1.0 TITLE PAGE

Forest Research Institute, Inc, an affiliate of Allergan, plc
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Jersey City, NJ 07311

An Open-label Long-term Safety Study of Vilazodone in Pediatric Patients With Major Depressive Disorder

VLZ-MD-23

IND # 54,613

NDA # 22,567

Original Protocol Date: 15 Dec 2014

Amendment #1 (Canada): 15 Apr 2015

Amendment #2: ***02 Nov 2016***

2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study VLZ-MD-23	
Title of Study	An Open-label Long-term Safety Study of Vilazodone in Pediatric Patients With Major Depressive Disorder
Study Centers (Country)	Approximately 60 study centers in the United States and Canada
Development Phase	3
Objective	To evaluate the long-term safety and tolerability of vilazodone for the treatment of major depressive disorder in pediatric outpatients (7-17 years)
Methodology	A multicenter, open-label, flexible-dose, 28-week study in pediatric patients
Number of Patients	Approximately ***315*** planned
Diagnosis and Main Criteria for Inclusion	Male and female outpatients who have completed Study VLZ-MD-22, or for de novo patients, male and female outpatients, ages 7 to 17 years, who meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria for major depressive disorder (confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime) and have a current depressive episode of ≥ 6 weeks duration at Screening (Visit 1). At both Screening (Visit 1) and Baseline (Visit 2), de novo patients must have a score of ≥ 40 on the a Children's Depression Rating Scale–Revised and a Clinical Global Impressions–Severity score ≥ 4
Test Product, Dosage, and Mode of Administration	Vilazodone HCl 5 mg and 10 mg tablets, taken orally as a single dose, once daily at the same time each day, with food
Duration of Treatment	The study will be 28 weeks in duration: approximately 1-week screening/washout period, 26-week open-label treatment period, and a 1-week down-taper period
Reference Therapy, Dosage, and Mode of Administration	None
Criteria for Evaluation	
Efficacy Measures	Children's Depression Rating Scale–Revised Clinical Global Impressions–Severity Clinical Global Impressions–Improvement
Safety Measures	Adverse event recording, clinical laboratory assessments, vital sign measurements (including height and weight), electrocardiograms, physical examinations, and Columbia–Suicide Severity Ratings Scale
Statistical Methods	Descriptive statistics will be presented for all efficacy and safety parameters. No inferential statistical analyses will be performed. All safety parameters will be summarized for the Safety Population, defined as all patients who receive at least 1 dose of open-label vilazodone. Efficacy parameters will be summarized using the Intent-to-Treat Population, defined as all patients in the Safety Population who had baseline and at least 1 postbaseline Children's Depression Rating Scale–Revised total score.

Table 2–1. SCHEDULE OF EVALUATIONS: Study VLZ-MD-23

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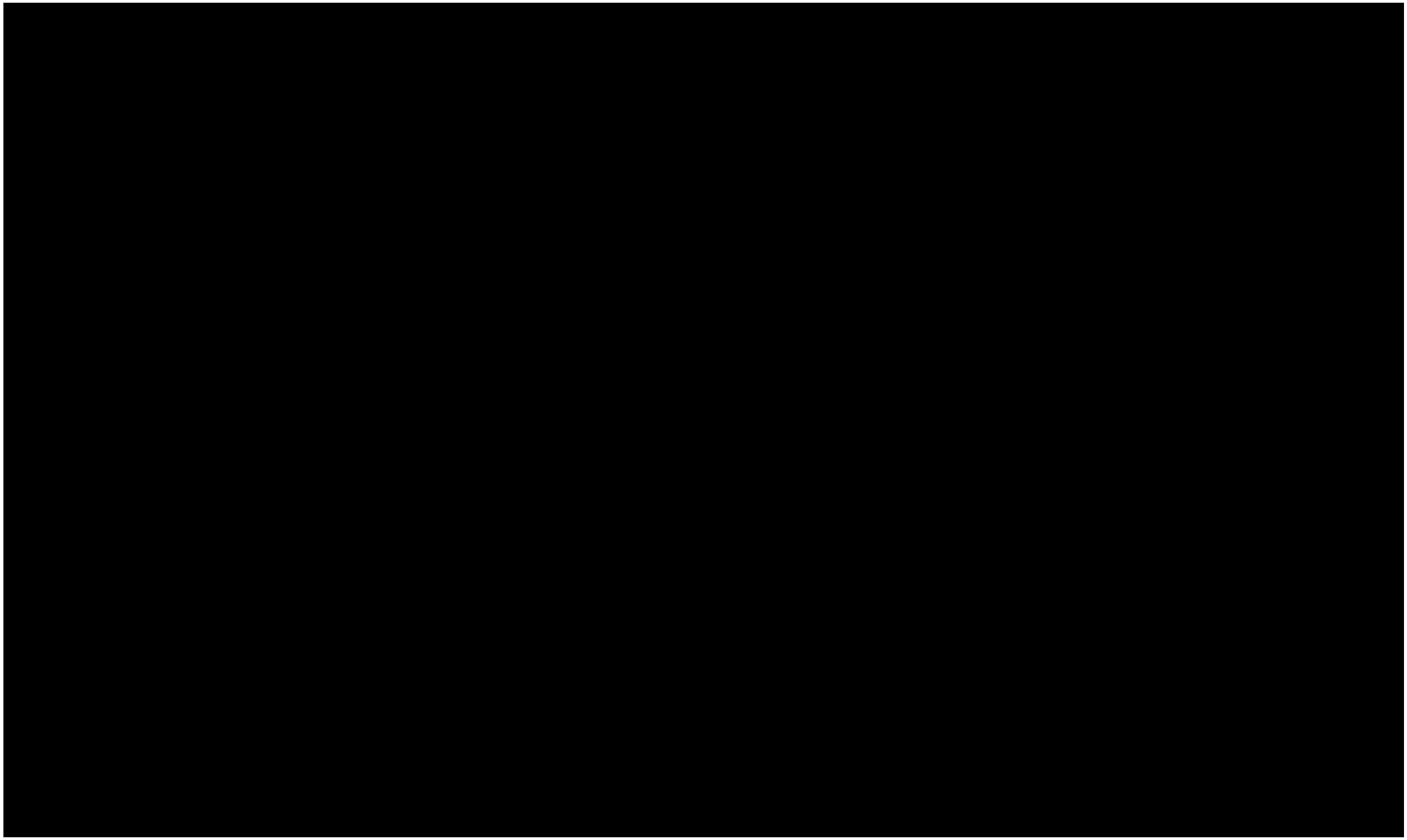


3.0 TABLE OF CONTENTS, TABLES AND FIGURES

3.1 OVERALL TABLE OF CONTENTS

3.2 LIST OF IN-TEXT TABLES

3.3 LIST OF IN-TEXT FIGURES

4.0 LIST OF ABBREVIATIONS

5-HT_{1A}	5-hydroxytryptamine 1A
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
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
CI	confidence interval
C-SSRS	Columbia–Suicide Severity Rating Scale
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, text revision
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	US Food and Drug Administration
FR	Federal Register
FRI	Forest Research Institute, Inc.
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent to treat
IWRS	interactive Web response system

K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime
LAR	legally authorized representative
MDD	major depressive disorder
NEAE	newly emergent adverse event
NDA	New Drug Application
PCS	potentially clinically significant
PID	patient identification
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
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, Inc. (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 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 CFR.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study and before participating in any study procedures, each patient, if developmentally appropriate, must provide written assent, and his or her parent(s), legal guardian(s), or legally authorized representative (LAR) (hereafter referred to as parent/guardian/LAR) must provide voluntary and written informed consent in compliance with 21 CFR, Parts 50 and 312 and give HIPAA authorization (or an equivalent of HIPAA authorization in non-US countries). The elements of informed consent are listed in Appendix I of this protocol.

The signed documents will be placed in the Investigator's study files. A unique patient identification (PID) number will be assigned [redacted]

5.3.1 Patient Assent Form

To participate in the study, the patient will read, assent to an understanding of, and sign the assent form. The patient will be made aware of the ability to withdraw from the study at any time, without prejudice. Patients who are unable to read the assent form will have the statements read to them. If the patient cannot sign the form, a witness will be allowed to provide written verification of oral assent. A copy of the signed assent form will be given to the patient's parent/guardian/LAR.

5.3.2 Parent, Legal Guardian, and Legally Authorized Representative Informed Consent

Written informed consent will be obtained from the patient's parent/guardian/LAR before the patient participates in any study-related procedure. To provide consent for the patient's participation in the study, the patient's parent/guardian/LAR will read, assent to an understanding of, and sign an ICF or other locally applicable regulations and authorization form after having had an opportunity to discuss the forms with the Investigator. The parent/guardian/LAR will be made aware that the patient may withdraw from the study at any time and will receive a copy of the signed ICF. Patients who reach the age of majority (ie, 18 years in most jurisdictions) during the course of the study are required to be re-consented.

5.3.3 Caregiver Consent

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, and may be a different individual than the parent/guardian/LAR. The caregiver must commit to accompanying the patient to each study visit. To be eligible for the study, the caregiver, whether or not he or she is the parent/guardian/LAR, must read and sign the caregiver consent and meet the relevant inclusion/exclusion criteria. If the parent/guardian/LAR is the caregiver, he or she will be asked to sign both the parent/legal guardian permission (ICF) and the caregiver consent. If a caregiver is replaced during the study, each caregiver must provide separate ICF/caregiver consents and will be given a signed copy of his/her caregiver consent.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 60 study centers.

The Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator 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 assent and informed consent for each patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at each study center 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 staff capabilities and performance is consistent with the study investigational plan. The Investigator at each study center 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

Vilazodone is a selective serotonin reuptake inhibitor and a partial agonist of the 5-hydroxytryptamine 1A (5-HT_{1A}) receptor. Vilazodone has greater in vitro potency for serotonin reuptake inhibition than compounds such as fluoxetine (0.2 nM versus 6.0 nM respectively). Vilazodone is more selective for inhibition of serotonin reuptake than dopamine or norepinephrine (0.2 nM, 60.0 nM and 90.0 nM, respectively). In vitro studies also indicate that vilazodone binds with high affinity and is a more potent agonist of 5-HT_{1A} receptors compared with specific 5-HT_{1A} ligands such as buspirone, with IC_{50} values of 0.5 nM and 30 nM, respectively. A detailed description of the pharmacokinetics, chemistry, pharmacology, safety, and efficacy of vilazodone for the treatment of major depressive disorder (MDD) is provided in the US prescribing information (Viibryd, 2014) and in the Investigator's Brochure (Vilazodone HCl, 2013). Viibryd was approved by the FDA for the treatment of MDD on 21 Jan 2011.

Approval for the use of Viibryd for the treatment of MDD was based on 2 pivotal, Phase 3, 8-week, multicenter, randomized, double-blind, placebo-controlled studies in adult outpatients with MDD. Vilazodone 40 mg/day demonstrated superiority over placebo in the improvement of depressive symptoms as measured by the mean change from baseline to Week 8 in the Montgomery-Åsberg Depression Rating Scale total score (Montgomery and Åsberg, 1979).

MDD is a common and serious illness in children and adolescents. Epidemiological studies from community and clinical samples estimate the prevalence of MDD as approximately 0.3%-1.4% of preschoolers (2-5 years of age) (Egger and Angold, 2006), 1%-2% of prepubertal children, and between 3% and 8% of adolescents (Zalsman et al, 2006). The American Academy of Child and Adolescent Psychiatry (1998) consensus estimated the cumulative incidence of MDD in adolescence by the age of 18 to be as high as 20%, while 65% report transient, less severe depressive symptoms. At any point in time, 1 in every 10 children and adolescents is affected by serious emotional disturbances (Substance Abuse and Mental Health Services Administration, 2009).

The National Comorbidity Survey Adolescent Supplement examined both dysthymic disorder and MDD together resulting in data showing approximately 11.2% of 13 to 18 year olds in the United States are affected at some point during their lives, and 3.3% have experienced a seriously debilitating depressive disorder. The Substance Abuse and Mental Health Services Administration examines the national prevalence of depression each year through the National Survey on Drug Use and Health. Their 2008 data show an 8.3% prevalence of depression among 12 to 17 year olds in the United States, noting that among 13 to 17 year olds the prevalence of depression among girls is nearly 3 times as high as that for boys. Additionally, while approximately 4% of 13 year olds experience depression, the rate increases to 11.6% among 16 year olds (Substance Abuse and Mental Health Services Administration, 2009).

MDD compromises the development process; feelings of worthlessness, low self-esteem, and thoughts of suicide are common. Patients also experience difficulties with concentration and motivation. Each year as many as 20% of adolescents have suicidal ideation, and 9% attempt suicide (Grunbaum et al, 2002). Suicide is a leading cause of death in adolescents and is a major public health concern (National Adolescent Health Information Center, 2006). A major risk factor for suicide in adolescents is major depression. In a review and meta-analysis of placebo controlled trials assessing use of antidepressant medications among children and adolescents, the FDA concluded that these medications pose an increased risk (4% vs 2%) for suicidal behavior or suicidal ideation, although no suicides were reported (Hammad et al, 2006). Subsequently, the FDA mandated a boxed warning be put on the labels of all antidepressants indicating an increased risk of suicidal thoughts and behavior in youth taking these medications, but did not prohibit their use.

MDD in children and adolescents can be chronic and recurrent. The mean length of pediatric depressive episodes appears to be 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).

Current drug treatment options for pediatric MDD are very limited (ie, FDA approved fluoxetine for children and adolescents 8-18 years of age and escitalopram for adolescents 12-17 years of age). Therefore, it is important that novel treatment options, such as vilazodone, be evaluated systematically for the treatment of MDD in children and adolescents to characterize their efficacy and safety profile in this population.

To address an unmet need of treating MDD in the pediatric population, this study of vilazodone in children and adolescent patients (7-17 years of age) with MDD was agreed upon with the FDA.

8.0 STUDY OBJECTIVE

The objective of this study is to evaluate the long-term safety and tolerability of vilazodone for the treatment of MDD in pediatric outpatients (7-17 years).

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

Study VLZ-MD-23 will be a multicenter, open-label, flexible-dose study in pediatric patients, ages 7 to 17 years with MDD. Eligible patients will include new patients meeting the inclusion/exclusion criteria defined in Section 9.3 and patients who completed the lead-in study (VLZ-MD-22). Study centers will enroll either de novo patients or patients who completed the lead in study. Patients who complete Study VLZ-MD-22 will have the option to participate in Study VLZ-MD-23. Entry into Study VLZ-MD-23 will continue until the enrollment goals are met.

The study will include a total of 17 visits and will be approximately 28 weeks in duration (Figure 9.1.3–1):

- Approximately 1-week screening/washout period
- 26-week open-label treatment period
- 1-week down-taper period

9.1.1 Screening Period

Patients who completed lead-in study VLZ-MD-22 will have completed a down-taper period at the end of study VLZ-MD-22 and will not be required to undergo a washout period.

For de novo patients, the screening/washout period will generally be 1 week prior to Visit 2 (Baseline), but may be extended up to a total of 5 weeks to accommodate prior medication washout or repeat assessments (with prior approval of the Study Physician or designee). At the end of Visit 2 (Baseline), patients who meet the eligibility criteria will be enrolled into the study.

9.1.2 Treatment Period

Approximately ***315*** patients are planned for enrollment in this open-label safety study.

[redacted]

[redacted]

9.1.3 Down-taper Period

All patients who complete the 26-week treatment period and patients who prematurely discontinue before completing 26 weeks of treatment will be eligible to enter the 1-week down-taper period.

[redacted]

If the Investigator determines that it is not clinically appropriate for a patient to enter the down-taper period, investigational product may be discontinued, and the patient should be managed in a clinically appropriate manner.

All enrolled patients must complete the Safety Follow-up Visit (Visit 17/Week 27). Additional follow-up visits may be scheduled within 30 days if necessary for safety reasons.

[redacted]

[redacted] **Study Design**

[redacted]

9.2 DISCUSSION OF STUDY DESIGN

This multicenter, flexible-dose study with a 26-week open-label treatment is designed to evaluate the long-term safety and tolerability of flexible doses of vilazodone (15 and 30 mg/day) in pediatric patients with MDD. An open-label study design with no control group was chosen to meet this objective.

The flexible-dose design was selected to examine the relative safety and tolerability of a range of doses of vilazodone based on the Investigator's judgment (ie, in a manner applicable to the expected clinical use). Also, this study was designed with reference to the FDA Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population.

In this pediatric study, Investigators will enroll pediatric patients ages 7 through 17 who met the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR) criteria for MDD. The MDD diagnosis will be confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime ([K-SADS-PL]; Kaufman et al, 1997), a reliable and valid semi-structured interview designed to assess current and past episodes of psychopathology in children and adolescents, covering a broad spectrum of psychiatric diagnoses through separate interviews with the patient and the caregiver. The Children's Depression Rating Scale-Revised (CDRS-R) (Section 9.5.1.2.1) will assess the MDD symptoms and severity.

[redacted]

[redacted] The 1-week down-taper has been included to allow a gradual reduction in the concentration of the investigational product to reduce the likelihood of emergence of discontinuation symptoms.

9.3 SELECTION OF STUDY POPULATION

The number of males and females will be approximately equal in both age groups (7-11 years and 12-17 years) with at least 40% of the patients between 7 to 11 years of age. There should be reasonable representation overall of ethnic and racial minorities, reflecting the proportions in the disease population.

9.3.1 Inclusion Criteria

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

Note: Inclusion criteria #2 through #5 are considered to have been met for patients who completed the lead-in study (VLZ-MD-22). For patients who completed the lead-in study (VLZ-MD-22), medical, psychiatric and medication histories from Screening (Visit 1) of the lead-in study will be used.

1. Be able to provide informed assent and their parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures (Section 5.3)

2. Be a male or female outpatient, 7 to 17 years of age, inclusive, at Screening (Visit 1; *de novo* patients only)

3. Meet DSM-IV-TR criteria for MDD, confirmed by K-SADS-PL, with a current depressive episode of ≥ 6 weeks duration at Screening (Visit 1; *de novo* patients only)

4. Have a score of ≥ 40 on the CDRS-R at Screening and Baseline (Visits 1 and 2, respectively; *de novo* patients only)

5. Have a Clinical Global Impressions–Severity (CGI-S) score ≥ 4 at Screening and Baseline (Visits 1 and 2, respectively; *de novo* patients only)

6. Have a caregiver who is willing and able and provides consent to be responsible for safety monitoring of the patient, providing information about the patient's condition, overseeing the administration of investigational product, and accompanying the patient to all study visits (Section 5.3)

7. Have normal physical examination findings, vital sign values, clinical laboratory test results, and electrocardiogram (ECG) results, or abnormal results that are determined by the Investigator not to be clinically significant

8. Have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result if patient is female ≥ 9 years of age or has had onset of menses

9.3.2 Exclusion Criteria

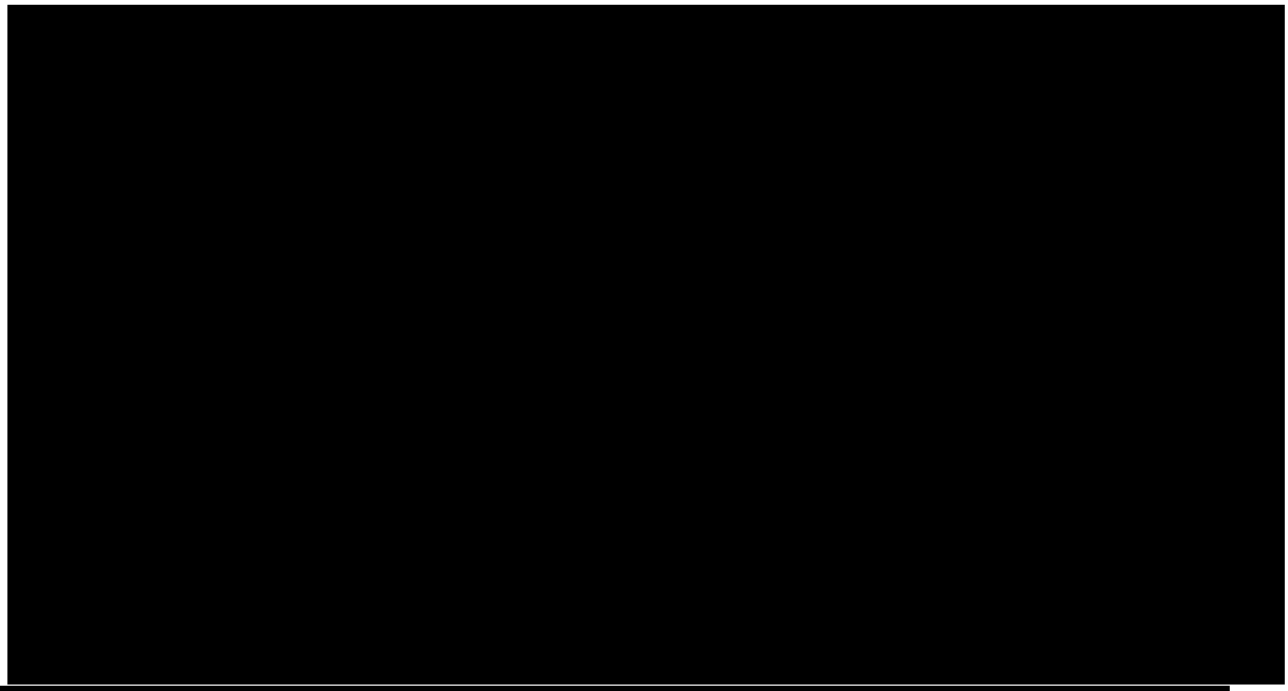
Patients who meet any of the following criteria will not be eligible to participate in the study:

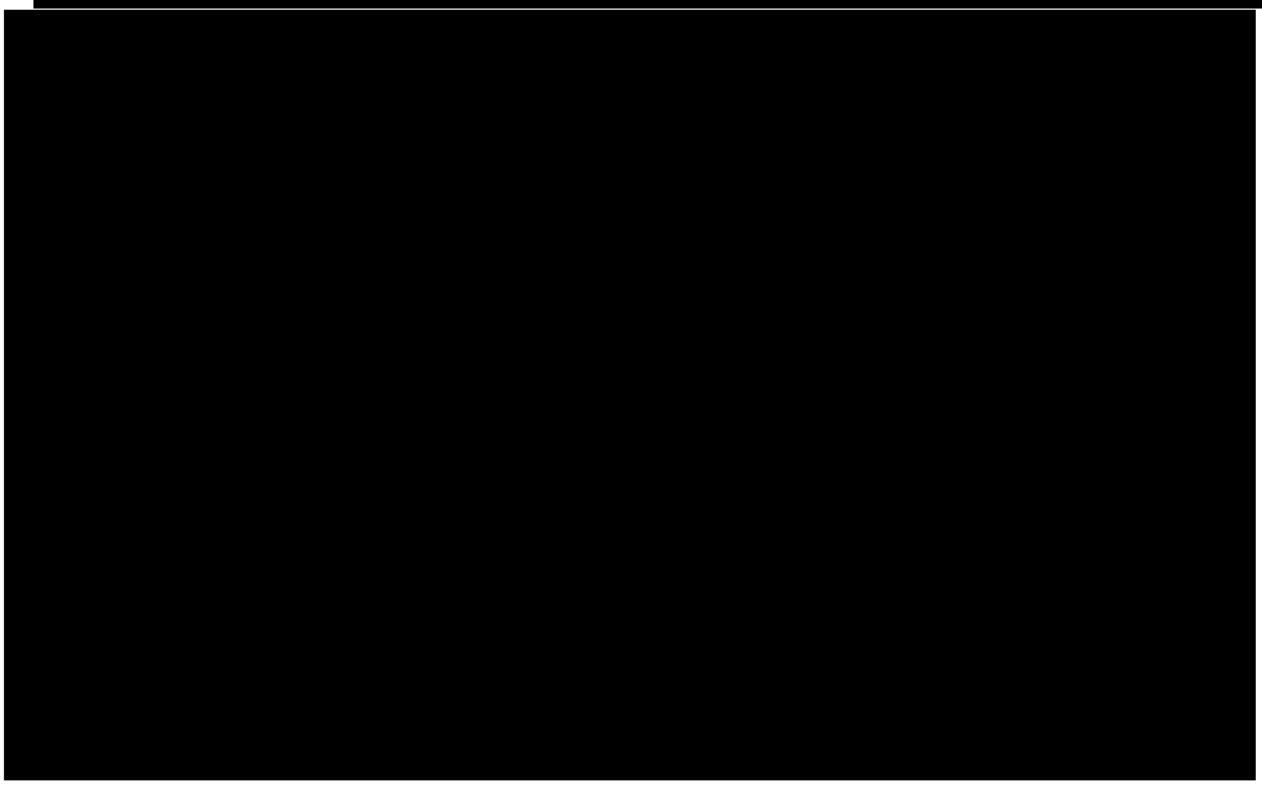
Note: For patients who completed the lead-in study (VLZ-MD-22), medical, psychiatric and medication histories from Screening (Visit 1) of the lead-in study will be used.

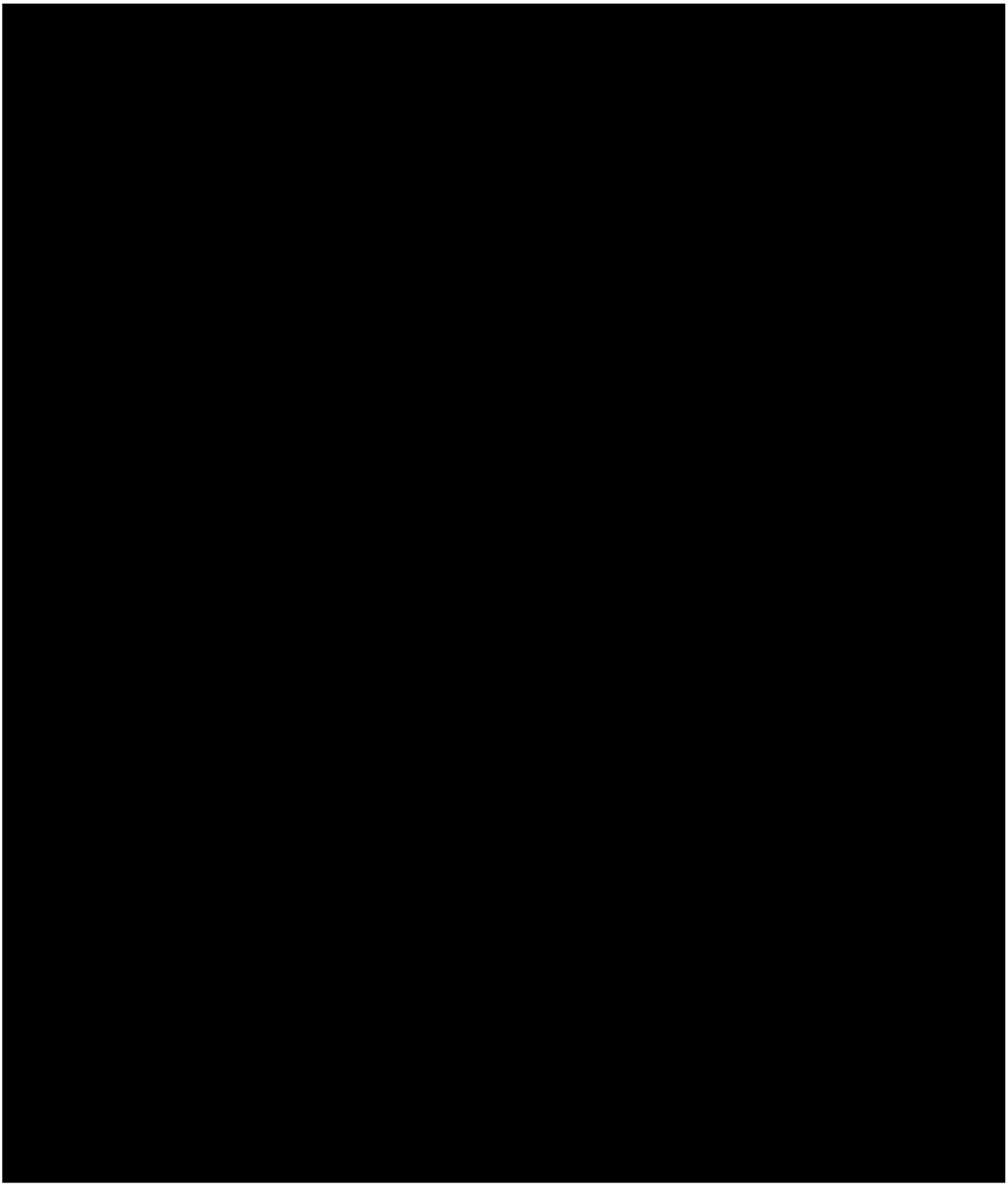
[redacted]

Psychiatric Criteria

1. A current (within 3 months of Screening) principal DSM-IV-TR–based diagnosis of an Axis I disorder other than MDD that is the primary focus of treatment (*de novo* patients only)
    - Patients with comorbid diagnoses of learning disorders, attention deficit disorder (with or without hyperactivity), communication disorders, separation anxiety disorder, oppositional defiant disorder, and anxiety disorders will be allowed to participate in the study if these conditions are not the primary focus of treatment and all concomitant medications/limitations comply with Appendix III
    - Patients with conduct disorder will not be allowed to participate
2. A prior diagnosis of mental retardation or amnesic or other cognitive disorders based on DSM-IV-TR criteria
3. An imminent risk of injuring self or others or causing damage to property as judged by the Investigator
4. A suicide risk as determined by meeting any of the following criteria:
    - Any suicide attempt within the past year
    - A significant risk, as judged by the Investigator on the psychiatric interview or information collected in the C-SSRS)







[redacted]

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

20. Females who are sexually active:

Who are not practicing a reliable method of contraception that will continue for the duration of the study and within 30 days following the end of study participation. Reliable contraception is defined as:

- Surgical sterilization (eg, tubal ligation or hysterectomy)
- Oral contraceptives (consisting of an estrogen-progestin combination or progestin alone)
- Transdermally delivered contraceptives (eg, Ortho-Evra), depot injections (eg, Depo-Provera)
- Vaginal contraceptive ring (eg, NuvaRing), contraceptive implants (eg, Implanon, Norplant II/Jadelle)

Note: Females using hormonal contraceptives must have been doing so for at least 1 month before Screening (Visit 1) and must follow that product's package insert instructions concerning additional protection at times when doses might be missed.

- Intrauterine device
- Double-barrier method (ie, diaphragm plus condom)
- Exclusively sexually active with a female partner

For females who are sexually active, rhythm, withdrawal, single-barrier methods (eg, contraceptive sponge, female condom or male condom, diaphragm alone or with spermicide), emergency contraceptives (eg, Plan B as the sole plan), and abstinence are not acceptable methods of contraception during study participation.

Criteria to be assessed at Baseline (Visit 2)
27. A suicide risk, as determined by meeting the following criterion:

- A significant risk, as judged by the Investigator, based on the psychiatric interview or information collected in the C-SSRS

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 signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study visits and procedures. Patients can be prematurely discontinued from the study for any of the following reasons:

- Failure to meet inclusion/exclusion criteria
- Withdrawal of assent or consent (a reason must be documented)
- Adverse event (AE)

- Worsening of MDD symptoms or insufficient therapeutic response
- Protocol deviation, including lack of compliance
- Lost to follow-up (every effort must be made to contact the patient; at least 2 documented telephone calls must be made and 2 registered letters must be sent)
- Study or study center prematurely terminated by FRI for any reason
- Other reasons, such as specified administrative reasons or pregnancy

All enrolled patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment at an Early Termination (ET) Visit. A final assessment will be defined as completion of the evaluations scheduled for all patients at the end of Week 26 (Visit 16). All patients discontinuing the study prematurely should enter the 1-week down-taper period when clinically appropriate.

Patients who discontinue from the study and do not return to the study center for final assessments must be requested in writing to return to the study center for a final assessment and return any unused investigational product. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study center staff will be contacted by FRI after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

9.3.4 Patient Replacement Procedures

Patients who prematurely discontinue treatment will not be replaced.

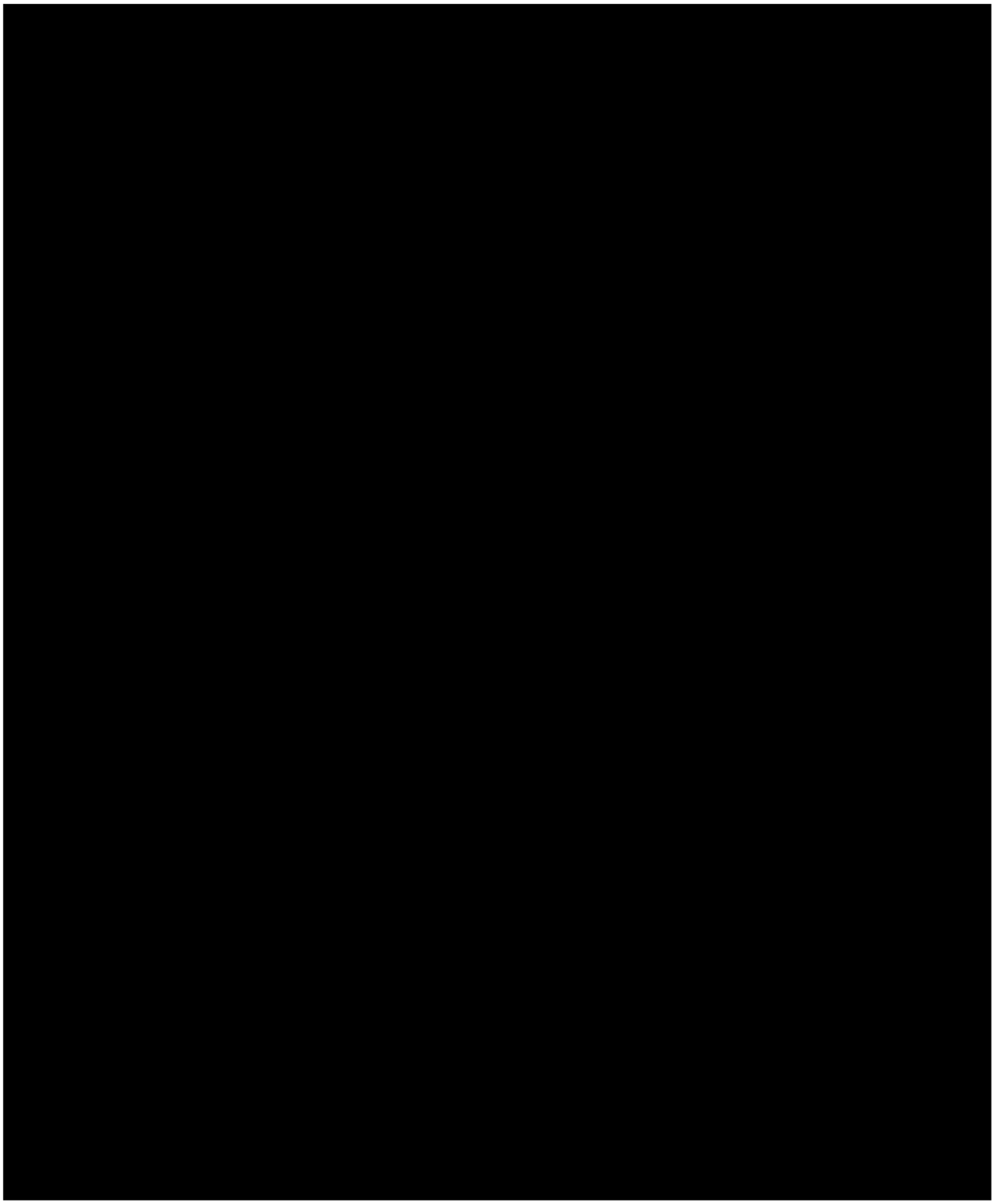
9.4 TREATMENTS

Patients who meet eligibility criteria at the end of Baseline (Visit 2) will be enrolled and receive open-label vilazodone.

9.4.1 Treatments Administered

Investigational product in the form of tablets [redacted]

9.4.2 Identity of Investigational Products



9.4.3 Method of Assigning Patients to Treatment

[redacted]

9.4.4 Selection of Dosages in the Study

Doses of vilazodone in pediatric patients (7-17 years of age) were selected based on modeling of available pharmacokinetic data from the adult healthy volunteers, as well as adult and adolescent patients (12-17 years of age) with MDD. [redacted]

[redacted]

9.4.5 Selection and Timing of Dose for Each Patient

9.4.5.1 Treatment Period

Patients who meet all eligibility criteria at Screening (Visit 1) and who continue to meet all the eligibility criteria for participation in the study at Baseline (Visit 2) will be dispensed [redacted] open-label investigational product for Week 1. [redacted]

9.4.5.2 Down-taper Period (Visit 17/End of Week 27)

Patients who complete 26 weeks of treatment at Visit 16 and patients who discontinue the study prematurely should enter the down-taper period when clinically appropriate.

[redacted]

[redacted]

9.4.6 Blinding

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

9.4.7 Unblinding

Not applicable.

9.4.8 Prior and Concomitant Therapy

[redacted]

9.4.9 Monitoring Treatment Compliance

[redacted]

9.4.10 Treatment Following Investigational Product Discontinuation

Patients whose MDD symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the open-label treatment period will be allowed to discontinue the investigational product, will be discontinued from the study, and may start an alternate treatment at the Investigator's discretion. An alternate treatment will not be provided by FRI. In addition, patients who need to start an alternate treatment will be discontinued from the study.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Diagnostic and Efficacy Assessments

No diagnostic and efficacy assessments are to be administered to the patient unless the patient is accompanied by his/her consented caregiver.

9.5.1.1 Diagnostic Assessments

The K-SADS-PL will be administered during the screening interviews by a child psychiatrist or doctoral level clinical psychologist or other clinician who has extensive professional training and experience in the diagnosis of mental illness in pediatric patients and who meets the training requirements and qualifications standards set by FRI and rater training vendor.

9.5.1.2 Efficacy Assessments

All efficacy assessments (CDRS-R, CGI-S, and Clinical Global Impressions–Improvement [CGI-I]) will be administered by the Investigator, Sub-investigator, or a child psychiatrist, doctoral level clinical psychologist, or other clinician who has extensive professional training and experience in the diagnosis of mental illness in pediatric patients and who meets the training requirements and qualifications standards set by FRI and rater training vendor.

9.5.1.2.1 Children's Depression Rating Scale–Revised

The CDRS-R (Poznanski and Mokros, 1996) is a semistructured, clinician-rated instrument designed for use with children and adolescents between 6 to 17 years of age and their caregivers. It contains 17 ordinally-scaled items that evaluate the presence and severity of symptoms commonly associated with depression in childhood.

The CDRS-R is administered separately to the patient and to the caregiver. The clinician selects a rating for each item that provides the best description of the patient's symptoms resulting in a score ranging from 17 to 113. The CDRS-R total score refers to the raw scale scores.

A copy of the CDRS-R is provided in Appendix IV.

9.5.1.2.2 The Clinical Global Impressions–Severity

The CGI-S (Guy, 1976) is a clinician-rated instrument used to rate the severity of the patient's current state of mental illness compared with the clinician's total experience with patients with MDD. The severity of the patient's MDD will be rated on a scale from 1 to 7, with 1 indicating a normal state and 7 indicating a patient who is *among the most extremely ill patients*. A copy of the CGI-S is provided in Appendix V.

9.5.1.2.3 Clinical Global Impressions–Improvement

The CGI-I (Guy, 1976) is a clinician rated instrument that will be used to rate total improvement or worsening of mental illness from Baseline (Visit 2), regardless of whether the Investigator considers it to be a result of treatment with the investigational product. The CGI-I will be used to rate the patient's improvement on a scale from 1 to 7, with 1 indicating that the patient is very much improved and 7 indicating the patient is very much worse. A copy of the CGI-I is provided in Appendix VI.

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. Safety assessments should not be administered to the patient unless the patient is accompanied by his or 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 the site's data collection responsibilities, any untoward event that is reported from the time the ICF was signed until 30 days after the final protocol-defined study visit or the last known dose of investigational product (if the final visit does not occur) 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 inform consent, 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

Particular attention must be given to AEs that were identified in the adult MDD vilazodone program: nausea, vomiting, decreased appetite, and weight loss.

Please note 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 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 [redacted]

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.

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 1 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.***

Fax the SAE Form for Clinical Trials to FRI.

United States and Canada: 631-858-7964
Medical Emergency phone number: 732-640-7482

9.5.2.7 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the ICF was signed until 30 days after the last dose of investigational product. Within 24 hours of learning of the pregnancy, the study center personnel must report the event to FRI Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE 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.

Any pregnancy of a patient treated with investigational product 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.

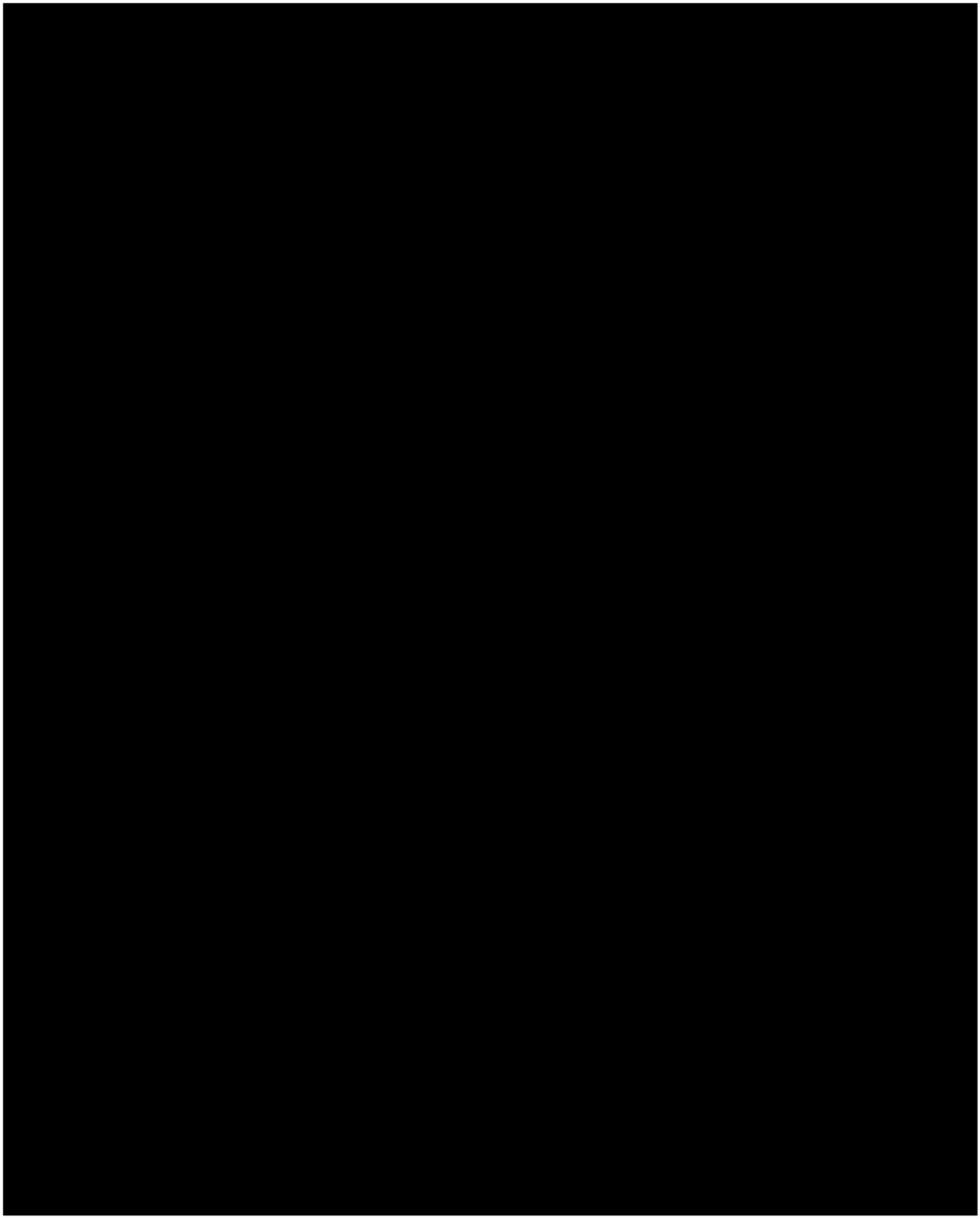
9.5.2.8 Potential Hy's Law Cases

[redacted]

[redacted]

9.5.2.9 Clinical Laboratory Determinations

[redacted]



9.5.2.10 Vital Signs Including Height and Weight

[redacted]

9.5.2.11 Electrocardiograms

[redacted]

9.5.2.12 Other Safety Assessments

9.5.2.12.1 Physical Examination

A complete physical examination will be done at Screening (Visit 1) and at Week 26 (Visit 16/ET) by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

9.5.2.12.2 Columbia–Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The paper version of the C-SSRS will be completed at all study visits. At Screening (Visit 1) the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior for *de novo* patients only; for rollover patients, patient's lifetime history of suicidal ideation and behavior data will be copied from Visit 1 in Study VLZ-MD-22 and kept with patients' source documents for this study. At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit (Appendix VIII). The C-SSRS will be evaluated and signed at each visit by a qualified staff member (ie, the Investigator or designee that has extensive professional training and experience in assessing mental illness) before the patient leaves the study center.

The patient should not be released from the study center until the results of the C-SSRS are reviewed and the patient is not considered to be at risk. If there is doubt about whether a patient is at risk, the Investigator must obtain appropriate psychiatric consultation. The results of the C-SSRS will be recorded in the eCRF. A copy of the C-SSRS is provided in Appendix VII.

9.5.3 Investigational Product Concentration Measurements

Not applicable.

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. Study procedures are for the patient only, unless otherwise specified.

[redacted]

9.5.5.1 Screening (Visit 1)

[redacted]

[redacted]

9.5.5.2 Baseline (Visit 2)

[redacted]

[redacted]

9.5.5.3 End of Weeks 2 and 3 (Visits 3 and 4)

[redacted]

[redacted]

9.5.5.4 End of Week 4 (Visit 5)

[redacted]

[redacted]

9.5.5.5 End of Week 6 (Visit 6)

At Visit 6, the following procedures will be performed:

[redacted]

9.5.5.6 End of Week 8 (Visit 7)

At Visit 7, the following procedures will be performed:

[redacted]

9.5.5.7 End of Week 10 (Visit 8)

[redacted]

[redacted]

9.5.5.8 End of Week 12 (Visit 9)

[redacted]

[redacted]

9.5.5.9 End of Week 14 (Visit 10)

[redacted]

9.5.5.10 End of Week 16 (Visit 11)

[redacted]

[redacted]

9.5.5.11 End of Week 18 (Visit 12)

At Visit 12, the following procedures will be performed:

[redacted]

9.5.5.12 End of Week 20 (Visit 13)

At Visit 13, the following procedures will be performed:

9.5.5.13 End of Week 22 (Visit 14)

[redacted]

9.5.5.14 End of Week 24 (Visit 15)

[redacted]

[redacted]

9.5.5.15 Final or Early Termination Visit, End of Week 26 (Visit 16)

[redacted]

- Schedule next visit:
    - Week 27 (Visit 17) (1 week [± 3 days] relative to Week 26 (Visit 16)

9.5.5.16 Down-taper, End of Week 27 (Safety Follow-up Visit/Visit 17)

All enrolled patients must complete a Safety Follow-up Visit (Week 27 [Visit 17]). [redacted]

[redacted]

Any clinical findings obtained during the final assessment, including clinically significant laboratory abnormalities, will be followed until the condition returns to prestudy status, resolves or stabilizes, or can be explained as being unrelated to the investigational product. If a follow-up visit is necessary, it should take place within 30 days of investigational product termination.

9.5.5.17 Unscheduled Visits

Unscheduled visits may be conducted by the Investigator as necessary for any safety reason. Assessments to be conducted at these visits will be at the discretion of the Investigator.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

[redacted]

9.6.2 Data Recording and Documentation

Data collection will involve the use of the Forest EDC system, to which only authorized personnel will have access. [redacted]

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 [redacted] 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 signed informed consent for this study.

9.7.1.2 Enrolled Population

The Enrolled Population will consist of all patients in the Screened Population who were dispensed investigational product.

9.7.1.3 Safety Population

The Safety Population will consist of all patients who took at least 1 dose of open-label 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 a 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 Enrolled, Safety, and ITT populations will be summarized by study center.

Screen failures (ie, patients who were screened but not included in the Enrolled Population) and the associated reasons for failure will be tabulated. The number and percentage of patients who complete the open-label treatment period and of patients who prematurely discontinue during the same period will be presented. The reasons for premature discontinuation from the open-label treatment period as recorded on the termination pages of the eCRF will be summarized (number and percentage) for the Safety Population.

All summaries in this section will be presented by patient cohort (rollover patients from Study VLZ-MD-22 and *de novo* patients) and overall.

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 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. Summaries of demographic parameters will be presented by patient cohort (rollover patients from Study VLZ-MD-22, *de novo* patients) and overall.

9.7.3.1 Prior and Concomitant Medication

9.7.4 Extent of Exposure and Treatment Compliance

All summaries in this section will be presented by patient cohort (rollover patients from Study VLZ-MD-22 and *de novo* patients) and overall.

9.7.4.1 Extent of Exposure

[redacted]

9.7.4.2 Measurement of Treatment Compliance

[redacted]

9.7.5 Efficacy Analyses

For patients who completed the lead-in study (VLZ-MD-22), the baseline for efficacy from the lead-in study will be used as the baseline for this study. For *de novo* patients, the latest nonmissing evaluation of efficacy variables before the first dose of open-label investigational product will be used as baseline.

The efficacy parameters will include the following at selected postbaseline visits:

- Change from baseline in CDRS-R total score
- Change from baseline in CGI-S score
- CGI-I score

Summaries of efficacy parameters will be presented by patient cohort (rollover patients from Study VLZ-MD-22 and *de novo* patients) and overall. Descriptive statistics will be provided by visit for efficacy parameters for the ITT Population during the open-label treatment period, using both last-observation-carried forward and observed-cases approaches. The last-observation-carried forward approach will be used to impute missing postbaseline values.

9.7.5.1 Primary Efficacy Parameter

No efficacy assessments are considered primary in this open-label safety study.

9.7.6 Safety Analyses

The safety analysis will be performed for the open-label treatment period and down-taper period separately using the Safety Population. The safety analyses will be presented by patient cohort (rollover patients from Study VLZ-MD-22 and *de novo* patients) and overall.

The safety parameters will include AEs, clinical laboratory parameters, vital sign measurements, ECG parameters, C-SSRS evaluations, and the change from baseline in the age- and gender-adjusted height (evaluation of growth). For patients who completed the lead-in study (VLZ-MD-22), the baseline for safety from the lead-in study will be used as the baseline for this study. For *de novo* patients, the latest nonmissing evaluation of safety variables before the first dose of open-label investigational product will be used as baseline.

9.7.6.1 Adverse Events

For patients who completed the lead-in study (VLZ-MD-22), an AE (classified by preferred term) that occurs during the open-label treatment period or during the down-taper 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 in the lead-in study or if it was present before the date of the first dose of double-blind investigational product in the lead-in study and increased in severity during the open-label treatment period or during the down-taper period. If more than 1 AE is reported before the date of the first dose of double-blind investigational product in the lead-in study 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 treatment period or during the 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 investigational product will not be counted as a TEAE.

For *de novo* patients, an AE (classified by preferred term) that occurs during the open-label treatment period or during the down-taper period will be considered a TEAE if the AE was not present before the date of the first dose of open-label investigational product or if it was present before the date of the first dose of open-label investigational product and increased in severity during the open-label treatment period or during the down-taper period,. If more than 1 AE is reported before the date of the first dose of open-label 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 open-label treatment period or during the 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 investigational product will not be counted as a TEAE.

An AE occurring during the down-taper period will be considered a newly emergent adverse event (NEAE) if it was not present before the start of the down-taper period or was present before the start of the down-taper period but increased in severity during the down-taper period. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a NEAE.

NEAEs reported during the down-taper period will be summarized separately by body system and preferred term.

The number and percentage of patients reporting TEAEs during the open-label treatment period and during the down-taper period will be tabulated separately 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 separately for the open-label treatment period and the down-taper period.

The incidence of common ($\geq$ 2% of patients) TEAEs during the open-label treatment period will be summarized separately by preferred term.

An SAE that occurred between the date of the first dose of open-label investigational product and 30 days after the date of the last dose of open-label investigational product in the study, inclusive, will be considered an on therapy SAE. The incidence of SAEs and AEs leading to premature discontinuation of the study will also be summarized by study period, system organ class and preferred term. Listings will be presented for patients with SAEs, patients with AEs leading to premature discontinuation, and patients who died. 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 open-label investigational product, and patients discontinuing due to AEs before the start of open label investigational product will be included in these listings.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented for each clinical laboratory parameter.

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS laboratory values will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (ie, sitting radial pulse rate, sitting systolic and diastolic BP, body weight, and height) and changes from baseline values at each visit and at end of study will be presented. In addition, height and weight z scores will be calculated based on growth charts (see Section 9.7.6.5.2).

Vital sign values will be PCS if they meet both the observed-value criteria and the change-from-baseline value criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS vital sign values will also be provided.

9.7.6.4 Electrocardiograms

Descriptive statistics for ECG parameters (ie, ventricular heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) and changes from baseline values at each assessment time point will be presented. The QTc is calculated using both the Bazett and Fridericia corrections.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated. The criteria for PCS ECG values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS ECG values will also be provided.

A listing of patients with postbaseline clinically significant ECG abnormalities, as reported by the Investigator or by the central cardiologist, will also be provided.

The number and percentage of patients with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcB or QTcF will be tabulated. A supportive listing of patients with postbaseline QTcB or QTcF increases > 30 msec will be provided, including the PID number, study center number, and all QTcB and QTcF values (including changes from baseline). A listing of all AEs that occur in patients who have postbaseline QTcB or QTcF increases > 30 msec will also be provided.

9.7.6.5 Other Safety Parameters

9.7.6.5.1 Columbia–Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of patients with suicidal ideation or suicidal behavior as recorded on the C-SSRS scale will be presented. The distribution of responses for most severe suicidal ideation and suicidal behavior during the lifetime history, the open-label treatment period, and the down-taper period will also be presented for the Safety Population. Supportive listings will be provided and will include the PID number, visit number, lifetime history, and postbaseline values for each patient. Intensity of ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

9.7.6.5.2 Growth Evaluation

Weight and height will be presented as standardized z scores adjusted for gender and age, using the lambda-mu-sigma method (Cole, 1990).

9.7.6.6 Investigational Product Plasma Concentration Parameters

Not applicable

9.7.7 Health Economics and Outcomes Research Analyses

Not applicable.

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

This is a long-term open-label study of the safety and tolerability of vilazodone in pediatric patients with MDD. ***To allow for all patients who complete the short-term lead-in study (VLZ-MD-22) to have the option to roll over into this extension study if eligible*** [redacted]

9.7.10 Computer Methods

[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

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
- Taking prohibited medications
- Departure from prescribed dosing or duration of treatment
- Failure to follow withdrawal criteria
- Failure to perform the required assessments at specified time points
- Scheduling of visits not in accordance with protocol specifications

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients 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 patients' 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 for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006.

10.0 STUDY SPONSORSHIP

This study is sponsored by Forest Research Institute, Inc.

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 FRI's standard operating procedures on publications.

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

[redacted]

11.2 PERFORMANCE

[redacted]

11.3 USE OF INVESTIGATIONAL MATERIALS

[redacted]

11.4 CASE REPORT FORMS

[redacted]

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, 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

[redacted]

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 for each patient participating in a clinical research study or from the patient's parent/guardian/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; 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/EC 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 permission, providing consent for the patient to participate (eg, "I agree to allow (my child) to participate . . .")

- A place for the patient's parent/guardian/LAR signature and date of signing of the ICF

- 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's parent/guardian/LAR.

In addition, the patient will be asked to provide assent that will include a statement agreeing to participate in the study.

APPENDIX II. CONTACT INFORMATION

Contact information for FRI personnel is maintained in the Study Reference Binder.

APPENDIX III. CONCOMITANT MEDICATIONS

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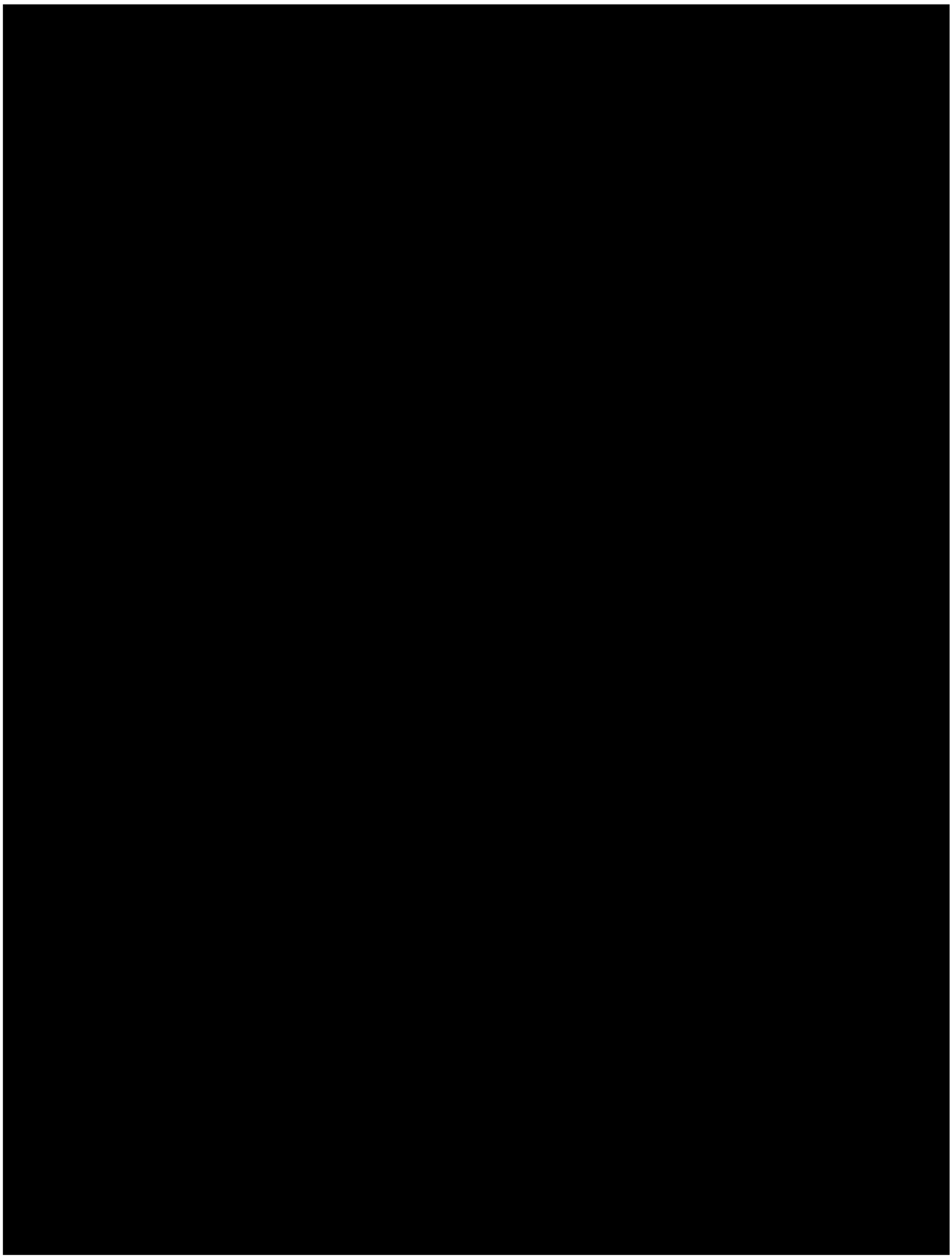
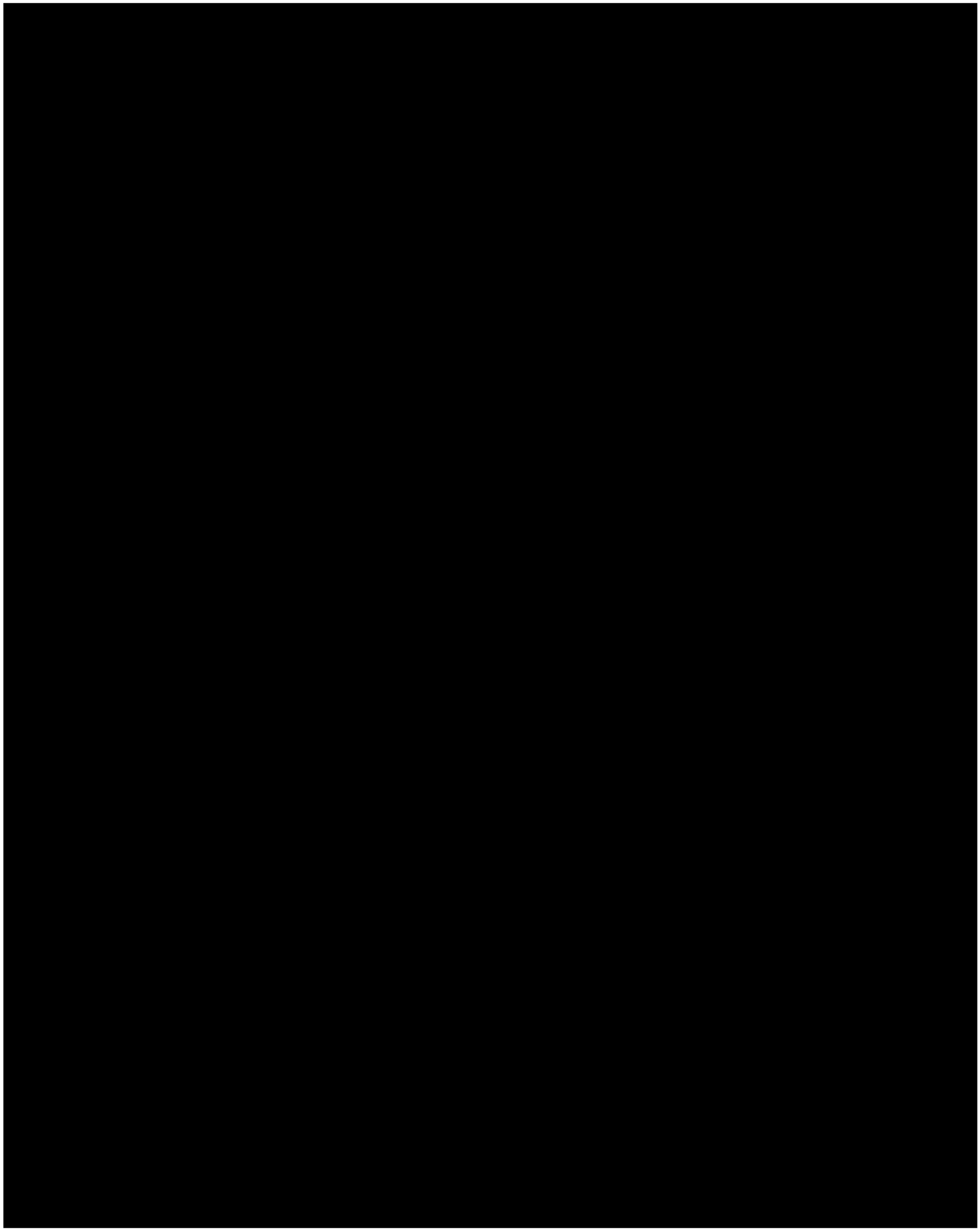
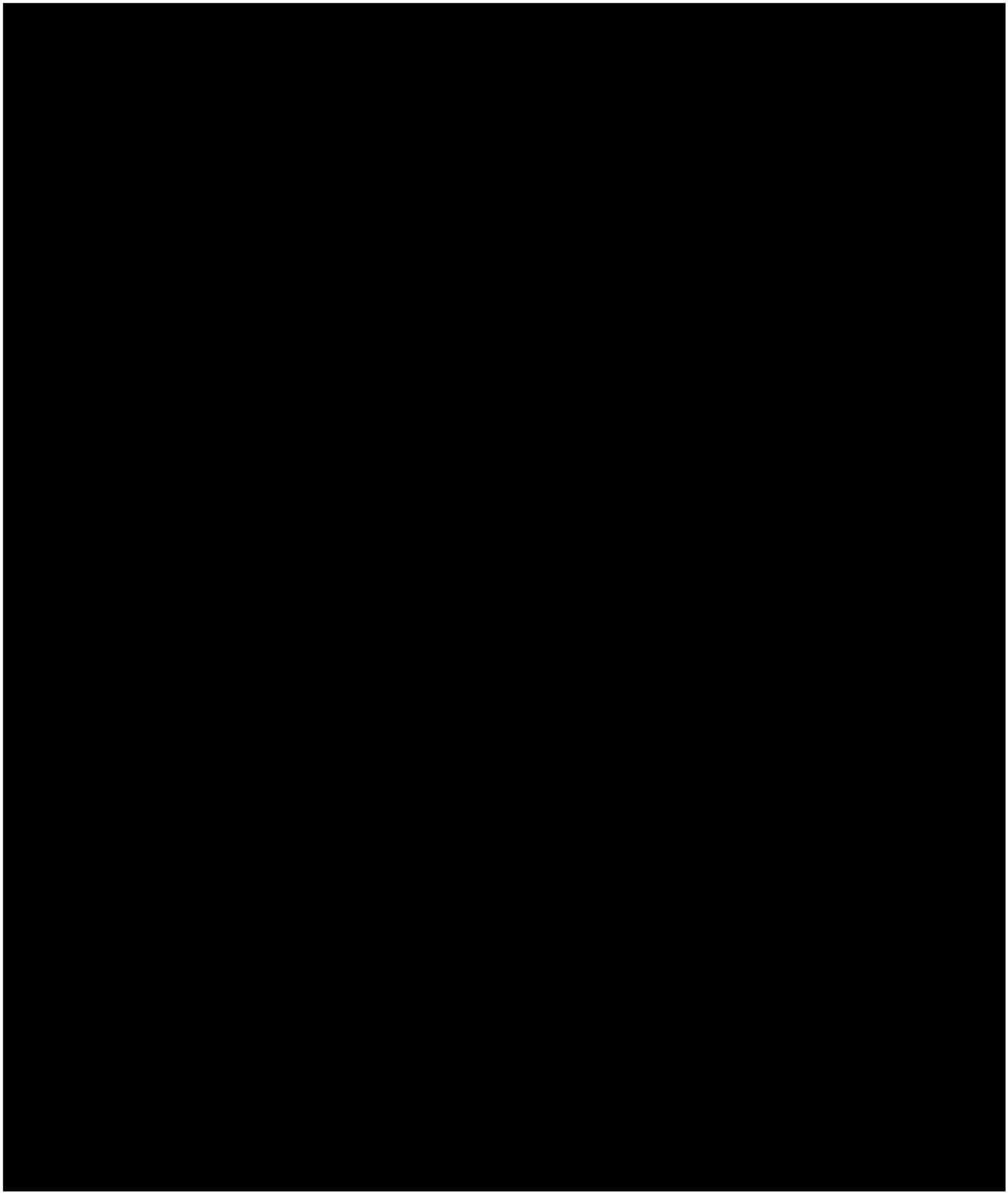
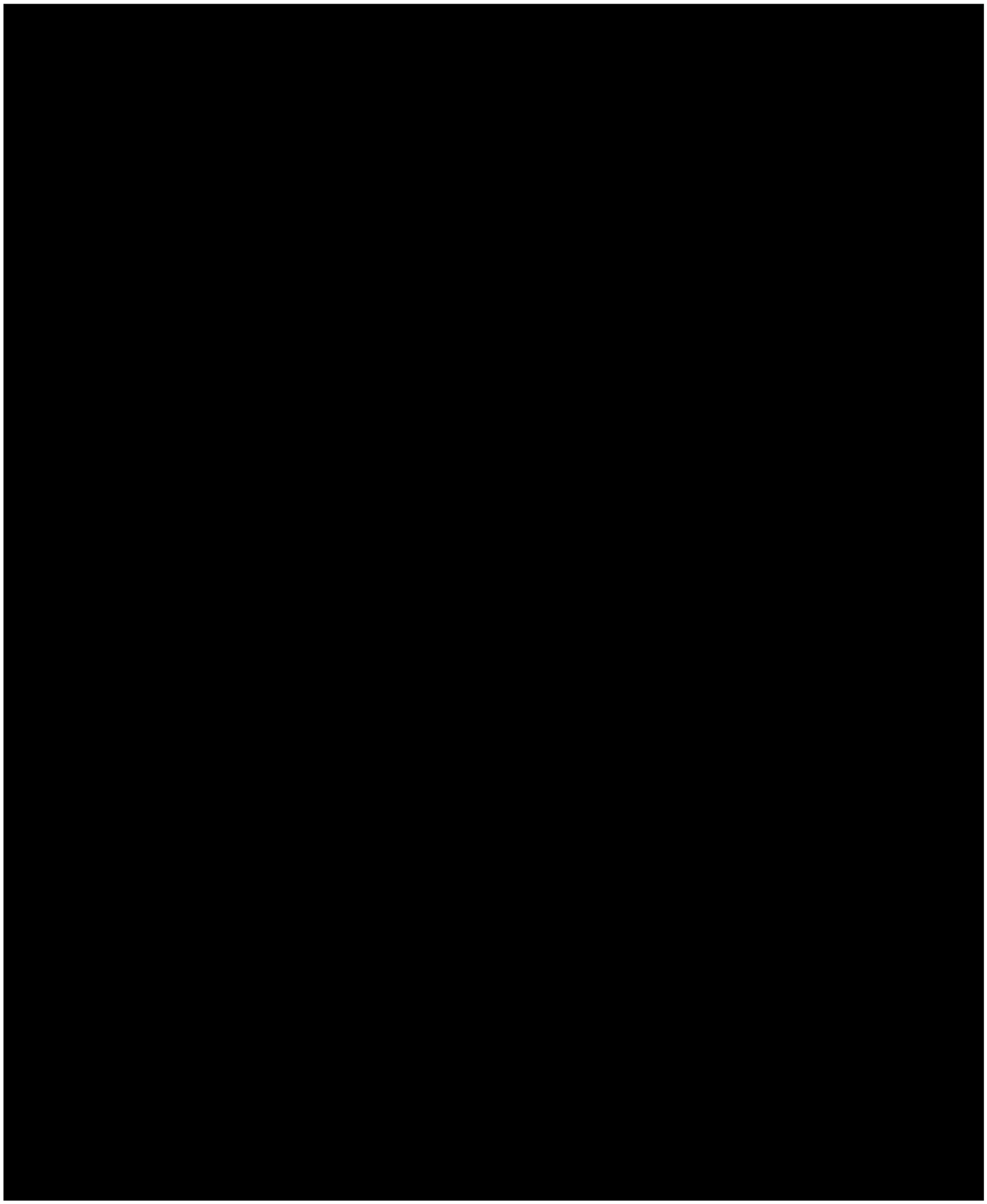






APPENDIX IV. CHILDREN'S DEPRESSION RATING SCALE–REVISED



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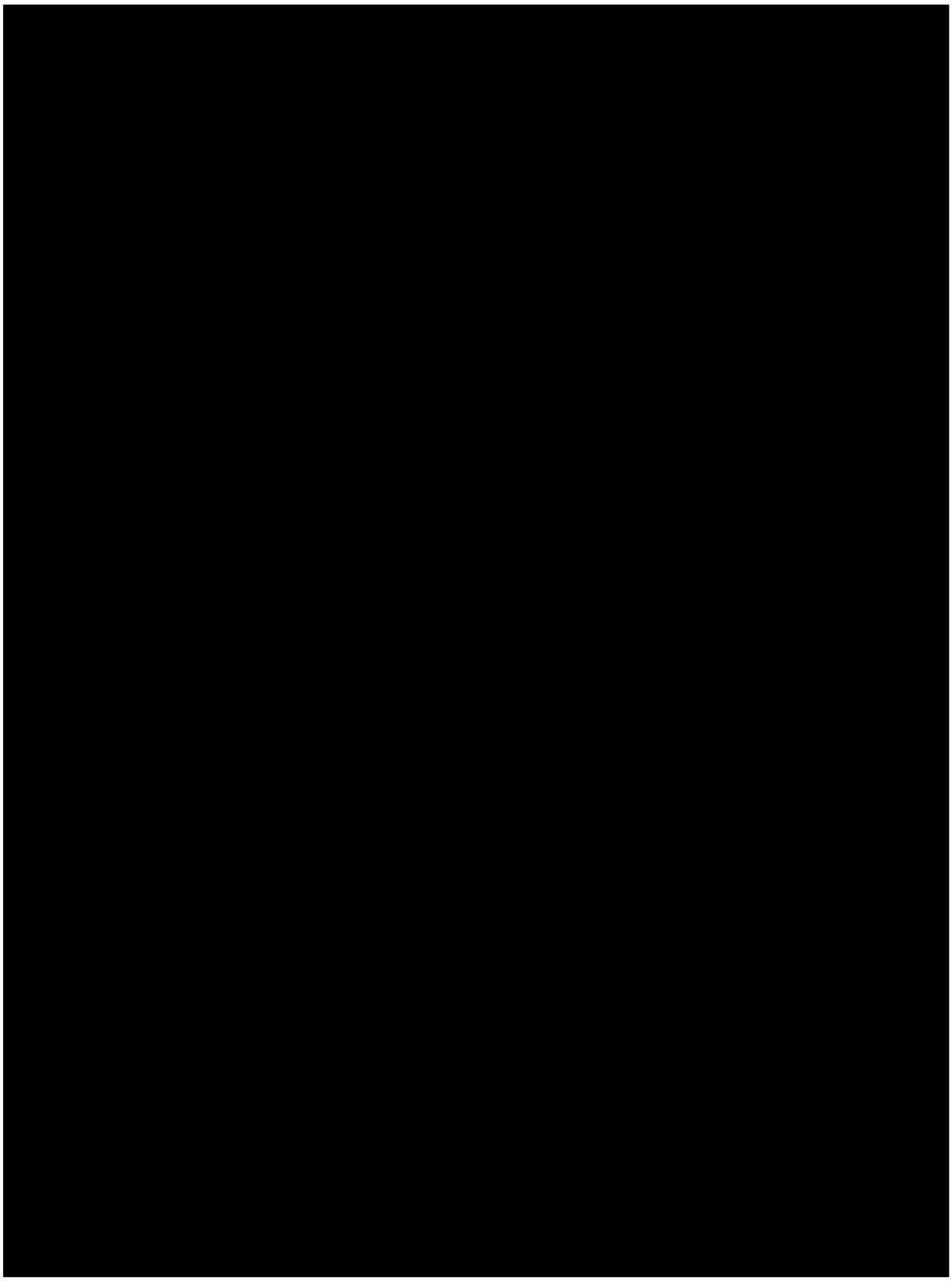
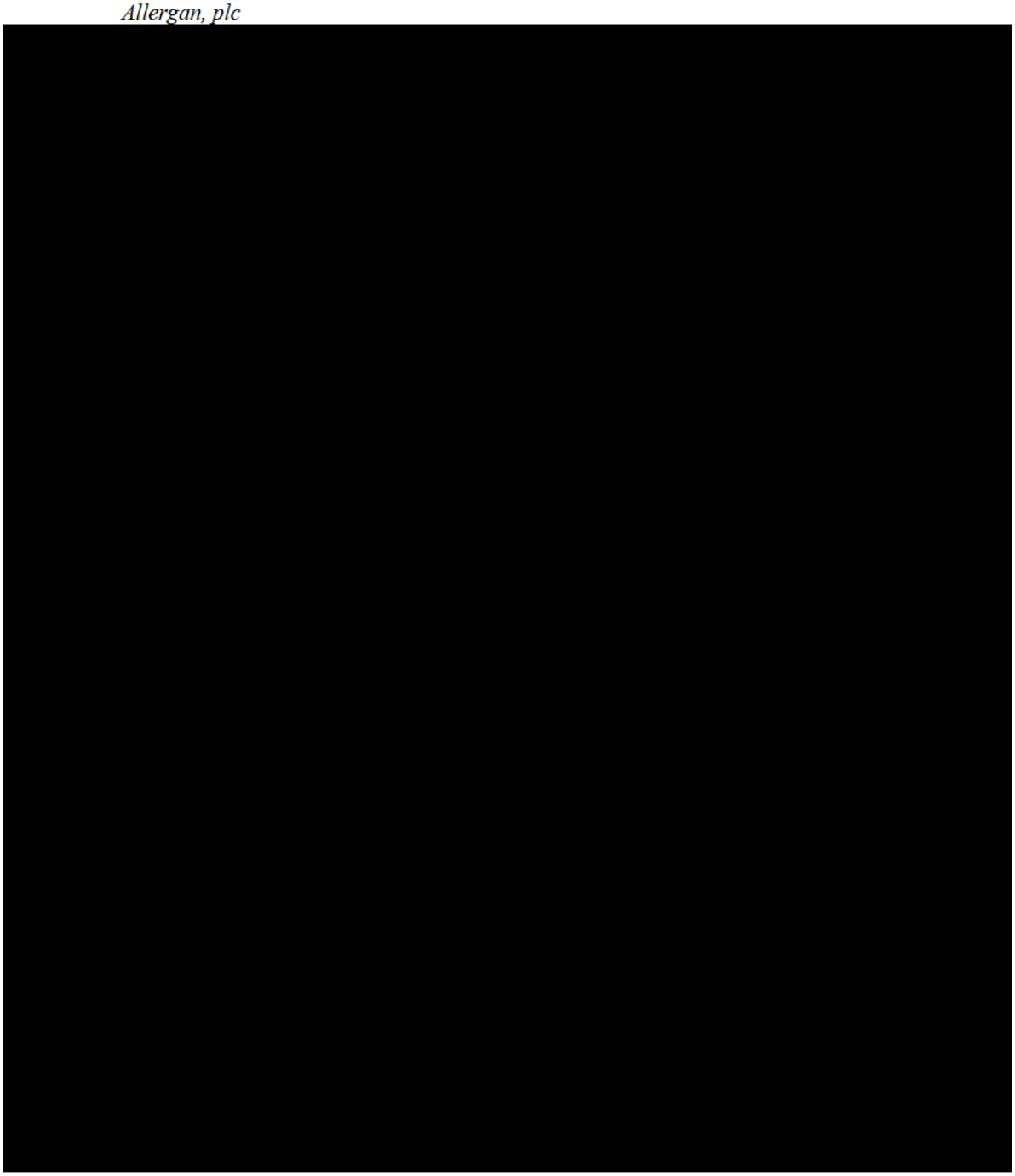
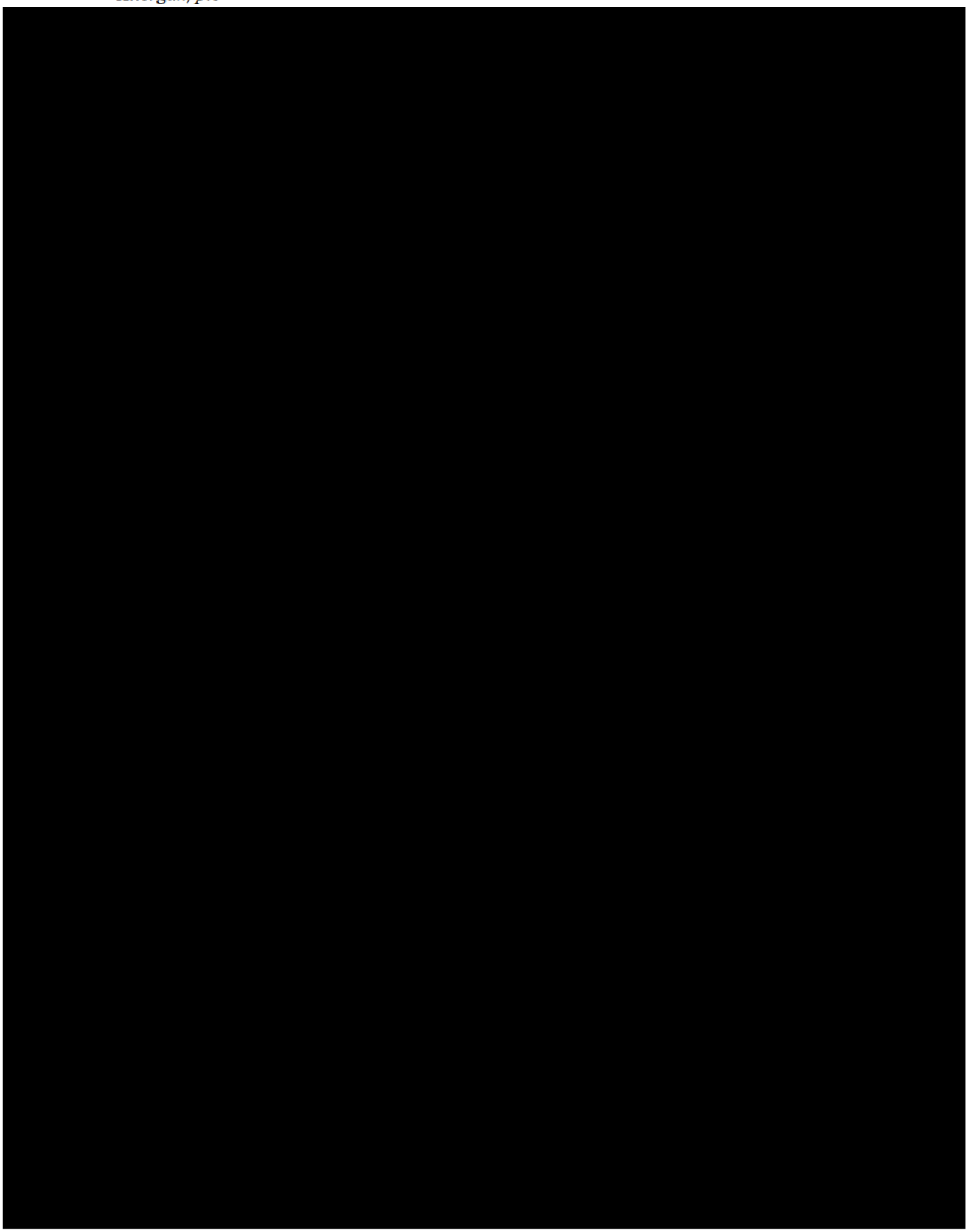
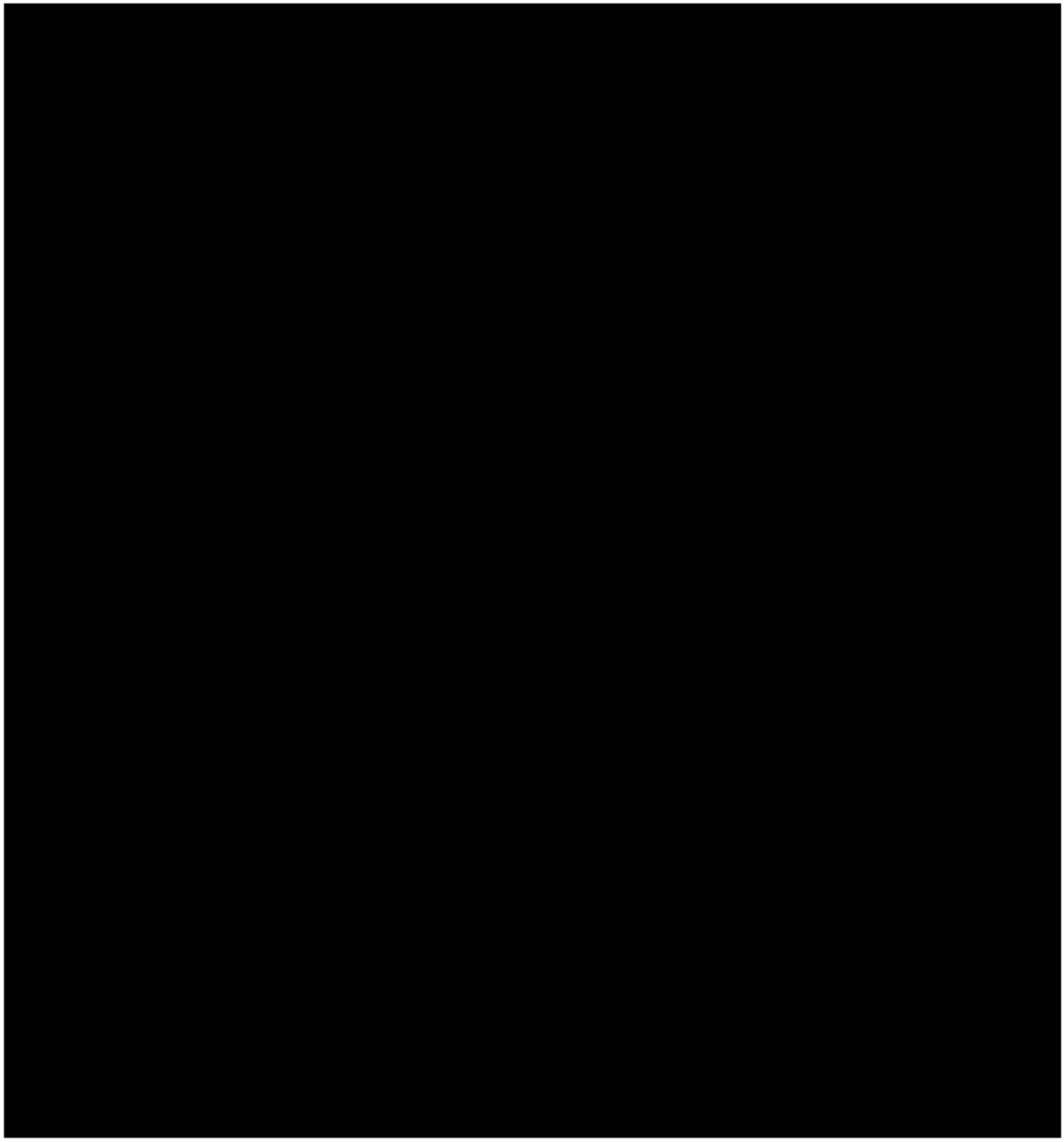








APPENDIX V. CLINICAL GLOBAL IMPRESSIONS–SEVERITY

APPENDIX VI. CLINICAL GLOBAL IMPRESSIONS–IMPROVEMENT

GLOBAL IMPROVEMENT

APPENDIX VII. COLUMBIA–SUICIDE SEVERITY RATING SCALE - BASELINE

COLUMBIA–SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline
Version 1/14/09

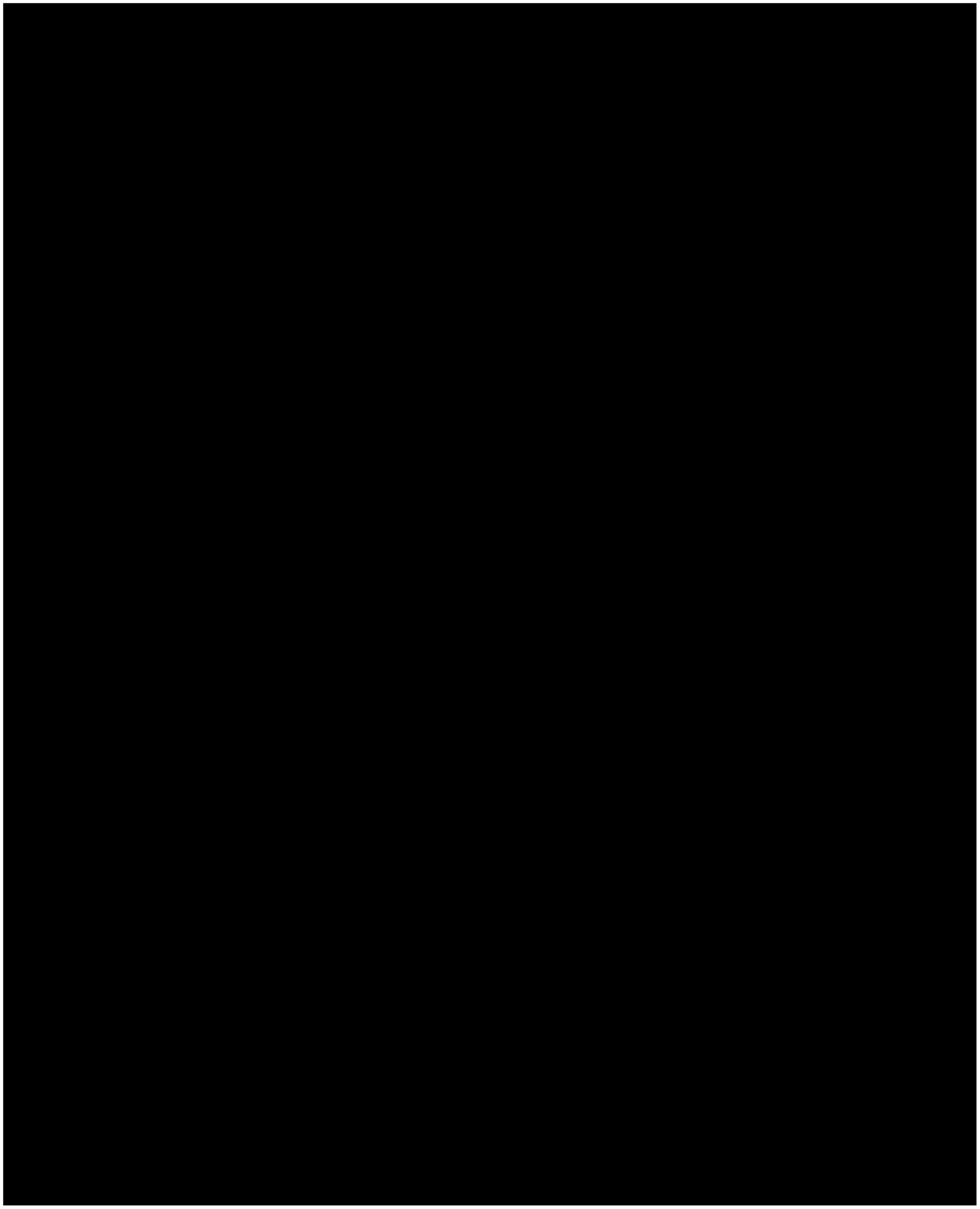
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu



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APPENDIX VIII. COLUMBIA–SUICIDE SEVERITY RATING SCALE - SINCE LAST VISIT

COLUMBIA–SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit
Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

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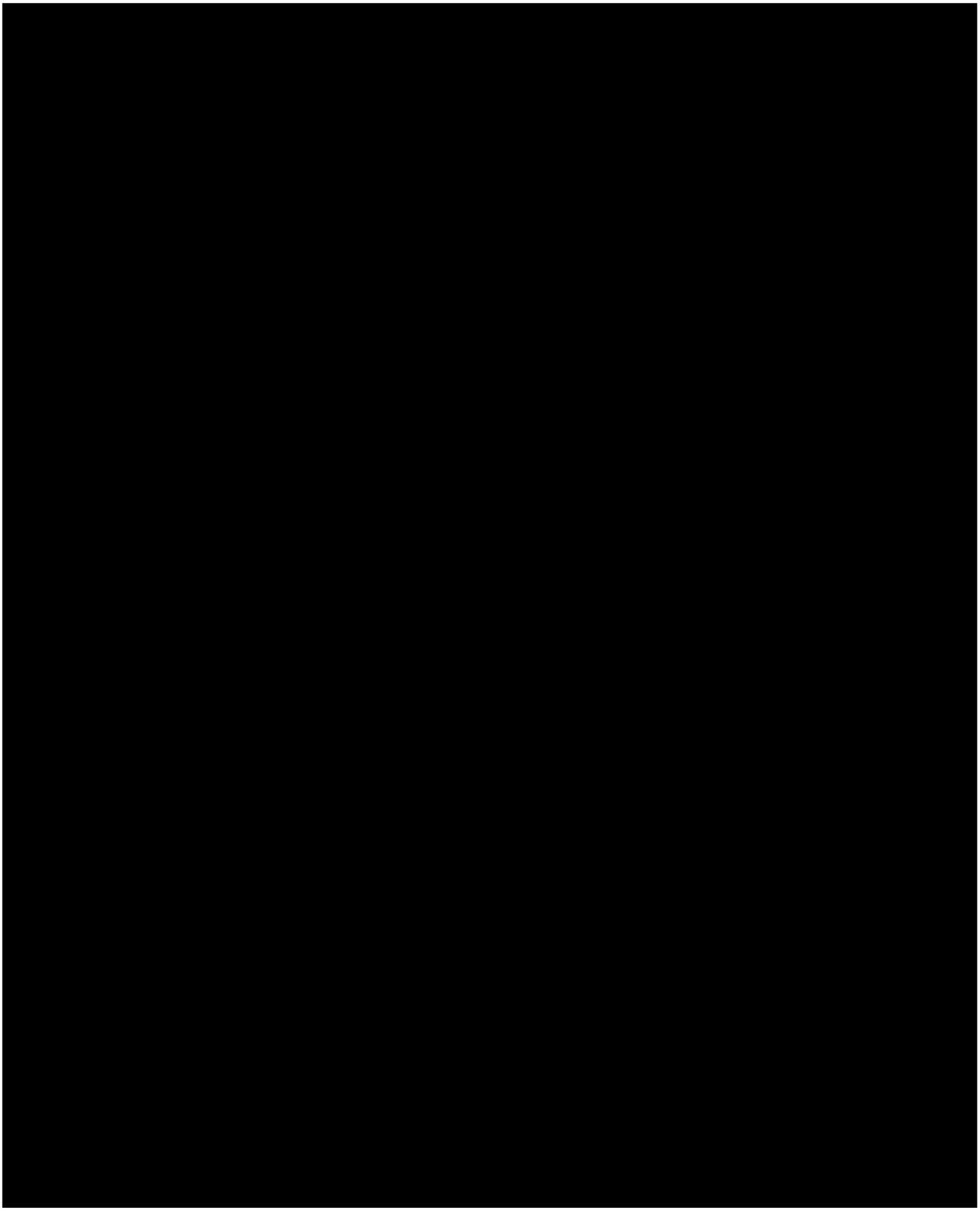

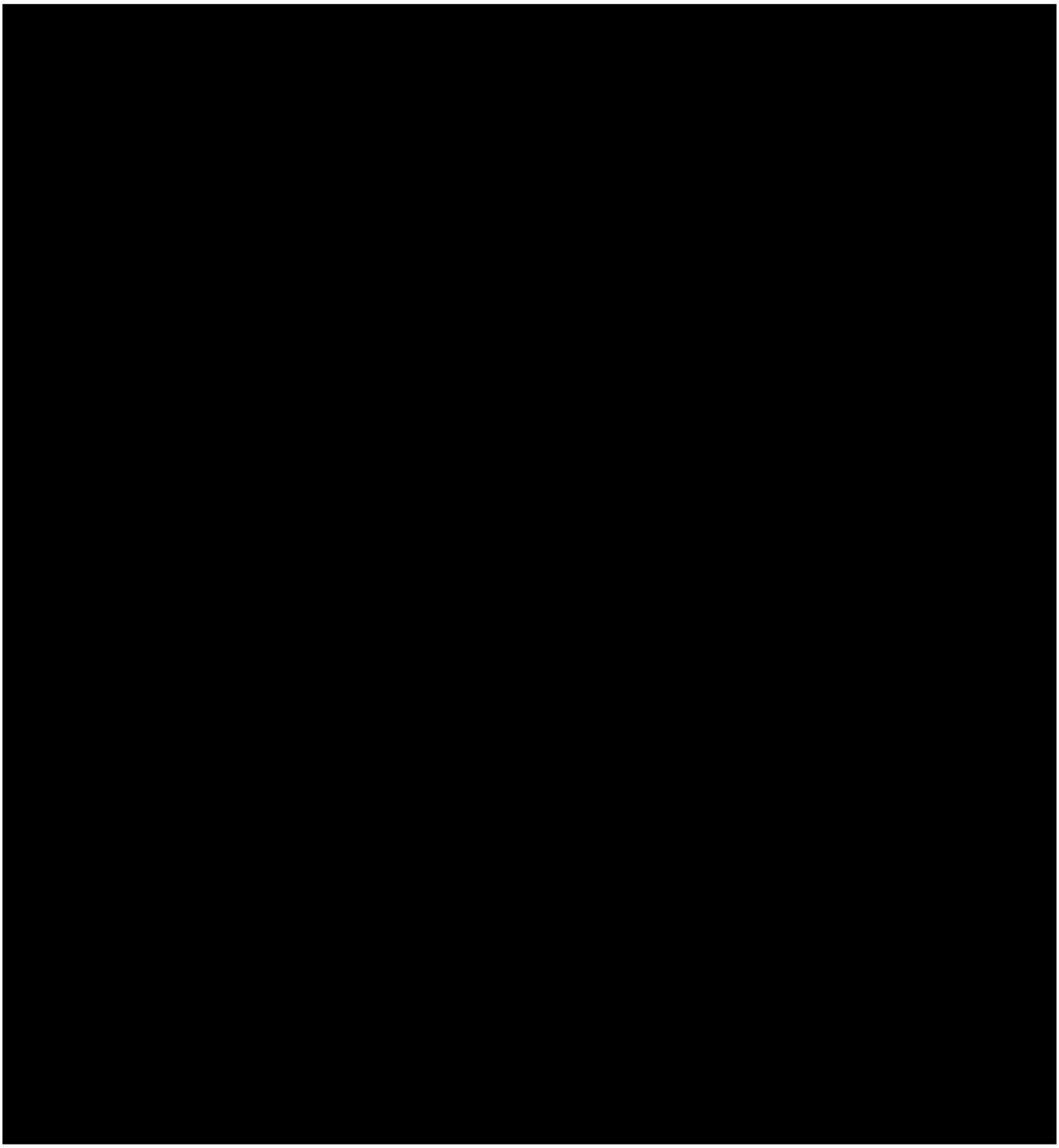

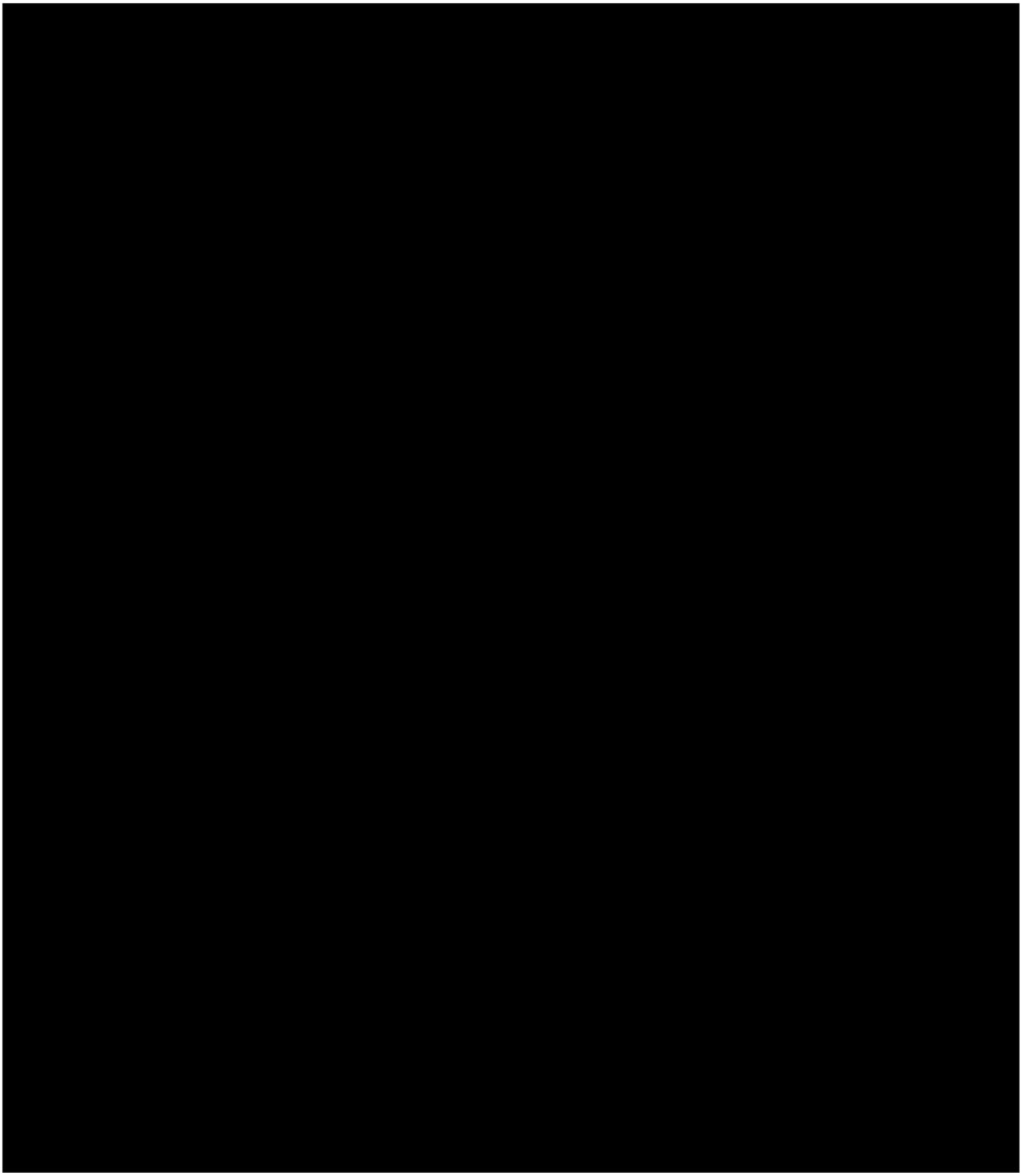

APPENDIX IX. INVESTIGATIONAL PRODUCT FORMULATION

- Ingredients of vilazodone [redacted]

[redacted]

14.0 LITERATURE CITED

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