TITLE PAGE

PROTOCOL

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF K0706 IN SUBJECTS WITH EARLY PARKINSON'S DISEASE

(PROSEEK: A **P**hase 2 Study In Early Parkinson's Disease Patients Evaluating The Safety And Efficacy Of Abl Ty**ros**in**e** Kinas**e** Inhibition Using **K**0706)

Protocol No.:	CLR_18_06
[redacted] EudraCT No:	[redacted] 2018-003337-15
CTRI Registration No.	CTRI/2019/10/021792
First Version No. /Date :	01/20 AUG 2018
Amendment No./Date:	06/23 October 2023
Investigational Product:	K0706
Study Phase:	2
Sponsor:	Sun Pharma Advanced Research Company Limited (SPARC) 17/B, Mahal Industrial Estate, Off Mahakali Caves Road, Andheri (E), Mumbai 400093

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Sponsor:	Sun Pharma Advanced Research Company Limited (SPARC) 17/B, Mahal Industrial Estate, Off Mahakali Caves Road, Andheri (E), Mumbai 400093
Protocol Title:	A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF K0706 IN SUBJECTS WITH EARLY PARKINSON'S DISEASE
Acronym and Brief Title:	PROSEEK: A **P**hase 2 Study In Early Parkinson's Disease Patients Evaluating The Safety And Efficacy Of Abl Ty**ros**in**e** Kinas**e** Inhibition Using **K**0706
Protocol No.:	CLR_18_06
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[redacted]

INVESTIGATOR'S SIGNATURE PAGE

Protocol Title:

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF K0706 IN SUBJECTS WITH EARLY PARKINSON'S DISEASE

(PROSEEK: A Phase 2 Study In Early Parkinson's Disease Patients Evaluating The Safety And Efficacy Of Abl Tyrosine Kinase Inhibition Using K0706)

I have read and agree to the protocol numbered, CLR_18_06 Amendment 6 as entitled above.

I am aware of my responsibilities as an Investigator under the guidelines of International Council on Harmonization (ICH) E6 Good Clinical Practice (GCP), Declaration of Helsinki, national regulations, and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff who will be involved in the study.

Principal Investigator

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date (dd mmm yyyy)

_____

_____

_____

Investigational site or name of institution and address

Please keep the signed original form in your study files, and return a copy to your local study monitor

KEY ROLES

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[redacted]

[redacted]

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[redacted]	[redacted]

1.0 PROTOCOL SYNOPSIS

Name of Sponsor: Sun Pharma Advanced Research Company Limited (SPARC)
Name of Investigational Product: K0706 / placebo
Name of Active Ingredient: K0706
Title of Trial: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of K0706 in Subjects With Early Parkinson's Disease **Acronym and Brief Title:** PROSEEK: A **P**hase 2 Study In Early Parkinson's Disease Patients Evaluating The Safety And Efficacy Of Abl Ty**ros**in**e** Kinas**e** Inhibition Using **K**0706
Phase of Development: 2
Trial Centers: Multicenter and multi-country study.
Objectives: **Part 1 (Day 0 to Week 40)** ***Primary Objective:*** To determine if K0706 reduces the rate of progression of early-stage Parkinson's disease (PD) versus placebo over 40 weeks, as assessed by the MDS-UPDRS (Movement Disorder Society – Unified Parkinson's Disease Rating Scale) Part III (motor examination) total score. ***Secondary Objectives:*** • To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients excluding mild-motor predominant sub-type (hereinafter Subgroup A). The rate of progression is assessed by the MDS-UPDRS Part III total score. • To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients with serum neurofilament light (NfL) value ≥ 13 pg/mL at baseline (hereinafter Subgroup B). The rate of progression is assessed by the MDS-UPDRS Part III total score. • To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks, as assessed by the sum of the MDS-UPDRS Parts II and III total scores. • To determine if K0706 slows early-stage PD progression compared to placebo by increasing the time to significant worsening on the MDS-UPDRS Parts I, II, and III. • [redacted] • To evaluate the efficacy of K0706 compared to placebo in terms of Health-Related Quality of Life (HRQoL) as measured by the European Quality of Life Questionnaire 5 level version (EQ-5D-5L). • To determine if K0706 slows the progression of early-stage PD compared to placebo over 40 weeks in terms of overall severity of PD as measured by the Clinician Global Impression Severity (CGIS) scale. • To evaluate the effect of K0706 compared to placebo on autonomic nervous system dysfunction related to PD as measured by the Scales for Outcome in PD - Autonomic (SCOPA-AUT).

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- To evaluate the safety and tolerability of K0706.
- To evaluate [redacted] the measures of efficacy and safety.

Exploratory Objectives:

- To evaluate the effect of K0706 on skin pathology biomarkers of PD.
- To evaluate the effect of K0706 on blood and cerebrospinal fluid (CSF) biomarkers linked to PD and target engagement of K0706.
- To investigate genetic and clinical markers that predict the degree of progression of early-stage PD and/or response to K0706.
- To evaluate the effect of K0706 on dopamine cell health in PD as detected via Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT) brain imaging.
- [redacted]

Part 2 (Weeks 40 to 80)

Primary Objective:

To assess the long-term safety/tolerability of K0706 in subjects with early PD

Secondary Objective:

To assess the initial and long-term efficacy of K0706 in subjects with early PD

Exploratory objective:

To assess the efficacy of K0706 in subjects with delayed treatment initiation relative to those with early treatment initiation

[redacted] **Part 1 (Day 0 to Week 40)**

To support the primary objective of the trial for Part 1, the [redacted] will be used. Part 1 of this trial is to clarify the efficacy of the K0706 in improving the MDS-UPDRS Part III total score [redacted]. See Section 9.6 (Efficacy Analysis) for details. Sensitivity analyses for the [redacted] will be specified in the statistical analysis plan (SAP) to further evaluate the robustness of the treatment effect attributable to K0706 therapy.

Study Endpoints: Part 1 (Day 0 to Week 40)

Primary Endpoint:

- Change from baseline to Week 40 in the MDS-UPDRS Part III total score.

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Secondary Endpoints:

- Change from baseline to Week 40 in the sum of the MDS-UPDRS Parts II and III total scores.
- Change from baseline to Weeks 8 through 40 in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, and Part III sub-scores.
- Change in MDS-UPDRS grand total score (sum of Parts I, II, and III) from the baseline.
- Evaluation of slopes of the mean MDS-UPDRS Parts II and III scores over time during Part 1 by treatment group.
- Time from the first dose in Part 1 to initiation of symptomatic PD medications
- Change in HRQoL using the EQ-5D-5L from Baseline to Week 40
- Change in CGIS from Baseline to Week 40
- Change in the SCOPA-AUT from Baseline to Week 40
- Pharmacokinetics – Plasma and CSF levels of K0706 and any relevant metabolites.

Safety / Tolerability Endpoints:

- Vital Signs
- Electrocardiography (ECG)
- Laboratory values
- Adverse Events (AEs)
- [redacted]

Exploratory Endpoints:

- Skin pathological findings that correlate with PD, [redacted]
- Blood and CSF levels of emerging biomarkers ([redacted]) that predict or track PD progression or target engagement of K0706.
- Brain DaT SPECT - an imaging tool that is a marker of dopaminergic cell health.
- [redacted]

Part 2 (Weeks 40 to 80)

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Primary endpoint:

- Incidence of treatment-emergent adverse events

Secondary endpoints:

- Change from Week 40 (Baseline for Part 2) to Week 76 of the long-term extension study in the MDS-UPDRS Part III score
- Change from Week 40 (Baseline for Part 2) to Week 76 of the long-term extension study in MDS-UPDRS Parts II and III sum score
- Change from Week 40 (Baseline for part 2) through Week 76 in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, and Part III sub-scores
- Change in MDS-UPDRS grand total score (sum of Parts I, II, and III) from Week 40 (Baseline for part 2) through Week 76
- Time from Week 40 (Baseline for Part 2) to initiation of symptomatic PD medications in the long-term extension study

Exploratory endpoints:

- Change in the mean MDS- UPDRS Parts I, II and III scores between the early-start and delayed-start groups at 76 weeks
- Evaluation of slopes of the mean MDS-UPDRS Parts II and III scores over time in part 2 for the early-start group as compared to the delayed-start group
- The proportion of patients starting symptomatic PD treatment

Study Design

This is a randomized, [redacted] double-blind, placebo-controlled, [redacted], to evaluate the efficacy, safety and tolerability of two doses of K0706 compared to placebo in subjects with early PD [redacted]. This study consists of two parts. Part 1 is designed to evaluate the efficacy, safety, and tolerability of two dose levels of K0706 compared to placebo in subjects with early PD who are not receiving dopaminergic therapy. Part 2 is an optional long-term extension study to assess the long-term safety/tolerability of K0706 in subjects with early PD.

[redacted]

Part 1:

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Subjects will visit the clinic for the part 1 Screening Visit for evaluation of the eligibility criteria. All the screening assessments will be conducted after the subject provides informed consent. Confirmation of eligibility at the Part 1 Baseline visit will require the availability of laboratory results, as well as interpretation by the investigator of a Magnetic Resonance Imaging (MRI) of the brain and by the central reader of a DaT SPECT scan (obtained prior to, or as part of this study).

[redacted]

The activities that are to be performed during the Screening period are summarized in the Screening Period Flow Diagram (Figure 17-1).

Following confirmation of eligibility at the Part 1 Baseline visit, all subjects will be randomized, have baseline assessments, and receive the first dose of study drug. Planned visits will occur according to the Schedules of Assessment. The part 1 treatment assessment for efficacy will be performed at Week 40.

[redacted]

Subjects will provide blood for measurement of standard safety laboratory parameters as well as levels of K0706. [redacted]

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Should an unusual circumstance such as public health emergency (i.e., pandemic with an infectious agent), natural disaster or any other serious unforeseeable circumstance preclude the safe participation at the investigative site in the opinion of the Sponsor and Principal Investigator, an evaluation by video or teleconference will be an acceptable alternative. The timing and the assessments performed during such a remote evaluation should follow the prescribed schedule of visits whenever possible.

Part 2 (Optional)

Subjects who complete the EoT visit of part 1 (V11/Week 40) and who confirm their willingness to participate in part 2 of the study will be screened according to Part 2 eligibility criteria. Subjects who had been randomized to placebo in Part 1 will be rolled over to a high dose K0706 ([redacted] at Week 40. Subjects that had been randomized to either dose of K0706 in part 1 of the study will continue on the same dosing regimen in Part 2 of the study. All subjects will continue treatment [redacted]. Subjects, Investigators, and site staff not directly providing kits on behalf of the Sponsor, and the Sponsor will remain masked to treatment assignments until the last subject completes the Week 40 assessments for efficacy and the database is locked for analysis of Part 1. In Part 2, all subjects will be informed that they are receiving the active study drug, but will not be informed of the dosage or the treatment received in Part 1.

At Week 40, all subjects in the placebo-randomized treatment arm in Part 1 who consent to participate in Part 2 of the study and who meet all eligibility criteria for participation in Part 2, will cross over to receive K0706 high dose ([redacted] once a day [redacted]. This will enable the collection of additional safety data for the high dose level. Subjects who had been randomized to either high-dose or low-dose K0706 in Part 1 of the study will remain on the same dosing regimen in Part 2, thus staying on the same dose [redacted] of the entire study.

Subjects will be followed for new AEs and serious adverse events (SAEs) up to 4 weeks following the last study drug administration. The end of the study is defined as the time the last subject completes the last study visit. [redacted] For subjects who discontinue the study agent prior to Part 2 [redacted] the last study visit is the final safety visit (4 weeks after the last administration of the study agent).

Study Treatments and Dosage:

Part 1

Subjects will be equally randomized (1:1:1) to receive K0706 low dose ([redacted], or high dose [redacted], or matching placebo. [redacted]

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[redacted]

Subjects will be instructed to take the study drug orally once daily. [redacted] Compliance with self-administration of the study drug will be verified by [redacted] counts and by examination of the subject diary.

[redacted]

Part 2

Subjects who had been randomized to either high dose or low dose K0706 in Part 1 of the study will continue to receive the same dose /equivalent dose [redacted] that they were receiving on V11/Week 40. [redacted]

Subjects who had been randomized to placebo in Part 1 of the study will be rolled over to high dose K0706 ([redacted] in Part 2. All subjects will receive active drug in the long-term extension study.

Duration of Treatment:

Part 1

Subjects will take the study drug (K0706 or placebo) orally, once daily, for 40 weeks.

Part 2

Subjects will take the study drug (K0706) orally, once daily, [redacted].

Study Population:

Subjects aged ≥ 50 years in whom an initial diagnosis of PD had been made within three years of the Screening visit, who score on a modified Hoehn and Yahr stage [redacted] 2 [redacted] will be eligible for screening.

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Number of Subjects Planned:

Approximately 506 subjects are planned in the [redacted] (placebo, low dose, and high dose K0706). [redacted]

Eligibility Criteria

Subjects aged ≥ 50 years with a diagnosis of PD within three years of the Screening visit, and modified Hoehn and Yahr stage [redacted] 2 who are [redacted] will be eligible for screening.

Part 1:

Inclusion Criteria:

1. The subject has given written informed consent and is willing to participate in the study
2. Subject is able to understand and comply with all study procedures (requires literacy in the available language of all patient-reported outcome measures);
3. Males or females aged ≥ 50 years;
4. Body mass index (BMI) greater than 18.5 kg/m^2 and less than 45 kg/m^2;
5. Diagnosed with "Clinically Probable PD" according to the MDS clinical diagnostic criteria, with a documented diagnosis of PD per the treating physician's records within three years of the Screening visit. Disease severity according to modified Hoehn & Yahr stage [redacted] 2;
6. Projected to not require to start dopaminergic therapy within [redacted] months from Baseline;
7. [redacted]

[redacted]

[redacted]

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Name of Investigational Product: K0706 / placebo

Exclusion Criteria:

1. Current, or within 60 days of Screening, use of any prescription, investigational, or over-the-counter medication for the symptomatic treatment of PD or to slow the progression of PD. Treatment with Monoamine Oxidase B (MAOB) inhibitors will be allowed if the dose is stable for at least 30 days prior to Screening and subjects agree to remain on it for the duration of the study;
2. Prior use of dopaminergic therapy (e.g., levodopa, dopamine agonist, amantadine) for 30 or more days at any time in the past;
3. A diagnosis of a significant central or peripheral nervous system disease affecting the subject's cognition or motor function at any time, such as another neurodegenerative disorder, multiple sclerosis or stroke. This does not include transient neurological deficits such as transient ischemic attacks or migraine aura;
4. A diagnosis of a medical condition that could interfere with the interpretation of the MDS-UPDRS during the trial (e.g., musculoskeletal disorders);
5. Contraindications to receiving an MRI;
6. Contraindications to receiving a DaT SPECT scan (e.g., hypersensitivity to the active substance, any of the excipients, or iodine) if a new DaT SPECT scan is required for the study;
7. Most recent DaT SPECT scans not compatible with PD (i.e., Scans Without Evidence of Dopaminergic Deficit [SWEDD]) based on a central reading by a study physician;
8. MRI of the brain performed after the onset of PD suggestive of secondary Parkinsonism (e.g., subdural hematoma, normal pressure hydrocephalus, or infarcts of the basal ganglia);
9. Severe tremors as defined by a score of "severe" on any of the MDS-UPDRS Parts II and III tremor severity (not constancy) items;
10. Montreal cognitive assessment score < 25;
11. History of any surgery on the brain itself, including deep brain stimulation for PD (note this does not include surgeries in the skull that do not affect the brain, e.g., small meningioma removal);
12. History of hypersensitivity (e.g., bronchospasm, anaphylaxis, serious drug rash) to contents of the study drug or other tyrosine kinase inhibitors;

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13. Clinically significant or unstable psychiatric or medical condition, vital sign, or laboratory abnormality that in the opinion of the Investigator, interferes with participation in the study;
14. [redacted]
15. [redacted]
16. [redacted]

[redacted]

18. History of surgery within 4 weeks prior to the Screening visit or expectation of a planned surgical or invasive diagnostic procedure during the course of the study;
19. Participation in other investigational drug trials within 30 days prior to Screening;
20. [redacted]
21. Recent use of medications that can cause Parkinsonism and suspicion of the investigator that it could have worsened the subject's Parkinsonism. This includes neuroleptics (e.g., olanzapine, risperidone, haloperidol), some anti-nausea medications (e.g., prochlorperizine, metoclopramide) and others (e.g., flunarizine, methyldopa);
22. Use of medications that affect the dopaminergic system within 60 days of Screening. This includes stimulants (e.g., methylphenidate, amphetamine derivatives, modafinil) and Monoamine Oxidase A (MAOA) inhibitors (e.g., phenelzine, and tranylcypromine). Note that antidepressants are acceptable as long as the subject has remained on them at a stable dose for over 60 days prior to Screening and plans to remain on them through the study;
23. Any malignant disease (other than basal cell carcinoma of the skin) with evidence of disease within the past 5 years and with the potential for recurrence;

[redacted]

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- [redacted]
- [redacted]

Part 2 - Long Term Extension Study:

Inclusion Criteria:

1. Subject has completed part 1 of the study.
2. Subject projected not to need dopaminergic treatment except for treatment with Monoamine Oxidase B (MAOB) inhibitors. MAOB inhibitors will be allowed if the patient was already taking the same during part 1 of the study.
3. Subject has received K0706/placebo, as appropriate, within 4 weeks prior to the end of part 1 of the study.
4. Male subjects enrolled in the study should not father a child and are advised to prevent the passage of semen to their sexual partner during intercourse using an effective method, as judged by the Investigator, for the duration of the study and for 3 months after the last dose of the study drug.

Exclusion Criteria:

1. Clinically significant or unstable psychiatric or medical condition, vital sign, or laboratory abnormality that in the opinion of the Investigator, interferes with participation in the study
2. Any condition that, in the opinion of the Investigator, represents an obstacle to study conduct and/or represents a potentially unacceptable risk for the subject.
3. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause continued treatment to be detrimental to the subject.

Statistical Method for [redacted]: Part 1 (Day 0 to Week 40)

Mean changes from baseline in the primary outcome measurement MDS-UPDRS Part III total score will be analyzed [redacted] The analysis will be performed by [redacted] the dependent variable based on the [redacted]. The analysis will include the treatment arm, analysis visit, region, baseline MAOB inhibitor user status, and the interaction term of treatment by analysis visit as the fixed, categorical effects, [redacted]. [redacted]

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[redacted]

A three-stage analysis of the primary efficacy endpoint will be as follows.

Stage 1: Administrative [redacted]

[redacted] The study team will remain blinded until the completion of Part 1. [redacted] Details about the [redacted] is documented in the statistical analysis plan (SAP).

Stage 2: Primary Efficacy Analysis for Part 1

The primary efficacy analysis will be performed when all the planned 506 randomized subjects have completed Part 1 of the study or been discontinued early from Part 1. The primary endpoint and all other efficacy and safety endpoints or outcomes will be analyzed. [redacted]

Stage 3: Efficacy Analyses for Part 2

All efficacy analyses for Part 2 will be considered exploratory. The primary efficacy endpoints of interest in Part 2 is the change from Part 2 baseline to Week 76 in the MDS-UPDRS Part III total score. The change from Part 2 baseline in the MDS-UPDRS assessments across all time points up to Week 76 will be summarized descriptively.

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Sample size estimate

Part 1

Part 1 sample size estimates for this study are based on information from [redacted] subjects in a large cohort study (Parkinson's Progression Markers Initiative) who remained off symptomatic PD medications from [redacted]

For this study, assuming a [redacted] improvement at Week [redacted] for the K0706 group mean over the placebo group mean of [redacted] points in change-from-baseline MDS-UPDRS Parts II and III sum score, the target delta is [redacted] points. [redacted]

Assuming a common standard deviation across treatment groups of [redacted] points, a sample size of [redacted] evaluable [redacted] subjects in the high dose and placebo groups will be required to achieve [redacted] power. The comparison for the low dose group ([redacted]) will also have at least [redacted] power under the same assumptions. Additional subjects may be enrolled. [redacted]

Based on the data of PASADENA trial in early PD subjects (www.clinicaltrials.gov NCT03100149), the contribution of the MDS-UPDRS Part II to the effect size is expected to be negligible or negative, thus by excluding Part II and using Part III alone as the primary efficacy outcome is expected to have at least the same power compared to using the sum of Parts II and III. .

[redacted] estimates in Part 2 are based on the number of subjects who complete Part 1 successfully and elect to participate in ongoing treatment rather than the number of subjects needed to test a statistical hypothesis of interest. [redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Expanded Form
AE	Adverse Event
ALT	Alanine Aminotransferase
ALL	Acute Lymphocytic Leukemia
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
c-Abl	Cellular Abelson Tyrosine Kinase
CGIS	Clinician's Global Impression Severity
C_{max}	Maximum concentration
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
[redacted]	[redacted]
CYP	Cytochrome P450
DB	Double Blind
DaT SPECT	Dopamine Transporter Single Photon Emission Computed Tomography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Early Discontinuation
EDC	Electronic Data Capture
EoT	End of Treatment
EQ-5D-5L	EuroQol - 5 Dimensional - 5 Level
FSH	Follicular Stimulating Hormone
GCP	Good Clinical Practice
hERG	Human Ether a-go-go Related Gene
HRQoL	Health-Related Quality of Life
[redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IP Manual	Investigational Product Manual
IRB	Institutional Review Board
[redacted]	[redacted]
IWRS	Interactive Web Response System
MAOB	Monoamine Oxidase B
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale

Mg/kg/day	Milligrams per kilogram per day
mL	Milliliter
[redacted]	[redacted]
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
ng/mL	Nanograms per Milliliter
Ph+ ALL	Philadelphia Chromosome Positive Acute Lymphocytic Leukemia
PD	Parkinson's Disease
PFF	Pre-formed Fibril
PK	Pharmacokinetics
PP	Per Protocol
PSP	Progressive Supranuclear Palsy
aPTT	Activated Partial Thromboplastin Clotting Time
QTc	Heart-rate corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCOPA-AUT	Scales for Outcome in Parkinson's disease – Autonomic
SOP	Standard Operating Procedure
SPARC	Sun Pharma Advanced Research Company
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWEDD	Scans Without Evidence of Dopaminergic Deficit
TEAE	Treatment Emergent Adverse Event
TH	Tyrosine Hydroxylase
TKI	Tyrosine Kinase Inhibitor
WBC	White Blood Cell
WHO	World Health Organization
°C	degrees Celsius
°F	degrees Fahrenheit

2.0 BACKGROUND INFORMATION

2.1 Background

Parkinson's disease (PD) is a neurodegenerative disease that typically presents in late life and is primarily characterized by progressive worsening of symptoms of slowness of movement, tremors, and postural instability. It also causes changes in mood, autonomic system dysfunction, and sleep. As the disease progresses, patients become progressively less mobile with high rates of falls and develop swallowing difficulty, hallucinations, and dementia. One study found that within 10 years, 55% had died, 68% had postural instability, and 46% had dementia [redacted]

Pathologically, PD is characterized by progressive loss of dopamine-producing neurons in the substantia nigra (part of the midbrain) and formation of Lewy Bodies also in the midbrain, but elsewhere in the brain as well. Loss of dopamine is thought to explain the motor symptoms of the disease, as dopamine replacement (through the dopamine precursor L-dopa or dopamine agonists) improves movement speed. The underlying pathophysiology of the disease is not fully understood but is thought to relate to the aggregation of a protein called α -synuclein, a major component of Lewy Bodies. Neuronal loss and dysfunction may be directly from α -synuclein aggregates or indirectly through multiple other pathways, including inflammation and programmed cell death.

Treatment for PD currently consists only of medications to replace the loss of dopamine production. These treatments can improve many (but not all) symptoms of the disease, but as the degeneration continues, the treatments become less and less effective. There are no interventions proven to slow disease progress (i.e., disease modification). To date, all attempts to modify the course of PD have been unsuccessful ([redacted]

One approach for disease modification is the inhibition of c-Abl (cellular [as opposed to viral] Abelson Tyrosine Kinase). C-Abl has multiple roles in the maintenance of neuronal health and function, but its over-activation has been shown to play a role in the pathophysiology of multiple neurodegenerative diseases, including PD, Alzheimer's disease, and others ([redacted] C-Abl can be activated by oxidative stress (a known predictor of neurodegenerative diseases) as well as by α-synuclein ([redacted] Activated c-Abl can then lead to neurodegeneration through its phosphorylation of parkin and α-synuclein, leading to cell death through a variety of pathways ([redacted]

Multiple lines of evidence suggest that inhibition of c-Abl will slow the degenerative process underlying PD and will do so through multiple pathways, including those involving parkin and α-synuclein. Ko and colleagues demonstrated that inhibition of c-Abl prevents phosphorylation of parkin and thereby reduces neurotoxicity in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) model of PD ([redacted] Parkin is a ubiquitin E3 ligase that

helps in the breakdown of proteins, and reduction in its function through phosphorylation or genetic mutations (e.g., autosomal recessive PD), is associated with the pathological underpinnings of PD. Brahmachari and colleagues further showed that c-Abl also acts via the α-synuclein pathway – levels of c-Abl activity regulated α-synuclein activity, promoting or inhibiting the pathology associated with PD [redacted] α-Synuclein is a widely expressed neuronal protein that has been found to aggregate in the Lewy bodies that define PD pathologically, and mutations in the α-synuclein gene are associated with autosomal dominant PD.

There are at least five c-Abl TKIs currently approved by the United States Food and Drug Administration as therapeutics in the clinical management of Chronic Myeloid Leukemia (CML), a disease driven by the constitutively active tyrosine kinase breakpoint cluster region/abelson murine leukemia viral oncogene homolog 1 (*BCR::ABL1*) ([redacted] Nilotinib has been shown to cross the blood-brain barrier and thus has been used in various preclinical models of neurodegenerative diseases. Nilotinib has been shown to protect dopamine neurons and reduce motor deficits in at least three animal models of PD ([redacted]). Nilotinib was also evaluated in an open-label clinical trial on 12 patients with PD or Lewy Body Dementia (a similar disease to PD also associated with α-synuclein), and was associated with improved cognitive and motor functions in > 90% of the patients in this small unblinded study [redacted]. Nilotinib, however, has significant risks, including an FDA black-box warning of QT prolongation, suggesting that safer alternatives should be developed for Parkinson's disease. Subsequent controlled studies of nilotinib failed to confirm efficacy and demonstrated inadequate penetration of the blood brain barrier in humans, unlike in rodents [redacted]

2.2 Investigational Product

2.2.1 Name and Description

K0706 is a novel Abl tyrosine kinase inhibitor developed by Sun Pharma Advanced Research Company Limited (SPARC). It is also being investigated for the treatment of patients with CML or Philadelphia Chromosome Positive Acute Lymphocytic Leukemia (Ph+ ALL). [redacted]

2.2.2 Non-clinical Data

2.2.3 Non-clinical Evidence of Efficacy

[redacted] MPTP is a toxin that leads to rapid destruction of dopaminergic substantia nigra pars compacta neurons, producing a Parkinsonian condition that mimics some, but not all features of PD. It was initially discovered

when it was inadvertently administered by heroin users leading to a rapid onset, severe, Parkinsonian state.

[redacted] Nilotinib, a second-generation c-Abl TKI, was included in the study as a reference as it has previously reported efficacy in this model [redacted] Administration of MPTP in mice caused a marked loss of SNpc dopaminergic neurons. K0706 administration significantly prevented the neurodegeneration induced by MPTP. [redacted]

[redacted]

K0706 was also studied in a rat model of PD based on the injection of a virus that has been engineered to produce large amounts of human α-synuclein; model described in [redacted]. In this model, [redacted] injection of the virus into the rat's substantia nigra produces progressive loss of dopamine-producing neurons and leads to a Parkinsonian state. After 6 weeks, animals were sacrificed, and dopamine neuron health was quantified using [redacted] to tyrosine hydroxylase (TH, the enzyme that produces dopamine). [redacted]

K0706 was also studied in a mouse model of PD based on injection of pre-formed fibrils (PFF) of α-synuclein model described in [redacted] The finding was that K0706 [redacted] dopaminergic neurons from α-synuclein-mediated toxicity [redacted].

[redacted]

[redacted]

2.2.4 Non-clinical Safety Data

Non-clinical safety data are available in the IB. Key findings from IB as well as findings obtained since the IB was published, are mentioned here.

[redacted] Overall, K0706 had [redacted] on CNS, cardiovascular, and respiratory functions. [redacted]

[redacted] clinical signs were observed in any animal, but [redacted]

K0706 was found to be [redacted] in ICH battery of [redacted] The high dose of K0706 [redacted]

[redacted] K0706 [redacted] appear to be a potent direct or time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. CYP inhibition profile for CYP2C8 is being investigated. [redacted].

2.2.5 Clinical Data

K0706 has been investigated [redacted]

[redacted]

[redacted] trial in subjects with early to late-stage PD. In this study, [redacted] Subjects [redacted] were the same, and

subjects in [redacted] were the same. A total of [redacted] subjects were enrolled in [redacted] part of the study.

Overall, a total of [redacted] reported [redacted] TEAEs. [redacted] subjects reported [redacted] drug-related TEAEs.

[redacted] subjects reported [redacted] TEAEs in [redacted] part: one subject each in [redacted]; 2 subjects each in [redacted]; 3 subjects each in [redacted]; and 5 subjects in [redacted] subjects reported [redacted] TEAEs in [redacted] part: 3 subjects each reported 10, 6, and 5 TEAEs in [redacted])

The most common TEAEs [redacted] subjects) in the [redacted] part of the study were [redacted]
The most common drug-related TEAEs occurring in [redacted] subject) were [redacted] These were of Grade 1 severity except for two events – [redacted]

The most common TEAEs occurring in ([redacted] subject) in the [redacted] part of the study were [redacted]. Drug-related TEAEs were [redacted]

The severity of TEAEs: [redacted], and the event was resolved. The other [redacted] TEAEs were of Grade 1 to Grade 2 intensity. Of these, TEAEs that had not resolved until database lock [redacted]

[redacted]

[redacted]. K0706 was overall well tolerated, with almost all subjects completing the trial. There was no overall trend for more AEs with dose, though [redacted] did occur in [redacted] subjects at the [redacted] doses. [redacted] also occurred in 3 subjects, with the only case of [redacted]. However, these were reported in a [redacted] subject only. Hence, there this [redacted] of any particular trend of dose-/relationship for AEs.

There were no deaths. Subject [redacted] reported 2 SAEs: troponin increased and chest pain. These events occurred before the administration of the study treatment. Hence, these events were not considered as TEAEs.

Overall, K0706 demonstrated reasonable safety and tolerability in the study.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted] study was designed to evaluate [redacted] K0706 [redacted]. There were [redacted] cohorts studied, [redacted] K0706 [redacted]

A total of [redacted] subjects were screened, of which [redacted] subjects were enrolled in the study. The safety population comprised [redacted] subjects, and the PK population comprised [redacted] subjects.

There were [redacted] deaths, SAEs, or other significant AEs reported during the study.

Overall, [redacted] clinically relevant or significant findings related to clinical laboratory results, vital signs, electrocardiograms, or physical examinations were observed.

[redacted] subjects [redacted] subjects reported [redacted] TEAEs. [redacted] subjects reported [redacted] treatment-related TEAEs. There were [redacted] SAEs. Of these, TEAEs unlikely related or unrelated to study treatment were reported in [redacted] of subjects, respectively. The TEAEs were mild ([redacted] subjects) to moderate ([redacted] subjects) in intensity, and [redacted] were more intense. [redacted] fatal or unknown outcomes were reported. Only one subject reported one TEAE, which had not been resolved by the end of the study. Overall, [redacted] clinically relevant or significant findings related to clinical laboratory results, vital signs, ECGs, or physical examinations were observed.

K0706 was safe and generally well tolerated at the doses administered in this study

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2.6 Summary of the Known and Potential Risks and Benefits, if any, to Human Subjects

Adverse events associated with K0706 are described in the IB and in sections 2.2.5 and 6.3.

K0706 is a BCR-ABL tyrosine kinase inhibitor with limited off-target effects. Based on its mechanism of action and the results of the pre-clinical toxicology studies, the anticipated potential toxicities in humans with K0706 include [redacted]. K0706 is a teratogen, as are other BCR-ABL tyrosine kinase inhibitors, in view of the role of ABL signaling in embryo-fetal development. Otherwise, non-clinical toxicology studies with K0706 demonstrate a safety profile that supports administration to human subjects.

In healthy controls, K0706 has been studied [redacted] Potentially-related TEAEs were mild and typically caused [redacted]. The [redacted]

In Parkinson's subjects, K0706 has been studied up to [redacted]. TEAEs were typically [redacted] and typically [redacted] across subjects. [redacted] is a common TEAE with other ABL inhibitors and is typically managed with stopping the treatment and often does not recur with restarting of the medication). [redacted]. In the Ph+ CML study population enrolled in [redacted], in the emerging clinical data, the most commonly observed TEAEs included the following:

[redacted]

Additionally, certain class effects are known with the clinical use of BCR-ABL tyrosine kinase inhibitors such as Imatinib mesylate, Dasatinib, Nilotinib, and Ponatinib in the treatment of Philadelphia-positive leukemia. While some of the observed AEs are common between the BCRABL tyrosine kinase inhibitors and contribute as a class effect, specific adverse reactions are associated with the structure of the BCRABL tyrosine kinase inhibitors and are unique for the particular TKI (e.g.: Thromboembolic episodes in patients treated with Ponatinib). Since K0706 is being developed as a tyrosine kinase inhibitor for the treatment of Philadelphia-positive leukemia, AEs commonly observed with the approved BCRABL tyrosine kinase inhibitors class of drugs may be observed with the clinical use of K0706. The following AEs have been reported

during clinical studies and clinical use of BCR-ABL TKIs such as imatinib, dasatinib, nilotinib, ponatinib, and bosutinib:

- Fluid retention: It is advised to monitor subjects for the development of signs and symptoms of fluid retention
- Myelosuppression: It is advised to monitor complete blood counts regularly
- Cardiac arrhythmias: Subjects should be advised to report signs and symptoms of slow or rapid heart rate.
- Hepatic impairment: Caution is recommended in subjects with hepatic impairment
- Heart failure: Subjects should be monitored for signs or symptoms consistent with cardiac dysfunction and should be treated appropriately
- Hepatotoxicity: It is advised to monitor liver function tests regularly
- Pancreatitis: Caution is recommended in subjects with a history of pancreatitis
- Hemorrhage: Caution is indicated in subjects requiring medications that inhibit platelet function or anticoagulants
- Pregnancy: Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant
- Compromised wound healing and gastrointestinal perforation

Nilotinib is approved for CML at doses up to 1200 mg daily (European Union) and up to 800 mg daily (United States of America), where it carries a black box warning for QT interval prolongation. Sudden cardiac death and electrolyte disturbances have been reported in patients taking nilotinib, and it can also cause myelosuppression. In non-clinical studies of nilotinib, potentially pro-arrhythmic effects as evidenced by inhibition of hERG current, prolongation of action potential duration, and induction of triangulation and beat-to-beat variability in the in-vitro assay systems were observed [redacted]

[redacted]

Ponatinib use is associated with hepatic impairment, neuropathy, ocular toxicity, and vascular occlusion (arterial and venous) [redacted]

There has been one open-label trial of nilotinib of five subjects with Dementia with Lewy Bodies (a similar condition to PD with early cognitive impairment) and 7 subjects with mid to late-stage PD (all but one with cognitive impairment) [redacted] SAEs in that study included myocardial infarction, hospitalization for urinary tract infection, and hospitalization for pneumonia. All other side effects were considered mild. Of note, most participants experienced increased psychotic symptoms and dyskinesias, which the authors noted suggested a symptomatic benefit of nilotinib (i.e., increased dopamine levels).

Regarding potential benefits, non-clinical evidence of efficacy in animal models of PD is described in section 2.2.3. There have been no studies in humans regarding the effectiveness of K0706 on Parkinson's disease.

2.3 Rationale

2.3.1 Rationale for the Trial and Selected Subject Population

This study is designed to serve as a [redacted] trial for the ability of K0706 to slow the progression of PD. Preclinical animal model data have already demonstrated that K0706 has neuroprotective activity, but further development will require human clinical experience. This study will also allow the determination of the safety and tolerability of K0706 over many months in subjects with PD. Finally, it will provide insights into relationships between blood and CSF levels of K0706 and efficacy, as well as other exploratory outcome measures, all of which will help in the design of pivotal phase 3 trials.

This trial is being performed in early-stage PD subjects as the primary outcome is based on symptoms and signs of PD (using the Movement Disorder Society - Unified PD Rating Scale [MDS-UPDRS]). Mid and late-stage PD subjects are not being studied as they are typically on dopamine replacement medication, which markedly ameliorates symptoms and signs of the disease, making the MDS-UPDRS no longer reflective of disease progression. There are no validated ways of tracking disease progression in patients on dopamine replacement medications, though it is an active area of research and may become available for future trials.

The study is a 40-week trial as clinical experience and prior clinical trials, e.g., The Parkinson Study Group, 2004 ([redacted]) and observational studies e.g., Parkinson Progression Marker Initiative, 2011 [redacted] suggest that the great majority of early-stage PD subjects can remain off of dopamine replacement medications for 40 weeks. An extension study has been designed to evaluate the safety and efficacy of the study drug at 76 weeks. This will help gather additional safety and efficacy data beyond 40 weeks.

This study is powered (i.e., number of subjects chosen) to detect a [redacted] slowing in PD progression over 40 weeks as measured by the sum of the MDS-UPDRS Parts II and III, when comparing the subjects on K0706 versus placebo. [redacted]

2.3.2 Rationale for Dose Selection

Subjects enrolled under Protocol Amendment 01 or 02 were treated with [redacted] K0706 (or placebo) [redacted] with Protocol Amendment 03, K0706 doses are changed [redacted] of K0706 (or placebo) [redacted] formulation. Dose selection is based on an attempt to [redacted] the human K0706 [redacted] concentration to the most effective [redacted] concentration in animal models of PD. [redacted] To determine the target CSF concentration, a separate group [redacted]

The [redacted] formulation will be used to allow for a higher dose but minimize [redacted] (as the [redacted] formulation is dosed with [redacted]). The high dose will be increased from [redacted] to [redacted], and the low dose will be increased from [redacted] to [redacted] Note that these are approximately [redacted] increases, as preliminary PK results from study [redacted] (Section 2.2.5.3 and the IB) shows that the [redacted]

[redacted]

Note that since animal studies suggest the potential for efficacy at doses less than [redacted], there is potential for subjects in the low-dose group to show efficacy as well.

K0706 will be administered once daily as the half-life is approximately [redacted]

Subjects are asked to take the study drug in the [redacted]

[redacted]

2.3.3 Rationale for the Use of Comparator

The comparator will be a placebo matched in appearance to K0706 to evaluate the efficacy of K0706 to slow PD progression accounting for the "placebo effect" of enrollment in the study and of taking of a daily medication. The use of a placebo is ethically justified as there are no medications proven to slow PD progression.

2.3.4 Rationale for DaT SPECT Scan as an Enrichment Tool

PD is a pathological diagnosis that can be challenging to diagnose as other syndromes have similar appearance, especially in the early stages. A recent study found that in subjects with a clinical phenotype of PD <5 years from onset with positive response to levodopa, only 8 out of 15 had PD when it came to autopsy [redacted] In that study and others, the alternative diagnoses included Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Alzheimer's Disease, Vascular Dementia, and multiple cases with no pathology found. Other conditions that can mimic PD in early stages include drug-induced Parkinsonism (typically from dopamine antagonists) and essential tremor. As K0706 has been shown only to act on the pathology that causes PD, it is essential to aim to limit this trial to subjects with the highest likelihood of having pathologically proven PD.

The first step for ensuring accurate diagnosis is based on the MDS clinical diagnostic criteria for PD ([redacted] using the "Clinically Probable PD" Criteria. This will ensure subjects have clinical features consistent with PD and not those clearly consistent with other causes of Parkinsonism.

To further rule out other causes of Parkinsonism, all subjects must have a Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT) consistent with the diagnosis of PD. A DaT SPECT scan is a brain scan that quantifies the binding of a radioactive "ligand" (a chemical) to the dopamine transporter and serves as an indirect measure of the health of dopamine-producing neurons. Subjects with PD or other disorders of dopamine-producing neurons will have a loss of binding of the ligand, typically asymmetrically. Patients with Parkinsonism but normal DaT SPECT scans (i.e., Scans without Evidence of Dopaminergic Deficit [SWEDD]) typically have essential tremor or drug-induced Parkinsonism and therefore will not be included in the study. One clinical trial of early-stage PD found that 15% of subjects who otherwise met the criteria for PD had negative DaT SPECT scans [redacted] However, DaT SPECT scanning cannot separate subjects with other neurodegenerative forms of Parkinsonism from those with PD.

2.3.5 Rationale for Primary Efficacy Endpoint

The MDS-UPDRS is a revision of the UPDRS [redacted] designed to be more [redacted] sound and have improved instructions. The MDS-UPDRS or its predecessor the UPDRS has been the primary outcome measure in the great majority of clinical trials in PD [redacted] and a large

ongoing cohort study ([redacted] thereby allowing a broader interpretation of the results of this study.

The MDS-UPDRS has a total of 4 parts – Part I is non-motor experiences of daily living, Part II is motor experiences of daily living, Part III is motor examination, and Part IV is motor complications. Only Parts II and III are the measures likely to be sensitive to change in early PD, while Part I shows only minimal change in early PD, and Part IV is only relevant for patients on symptomatic medication [redacted] Parts II and III both quantify the severity of movement deficits typical of PD, with Part II focusing on how these deficits are experienced by the patient (i.e., symptoms) while Part III is how they are observed by the examiner (i.e., signs).

One recent study [redacted] recommends against summing parts of the MDS-UPDRS scores as the primary or secondary clinical outcomes for the PD clinical trials. Based on the concept of clinimetrical validity, the authors advocate using the MDS-UPDRS as it was originally envisioned and soundly tested, that is, reporting the individual parts of the MDS-UPDRS scores separately. By taking the up-to-date external information into account, the MDS-UPDRS Part III total score is taken as the primary efficacy outcome.

2.3.6 Rationale for Secondary Efficacy Endpoints

Parts I, II, and III of MDS-UPDRS, and combinations of these scores will also be evaluated from baseline to earlier visits to determine the onset and time course of effect of K0706 on PD progression versus placebo.

The Clinician's Global Impression of Severity (CGIS) ([redacted] is a single-question, clinician-scored measure of overall disease severity widely used in neurological and clinical trials and validated in PD [redacted] The CGIS will serve as an overall measure of PD severity in the view of the investigator. It is possible that the effect of K0706 on PD progression over [redacted] months may not be detectable by a change in the CGIS, so results from this study will determine its potential utility in a future pivotal trial.

PD affects autonomic nervous function causing constipation, orthostatic hypotension, and other symptoms. To measure this, subjects will fill out the Scales for Outcomes in PD - Autonomic questionnaire (SCOPA-AUT) questionnaire, which measures symptoms over the past month [redacted]. This is a validated scale of autonomic symptoms recommended by the Movement Disorders Society [redacted]

Time to initiation of PD symptomatic medication will also be measured as this is an indirect measure of the progression of disability. This measure was used as the primary outcome measure in earlier trials ([redacted] though its interpretation can be confounded

by the subject's work status/profession as well as treating physician preference ([redacted] 2011).

Health-Related quality of life (HRQoL) will be measured using the European Quality of Life Questionnaire 5 level version (EQ-5D-5L) [redacted] The scale has a total of six questions, 5 with a 5-level response and one with a visual analog scale response. It is a generic HRQoL scale that was initially validated in PD using the 3-level version [redacted] and more recently with the 5-level version [redacted] designed to have less of a ceiling effect than the 3-level version. By using this generic HRQoL scale rather than a PD-specific scale, the results of this study will be able to be incorporated into cost-utility analysis models. A literature review in April 2018 suggested that there is no data on the ability of the EQ-5D-5L to detect change in early-stage PD subjects, so results from this study will determine the potential utility of this measure in a future pivotal trial of K0706.

2.3.7 Rationale for Exploratory Efficacy Endpoints

Blood will be collected at multiple time points and stored frozen for later analysis. There are currently no validated blood-based tests that can predict the rate of PD progression, objectively track PD progression, or identify target engagement of K0706, but this is an active area of research. Possible tests include neurofilament light chains, genetic markers of different PD subtypes and neuronal-origin "exosomes" which allow quantification of substances in the brain [redacted] Once putative tests become available, stored samples will be analyzed to validate them in this dataset.

Subjects may be provided with smartphone applications, which will be used to track their motor behavior. Smartphones (e.g., using Android or iOS operating systems) contain sensors that can be used to quantify movement and speech, including touch screens, accelerometers, GPS, gyroscopes, and microphones. Behavior can be quantifiable through active tasks (e.g., asking subjects to tap on the screen or walk a set path with the phone in a pants pocket), or passive (e.g., recording gait throughout the day with the phone in the pants pocket). Compared to the standard outcome measures performed in the clinic by an expert rater, use of smartphones offers the potential to quantify motor behavior more accurately and objectively, as well as at a much higher frequency (as the devices can be used at home) [redacted] While still in the early stage of development, smartphone measures have been shown to distinguish patients with PD from controls [redacted] and quantify disease severity in a cross-sectional study [redacted] Another study also showed the feasibility of using smartphones in a longitudinal clinical trial [redacted] This approach is still considered exploratory as the best combination of outcome measures is not known, and validity has not been definitively shown. Therefore, feasibility analyses will be conducted during this trial, likely leading to modifications throughout the trial.

[redacted] DaT SPECT scan (described in Section 2.3.4) will be used as a marker of disease progression as it has in previous trials [redacted] CSF will be used to measure K0706 levels (as a marker of brain penetration), as well as stored frozen for later analysis of biomarkers of PD progression or target engagement of K0706. There are currently no validated [redacted] biomarkers for these purposes, but there are multiple under active development, such as markers of cell death, gene expression arrays, and others [redacted]

Skin punch biopsy (Section 7.6) will be sent for pathological analysis, including quantification of [redacted] deposition in the autonomic nerves. Multiple studies have shown that the presence of phosphorylated α-synuclein in the autonomic nerves of the skin is highly specific for diseases caused by abnormal α-synuclein deposition (e.g., PD, MSA, Primary Autonomic Failure) and, therefore, should be able to exclude conditions not due to α-synuclein deposition (e.g., PSP or vascular Parkinsonism) and therefore progress differently [redacted] Total α-synuclein deposition in the autonomic nerves has been shown to correlate with the severity of PD [redacted] so progression of this marker may prove useful as a marker of target engagement of K0706. Biopsies will be performed from a proximal site, such as the posterior neck, as proximal sites are more sensitive to α-synuclein deposition than distal ones [redacted]

[redacted]

2.3.8 Rationale for the long-term extension study

The long-term extension study is designed to evaluate the long-term safety and efficacy of K0706 in subjects who have completed part 1 of the study.

2.4 Compliance Statement for Study Conduct in Accordance With Protocol, GCP and Applicable Regulatory Requirements

The study protocol, amendments to the protocol, IB, procedures for the recruitment of subjects (e.g., advertisements), the subjects' information and informed consent form as well as consent form updates (if applicable), written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC), which is constituted according to local law to obtain approval before initiation of the study and as applicable thereafter.

The study will only be initiated after receipt of approval from the IRB or EC and/or regulatory authority. The investigator will report promptly to the IRB/EC new information that may adversely affect the safety of the subjects or the conduct of the study.

The Principal Investigator (PI) will follow the protocol in conformity with Good Clinical Practice (GCP) described in Guideline E6 of the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) and applicable regulatory requirements.

Before admission into the study, the written informed consent form must be signed and personally dated by the subject and by the PI or designee who conducted the informed consent discussion.

In obtaining and documenting informed consent, the Principal Investigator must comply with the applicable regulatory requirement(s) and adhere to GCP.

The PI must inform the subject of all pertinent aspects of the study, including the written information approved/favorably assessed by the IRB/EC.

3.0 STUDY OBJECTIVES

3.1 Part 1 (Day 0 to Week 40)

3.1.1 Primary Objective

- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks, as assessed by the MDS-UPDRS (Movement Disorder Society – Unified Parkinson's Disease Rating Scale) Part III (motor examination) total score.

3.1.2 Secondary Objectives

- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients excluding mild-motor predominant sub-type ([redacted]). The rate of progression is assessed by the MDS-UPDRS Part III total score.
- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks by a greater magnitude in the subgroup of patients with serum NfL value ≥ 13 pg/mL at baseline ([redacted]). The rate of progression is assessed by the MDS-UPDRS Part III total score.
- To determine if K0706 reduces the rate of progression of early-stage PD versus placebo over 40 weeks, as assessed by the sum of the MDS-UPDRS Parts II and III total scores.
- To determine if K0706 slows early-stage PD progression compared to placebo by increasing the time to significant worsening on the MDS-UPDRS Parts I, II, and III.
- [redacted]
- To evaluate the efficacy of K0706 compared to placebo in terms of Health-Related Quality of Life (HRQoL) as measured by the European Quality of Life Questionnaire 5 level version (EQ-5D-5L).
- To determine if K0706 slows the progression of early-stage PD compared to placebo over 40 weeks in terms of overall severity of PD as measured by the Clinician Global Impression Severity (CGIS) scale.
- To evaluate the effect of K0706 compared to placebo on autonomic nervous system dysfunction related to PD as measured by the Scales for Outcome in PD - Autonomic (SCOPA-AUT).
- To evaluate the safety and tolerability of K0706.
- To evaluate the relationship between plasma and cerebrospinal fluid (CSF) concentrations of K0706 and the measures of efficacy and safety.

3.1.3 Exploratory Objectives:

- To evaluate the effect of K0706 on skin pathology markers of PD.
- To evaluate the effect of K0706 on blood and cerebrospinal fluid (CSF) biomarkers linked to PD and target engagement of K0706.

- To investigate genetic and clinical markers that predict the degree of progression of early-stage PD and/or response to K0706.
- To evaluate the effect of K0706 on dopamine cell health in PD as detected via Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT) brain imaging.
- [redacted]

3.2 Part 2 (Week 40 to Week 80)

3.2.1 Primary Objective

To assess the long-term safety/tolerability of K0706 in subjects with early PD

3.2.2 Secondary Objective

To assess the initial and long-term efficacy of K0706 in subjects with early PD

3.2.3 Exploratory Objective

To assess the efficacy of K0706 in subjects with delayed treatment initiation relative to those with early treatment initiation

3.3 [redacted] Events: Part 1 (Day 0 to Week 40)

To support the primary objective of the trial for Part 1, the [redacted] will be used for the [redacted] analysis. Part 1 of this trial is to clarify the efficacy of the K0706 in improving the MDS-UPDRS Part III score in a [redacted] situation had [redacted] subjects had an [redacted]

4.0 SELECTION OF SUBJECTS

4.1 Description of the Study Population

Subjects aged ≥ 50 years with a diagnosis of PD made [redacted] and modified Hoehn and Yahr stage [redacted] 2 who are [redacted] will be eligible for screening.

4.2 Part 1

4.2.1 Inclusion Criteria

1. The subject has given written informed consent and is willing to participate in the study;
2. Subject is able to understand and comply with all study procedures (requires literacy in the available language of all patient-reported outcome measures);
3. Males or females aged ≥ 50 years;
4. Body mass index (BMI) greater than 18.5 kg/m^2 and less than 45 kg/m^2;
5. Diagnosed with "Clinically Probable PD" according to the MDS clinical diagnostic criteria, with a documented diagnosis of PD per the treating physician's records within three years of the Screening visit. Disease severity according to modified Hoehn & Yahr stage [redacted] 2;
6. Projected to not require starting dopaminergic therapy within [redacted] months from Baseline;
7. [redacted]
8. [redacted]
9. [redacted]

4.2.2 Exclusion Criteria

1. Current, or within 60 days of Screening, use of any prescription, investigational, or over-the-counter medication for the symptomatic treatment of PD or to slow the progression of PD. Treatment with Monoamine Oxidase B (MAOB) inhibitors will be allowed if the dose is stable for at least 30 days prior to Screening and subjects agree to remain on it for the duration of the study;

2. Prior use of dopaminergic therapy (e.g., levodopa, dopamine agonist, amantadine) for 30 or more days any time in the past;
3. A diagnosis of a significant central or peripheral nervous system disease affecting the subject's cognition or motor function at any time, such as another neurodegenerative disorder, multiple sclerosis, or stroke. This does not include transient neurological deficits such as transient ischemic attacks or migraine aura;
4. A diagnosis of a medical condition that could interfere with the interpretation of the MDS-UPDRS during the trial (e.g., musculoskeletal disorders);
5. Contraindications to receiving an MRI;
6. Contraindications to receiving a DaT SPECT scan (e.g., hypersensitivity to the active substance, any of the excipients, or iodine) if a new DaT SPECT scan is required for the study;
7. Most recent DaT SPECT scans are not compatible with PD (i.e., Scans Without Evidence of Dopaminergic Deficit [SWEDD]) based on a central reading by a study physician;
8. MRI of the brain obtained after the onset of PD suggestive of secondary Parkinsonism (e.g., subdural hematoma, normal pressure hydrocephalus, or infarcts of the basal ganglia);
9. Severe tremors as defined by a score of "severe" on any of the MDS-UPDRS Parts II or III tremor severity (not constancy) items;
10. Montreal cognitive assessment score < 25;
11. History of any surgery on the brain itself, including deep brain stimulation for PD (note this does not include surgeries in the skull that do not affect the brain, e.g., small meningioma removal);
12. History of hypersensitivity (e.g., bronchospasm, anaphylaxis, serious drug rash) to contents of the study drug or other tyrosine kinase inhibitors;
13. Clinically significant or unstable psychiatric or medical condition, vital sign, or laboratory abnormality that, in the opinion of the Investigator interferes with participation in the study;
14. [redacted]
15. [redacted]

[redacted]

18. History of surgery within 4 weeks prior to the Screening Visit or expectation of a planned surgical or invasive diagnostic procedure during the course of the study;
19. Participation in other investigational drug trials within 30 days prior to Screening;
20. Any concomitant medication or medication excluded that could put the subject at risk or interfere with study evaluations (Section 6.4);
21. Recent use of medications that can cause Parkinsonism and suspicion of the investigator that it could have worsened the subject's Parkinsonism. This includes neuroleptics (e.g., olanzapine, risperidone, haloperidol), some anti-nausea medications (e.g., prochlorperizine, metoclopramide), and others (e.g., flunarizine, methyldopa);
22. Use of medications that affect the dopaminergic system within 60 days of Screening. This includes stimulants (e.g., methylphenidate, amphetamine derivatives, modafinil) and Monoamine Oxidase A (MAOA) inhibitors (e.g., phenelzine, and tranylcypromine). Note that antidepressants are acceptable as long as the subject has remained on them at a stable dose for over 60 days prior to Screening and plans to remain on them through the study;
23. Any malignant disease (other than basal cell carcinoma of the skin) with evidence of disease within the past 5 years and with the potential for recurrence;

[redacted]

4.3 Part 2

4.3.1 Inclusion Criteria

1. Subject has completed part 1 of the study
2. Subject projected not to need dopaminergic treatment except for treatment with Monoamine Oxidase B (MAOB) inhibitors. MAOB inhibitors will be allowed if the patient was already taking the same during part 1 of the study.
3. Subject has received K0706/placebo within 4 weeks prior to the end of part 1 of the study.

4. Male subjects enrolled in the study should not father a child and are advised to prevent the passage of semen to their sexual partner during intercourse using an effective method, as judged by the Investigator, for the duration of the study and for 3 months after the last dose of study drug.

4.3.2 Exclusion Criteria

1. Clinically significant or unstable psychiatric or medical condition, vital sign, or laboratory abnormality that, in the opinion of the Investigator interferes with participation in the study
2. Any condition that, in the opinion of the Investigator, represents an obstacle for study conduct and/or represents a potentially unacceptable risk for the subject.
3. Subject has any concurrent medical condition or uncontrolled, clinically significant systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, or anemia) that, in the opinion of the Investigator, could cause continued treatment to be detrimental to the subject.

5.0 STUDY DESIGN

5.1 Description of Type and Design of Study

This is a randomized, multicenter, double-blind, placebo-controlled, [redacted] study to evaluate the efficacy, safety, and tolerability of two dose levels of K0706 in subjects with early PD who are not receiving symptomatic therapy. This study consists of two parts. Part 1 is designed to evaluate the efficacy, safety, and tolerability of two dose levels of K0706 compared to placebo in subjects with early stage PD. Part 2 is an optional long-term extension study assess the long-term safety/tolerability of K0706 in subjects with early PD.

[redacted]

Part 1

Subjects will visit the clinic for the part 1 Screening Visit, be screened based on the eligibility criteria, and provide written informed consent. Confirmation of eligibility at the Part 1 Baseline visit will require the availability of laboratory results, as well as Investigator interpretation of Magnetic Resonance Imaging (MRI) of the brain and central reading of a DaT SPECT scan (obtained prior to or as part of this study).

[redacted]. The screening period is summarized in the Screening Period Flow Diagram (Figure 17-1). Following confirmation of eligibility at the Part 1 Baseline visit, all subjects will be randomized, have baseline assessments performed, and receive the first dose of the study drug. This will be followed by planned visits as per the Schedule of Assessments. The part 1 treatment assessment for efficacy will be performed at Week 40. Subjects choosing not to continue in part 2 will return for a follow-up visit at Week 44.

Subjects will provide blood for the measurement of standard safety laboratory parameters and of levels of K0706. [redacted]

[redacted]

If a subject chooses to begin taking symptomatic PD medication during the trial, they will be discontinued from the study and will be asked to come in for an Early Discontinuation (ED) visit for their final assessment. They will be requested to perform this visit prior to initiation of symptomatic medication. The date of initiation of symptomatic medication will be documented appropriately in source notes and eCRF.

Should an unusual circumstance such as public health emergency (i.e., pandemic with an infectious agent) or a natural disaster, or any other serious unforeseeable circumstances arise, video conference or teleconference between the subject and site Investigator will be permitted to ensure the safe participation of the subjects in case onsite visits are not possible as assessed by a visit at the Investigative site in the opinion of the Sponsor and PI. The timing of these tele/videoconferences should be as per the visit schedule so far as possible. The assessments which are possible to be done remotely should be completed in so far as possible. These remote evaluations should follow the schedule of visits whenever possible.

Part 2 (Optional)

Subjects who complete the EoT visit of part 1 (v11/Week 40) and who consent to participate in part 2 of the study will be screened according to Part 2 eligibility criteria. Subjects who had been randomized to placebo dosing in Part 1 will be rolled over to a high dose [redacted] at Week 40 or their first dosing opportunity in Part 2. This will enable the collection of additional safety data for the high dose level. Subjects who were randomized to K0706 (either dose level) in Part 1 of the study will remain on the same dosing regimen in Part 2. All part 2 subjects will continue treatment for up to 36 additional weeks. Treatment assignments will remain masked to subjects, Investigators, and site staff not directly provisioning kits on behalf of the Sponsor, and the Sponsor will remain masked to treatment assignments until the last subject completes the Week 40 assessments for efficacy and the clinical database is locked for the analysis of part 1. In Part 2, all subjects will be informed that they are receiving the active study drug but will not be informed of the dosage or the treatment received in Part 1.

5.2 General Instructions for Study Visits

The Schedule of Assessments (Appendix 1) provides an overview of the timing of each visit, with an allowed time window for the visit, along with events to occur at each visit. Individual

trial procedures are described below, though efficacy assessments are described in more detail in Section 7.0, and AE reporting is described in more detail in Section 8.0.

If a subject misses a visit, they should be asked to come in as soon as possible for that visit, but no later than 2 weeks prior to the subsequent visit for visits spaced 4 or 8 weeks apart, and no later than 1 week prior to the subsequent visit for visits spaced 2 weeks apart.

If a subject misses two visits in a row without making the visit for a reasonable amount of time, the Sponsor should be notified; in these cases, the Sponsor has the right to remove the subject from the study.

If a subject misses a visit with extra testing (e.g., K0706 blood level or CSF collection), then that testing can be performed before the subsequent visit and should be marked as an unscheduled visit.

Instructions on the collection, processing, storage, and shipment of samples are provided in a separate Laboratory Manual.

Table 5-1 summarizes the approximate blood volumes for sampling during part 1 of the study. Additional samples may be drawn if needed for safety purposes at the discretion of the Investigator.

[redacted]

Table 5-2 summarizes the approximate blood volume sampling for the long-term extension study. Additional samples may be drawn if needed for safety purposes or based on the Investigator's discretion.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Some visits require a blood draw for determination of K0706 levels prior to administration of a dose (i.e., trough level). If the subject inadvertently takes the study drug prior to the visit, the subject should be asked to return within the following week for a blood draw for a pre-dose PK sample.

Subjects should be called within 1 week prior to each scheduled visit to remind them of the visit date, as well as to bring in their diary, [redacted] and any remaining study drug for [redacted] count. Remind the subject to perform the s[redacted] tasks when relevant (Section 7.10). Remind subjects to have a typical amount of caffeine intake on all visits days to avoid caffeine withdrawal as well as excessive use exacerbating any tremor.

5.3 Schedule of Assessments

Part 1 (Day 1 to Week 40)

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

For subjects choosing to participate in part 2 long-term extension, please see Section 5.3.17

[redacted]

[redacted]

[redacted]

5.3.16 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site outside of the protocol-specified time points because of safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, confirmation of out-of-range results), or if a test is missed at a visit and needs to be performed, or for dispensing study drug to the subject, where the subject is seen by study personnel.

All unscheduled visits and assessments performed during the visits will be recorded in the subject's source documents and electronic Case Report Form (eCRF). During any unscheduled visits the Investigator will record any AEs and concomitant medications. They will also perform any assessments, collect samples that they deem necessary and will record having done so.

Part 2 (Weeks 40 – 80)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.4 Measures Taken to Avoid Bias

5.4.1 Subject Number

Subjects will be allotted a unique Subject number at the time of consent. The Subject Number will appear on all study documents relating to that subject and will be cross-referenced by the subject's year of birth.

5.4.2 Randomization

A computer-generated randomization scheme will be produced by the Sponsor or its designee.

Randomization will be 1:1:1 to each dose group and [redacted] based on assignment to [redacted] region (United States or non-United States), and use of a Monoamine Oxidase B (MAOB) Inhibitor.

5.4.3 Blinding

In order to maintain the double-blind nature of the study, all study-related individuals, including the subjects, ancillary study center staff, clinical monitor(s), Investigator, Sponsor and Contract Research Organization (CRO) staff, will remain blinded to the administered treatment. The blinding code will be stored in the IWRS system, available only to parties independent of study conduct. The bioanalytical team will remain unblinded to obviate the need to analyze samples from subjects assigned to placebo.

The treatment code will be broken after Part 1 database is cleaned and locked. Before the database lock for the final analysis of Part 1, a data review will be undertaken to identify the per-protocol population (Section 9.5). After the database lock for the final analysis of Part 1, unblinding will be performed by matching the randomization codes to the data in the database, and the results will be analyzed.

The treatment code may be revealed on an individual basis in the case of an SAE, for which the investigator must know the identity of the study medication to initiate appropriate treatment. The investigator will use the IWRS to unblind the subject. Only Principal Investigators or appropriately delegated sub-Investigators will be given access to open the blind for an individual subject. If the blind is broken, the site must inform the medical monitor or designee and report the reason for unblinding. The date, time and reason for unblinding, with the Investigator's signature, must be recorded. All SAEs will be evaluated for causality by the investigator or designee. A designated Sponsor's safety team member will be unblinded for any SUSAR for regulatory reporting purposes. Unblinding is for regulatory reporting purposes only and all other study-related individuals, including the subjects, ancillary study center staff, clinical monitor(s), Investigator, Sponsor, and CRO staff, will remain blinded to the administered treatment.

To ensure blind maintenance, all products will have identical packaging with a similar label. [redacted]

Subjects who are willing to participate in Part 2 of the study will be rolled over from Part 1 into Part 2. All subjects will receive K0706 therapy in Part 2. Part 2 will remain double-blind until database lock for the final analysis of Part 1.

5.5 Withdrawal and Replacement Rules

The Investigator will make every effort to keep each subject in the study. However, a subject may withdraw from the study at any time without giving any reason; should a subject be removed from the study or elect to decline further study participation, the Sponsor will be notified and the reason(s) for discontinuing the study will be recorded in the source documents and eCRF. Subjects who withdraw or are removed from the study should perform all assessments scheduled for the Early Discontinuation Visit within 30 days.

The following are justifiable reasons for removing a subject from the study:

- Occurrence of AE or SAE that do not justify the subject continuation of the study
- Major protocol deviation (to be defined in the Statistical Analysis Plan)[redacted]
- Subject becomes pregnant during the study.
- Subject elects to discontinue his/her participation in the study by withdrawing consent
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- Subjects who take less than [redacted] of study drug (i.e., for non-compliance).

Sponsor notification is required upon removing subjects for **any** of the reasons noted above. Sponsor written approval is required prior to the removal of a subject for study drug compliance reasons.

Subjects who are discontinued from the study due to an AE will be treated according to established acceptable medical practice and followed for outcome. All pertinent information concerning the outcome of such treatment will be entered in the source document and eCRF.

5.5.1 Lost to Follow-Up

Randomized subjects who have received at least one dose of the study drug but not evaluated for subsequent visits will be considered as lost to follow-up. The Investigator will make every effort to contact subjects lost to follow-up and ask them to return for an Early Discontinuation Visit. Subjects lost to follow-up will not be replaced.

5.5.2 Discontinued due to Adverse Event

Subjects who discontinued the study drug due to the occurrence of an AE will be recorded as dropouts. The AE will be recorded. All subjects, irrespective of the time of dropout (after being randomized and having taken at least one dose of study treatment), will be considered for inclusion in the safety analysis.

5.5.3 Replacement of Subjects

Subjects who drop out after randomization or who are discovered to have major protocol deviations (defined in Statistical Analysis Plan) may be replaced as per Sponsor preference.

5.5.4 Premature Discontinuation of the Complete Study

If the trial is prematurely terminated 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). Additionally:

1) If the investigator terminates or suspends a trial without the prior agreement of the Sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/EC and should provide the sponsor and the IRB/EC a detailed written explanation of the termination or suspension.

The sponsor may discontinue the entire study at any time, for business, ethical, or scientific reasons, in agreement with the investigator. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution where applicable, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

5.6 The Identification of Any Data to be Recorded Directly in the eCRF

No data will be directly recorded in eCRF. Subjects' information will be documented on source documents and then transferred to the individual eCRFs. The original reports, e.g., laboratory

reports, will be kept at the study site. The date and time of the report will be transcribed to specific sections in the eCRF.

6.0 TREATMENT OF SUBJECTS

6.1 Investigational Medicinal Products

6.1.1 Study Medication

The study medication comes as a [redacted] Other formulations are being developed. [redacted] (Table 6-1).

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

The placebo [redacted] formulation will contain the same excipients as that of the K0706 formulation and match the K0706 formulation in shape, size, and color.

[redacted]

6.1.2 Handling Requirements of the Investigational Product

The study drug will be stored [redacted] in the storage area of the study center, in a secure, [redacted] and locked environment with restricted access. Other handling and excursion requirements for the study drug are described in the Investigational Product (IP) manual.

No special procedures for the safe handling of K0706/placebo are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures, and records provided that the blind of the study is not compromised.

6.1.3 Dispensing (Labeling and Packaging) and Compliance

The study drug will be supplied to the study centers by a CRO appointed by the Sponsor. The IWRS (Interactive Web Response System) supports drug supply process.

A sufficient quantity of K0706 and a matching placebo prepared for human studies will be supplied to study centers. Study drug will be supplied and stored in compliance with Good Manufacturing Practice conditions and labeled in accordance with local regulations.

The study center pharmacist / appropriately qualified designee will dispense individual subject treatments [redacted].

All clinical study materials will be packaged and labeled to comply with applicable regulations. The study drug will be clearly labeled according to local requirements regarding use for clinical study investigation only.

The following minimum information will be given on the label:

- Sponsor name
- Protocol number
- IP name
- Study medication / IP number
- Manufacturing / Expiry date (as per local regulatory requirement)
- Storage conditions
- Subject number
- Investigator's name

Other information as per the local regulatory requirements may be added, e.g., caution statement for USA "Caution: New Drug-- Limited by Federal (or United States) law to investigational use."

For further details see the IP Manual.

6.1.4 Investigational Product Numbering

Each investigational product container will be uniquely numbered. The study medication number(s) will be recorded in the source documents.

6.1.5 Accountability Procedures for the Investigational Product

The Sponsor will supply sufficient quantities of the study drug to allow the completion of this study in an appropriate package deemed to maintain the integrity of the products. In accordance with GCP, the study site will account for all supplies of the study drug. The supplies will be stored as per label instructions until dispensed, in a secure, temperature-controlled, and locked environment with restricted access, accessible only to the pharmacist or other authorized person. Details of receipt, storage, assembly, dispensing, and return will be recorded. All unused supplies of study drug will either be destroyed by a designated vendor or will be returned to the study Sponsor at the end of the study in accordance with instructions by the Sponsor. The end of the study is defined as the time the last subject completes the last study visit.

6.2 Dosage and Dosage Regimen

6.2.1 General Dosing Instructions

See IP manual regarding instructions for dispensation of study drug at each visit.

Subjects will be instructed to self-administer the study drug once daily, [redacted]. The date and time of study drug self-administration will be recorded in the subject's daily diary. The study drug will be administered under the supervision of in-clinic staff at certain visits (Appendix 1). [redacted]

[redacted]. Alternate formulations under development will require different dosing instructions and preparation of matching placebos. Subjects are to bring the daily diary and remaining study drug and used / unused containers with them to each visit to allow for [redacted] count and compliance check.

6.2.2 Dose

In earlier versions of this protocol (Amendment 01 and 02), subjects were dosed on [redacted] (low dose) or [redacted] (high dose) of K0706 or matching placebo. The study continued with that formulation and dose until [redacted], at which point newly enrolled subjects were randomized to [redacted] (low

dose) or [redacted] (high dose) of K0706 or placebo [redacted] Subjects who started the study on [redacted] formulation were switched to the [redacted] dose for their corresponding dose group (placebo stays on placebo, [redacted]). Subjects who had a [redacted] dose reduction to [redacted] or to placebo (from placebo) remained on the same dose level of the [redacted] formulation. Subjects who had a dose reduction from [redacted] were discontinued from the study [redacted]

An [redacted] development may further displace the current [redacted] formulation. Transitions will occur in a blinded manner via the IWRS and will occur at the subject's subsequent visit.

[redacted]

6.2.3 Dose Holding and Dose Reduction Guidance for TEAEs

TEAEs (AEs occurring after the first dose of the study drug) considered mild (Section 8.5) should be managed supportively. For moderate or more severe TEAEs, the Investigator has the option to withhold the study drug for up to [redacted] weeks and then rechallenge the subject at the same dose if deemed safe or start the subject at a lower dose. Investigators will be allowed to reduce a subject's dose once during the trial, and it will be enacted in a blinded fashion via the IWRS. The dose may not be increased once it has been reduced. If the AE recurs, the dose can then be reduced (if not reduced already) or the subject should be withdrawn from the study. See the IP Manual for more details on dose reduction. For dose reductions, subjects' daily dose will be reduced in half from their current dose, though subjects on a placebo will remain on a placebo.

6.3 Warnings and Precautions

Potential adverse reactions from K0706 based on limited existing data, and similar medications, are described in section 2.2.6.

[redacted]. It occurred within the first [redacted]-day cycle. It is likely that this [redacted] was due to the intended effect of [redacted] reducing the numbers of [redacted] but it is not possible to rule out at this time that it may be seen in subjects without leukemia. [redacted] was not seen in subjects with PD treated for up to 2 weeks in study [redacted], though one subject [redacted] had a reduction in total [redacted] that resolved after stopping the study drug and was not felt to be an AE by the investigator. If [redacted] occurs, subjects will be at increased [redacted]. For [redacted] Once values have returned to normal, subjects may be restarted on the study drug at the same or lower dose if deemed safe by the investigator (Section 6.2.3).

6.4 Medication(s)/Treatment(s) Permitted and Not Permitted Before and/or During the Study

Concomitant medications are any medications taken by the subject other than the assigned study drug, and these will be recorded in the source document as concomitant medications.

Any medications (other than those excluded by the inclusion/exclusion criteria) that are considered mandatory for the subjects' welfare and that are not anticipated by the Investigator to be likely to interfere with the pharmacokinetics of K0706 may be given at the discretion of the Investigator.

Medications other than those specifically excluded in this study may be administered for the management of concomitant illness, AEs, or symptoms associated with the administration of K0706 as needed. These medications include, but are not limited to, analgesics, anti-nausea medications, antihistamine, antianxiety medications, and medication for pain management (narcotic agents are included). For nausea, medications that inhibit dopamine (e.g., metoclopramide, chlorpromazine) should be avoided.

6.4.1 Use of Medications for Parkinson's Disease (Symptomatic or Disease Modifying)

During the trial, subjects are not permitted to take any prescription, investigational, or over-the-counter medication for the symptomatic treatment of PD or disease modification (to slow the progression of PD). The only exception is an [redacted] inhibitor they are on at [redacted] (Section 4.2.2), though subjects are not permitted to increase the dose. If a subject stops the use of an MAOB inhibitor or switches to an equivalent dose of a different MAOB inhibitor during the study, the timing and reason should be noted, but the subject can continue in the study.

6.4.2 Use of Anti-clotting Agents

Serious bleeding events, including fatalities, have occurred in patients treated with K0706 in [redacted] (section 2.2.5), as well as other Abl TKIs used for leukemia. Cerebral hemorrhage and gastrointestinal hemorrhage were the most commonly reported serious bleeding events in studies of other Abl tyrosine kinase inhibitors, with most hemorrhagic events occurring in patients with Grade 4 thrombocytopenia. Most likely, the cause of bleeding in these subjects was disease progression, but until further information is available, caution is indicated in patients requiring medications that inhibit platelet function or anticoagulants.

6.4.3 Use of Substances Related to Specific Transporters

K0706 inhibits the transporters P-gp (p-glycoprotein) and Breast Cancer Resistance Protein (BCRP), so medications affected by these transporters should be avoided or used with caution. P-gp and BCRP transport substances out of the brain, so medications with CNS penetration and side effects should be avoided or used with caution, especially digoxin.

[redacted]

Reference:

[redacted].

6.4.4 Use of Substances Related to Specific Cytochrome Inhibitors

K0706 is only weakly metabolized by cytochrome P450 enzymes, so there is minimal concern about the use of inhibitors of these enzymes.

Based on preliminary investigation, K0706 may be an inhibitor of the enzyme CYP2C8, and further investigation is ongoing to confirm its inhibition potential. However, to be cautious, sensitive substrates of CYP2C8 with a narrow therapeutic index should be avoided or used with caution. Clinically significant CYP2C8 substrates include, but are not limited to those listed [redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

K0706 may have the potential to [redacted] CYP3A4 enzyme expression. Most common CYP3A4 [redacted] include drugs such as dexamethasone, anti-epileptic agents (e.g., phenobarbital and phenytoin), and St. John's Wort, among many others. The serum/plasma levels of concomitantly consumed medications that are substrates of CYP3A4 (i.e., metabolized by CYP3A4) may [redacted] and this may require a dose adjustment. Examples of concomitant drugs that may be so affected include many statins (e.g., lovastatin, simvastatin, atorvastatin), some antidepressants (e.g., venlafaxine, amitriptyline, citalopram, sertraline), antiplatelet-agents (clopidogrel) and calcium channel blockers (e.g., amlodipine, diltiazem). [redacted]

Subjects receiving such medications [redacted] by CYP3A4 should be closely monitored, and the dosage of such medications should be adjusted if necessary after consultation with their treating physician.

6.4.5 Use of Substances Related to Uridine Diphosphate Glucuronosyl Transferase (UGT1A1) Enzyme

K0706 may have the potential to [redacted] the uridine diphosphate glucuronosyl transferase (UGT1A1) enzyme. K0706 may [redacted] the drug levels of concomitant medications that are predominately metabolized by UGT1A1, which may lead to toxicities.

More commonly used drugs whose levels might increase without significant safety concerns include naproxen, estradiol, ethinylestradiol, raloxifene, and some statins (See extensive list https://go.drugbank.com/categories/DBCAT003871).

6.4.6 Additional Treatments Not Permitted

The following non-drug therapies must not be undertaken or administered during the study (or within 4 weeks before the start of study drug administration):

- [redacted];
- [redacted].
- Major surgery (excluding diagnostic biopsy)
- [redacted]

- [redacted]

All subjects will be questioned about the use of any pre-study and concomitant treatments that might interfere with the study outcome. All concomitant treatments must be appropriately recorded in the source documents and described in the eCRF.

6.4.7 Use of Calcium and Magnesium-Containing Medications and Supplements

In vitro data suggest that calcium may reduce the absorption of K0706 and therefore lead to reduced blood and brain concentrations. Therefore, subjects taking calcium or magnesium-containing medications or supplements should be requested to take those substances at a different time of day from K0706, ideally at least 2 hours apart. The sponsor is conducting additional studies to better understand the role of magnesium and calcium-containing substances in K0706 pharmacokinetics. If these studies reveal the effect to be non-significant, then sites will be notified in writing to notify the subjects that no restriction on their co-administration is necessary.

6.5 Procedure(s) for Monitoring Subject Compliance

Study medication will be dispensed by the site personnel. Dispensation will be documented in the drug accountability log or equivalent document. Subjects will be instructed to bring their daily diary and used and unused study drug containers at all scheduled visits to allow for [redacted] count and compliance checks. If the subject fails to bring the study drug container on the designated day, non-compliance to the protocol will be recorded. Subjects will also be asked to record in a daily diary the date and time at which they took the study drug and their adherence to [redacted]. For scheduled visits greater than 4 weeks apart, subjects will be called and asked about compliance with the study drug.

7.0 ASSESSMENT OF EFFICACY

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments (Appendix 1). The rationale for the choice of these outcome measures is in Section 2.3.

7.1 MDS-UPDRS

MDS-UPDRS (Goetz et al., 2008) Parts I and II can be performed by a clinician or a coordinator; Part III must be performed by a trained clinician who has completed the MDS formal training program [redacted] within 1 year of their first subject (exceptions to this may be made in writing by the Sponsor). Part III should be performed by the same examiner at all visits. The examiner performing the scale will place their name on the scoring form to track who performed it.

At the Part 1 Screening visit, only the MDS-UPDRS tremor severity (not constancy) items will be performed (items 2.10, 3.15, 3.16, and 3.17). They will be performed by a trained clinician, though not necessarily the same clinician who will perform the remainder of the assessments, i.e., at later visits.

Performance of MDS-UPDRS Part III may be video-recorded for one or more assessments per clinician. Whenever possible, the video record will be transmitted to an expert rater who will then give feedback to the clinician on performance and scoring of the assessment to improve future testing. Typically, the clinician's first subject's first assessment [redacted] may be recorded, though subsequent subjects or visits may be recorded if requested by the expert rater to ensure implementation of feedback or as requested by the Sponsor. Final decisions on the scoring of subjects will be with the clinician at the site.

Subjects will be notified about the purpose and use of the video and be given the opportunity to decline to have it performed. Sites, where sharing of subject video is not permitted (e.g., by the ethics committee or regulatory authority) will not participate in video recording the assessment.

This video recording for quality assurance is useful as the MDS-UPDRS Part III is a relatively new scale, and accurate performance and scoring are essential for the validity of the trial. Recording of the subjects' face and body is required to score the test accurately (e.g., facial expression is scored). To limit the loss of privacy, the video will only be accessible to staff at the site where the subject is participating and to the expert rater and their video support team. Video will be recorded and stored within a Health Insurance Portability and Accountability Act and General Data Protection Regulation Act-compliant smartphone application that prohibits local storing of the video on the phone and therefore sharing of the file with other applications (see separate manual for instructions). The application will permit a full audit trail of everyone who accessed every video file.

7.2 CGIS

The CGIS (Appendix 4) should be scored by the same examiner who performs the MDS-UPDRS Part III, which should be done by the same examiner at all time points. The examiner should score the subject's severity of Parkinson's disease using all information available about the subject [redacted] Scoring should only be based on the subject's symptoms and signs related to Parkinson's disease ([redacted]

7.3 Time to Initiation of Symptomatic PD Medications

This will be defined by the day the subject reports they begin taking symptomatic PD medications. These medications include: levodopa, dopamine agonists, amantadine, or an MAOB inhibitor started or when the dose is increased after randomization.

7.3.1 EQ-5D-5L (HRQoL Measure)

The ED-QD-5L is available in multiple languages and is filled out by the subject following the instructions in the document.

7.4 DaT SPECT

Subjects in the Biomarker sub-study will have a DaT SPECT scan performed at visits described in the Schedule of Assessment as an exploratory outcome measure. DaT SPECT scans are to be performed using the ^{123}I-FP-CIT tracer; other tracers may be approved with written approval from the Sponsor. Scans will be uploaded to the Sponsor or Sponsor's collaborating imaging laboratory (see relevant manual) for quantitative analysis.

7.5 SCOPA-AUT

The SCOPA-AUT is an instrument that is used to evaluate autonomic symptoms in patients with Parkinson's disease as well as patients with MSA. The scale is self-completed by patients and consists of 25 items assessing the following domains: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2 items for men and 2 items for women). The development of the SCOPA-AUT is part of a larger research project, the Scales for Outcomes in Parkinson's disease (SCOPA), in which practical and clinimetric sound instruments for all relevant regions in PD are selected or developed.

[redacted]

[redacted]

7.7 Blood Tests of PD Progression and K0706 Target Engagement

For subjects who provide consent in Part 1, blood will be collected for genetic markers and future tests at the Baseline visit and at other visits as described in the Schedule of Assessments. Details of the collection and processing of blood will be in the separate lab manual. The specific genetic and other future tests (e.g., proteins, nucleic acids, metabolites, or sugars) to be tested have not yet been determined at the time of the writing of the protocol. Markers tested will be ones that have been shown to link to PD or efficacy or safety of K0706 and may include substances associated with PD pathology, such as misfolded or phosphorylated α-synuclein, or may include markers of the types of cell death that occur in PD. Exploratory analyses may be performed at a later date by the Sponsor or collaborating entity.

7.8 CSF Biomarkers of PD Progression and K0706 Target Engagement

[redacted] Subjects will need to consent to have future tests of the CSF performed. Details of the collection and processing of CSF will be in the separate lab manual. The specific biomarkers (e.g., proteins, nucleic acids, metabolites, or sugars) to be tested have not yet been determined at the time of the writing of the protocol. Markers tested will be ones that have been shown to link to PD or target engagement of K0706 and may include substances associated with PD pathology, such as misfolded or phosphorylated α-synuclein, or may include markers of the types of cell death that occur in PD. Exploratory analyses may be performed at a later date by the Sponsor or collaborating entity. If subjects experience an adverse event related to the first or second spinal tap, they may be permitted to skip the subsequent spinal tap(s).

7.9 Pharmacokinetic Analysis

Plasma and CSF samples will be sent to the sponsor or a collaborating entity in a coded fashion and analyzed for levels of K0706 and any relevant metabolites. Details are in the Lab Manual.

[redacted]

[redacted]

8.0 ASSESSMENT OF SAFETY

8.1 Description of Safety Parameters

The following safety parameters will be assessed during the study as per the Schedules of Assessments and are described below:

8.1.1 Vital Signs Measurements

Blood pressure and pulse will be measured at each clinic visit throughout study participation. Measurements will be made with the subject in a supine position for at least 5 minutes, followed by standing after 3 minutes. Weight will also be measured at each visit. Results will be evaluated against pre-specified criteria for clinically significant change.

8.1.2 Clinical Laboratory Testing

The following tests will be performed by a central laboratory:

Hematology

- Hemoglobin, hematocrit
- Total WBC count
- Automated differential WBC count with reflex to manual differential if abnormality seen
- Platelet count

Chemistry

- Sodium
- Potassium
- Chloride
- CO_2
- Glucose
- Blood Urea Nitrogen (BUN)
- Creatinine
- Calcium
- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Alkaline phosphatase
- Total bilirubin

- Total protein
- Albumin
- Amylase
- Lipase

Lipid Profile

- Total Cholesterol
- High-Density Lipoprotein (HDL)
- Low-Density Lipoprotein (LDL)
- Triglyceride

Urinalysis

- Routine testing, including dipstick for pH, specific gravity, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase
- Microscopic examination of the sediment only if abnormality seen on routine tests

Serology

- HIV, hepatitis panel

Results for clinical laboratory parameters will be evaluated for clinically significant values according to pre-specified criteria. Laboratory tests may also be repeated between scheduled visits at the discretion of the Investigator. In addition, repeat testing should be performed at the end of the study to follow any clinically significant abnormality to resolution/stabilization. Clinically significant results will be reported as AEs.

8.1.3 12-Lead ECG

12-lead ECG measurements will be collected in triplicate in a supine position after 5 minutes of rest. Within the triplicate series, ECGs are to be spaced no more than 2 minutes apart. The QTc data will be corrected using Fridericia's correction. In addition to the QT interval, the following parameters will be collected: PR interval, QRS, and ventricular rate, the presence of T-waves.

Clinically significant abnormalities will be reported as AEs.

8.1.4 Physical Examination

A complete physical examination is to be performed at Screening. It must include, at minimum examination of skin, musculoskeletal, neurological, cardiovascular, and respiratory systems, with other systems optional. At other visits, targeted physical examinations are to be performed only as necessary in response to AEs.

[redacted]

8.2 Definitions of Adverse Events

8.2.1 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans in a clinical investigation, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Untoward medical experience occurring during medication-free pre-treatment periods does not meet the above-mentioned definition of an AE. Nevertheless, they have to be documented in the same way as AE. Each subject will be queried generally for the occurrence of adverse experiences prior to study drug administration and throughout the subject's participation in the study. During and following a subject's participation in this study, the Investigator has to ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values. The subject will be treated and/or followed up until the symptom(s) return to normal, as judged by the Investigator.

8.2.2 Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.), convulsions that do not result in hospitalization or the development of drug dependency or drug abuse.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

*A planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social/logistic reason) is not to be considered as SAEs.

8.3 Pregnancy

Male subjects enrolled in the study will be instructed to avoid the passage of semen to their partner by using an acceptable contraceptive method to avoid fathering a child. If a female subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedures, and the subject will be withdrawn from the study immediately. If a female partner of a male subject becomes pregnant during the study, the medical event will be recorded appropriately with the 'Pregnancy Reporting Form' and submitted to the Sponsor's safety physician/CRO. All pregnancies shall be followed every three months until the outcome and up to one-month post-delivery to assess the functional status of the child. If any SAE occurs during pregnancy, then it will be reported using SAE forms as per section 8.6. Any congenital abnormalities or birth defects in the newborn will be followed three months post-delivery.

8.4 Eliciting, Documentation and Reporting of Adverse Events

Information on AEs will be derived by questioning the subjects in general terms (e.g., "How do you feel?" or "How have you been feeling since the last questioning?" respectively), by subjects' spontaneous reports, or by observation.

AEs will be documented on the source document. Trained monitors will check the entries on the source document. The AE will be transcribed to the AE eCRF-sections. The following information will be given for each AE: Description of the AE, start date, stop date, severity, pattern, action taken, outcome, seriousness, dose of study drug, and relationship to the study medications. The dose of the study drug assigned to an AE will be the dose the subject was assigned to take on the date the subject reported the AE first began.

The AE / SAE collection period for safety surveillance begins when the subject signs the Informed Consent Form and continues until the follow-up visit, or if the follow-up visit does not occur within the defined time window, then 30 days post the end of treatment visit or 30 days post the last dose of study drug for subjects with early discontinuation.

8.5 Rating of Adverse Events

The following system will be used to assess the treatment relationship: Unrelated, unlikely, possibly, probably, and certainly.

TERM	DEFINITION	CLARIFICATION
Unrelated	Those AEs which, after careful consideration, are clearly due to extraneous causes (medical history, demography details, disease, environment, *etc*.)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from the administration of the drug. 2. It could also be explained by the patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals, including food-drug interactions
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from the administration of the drug. 2. It could also be explained by the patient's concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.	1. It follows a reasonable temporal sequence from the administration of the drug. 2. It could not be readily explained (unlikely) by the patient’s concurrent disease, environmental factors, medical history, and other concomitant drugs or chemicals, including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No rechallenge information is available or possible.

TERM	DEFINITION	CLARIFICATION
Certainly	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to the withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	1. It follows a plausible time sequence to drug intake; this means that there is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically, e.g., pharmacokinetics and type of reaction. 2. It could not be explained by the patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals, including food-drug interactions (i.e., no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance, 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. *This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation).* 5. It reappears on re-administration of the drug (only if ethically correct i.e., in case of non-serious and easily treatable AEs).

The severity of an AE is characterized as:

- Mild: AE, which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE, which prevents normal daily activities.
- Life-threatening: The subject is at risk of death due to the AE as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.
- Death: Death related to AE

Event outcome at time last follow-up is recorded is categorized as "Fatal", "Resolved", "Resolved with Sequelae", "Resolving", "Not Resolved", or "Unknown".

Action taken with respect to study drug is categorized as "none", "study drug discontinued / withdrawn", "study drug discontinued and restarted", "dose reduced", "required concomitant medication", "required procedure", or "other".

Assessment of Expectedness will be determined by the version of the IB effective at the time of onset of the adverse event.

8.6 Documentation and Reporting of Immediately Reportable Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's safety physician / CRO to file a report which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24 hours of his / her awareness to the Sponsor's safety physician / CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE Report Form in the eCRF and source documents.

As much information as possible should be supplied at the time of the initial report with at least the following information using SAE Report Form.

- Name, address, and telephone number of the reporting Investigator
- Investigational product(s)
- Protocol number
- Subject identification number, initials, sex, and date of birth
- Description of the AE, reason considered serious, measures taken, and outcome (if resolved)
- Likelihood of drug causation of the AE was assessed by the Investigator.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor's safety physician/CRO.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by e-mail to the Sponsor's safety physician/CRO.

Relevant pages from the source document and eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor's safety physician / CRO may have on the SAE. This is necessary to ensure prompt assessment of the event by the Sponsor's safety physician to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the Sponsor's safety physician / CRO.

8.6.1 Serious Adverse Events/Suspected Unexpected Serious Adverse Reactions (SUSARs) Reporting to Regulatory Authorities/EC/IRBs/Participating Investigators

The Sponsor's Safety Physician/CRO shall notify the applicable Regulatory Authorities of any SAE/SUSAR, as per local Regulatory Authorities' guidelines and timeframe specified as per local regulation.

All participating Investigators, EC/IRB, and other stakeholders shall be notified of any SAE/ SUSAR by CRO as per local regulatory requirements.

The contact details of the Sponsor's Safety Physician and CRO's Medical Monitor are listed on Page 5.

Progress reports: Where required by 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/EC annually or more frequently, as requested. The investigator should promptly provide written reports to the Sponsor, the IRB or EC, 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 the subjects.

8.7 Analysis of Adverse Events

The Sponsor and/or CRO will perform an approximately monthly review of safety data. Any suspicious signals will be analyzed further.

If approximately 15% or more of subjects have a dose reduction or a similar degree of concern regarding adverse events, an appropriately qualified independent data safety monitoring board (DSMB) will be convened to review the unblinded safety data. Should the DSMB recommend a dose reduction, ongoing subjects who have not already had a dose reduction would undergo a dose reduction as detailed in Section 6.2.3), and newly enrolled subjects would be dosed at 1/2 of the current dose of the [redacted] formulation; no further dose reductions would be allowed. Further use of the DSMB will depend upon their recommendations and any future safety signals.

8.8 Follow-Up of Subjects After Adverse Events (Serious and Non-Serious)

8.8.1 Unresolved Events

If an AE/SAE is continuing when the subject has completed the study, the event must be followed and reported until resolution/stabilization as per the medical judgment of the Investigator.

8.8.2 Post-study Events

Any AE/SAE that occurs up until the follow-up visit, or if the follow-up visit does not occur within the defined time window, then 30 days post the end of treatment visit or 30 days post the last dose of study drug for subjects with early discontinuation, should be reported and included in the safety analysis of the study.

Any AE/SAE which occurs past this date will be reported if it is considered related to study drug by the Investigator.

9.0 STATISTICAL ANALYSES

A detailed SAP will be written and finalized in advance of any database lock. The plan will follow the outline of the statistical analyses, including but will not be limited to points presented below, and all the details necessary to complete the statistical analyses will be provided.

Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages. All subject data will be presented in by-subject data listing(s). For time-to-event variables, [redacted], [redacted], and other [redacted] will be presented.

9.1 Subject Disposition

Subject disposition will be based on all subjects who are screened for this study. The number of subjects randomized, completed, and the number discontinuing at each visit will be presented. A summary of reasons for early discontinuation will be provided. Reasons for early discontinuation include adverse events, lack of efficacy, protocol deviation or non-compliance with IP, subject's withdrawal of consent, or other (to be specified by the Investigator). The number of subjects in each of the [redacted] (Parts 1 and 2), PP, PK, and safety analysis sets will be presented.

9.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively overall and by treatment in the 'all randomized subjects' set, comprising all subjects randomized in the study. The following demographic and Baseline variables will be included:

- Age (years)
- Gender
- Race
- Ethnicity
- Weight (kg)
- Weight category (≤90 kg or >90 kg)
- Height (cm)
- BMI (kg/m^2)
- Baseline MDS-UPDRS (Parts I, II, and III)

9.3 Study Drug Exposure and Compliance

Study drug exposure will be evaluated using the [redacted] formulation dosing separately and as pooled per visit total number of doses administered for Part 1 and [redacted] Part 2. All exposures will be summarized using nominal units (mg) as well as equivalence-adjusted units in periods for each study part and overall for the entire treatment

period. The number and percent of doses administered per subject and the number of subjects with doses administered at each scheduled visit will be summarized using descriptive statistics by treatment arm (Part 1 and Part 2 separately) and in total for the Safety Population.

Cumulative observed exposure will sum per visit for nominal and equivalence-adjusted dosing separately at each visit, study part, and overall by formulation and as pooled across both formulations as applicable.

For Part 1, the percentage of doses administered per subject will also be summarized descriptively, defined as the total number of doses received per visit and overall in Part 1 divided by the total planned dose per visit and overall in Part 1, expressed as a percentage. Part 2 will be handled similarly, and the total overall in the pooled periods will also be described similarly.

Relative dosing intensity will be calculated as the cumulative observed exposure per visit, study part and overall divided by the expected per visit, study part, and overall exposure, respectively. The result will be expressed in units of percentage.

Incomplete [redacted] dosing and its impact on exposure and compliance metrics will be evaluated as a potential protocol deviation prior to unblinding for any planned analysis. If confirmed, relevant exposure and compliance metrics will be adjusted accordingly.

All study drug administration data will be listed by subject.

9.4 Prior and Concomitant Medications

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the World Health Organization (WHO) Drug Dictionary. The incidence of concomitant medication usage will be summarized for each therapeutic drug class and each preferred drug name. Prior medications will include medications with a documented stop date/time prior to the first dose of IP. Concomitant medications are those with start date/time on or after the date/time of dosing or that started prior to the date/time of dosing but are indicated as continuing into the treatment period. Any medications with partial start and/or stop dates will be considered concomitant if the assignment is uncertain.

9.5 Analysis Populations

Part 1 (Week 0 to Week 40) and Part 2 (Week 40 to Week 80)

Intent-To-Treat Population: [redacted]

Per Protocol Population: The Per Protocol (PP) population comprises all subjects in the [redacted] population who have completed the Part 1, 40-week placebo-controlled treatment without any major protocol deviation that could impact data interpretability for the primary efficacy endpoint.

[redacted]:

- any violation of important entry criteria
- non-compliance with study medication in Part 1 (i.e., missed multiple successive daily doses of study medication or partial powder doses),
- discontinuing prior to the Week 4 visit, receiving a misallocated medication kit in Part 1,
- use of prohibited medication, and
- meeting specific exclusion criteria (e.g., having an underlying medical condition that would interfere with evaluating MDS-UPDRS).

The PP population will be used as a supportive analysis of primary and secondary endpoints for Part 1 Stage 2 only.

Safety Population: The safety population will be all subjects who were randomized and received at least one dose of study medication, [redacted]

Pharmacokinetic Population: The pharmacokinetic population will include all subjects who received at least one dose of the study drug [redacted]

9.6 Efficacy Analysis

Analyses for both Part 1 and Part 2 are described. Endpoints to be analyzed are described in Table 9-1.

Table 9-1: Efficacy Analyses

Endpoint	**Endpoint status: Primary / Secondary / Exploratory**	[redacted]	[redacted]
MDS-UPDRS Part III score	Primary	[redacted]	[redacted]
MDS-UPDRS Part III score	Primary	[redacted]	[redacted]
MDS-UPDRS Part I, Part II, Part III sub-	Secondary	[redacted]	[redacted]

Endpoint	Endpoint status: Primary / Secondary / Exploratory	Primary/Secondary Analysis	Sensitivity Analysis Method
scale, sum of Parts II and III, sum of Parts I, II and III			
Symptom med TTE	Secondary	[redacted]	[redacted]
EQ-5D-5L	Secondary	[redacted]	[redacted]
Skin biopsies	Secondary	[redacted]	[redacted]
CGIS	Secondary	[redacted]	[redacted]
SCOPA-AUT	Secondary	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
DaT SPECT	Secondary/Exploratory	[redacted]	[redacted]
MDS-UPDRS Parts I, II w/ alternate covariates	Secondary	[redacted]	[redacted]
Evaluation of slopes of MDS-UPDRS (Part III, and sum of Parts II and III)	Exploratory	[redacted]	[redacted]
Proportion of patients starting symptomatic treatment	Exploratory	[redacted]	[redacted]

[redacted]

9.6.1 Primary Endpoint (Part 1)

The primary endpoint is the change from baseline to Week 40 in the MDS-UPDRS Part III total score.

9.6.1.1 [redacted] and Method of Estimation (Part 1)

This trial seeks to clarify the efficacy of K0706 in delaying the progress of PD in the ideal scenario of [redacted] adherence to the assigned 40-week treatment regimen dosed once daily in all randomized subjects. It is thus appropriate to use the [redacted] for the primary efficacy analysis. The primary estimand is described by five attributes as follows.

- **Treatment**: the treatment condition of interest includes the [redacted] high dose and the [redacted] low dose of K0706 in [redacted] administered once daily for 40 weeks. The alternative treatment condition to which the comparison will be made is Placebo [redacted] administered once daily for 40 weeks.

- **Target Population**: subjects aged ≥ 50 years in whom an initial diagnosis of PD was within 3 years of the screening visit, who score on a modified Hoehn and Yahr stage [redacted] 2, [redacted] who meet the protocol-specified inclusion and exclusion criteria.
- **Endpoint**: Change from Baseline to Week 40 in the MDS-UPDRS Part III total score
- [redacted] follow-up prior to Week 40.
- **Population-level summary**: difference in endpoint means between each of the two K0706 treatment arms (high dose, low dose) and placebo treatment arm.

Estimation for the [redacted] will be carried out as follows.

Mean changes from baseline in the MDS-UPDRS Part III total score will be analyzed [redacted] The analysis will include the treatment arm, analysis visit, region, baseline MAOB inhibitor user status (yes/no), and the interaction term of treatment by analysis visit as the fixed, categorical effects, and will include the interaction term of baseline Part III score by analysis visit as the continuous, fixed covariates. An unstructured covariance structure will be used to model the within-subject error. [redacted]

[redacted] to estimate the denominator degrees of freedom. Three contrasts of group means (i.e., the difference in least-square means for each active dose and the pooled dose of the K0706 *vs.* placebo) at Week 40 will be estimated from the interaction term of treatment by analysis visit [redacted]. These contrasts at Week 40 will serve as the primary comparisons. [redacted]

9.6.2 Analyses of the Primary Efficacy Endpoint [redacted]

[redacted]. [redacted] proposed

clinical criteria for dividing [redacted] patients into "[redacted]. The proposed criteria for the mild motor-predominant subtype will be adapted to define Subgroup A for the Proseek trial. The Proseek cohort is considerably similar in demographics and baseline disease characteristics to the de novo PD cohort of the PPMI study. This similarity justifies the use of the subtype criteria developed in [redacted] Specific criteria will be specified in the SAP. Per [redacted], the intermediate and diffuse malignant subtype had faster PD progression compared to the mild motor-predominant subtype. Thus, [redacted] is considered at risk of faster PD progression relative to its complement.

[redacted] is determined by having baseline serum NfLvalue ≥ 13 pg/mL, which is the mean NfL from the baseline data of the de novo PD patients of the PPMI study. Several studies (including [redacted]) reported positive correlations between serum NfL value and clinical measures of PD severity. Built on the longitudinal data of the de novo PD patients in the PPMI study, the predictive modeling of [redacted] quantified that for each increase of 10 pg/mL in serum Nfl at baseline, there was an yearly increase of 0.52 points in the MDS-UPDRS Part III score [redacted]

The [redacted] analysis of the primary efficacy endpoint performed on the overall sample will be repeated for the two subgroups. Multiplicity adjustment will be applied to the testing of the same primary efficacy endpoint in 3 populations (i.e., the overall sample, Subgroup A, and Subgroup B). See Section 9.10.

9.6.3 Secondary Endpoints (Part 1)

Secondary endpoints in Part 1 include the following:

- Change from baseline to Week 40 in the sum of the MDS-UPDRS Parts II and III total scores.
- Change from baseline to Weeks 8 through 40 in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, and Part III sub-scores.
- Change in MDS-UPDRS grand total score (sum of Parts I, II, and III) from the baseline.
- Evaluation of slopes of the mean MDS-UPDRS Parts II and III scores over time during Part 1 by treatment group.
- Time from the first dose in Part 1 to initiation of symptomatic PD medications
- Change in HRQoL using the EQ-5D-5L from Baseline to Week 40
- Change in CGIS from Baseline to Week 40
- Change in the SCOPA-AUT from Baseline to Week 40
- Pharmacokinetics – Plasma and CSF levels of K0706 and any relevant metabolites.

Comparison of MDS-UPDRS Part III total score among treatment groups at all other time points are secondary. A similar [redacted] approach will be used for the secondary analyses of the MDS-UPDRS Part IA, Part IB, Part I, Part II, Part III sub-domain scales, and the sum of the individual scales (i.e., Parts II and III, Parts I, II and III). Note that any MDS-UPDRS assessments captured for a subject after the start of symptomatic PD medications (e.g., at the ED visit for a subject leaving the study early) are treated as missing when implementing the [redacted] approach. These assessments, however, may be utilized as part of an exploratory analysis. [redacted]

In addition to these analyses, all modeling and testing will be repeated on the Per Protocol population as secondary analyses, along with alternative models which implement multiple imputation methods to account for missing observations at various time points.

A random coefficients regression analysis with random terms for intercept and slope (i.e., time is treated as a linear random effect) will be used to estimate mean changes from baseline in UPDRS Part III total score over time (in weeks) during Part 1 by treatment group, and the linear trend of the estimated mean change-from-baseline in the MDS-UPDRS Part III total score will be displayed graphically. This analysis will be repeated for the sum of Parts II and III total scores.

A secondary outcome measure will be defined as the waiting time from the first administration of the study drug in Part 1 to the time-point when a subject begins taking symptomatic PD medications. These symptomatic medications include levodopa, dopamine agonists, amantadine, or initiation or increase in the dose of an MAOB inhibitor. If a subject does not go on any symptomatic PD medications through completion of Part 1, the waiting time variable will be censored at the time of the last available data point. This secondary endpoint will be summarized and analyzed by treatment group [redacted] The proportion of non-censored subjects within each treatment group will also be compared [redacted]

The EQ-5D-5L score, CGIS score, and the SCOPA-AUT score will be summarized within each treatment group and will be tested for differences between groups for change from baseline to end of Part 1 [redacted]. As with the MDS-UPDRS endpoints, all assessments captured after the start of symptomatic PD medications will be treated as missing values for the Part 1 analyses.

K0706 plasma and CSF concentration data will be summarized by treatment group and assessment time-point by using descriptive statistics (such as number of subjects, mean, standard deviation, geometric mean, coefficient of variation (CV%), minimum, median, and maximum values).

9.6.4 Exploratory Endpoints (Part 1)

Exploratory endpoints for Part 1 include the followings:

- Skin pathological findings that correlate with PD, [redacted]
- Blood and CSF levels of emerging biomarkers ([redacted]) that predict or track PD progression or target engagement of K0706.
- Brain DaT SPECT - an imaging tool that is a marker of dopaminergic cell health.
- [redacted]

[redacted] parameters will be summarized descriptively by treatment group and time point (visit). [redacted] parameters or characteristics that may be predictive of PD progression in terms of MDS-UPDRS scores, such as genetic tests, blood and CSF biomarkers, DaT SPECT quantitative results of DaT SPECT scans will be examined by using summary statistics, graphical display [redacted]), and linear models ([redacted]). When relevant based on existing data, some of these outcomes may be treated as secondary endpoints and, hence, summarized and tested for differences between treatment groups. [redacted]. These methods will be described in detail within SAP.

[redacted]

9.6.5 Efficacy Endpoint Analyses (Part 2)

All efficacy analyses in Part 2 will be considered secondary or exploratory.

Part 2 efficacy analyses will be performed for the following secondary endpoints:

- Change from Week 40 (Baseline for Part 2) to Week 76 of the long-term extension study in the MDS-UPDRS Part III score
- Change from Week 40 (Baseline for Part 2) to Week 76 of the long-term extension study in MDS-UPDRS Parts II and III sum score
- Change from Week 40 (Baseline for Part 2) through Week 76 in MDS-UPDRS Part IA, Part IB, Part I total, Part II total, and Part III sub scores
- Change in MDS-UPDRS grand total score (sum of Parts I, II, and III) from Week 40 (Baseline for part 2) through Week 76
- Time from Week 40 (Baseline for Part 2) to the initiation of symptomatic PD medications in the long-term extension study

Part 2 efficacy analyses will be performed for the following exploratory endpoints:

- Change in the mean MDS-UPDRS Parts I, II and III scores between the early-start and delayed-start groups at 76 weeks
- Evaluation of slopes of the mean MDS-UPDRS Parts II and III scores over time in part 2 for the early-start group as compared to the delayed-start group.
- The proportion of patients starting symptomatic PD treatment

The change from Part 2 baseline value in the MDS-UPDRS assessments (including Part IA score, Part IB score, Part-I total score, Part II total score, Part III sub-domain scores, Part III total score, Parts II and III sum score, and Parts I, II and III sum score) across all time points (visits) up to the Week 76 visit will be summarized by treatment group (early-start of K0706 Low Dose, early-start of K0706 High Dose, and delayed-start of K0706) Mean difference in the above-mentioned MDS-UPDRS scores between treatment groups will be extracted from the [redacted] models for each scheduled visit in Part 2.

The same random coefficients [redacted] analysis for Part 1 (see Section 9.6.3) will be used for Part 2, with Part 2's treatment groups being the early-start of K0706 (that is, the previous Low Dose group and High Dose group in Part 1) and the delayed-start of K0706 (that is, the previous Placebo group in Part 1). Note that Part 2's baseline will be used as the baseline value for this analysis. Time (in weeks) from first dose of the study drug in Part 2 to the initiation of symptomatic PD medications in Part 2 will be analyzed by treatment group (the early-start with Low Dose, early-start with High Dose, and the delayed-start of K0706) by using the [redacted] method.

The difference and its [redacted] CI between treatments in the binomial proportion of subjects starting symptomatic PD medication in Part 2 will be calculated for the K0706 early-start group vs the delayed-start group.

[redacted]

9.7 Pharmacokinetic Analysis

Blood in all subjects, [redacted] will be analyzed for levels of K0706 and any relevant metabolites. Exploratory analyses will be performed to determine the relationship between these values and the safety and efficacy endpoints. The PK analysis population will be used.

9.8 Safety Analyses

The analysis of safety parameters will be based on the Safety Population. In general, missing safety data will be analyzed without imputation or substitution. Treatment-emergent events will be described for Part 1 separately and for Parts 1 and 2 overall. Events will be considered

treatment-emergent if first appearing or worsening following initiation of study therapy and within 4 weeks after study therapy discontinues. See additional details in the SAP.

9.8.1 Adverse Event Analysis

An AE is considered treatment-emergent if it was not present prior to the first dose of treatment or, if it was present, it worsened in severity or treatment attribution. AEs will be coded using the most recent version available of Medical Dictionary for Regulatory Activities (MedDRA) and assigned severity levels as described in Section 8.5.

The number and percentage of subjects reporting TEAEs will be tabulated by severity, system organ class, causality, and preferred term, with a breakdown by treatment group. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study drugs.

Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study drugs, will be listed. AEs will also be summarized by actual dose at the time of onset of the AE to account for possible dose reductions over the course of the study.

9.8.2 Clinical Laboratory Evaluation, Vital Signs Analysis, and ECG

Individual data for clinical laboratory, vital signs, and ECG parameters will be presented in tabular form with descriptive statistics, including the number of observations, arithmetic mean, median, standard deviation, and range (minimum and maximum) as appropriate. The data will be summarized by treatment groups and scheduled visits. For the laboratory safety data, out-of-range values will be flagged in the data listings, and a list of clinically significantly abnormal values will be presented. Individual results will be reviewed for any treatment-emergent changes of possible clinical significance.

9.8.3 Physical Examination

Findings from the physical examination at baseline will be summarized by the treatment group. A listing of physical examinations will also be provided.

[redacted]

9.8.5 Other Safety Analysis

Concomitant medications will be coded using the current version of the WHO drug dictionary. The number and percentage of subjects taking concomitant medications will be summarized by treatment group.

9.9 Sample Size and Power Calculations

Sample size estimates for this study are based on information from [redacted] subjects in an ongoing large cohort study (Parkinson's Progression Markers Initiative) who remained off symptomatic medication from study entry to the [redacted]-month visit. In these subjects, the mean change from baseline in the sum of the MDS-UPDRS Parts II and III was [redacted] points with a standard deviation of [redacted] points at the [redacted]-month assessment. The results from a clinical trial called the [redacted] trial ([redacted]) were also analyzed. In this study, a group of 70 early-stage PD subjects receiving a placebo showed a change on the sum of the UPDRS Parts II and III (older but similar scale to the MDS-UPDRS) of [redacted] points with a standard deviation of [redacted] points over [redacted] weeks (data for analysis obtained from the National Institute of Neurological Disorders and Stroke, National Institute of Health, United States of America).

For this study, assuming [redacted] improvement at Week 40 for the K0706 group mean over the placebo group mean of [redacted] in change-from-baseline MDS-UPDRS Parts II and III sum score, the target delta is [redacted]. [redacted]

Assuming a common standard deviation across treatment groups [redacted], a sample size of [redacted] in the high-dose and placebo groups will be required to achieve [redacted] power. The comparison for the low-dose group ([redacted]) will also have [redacted] power under the same assumptions. Additional subjects may be enrolled.

With an evaluable sample size of [redacted], the target [redacted] of [redacted] is considered to be the minimal improvement that would be considered clinically meaningful.

[redacted]

Based on the data of PASADENA trial in early PD subjects ([redacted] the contribution of the MDS-UPDRS Part II to the effect size is expected to be negligible or negative, thus by excluding Part II and using Part III alone as the primary efficacy outcome is expected to have at least the same power compared to using the sum of Parts II and III.

Sample size estimates for Part 2 [redacted] consideration but are based on the [redacted] successfully and elect to participate in ongoing treatment.

9.10 Planned Three-Stage Analysis

The data for this study will be evaluated in three stages as follows:

Stage 1 - [redacted]. The study team will remain blinded until the completion of Part 1. Details will be provided in the SAP along with the [redacted]

Stage 2 – At the completion of Part 1. The primary efficacy analysis will be performed at this stage. The primary efficacy analysis will be performed when all the planned [redacted] subjects have completed Part 1 or been discontinued early from Part 1. The primary efficacy endpoint will be analyzed together with all other efficacy and safety endpoints or outcomes. An overall alpha of 0.099 (two-sided) will be allocated to the primary efficacy analysis at this stage. A parallel gatekeeping procedure will be used to test the combined family of 6 hypotheses (i.e., cross-combination of 2 dose comparisons and 3 patient populations) pertaining to the primary endpoint, aiming for a strong control of the familywise error rate at 9.9% level (two-sided). The combined family for inferences includes 2 comparisons (High Dose vs Placebo, Low Dose vs Placebo) in Gate-1 family concerning the overall sample, and the same 2 comparisons in Gate-2a family concerning [redacted] and the same 2 comparisons in Gate-2b family concerning [redacted]

Stage 3 – At the completion of Part 2. This analysis will evaluate the long-term extension data and will constitute the final analysis of Part 2. The primary efficacy endpoints of interest for Part 2 is the change from Part 2 baseline to Week 76 in the MDS-UPDRS Part III score. The change from Part 2 baseline in the MDS-UPDRS assessments (including Part I score, Part IA score, Part IB score, Part II score, Part III score, Part III sub-domain scores, Parts II and III sum score, and Parts I, II and III sum score) across all time points up to Week 76 will be summarized by treatment group.

10.0 STUDY MANAGEMENT

10.1 Monitoring

On-site or remote monitoring will be performed during the study. Remote monitoring may be necessary for data sites due to the impact of a pandemic (COVID-19) or natural disaster. The monitor will ensure that the study is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedure (SOP), GCP, and the applicable regulatory requirements. The monitor will check the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The monitor will follow written SOPs as well as those procedures that are specified by CRO for monitoring a specific study. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

Considering the COVID pandemic situation, remote monitoring will be allowed wherever possible.

The Investigator will provide direct access to source data/documents for study-related monitoring. It is important that the Investigator and/or other staff are available at these visits. The Investigator should maintain source documents such as laboratory reports, history, and physical examination reports, etc., for possible review.

10.2 Documentation at the Study Site

Data relating to the study will be documented in the source documents and eCRFs. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the source documents and eCRFs. Any change or correction to a source document or eCRF will be dated, initialed, and explained (if necessary) and will not obscure the original entry.

At the beginning of the study, a site master file will be established at the investigational site. The Investigator will maintain the study documents as specified in the ICH Guideline of GCP and as required by the applicable regulatory requirements. The Investigator will take measures to prevent accidental or premature destruction of these documents. The Investigator will permit study-related monitoring, audits, and IRB/EC or regulatory inspection, providing direct access to source data or documents.

Prior to the start of the study, a Signature and Delegation Log will be completed showing the signatures and hand-written initials of all study staff. This log allows the PI to delegate study tasks to individual members of his/her team, identifies site staff participating in the study and the start/stop times of their participation, and provides a handwriting sample for all site staff participating in the study.

10.3 Subject Data and Data Protection

To protect the subject's identity, a subject number will be assigned by the Investigator to each study subject and used in lieu of the subject's name when the Investigator reports AEs and/or other study-related data. Personal information will be treated as confidential but may need to be reviewed by authorized representatives of CRO (if applicable) (monitor and auditor), IRB/EC, and regulatory authorities. The subject's consent for direct access to his/her original medical records for data verification purposes has to be obtained prior to a subject's participation in the study.

The Investigator must maintain a list of names and identifying information (e.g., initials, date of birth, subject identification code, and date of study randomization) of all subjects enrolled in the study. The Investigator will keep the subject identification code list in the site master file.

10.4 Data Management

A Code of Federal Regulations Title 21 Part 11-compliant EDC (Electronic Data Capture) system will be used for this study. The eCRFs will be produced for each subject. The majority of study data collected on the source documents will be entered by the study center staff or directly captured from devices and submitted to the database. Data will be available for Sponsor review via predefined reports extracted from the database at agreed intervals. The eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

All source documents will be retained. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor.

Safety laboratory data are managed and stored within the appropriate system and the date and time of sampling will be recorded in the eCRF. Safety laboratory data will be integrated with the consolidated clinical data before interim and final database locks.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided by the sponsor/designated personnel; alternately a note to indicate where the records are located will be provided by the sites. All records should be kept in conformance to applicable national laws and regulations.

Data validity and consistency will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct per the source document. At the interim 40-week time point and after completion of the study, when all collected data is validated, the database will be locked. Interim and Final data will be extracted from the EDC system in the form of SAS® datasets for the purpose of analysis. A portable document format copy of the eCRF will be produced for each study subject and included in the interim and final deliveries as required.

All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized, study center staff and only by individuals who have received training to use the EDC system. Study center staff may only be allowed access to the system after the relevant training is completed. Training must be documented, and a log of all EDC users and their rights within the system must be maintained.

Adverse events will be coded using the current MedDRA thesaurus; concomitant medications will be coded using World Health Organization's Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query entry and resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside the data.

10.5 Compliance with Protocol

The investigator or 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 approved or given a favorable opinion by the IRB/EC.

The Investigator will not implement any deviation from or changes to the protocol without agreement by the Sponsor and prior review and receipt of documented approval or a favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate immediate hazards to a study subject or when the changes involve only logistical or administrative aspects of the study (e.g. change in monitor(s), change in telephone numbers).

10.6 Amendments to the Protocol

All changes to or deviations from the trial protocol must be confirmed in writing. The amendments to the protocol will be made jointly among the CRO (if applicable), the Sponsor, and Investigator(s). Protocol amendment(s) will be signed off in the same way as the original protocol.

10.7 Investigator Responsibilities

10.7.1 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor or designee and given approval/approval/favorable opinion by the IRB/EC and the appropriate regulatory authorities. The Investigator will sign this protocol to confirm the agreement (see Principal Investigator Signature Page).

10.7.2 Protocol Deviations

The Investigator should not implement any deviation from or change to the protocol without prior agreement with the Sponsor or designee. When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact Sponsor or

designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented and submitted to the IRB/EC in accordance with the IRB/EC's reporting requirements.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems are implemented and maintained using written SOPs to ensure that the study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11.1 Audit

Sponsor or designee may conduct an internal or external audit. In such an instance, the auditor will be allowed direct access to the source medical records, the study drug storage area, the eCRFs, and the Site's master file for the study.

12.0 ETHICS

Before initiation of the study, Sponsor will seek permission from the regulatory authorities and EC for conducting the study. All documents required by the appropriate authorities will be submitted. Any notification/submission will be dated and contain sufficient information to identify the protocol.

12.1 Ethics Committee (EC) or Institutional Review Board (IRB)

This study will be initiated after the protocol is reviewed and approved by the concerned IRB or EC. All documents required by the appropriate authorities will be submitted. Any notifications/submission will be dated and contain sufficient information to identify the protocol.

12.2 Ethical Conduct of the Study

This study will be carried out in conformity with GCP described in Guideline E6 of the ICH. This study will also be carried out in conformity with the laws, rules and regulations prevailing in the state and country of the investigational site.

12.3 Subject Information and Consent

Subjects will be screened and included in Part 1 and/or Part 2 of the study only after having been given adequate and appropriate information, and having obtaining a written informed consent form. The subject will be given sufficient time to consider the study's implications before deciding whether to participate. The subject will be provided with a copy of the signed informed consent form. The confidentiality of the subject's records will be maintained. If there is any major amendment in the protocol affecting the subject's participation in the study e.g., a change in any procedure, the ICF will be amended to incorporate this modification and previously consented subjects will sign an amended consent form (when relevant). The Investigator is responsible for obtaining the subject's freely given written consent.

13.0 DATA HANDLING AND RECORD KEEPING

The Investigator must maintain all documentation relating to this study. Essential documents (as defined in the ICH Guideline of GCP) must 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 must be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Sponsor.

In any case, all study records such as, but not limited to: CRFs, regulatory documents, the subject identification code list, subject files and other source data that support CRFs must be retained for at least 15 years after the completion or discontinuation of the study. If the Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred and Sponsor notified in writing. The Sponsor will notify the Investigator in writing when the study-related records are no longer needed.

14.0 FINANCING AND INSURANCE

The Sponsor is covered by a liability insurance that also covers liability towards subjects in clinical trials. Sponsor is covered by a General and Products liability insurance that includes clinical trials.

15.0 PUBLICATION POLICY

The CRO and Investigator agree to keep strictly confidential all unpublished information and results concerning this study. In the event Institution or Investigator wants to publish or present any or all of the technical developments, it shall submit to Sponsor the manuscript, abstract or other proposed publication at least 30 days prior to submission, and in the case of poster boards or other presentations, at least 45 days prior to the presentation itself. Sponsor shall timely review the proposed publication, and may revise the manuscript or other proposed publication to ensure protection of Sponsor's confidential information. Any publication or disclosure by the investigator contrary to the provisions of this section or without prior written consent of Sponsor shall be void-ab-initio. Sponsor reserves all the rights to declare any of its data confidential or of business importance and will provide it only to the regulatory authorities of concern on request/demand.

16.0 REFERENCES

Adler, C. H., et al. (2014). Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. (1526-632X (Electronic)).

Alvarado-Bolaños, A., et al. (2015). Convergent validation of EQ-5D-5L in patients with Parkinson's disease. (1878-5883 (Electronic)).

Arora, S., et al. (2018). Smartphone motor testing to distinguish idiopathic REM sleep behavior disorder, controls, and PD. *Neurology, 91*, 10.1212/WNL.0000000000006366. doi:10.1212/WNL.0000000000006366

Athauda, D., et al. (2017). Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. (1474-547X (Electronic)).

Beal, M. F., et al. (2014). A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. (2168-6157 (Electronic)). doi:10.1001/jamaneurol.2014.131

Biglan, K., et al. (2017). A novel design of a Phase III trial of isradipine in early Parkinson disease (STEADY‐PD III). *Annals of Clinical and Translational Neurology, 4*. doi:10.1002/acn3.412

Bosulif [bosutinib] PI. (2023). Bosulif PI. Retrieved from https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=adc84ad5-a04d-4fee-9ba8-91f7abd928e3&type=display

Brahmachari S Fau - Ge, P., et al. (2016). Activation of tyrosine kinase c-Abl contributes to α-synuclein-induced neurodegeneration. (1558-8238 (Electronic)). doi:10.1172/JCI85456

Brahmachari, S., et al. (2017). c-Abl and Parkinson's Disease: Mechanisms and Therapeutic Potential. (1877-718X (Electronic)). doi:10.3233/JPD-171191

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont), 4*(7), 28-37.

Busner, J., Targum Sd Fau - Miller, David S. Miller, D. S. (2009). The Clinical Global Impressions scale: errors in understanding and use. (1532-8384 (Electronic)). doi:10.1016/j.comppsych.2008.08.005

Daily, E. B., & Aquilante, C. L. (2009). Cytochrome P450 2C8 pharmacogenetics: a review of clinical studies. (1744-8042 (Electronic)).

Donadio, V., et al. (2014). Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson disease. (1526-632X (Electronic)). doi:10.1212/WNL.0000000000000316

Dorsey, E. R., Papapetropoulos, S., Xiong, M., & Kieburtz, K. (2017). The First Frontier: Digital Biomarkers for Neurodegenerative Disorders. (2504-110X (Electronic)). doi:10.1159/000477383

Eusebi, P., et al. (2017). Diagnostic utility of cerebrospinal fluid α-synuclein in Parkinson's disease: A systematic review and meta-analysis. (1531-8257 (Electronic)). doi:10.1002/mds.27110

Fahn, S., et al. (2004). Levodopa and the progression of Parkinson's disease. (1533-4406 (Electronic)). doi:10.1056/NEJMoa033447

Fahn S, Elton R. (1987). UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease. . 153-163 293-304.

Gibbons, C. H., Garcia, J., Wang, N., Shih, L. C., & Freeman, R. (2016). The diagnostic discrimination of cutaneous α-synuclein deposition in Parkinson disease. (1526-632X (Electronic)). doi:10.1212/WNL.0000000000002919

Gleevec [imatinib] PI. (2016). Gleevec (imatinib) prescribing information. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021588s047lbl.pdf

Goetz, C. G., et al. (2023). It Is as It Was: MDS-UPDRS Part III Scores Cannot Be Combined with Other Parts to Give a Valid Sum. *Mov Disord, 38*(2), 342-347. doi:10.1002/mds.29279

Goetz, C. G., et al. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. (0885-3185 (Print)). doi:10.1002/mds.21198

Goetz, C. G., et al. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. (0885-3185 (Print)). doi:10.1002/mds.20213

Goetzl, E. J., et al. (2015). Altered lysosomal proteins in neural-derived plasma exosomes in preclinical Alzheimer disease. (1526-632X (Electronic)). doi:10.1212/WNL.0000000000001702

Guy, W., National Institute of Mental Health . Psychopharmacology Research Branch. Division of Extramural Research, P., & National Institute of Mental Health . Psychopharmacology Research, B. (1976). *ECDEU Assessment Manual for Psychopharmacology*: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Hebron, M. L., Lonskaya I Fau - Moussa, C. E. H., & Moussa, C. E. (2013). Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson's disease models. (1460-2083 (Electronic)). doi:10.1093/hmg/ddt192

Herdman, M., et al. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research, 20*(10), 1727-1736. Retrieved from http://www.jstor.org/stable/41488243

Iclusig [ponatinib] PI. (2016). Iclusig (ponatinib) prescribing information. Retrieved from https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=807f988e-117b-4497-934d-73aa78baac71&type=display

Janssen, M. F., et al. (2013). Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. (1573-2649 (Electronic)). doi:10.1007/s11136-012-0322-4

Karuppagounder, S. S., et al. (2013). The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. (2045-2322 (Electronic)). doi:10.1007/s11136-012-0322-4

Kenneth Marek, D. J., Shirley Lasch, Andrew Siderowf, Caroline Tanner, Tanya Simuni, Chris Coffey, Karl Kieburtz, Emily Flagg, Sohini Chowdhury, Werner Poewe, Brit Mollenhauer, Paracelsus-Elena Klinik, Todd Sherer, Mark Frasier, Claire Meunier, Alice Rudolph, Cindy Casaceli, John Seibyl, Susan Mendick…Peggy Taylor. (2011). The Parkinson Progression Marker Initiative (PPMI). *Prog Neurobiol, 95*(4), 629-635. doi:10.1016/j.pneurobio.2011.09.005

Ko, H. S., et al. (2010). Phosphorylation by the c-Abl protein tyrosine kinase inhibits parkin's ubiquitination and protective function. (1091-6490 (Electronic)). doi:10.1073/pnas.1006083107

Koprich, J. B., Johnston Th Fau - Reyes, M. G., Reyes Mg Fau - Sun, X., Sun X Fau - Brotchie, J. M., & Brotchie, J. M. (2010). Expression of human A53T alpha-synuclein in the rat substantia nigra using a novel AAV1/2 vector produces a rapidly evolving pathology with protein aggregation, dystrophic neurite architecture and nigrostriatal degeneration with potential to model the pathology of Parkinson's disease. (1750-1326 (Electronic)). doi:10.1186/1750-1326-5-43

Koprich, J. B., Kalia, L. V., & Brotchie, J. M. (2017). Animal models of α-synucleinopathy for Parkinson disease drug development. (1471-0048 (Electronic)). doi:10.1038/nrn.2017.75

Lee, S., et al. (2018). The c-Abl inhibitor, Radotinib HCl, is neuroprotective in a preclinical Parkinson's disease mouse model. (1460-2083 (Electronic)). doi:10.1093/hmg/ddy143

Lipsmeier, F., et al. (2018). Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. (1531-8257 (Electronic)). doi:10.1002/mds.27376

Luk, K. C., et al. (2012). Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. (1095-9203 (Electronic)). doi:10.1126/science.1227157

Marras, C., et al. (2011). Predictors of Time to Requiring Dopaminergic Treatment in 2 Parkinson's Disease Cohorts. *Movement Disorders, 26*, 608-613. doi:10.1002/mds.23581

Martínez-Martín, P., et al. (2016). Analysis of four scales for global severity evaluation in Parkinson's disease. (2373-8057 (Print)). doi:10.1038/npjparkd.2016.7. eCollection 2016

Mary E. Nilsson, S. S., Cristiana Gassmann-Mayer, Sarah, & Dubrava, P. M., and Kaihong Jiang. . (2013). Columbia–Suicide Severity Rating Scale

Scoring and Data Analysis Guide. Retrieved from https://cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.pdf

Mollenhauer, B., et al. (2017). Longitudinal CSF biomarkers in patients with early Parkinson disease and healthy controls. (1526-632X (Electronic)). doi:10.1212/WNL.0000000000004609

Mollenhauer, B., et al. (2020). Validation of Serum Neurofilament Light Chain as a Biomarker of Parkinson's Disease Progression. *Mov Disord, 35*(11), 1999-2008. doi:10.1002/mds.28206

Mustapic, M., et al. (2017). Plasma Extracellular Vesicles Enriched for Neuronal Origin: A Potential Window into Brain Pathologic Processes. *Frontiers in Neuroscience, 11*. doi:10.3389/fnins.2017.00278

NINDS exploratory trials. (2015). Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. (1474-4465 (Electronic)). doi:10.1016/S1474-4422(15)00144-1

Olanow, C. W., et al. (2009). A double-blind, delayed-start trial of rasagiline in Parkinson's disease. (1533-4406 (Electronic)). doi:10.1056/NEJMoa0809335

Pagan, F., et al. (2016). Nilotinib Effects in Parkinson's disease and Dementia with Lewy bodies. (1877-718X (Electronic)). doi:10.3233/JPD-160867

Parkinson study group. (1993). Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. (0028-4793 (Print)). doi:10.1056/NEJM199301213280305

Parkinson Study Group. (2002). Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. (0098-7484 (Print)). doi:10.1001/jama.287.13.1653

Parkinson study group. (2007). Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. (1526-632X (Electronic)). doi:10.1212/01.wnl.0000277648.63931.c0

Pavy-Le Traon, A., et al. (2011). The Movement Disorders task force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension. (1531-8257 (Electronic)). doi:10.1002/mds.23742

Postuma, R. B., et al. (2015). MDS clinical diagnostic criteria for Parkinson's disease. (1531-8257 (Electronic)). doi:10.1002/mds.26424

Schrag, A., Selai C Fau - Jahanshahi, M., Jahanshahi M Fau - Quinn, N. P., & Quinn, N. P. (2000). The EQ-5D--a generic quality of life measure-is a useful instrument to measure quality of life in patients with Parkinson's disease. (0022-3050 (Print)). doi:10.1136/jnnp.69.1.67

Shahnawaz, M., et al. (2017). Development of a Biochemical Diagnosis of Parkinson Disease by Detection of α-Synuclein Misfolded Aggregates in Cerebrospinal Fluid. (2168-6157 (Electronic)). doi:10.1001/jamaneurol.2016.4547

Simuni, T., et al. (2018). Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort. (1468-330X (Electronic)). doi:10.1136/jnnp-2017-316213

Simuni, T., et al. (2018). Longitudinal Change of Clinical and Biological Measures in Early Parkinson's Disease: Parkinson's Progression Markers Initiative Cohort. *Movement Disorders, 33*(5), 771-782. doi:https://doi.org/10.1002/mds.27361

Sprycel [dasatinib] PI. (2023). Dasatinib Prescribing Information. Retrieved from https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=4764f37b-c9e6-4ede-bcc2-8a03b7c521df&type=display

Tasigna [nilotinib] PI. (2021). <Tasigna (nilotinib) prescribing information.pdf>. Retrieved from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6093952a-5248-45cb-ad17-33716a411146

Tasigna NDA#022068. (2007). Nilotinib drug approval package.

The Parkinson Progression Marker Initiative. (2011). PPMI Collaborators. (1873-5118 (Electronic)). doi:10.1016/j.pneurobio.2011.09.005

Vijiaratnam, N., Simuni, T., Bandmann, O., Morris, H. R., & Foltynie, T. (2021). Progress towards therapies for disease modification in Parkinson's disease. (1474-4465 (Electronic)). doi:10.1016/S1474-4422(21)00061-2

Visser, M., Marinus J Fau - Stiggelbout, A. M., Stiggelbout Am Fau - Van Hilten, J. J., & Van Hilten, J. J. (2004). Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. (0885-3185 (Print)). doi:10.1002/mds.20153

Walsh, R. R., et al Walsh, R. R., et al. (2023). Plasma and cerebrospinal fluid pharmacokinetics of vodobatinib, a neuroprotective c-Abl tyrosine kinase inhibitor for the treatment of

Parkinson's disease. *Parkinsonism Relat Disord, 108*, 105281. doi:10.1016/j.parkreldis.2023.105281

Williams-Gray, C. H., et al. (2013). The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. (1468-330X (Electronic)). doi:10.1136/jnnp-2013-305277

Ye, R., et al. (2021). Serum NFL levels predict progression of motor impairment and reduction in putamen dopamine transporter binding ratios in de novo Parkinson's disease: An 8-year longitudinal study. *Parkinsonism Relat Disord, 85*, 11-16. doi:10.1016/j.parkreldis.2021.02.008

Zhan, A., et al. (2018). Using Smartphones and Machine Learning to Quantify Parkinson Disease Severity: The Mobile Parkinson Disease Score. (2168-6157 (Electronic)). doi:10.1001/jamaneurol.2018.0809

Zhao, Y. J., et al. (2010). Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. (1531-8257 (Electronic)). doi:10.1002/mds.22875

17.0 APPENDICES

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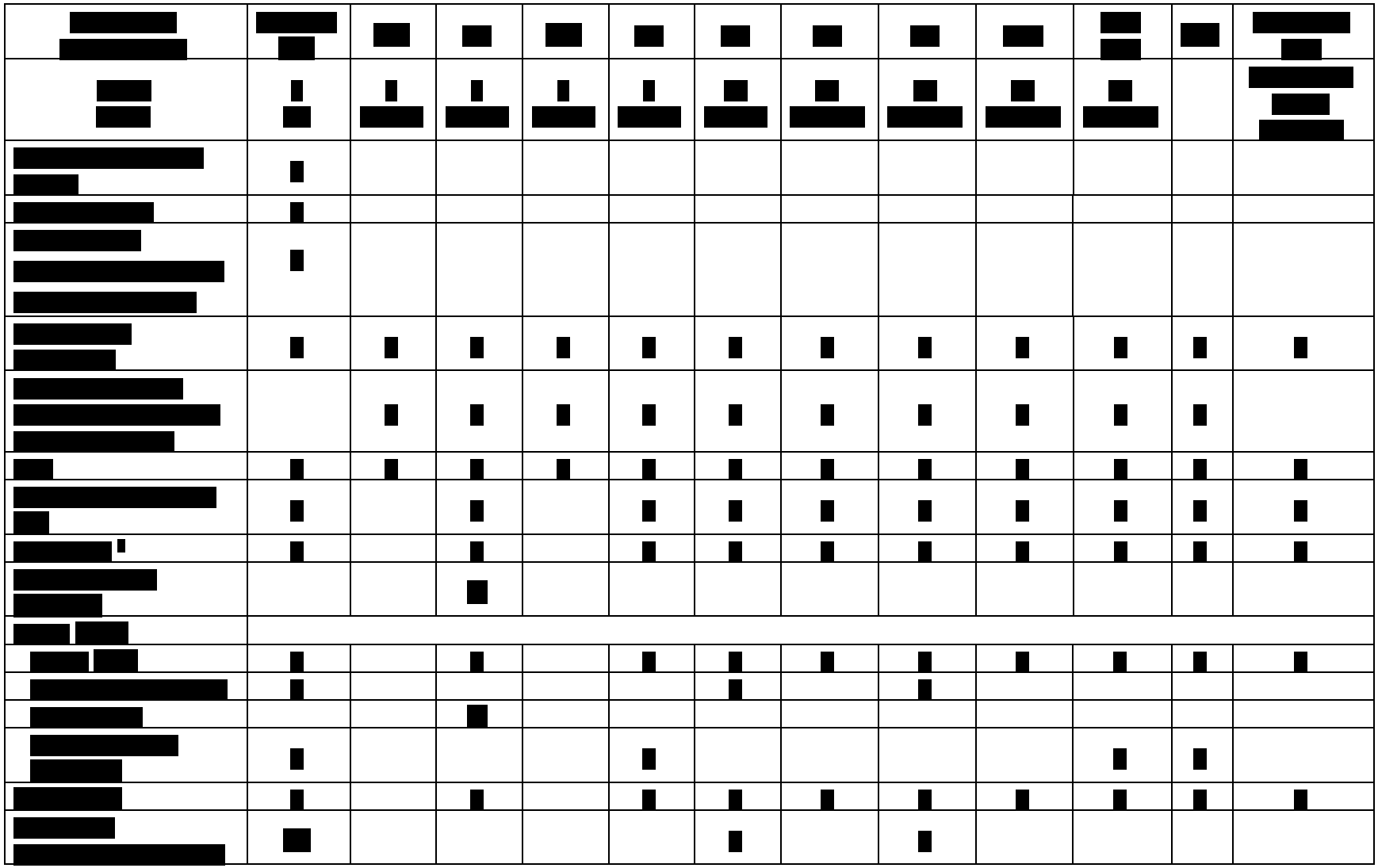

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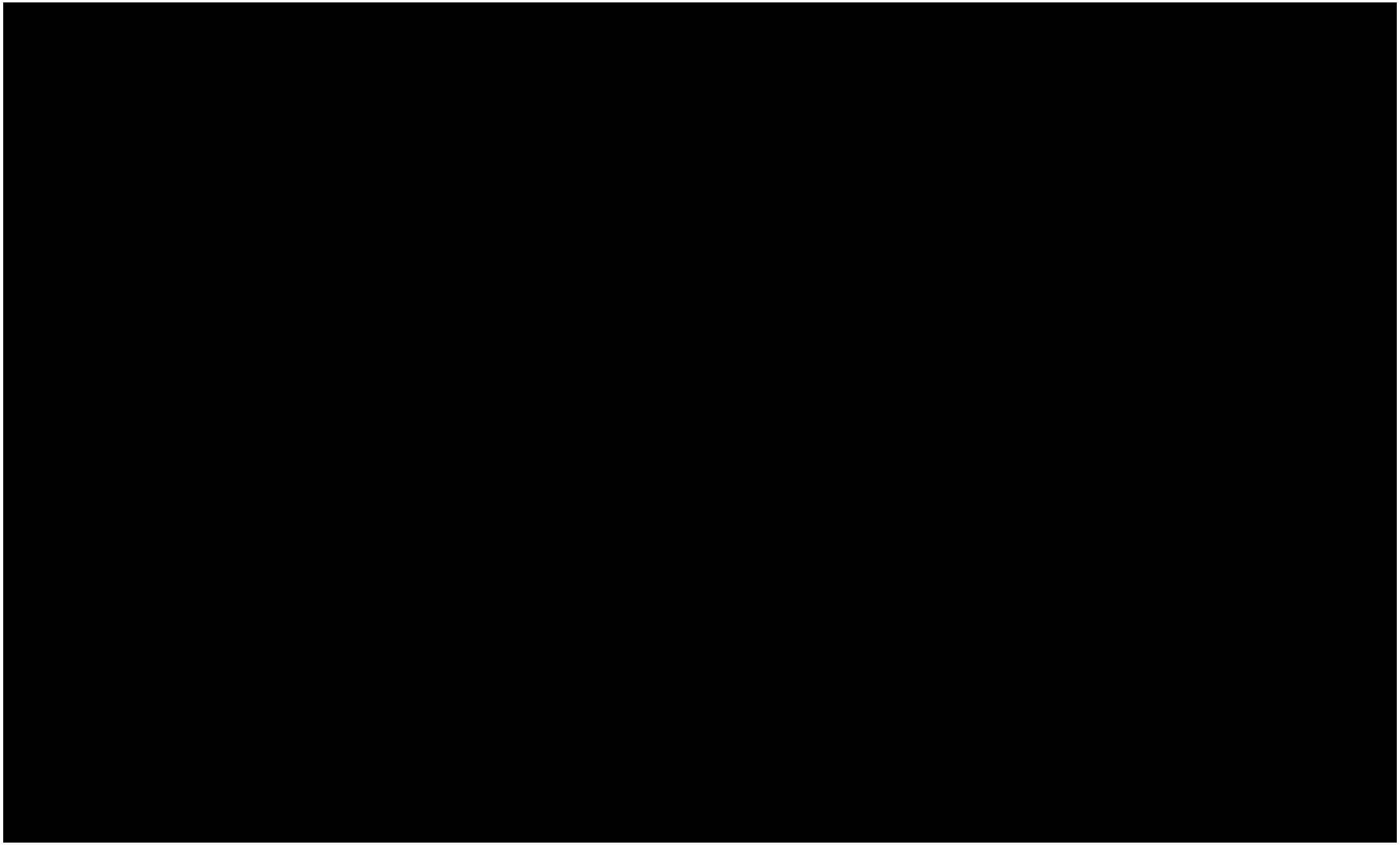

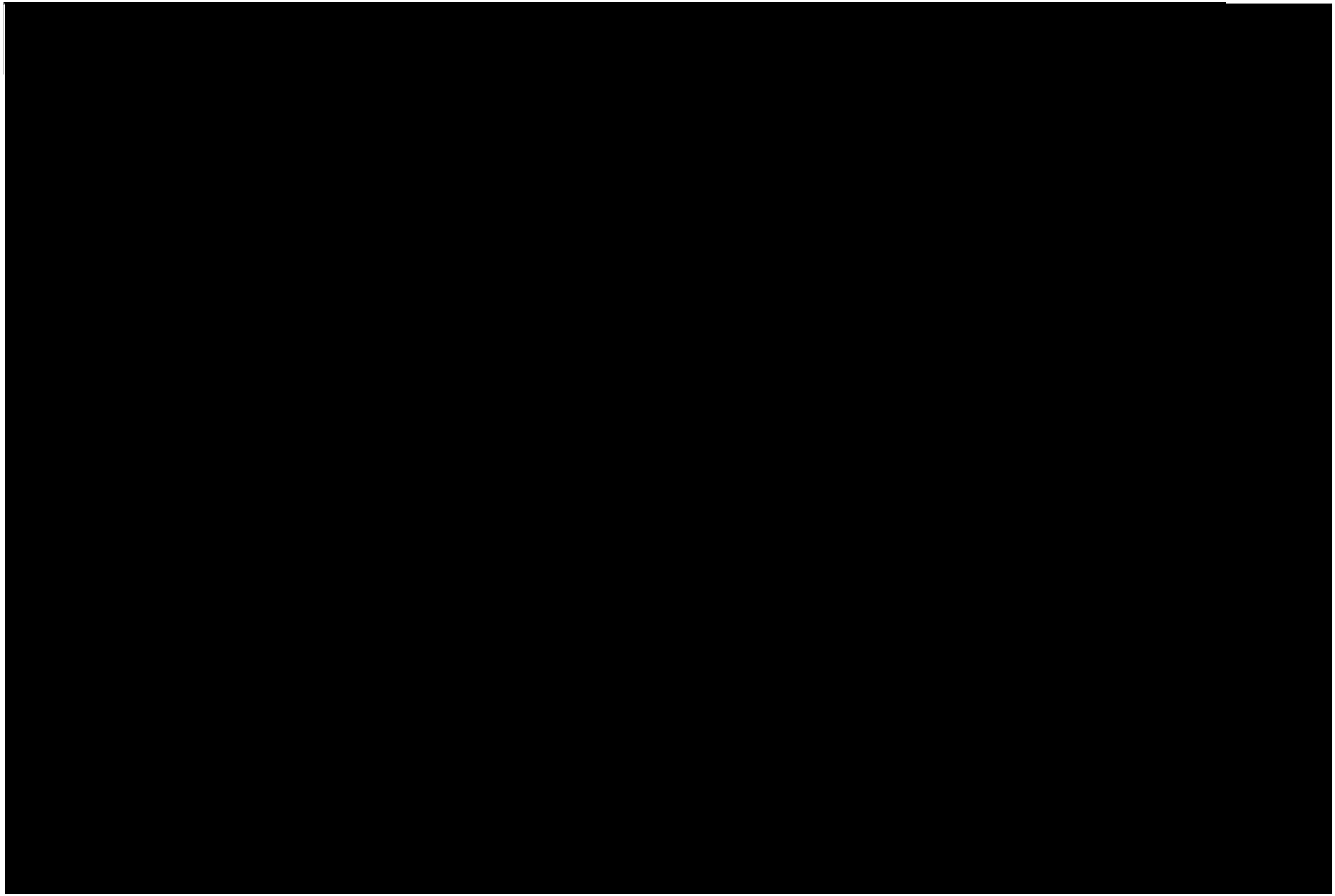

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APPENDIX 4: CLINICIAN GLOBAL IMPRESSION SCALE

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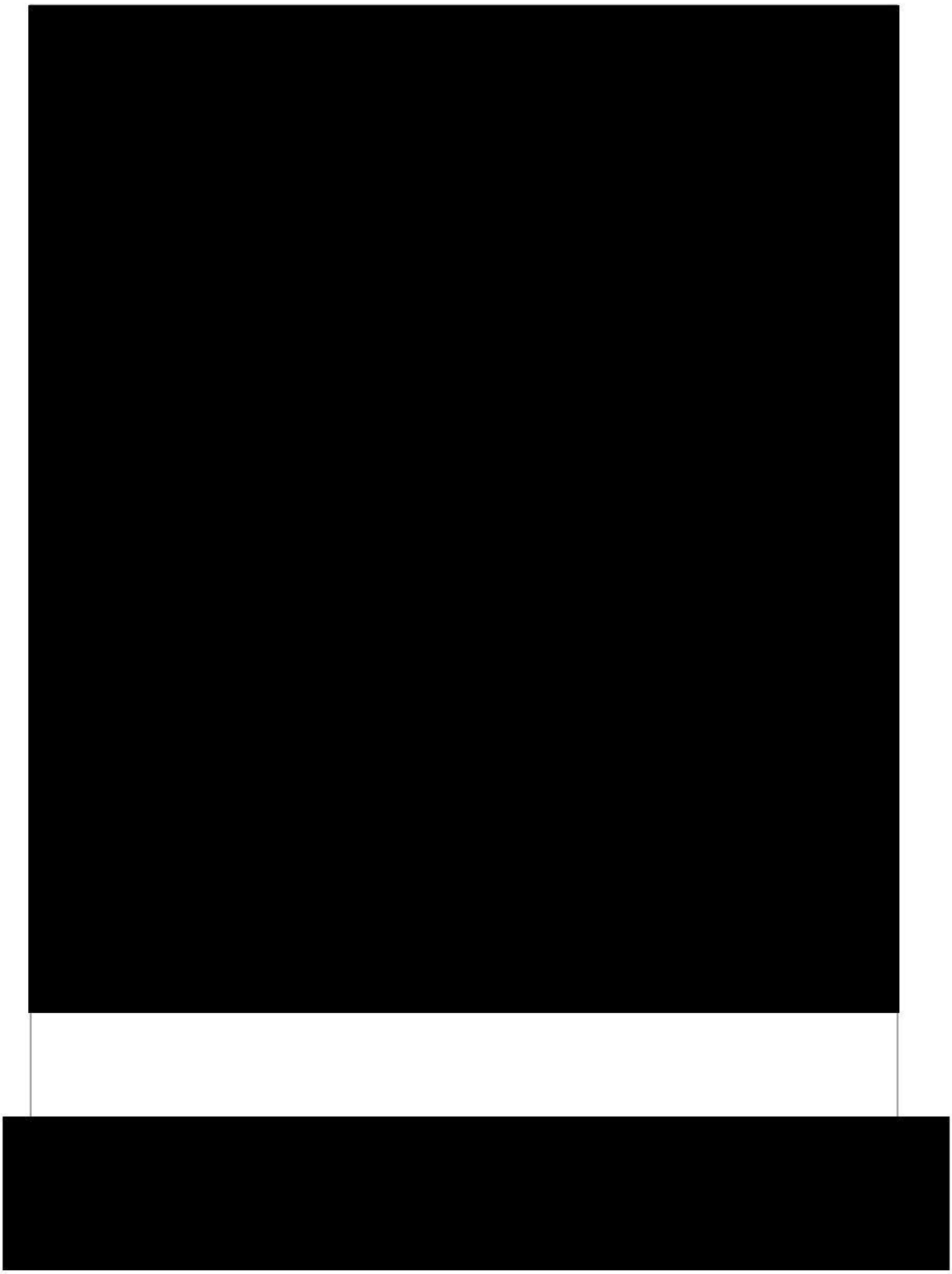

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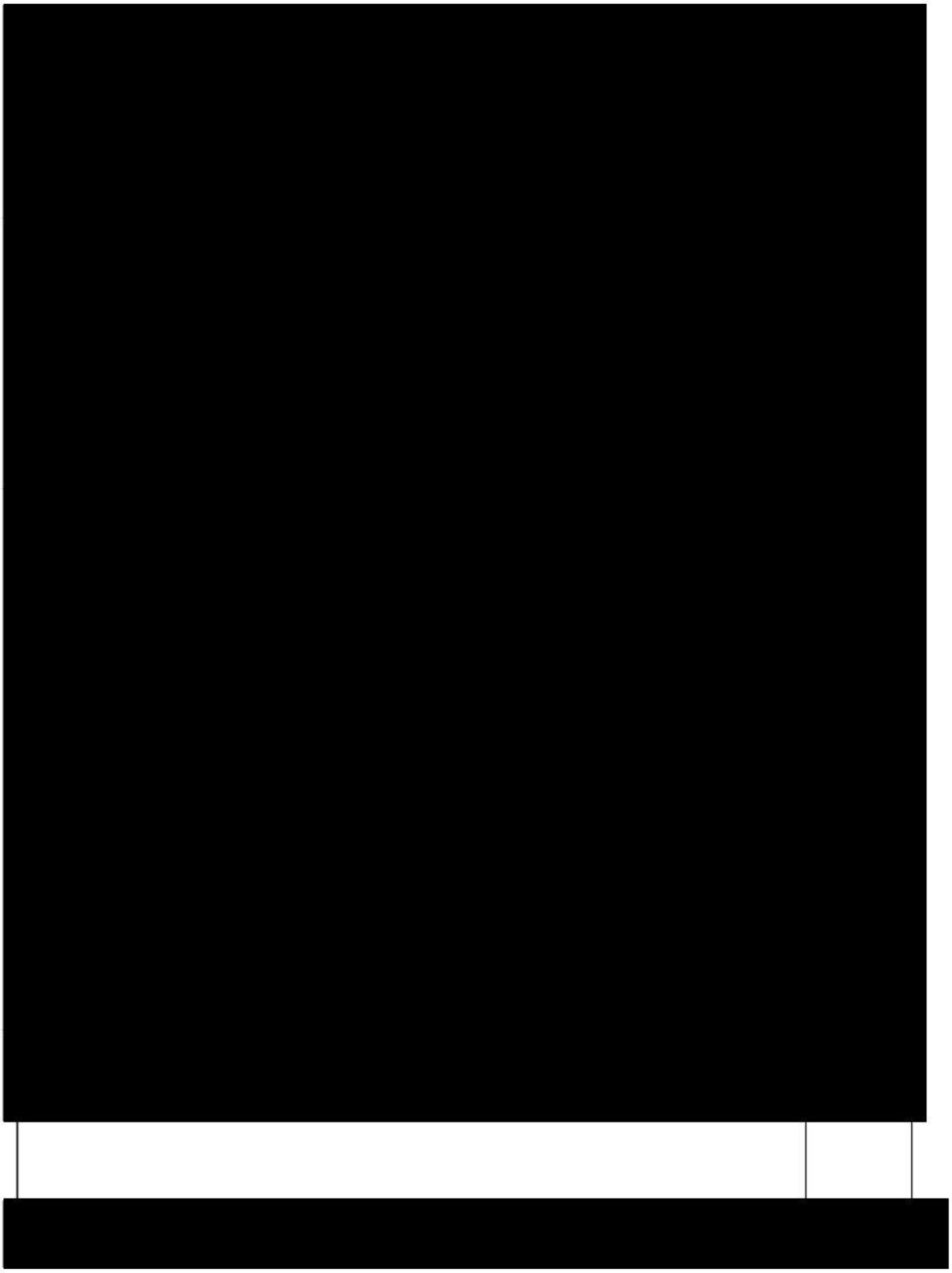

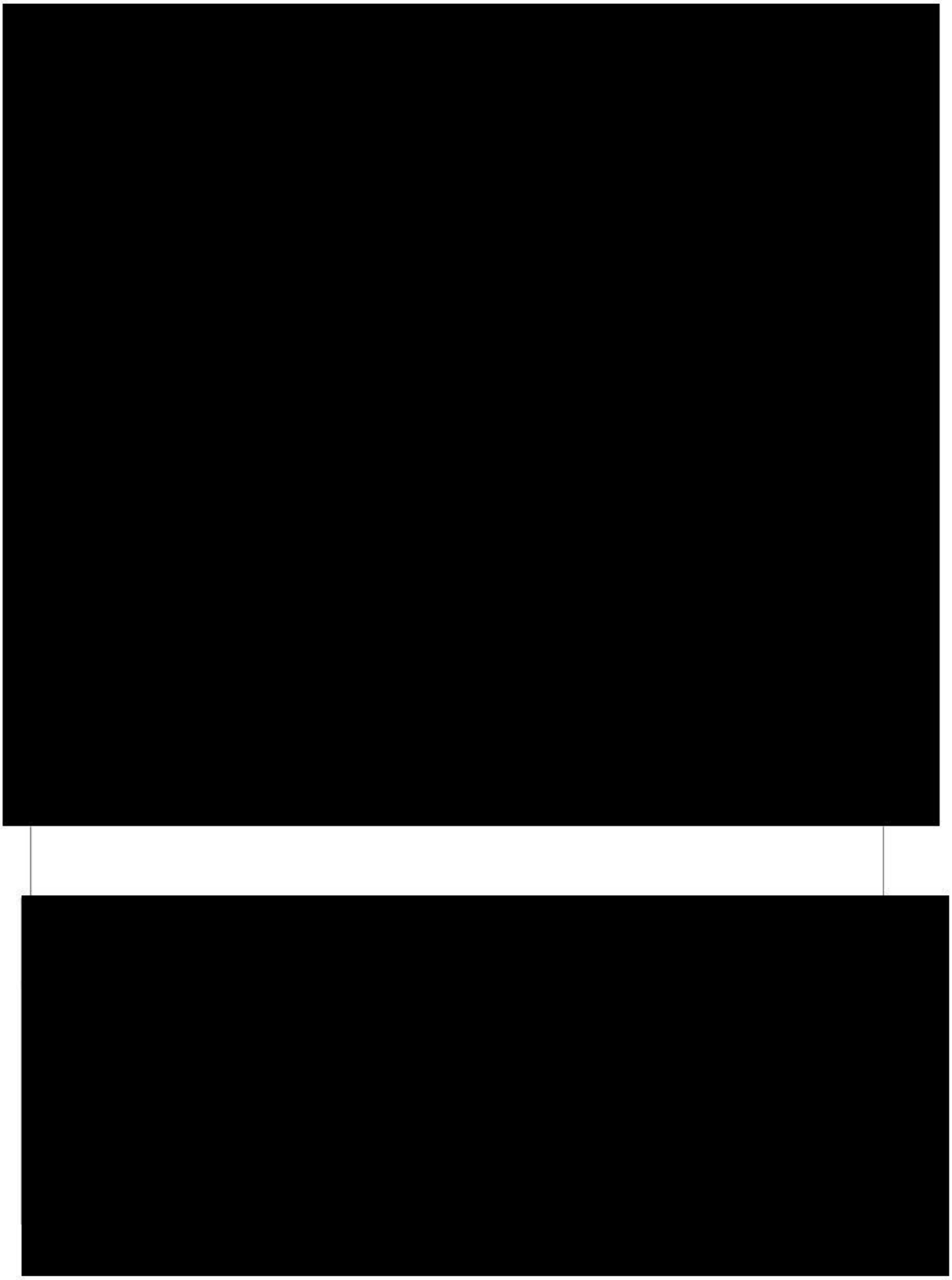
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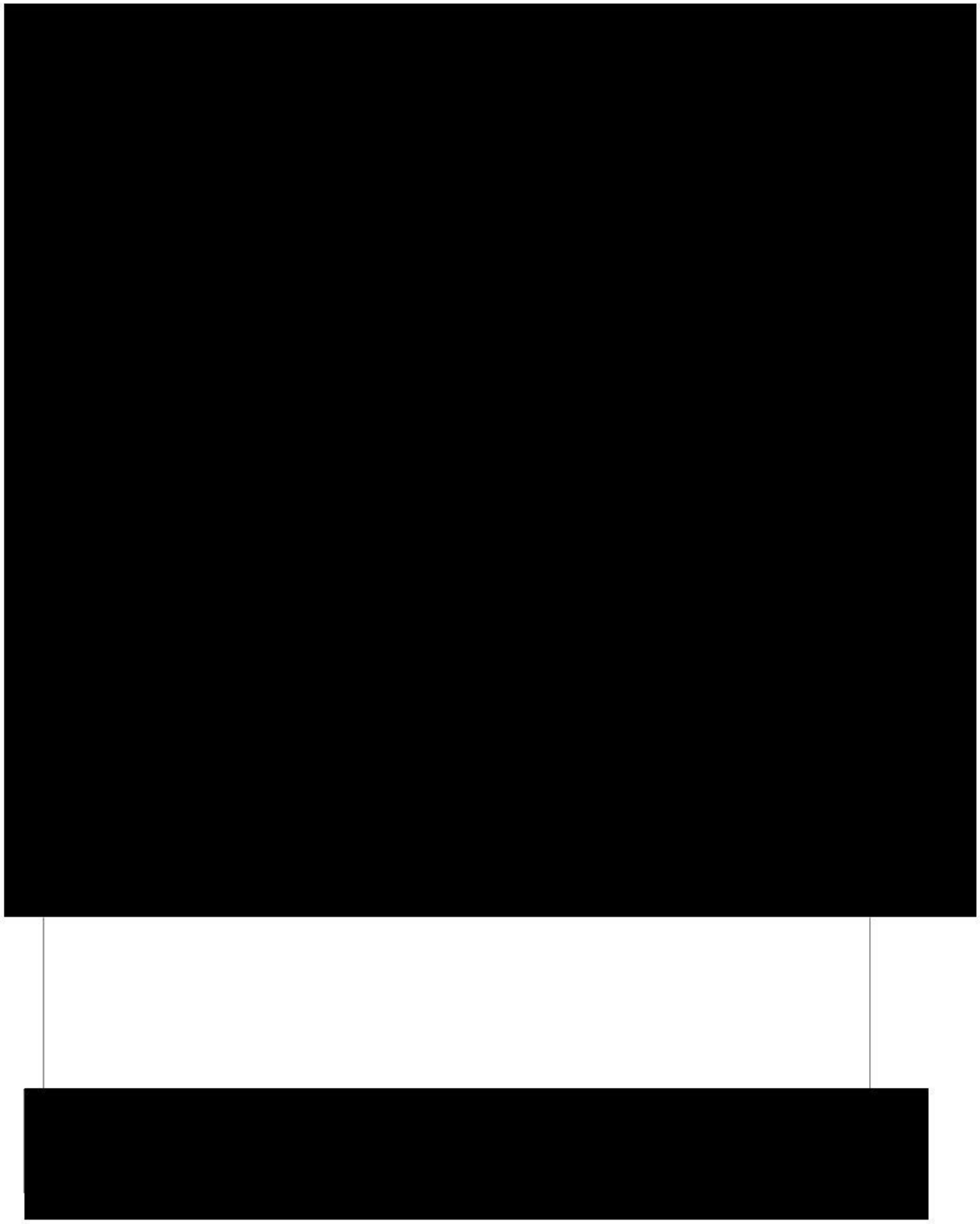
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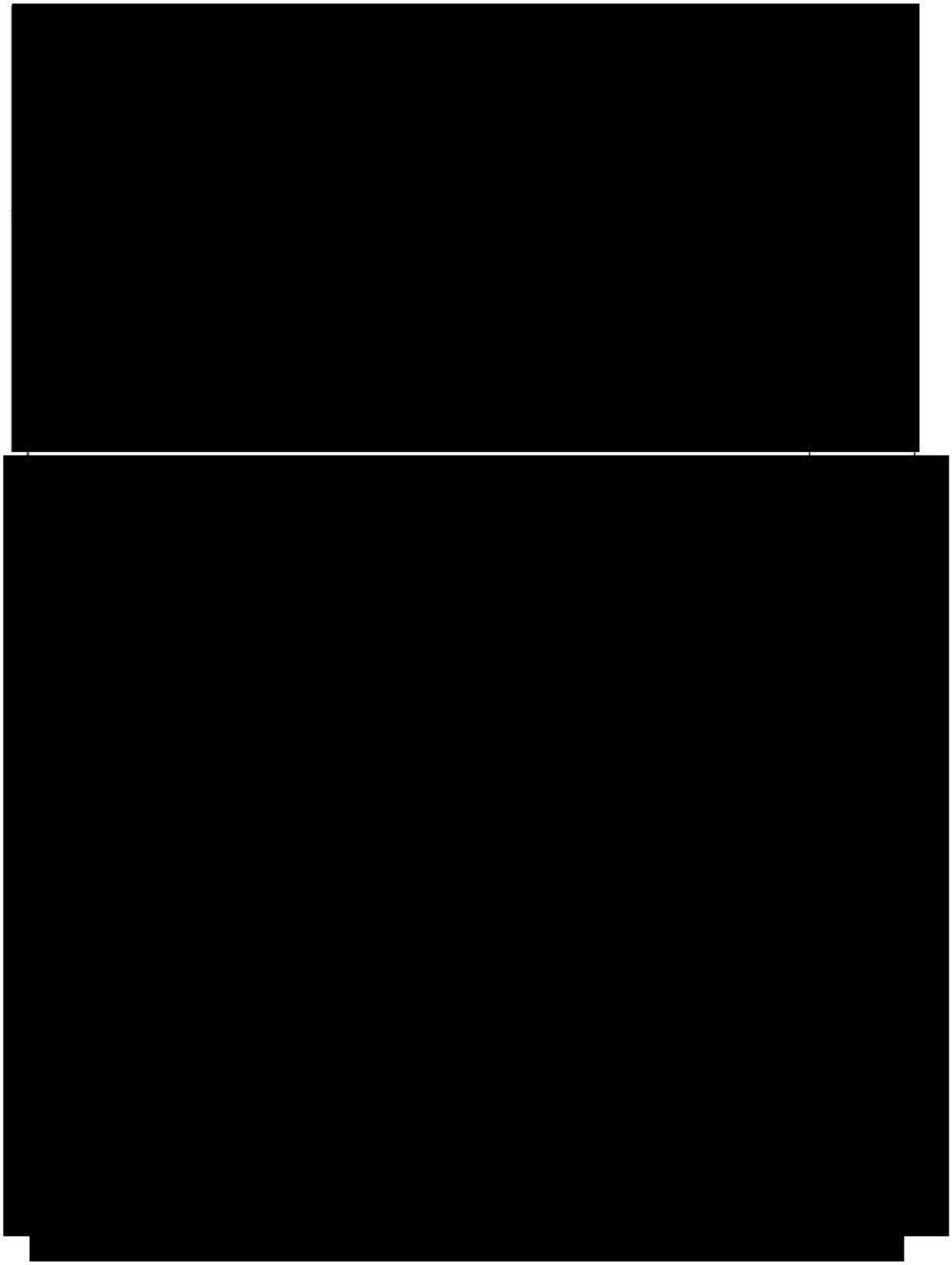

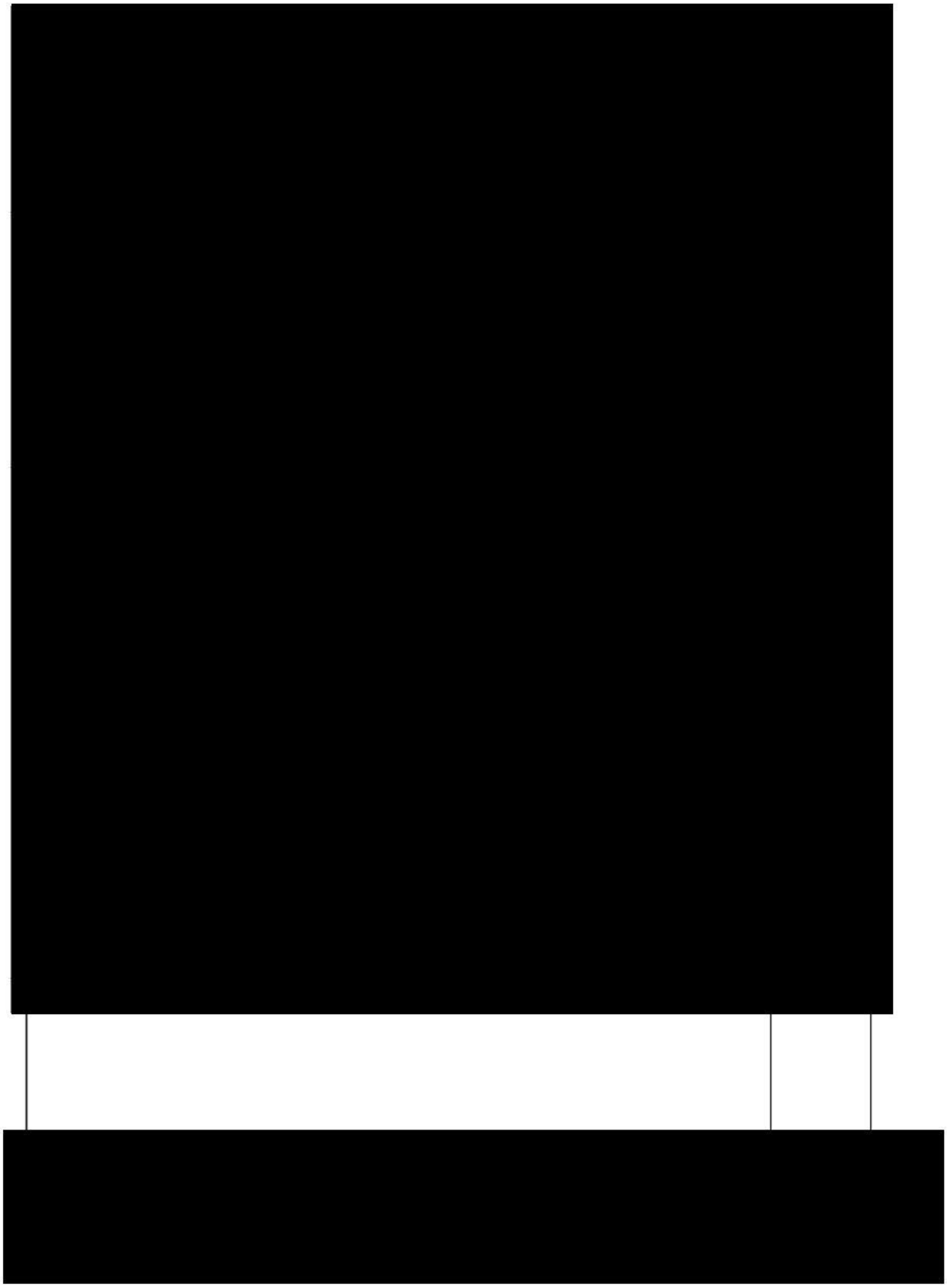
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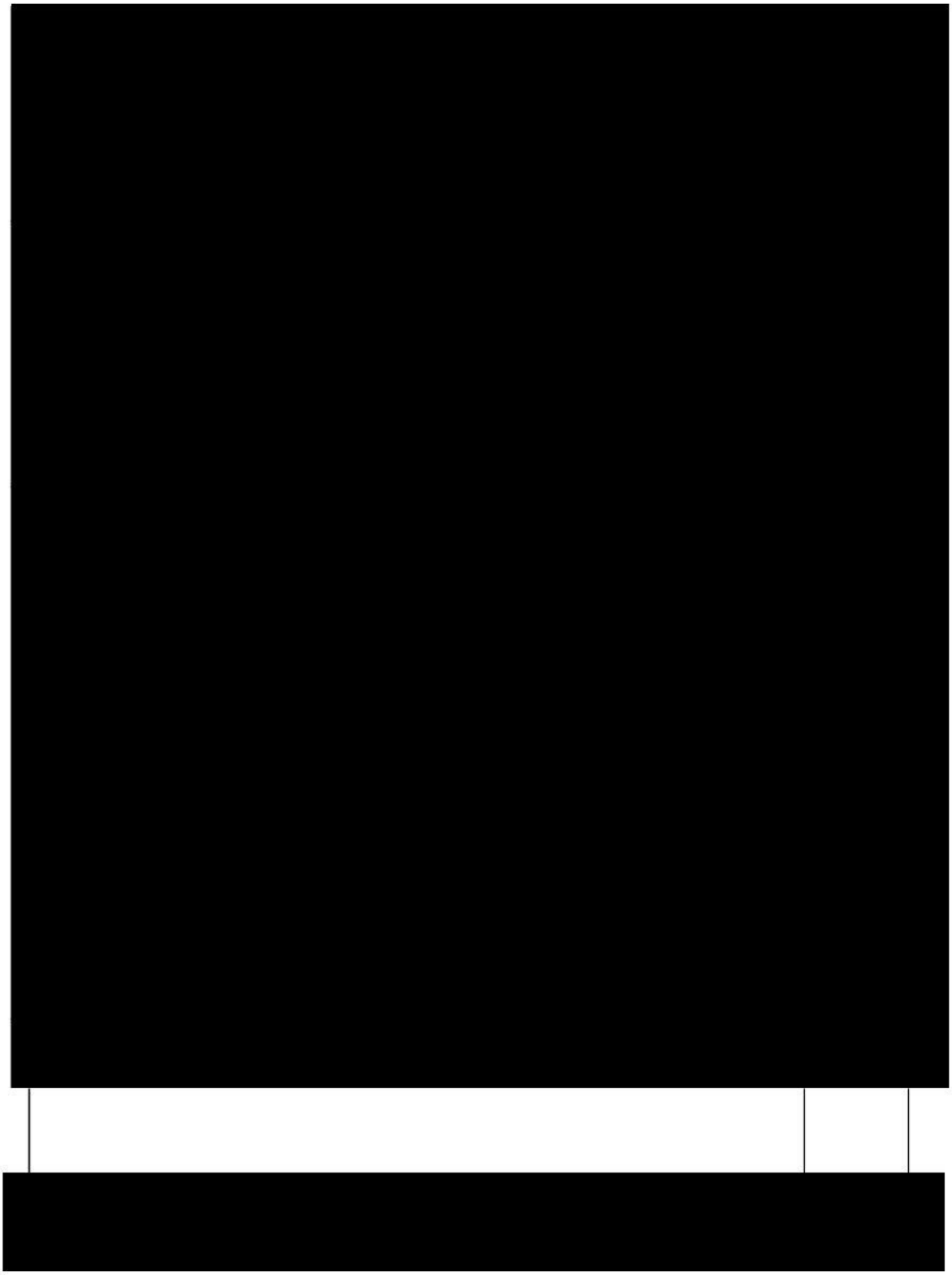
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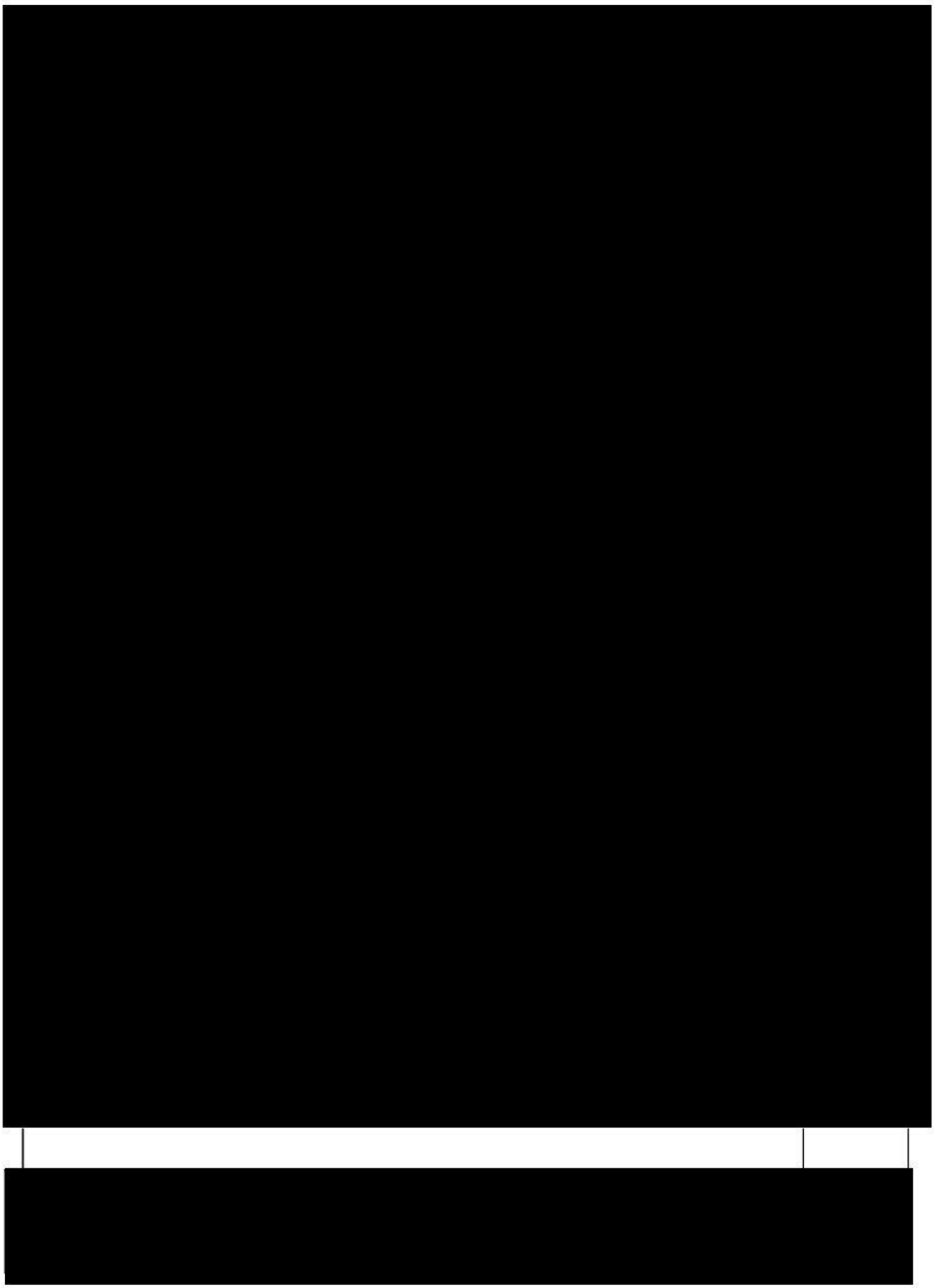
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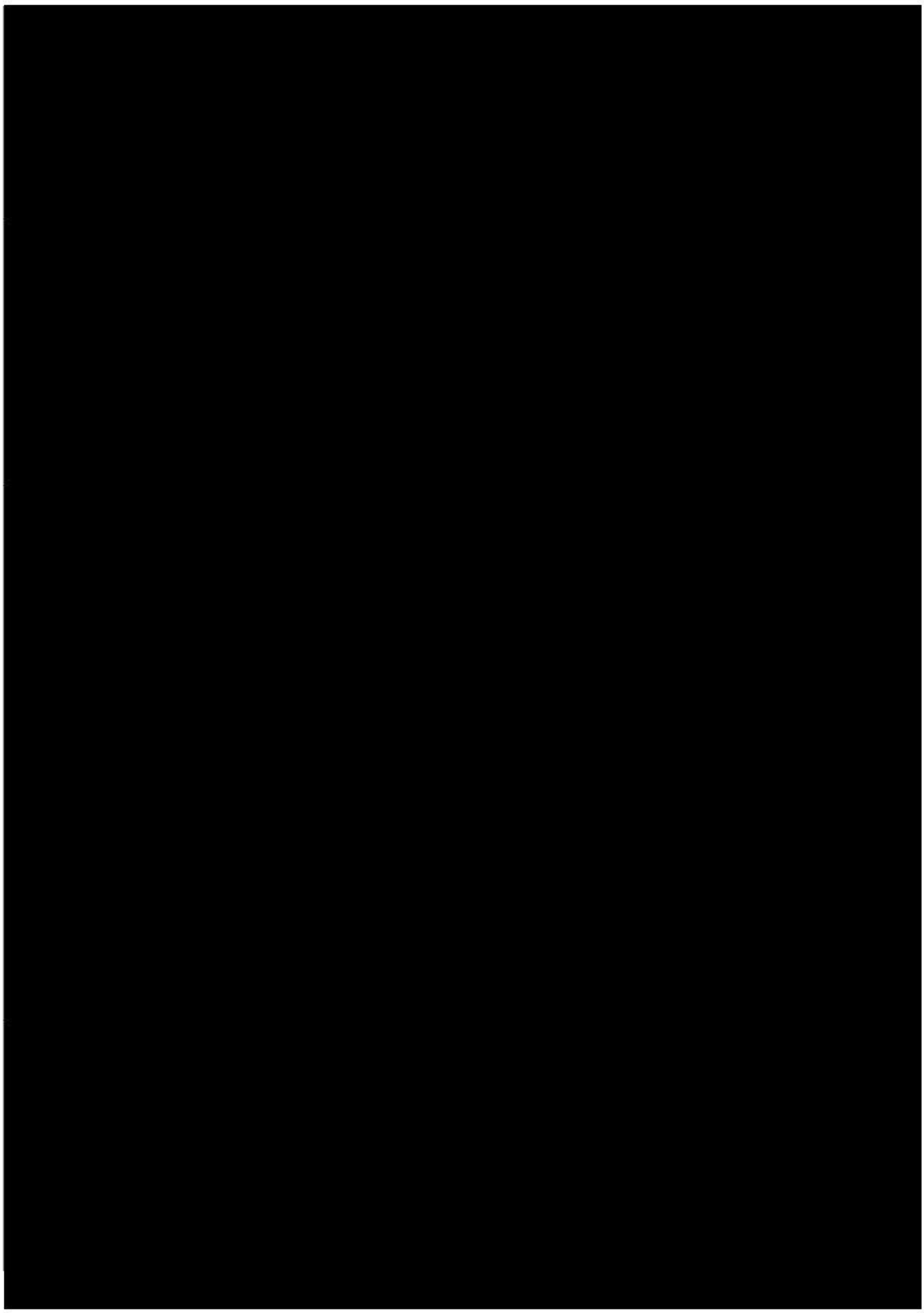

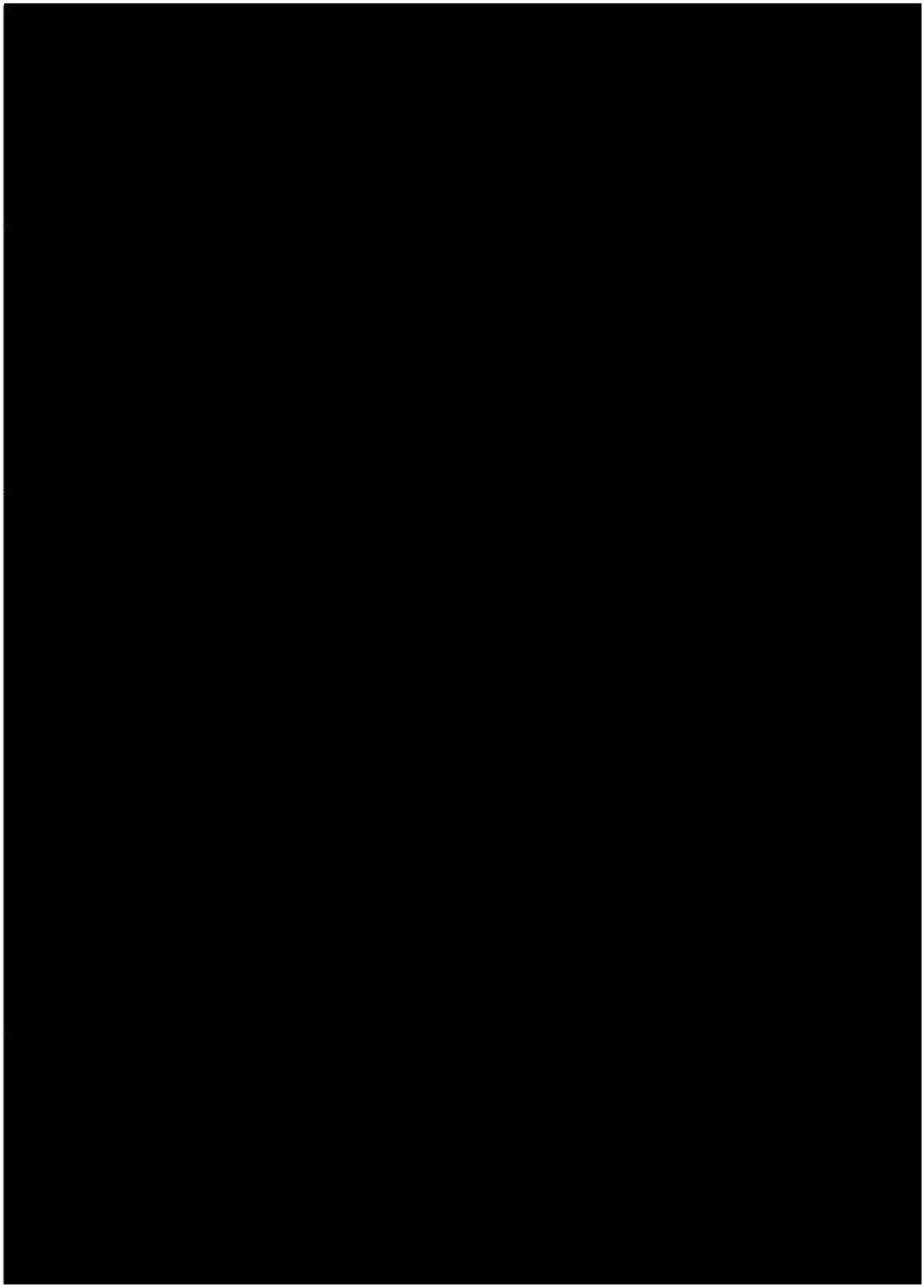

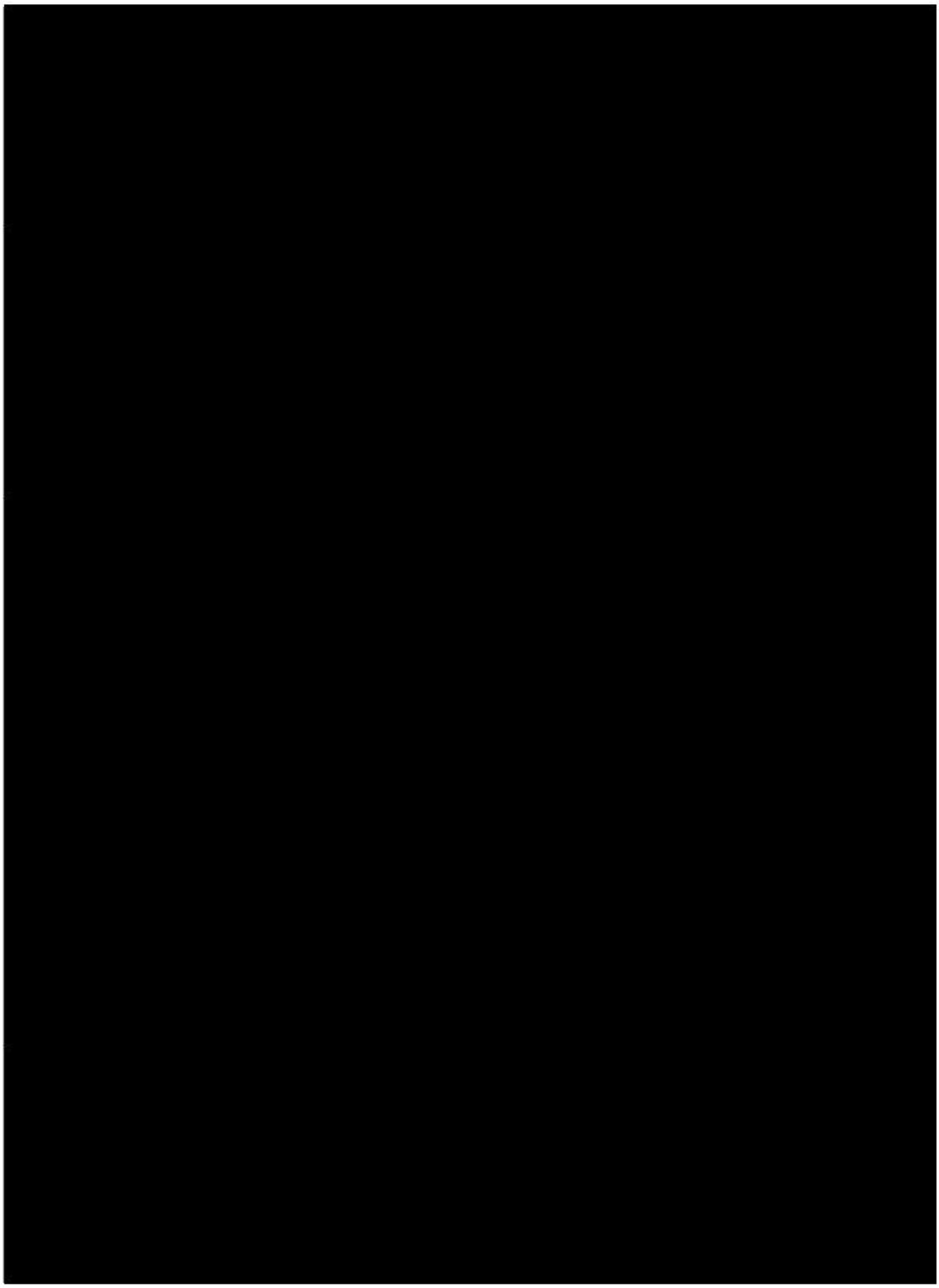

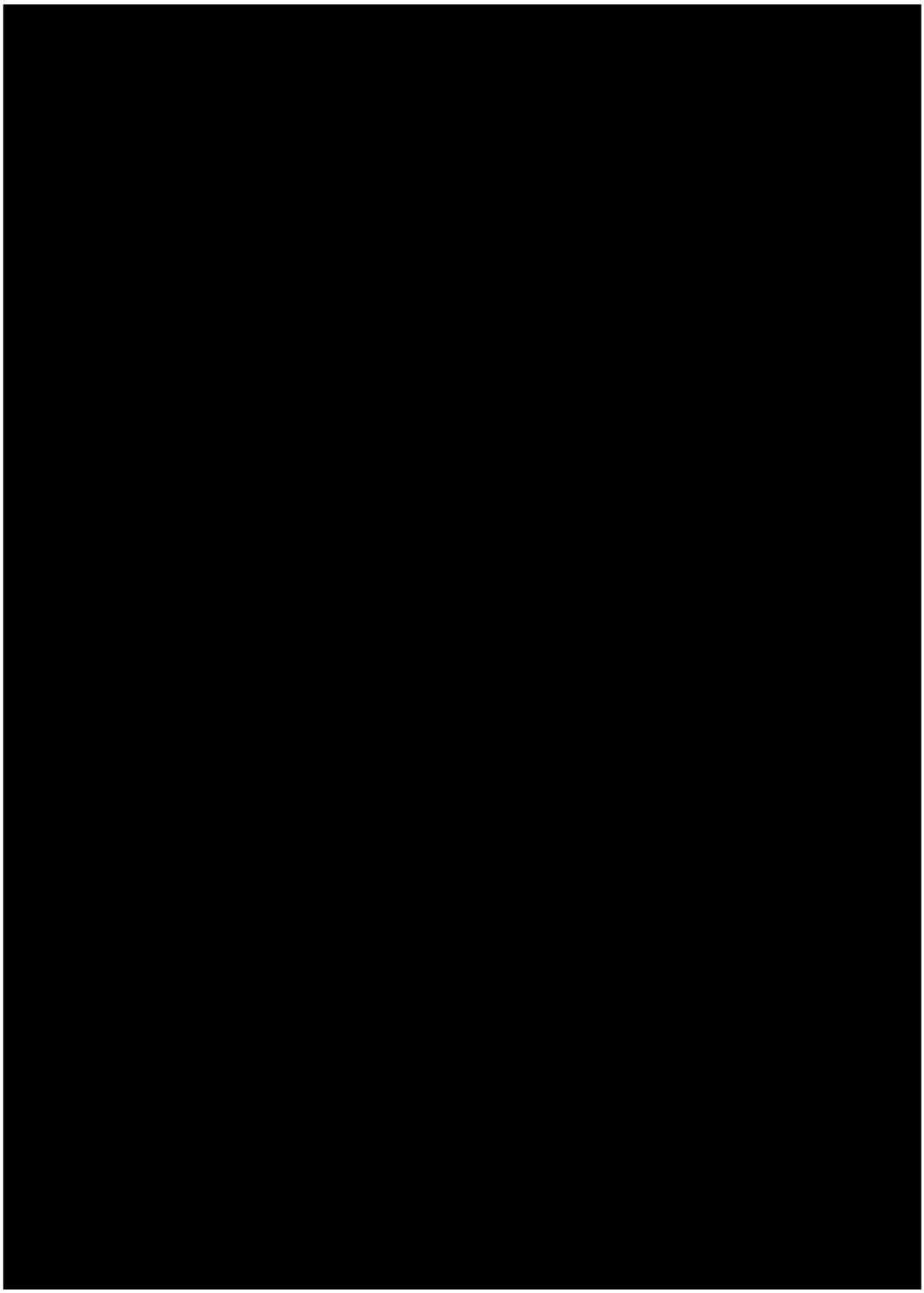

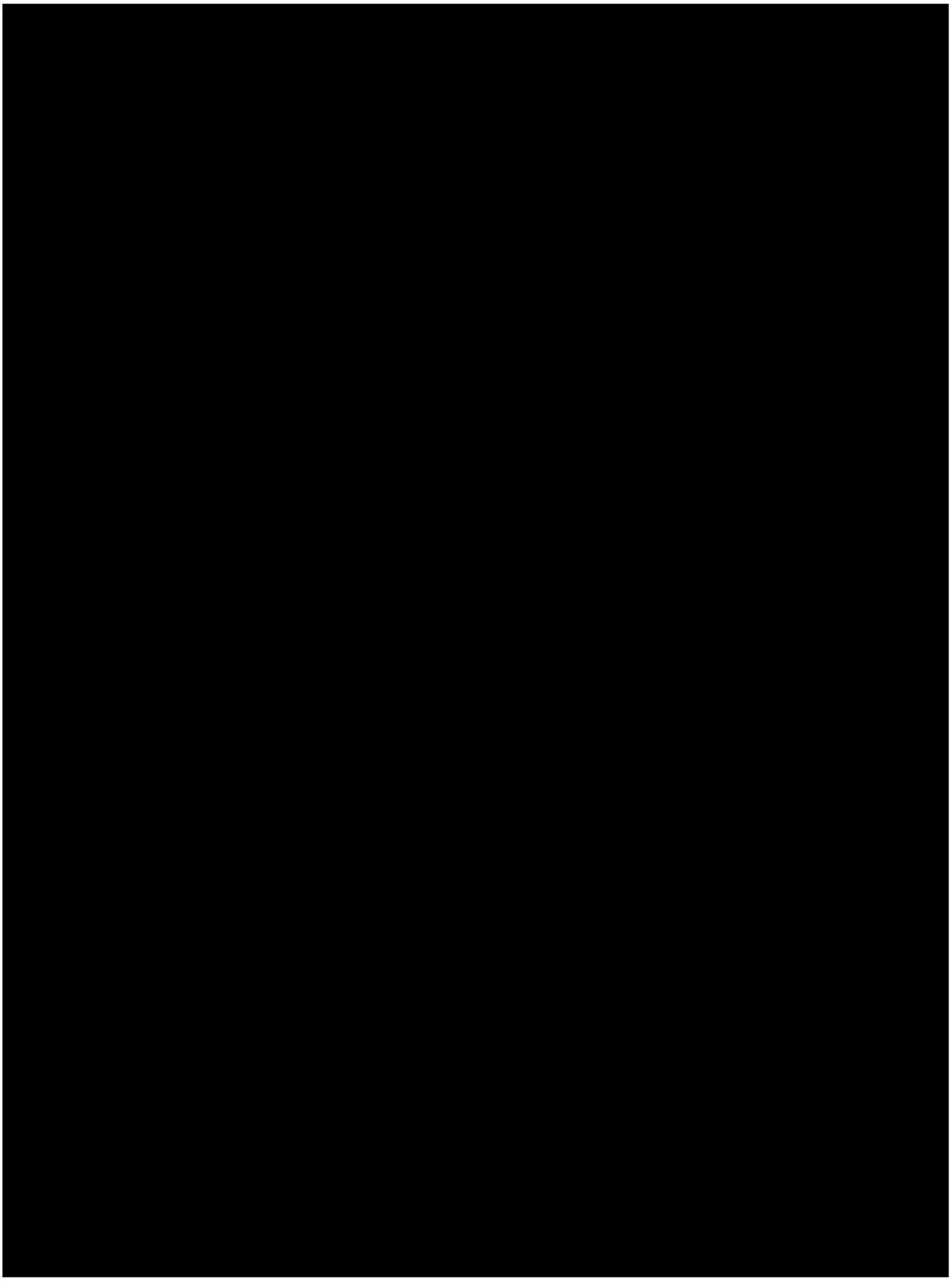

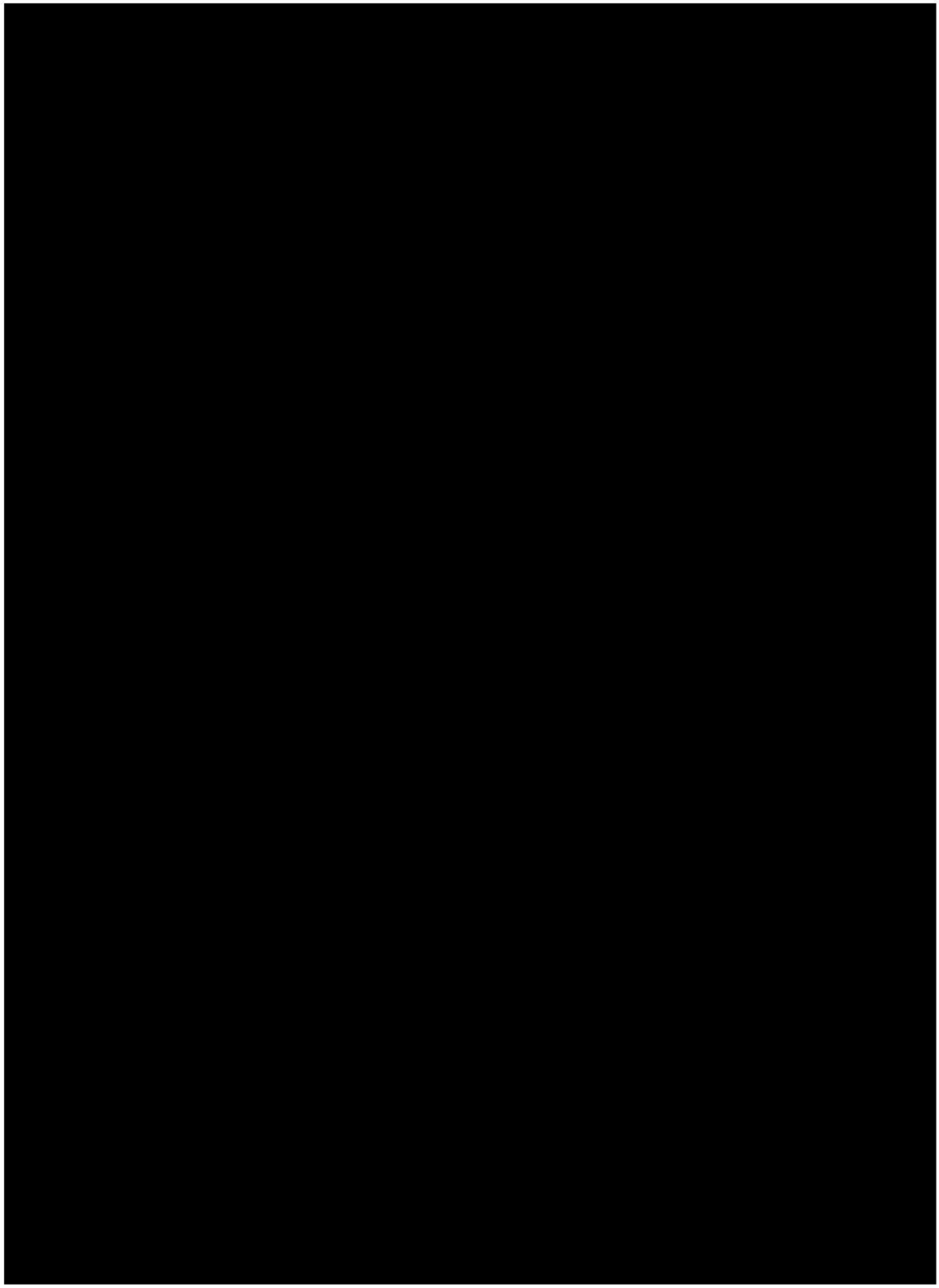

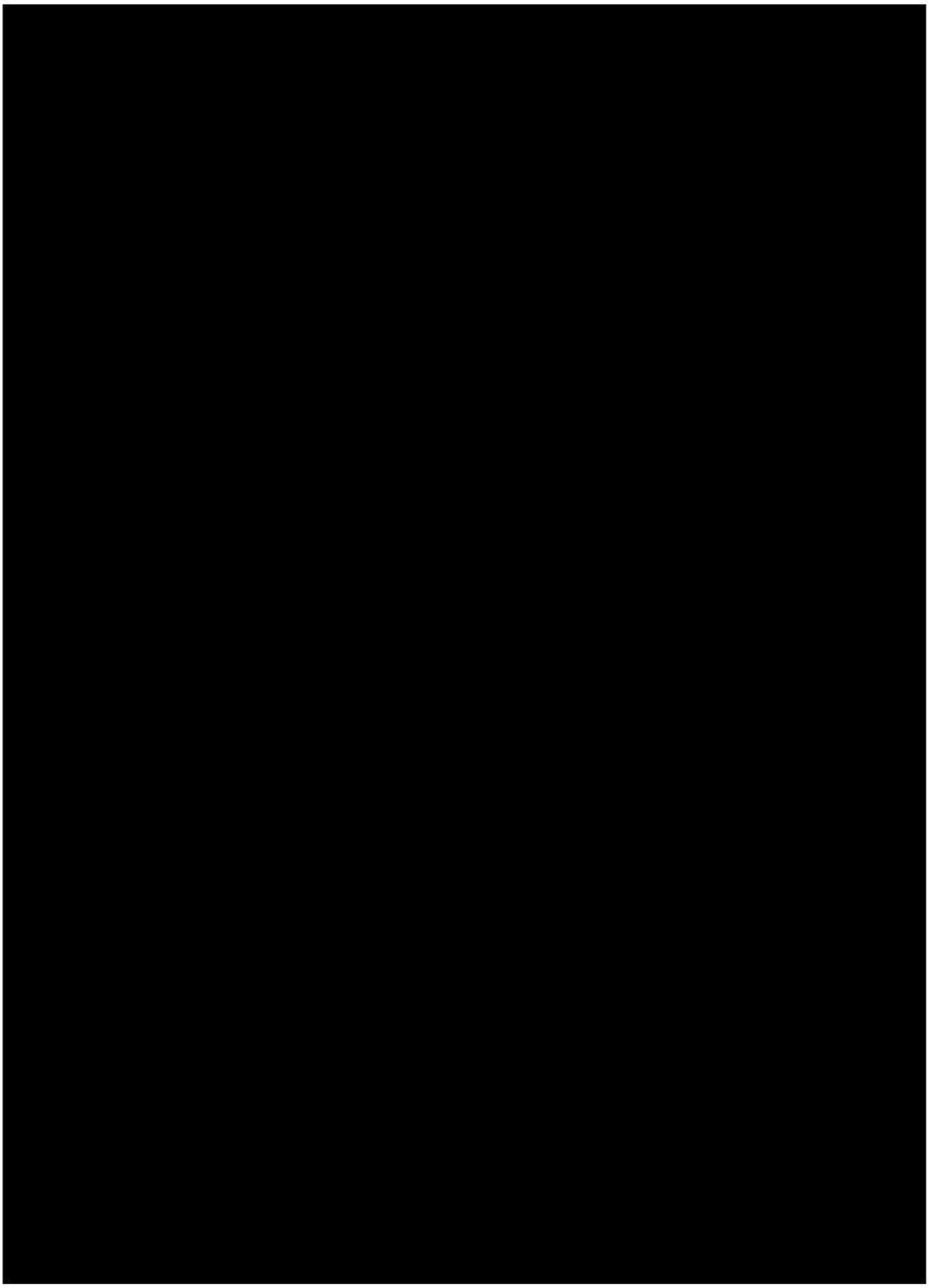

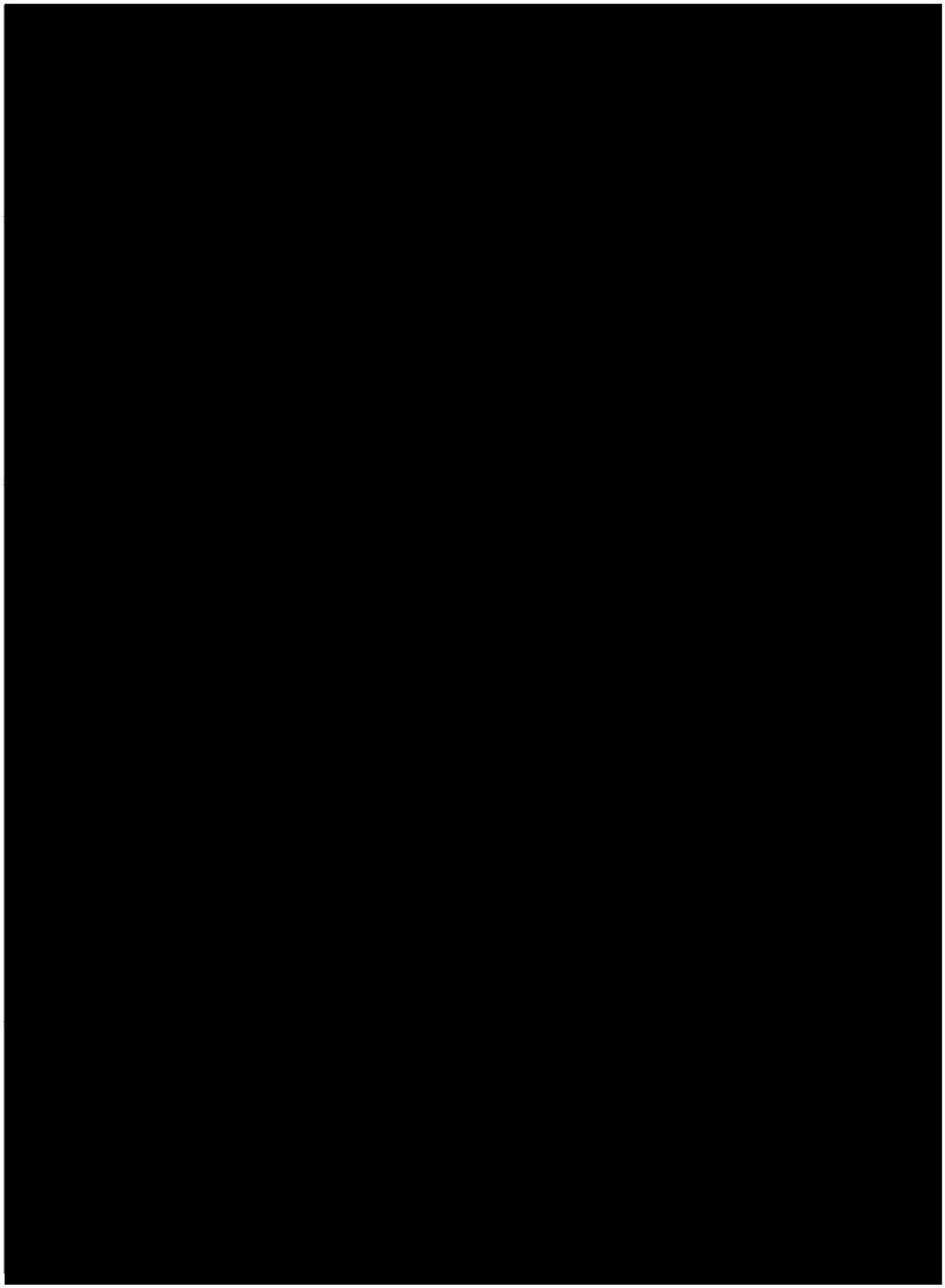

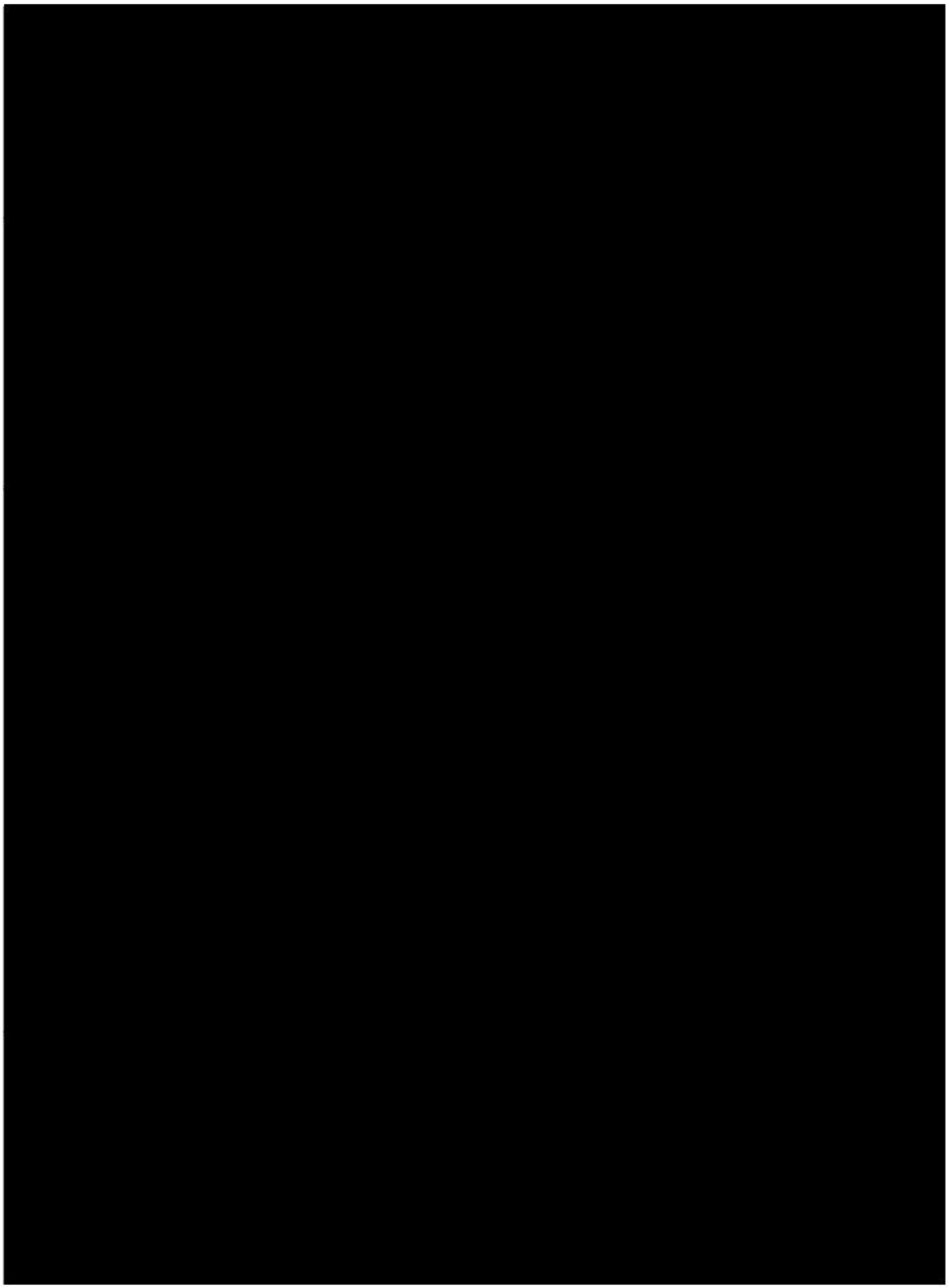

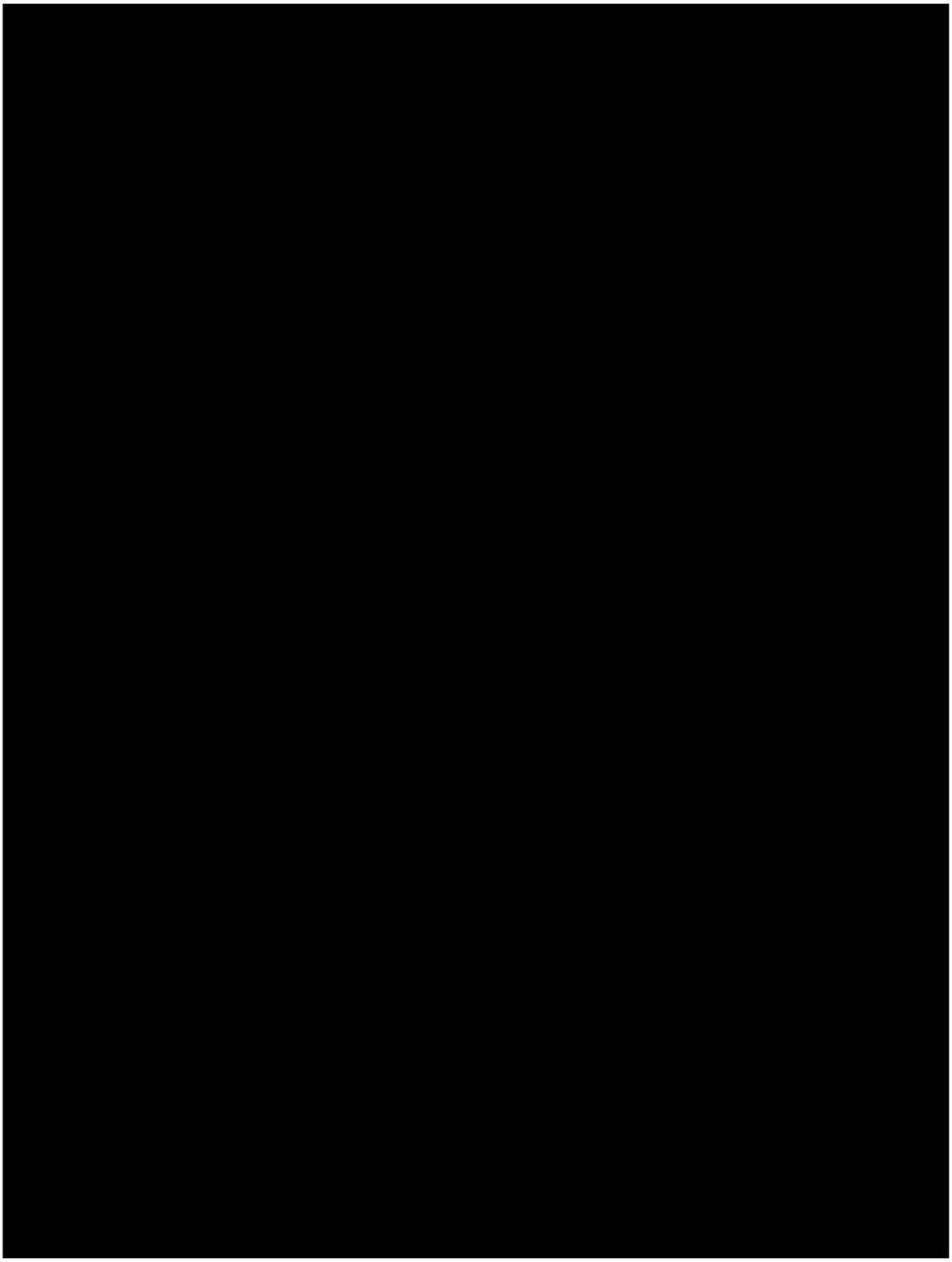

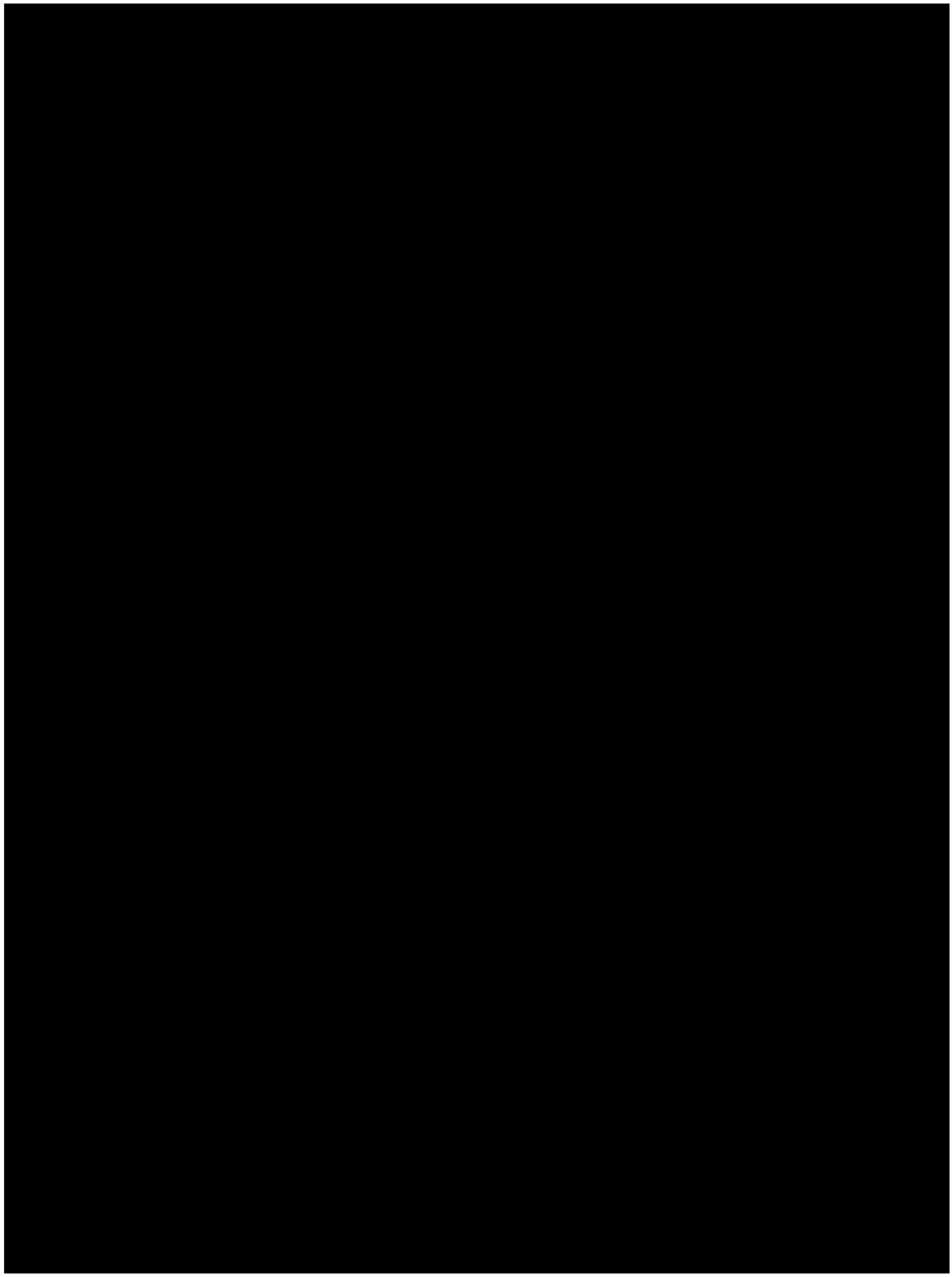

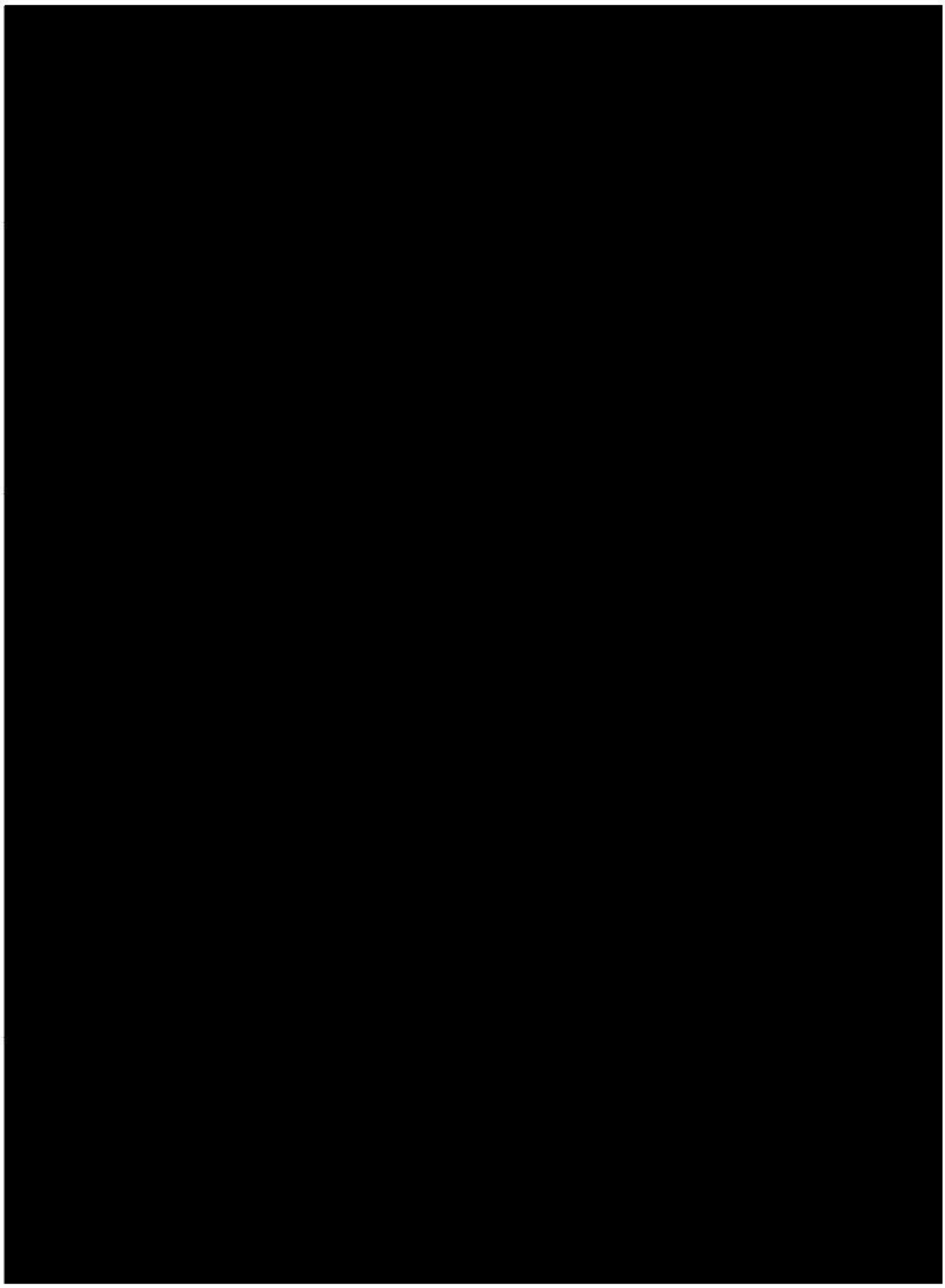

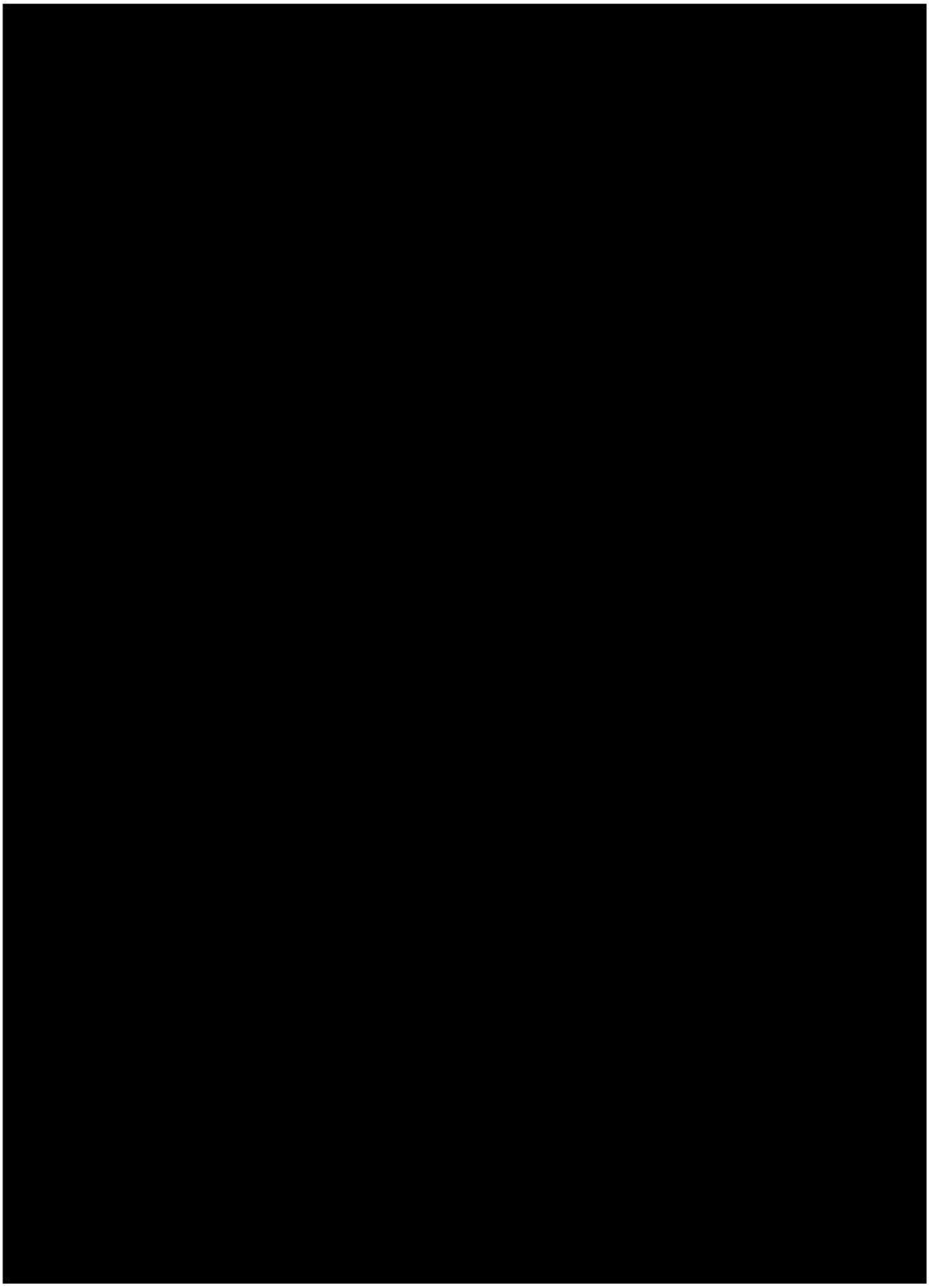

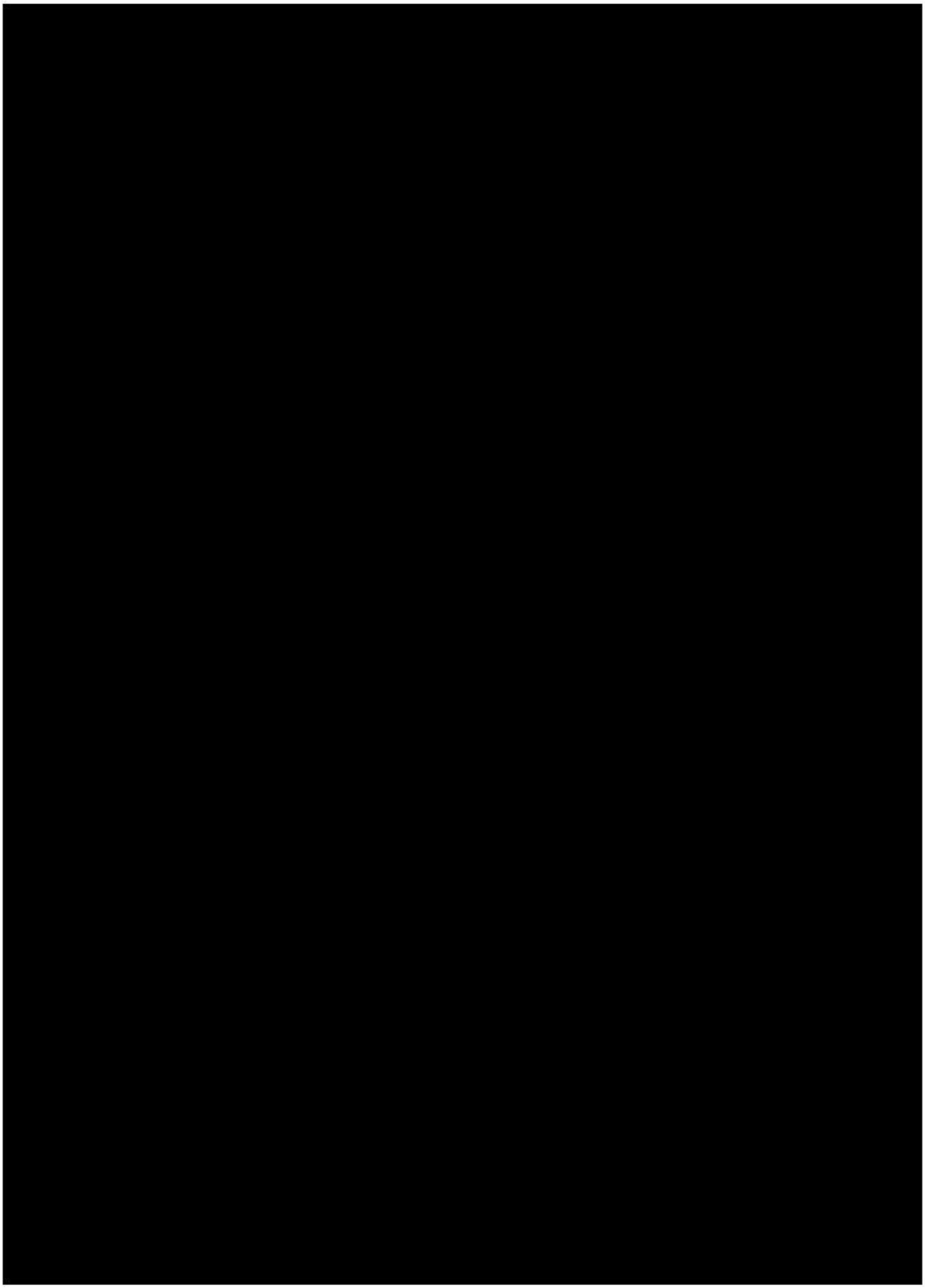

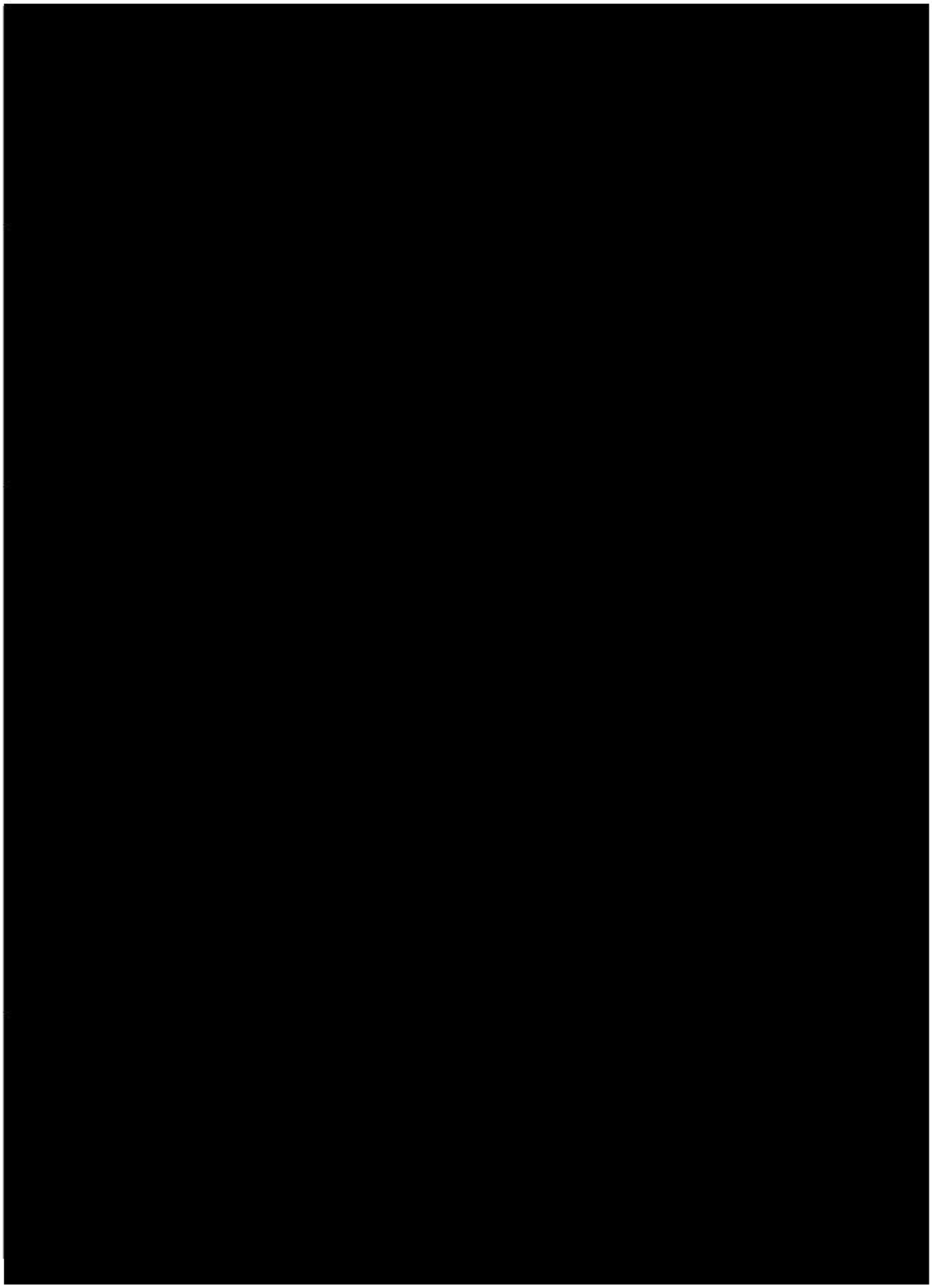

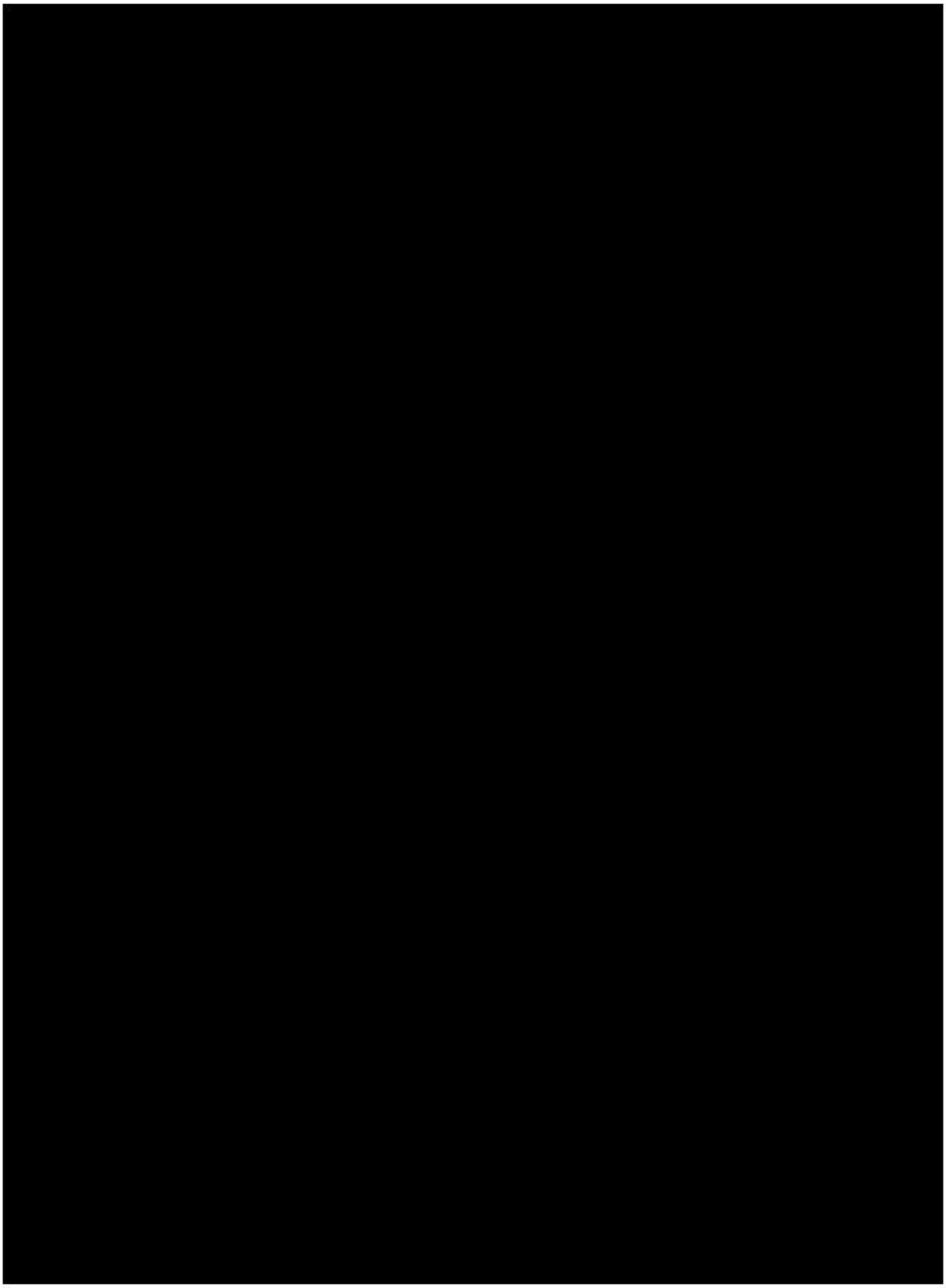

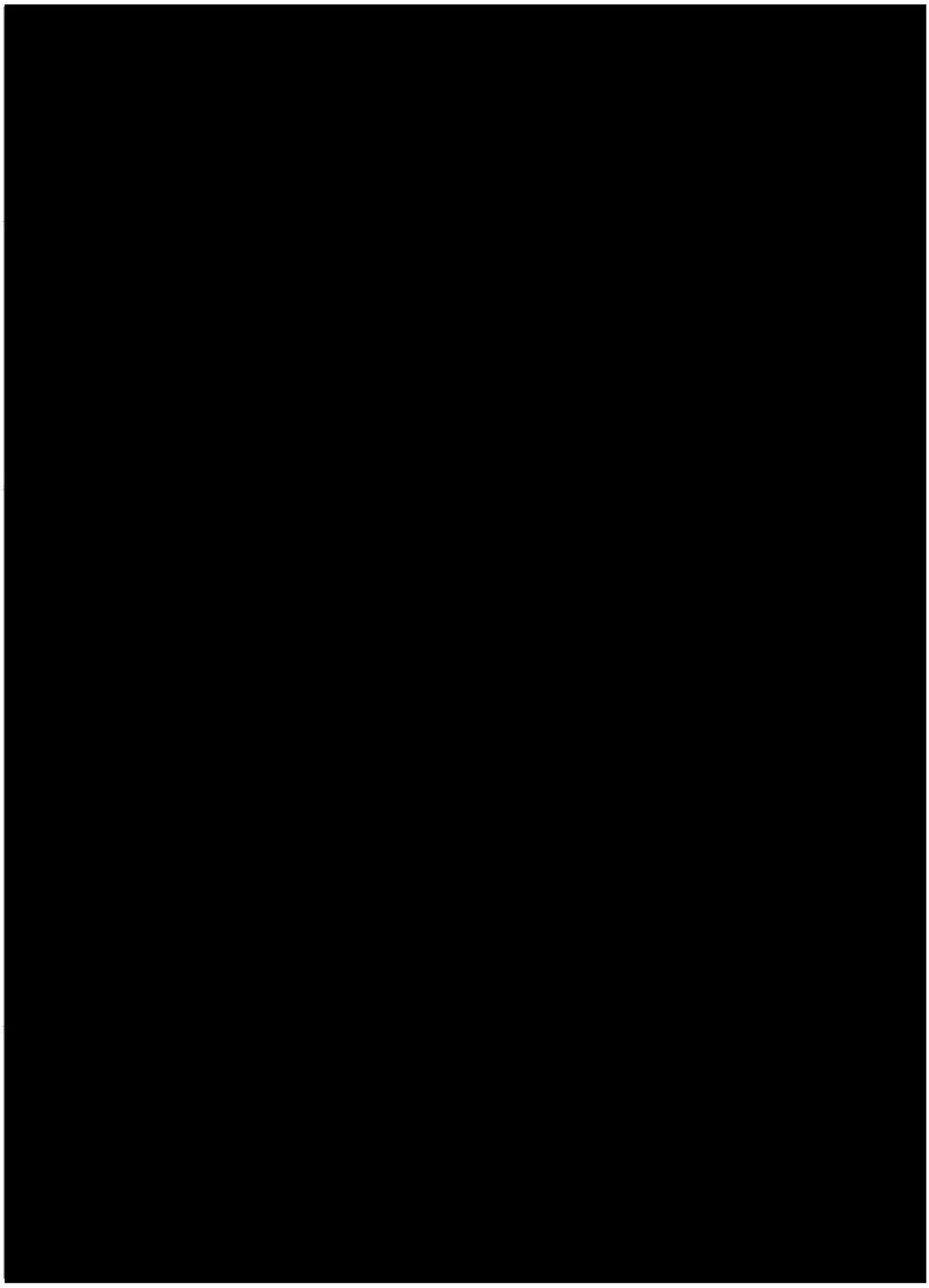

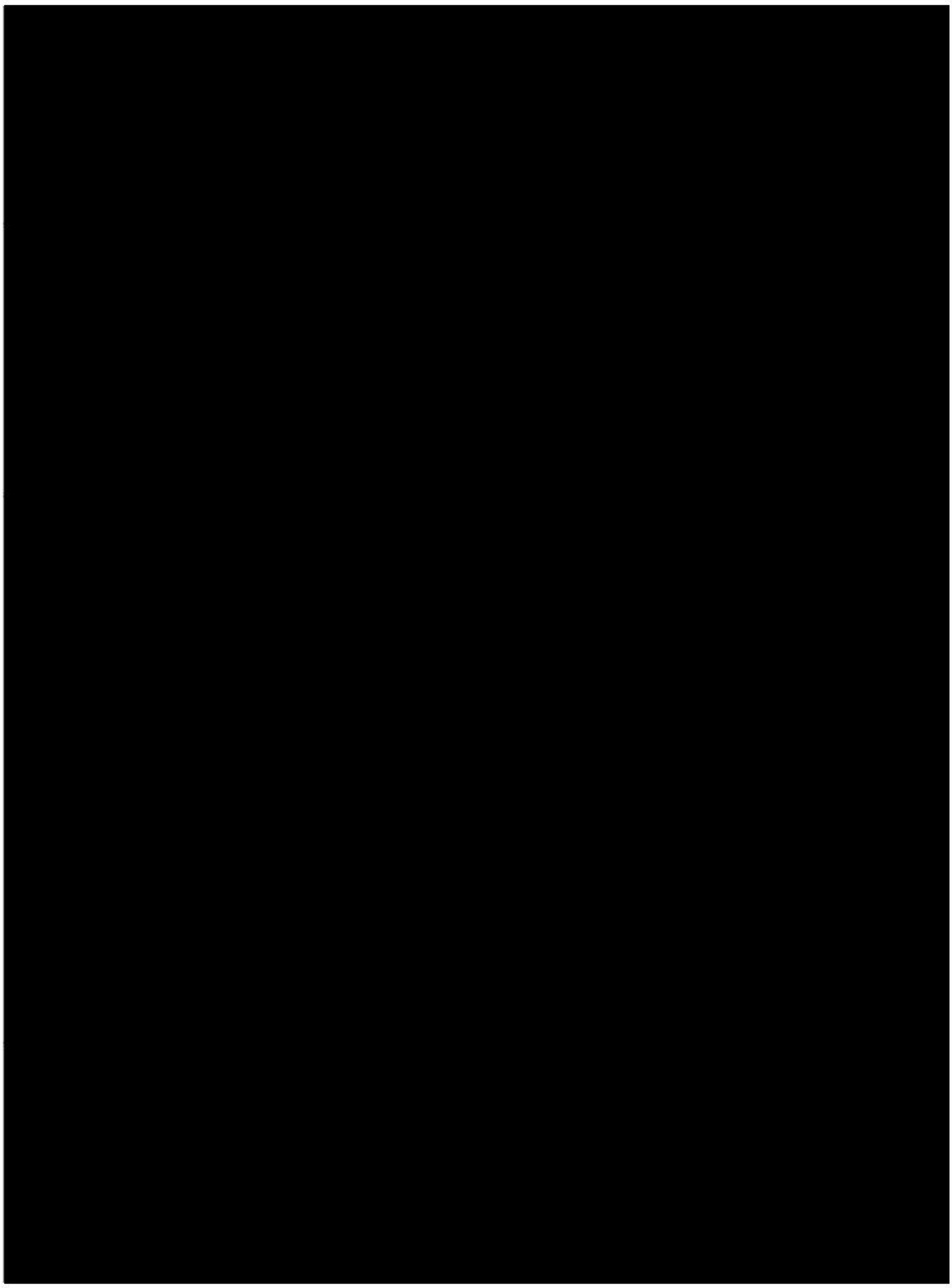

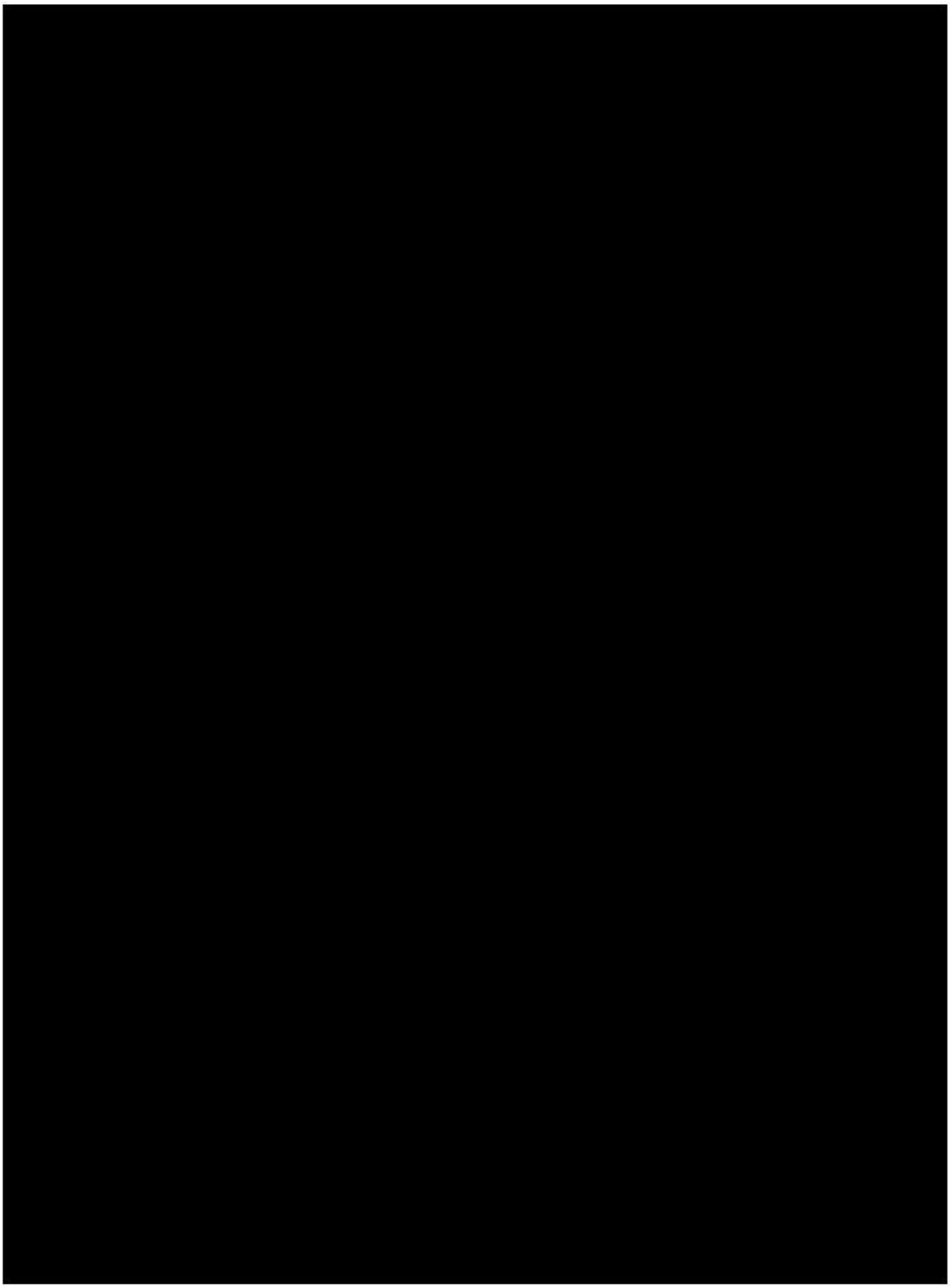

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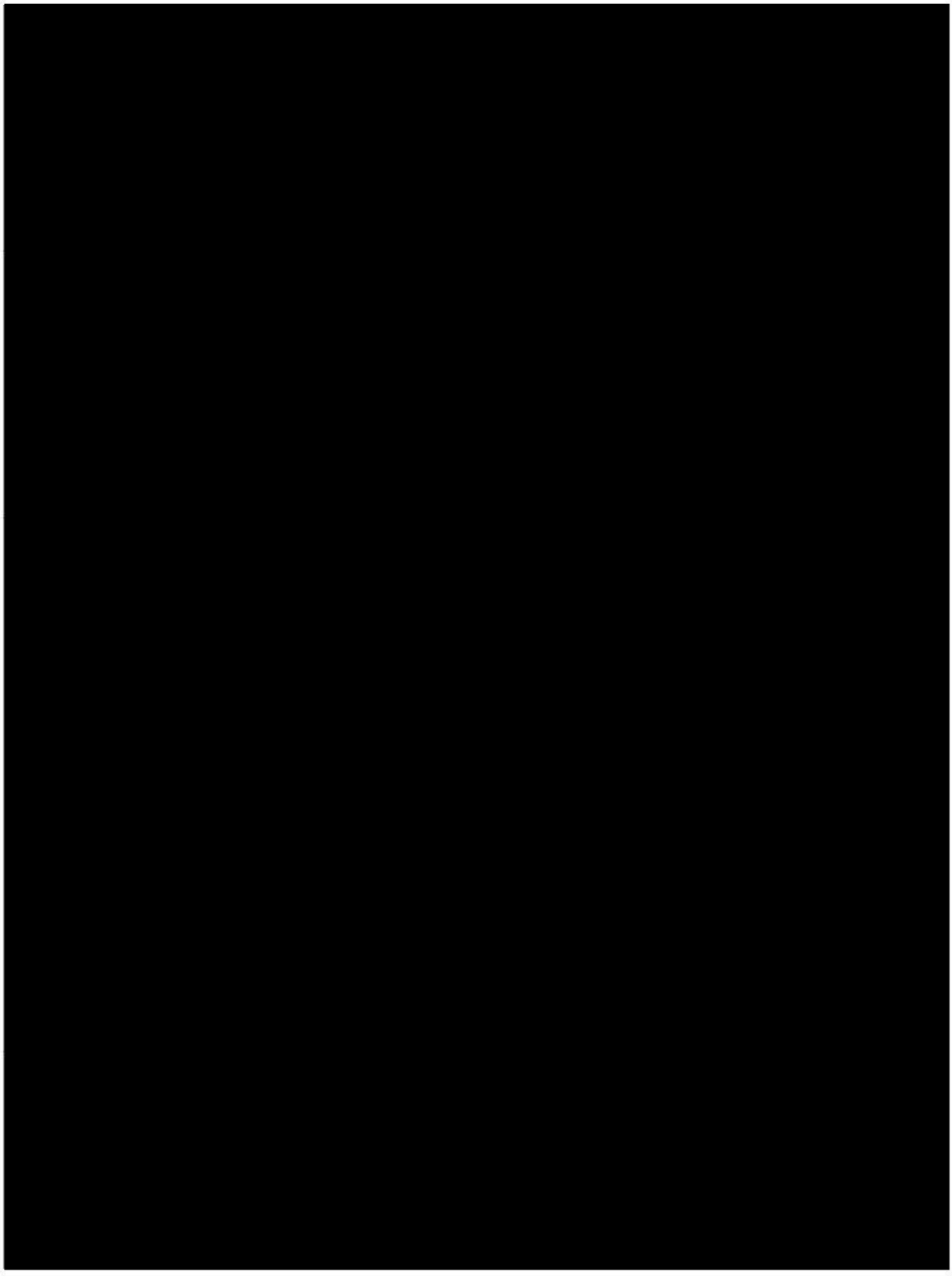

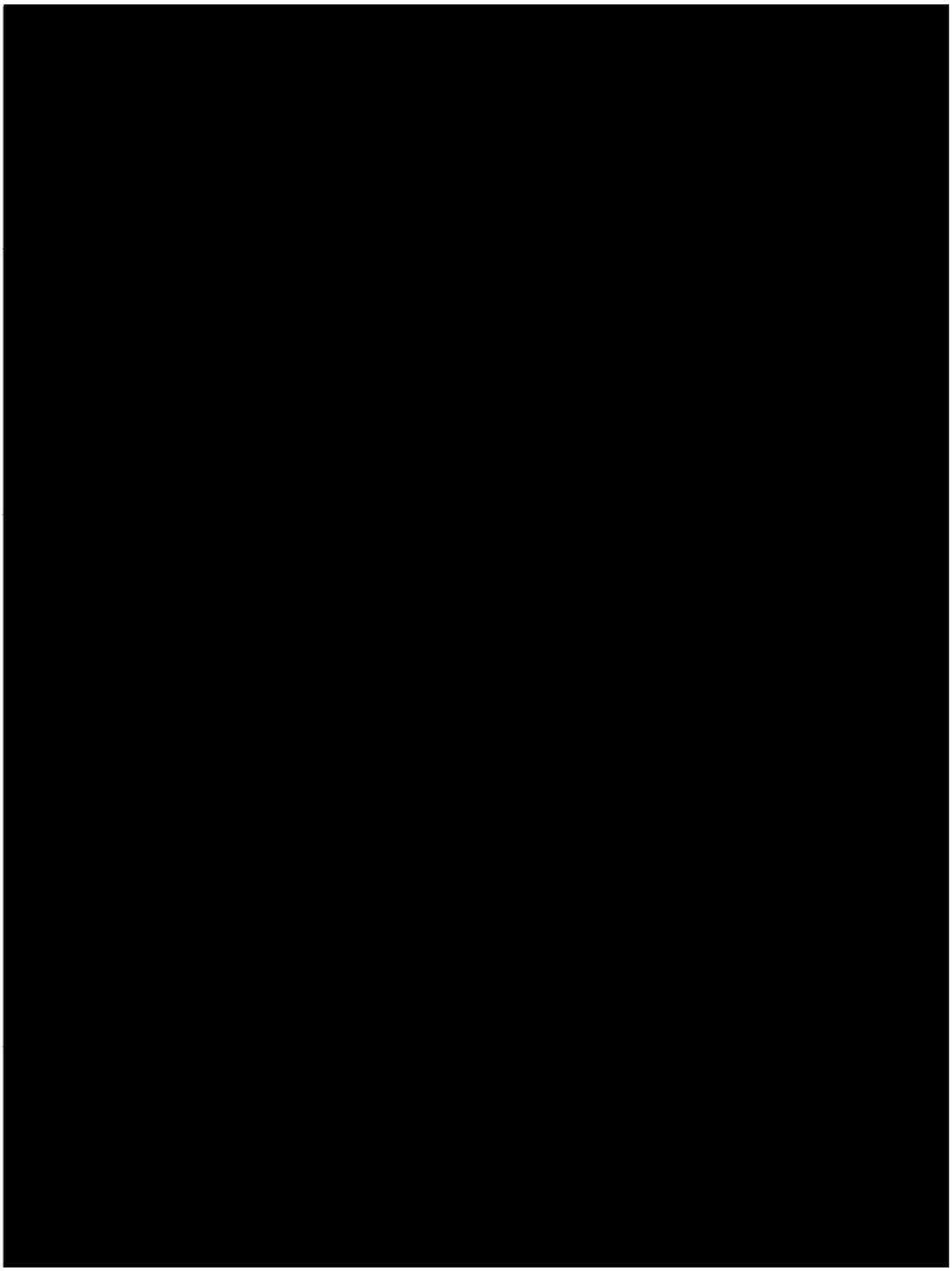

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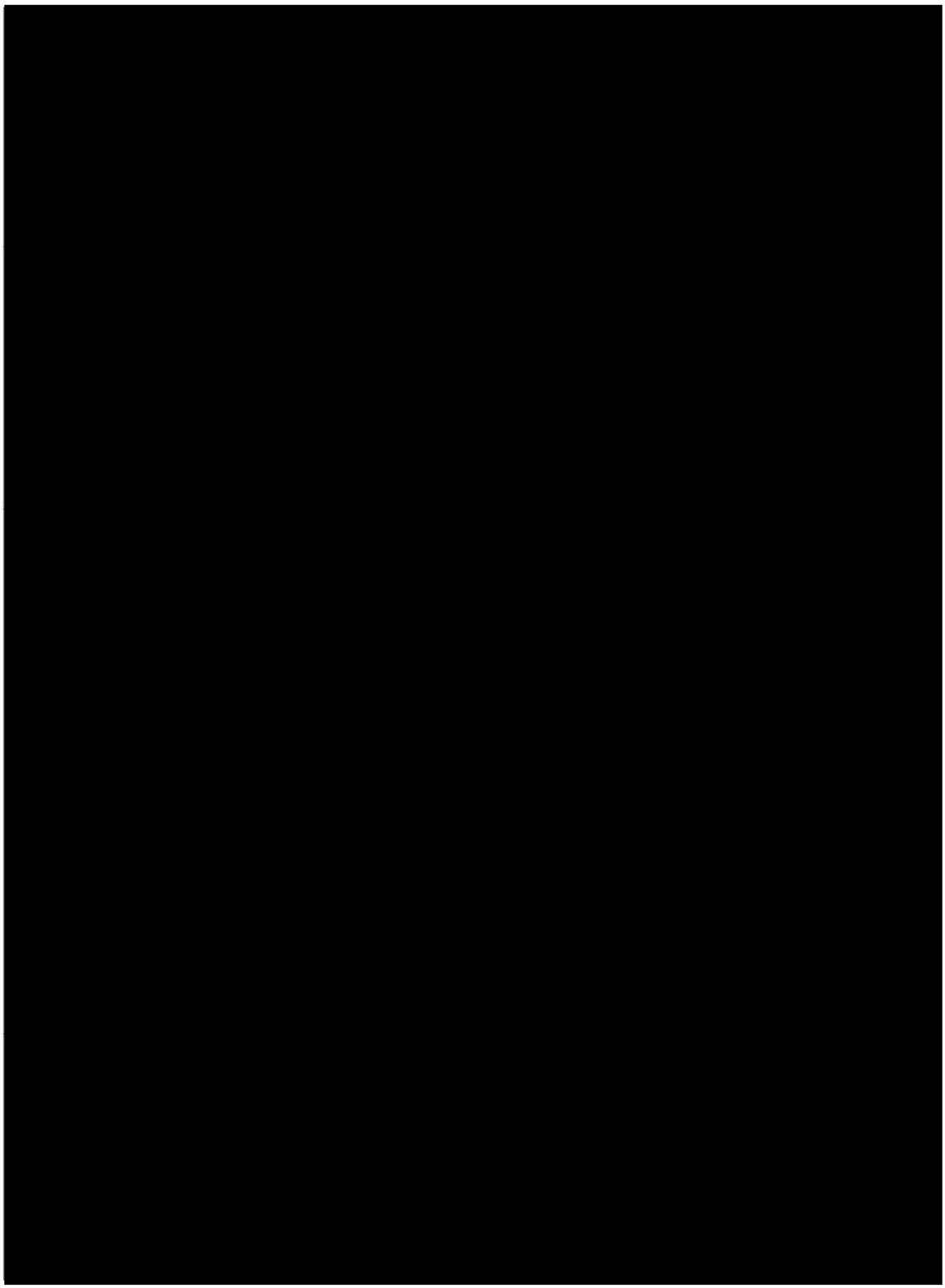

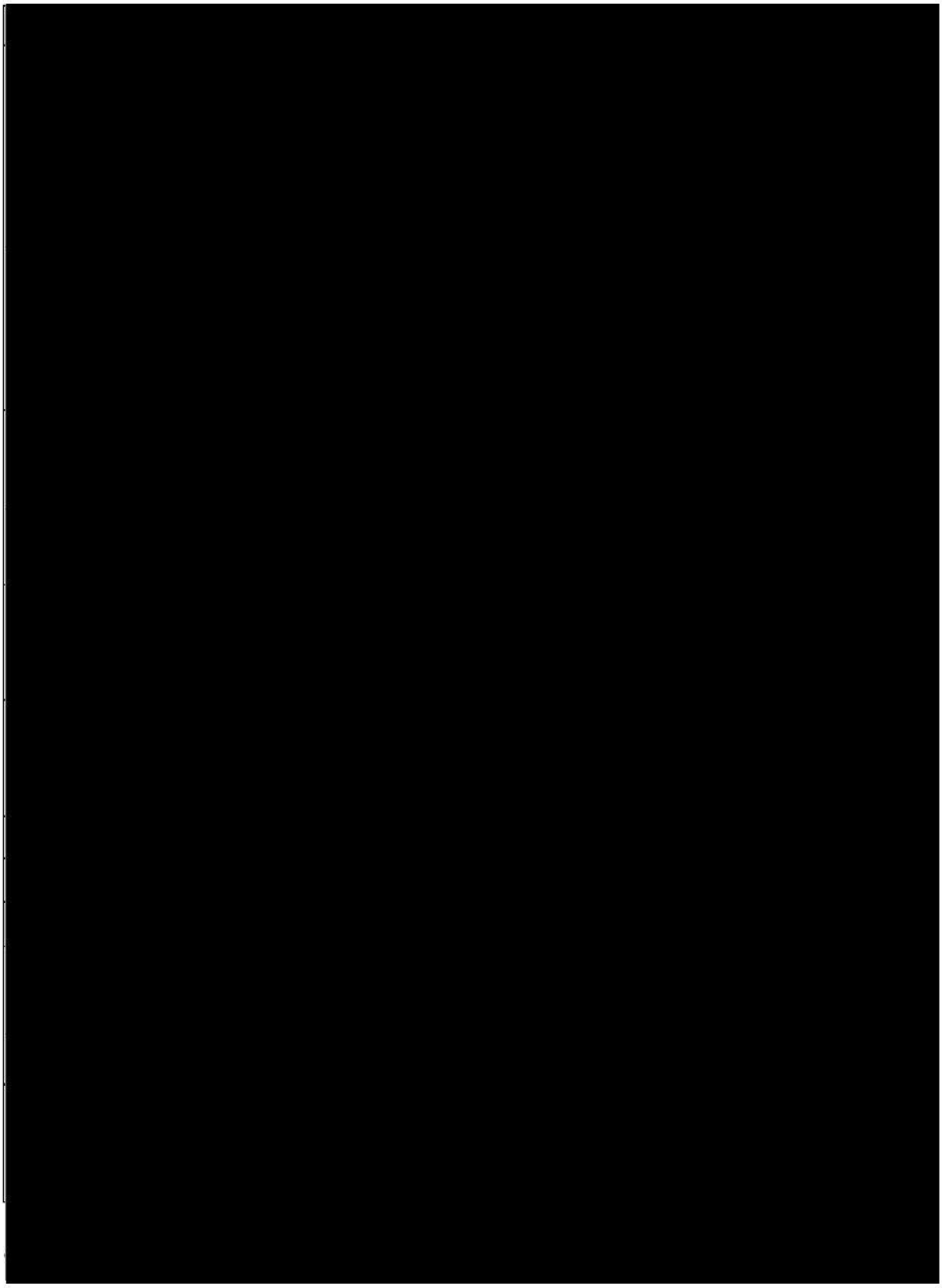

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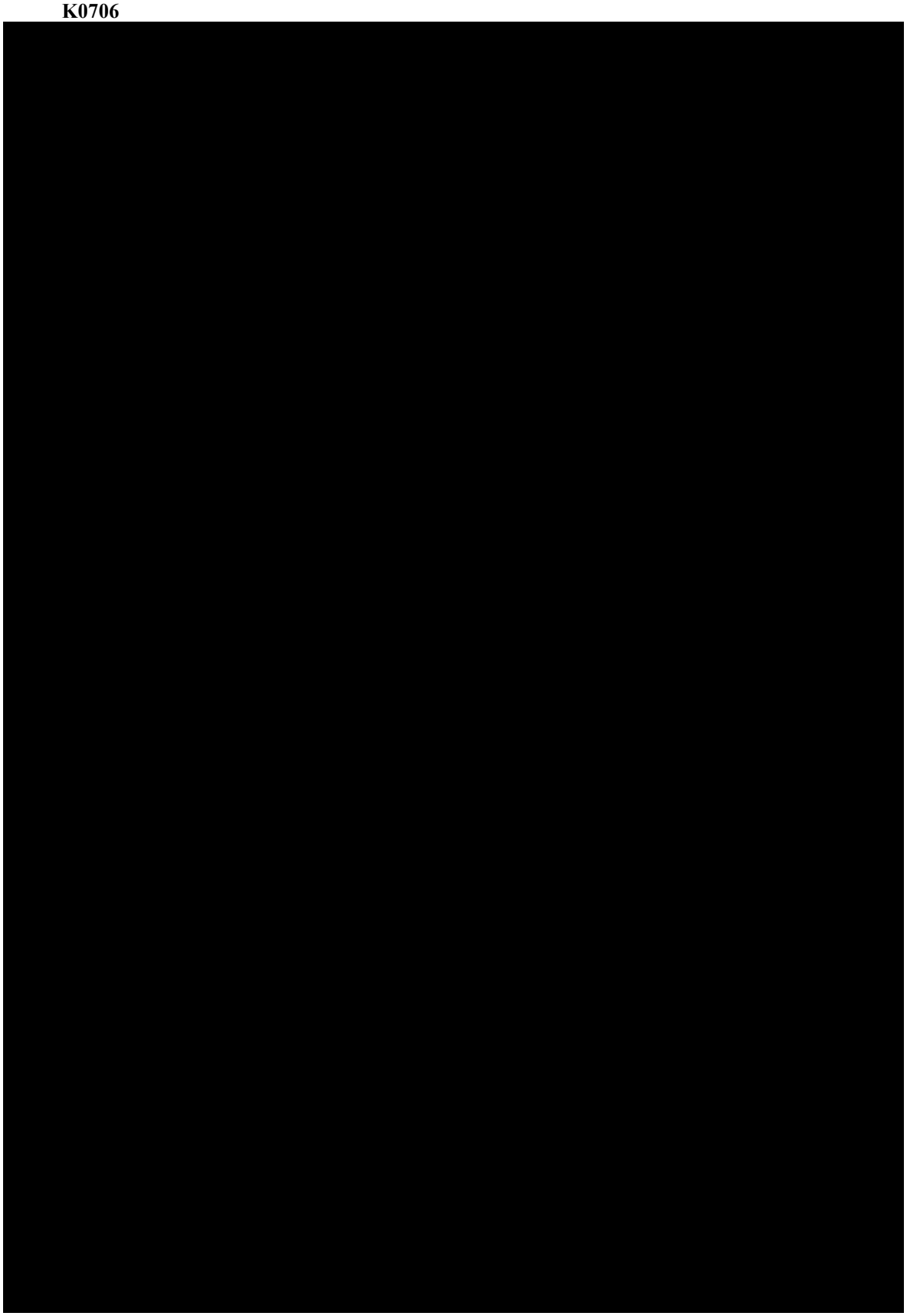

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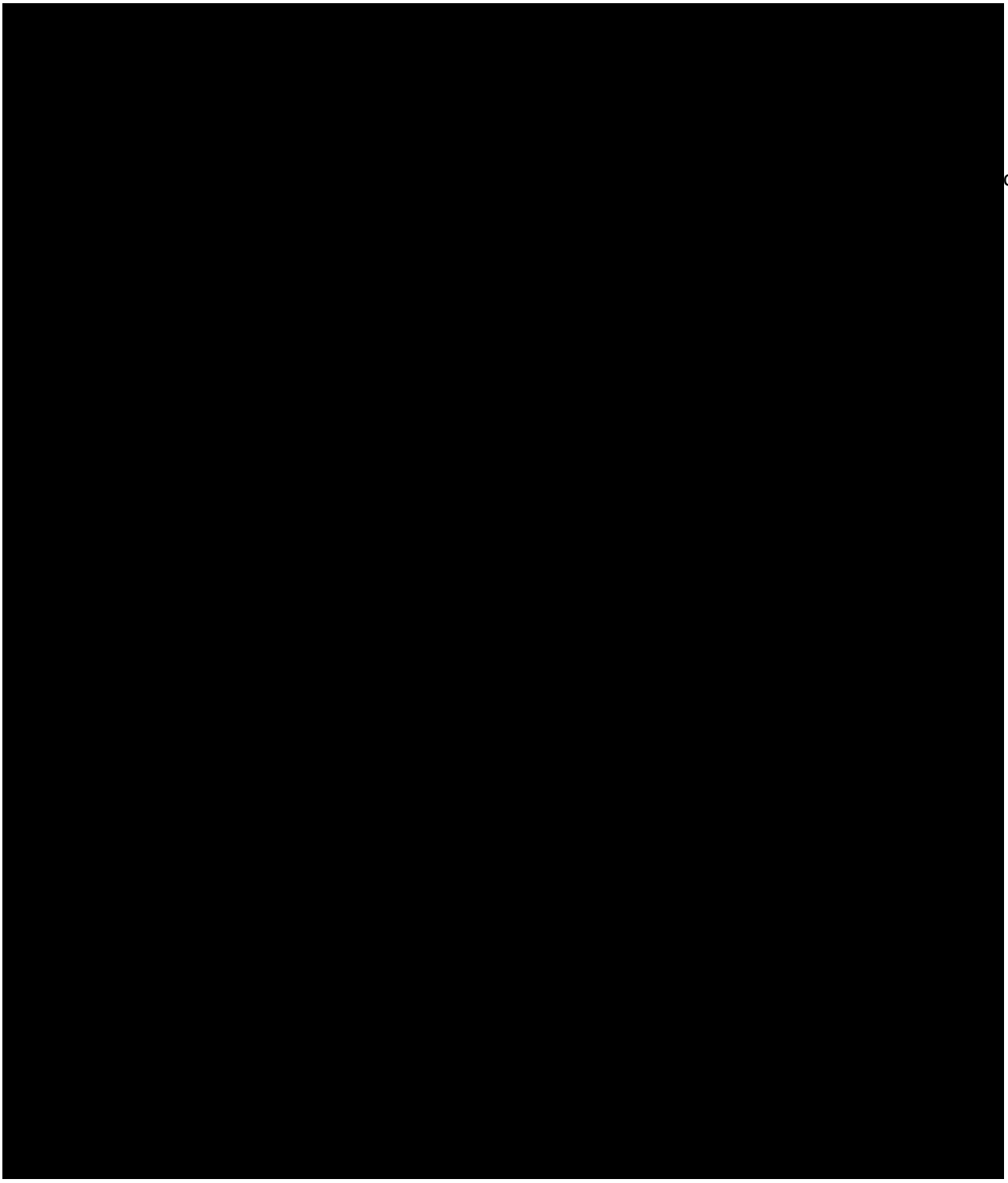
SCOPA-AUT



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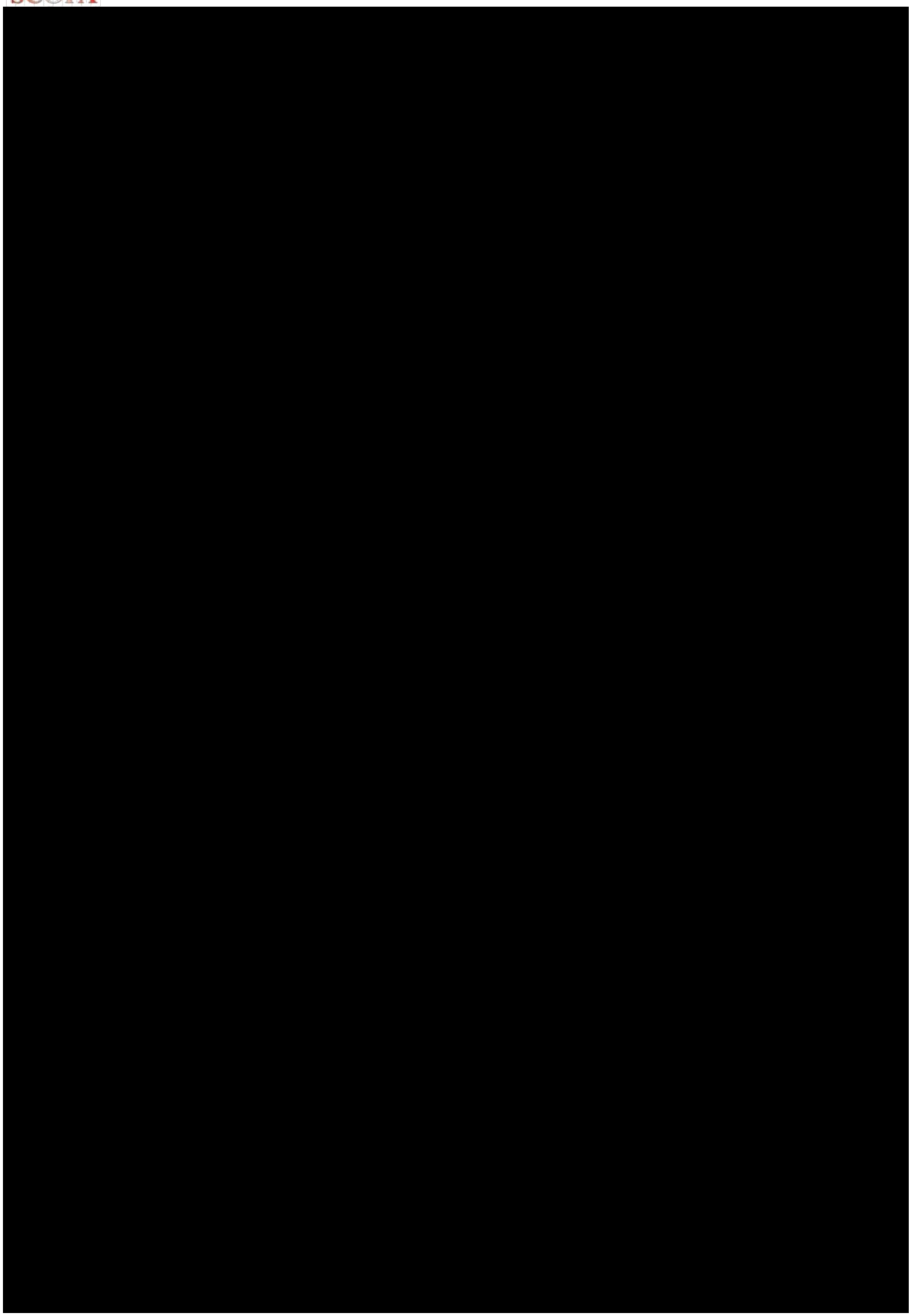

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