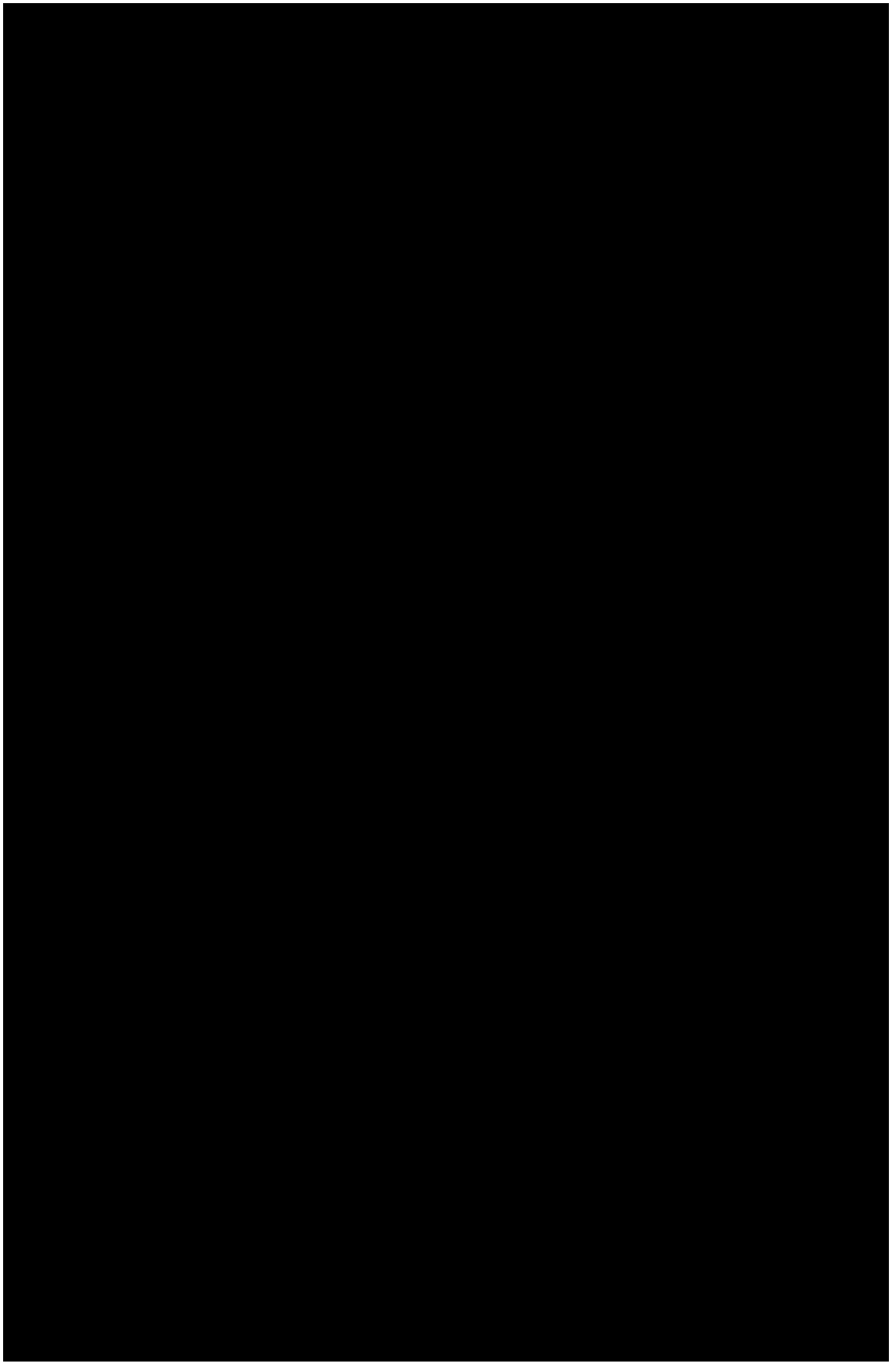


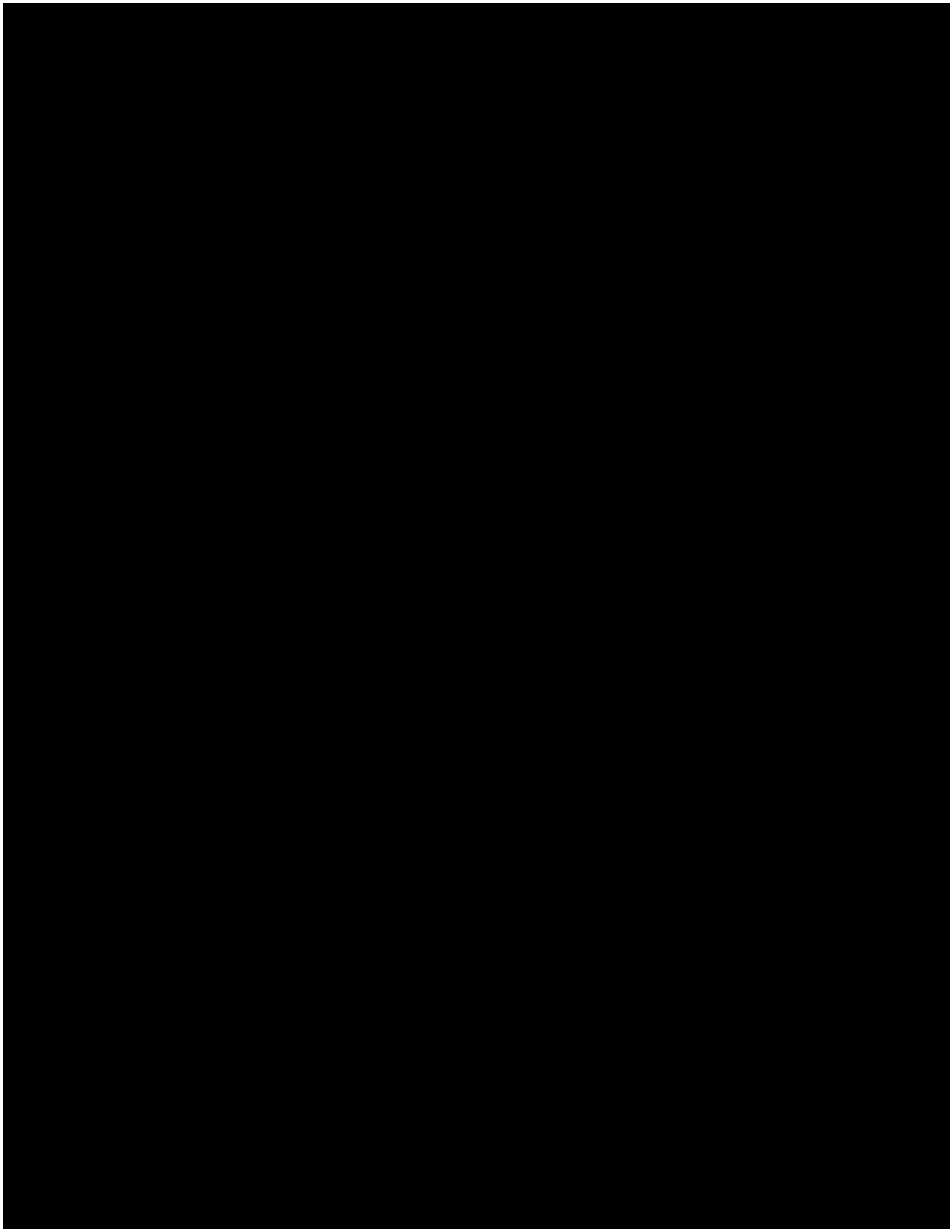


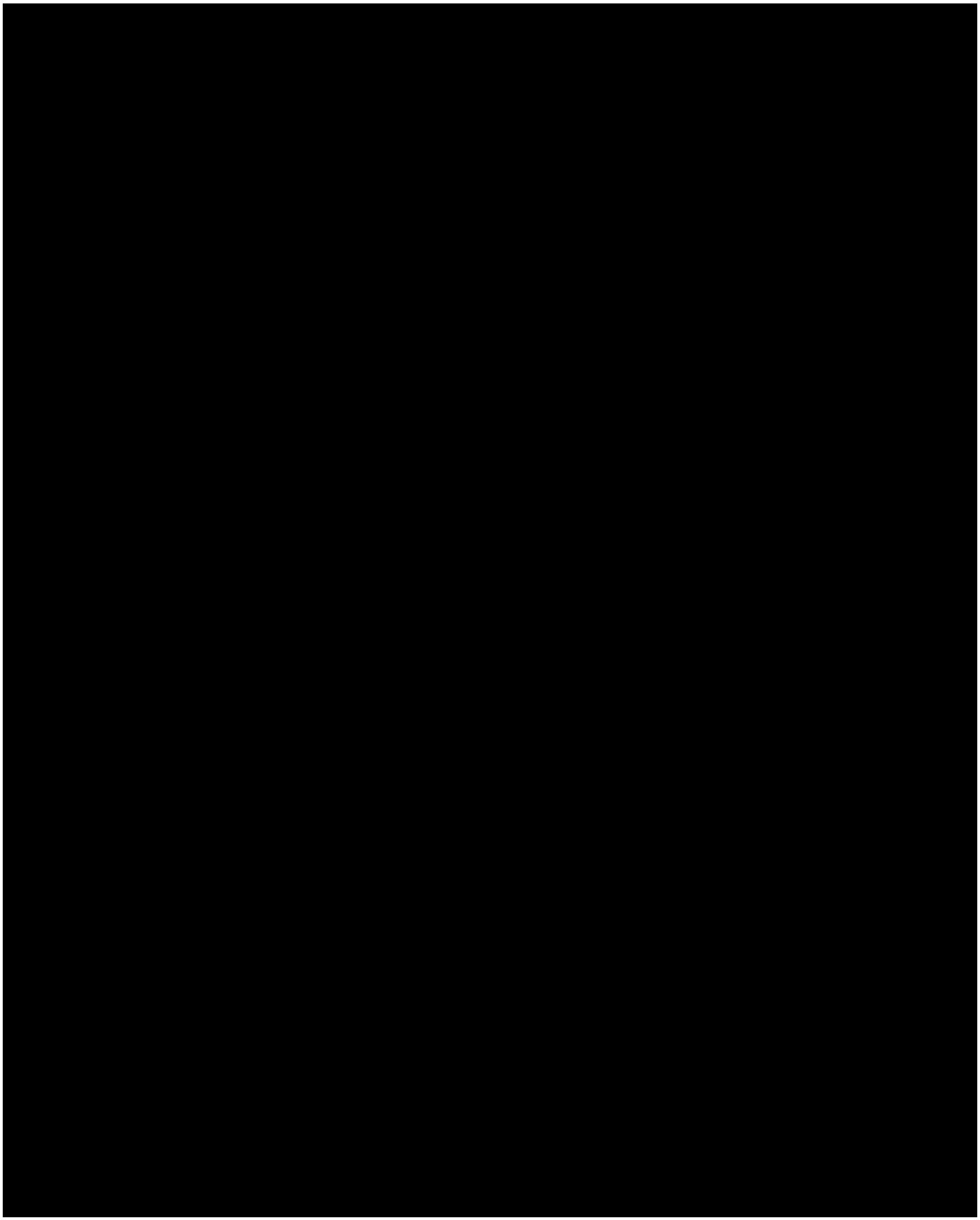


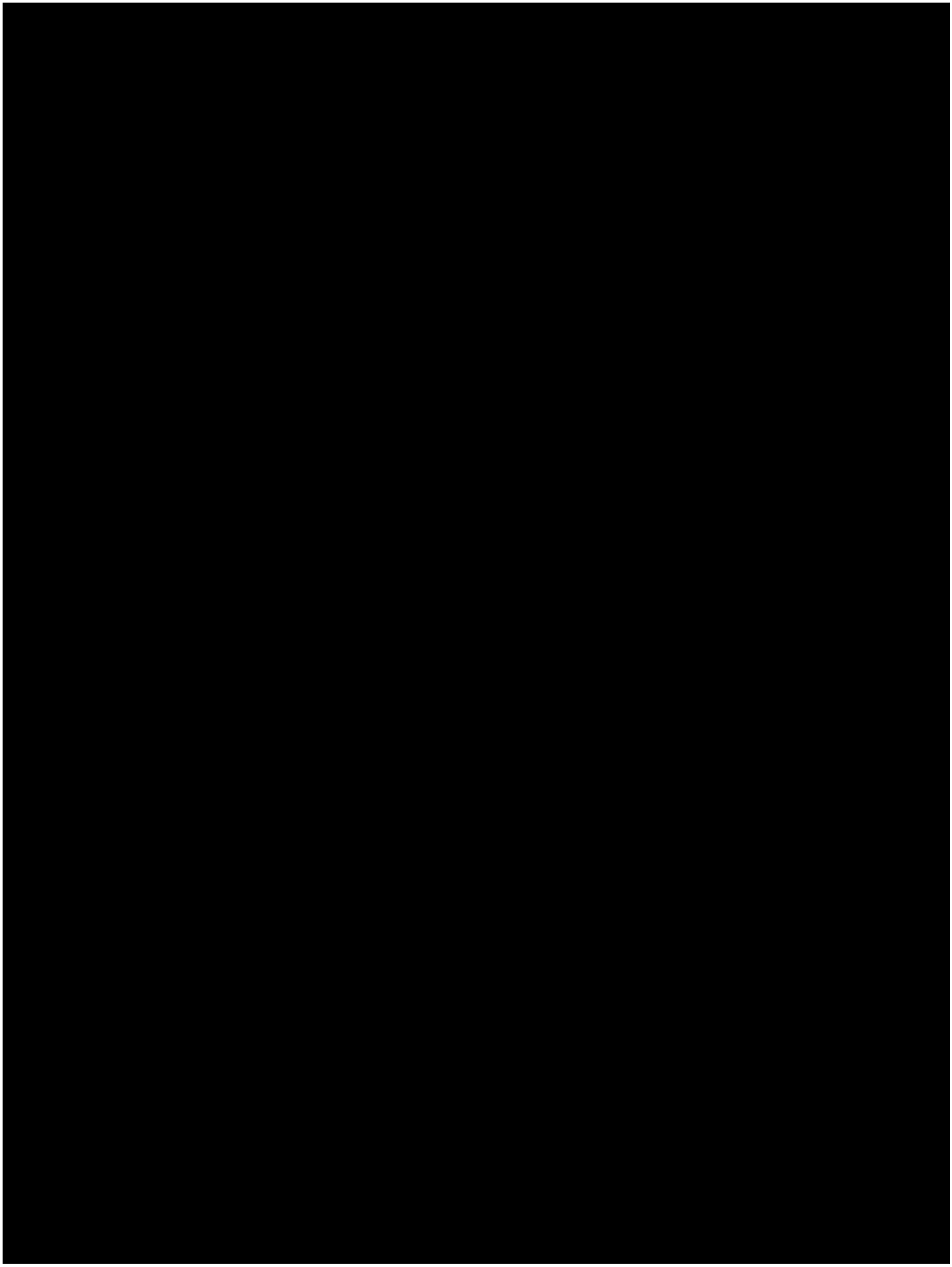


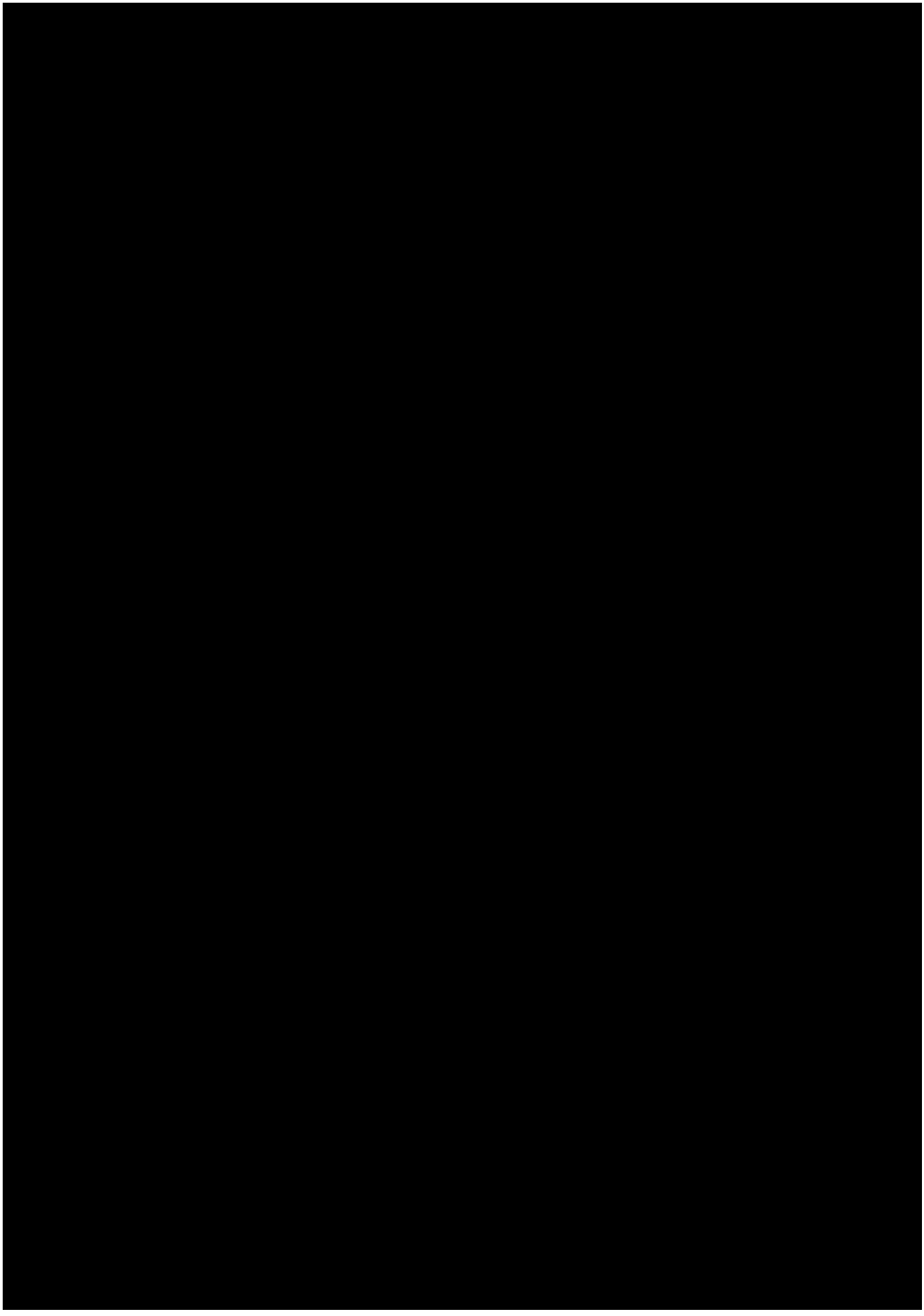


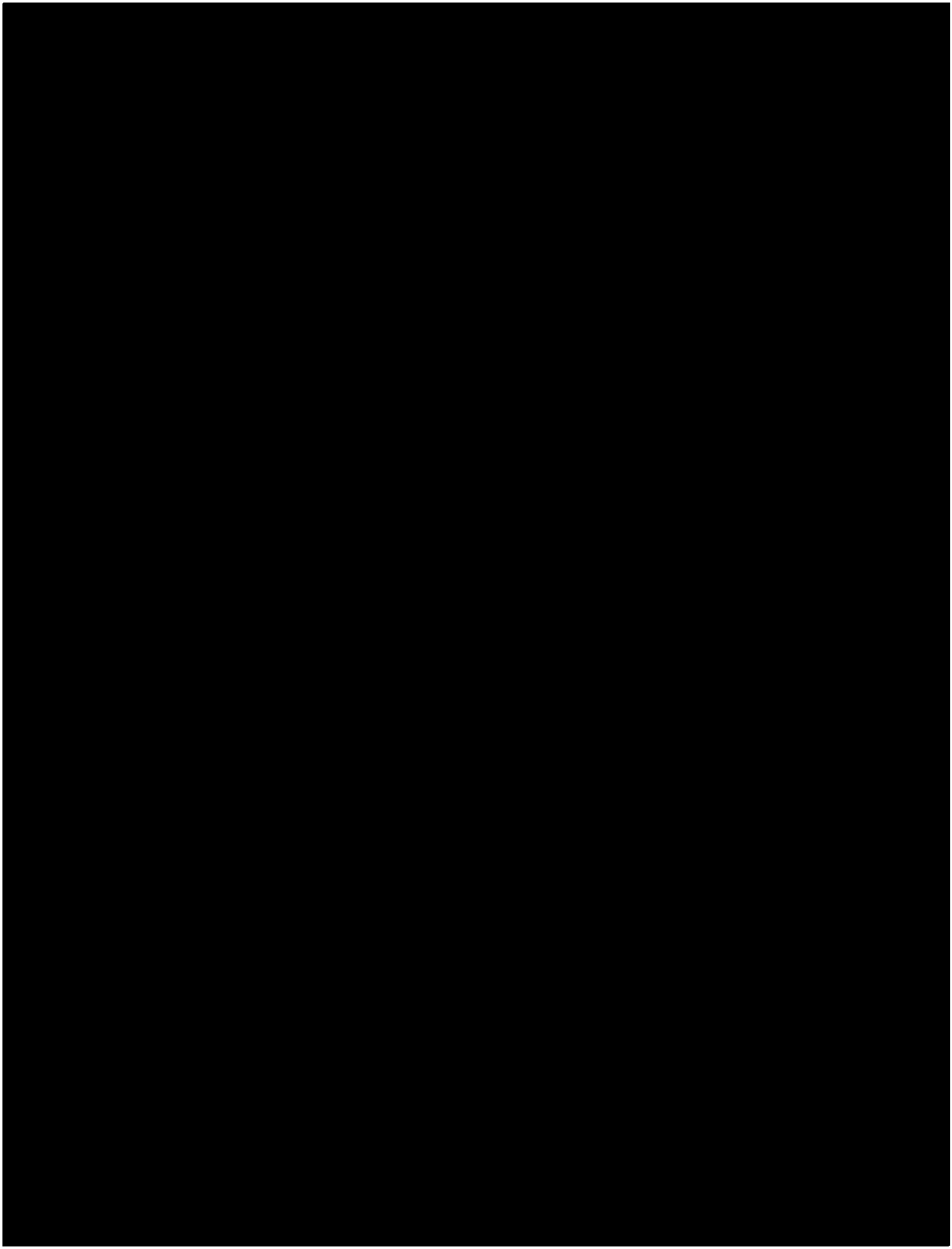


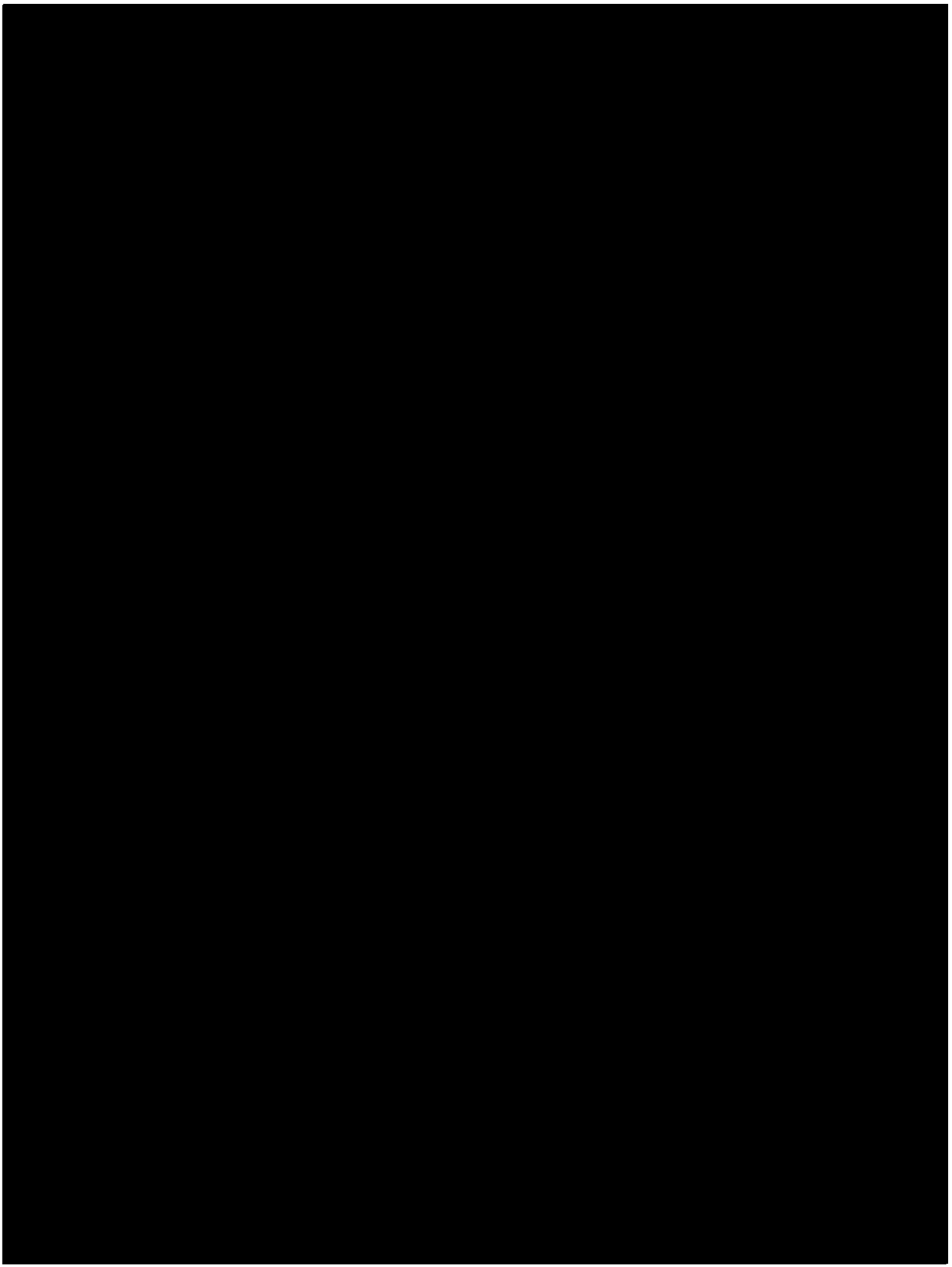


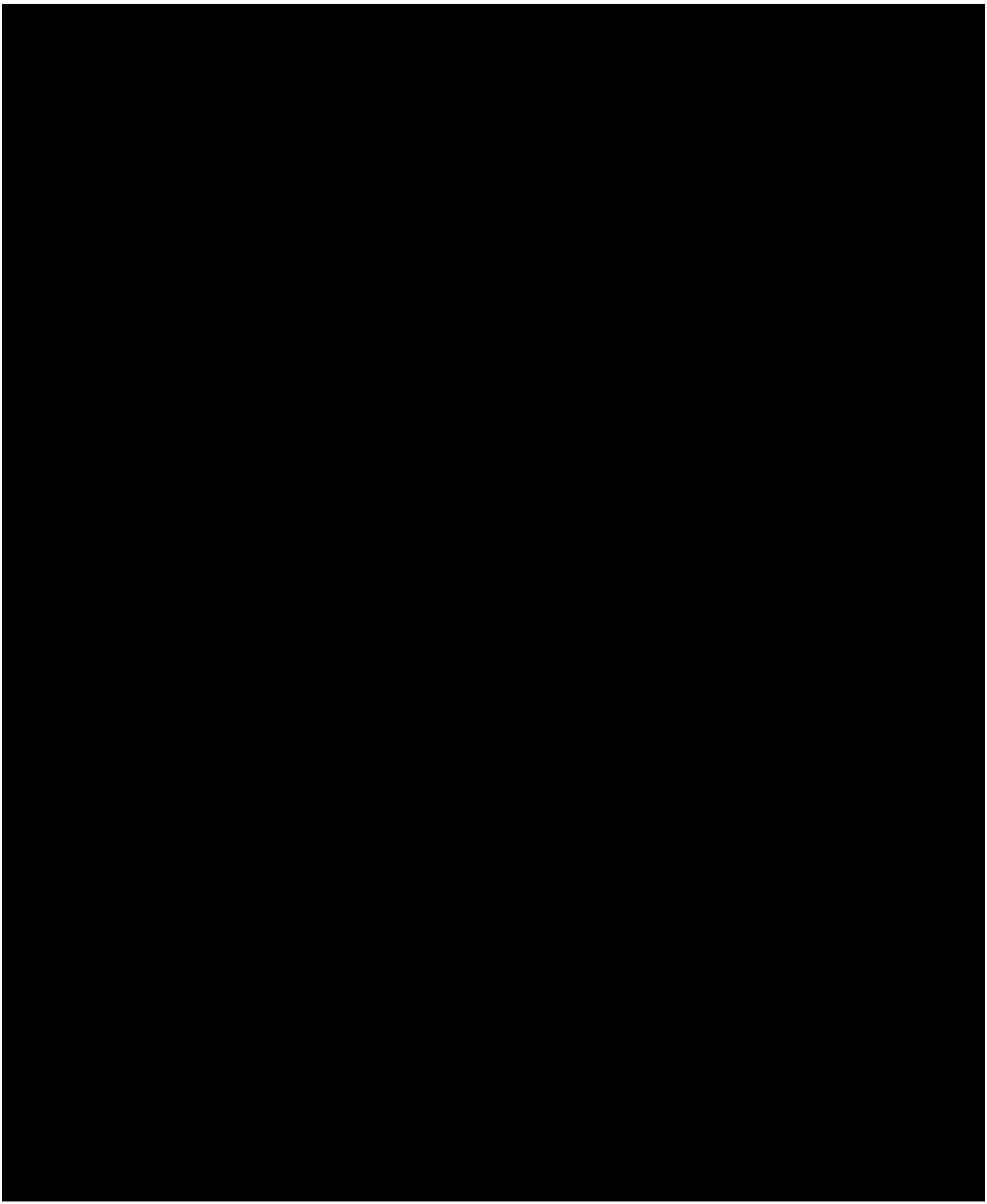


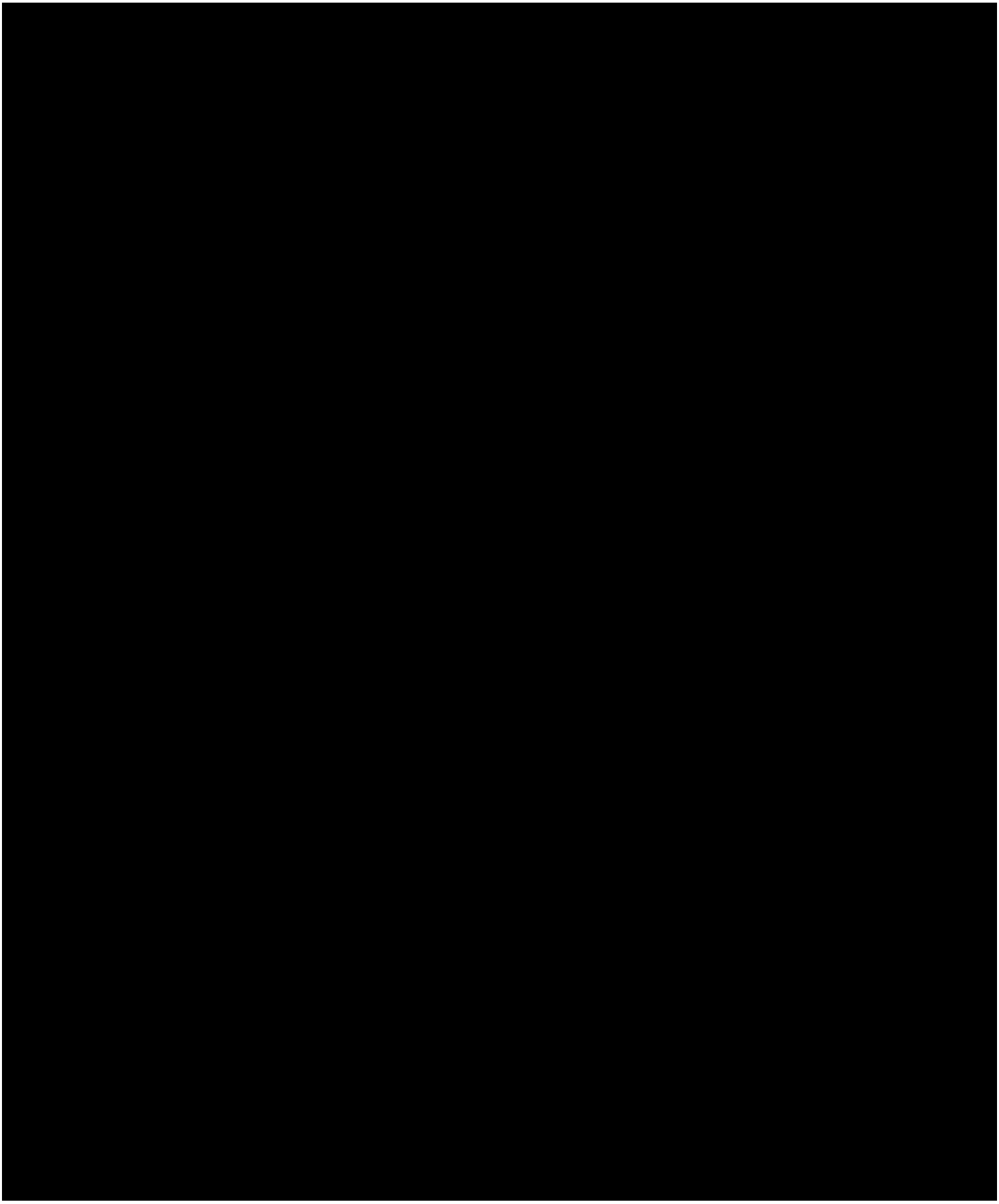








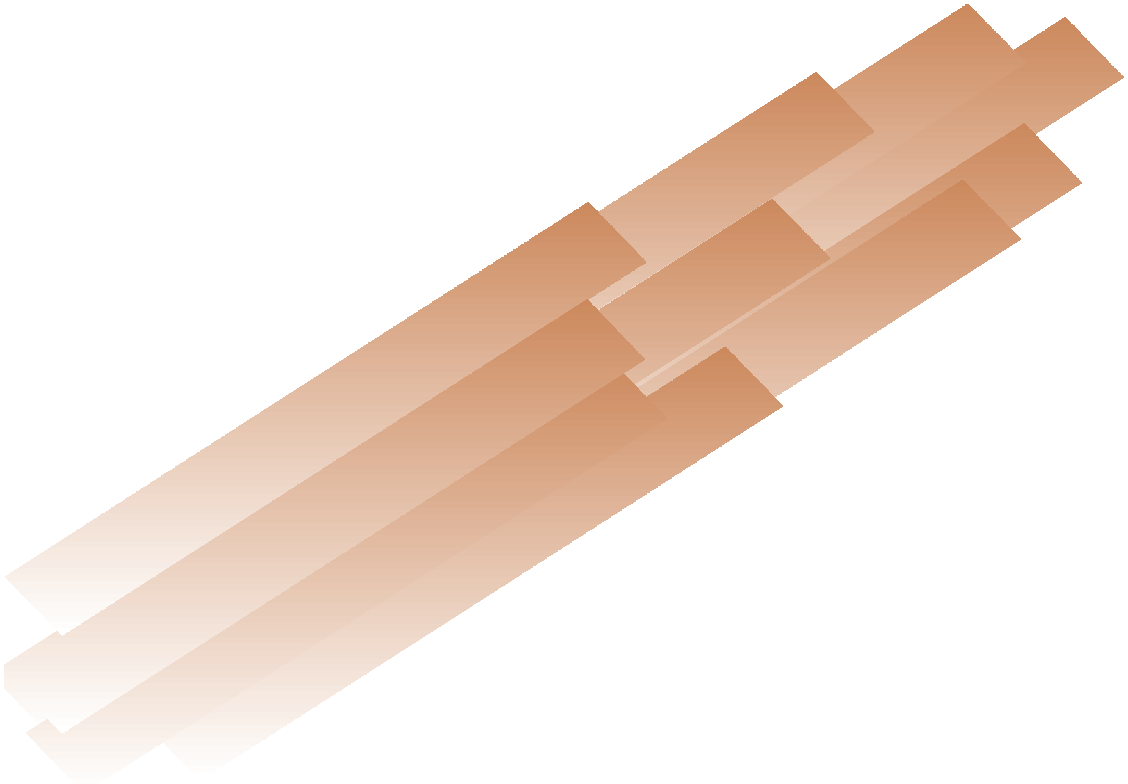




Appendix 15: Investigator Responsibilities

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.

Appendix 16: World Medical Association Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

Corresponding Author: World Medical Association, 13, ch. du Levant, CIB - Bâtiment A, 01210 Ferney-Voltaire, France; wma@wma.net.

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