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Study ID: LVM-MD-11

Title: A Double-blind, Placebo- and Active-Controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Adolescent Patients With Major Depressive Disorder

Protocol Amendment 3 Date: 25 Mar 2019

1.0 TITLE PAGE

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A Double-blind, Placebo- and Active-Controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Adolescent Patients with Major Depressive Disorder

LVM-MD-11

Original Protocol Date:	01 Dec 2014
Amendment #1:	08 Jun 2015
Amendment #2:	08 Aug 2016
Amendment #3:	25 Mar 2019

25 Mar 2019

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study LVM-MD-11	
Title of Study	A Double-blind, Placebo- and Active-Controlled Evaluation of the Safety and Efficacy of Levomilnacipran ER in Adolescent Patients With Major Depressive Disorder
Study Centers	Approximately 80 study centers
Development Phase	3
Objective	To evaluate the efficacy, safety, and tolerability of levomilnacipran relative to placebo in adolescent outpatients (12-17 years) with major depressive disorder (MDD). In addition, the study is designed to obtain pharmacokinetic (PK) data to guide dose selection for future pediatric studies of levomilnacipran.
Methodology	Multicenter, randomized, double-blind, placebo- and active-controlled, fixed-dose study
Number of Patients	544 planned (136 per treatment group for placebo, levomilnacipran 40 mg/day, levomilnacipran 80 mg/day, and fluoxetine 20 mg/day)
Diagnosis and Main Criteria for Inclusion	Male and female outpatients, 12 to 17 years of age, who meet *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD; have a score of ≥ 40 on the Children's Depression Rating Scale–Revised (CDRS-R) at Visits 1 and 2, and Clinical Global Impressions-Severity (CGI-S) ≥ 4 at Visits 1 and 2. The Kiddie Schedule for Affective Disorders–Present and Lifetime (K-SADS–PL) will be used to confirm the diagnosis of MDD and to document the patient's psychiatric history.
Test Product, Dosage, and Mode of Administration	Encapsulated Levomilnacipran extended release (ER) 10 mg, 20 mg, and 40 mg capsules; once daily oral administration, at the same time each day
Duration of Treatment	9 weeks in duration: 8 weeks of double-blind treatment and a 1-week double-blind down-taper period
Reference Therapy, Dosage, and Mode of Administration	Placebo capsules, once-daily oral administration, at the same time each day Encapsulated fluoxetine 10 mg ***capsules*** and ***encapsulated fluoxetine*** 20 mg tablets; once-daily oral administration, at the same time each day
Criteria for Evaluation	
Primary Outcome Measure	CDRS-R change from baseline at Week 8
Secondary Outcome Measure	CGI-S change from baseline at Week 8
[redacted]	[redacted]
[redacted]	[redacted]

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Statistical Methods	The primary efficacy parameter is the change from baseline to end of Week 8 of the double-blind treatment period in the CDRS-R total score. The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as the fixed effects and the baseline value and baseline value–by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. This analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values. The secondary efficacy parameter is the change from baseline to end of Week 8 of the double-blind treatment period in CGI-S. This parameter will be analyzed using an MMRM similarly to the primary efficacy parameter. Multiple comparisons for the primary and secondary efficacy parameters will be addressed using the matched parallel gatekeeping procedure. All safety parameters will be analyzed descriptively. The safety analysis will be performed using the *Safety Population,* defined as all randomized patients who received at least 1 dose of the investigational product. Efficacy analyses will be performed using the *Intent-to-Treat (ITT) Population,* defined as all patients in the Safety Population who had the baseline and at least 1 postbaseline assessment of CDRS-R total score. [redacted]

[redacted]

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4.0 LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
AUC	area under the plasma concentration versus time curve
CDRS-R	Children's Depression Rating Scale-Revised
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
[redacted]	[redacted]
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ER	extended release
ET	early termination
FDA	Food and Drug Administration
FR	Federal Register
FRI	Forest Research Institute, Inc.
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

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IRB	Institutional Review Board
ITT	intent to treat
IVRS	interactive voice response system
IWRS	interactive Web response system
K-SADS-PL	Kiddie Schedule for Affective Disorders–Present and Lifetime
LAR	legally authorized representative
LOCF	last observation carried forward
MDD	major depressive disorder
MMRM	mixed-effects model for repeated measures
NDA	New Drug Application
NE	norepinephrine
PCS	potentially clinically significant
PID	patient identification
PK	pharmacokinetic, pharmacokinetics
PVC	premature ventricular contraction
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/[RR]^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/[RR]^{1/3}$)
SAE	serious adverse event
SFU	safety follow-up
SNRI	serotonin and norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

United States
Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Forest Research Institute (FRI [the Sponsor]) along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with the US CFR, Title 21, Part 56.

Outside the United States
This study will be carried out in full compliance with the guidelines of the independent ethics committee (IEC) and government agencies of each respective country as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the study center will require approval from an IEC and government agency. During the course of the study, FRI or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, ICF, information sheet advertisements, and amendments (if any) will be approved by the IEC at the study center in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

5.2 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the US CFR.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study, patients will give voluntary and written informed assent and the parent(s)/legal guardian, or legally authorized representative (LAR) will provide voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) before participating in any study-related procedures.

Patients unable to give written informed assent must orally assent to the procedures; and written consent must be obtained from their parent(s)/legal guardian (either parent or legal guardian will be referred to as the LAR) in accordance with the appropriate local laws, where applicable.

Each patient and his/her LAR will read, assent to an understanding of, and sign an assent/ICF, the HIPAA authorization form, or other locally applicable regulations and authorization form after having had an opportunity to discuss the documents with the study staff before signing. Each patient and his/her LAR will be made aware that he or she may withdraw from the study at any time.

A caregiver is a person identified as able and willing to provide safety and efficacy information about the patient and oversee the administration of investigational product. He/she may be a different individual than the LAR. In order for the patient to be eligible for the study, the caregiver, whether or not the LAR, must read and sign the caregiver consent and meet the relevant inclusion/exclusion criteria. If the LAR is the caregiver, he/she will be asked to sign both the parent/legal guardian consent and the caregiver consent.

Signed copies of the ICF will be given to the patient and LAR. In addition, a signed copy of the caregiver consent will be given to the caregiver. All original ICF documents will be placed in the Investigator's study files. The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 80 study centers.

The Investigator is responsible for ensuring that the investigation is conducted according to the signed Investigator's Statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at each site must meet his or her obligations to the patients, ethics committee, FRI, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance consistent with the study investigational plan. The Investigator at each site will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB/IEC, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

Major depressive disorder (MDD) is a common and serious illness in children and adolescents. Epidemiological studies and clinical samples estimate the prevalence of MDD as approximately 1%-2% of prepubertal children, and between 3% and 8% of adolescents (Zalsman et al, 2006). By the ages of 10 to 15, girls appear to be more likely to experience depression than boys (Angold et al, 1998).

MDD is commonly associated with feelings of worthlessness, low self-esteem, and thoughts of suicide and its psychosocial burden in the formative years can compromise the developmental process. Patients also experience difficulties with concentration and motivation, impairing functioning in this critical period. Each year as many as 20% of adolescents have suicidal ideation and 9% attempt suicide (Grunbaum JA, 2002). Suicide is a leading cause of death in adolescents and is a major public health concern (CDC, 2014). A major risk factor for suicide in adolescents is major depression.

MDD in children and adolescents can be chronic and recurrent. The mean length of pediatric depressive episodes is approximately 7 months, and in the course of a first episode, up to 40% of patients appear to recover without specific treatment. However, patients who do not recover appear to be at high risk of chronic depression, and those who do recover have high rates of recurrence and dysthymia (Zalsman et al, 2006).

As a pharmacological treatment, the use of selective serotonin reuptake inhibitors (SSRIs) for children and adults increased approximately 7-fold during the 1990s. Fluoxetine (Prozac®), an SSRI, is approved by the FDA for the treatment of MDD in children and adolescents 8 years and older. Escitalopram (Lexapro®), another SSRI, is approved for the treatment of MDD in patients aged 12 and over. Currently, no serotonin and norepinephrine reuptake inhibitors (SNRIs) have been approved for the treatment of MDD in children or adolescents.

Levomilnacipran is an SNRI approved for the treatment of MDD in adults in the United States. The pharmacologic mechanism of the antidepressant activity of levomilnacipran and other SNRIs (ie, duloxetine, venlafaxine, and desvenlafaxine) is thought to be mediated through inhibition of norepinephrine (NE) and 5-hydroxytryptamine (serotonin) (5-HT) reuptake in the central nervous system. Although all SNRIs (as a class) block 5-HT and NE reuptake, currently marketed SNRIs (duloxetine, venlafaxine, and desvenlafaxine) are more potent inhibitors of 5-HT reuptake than of NE reuptake (Deecher et al, 2006; Vaishnavi et al, 2004). Levomilnacipran exhibits a distinct *in vitro* profile, exhibiting more potent inhibition of NE reuptake than 5-HT reuptake (Auclair et al, 2013). This greater potency at the NE transporter may confer additional improvements specifically in those domains associated with noradrenergic neurotransmission; for example: alertness, energy, attention, and anhedonia (Montgomery and Briley, 2011).

The efficacy of levomilnacipran as measured by the Montgomery-Åsberg Depression Rating Scale total score was established in 3 pivotal studies of adult patients with MDD. Levomilnacipran also demonstrated superiority over placebo as measured by improvement in the Sheehan Disability Scale functional impairment total score. These studies, which were conducted in the United States and Canada, were placebo-controlled; no active comparator was included. Two of the studies were fixed-dose studies (LVM-MD-01: placebo, levomilnacipran 40 mg/day, 80 mg/day, and 120 mg/day, and LVM-MD-10: placebo, levomilnacipran 40 and 80 mg/day) and 1 study was flexible-dose (LVM-MD-03: placebo, levomilnacipran 40 mg/day to 120 mg/day).

In summary, MDD is a condition common in children and adolescents and is a major public health concern. Current approved treatment options for this condition are limited to the 2 aforementioned SSRI products. Since the modulation of energy, vigilance, and arousal can be directly linked to the noradrenergic system, it has been suggested that antidepressants with a prominent noradrenergic component, such as levomilnacipran, may be particularly effective in addressing functional impairment, decreased concentration, lassitude, mental and physical slowing, and decreased self-care (Citrome, 2013). Brain serotonin and norepinephrine systems continue to mature through childhood and adolescence, however, and these maturational effects may generate age-related differences in patients' responses to pharmacotherapy. Thus, it is important that further investigation of SNRI treatment options such as levomilnacipran be evaluated systematically for the treatment of MDD in children and adolescents, so that an SNRI's efficacy and safety profile can be characterized in this population.

The current study of levomilnacipran extended release (ER) in adolescent patients (12-17 years old) with MDD will be conducted as required under the Pediatric Research Equity Act and as agreed upon with the FDA as a part of Postmarketing Requirement studies.

8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and tolerability of levomilnacipran relative to placebo in adolescent outpatients (12-17 years) with MDD. In addition, the study is designed to obtain pharmacokinetic (PK) data to guide dose selection for future pediatric studies of levomilnacipran.

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

Study LVM-MD-11 will be a randomized, double-blind, placebo- and active-controlled, parallel group, fixed-dose study in adolescent patients, ages 12-17 years. The study will be approximately 10 weeks in duration:

- 1-week screening/washout period
- 8-week double-blind treatment period
- 1-week double-blind down-taper period

The screening/washout period will generally be 1 week (± 3 days) prior to Visit 2, but may be extended up to a total of 5 weeks to accommodate prior medication washout or to repeat assessments. Patients will not receive any investigational product during the screening period.

Patients who meet the eligibility criteria at Visit 2 (Baseline) will be randomized to 1 of 4 treatment groups: placebo, levomilnacipran 40 mg/day, levomilnacipran 80 mg/day, or fluoxetine 20 mg/day. See Section 9.4.5 for details regarding dose selection and timing.

All randomized patients who complete the 8-week double-blind treatment period and patients who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week, double-blind down-taper period unless it is considered not clinically appropriate by the Investigator.

All patients must complete Visit 8/Early Termination (ET) Visit and, at the end of the down-taper period, return for Visit 9/Safety Follow-up (SFU) Visit. Patients who do not enter the down-taper period must return for Visit 9/SFU Visit approximately 1 week after Visit 8/ET Visit.

Approximately 544 patients (136 per treatment group) are planned to be randomized in the study.

Figure 9.1–1 provides a schematic of the study design. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit are provided in Section 9.5.5.

[redacted]

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This placebo- and active-controlled, fixed-dose design with an 8-week, double-blind treatment period was chosen based on prior studies that established the efficacy and safety of levomilnacipran in adult patients with MDD. In this study, Investigators must use a valid and reliable diagnostic method for recruiting and enrolling adolescents meeting *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD.

A placebo arm is included for comparison since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes than non-inferiority comparisons to a previously approved drug (Feifel, 2008; Laughren, 2001; Gispen-de Wied et al, 2012). In addition, placebo in place of the (limited) standard therapy should not cause irreversible health problems or extreme suffering (depression is recognized by the FDA as a condition in which there is substantial improvement and variability in placebo groups; see FDA Guidance for Industry: E10, May 2001).

Fluoxetine was selected as an active comparator for the present study because it is an SSRI approved by the FDA for the treatment of MDD in children and adolescents 8 years and older.

In the current study, safety and efficacy assessments are included in every visit to determine adequacy of response, safety, and tolerability for all patients.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

Patients must provide assent to participate and their LAR and caregiver (even if the same as the LAR) must provide written informed consent prior to the conduct of any study-specific procedures (see also Section 5.3).

To be eligible to participate in the study, patients must meet the following criteria:

1. Male or female outpatients between 12-17 years of age, inclusive, at Visit 1
2. Patients must meet DSM-IV-TR criteria for MDD, confirmed by K-SADS-PL
3. Patients must have a score ≥ 40 on the Children's Depression Rating Scale-Revised (CDRS-R) at Visits 1 and 2
4. Patients must have a Clinical Global Impressions-Severity (CGI-S) score ≥ 4 at Visits 1 and 2
5. Patients must have a caregiver who can and is willing to consent to be responsible for safety monitoring of the patient, provide information about the patient's condition, oversee the administration of investigational product, and accompany the patient to all study visits (see Section 5.3)
6. Patients must have normal physical examination findings, vital sign values, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that are judged not clinically significant by the Investigator
7. Female patients must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result at Visit 1

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria at Visit 1 (Screening) or Visit 2 (Baseline) will not be eligible to participate in the study**:**

Psychiatric Criteria

1. DSM-IV-TR–based diagnosis of an axis I disorder other than MDD that is the primary focus of treatment. Patients with conduct disorder will *not* be allowed to participate. Patients with comorbid diagnoses of learning disorders, attention deficit disorder (with or without hyperactivity), communication disorders, separation anxiety disorder, dysthymic disorder, oppositional defiant disorder, and anxiety disorders *will be allowed to participate in the study as long as these conditions are not the primary focus of any treatment* and they comply with concomitant medication limitations as listed in Appendix III

2. Prior diagnosis of mental retardation or amnestic or other cognitive disorders based on DSM-IV-TR criteria

3. [redacted]

4. Suicide risk as determined by meeting either of the following criteria:

   - Any suicide attempt within the past year
   - Significant risk at Visit 1 (Screening) or Visit 2 (Baseline), as judged by the Investigator based on the psychiatric interview or information collected in the Columbia-Suicide Severity Rating Scale (C-SSRS)

Treatment-Related Criteria

5. History of allergy, intolerance, or hypersensitivity to levomilnacipran, milnacipran, fluoxetine, or any other SSRI or SNRI or known hypersensitivity to the investigational products' non-medicinal ingredients including gelatin and cellulose

6. Patients requiring prohibited concomitant medication or herbal supplements that could not be discontinued or switched to an allowable alternative medication and stabilized for at least 2 weeks preceding Visit 2 (Baseline)

[redacted]

Other Medical criteria

9. Any concurrent medical condition that might interfere with the conduct of the study, confounds the interpretation of study results, or endangers the patient's well-being. [redacted]

10. Any cardiovascular disease or condition that is clinically significant, unstable, or decompensated. Additionally, patients with any of the following conditions are excluded from participation in the study:

[redacted]

[redacted]

13. History of seizure disorder (except simple childhood febrile seizures before age 5), unexplained syncope or black-out episodes, stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes the patient toward a risk for seizure

14. Liver enzyme tests (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) > 2 times the upper limit of normal (ULN)

[redacted]

16. History of drug or alcohol abuse or dependence within the past year

17. Positive result from the blood alcohol test or the urine drug screen (UDS) for prohibited substance, with the following exceptions:

[redacted]

18. Pregnant, breastfeeding, and/or planning to become pregnant and/or breastfeed during the study or within 30 days following the end of study participation

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[redacted]

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[redacted]

9.3.3 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who gave voluntary assent and/or whose LAR and/or caregiver signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study. Patients can be prematurely discontinued from the study for any of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Withdrawal of consent
- Adverse event (AE)
- Lack of efficacy
- Protocol violation
- Non-compliance with investigational product
- Lost to follow-up
- Study terminated by Sponsor
- Site terminated by Sponsor
- Other

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at ET (see Section 9.5.5.6 for details on assessments performed at Visit 8/ET). Patients who discontinued from the study and did not return to the site for final assessments must be requested in writing to do so and to return any unused investigational product. A copy of the letter, together with the source documentation, will be kept by the Investigator. The reasons for premature discontinuation from the study will be recorded on the Study Disposition Pages of the eCRF.

All randomized patients must complete Visit 8/ET Visit and return for Visit 9/SFU at the end of the down-taper period. Patients who do not enter the down-taper period must return for Visit 9/SFU approximately 1 week after Visit 8/ET Visit.

9.3.4 Patient Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

9.3.5 Demographic Considerations

Efforts will be made to have reasonable representation with respect to gender, race, and ethnicity, reflecting the proportions in the disease population. FRI will monitor enrollment and may instruct the sites accordingly.

9.4 TREATMENTS

Patients meeting the eligibility criteria at Visit 2 (Baseline) will be randomized in a double-blind fashion to 1 of 4 treatment groups: placebo, levomilnacipran 40 mg/day, levomilnacipran 80 mg/day, or fluoxetine 20 mg/day.

9.4.1 Treatments Administered

Investigational product in the form of over-encapsulated capsules and tablets will be packaged in blister cards and provided by FRI. Patients will be supplied with blinded investigational product and will be instructed to take 2 capsules orally each morning (see Section 9.4.5 for details). Confirmation that dosing scheme (including titration and down-taper) and dosing instructions were discussed with the patient and caregiver and that dosing instructions were provided will be recorded in the source documents.

9.4.2 Identity of Investigational Products

Investigational product will be supplied by FRI as capsules containing placebo or levomilnacipran 10 mg capsules, levomilnacipran 20 mg capsules, levomilnacipran 40 mg capsules, fluoxetine 10 mg ***capsules***, or fluoxetine 20 mg tablets packaged in blister cards.

The blister cards will contain sufficient numbers of doses for the interval of days between scheduled visits plus additional doses to accommodate visit scheduling.

The blister cards will be labeled with the protocol number, storage information, warning language (viz, "Caution: New Drug—Limited by Federal Law to Investigational Use"), and instructions to take as directed. The Investigator will write the date, visit number, study week, and patient identification (PID) number on the label.

All investigational product will be provided and shipped to the study centers by FRI and must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) at room temperature [redacted] and must be protected from light, heat, and moisture.

The Investigator is responsible for recording the receipt and use of all investigational product supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused investigational product must be returned; and, whenever investigational product are returned, unit counts must be performed. All investigational product must be accounted for. At the end of the study, all unused investigational product and empty investigational product packages must be returned to the Sponsor at the address provided in the Study Reference Binder.

9.4.3 Method of Assigning Patients to Treatment Groups

After the patient, LAR, and caregiver provide assent and sign the ICF at Visit 1 (Screening), study personnel will register the patient in the interactive Web response system (IWRS) system, and the system will assign the patient a sequential PID number. The first patient entered into the system at each site will be assigned the first number in the sequence by the system. [redacted]

The study center must contact the IWRS at Baseline (Visit 2) and all subsequent study visits in order to obtain the instructions on kit number for the investigational product to be dispensed to the patient at that visit.

A detailed description of IWRS procedures is contained in the IWRS ***Site User Guide*** that should be stored in the Study Reference Binder.

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9.4.4 Selection of Dosages in the Study

Doses were selected based on the population PK model submitted with NDA 204,168 (Study LVM-MS-01, 2012). To determine the doses for this adolescent study, a simulation was performed to infer adolescent plasma concentrations from adult plasma concentrations for the 120-mg dose. The simulation found that comparable concentrations are expected to be obtained in adolescents at 75% of the adult dose. Levomilnacipran has linear PK in adults and a linear PK profile is expected in children and adolescents. Therefore, plasma concentrations from doses of 30 mg to 90 mg per day in adolescents are expected to correspond to the adult plasma concentrations for the approved adult therapeutic range of 40-120 mg/day.

Levomilnacipran is currently available in 20 mg, 40 mg, 80 mg, and 120 mg capsules. In order to use existing strengths and to have more than 1 arm of levomilnacipran in this fixed-dose study, doses of 40 mg and 80 mg per day have been selected for the adolescent age range. A 10 mg capsule formulation is currently under development for the purpose of titration in this study. The corresponding plasma concentrations of these doses in adolescents are expected to remain within the plasma concentrations associated with the approved therapeutic dose range for adults.

9.4.5 Selection and Timing of Dose for Each Patient

Patients who meet all eligibility criteria at Screening (Visit 1) and who continue to meet all the eligibility criteria for participation in the study will be assigned a randomization number at Baseline (Visit 2) and dispensed the corresponding blister card containing capsules of double-blind investigational product for Week 1. Patients will begin dosing with double-blind capsules on the next day. Patients will be instructed to take 2 capsules orally as a single dose, once daily at approximately the same time each day (morning dosing recommended), with or without food.

Dosing may be switched from the morning to another time of day if a patient prefers or if tolerability issues arise. However, any switch must allow at least 20 hours between 2 consecutive doses.

9.4.5.1 Double-blind Treatment Period

The titration schedule is as follows:

- Levomilnacipran 40 mg/day treatment group: Days 1-2, 10 mg/da**y**; Days 3-7, 20 mg/day; Week 2 through Week 8, 40 mg/day

- Levomilnacipran 80 mg/day treatment group: Days 1-2, 10 mg/day; Days 3-4, 20 mg/day; Days 5-7, 40 mg/day; Week 2 through Week 8, 80 mg/day

- Fluoxetine 20 mg/day (active comparator): Week 1, 10 mg/day; Week 2 through Week 8, 20 mg/day

Patients will be assigned a randomization number at Visit 2 and dispensed the corresponding blister card containing capsules of double-blind investigational product for Week 1. Patients will begin dosing with double-blind capsules on the next morning. Patients will be instructed to take 2 capsules from each column (1 each from Row A and Row B) as a single dose daily each morning with or without food. The double-blind dosing regimen is presented in Table 9.4.5.1–1.

Patients will be instructed to return the blister card with any remaining investigational product, and to return it even if it is empty, preferably at the next study visit. Additional investigational product will be dispensed as per the schedule shown in Section 2.0.

If a patient experiences an AE, the investigational product may be stopped for up to a maximum of 4 consecutive days. The date and reason for missed doses must be recorded on the appropriate page of the eCRF.

9.4.5.2 Double-Blind Down-Taper Period

All randomized patients who complete the 8-week double-blind treatment period and patients who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week, double-blind down-taper period unless it is considered not clinically appropriate by the Investigator. The double-blind down-titration regimen is as follows:

- Levomilnacipran 40 mg/day and 80 mg/day treatment groups: Days 1-2, 40 mg/day; Days 3-7, 20 mg/day

- Fluoxetine 20 mg/day: Days 1-7, 10 mg/day

9.4.6 Blinding

A list of patient randomization codes will be generated by Statistical Programming at FRI and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

9.4.7 Unblinding

Any unblinding at the study center level should be done only in an emergency that requires for the investigational product to be identified for the medical management of the patient. The Investigator must notify the Study Physician immediately (see Appendix II) and a full written explanation must be provided if the blind is broken. Before the investigational product is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study center will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Global Drug Safety at FRI for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the patient will not need to be disqualified from the study.

In an emergency, the Investigator can obtain the treatment assignment of any patient at his/her study center through the IWRS. In an emergency, the Investigator should access the IWRS to break the blind.

9.4.8 Prior and Concomitant Therapy

A list of concomitant medications that are allowed and not allowed for either episodic or chronic use is provided in Appendix III. Medication history (psychotropic medication history during the previous 5 years and all other medications during the past 12 months) will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

9.4.9 Monitoring Treatment Compliance

Investigational product compliance during any treatment period will be closely monitored by counting the number of capsules dispensed and returned. Before new investigational product is dispensed at each visit, every effort will be made to collect all unused investigational product. Patients who do not take investigational product for 5 or more consecutive days, or consistently demonstrate poor compliance (< 80% or > 120% in 2 consecutive visit intervals, measured by capsule count) should be considered for study discontinuation. Investigators should consult with the Study Physician before discontinuing a patient due to poor compliance.

9.4.10 Treatment After Discontinuation

Patients whose MDD symptoms worsen or are determined by the Investigator to be inadequately controlled before completing the double-blind treatment period are allowed to discontinue investigational product and start appropriate treatment at the Investigator's discretion. This new treatment will not be provided by FRI. Patients who initiate a new treatment for MDD must be discontinued from the study.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

The efficacy assessments will include the CDRS-R, CGI-S, and Clinician Global Impressions-Improvement (CGI-I). Efficacy assessments are not to be administered if the patient is not accompanied by his/her consented caregiver. The K-SADS-PL and all efficacy assessments will be conducted by experienced clinicians meeting training requirements and qualifications standards established by FRI and rater training vendor.

9.5.1.1 Primary Efficacy Assessment

The CDRS-R (Appendix V; Poznanski and Mokros, 1996) is a semi-structured, clinician-rated instrument designed for use with children and adolescents between the ages of 6-17 years and contains 17 ordinally-scaled items that evaluate the presence and severity of symptoms commonly associated with childhood depression. The CDRS-R total score ranges from 17 to 113.

The CDRS-R will be administered separately to the patient and to the caregiver. For each item, the clinician administering the interviews will select the rating that provides the best description of the patient and will then determine the total score.

9.5.1.2 Secondary Efficacy Assessment

The CGI-S (Appendix VI; Guy, 1976) is a clinician-rated scale used to rate the severity of the patient's current state of mental illness compared with an MDD patient population. The patient will be rated on a scale from 1 to 7, with 1 indicating a "normal, not at all ill" and 7 indicating "among the most extremely ill patients."

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9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits. Scheduled safety assessments are not to be administered if the patient is not accompanied by his/her consented caregiver.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of data collection for this study, any untoward event that was reported from the time the patient signed the ICF until 30 days after the last dose of treatment is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study center personnel

- All diseases that occur after signing ICF, including any change in severity or frequency of preexisting disease

- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note that medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

9.5.2.2 Causality Assessment

For each AE, the Investigator must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility that the investigational product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

9.5.2.4 Serious Adverse Events

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of investigational product dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.5 Reporting Adverse Events and Serious Adverse Events

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study center personnel will record all pertinent information in the patient's eCRF.

In addition, any SAEs reported by the patient (or patient representative) or otherwise identified by the Investigator after the study period (ie, after 30 days post last dose) should be documented and reported.

All AEs must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to the investigational product.

For every AE, the Investigator must:

- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, patients are to be reminded, as described in the ICF and in accordance with Section 9.5.2.1, to notify site personnel of any AEs occurring during the 30 day post-study period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least one of the following conditions is met: 1) the event meets the criteria for an SAE (see Sections 9.5.2.4 and 9.5.2.6), and/or 2) the event is judged by the Investigator to be potentially causally related to investigational product.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

9.5.2.6 Immediate Reporting of Serious Adverse Events and Events of Special Interest

FRI is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, FRI must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to Global Drug Safety on the SAE Form for Clinical Trials. The Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The study center must transmit the SAE Form for Clinical Trials to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study center.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. ***FRI may contact the study center to solicit additional information or follow up on the event.***

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9.5.2.7 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the patient signs the ICF until 30 days after the last dose of investigational product. Within 24 hours of learning of a pregnancy, the study center personnel must report the event to Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in Section 9.5.2.6, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 9.5.2.6 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

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9.5.3 Investigational Product Concentration Measurements

For patients enrolled under protocol amendment #3, no PK sampling will be conducted. For patients enrolled prior to protocol amendment #3, the following procedures should be followed:

PK blood samples will be collected from assented/consented patients to determine plasma concentrations of levomilnacipran. The blood sample will be processed, stored, and shipped as indicated in Appendix IV. The population PK of levomilnacipran will be characterized using serial and sparse plasma concentration-time data. Non-compartmental analysis using the serial concentration-time data will also be performed. The plasma concentration-time data collected will provide estimates of PK parameters, eg, area under the curve (AUC), half-life, maximum plasma drug concentration, and time of maximum plasma concentration.

Sparse PK blood samples will be collected during Visits 5, 6, 7, and 8, or ET as follows:

- Visit 5, a pre-dose and at 1-4 hours post-dose
- Visit 6, 4-6 hours post-dose
- Visit 7, 6-8 hours post-dose
- Visit 8, random post-dose sample

In case of scheduling constraints, the sampling times above may be collected in a different sequence among the specified visits.

From a subset of consented patients, instead of sparse PK samples, 7 serial PK blood samples will be collected at Visit 5 (or at any 24-hour period between Visit 5 and Visit 7, inclusive) at the following time points: pre-dose (20-24 hours after the most recent dose), and 2, 4, 6, 8, 10-12, and 24-hours post-dose.

To allow for a pre-dose sampling, patients who take their daily dose in the morning will be instructed to hold their daily dose on the sampling day and take it when instructed at the study center. Patients who take their dose in the evening will be instructed to not take their dose on the evening before the pre-dose sampling visit and to bring the daily dose to the site.

PK samples will not be obtained from patients who missed investigational product dosing for 2 or more consecutive days before the sampling date.

The actual date and clock times of the reference dose (the last dose taken before the PK sample) and all blood draws will be recorded in the eCRF along with the date and time of the dose before the reference dose for each patient who undergoes PK sampling.

9.5.4 Health Economic and Outcomes Research Assessments

Not applicable.

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in Section 2.0. The descriptions of the procedures to be performed at each visit are provided below.

The screening period should be 1 week (± 3 days) before Visit 2, but may be extended up to a total of 5 weeks to accommodate prior medication washout or to repeat assessments. The reason for the extended screening will be recorded in the source documents.

If necessary, visits may be conducted up to 3 days before or after the indicated postbaseline weeks relative to Visit 2 (Baseline).

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9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the study, a representative of FRI will meet with the Investigator and the study center staff to review the procedures to be followed during the study. Electronic data capture (EDC) functionality training is provided via computer-based training to train Investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first patient is enrolled, the FRI representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the Investigator and the study center staff. The Investigator will make available to the RSM or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study center staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system, and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of the FRI EDC system, to which only authorized personnel will have access. Patient's data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring, and reviews, queries may be electronically issued to the site and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date, and time) to assist FRI and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator before the final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by FRI, its authorized representatives, and the FDA or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Patient Populations

Four populations will be considered in the statistical analysis of the study as specified below.

9.7.1.1 Screened Population

The Screened Population will consist of all patients who underwent a Screening Visit and received a screening number, and for whom informed consent was obtained.

9.7.1.2 Randomized Population

The Randomized Population will consist of all patients in the Screened Population who were randomized to a treatment group in the study.

9.7.1.3 Safety Population

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product.

9.7.1.4 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had the baseline and at least 1 postbaseline assessment of the CDRS-R total score.

9.7.2 Patient Disposition

The number of patients in the Screened Population will be summarized overall by study center. The number of patients in the Randomized, Safety, and ITT Populations will be summarized by treatment group and study center.

Screen failures (ie, patients who were screened but not included in the Randomized Population) and the associated reasons for failure will be tabulated overall. Patients completing 8 weeks of double-blind treatment (Visits 2-8) will be considered completers. The number and percentage of patients who complete the double-blind treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups. The reasons for premature discontinuation from the double-blind treatment period as recorded on the disposition pages of the eCRF will be summarized (number and percentage) by treatment group for the safety population. The percentage of premature discontinuations will be compared overall and for each discontinuation reason between treatment groups using Fisher's exact test.

The number and percentage of patients with important protocol deviations will be summarized overall and by treatment group for the Safety Population. Deviations related to the following categories will be included:

- Inclusion or exclusion criteria
- Withdrawal criteria
- Treatment or dose
- Concomitant medications

These and any additional important protocol deviations will be reviewed and documented before database lock and unblinding of treatment codes.

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented for continuous variables, and frequency distributions (counts and percentages) will be presented for categorical variables.

Comparability among treatment groups will be tested using a two-way analysis of variance model, with treatment group and study center as the factors for continuous variables and the Cochran-Mantel-Haenszel test, controlling for study center, for categorical variables.

Prior medication is defined as any recorded medication taken before the date of the first dose of double-blind investigational product. Concomitant medication is defined as any recorded medication taken on or after the date of the first dose of double-blind investigational product.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a patient will only be counted once. Any recorded medications started after last dose of double-blind investigational product will not be summarized but will be included in listings.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

9.7.4.1.1 Investigational Product

Exposure to double-blind investigational product for the Safety Population during the double-blind treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind investigational product taken to the date of the last dose taken, inclusive. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be presented by treatment group.

In addition, weekly and overall mean daily dose of investigational product will be summarized by treatment group for the Safety Population.

9.7.4.2 Measurement of Treatment Compliance

Dosing compliance for a specified period will be defined as the total number of ***capsules or*** tablets actually taken by a patient during that period divided by the number of ***capsules or*** tablets prescribed to be taken for the same period multiplied by 100. This information will be obtained from the investigational product record of the patient's eCRF.

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The total number of ***capsules or*** tablets actually taken during a specific time period is calculated based on the study medication record. The number of ***capsules or*** tablets prescribed to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of ***capsules or*** tablets to be taken per day.

Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the entire double-blind treatment period.

9.7.5 Efficacy Analyses

The efficacy analyses will be based on the ITT Population. Baseline for efficacy is defined as the last nonmissing efficacy assessment recorded at or prior to Visit 2. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with less than 2 patients in at least 1 treatment group in the ITT population. Small centers will be pooled to form pseudo-centers so that each treatment group includes at least 2 ITT patients within the center. Pooling will be done using the following algorithm:

Based on the number of ITT patients, small centers will be ordered from the largest to the smallest, and centers of the same size will be ordered from the largest center code to the smallest center code. The pooling process starts with the largest small center from the top, which will be pooled with the smallest from the bottom until a non-small center is formed. The process will be repeated using the small centers left out after the first pass. If any centers are left out at the end of the process, they will be pooled with the smallest pseudo center. If there is more than 1 smallest pseudo center, the pseudo center with the smallest center code will be selected. In case the pseudo center formed by pooling all small centers is still a small center, it will be pooled with the smallest non-small center. If there is more than 1 smallest non-small center, the one with the smallest center code will be selected.

By-visit analysis based on the mixed-effects model for repeated measures (MMRM) using the observed case approach will be performed for all continuous efficacy parameters.

In addition, by-visit analyses using the last-observation-carried-forward (LOCF) approach will be presented for all continuous efficacy parameters. For the LOCF approach, only the postbaseline total score of a parameter will be imputed using the LOCF approach; individual item scores will not be carried forward. Baseline total score will be carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values are missing, the baseline value will not be carried forward.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the change from baseline to end of Week 8 in the CDRS-R total score. The primary analysis will be performed using an MMRM with treatment group, study center, visit, and treatment group–by-visit interaction as the fixed effects and the baseline value and baseline value-by-visit interaction as the covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom. This analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values. The multiple comparison issues will be addressed using the matched parallel gatekeeping procedure (Chen et al, 2005).

In addition, 2 sensitivity analyses, LOCF and pattern-mixture model, will be performed on the primary efficacy parameter. For the LOCF approach, the between-treatment group comparison will be performed by means of an analysis-of-covariance model with treatment group and pooled study center as factors and the baseline CDRS-R total score as the covariate. The LOCF approach will be used to impute missing postbaseline values, provided that at least 1 postbaseline assessment is available. Missing values between the baseline and the first nonmissing postbaseline will be imputed with the baseline value. If all the postbaseline values are missing, baseline value will not be carried forward. Only the total score of a parameter will be imputed using the LOCF approach; individual item scores will not be carried forward.

In the other sensitivity analysis, a pattern-mixture model based on non-future dependent missing value restrictions (Kenward et al, 2003) will be performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at–random missingness assumption. The non-future dependent missing value restriction states that the probability of drop-out at a specific visit can only depend on the observed value and the possibly missing value up to that visit, but not future values beyond that visit. The details of this sensitivity analyses are as follows:

The pattern for the pattern-mixture model will be defined by the patient's last visit with observed value. The observed CDRS-R total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The dataset with missing values will be imputed under the assumption that the distribution of a missing observation differs from the observed only by a shift parameter value Δ. The dataset with missing values will be analyzed using the same model as the primary analysis for between-treatment group comparisons at Week 8. The imputation of missing values and the analysis will be performed multiple times and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values for Δ will be selected as 0 to 6 based on experience with historical data.

9.7.5.2 Secondary Efficacy Parameter

The secondary efficacy parameter is the change from baseline to the end of Week 8 in CGI-S score. This parameter will be analyzed similarly to the primary efficacy parameter.

To control the overall type I error rate for multiple comparisons across the primary and the secondary efficacy parameters, the matched parallel gatekeeping procedure (Chen et al, 2005) will be implemented.

A sensitivity analysis will also be performed using the LOCF approach as described in Section 9.7.5.1.

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9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the double-blind treatment period or during the double-blind down-taper treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of double-blind investigational product or was present before the date of the first dose of double-blind investigational product and increased in severity during the double-blind treatment period or during the double-blind down-taper period, respectively. If more than 1 AE is reported before the date of the first dose of double-blind investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the double-blind treatment period or during the double-blind down-taper period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of double-blind investigational product will not be counted as a TEAE.

An AE occurring during the double-blind down-taper period will be considered a newly emergent AE if it was not present before the start of the double-blind down-taper period or was present before the start of the double-blind down-taper period but increased in severity during the double-blind down-taper period. The newly emergent AEs during the double-blind down-taper period will be summarized by body system, preferred term, and treatment group.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs during the double-blind treatment period will be summarized separately by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind investigational product and within 30 days of the date of the last dose of double-blind investigational product.

The incidence of SAEs and AEs leading to premature discontinuation of the study will also be summarized by study period, system organ class, preferred term, and treatment group.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any). All patients with SAEs, including those reported during the screening period or more than 30 days after the date of the last dose of the double-blind investigational product, and patients discontinuing due to AEs before the start of double-blind investigational product, will be included in these listings.

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9.7.6.6 Investigational Product Plasma Concentration Parameters

Plasma samples will be analyzed for the concentrations of levomilnacipran using validated bioanalytical methods. Population PK parameters will be estimated using nonlinear mixed-effects modeling methods. The study will be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for levomilnacipran ER, with at least 80% power.

9.7.7 Health Economics and Outcomes Research Analyses

Not applicable.

9.7.8 Blinded Interim Analysis

A blinded interim analysis will be conducted when approximately 75% of randomized patients have either completed or discontinued the study. The blinded interim analysis is to obtain an estimate of the pooled SD on change from baseline to Week 8 in the CDRS-R total score. If the estimated pooled SD is larger than the assumed pooled SD specified in the sample size estimation (Determination of Sample Size, Section 9.7.9), sample sizes may be increased to ensure an adequate power. However, due to the difficulties in recruiting pediatric patients with MDD, the total number of patients of the study will be capped at 800 (200 per treatment group).

In addition, an interim PK analysis will be performed by updating the adult population PK model with PK data from this adolescent pediatric study to establish the doses to be used in future studies.

9.7.9 Determination of Sample Size

Original sample size calculation: The effect size (treatment group difference relative to pooled SD) of 0.36 for both levomilnacipran and fluoxetine is based on a treatment difference of 4 units with a common pooled SD of 11.1 for the primary efficacy parameter, change from baseline to Week 8 in CDRS-R total score. Adjusting for multiple comparisons of 2 levomilnacipran groups with placebo across the primary and secondary endpoints by using the matched parallel gatekeeping procedure, a sample size of 660 patients (165 per treatment group) will be needed to provide 85% power for primary analysis (levomilnacipran vs placebo) and for assay sensitivity analysis (fluoxetine vs placebo) based on an MMRM model using simulation method (Lu, 2012). The simulation assumed a correlation of 0.7 between the repeated measures and a dropout rate of 17% based on historical data in pediatric patients. Following discussions with FDA, the study will be deemed to be successful if at least 1 of 2 levomilnacipran doses (40 mg/day and 80 mg/day) is shown to be statistically significant versus placebo based on the primary efficacy endpoint. Therefore, the study will be powered at 85% based on at least one of the two dose levels achieving statistical significance, which yields a resultant sample size of 520 patients using the same assumptions.

Sample size recalculation: Following a blinded interim analysis, the sample size has been re-estimated. The MMRM model is used to estimate the pooled variance for change from baseline in CDRS-R total score at Week 8; it includes pooled study site and week as factors, and baseline CDRS-R total score and baseline value-by-week interaction as covariates.

A total of 421 subjects were included in the ITT analysis. Of these 421 patients, 347 (82.4%) patients have observed data at Week 8, so the estimated dropout rate at Week 8 is 17.6%. Based on the MMRM model, the variance estimate for the change from baseline in CDRS-R total score at Week 8 is 129.53, and the estimated pooled standard deviation is 11.38. Thus, the estimated effect size is 0.35 based on a treatment difference of 4 units and a pooled standard deviation of 11.38.

Assuming an effect size of 0.35, a common dropout rate of 17.6%, and a correlation of 0.7 between the repeated measures, an estimated total sample size of 544 patients (136 per group) will be needed to maintain the 85% power to detect the treatment difference of 4 units in at least 1 of the 2 doses of levomilnacipran versus placebo.

9.7.10 COMPUTER METHODS

Statistical analyses will be performed using version [redacted].

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by FRI. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the Investigator, has been received by FRI. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS AND VIOLATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing, or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patient and must immediately be reported to FRI. Protocol deviations should be reported to FRI (either verbally or electronically) in a timely manner from the date of discovery.

Protocol deviations that may impact a patient's rights (eg, failure to obtain informed consent prior to initiating study procedures), safety or well-being (eg, deviations that resulted in an SAE, exposure during pregnancy), or the integrity and authenticity of the study data should be reported to FRI within 24 hours, if possible.

The IRB/IEC must be notified according to the criteria and time period dictated by the IRB/IEC associated with this study.

9.10 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee to evaluate safety study outcomes such as suicidal ideation and suicidal behavior during study conduct will be established and will operate based on a charter drafted to comply with FDA guidance *(*http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf*)*.

10.0 STUDY SPONSORSHIP

This study is sponsored by FRI.

10.1 STUDY TERMINATION

FRI reserves the right to terminate the study in its entirety or at a specific study center before study completion.

10.2 REPORTING AND PUBLICATION

All data generated in this study are the property of FRI. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and FRI and will follow the FRI's Standard Operating Procedure on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must provide the following to FRI before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to FRI for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all Subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 5.1
- A copy of the IRB/IEC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all Subinvestigators listed on Form FDA 1572. The Investigator and all Subinvestigators will provide an updated financial disclosure agreement to FRI 1 year after the completion of the study

11.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Subinvestigators listed on Form FDA 1572. The investigational products must be stored and locked in a secured location. At study initiation, a representative from FRI will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. FRI will supply forms on which to record the date the investigational products were received and a dispensing record in which to record each patient's use. All unused investigational products must be returned to FRI. It is the Investigator's responsibility to ensure that patients return their investigational product.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by FRI through the EDC system. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to FRI. The Investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and ECGs) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by FRI.

No study records shall be destroyed without notifying FRI and providing FRI the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of FRI or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. FRI must be notified in writing of the name and address of the new custodian in advance of the transfer.

For Canadian study centers only: All records and documents pertaining to the conduct of the study must be retained for a 25-year period in accordance with the Canadian Food and Drugs Act and Regulations.

11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and PID number. Patients' names are not to be transmitted to FRI. The Investigator will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol amendment (Protocol LVM-MD-11, Amendment #3) dated 25 Mar 2019 and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

13.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's LAR. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; FRI; the IRB/IEC; or an authorized contract research organization may inspect the records

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB/IEC may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate . . .")

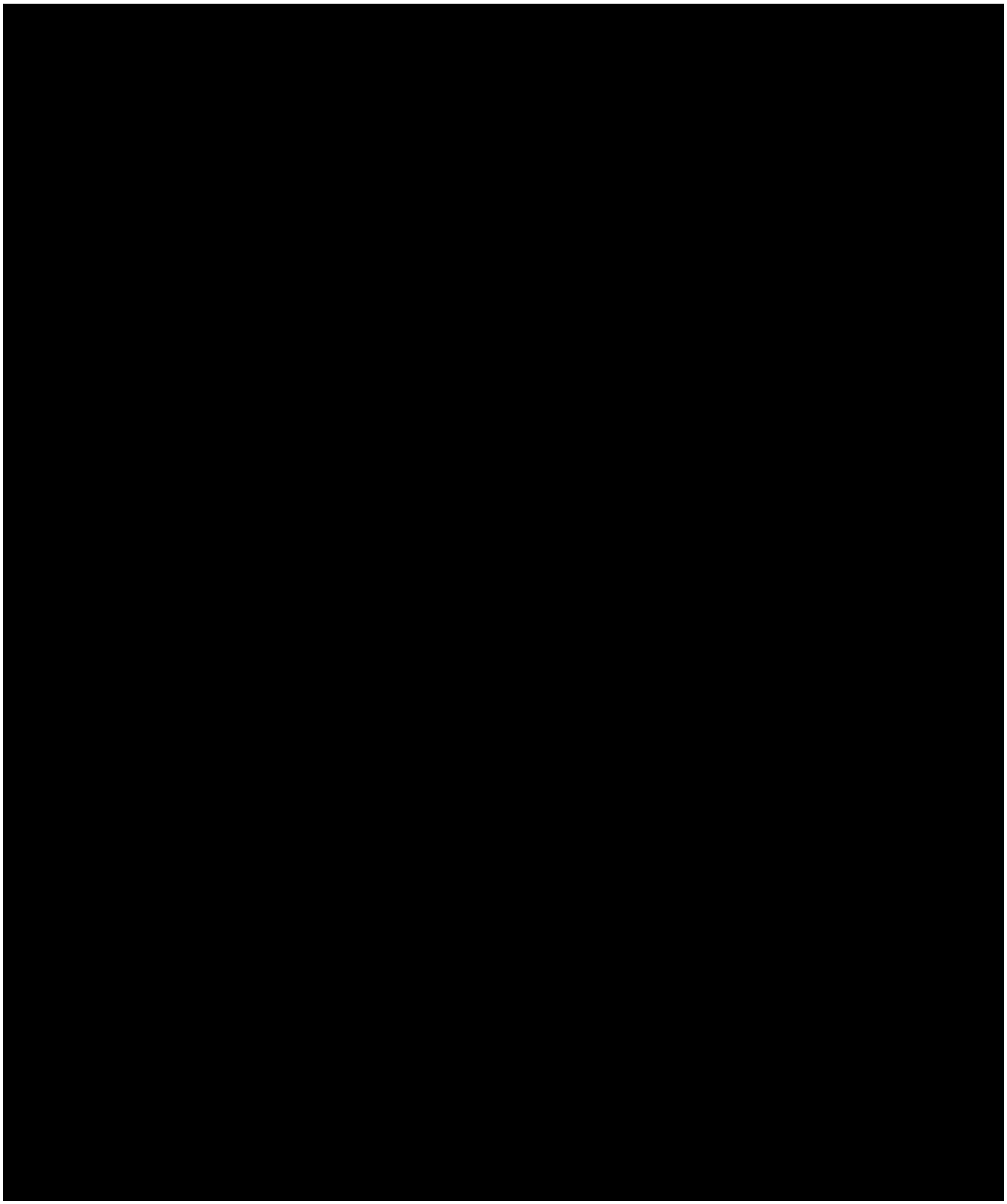
- A place for the patient's signature and date of signing

- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient.

APPENDIX II. CONTACT INFORMATION

Contact information for FRI personnel will be provided in the study reference binder.



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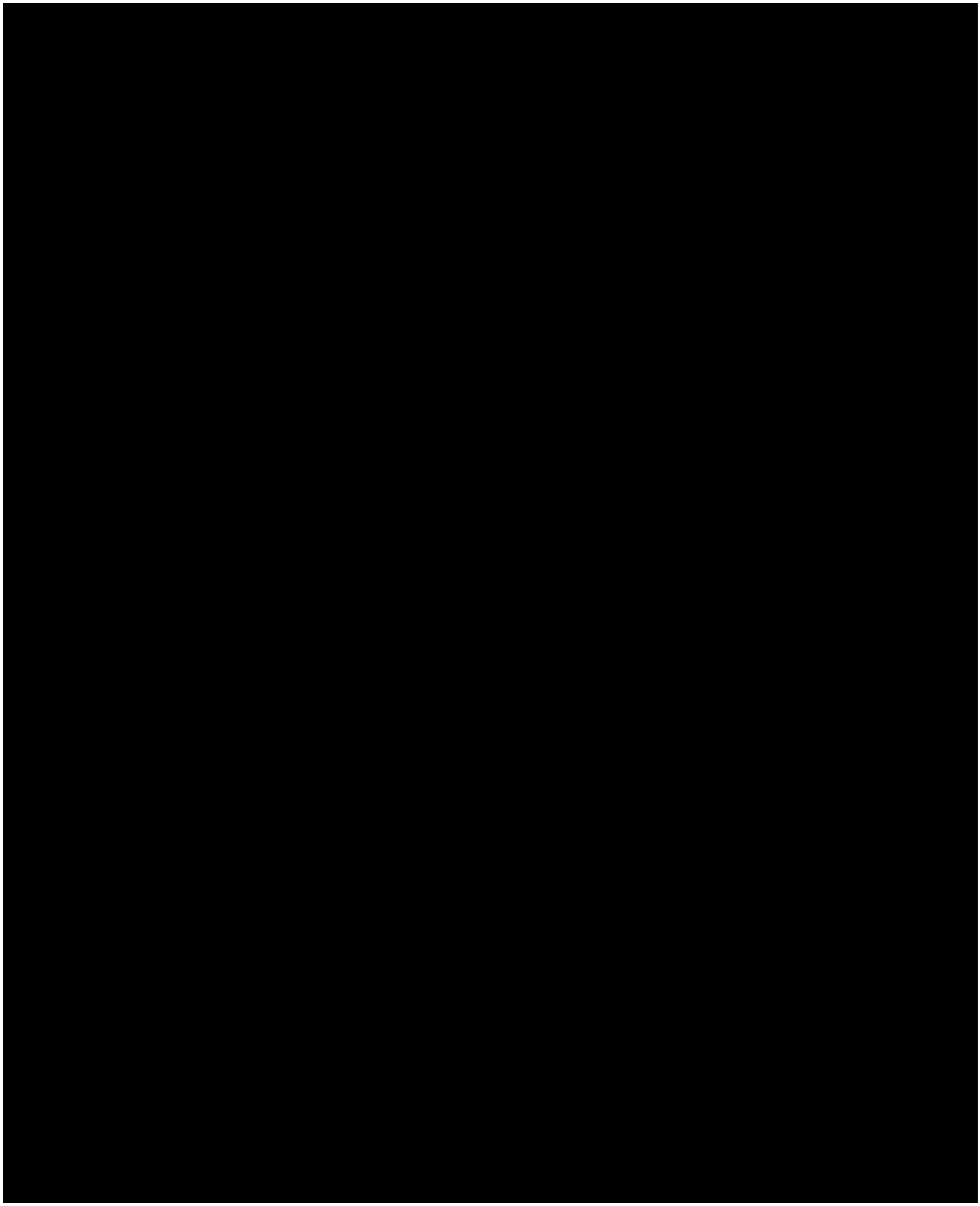

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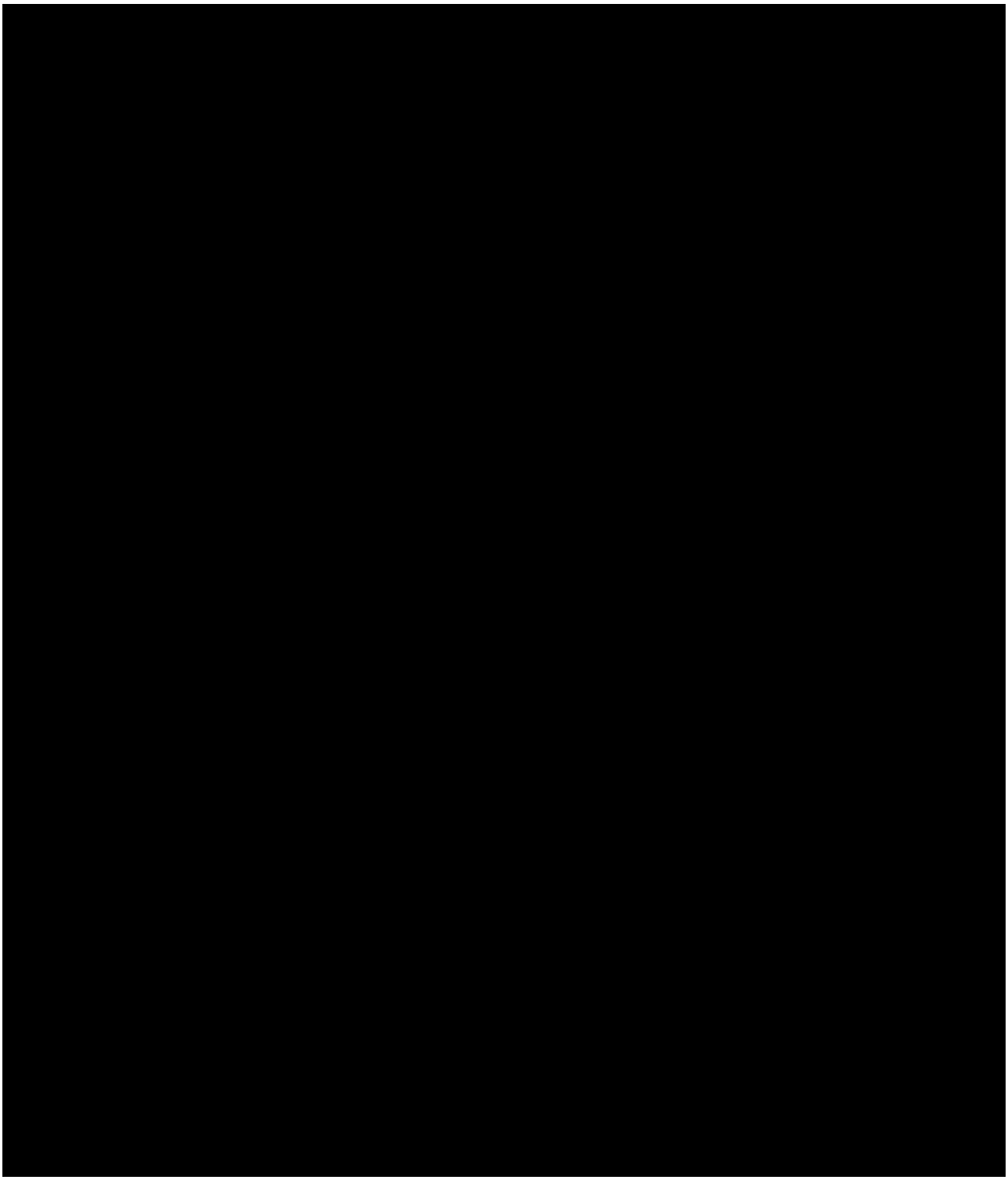

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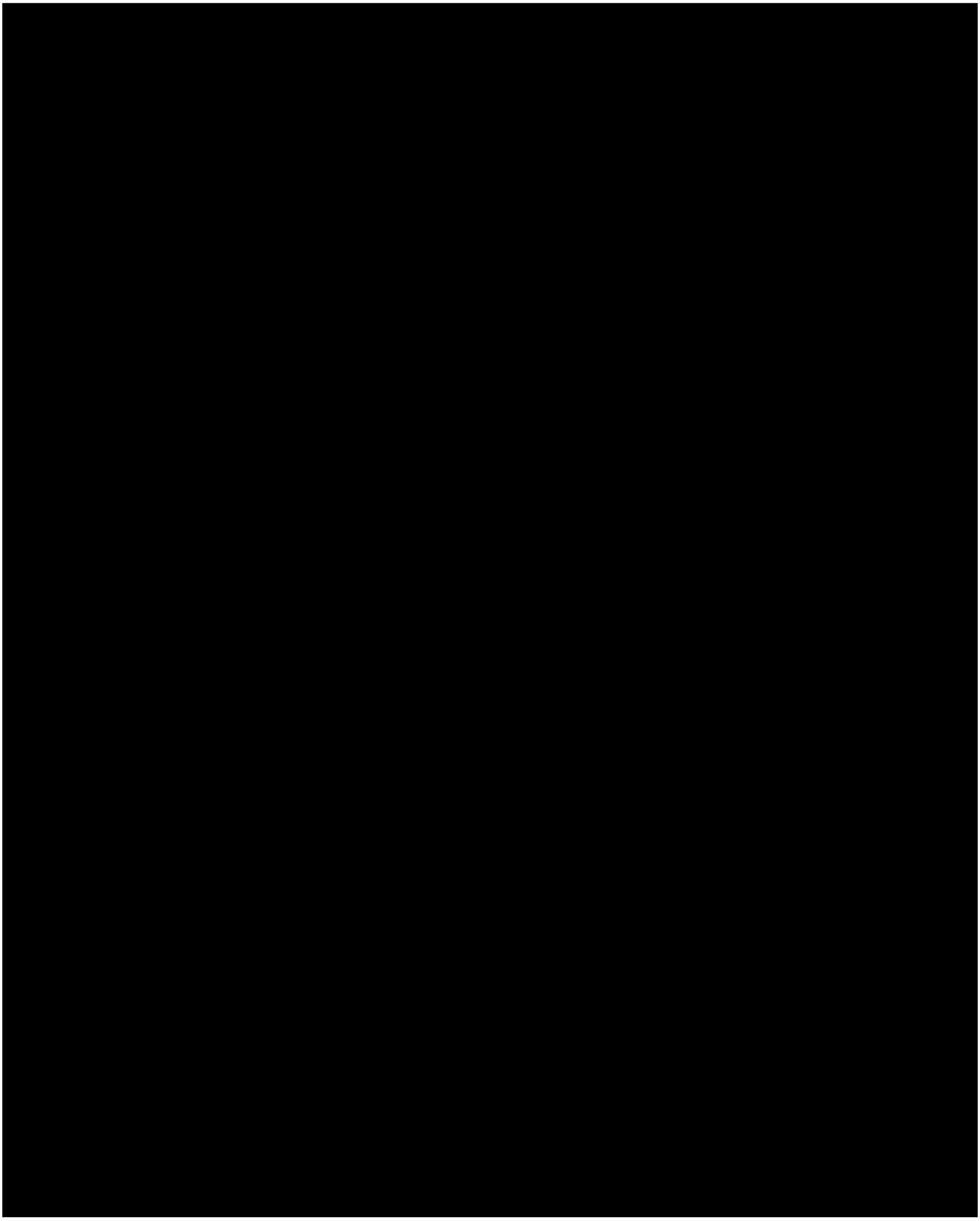

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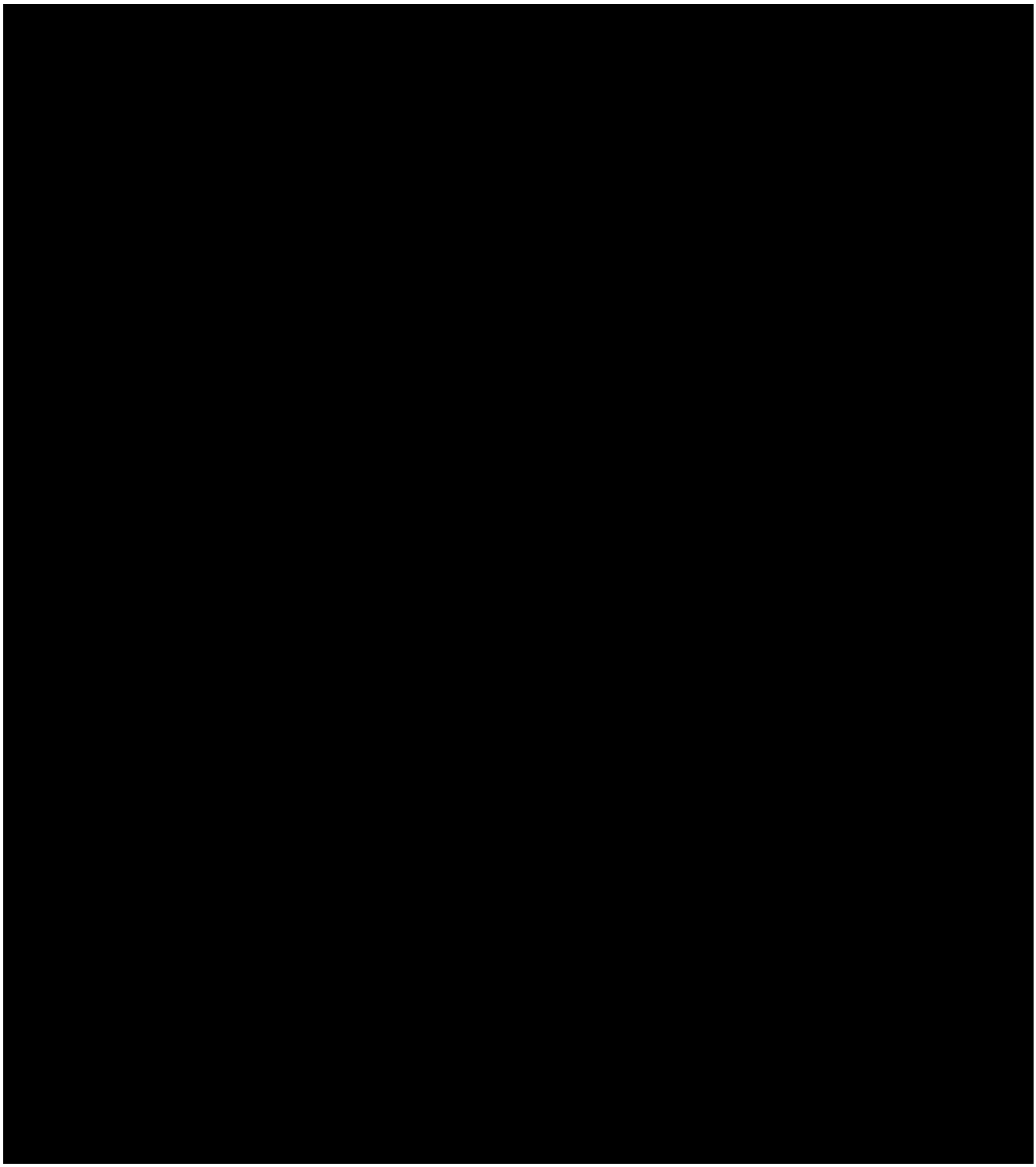

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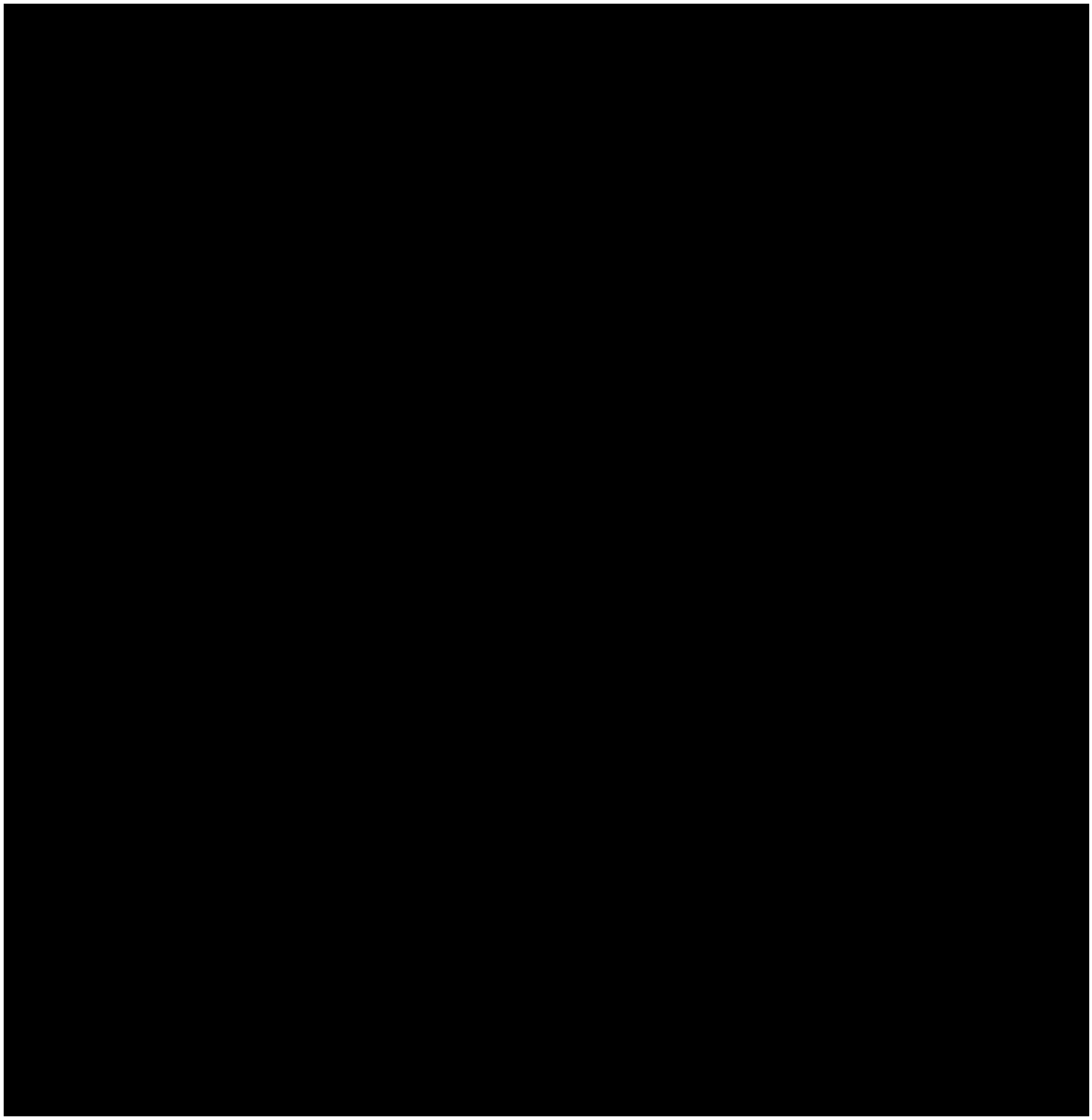

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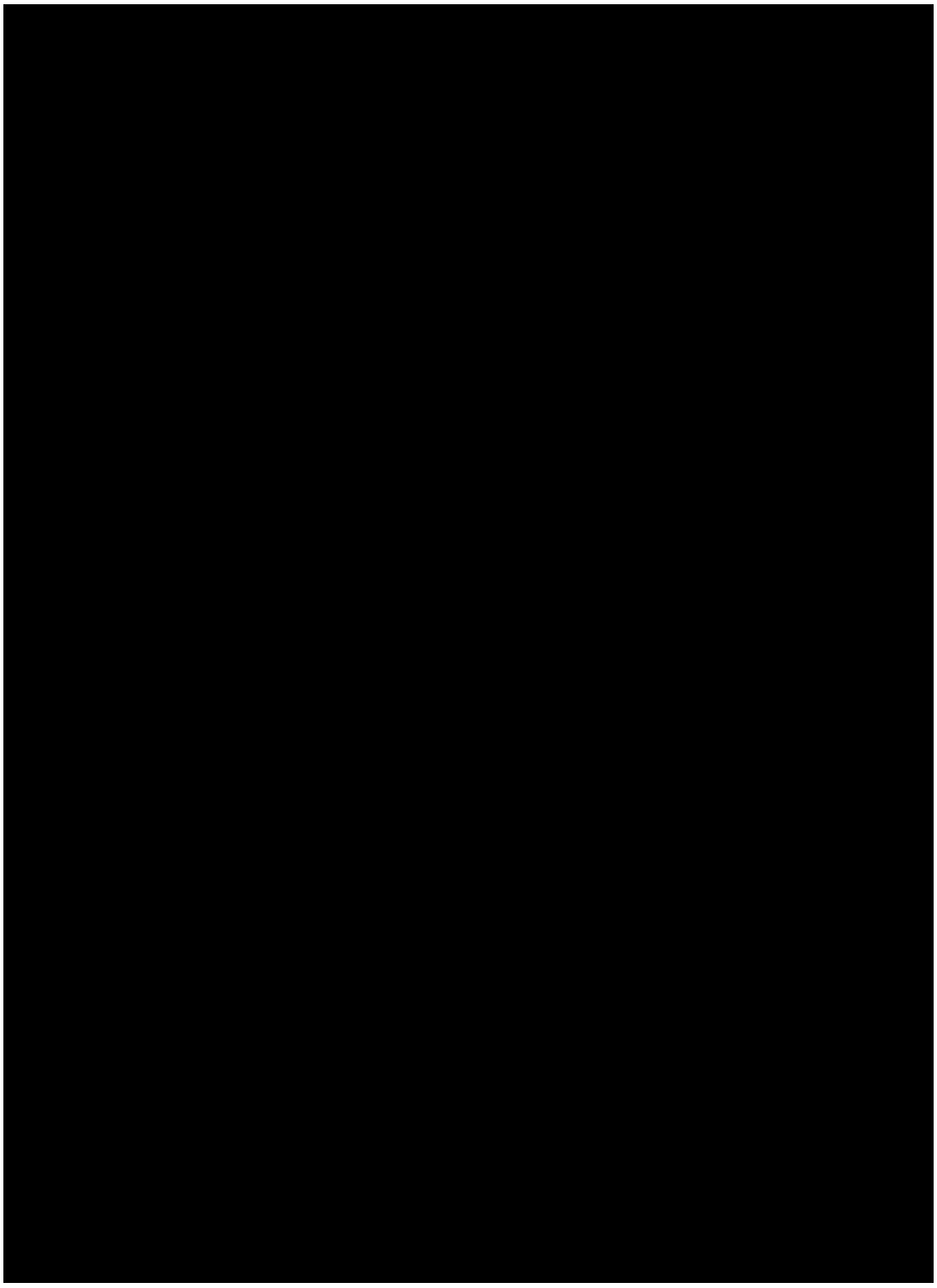

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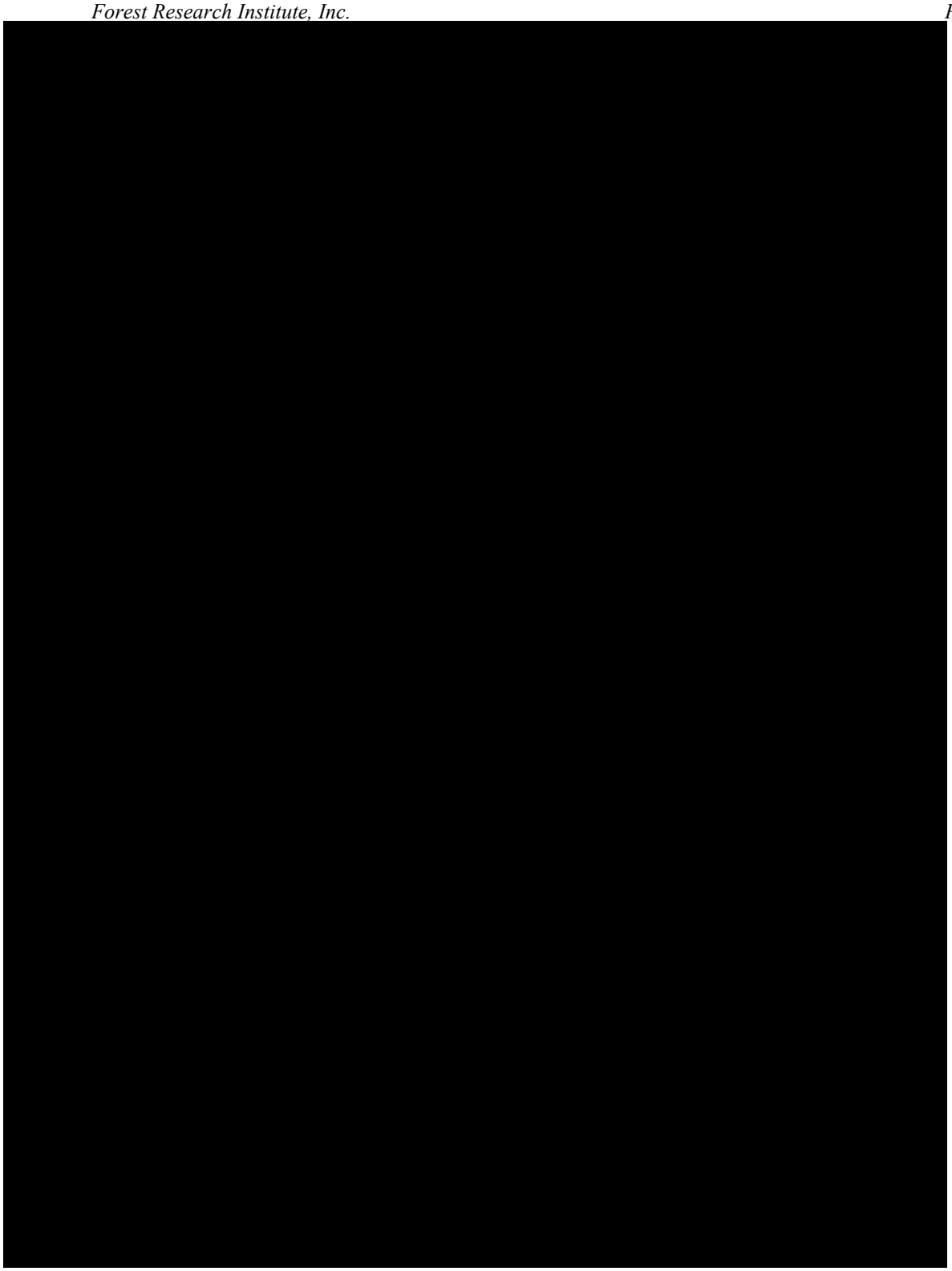

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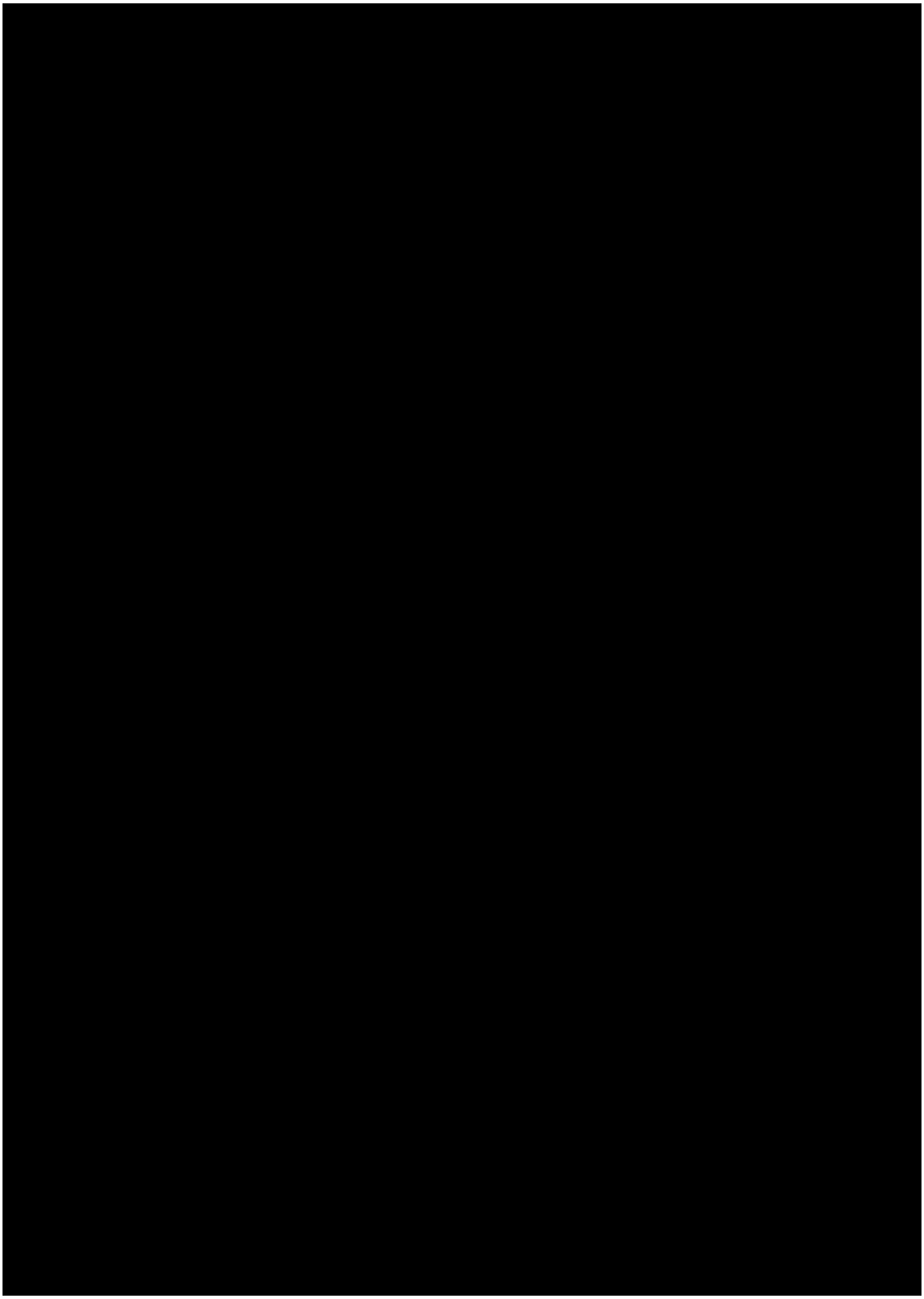

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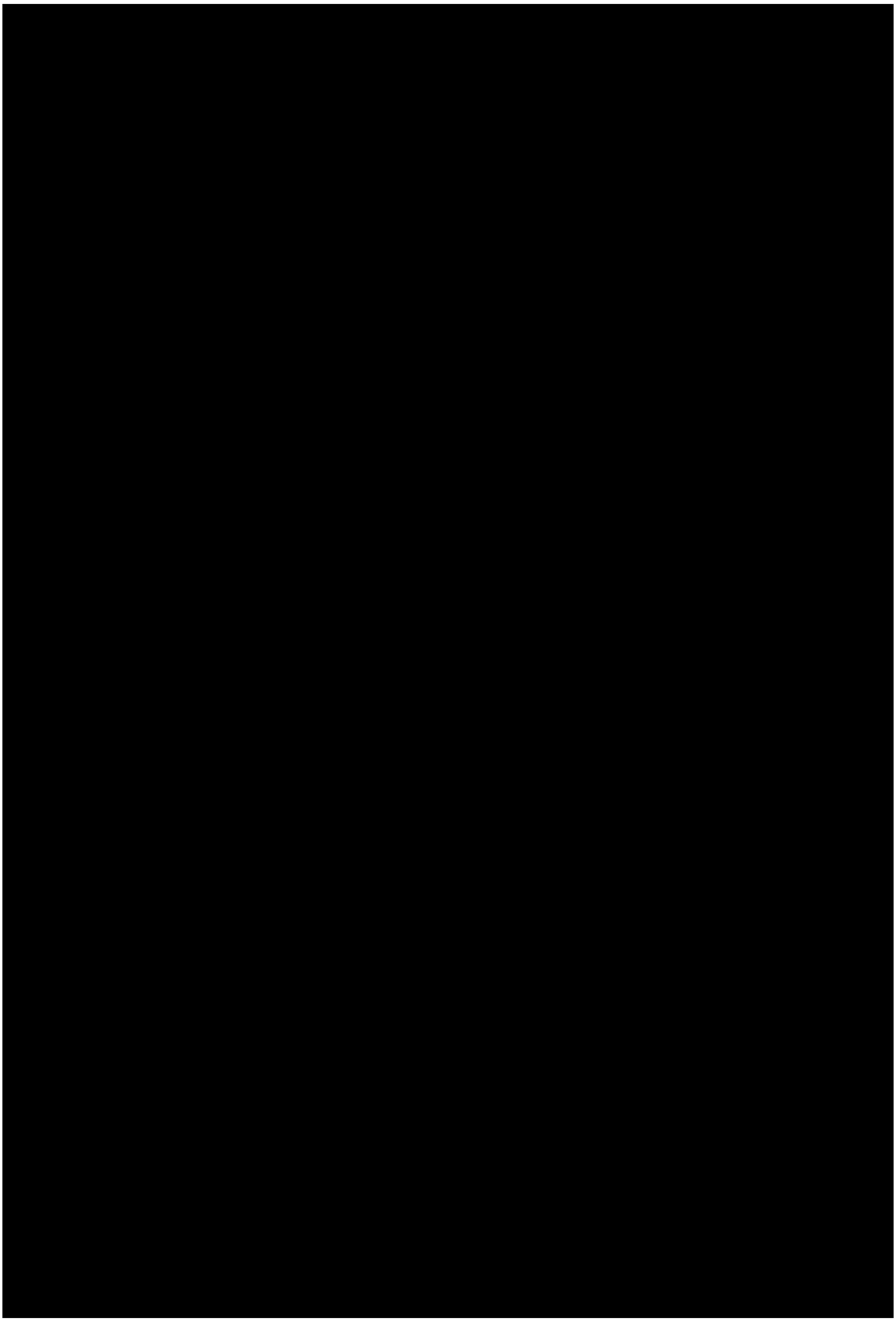

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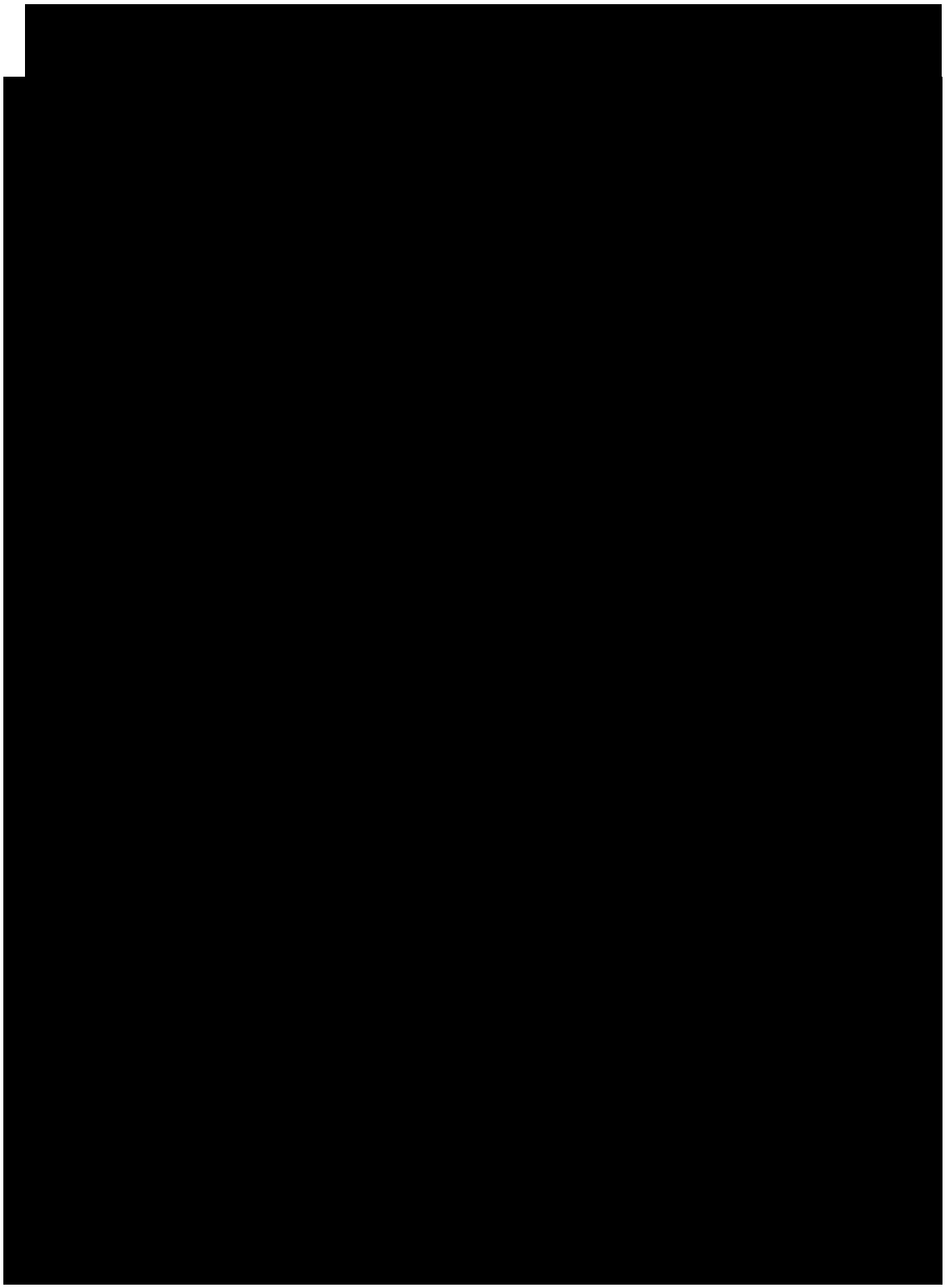

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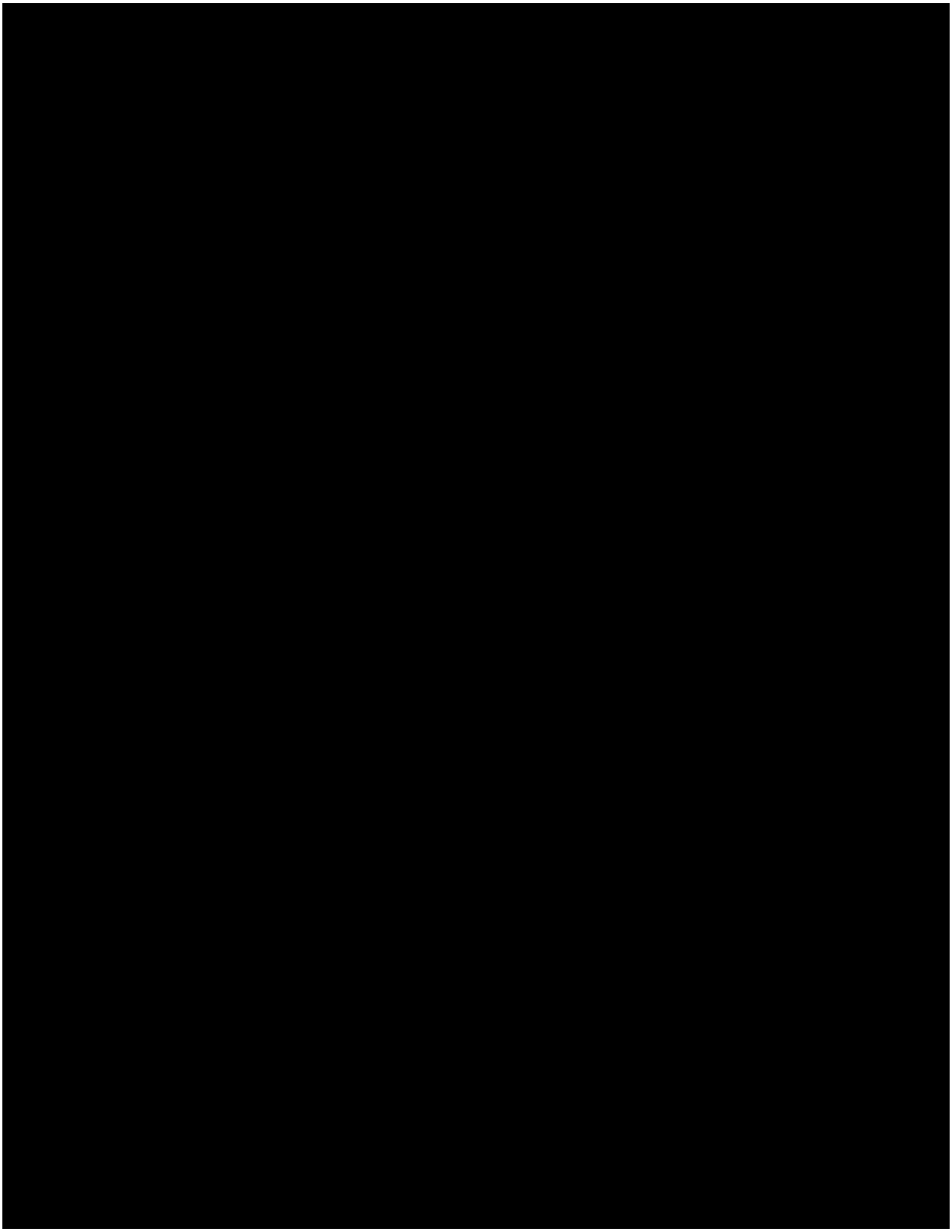

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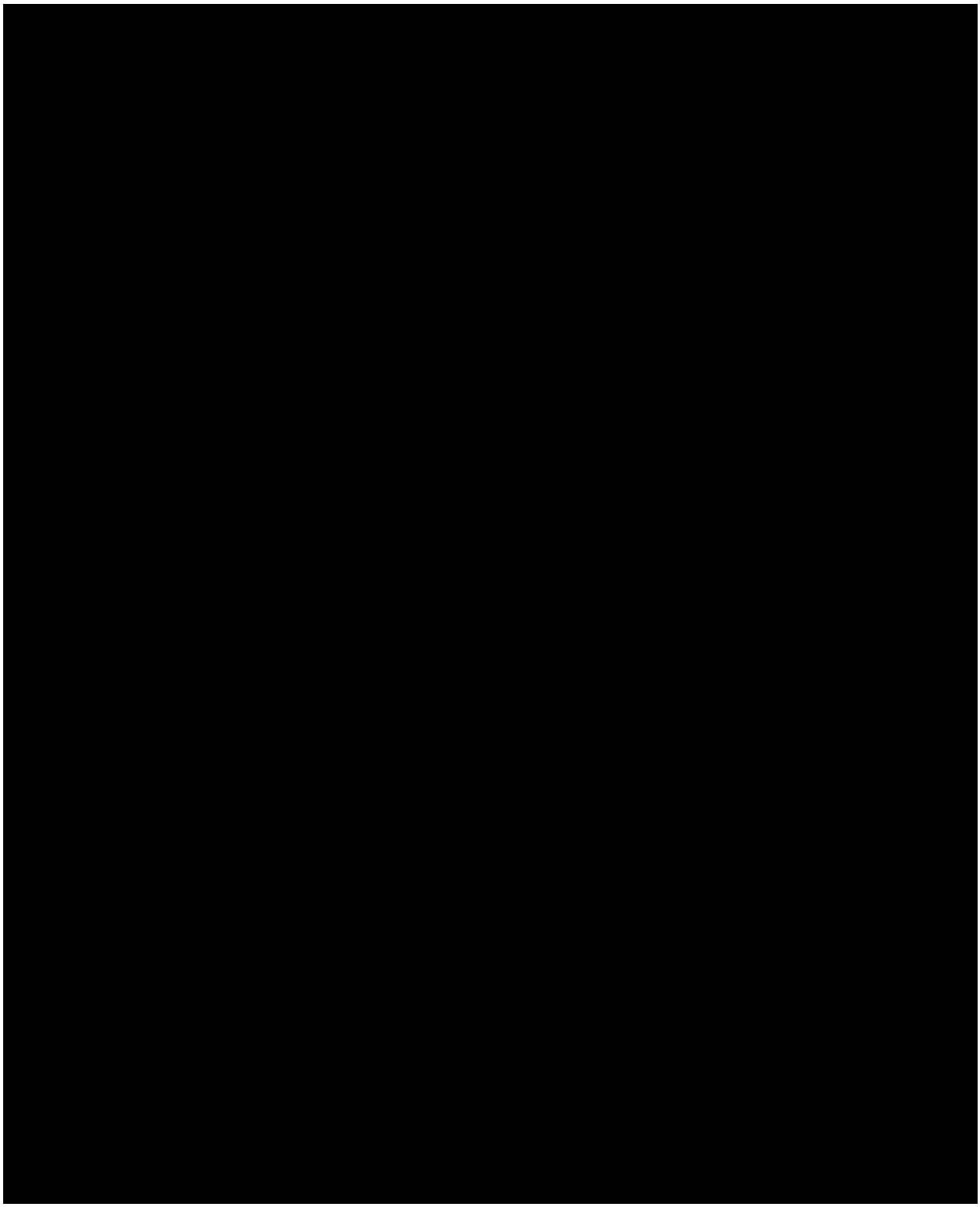

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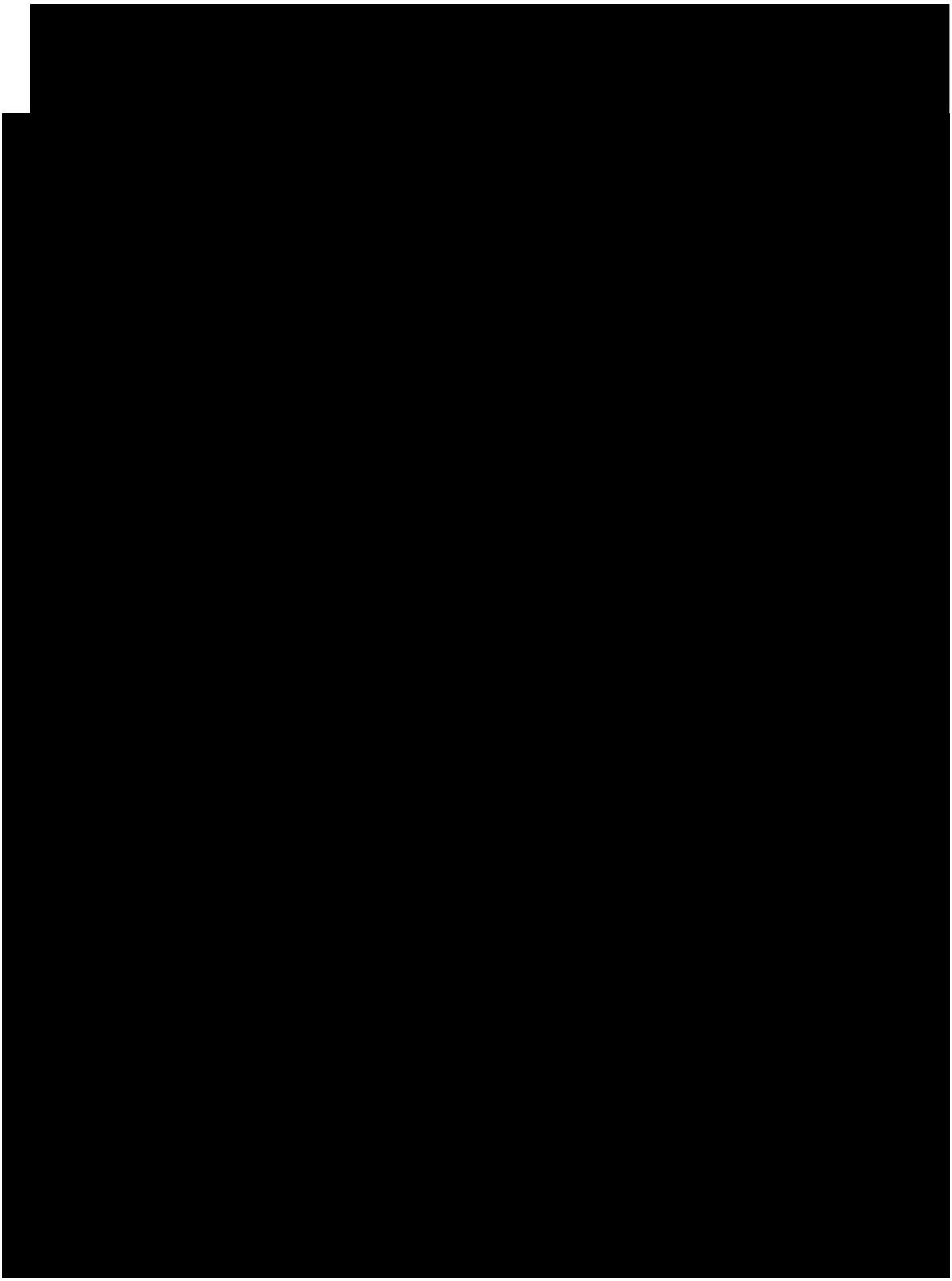

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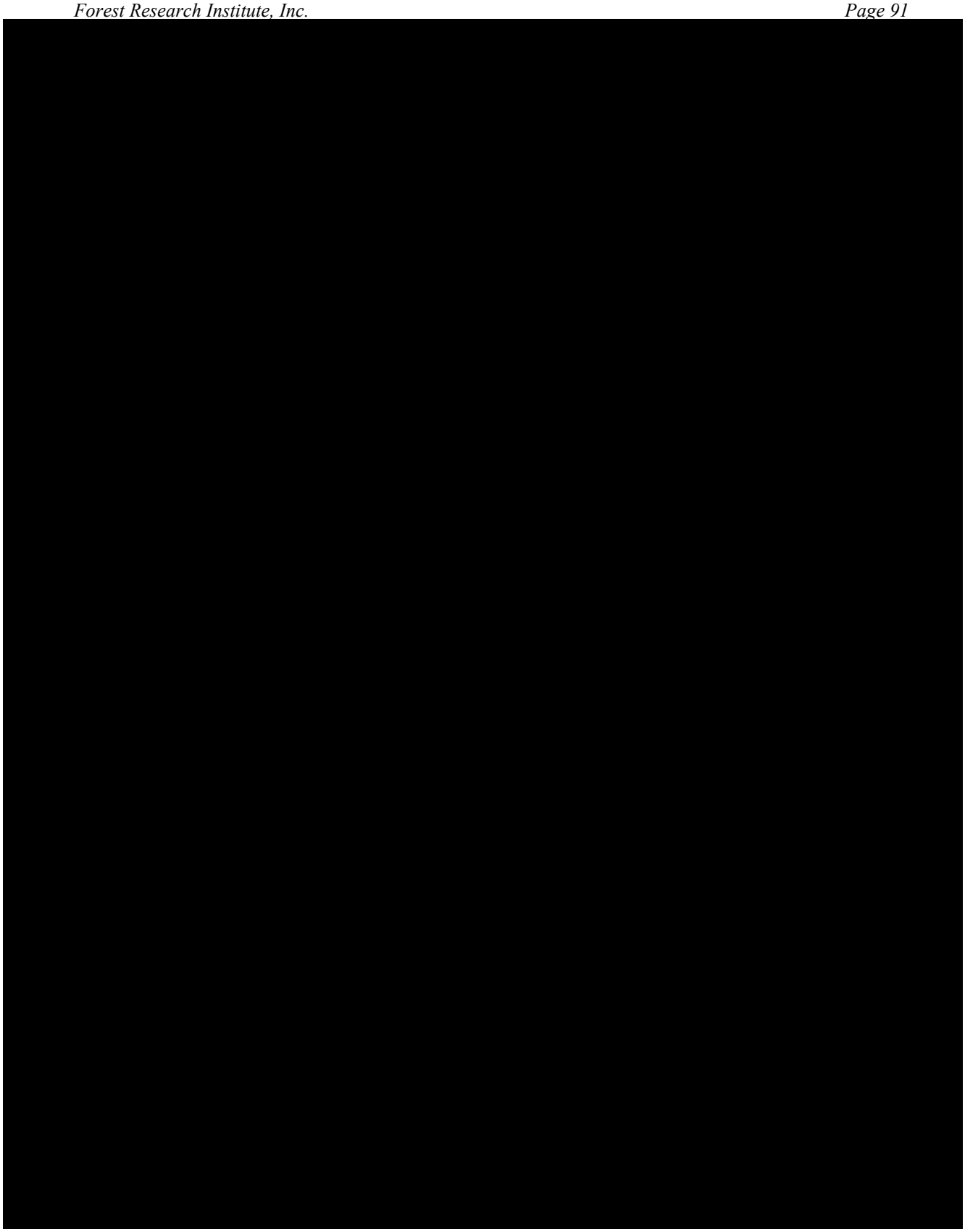

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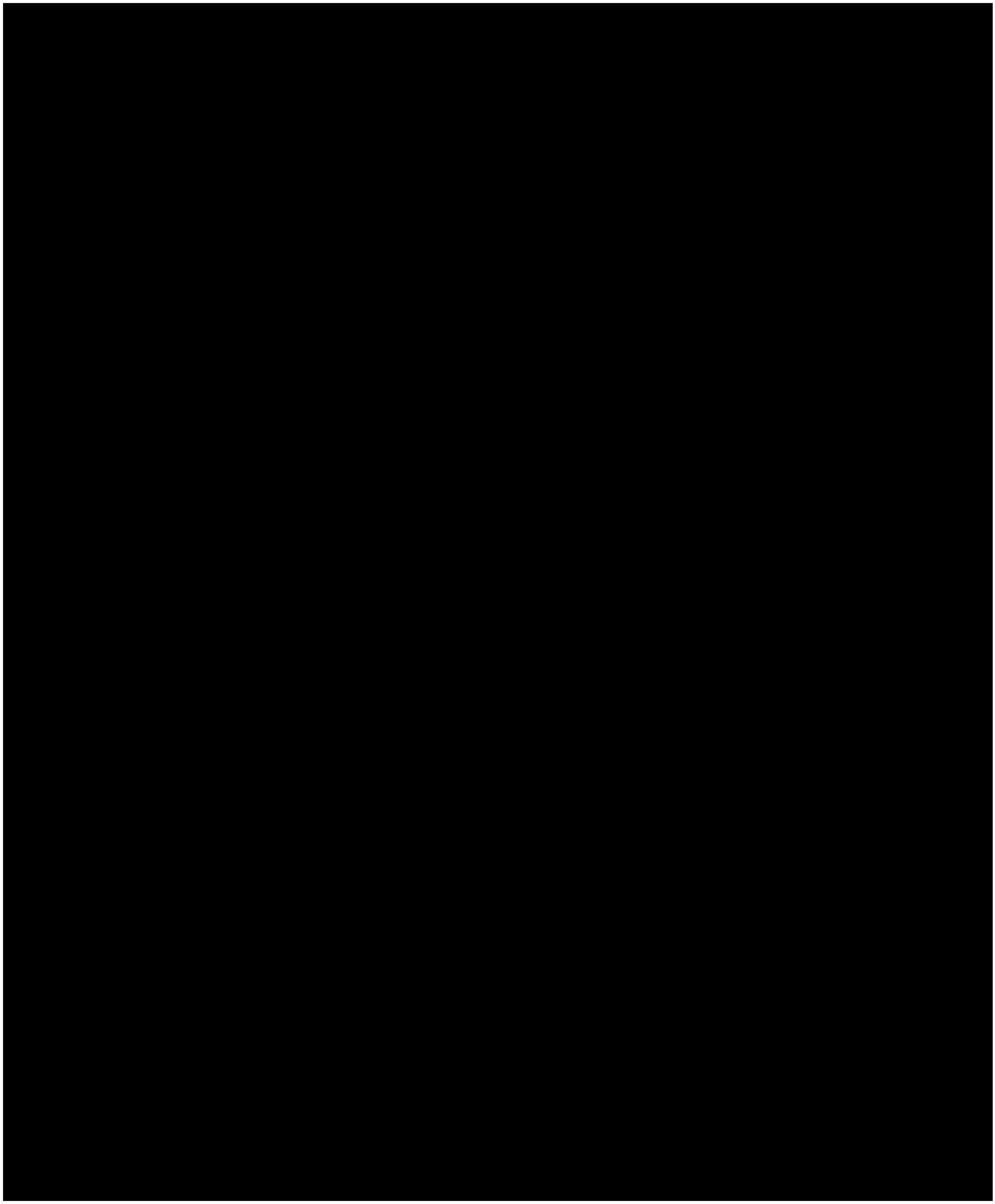

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