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**Title:** A Multicenter, Double-blind, Placebo- and Active-Controlled Parallel-Group  
Evaluation of the Safety and Efficacy of Vilazodone in Pediatric Patients With  
Major Depressive Disorder

**Protocol Amendment 1 Date:** 15 April 2015

**1.0**

**TITLE PAGE**



**Forest Research Institute, Inc., a subsidiary of Actavis, Inc.  
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**A Multicenter, Double-blind, Placebo- and Active-Controlled Parallel-Group  
Evaluation of the Safety and Efficacy of Vilazodone in Pediatric Patients With  
Major Depressive Disorder**

**VLZ-MD-22**

**IND # 54,613**

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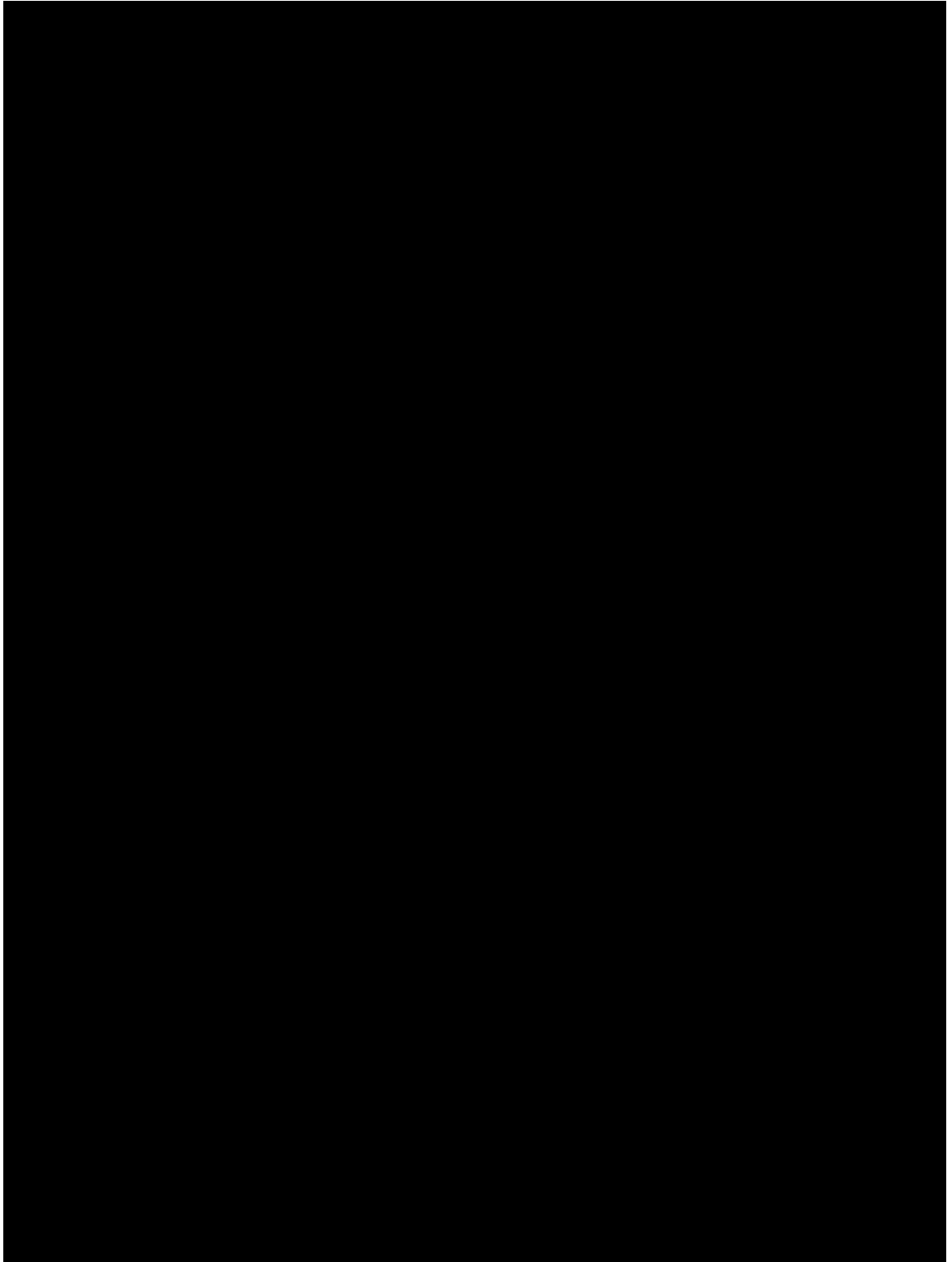
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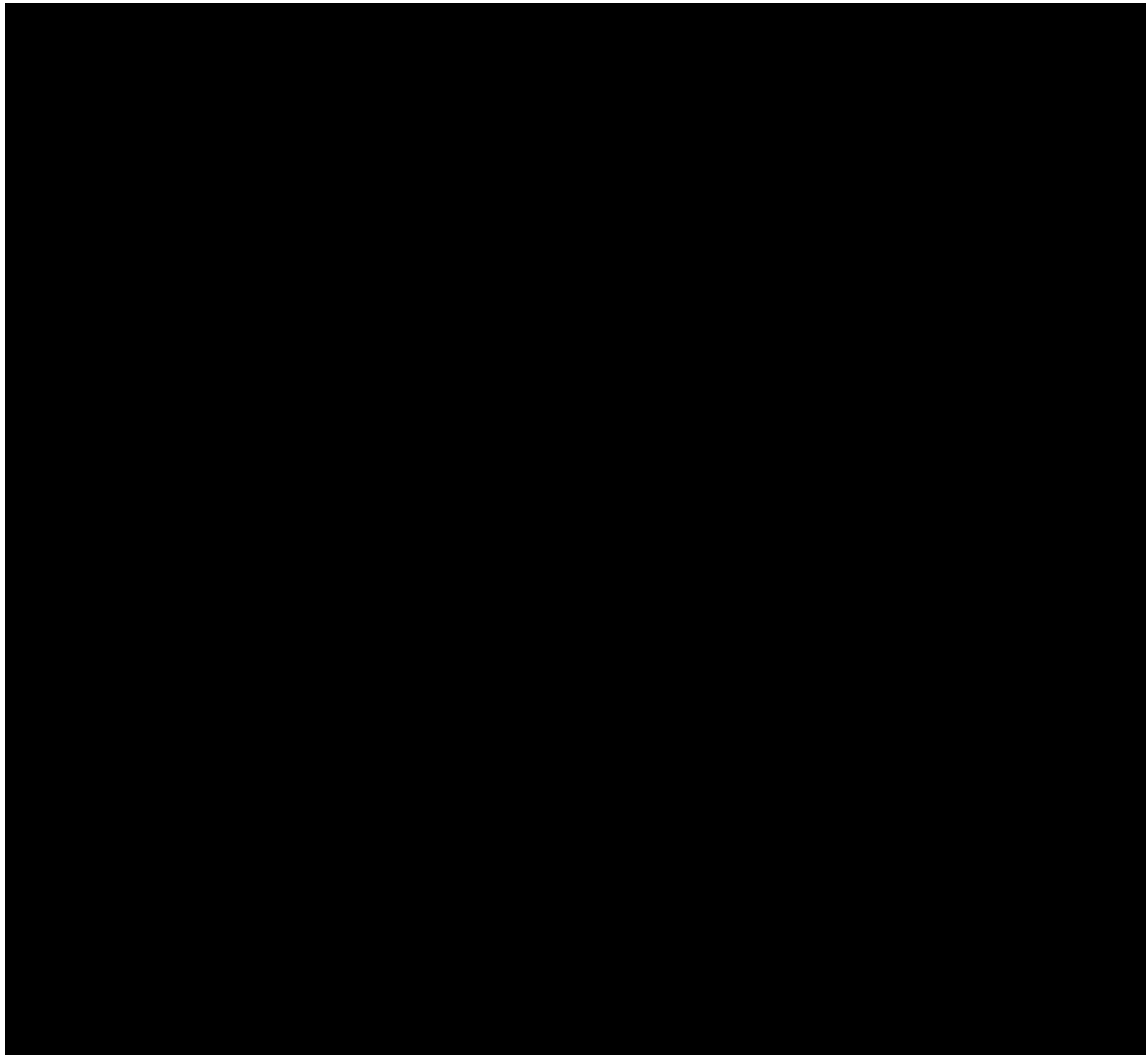
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## 2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study VLZ-MD-22	
<b>Title of Study</b>	A Multicenter, Double-blind, Placebo- and Active-Controlled, Parallel-group Evaluation of the Safety and Efficacy of Vilazodone in Pediatric Patients With Major Depressive Disorder
<b>Study Centers</b>	Approximately 60 study centers in the United States and Canada
<b>Development Phase</b>	3
<b>Objective</b>	To evaluate the efficacy, safety, and tolerability of vilazodone compared with placebo in pediatric outpatients (7-17 years of age) with major depressive disorder (MDD)
<b>Methodology</b>	A multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, flexible-dose study in pediatric patients
<b>Number of Patients</b>	Approximately 400 patients are planned (160 placebo patients, 160 vilazodone patients, and 80 fluoxetine patients)
<b>Diagnosis and Main Criteria for Inclusion</b>	Male and female outpatients, ages 7 to 17 years, who meet <i>Diagnostic and Statistical Manual of Mental Disorders</i> , Fourth Edition, Text Revision criteria for MDD (confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime [K-SADS-PL]) and have a current depressive episode of $\geq 6$ weeks duration at Screening (Visit 1). At Screening (Visit 1) and Baseline (Visit 2), the patient must have a Children’s Depression Rating Scale–Revised (CDRS-R) score $\geq 40$ and a Clinical Global Impressions–Severity (CGI-S) score $\geq 4$ .
<b>Test Product, Dosage, and Mode of Administration</b>	Vilazodone HCl 5 mg, 10 mg, and 20 mg tablets, taken orally as a single dose, once-daily at the same time each day, with food
<b>Duration of Treatment</b>	The study will be 10 weeks in duration: approximately 1-week screening/washout period, 8 weeks of double-blind treatment, and a 1-week double-blind down-taper period.
<b>Reference Therapy, Dosage, and Mode of Administration</b>	Encapsulated fluoxetine 10 and 20 mg, taken orally as a single dose, once-daily at the same time each day, with food Matching placebo tablets for vilazodone HCl and matching placebo capsules for encapsulated fluoxetine, taken orally as a single dose, once-daily at the same time each day, with food
<b>Criteria for Evaluation</b>	
<b>Primary Outcome Measure</b>	Change from baseline to Week 8 of the double-blind treatment period in CDRS-R total score
<b>Key Secondary Outcome Measure</b>	Change from baseline to Week 8 of the double-blind treatment period in CGI-S score
<b>Safety Measures</b>	Adverse event (AE) recording, clinical laboratory tests, vital sign measurements including height and weight, electrocardiograms (ECGs), physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS)
	

<b>Statistical Methods</b>	<p>The primary analysis for comparing vilazodone versus placebo, based on change from baseline to Week 8 in CDRS-R total score, will be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, pooled 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.</p> <p>The secondary efficacy analysis for comparing vilazodone versus placebo based on change from baseline to Week 8 in CGI-S score will be performed using an MMRM model similar to the one used for the primary efficacy parameter.</p> <p>All safety parameters will be analyzed descriptively for the <i>Safety Population</i>, defined as all randomized patients who received at least 1 dose of the investigational product. Efficacy analyses will be performed using the <i>Intent-to-Treat (ITT) Population</i>, defined as all patients in the Safety Population who had baseline and at least 1 postbaseline assessment of CDRS-R total score.</p>
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### 3.1 OVERALL TABLE OF CONTENTS

	Page
1.0 TITLE PAGE .....	1
2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS .....	2
3.0 TABLE OF CONTENTS, TABLES AND FIGURES	
3.1 OVERALL TABLE OF CONTENTS .....	6
3.2 LIST OF IN-TEXT TABLES .....	12
3.3 LIST OF IN-TEXT FIGURES .....	13
4.0 LIST OF ABBREVIATIONS .....	14
5.0 ETHICAL CONSIDERATIONS .....	16
5.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE .....	16
5.2 ETHICAL CONDUCT OF THE STUDY .....	16
5.3 PATIENT INFORMATION AND INFORMED CONSENT .....	17
5.3.1 Patient Assent Form .....	17
5.3.2 Parent, Legal Guardian, and Legally Authorized Representative Informed Consent .....	17
5.3.3 Caregiver Consent .....	18
6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE .....	19
7.0 INTRODUCTION .....	20
8.0 STUDY OBJECTIVES .....	22
9.0 INVESTIGATIONAL PLAN .....	23
9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION .....	23

9.1.1 Screening Period .....	23
9.1.2 Double-blind Treatment Period.....	23
9.1.3 Double-blind Down-taper Period .....	24
9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS .....	25
9.3 SELECTION OF STUDY POPULATION.....	26
9.3.1 Inclusion Criteria.....	26
9.3.2 Exclusion Criteria.....	27
9.3.3 Removal of Patients from Therapy or Assessment .....	31
9.3.4 Patient Replacement Procedures .....	32
9.4 TREATMENTS.....	32
9.4.1 Treatments Administered .....	32
.....	32
.....	33
9.4.4 Selection of Dosages in the Study.....	34
9.4.5 Selection and Timing of Dose for Each Patient .....	34
9.4.5.1 Screening Period .....	35
9.4.5.2 Double-blind Treatment Period .....	35
9.4.5.3 Double-blind Down-taper Period (End of Week 8/(Visit 8)).....	36
9.4.6 Blinding.....	37
9.4.7 Unblinding.....	37
.....	38
.....	38



9.4.10 Treatment Following Investigational Product Discontinuation .....	38
9.5 EFFICACY AND SAFETY VARIABLES.....	38
9.5.1 Diagnostic and Efficacy Assessments.....	38
9.5.1.1 Diagnostic Assessments.....	39
9.5.1.2 Efficacy Assessments.....	39
9.5.2 Safety Assessments .....	40
9.5.2.1 Adverse Events .....	40
9.5.2.2 Causality Assessment.....	41
9.5.2.3 Severity Assessment .....	42
9.5.2.4 Serious Adverse Events .....	42
9.5.2.5 Reporting Adverse Events and Serious Adverse Events .....	43
9.5.2.6 Immediate Reporting of Serious Adverse Events and Events of Special Interest .....	44
9.5.2.7 Reporting of Pregnancies Occurring During the Study .....	44
[REDACTED] .....	45
[REDACTED] .....	45
[REDACTED] .....	47
[REDACTED] .....	48
[REDACTED] .....	48
9.5.3 Investigational Product Concentration Measurements.....	49
9.5.4 Health Economic and Outcomes Research Assessments.....	50
9.5.5 Schedule of Assessments .....	50
[REDACTED] .....	50

[REDACTED]	51
[REDACTED]	52
[REDACTED]	53
[REDACTED]	54
[REDACTED]	54
[REDACTED]	55
9.6 DATA QUALITY ASSURANCE .....	56
[REDACTED]	56
9.6.2 Data Recording and Documentation .....	56
9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE .....	57
9.7.1 Patient Populations .....	57
9.7.1.1 Screened Population.....	57
9.7.1.2 Randomized Population .....	57
9.7.1.3 Safety Population .....	57
9.7.1.4 Intent-to-Treat Population.....	58
9.7.2 Patient Disposition .....	58
9.7.3 Demographics and Other Baseline Characteristics .....	58
[REDACTED]	58
9.7.4 Extent of Exposure and Treatment Compliance .....	59
[REDACTED]	59
[REDACTED]	59
9.7.5 Efficacy Analyses.....	60

9.7.5.1 Primary Efficacy Parameter .....	61
9.7.5.2 Secondary Efficacy Parameter .....	61
.....	62
9.7.6 Safety Analyses .....	62
9.7.6.1 Adverse Events .....	63
.....	64
.....	64
.....	65
.....	66
9.7.6.6 Investigational Product Plasma Concentration Parameters and Exposure-Response Evaluation.....	66
9.7.7 Health Economics and Outcomes Research Analyses .....	66
9.7.8 Interim Analysis .....	67
9.7.9 Determination of Sample Size.....	67
.....	67
9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES .....	67
9.9 PROTOCOL DEVIATIONS AND VIOLATIONS .....	68
9.10 DATA MONITORING COMMITTEE.....	68
10.0 STUDY SPONSORSHIP.....	69
10.1 STUDY TERMINATION .....	69
10.2 REPORTING AND PUBLICATION .....	69
11.0 INVESTIGATOR OBLIGATIONS .....	70
.....	70

[REDACTED]	70
[REDACTED]	71
[REDACTED]	71
11.5 RETENTION AND REVIEW OF RECORDS .....	71
11.6 PATIENT CONFIDENTIALITY .....	72
12.0 INVESTIGATOR'S STATEMENT .....	73
13.0 APPENDICES .....	
APPENDIX I. ELEMENTS OF INFORMED CONSENT .....	74
APPENDIX II. CONTACT INFORMATION .....	76
[REDACTED] .....	77
APPENDIX IV. BLOOD SAMPLING AND SHIPPING INSTRUCTIONS .....	81
[REDACTED]	82
[REDACTED]	88
[REDACTED]	89
[REDACTED]	90
[REDACTED]	94
APPENDIX X. INVESTIGATIONAL PRODUCT FORMULATION ...	98
14.0 LITERATURE CITED .....	99

**3.2 LIST OF IN-TEXT TABLES**

	<b>Page</b>
Table 9.4.5.3–1. Double-blind Dosing Regimen .....	<b>36</b>

**3.3 LIST OF IN-TEXT FIGURES**

	<b>Page</b>
Figure 9.1.3–1. Study Design .....	24

**4.0**

**LIST OF ABBREVIATIONS**

5-HT1A	5-hydroxytryptamine 1A
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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	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

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
LOCF	last-observation-carried-forward
MDD	Major Depressive Disorder
MMRM	Mixed-effect model for repeated measures
NDA	New Drug Application
PCS	potentially clinically significant
PID	patient identification
PK	pharmacokinetic
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
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 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 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 signed documents will be placed in the Investigator's study files. A unique patient identification (PID) number will be assigned according to Section [9.4.3](#).

#### **5.3.1 Patient Assent Form**

To participate in the study, the patient will read, assent understanding of, sign the assent form, and be made aware they can withdraw from the study at any time. 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 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 instrument of informed consent or other locally applicable regulations and authorization form after having had an opportunity to discuss the forms with the Investigator before signing. 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 of age 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 (SSRI) and a partial agonist of the 5-hydroxytryptamine 1A (5-HT<sub>1A</sub>) 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 for 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<sub>1A</sub> receptors compared with specific 5-HT<sub>1A</sub> ligands such as buspirone, with IC<sub>50</sub> values of 0.5 nM for vilazodone and 30 nM for buspirone. A detailed description of the pharmacokinetics, chemistry, pharmacology, safety, and efficacy of vilazodone for the treatment of MDD is provided in the US prescribing information (Viibryd<sup>®</sup>, 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 (AACAP) consensus ([AACAP, 1998](#)) 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 are affected by serious emotional disturbances ([Substance Abuse and Mental Health Services Administration \[SAMHSA\], 2009](#)).

The National Comorbidity Survey – Adolescent Supplement (NCS-A) examines 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. SAMHSA examines the national prevalence of depression each year through the National Survey on Drug Use and Health (NSDUH). 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.

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, 2002](#)). Suicide is a leading cause of death in adolescents and is a major public health concern ([NAHIC, 2006](#)). A major risk factor for suicide in adolescents is major depression. In its 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 its 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 OBJECTIVES**

The objective of this study is to evaluate the efficacy, safety, and tolerability of vilazodone compared with placebo in pediatric outpatients (7-17 years of age) with MDD.

In addition, the study is designed to obtain pharmacokinetic (PK) data to define the PK profile of vilazodone in the pediatric population (7–17 years of age).

## **9.0** **INVESTIGATIONAL PLAN**

### **9.1** **OVERALL STUDY DESIGN AND PLAN: DESCRIPTION**

Study VLZ-MD-22 will be a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, flexible-dose study in pediatric patients, 7 to 17 years of age. The study will include a total of 9 visits and will be approximately 10 weeks in duration ([Figure 9.1.3–1](#)):

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

#### **9.1.1** **Screening Period**

The screening/washout period will generally be 1 week prior to Baseline (Visit 2), but may be extended up to a total of 5 weeks to accommodate prior medication washout or to repeat assessments (with prior approval of the Study Physician or designee). Patients will not receive any investigational product during the screening period. Patients meeting the eligibility criteria at the end of Baseline (Visit 2) will be randomized in a ratio of 2:2:1 to 1 of 3 treatment groups: placebo, vilazodone, or fluoxetine.

#### **9.1.2** **Double-blind Treatment Period**

Approximately 400 patients are planned for enrollment in the double-blind treatment period (160 placebo patients, 160 vilazodone patients, and 80 fluoxetine patients); randomization will be stratified by study center and by country.

[REDACTED]

[REDACTED]

[REDACTED]



### **9.1.3 Double-blind Down-taper Period**

All patients who complete the 8-week double-blind treatment period and patients in the double-blind treatment period who prematurely discontinue from the study before completing 8 weeks of double-blind treatment should enter the 1-week, double-blind down-taper period when clinically appropriate (eg, when patients have not received investigational product for  $\leq 3$  days). Patients who complete 8 weeks of double-blind treatment may be eligible to enter a 6-month, open-label, extension study (Study VLZ-MD-23).

[REDACTED]

All randomized patients must complete Week 9 (Visit 9). Additional follow-up visits may be scheduled within 30 days, if necessary for safety reasons.

[REDACTED]

[REDACTED]

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

This multicenter, randomized, placebo- and active-controlled, parallel-group, flexible-dose study with an 8-week double-blind treatment was designed based on prior studies that established vilazodone efficacy and safety in adult patients with MDD. Additionally, 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 9.5.1.1) will assess the MDD symptoms and severity.

Study centers will have experience with the study population and will be encouraged to apply available guidelines to minimize patient risk or distress (See [European Medicines Agency \(EMA\)](#): ICH Topic E 11, Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population, January 2001). To ensure accurate MDD diagnosis, both the K-SADS-PL and CDRS-R 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.

Dose selection information is presented in Section 9.4.4. The planned titration regimen is based on experience from vilazodone studies ([Viibryd Package Insert, 2014](#); [Study VLZ-MD-21](#), in progress). A titration period has been included to reduce the possibility of tolerability issues that may accompany the start of investigational product treatment at the dose levels to be studied. The 1-week, double-blind 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.

A placebo treatment group is included in the study to comply with worldwide regulatory preferences (Laughren, 2001; Gispen-de Wied et al, 2012), since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes (Feifel, 2008; Laughren, 2001; Gispen-de Wied et al, 2012). Additionally, from a scientific point of view, randomized double-blind comparisons versus placebo are needed to permit adequate evaluation of efficacy. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions of the investigational product (EMA guidance, 2013). The use of placebo in place of the standard therapy (fluoxetine) 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) (FDA Guidance for Industry: E10, May 2001).

The fluoxetine active comparator group is included as a reference treatment, since fluoxetine is currently the only drug approved in the United States for the treatment of MDD in both children and adolescents.

In Study VLZ-MD-22, safety and efficacy assessments are included during every visit to determine adequacy of response, safety, and tolerability. In the event of insufficient therapeutic response or worsening of the patient's initial condition, investigational product should be discontinued, and an alternative treatment will then be allowed (Section 9.4.10). An independent Data Monitoring Committee will evaluate safety data during the study (Section 9.10).

### **9.3 SELECTION OF STUDY POPULATION**

The number of males and females will be approximately equal in both age groups (7-11 years of age and 12-17 years of age) 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:

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)
3. Meet DSM-IV-TR criteria for MDD, confirmed by K-SADS-PL, with a current depressive episode of  $\geq 6$  weeks duration at Screening (Visit 1)
4. Have a score of  $\geq 40$  on the CDRS-R at Screening (Visit 1) and Baseline (Visit 2)
5. Have a Clinical Global Impressions-Severity (CGI-S) score  $\geq 4$  at Screening (Visit 1) and Baseline (Visit 2)

6. Have a caregiver who is willing and able 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 (Section 5.3)
7. Have normal physical examination findings, vital sign values, clinical laboratory test results, and electrocardiograms (ECG) results, or abnormal results that are determined by the Investigator not to be clinically significant
8. Must have a negative serum pregnancy test result if patient is female  $\geq 9$  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:

#### Criteria to be assessed at Screening (Visit 1 [unless otherwise specified])

##### *Psychiatric Criteria*

1. A current (within 3 months of Screening) principal DSM-IV-TR–based diagnosis of an Axis I disorder other than MDD within 6 months before Screening (Visit 1) that is the primary focus of treatment.
  - 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]

[REDACTED]

these cases):

- o [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

○ [REDACTED]

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1. **Identify the subject and predicate.**  
 2. **Identify the object and complement.**  
 3. **Identify the modifier.**  
 4. **Identify the clause.**  
 5. **Identify the sentence.**

1. **Identify the main topic or purpose of the text.**  
 2. **Summarize the key points or findings.**  
 3. **Identify any specific data or evidence presented.**  
 4. **Discuss the implications or conclusions drawn from the information.**  
 5. **Provide a clear and concise conclusion or recommendation.**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

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 parent/guardian/LAR and/or caregiver 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 after careful consideration for one of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Withdrawal of consent
- AE
- Lack of efficacy
- Protocol violation
- Noncompliance 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 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 8 (Visit 8). All patients discontinuing the study prematurely should enter the 1-week, double-blind 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 the Sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

#### **9.3.4 Patient Replacement Procedures**

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

### **9.4 TREATMENTS**

Patients meeting the eligibility criteria at the end of Baseline (Visit 2) will be randomized in a double-blind fashion to 1 of 3 treatment groups: placebo, vilazodone, or fluoxetine.

#### **9.4.1 Treatments Administered**

At Screening (Visit 1) and after consent/assent is obtained, patients will be given 3 placebo tablets and 1 placebo capsule to swallow to confirm their ability to swallow investigational product.

Investigational product in the form of tablets and capsules

[REDACTED]

Throughout the study, it is recommended that patients take the investigational product at the same time each day with food (Section 9.4.5).

Patients should participate in the double-blind down-taper period unless it is deemed not to be clinically appropriate by the Investigator.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 PK data from the adult healthy volunteers, as well as adult and adolescent patients (12-17 years of age) with MDD.

[REDACTED]

#### **9.4.5 Selection and Timing of Dose for Each Patient**

All investigational products should be taken orally as a single dose of 3 tablets and 1 capsule, once-daily at the same time each day, with food (see Section 9.1).

[REDACTED]

[REDACTED]

[REDACTED]

**9.4.5.1 Screening Period**

At Screening (Visit 1) after consent/assent is obtained, placebo capsules and placebo tablets will be administered for the purposes of eligibility determination. Patients will be given 3 placebo tablets and 1 placebo capsule to swallow. If a patient is unable to swallow either the placebo capsule and/or all placebo tablets, the patient will be ineligible for study participation.

**9.4.5.2 Double-blind 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 the Baseline visit will be assigned a randomization number at Baseline (Visit 2) and dispensed the corresponding blister card containing tablets and capsules of double-blind investigational product for Week 1.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

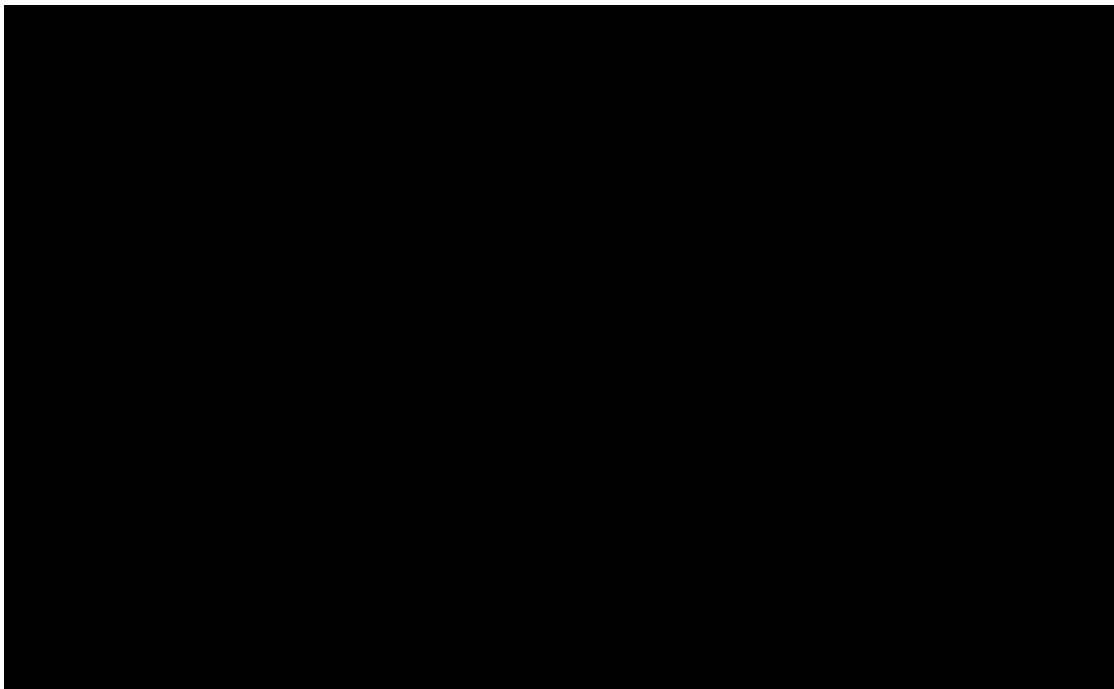
[REDACTED]

**9.4.5.3                      *Double-blind Down-taper Period (End of Week 8/(Visit 8)***

Patients who complete 8 weeks of double-blind treatment at Week 8 (Visit 8) or patients who discontinue the study prematurely should enter the double-blind down-taper period when clinically appropriate.

[REDACTED]

[REDACTED]



#### **9.4.6 Blinding**

A list of patient randomization codes will be generated by [REDACTED] (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 (refer to [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 FRI Global Drug Safety 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.

[REDACTED]

#### **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 double-blind treatment period will be allowed to discontinue the investigational product and start appropriate treatment at the Investigator's discretion. This new treatment will not be provided by FRI. Patients who need to initiate a new treatment will be discontinued from the study.

### **9.5 EFFICACY AND SAFETY VARIABLES**

#### **9.5.1 Diagnostic and Efficacy Assessments**

All diagnostic and efficacy assessments are not 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, Subinvestigator, or 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.

##### **9.5.1.2.1                      *Primary Efficacy Assessment: Children's Depression Rating Scale-Revised***

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

The CDRS-R will be administered separately to the patient and to the caregiver. For each item, the rating that provides the best description of the patient will be selected by the clinician administering the interviews.

A copy of the CDRS-R is provided in [Appendix V](#).

##### **9.5.1.2.2                      *Secondary Efficacy Assessment: 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 VI](#).



**9.5.1.2.3**                      *Additional Efficacy Assessment: 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 VII](#).

**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 adverse event (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 was 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 informed 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 of the patient's eCRF.

[REDACTED]

[REDACTED]

[REDACTED]

[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 poststudy 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.

[REDACTED]

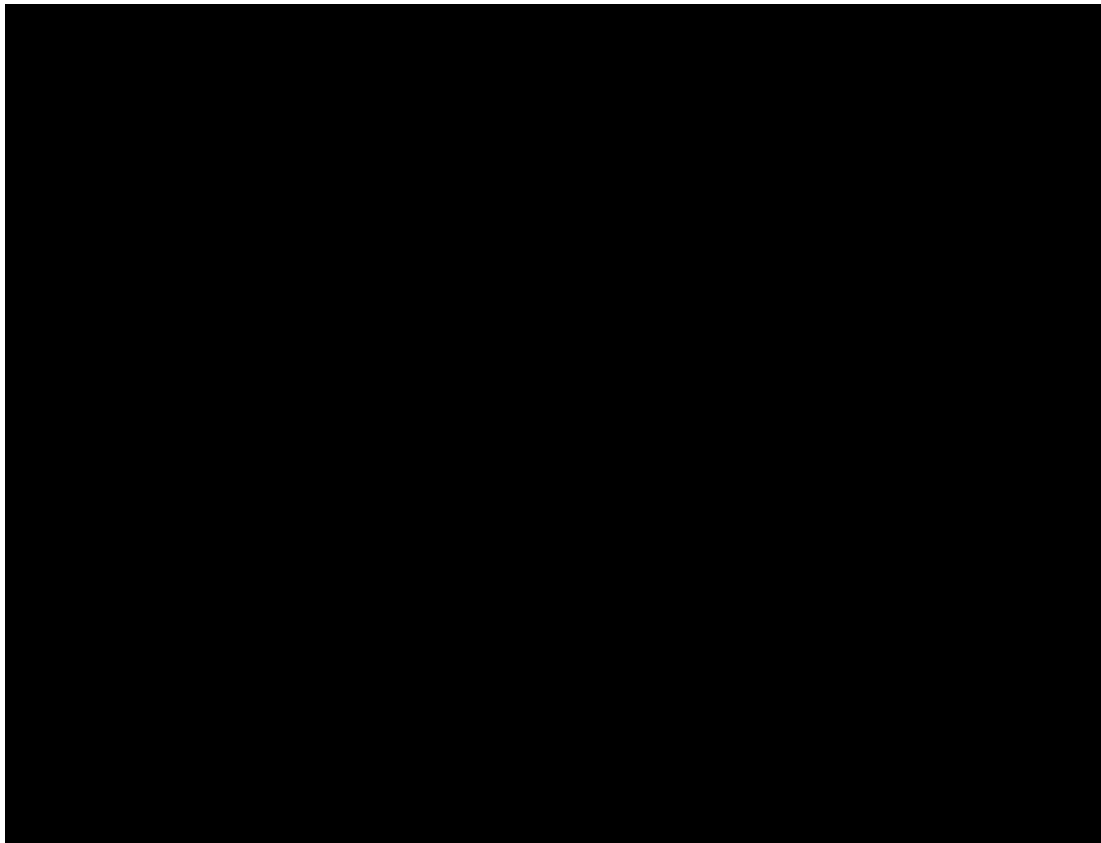
[REDACTED]

[REDACTED]

**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/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.

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.



[illegible]

[illegible]



[REDACTED]

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## **9.6 DATA QUALITY ASSURANCE**

[REDACTED]

### **9.6.2 Data Recording and Documentation**

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

[REDACTED]

[REDACTED]

[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 study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by 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, 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 this 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 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 (Baseline through Week 8 [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 termination 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.

#### **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.

[REDACTED]

[REDACTED]

#### **9.7.4                    Extent of Exposure and Treatment Compliance**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **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 Baseline (Visit 2). All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with  $< 2$  patients in  $\geq 1$  treatment group in the ITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes  $\geq 2$  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  $> 1$  smallest pseudo-center, the pseudo-center with the smallest center code will be selected. In case that 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  $> 1$  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 with multiple postbaseline measurements.

In addition, by-visit analyses using the last-observation-carried-forward (LOCF) approach will be presented for all 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 change from baseline to Week 8 of the double-blind treatment period in CDRS-R total score will be the primary efficacy parameter. The primary analysis for comparing vilazodone versus placebo will be performed with treatment group, pooled 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.

In addition, 2 sensitivity analyses, LOCF and pattern-mixture model approaches, will be performed on the primary efficacy parameter. The LOCF approach is based on an analysis-of-covariance model including treatment group and pooled study center as factors and baseline CDRS-R total score as a covariate.

The other sensitivity analysis using a pattern-mixture model based on nonfuture 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 assumption. 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 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  $\Delta$ . The dataset with missing values will be analyzed using an analysis-of-covariance model with treatment group and pooled study center as factors and baseline CDRS-R total score as a covariate 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  $\Delta$  will be selected as 0 to 6 based on experience with historical data.

The comparison of fluoxetine versus placebo will be performed to assess study assay sensitivity.

#### **9.7.5.2                      *Secondary Efficacy Parameter***

The key secondary efficacy parameter is the change from baseline to Week 8 in CGI-S score, which will be analyzed using the MMRM approach similar to the one used for the primary efficacy parameter.

The overall family-wise type I error rate for testing the primary and secondary efficacy parameters will be controlled at the 0.05 significance level by using the fixed sequence testing procedure. The efficacy analysis of the secondary efficacy parameter will be carried out inferentially only if the null hypothesis for the primary efficacy parameter is rejected.

[REDACTED]

#### **9.7.6 Safety Analyses**

The safety analysis will be performed for the double-blind treatment period and double-blind down-taper period separately using the Safety Population. 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 each safety parameter, the last assessment made before the first dose of double-blind investigational product will be used as the baseline for all analyses of that safety parameter.

#### **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 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 is 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 ( $\geq 2\%$  of patients in any treatment group) TEAEs during the double-blind treatment period will be summarized separately by preferred term, and treatment group.



An SAE that occurred between the date of the first dose of double-blind investigational product and 30 days after the date of the last dose of double-blind 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, preferred term, and treatment group. 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 double-blind investigational product, and patients discontinuing due to AEs before the start of double-blind 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).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

### ***Investigational Product Plasma Concentration Parameters and Exposure-Response Evaluation***

Vilazodone plasma concentration data will be used to estimate population PK parameters, inter-patient, and residual variability using nonlinear mixed-effects modeling software. The study will be prospectively powered to target a 95% CI within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for vilazodone, with at least 80% power. The effect of covariates on the vilazodone pharmacokinetics will also be investigated. The maximum plasma drug concentration, area under the plasma concentration versus time curve, time of maximum plasma drug concentration, half-life, apparent oral clearance and apparent volume of distribution for vilazodone will be determined and a summary (mean, median) will be reported. Vilazodone PK data will be used to support the evaluation of a potential exposure/dose-response relationship. The analysis results will be provided in a separate report.

## Health Economics and Outcomes Research Analyses

Not applicable.

A blinded interim analysis will be conducted when approximately 75% of randomized patients have either completed the study or discontinued to obtain an estimate of the pooled standard deviation on change from baseline in the CDRS-R total score to Week 8 of the double-blind treatment period. If the estimated pooled standard deviation is larger than the assumed pooled standard deviation in the sample size calculation (see Section 9.7.9), sample sizes in placebo and vilazodone treatment groups may be increased to ensure an adequate power. However, due to the difficulties in recruiting pediatric patients with MDD, the number of patients in placebo and vilazodone treatment groups will be capped at 200.

The primary efficacy parameter will be the change from baseline to Week 8 of the double-blind treatment period in CDRS-R total score. [REDACTED]

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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.

*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 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 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.

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.

[illegible]

\_\_\_\_\_

[REDACTED]

[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**

I agree to conduct the study in accordance with this protocol ***amendment*** (VLZ-MD-22, ***Amendment #1***, dated ***15 Apr 2015***) 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 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](http://www.ClinicalTrials.gov).

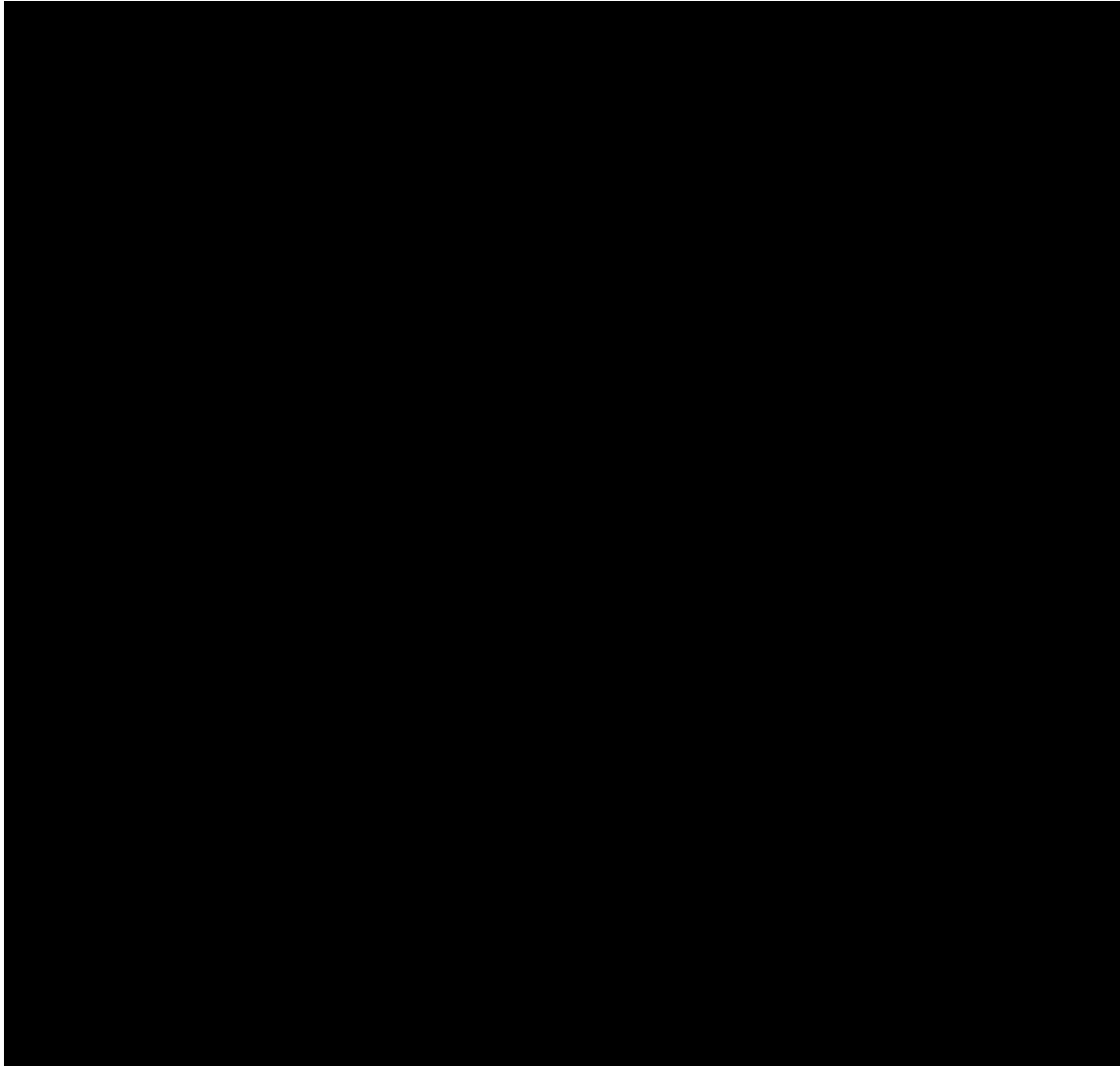
A copy of the signed consent form must be given to the patient's parent/guardian/LAR.

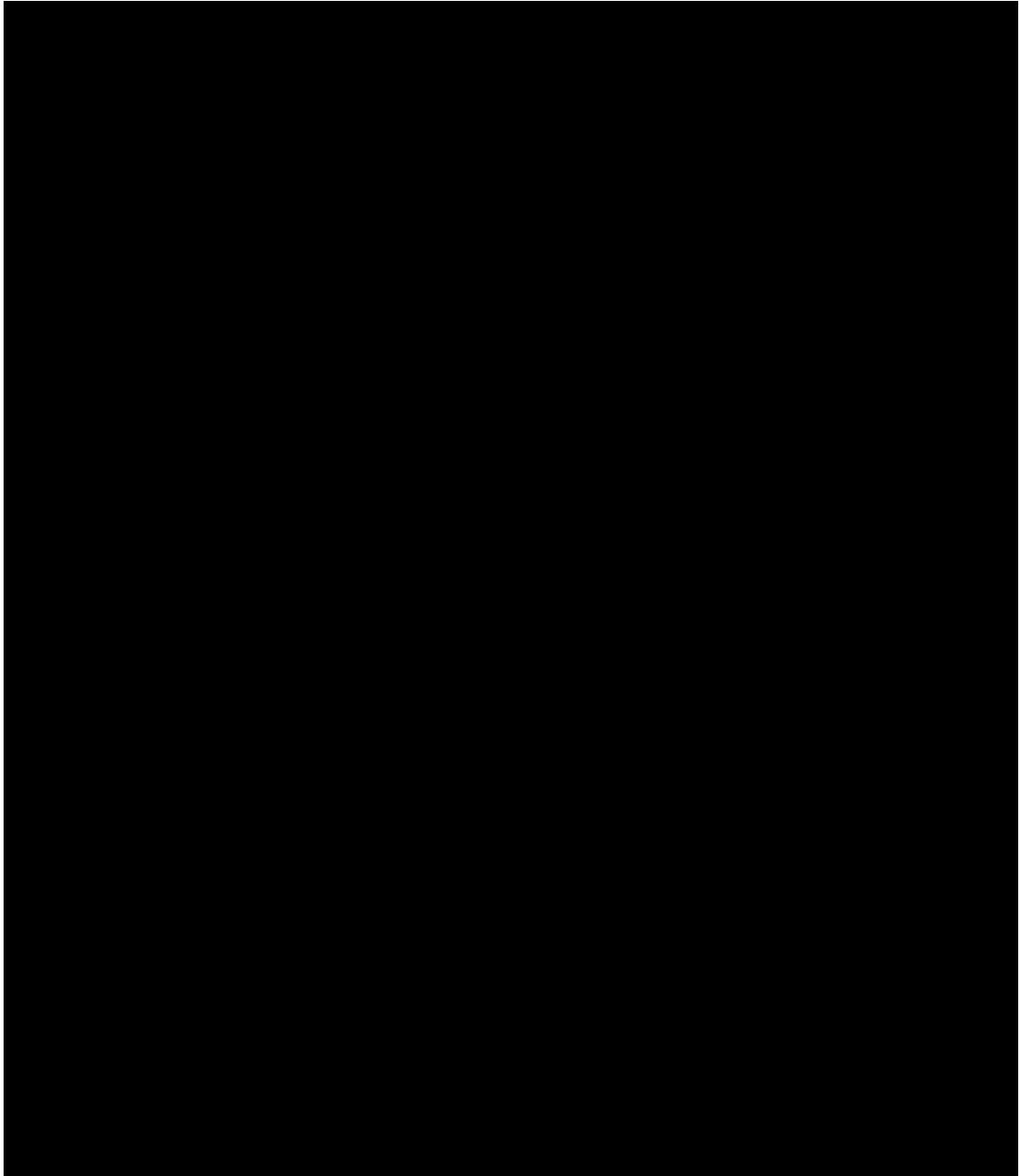
In addition, the patient will be asked to provide assent that will include a statement agreeing to participate in the study.

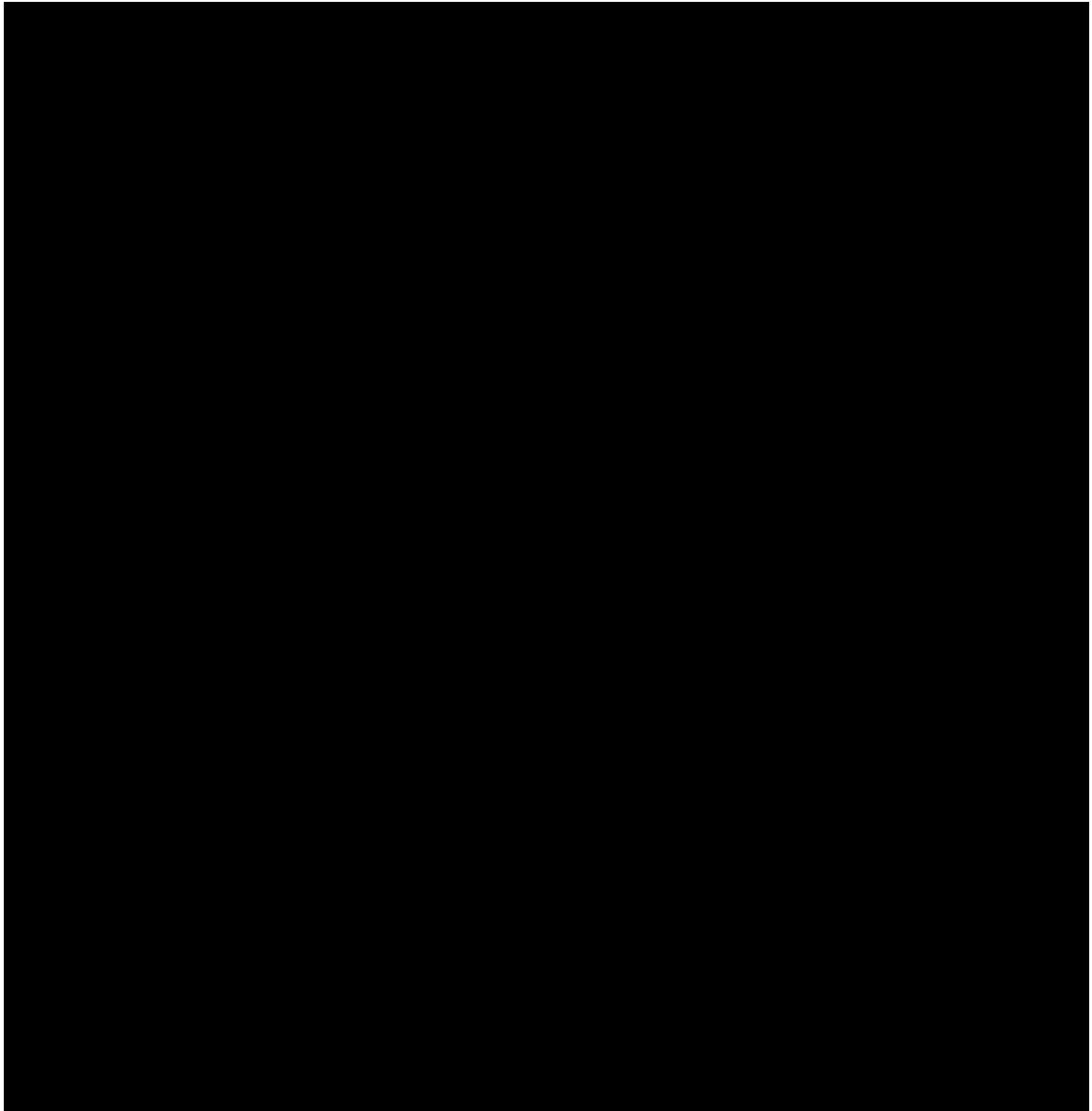
**APPENDIX II. CONTACT INFORMATION**

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

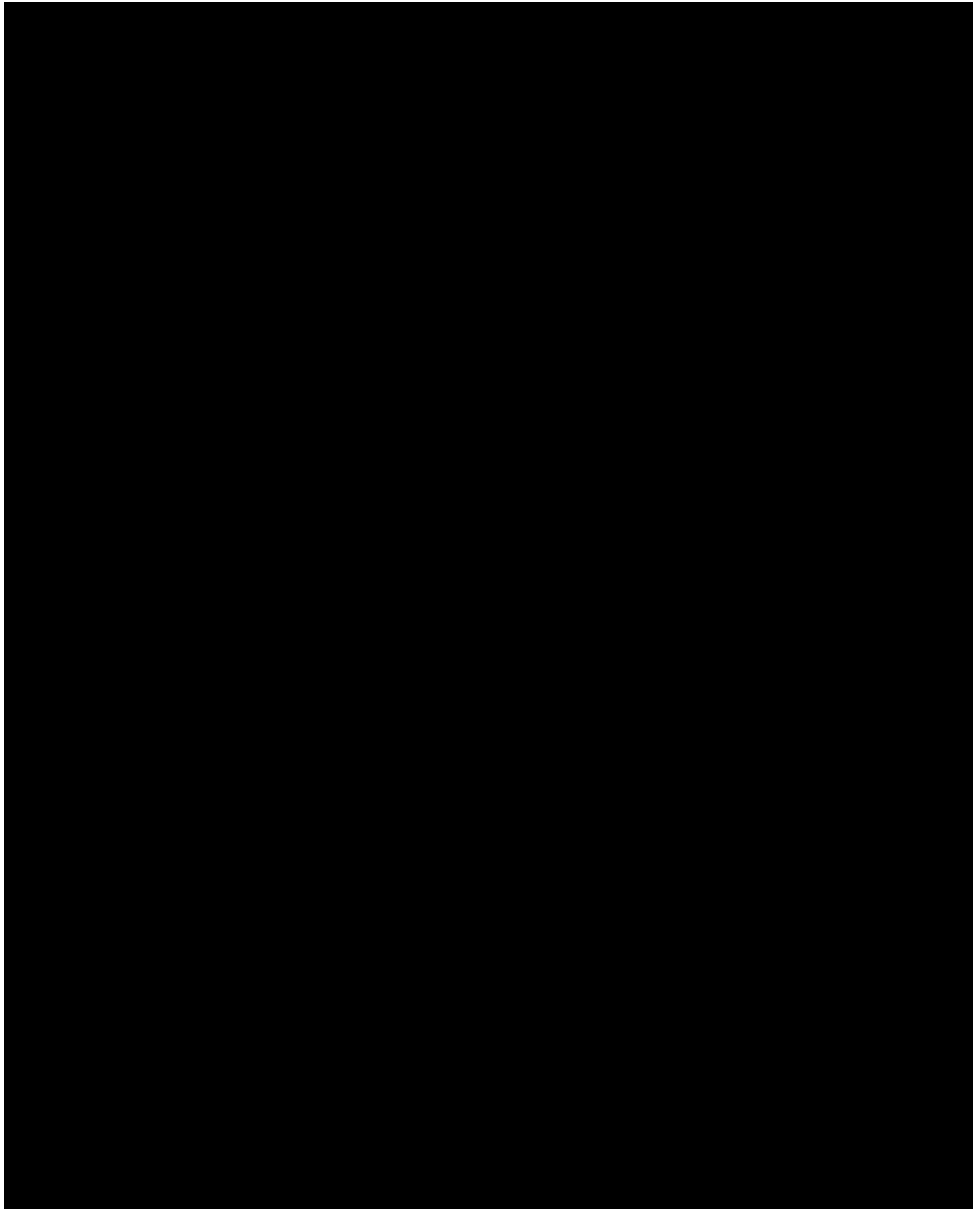
**APPENDIX III. CONCOMITANT MEDICATIONS**











## **APPENDIX IV. BLOOD SAMPLING AND SHIPPING INSTRUCTIONS**

### **Pharmacokinetic Blood Collection and Processing Procedure**

#### **Specimen Tube Collection Preparation**

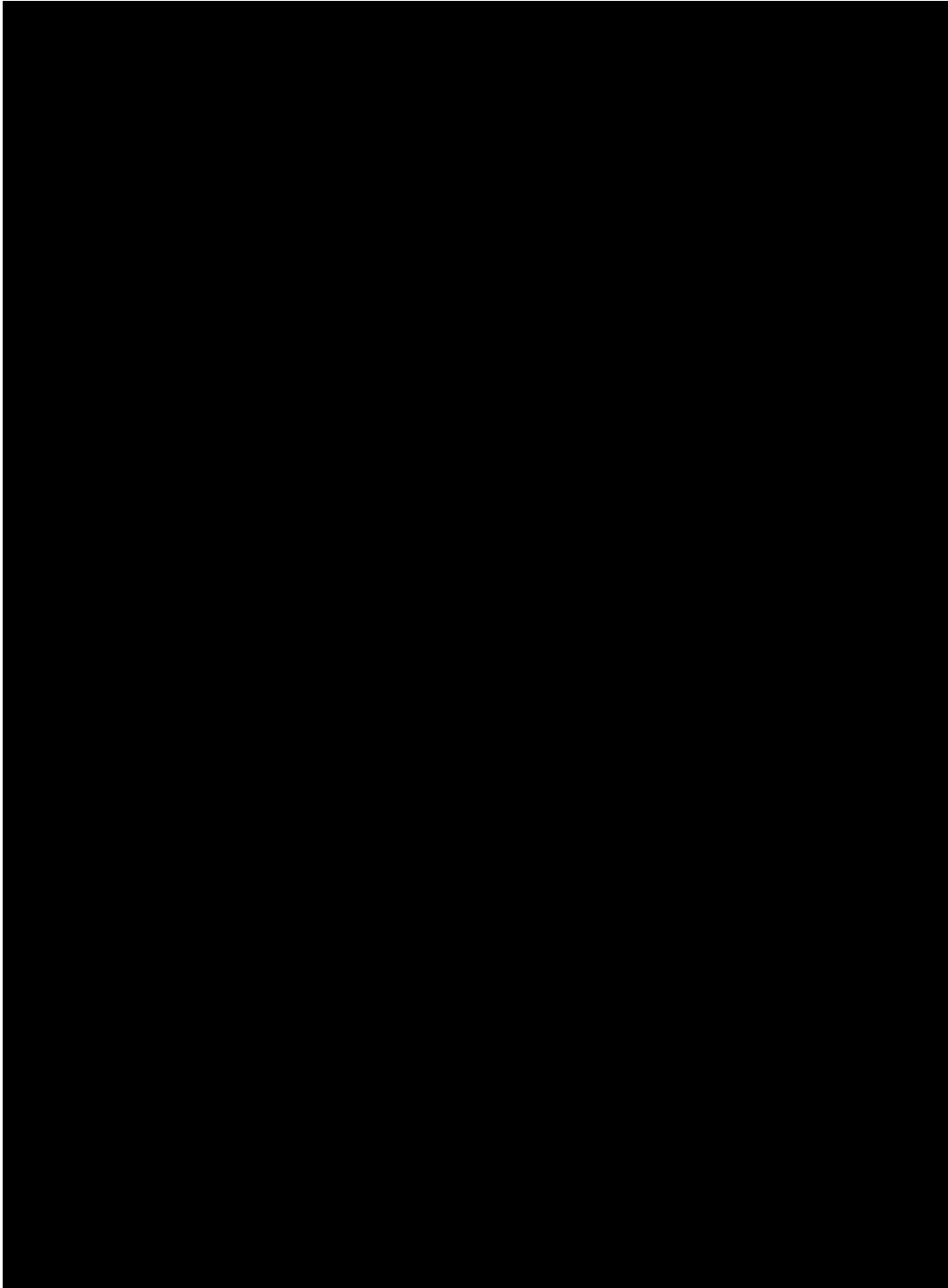
- Adhere the FRI provided label to a Vacutainer<sup>®</sup> tube containing K<sub>2</sub>EDTA
- Prechill (eg, in an ice bath or refrigerator) the labeled Vacutainer tube and a polypropylene tube

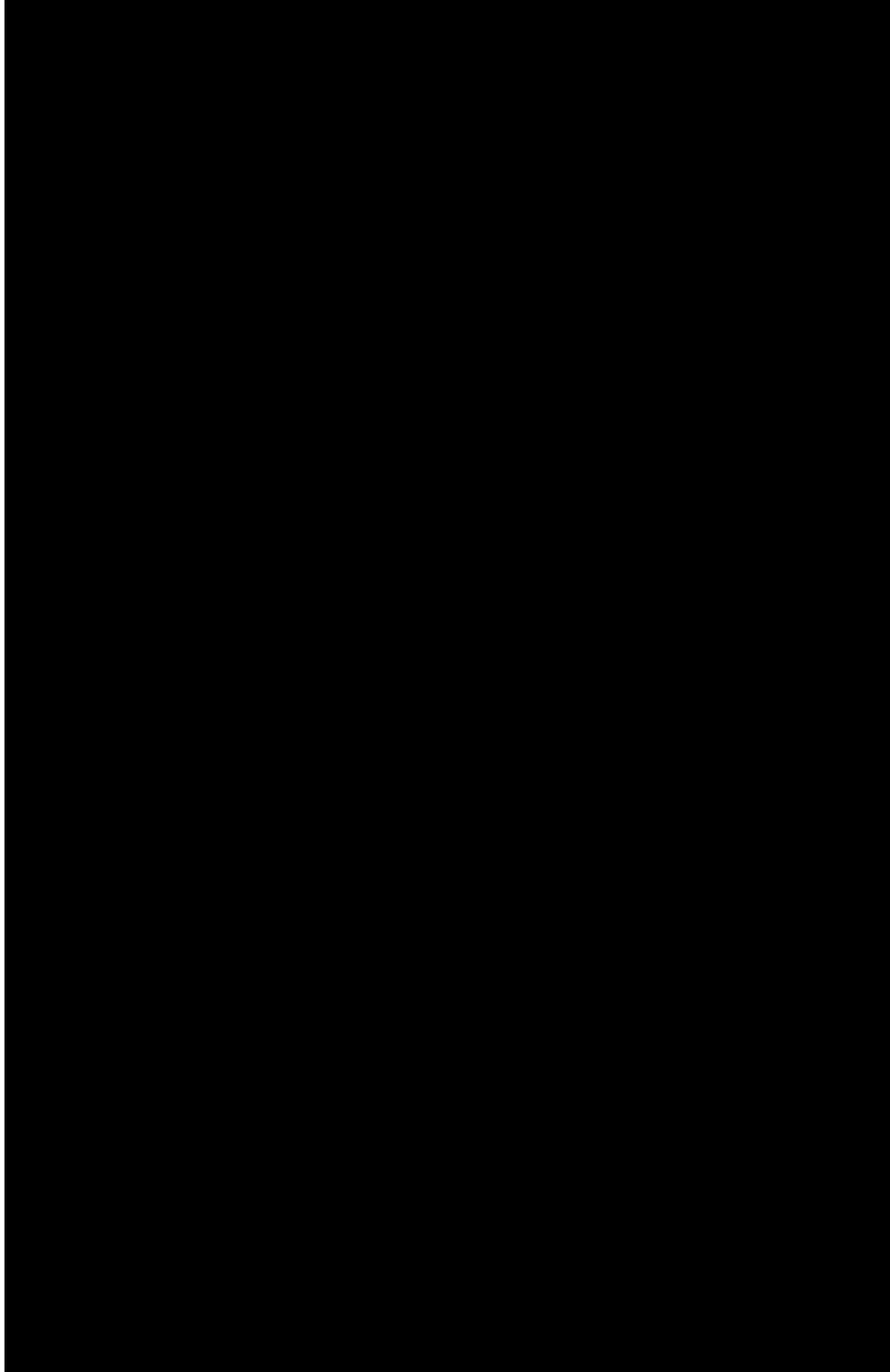
#### **Plasma Collection Procedure**

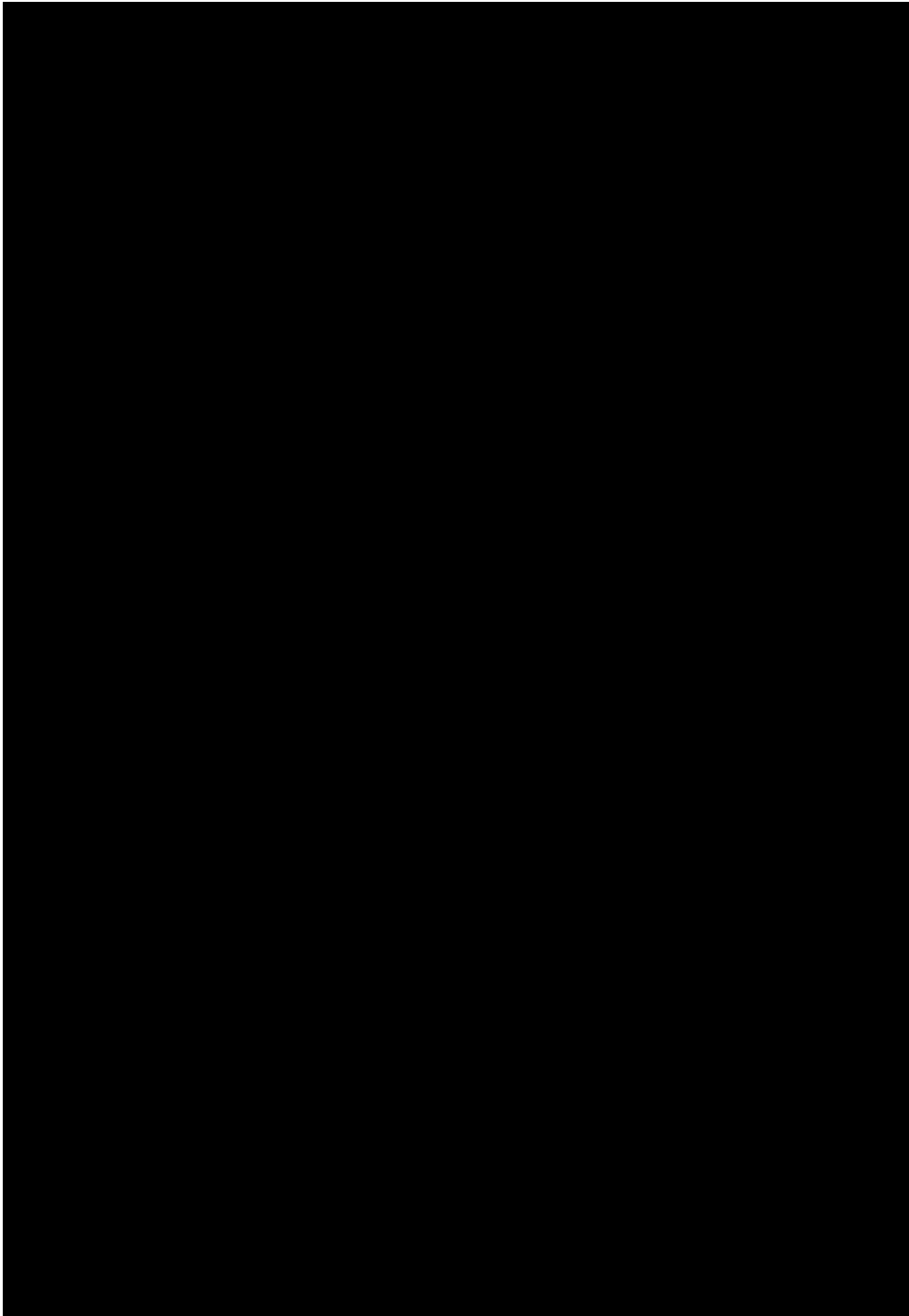
- Collect blood into the prechilled Vacutainer tube; invert the tube gently 8-10 times to mix the blood and anticoagulant. Place the tube in an ice-water bath (use crushed ice).
- Centrifuge the tube (within 30 minutes from the time the blood is drawn) at a minimum 2500 rpm for 10 minute at approximately 4°C (ie, refrigerated centrifuge). In absence of a refrigerated centrifuge, the blood tubes should be chilled in ice for at least 10 minutes prior to centrifuging. Blood samples should still be centrifuged within 30 minutes of blood collection.
- After centrifugation, transfer harvested plasma immediately into a prechilled, labeled, polypropylene tube provided by the central laboratory. Ensure the tube has the appropriate label marked with study number, subject identification number, date, and time of collection.
- The tube will then be flash-frozen in a dry ice and alcohol bath (with isopropyl alcohol, ethanol, acetone, or methanol) and should be stored at approximately –70°C (or up to 6 weeks at –20°C).
- Enter the actual time that the blood sample was collected on the appropriate form of the eCRF.
- Send the frozen sample to the central laboratory according to the central laboratory sample shipment guide.

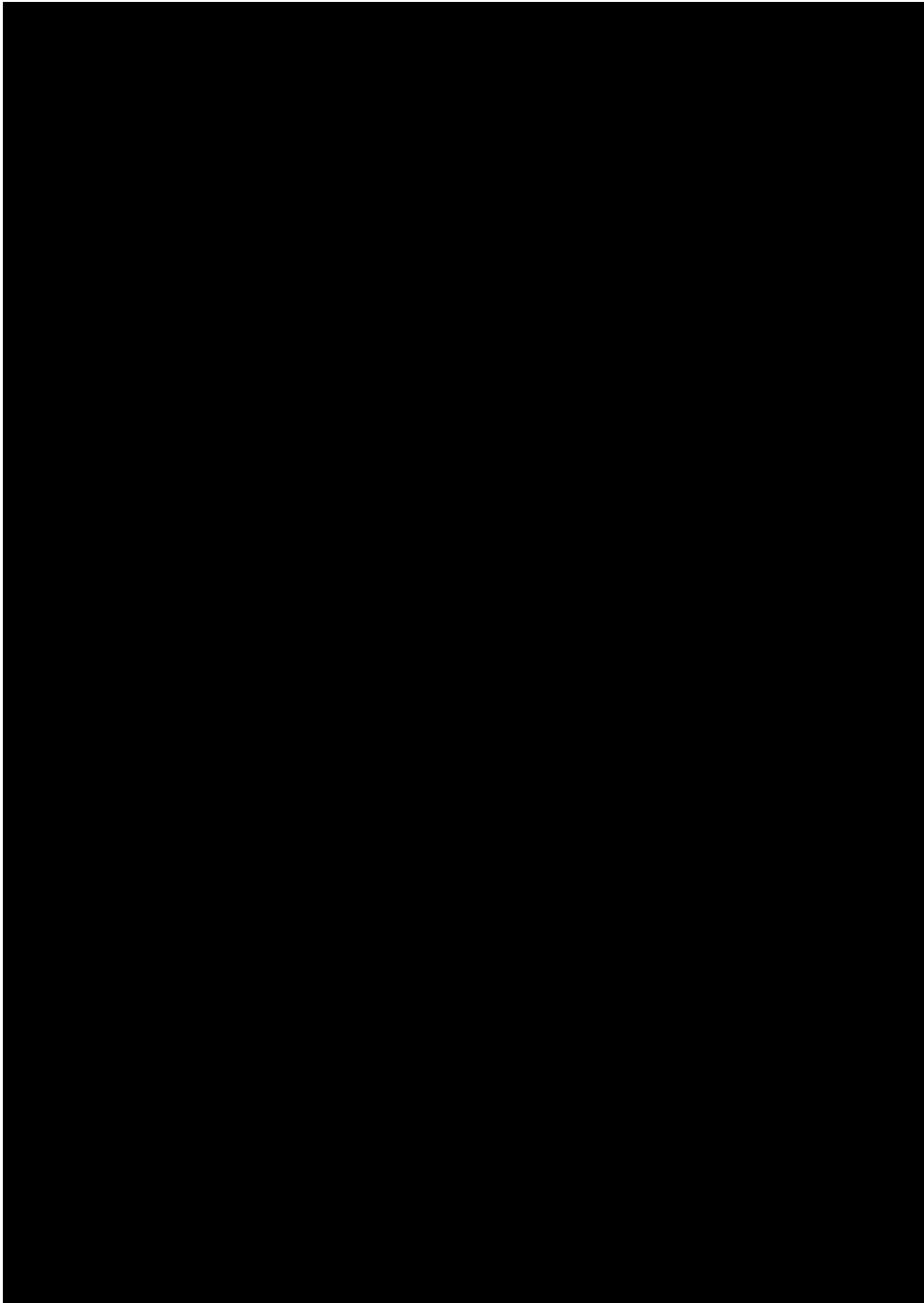
#### **Shipping Guide from the Study Center to the Central Laboratory**

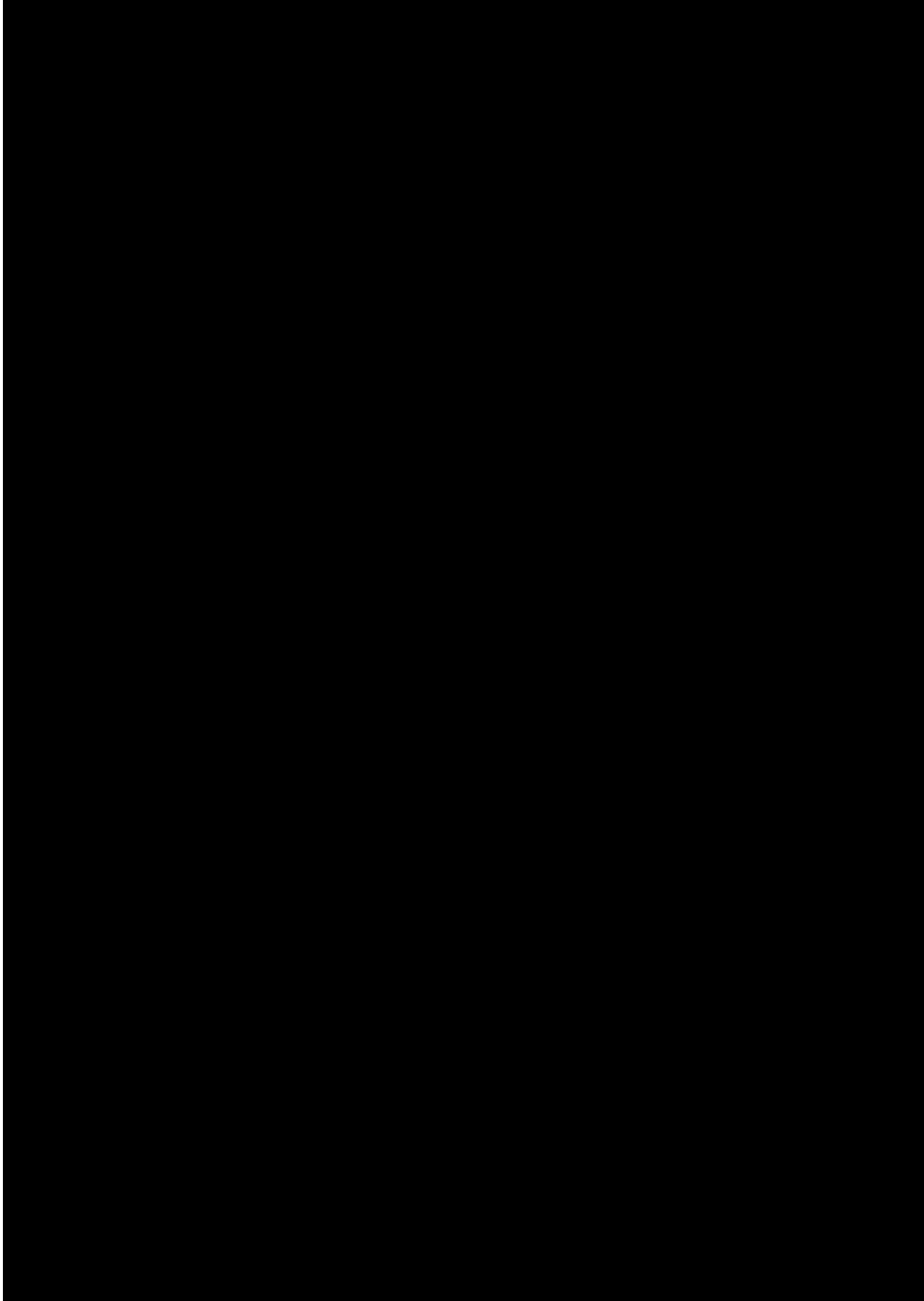
Samples will be shipped from the study center to the central laboratory on the first available appropriate date after sample collection, and can be batch-shipped but no later than six weeks after sample collection if stored at a temperature approximately –20°C. The central laboratory will provide packaging, labeling, and shipping instructions to the study center. Plasma samples will be shipped on sufficient dry ice to keep them frozen for at least 96 hours.

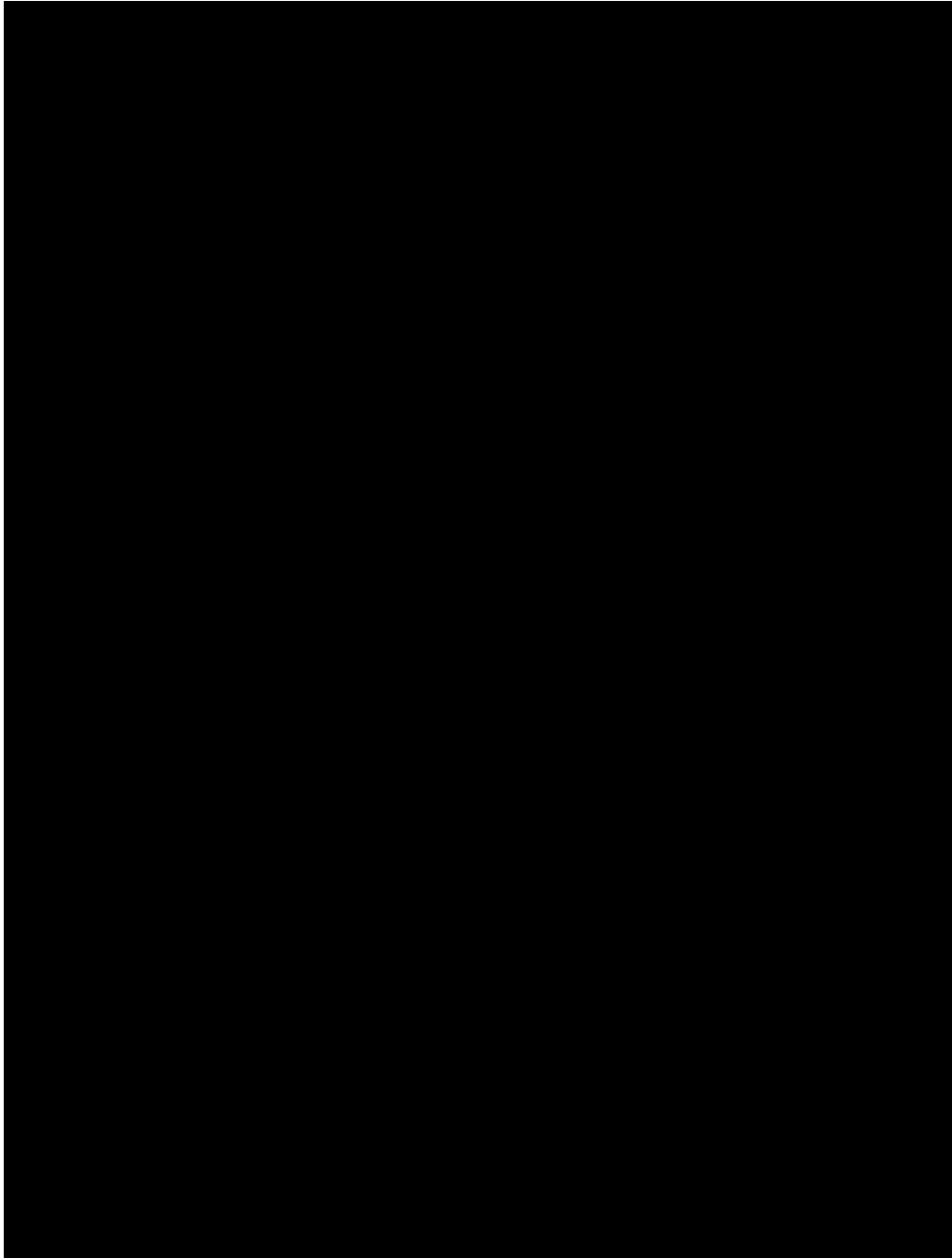




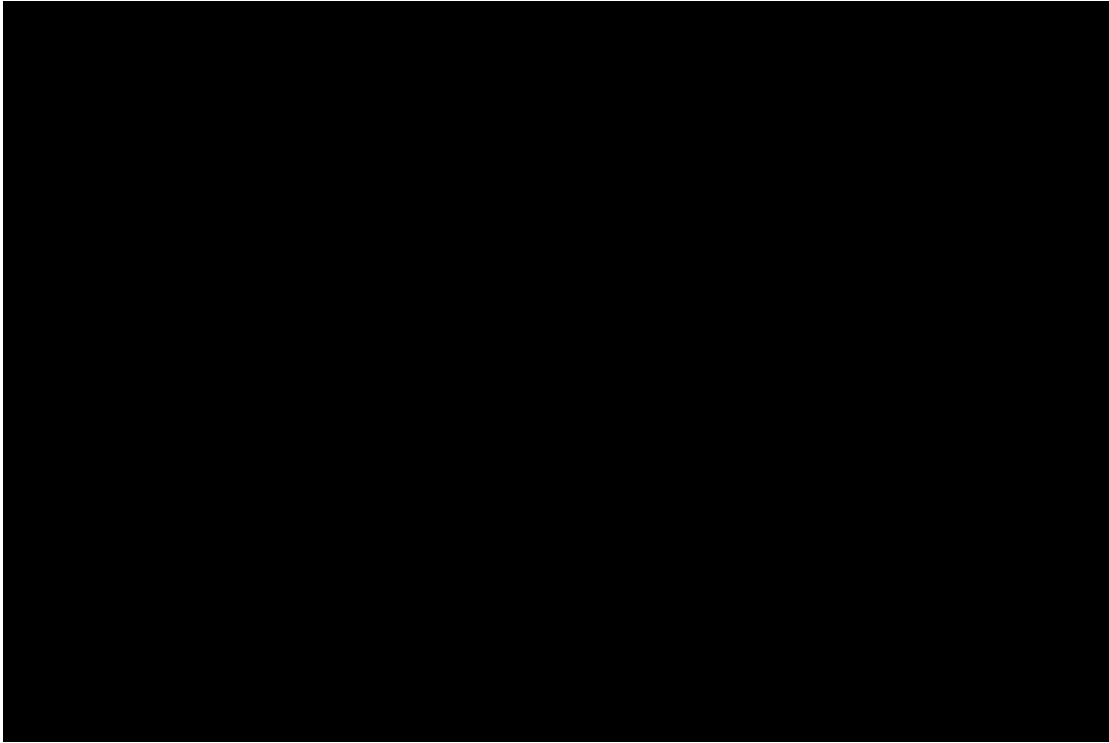














**APPENDIX VIII. COLUMBIA-SUICIDE SEVERITY RATING SCALE -  
BASELINE**

**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.***

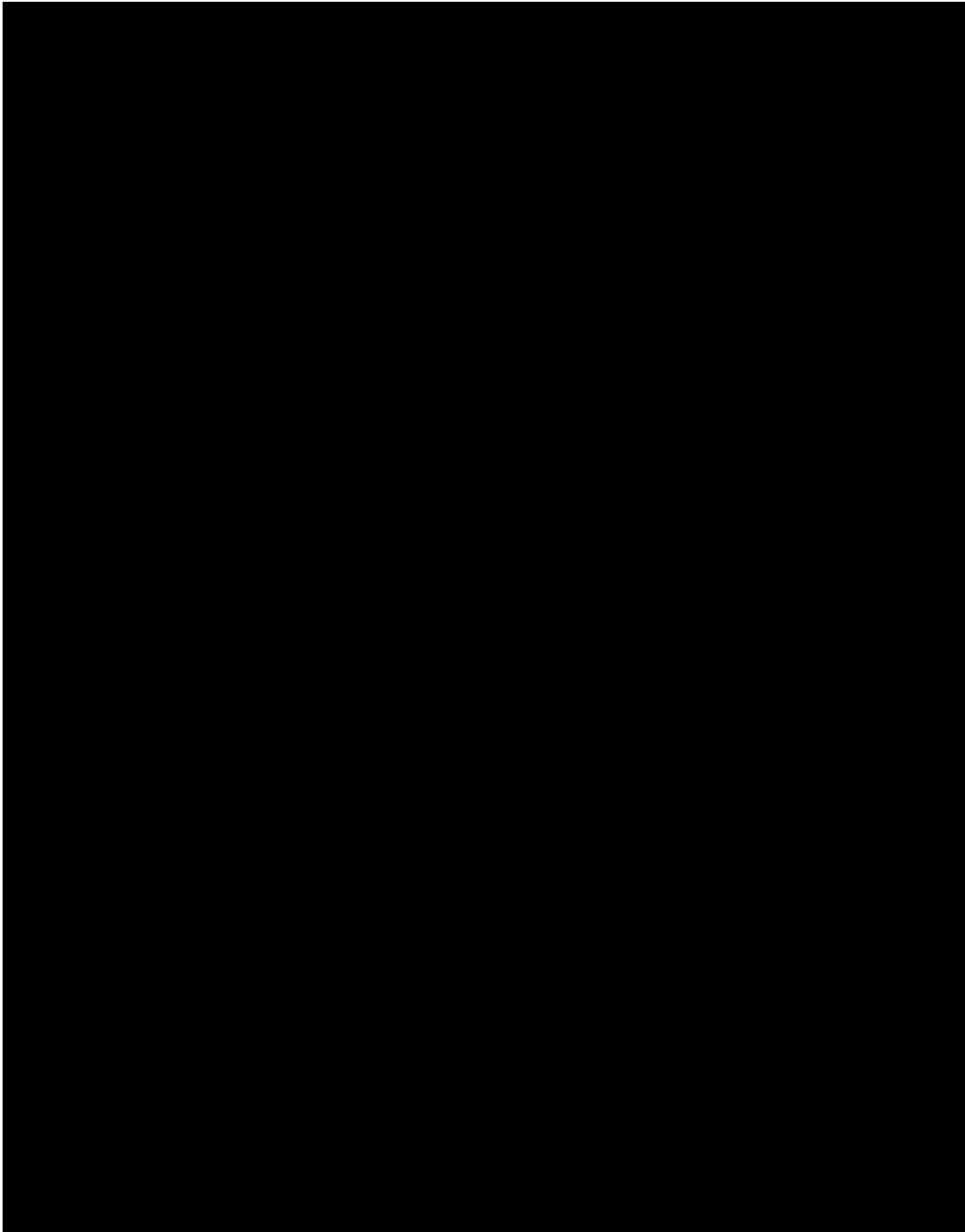
*Disclaimer:*

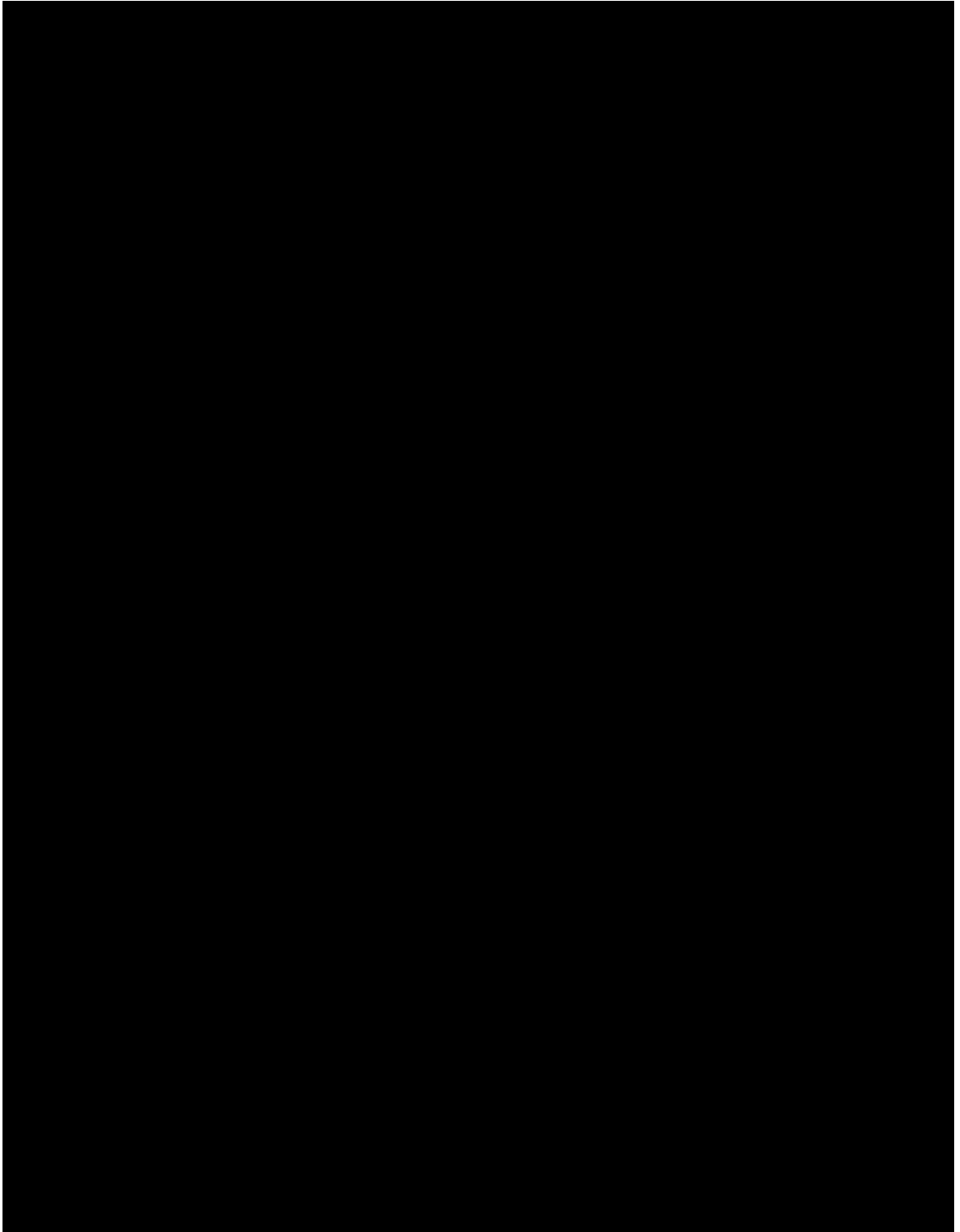
*This scale is intended for use by trained clinicians. The questions contained in the  
Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the  
determination of the presence of suicidality depends on clinical judgment.*

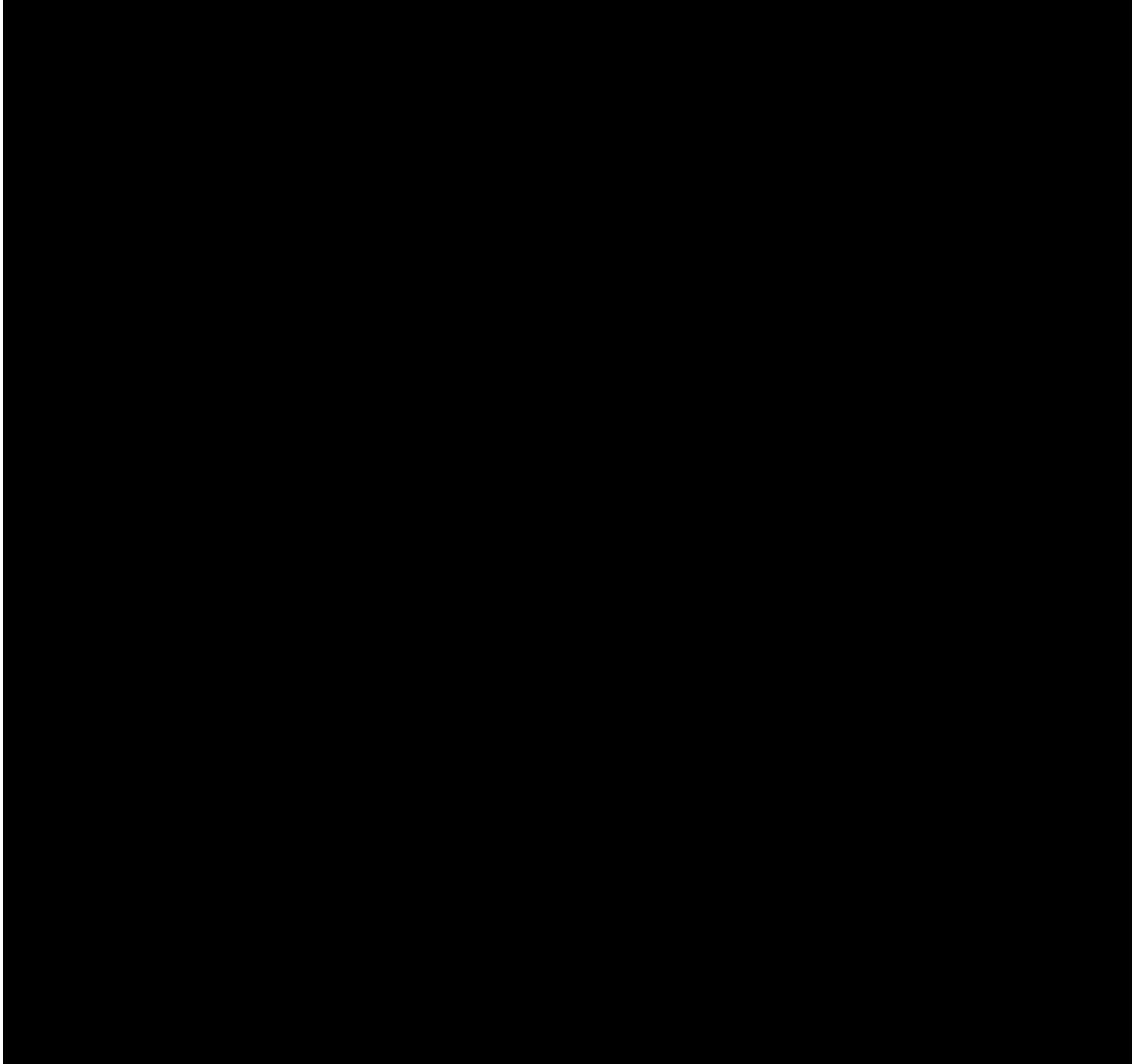
*Definitions of behavioral suicidal events in this scale are based on those used in **The  
Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo,  
MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State  
Psychiatric Institute, 1051 Riverside Drive, 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](mailto:posnerk@childpsych.columbia.edu)*

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**APPENDIX IX. 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.***

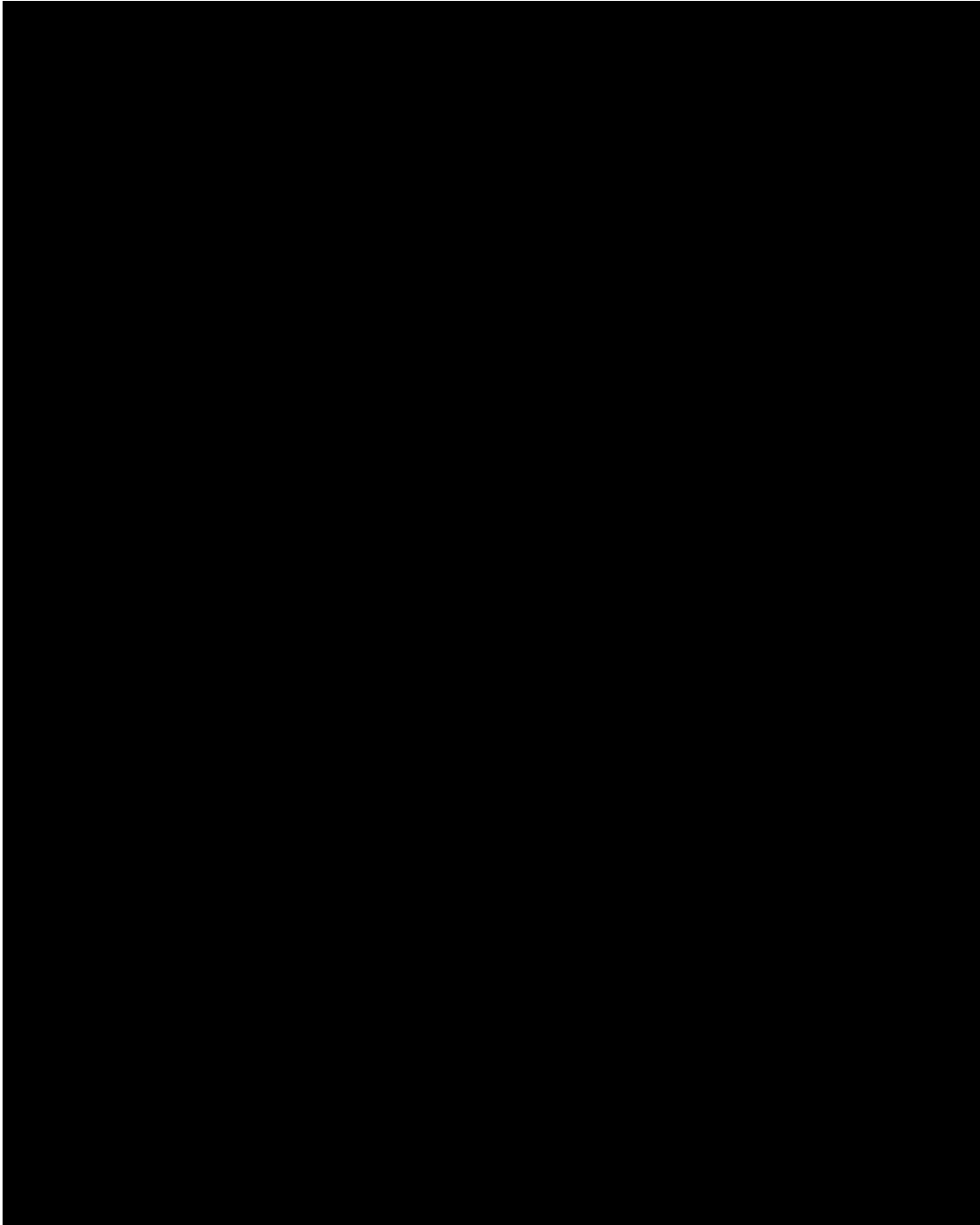
*Disclaimer:*

*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.*

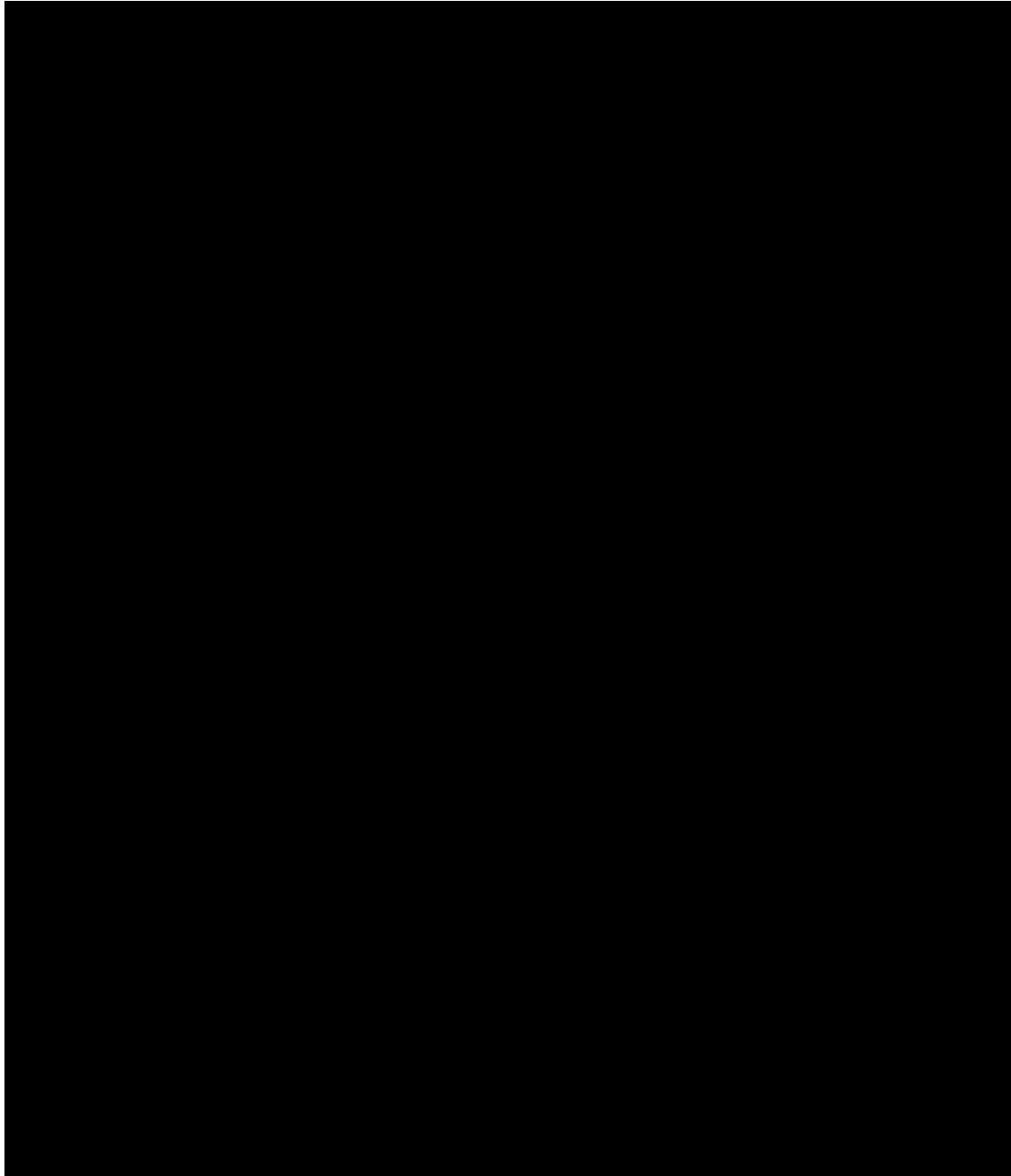
*Definitions of behavioral suicidal events in this scale are based on those used in **The  
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research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice,  
pp. 103 -130, 2003.)*

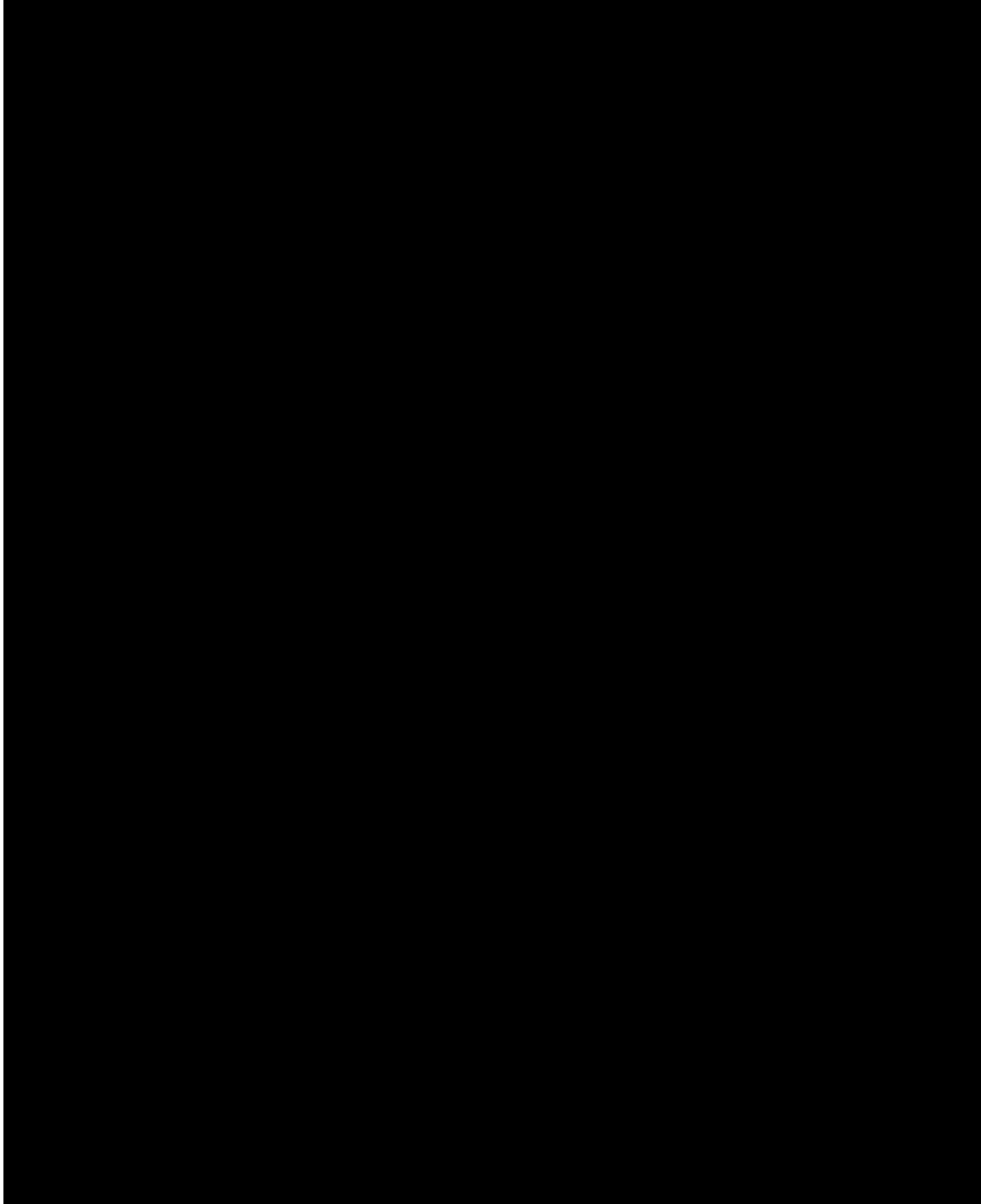
*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric  
Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training  
requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)*

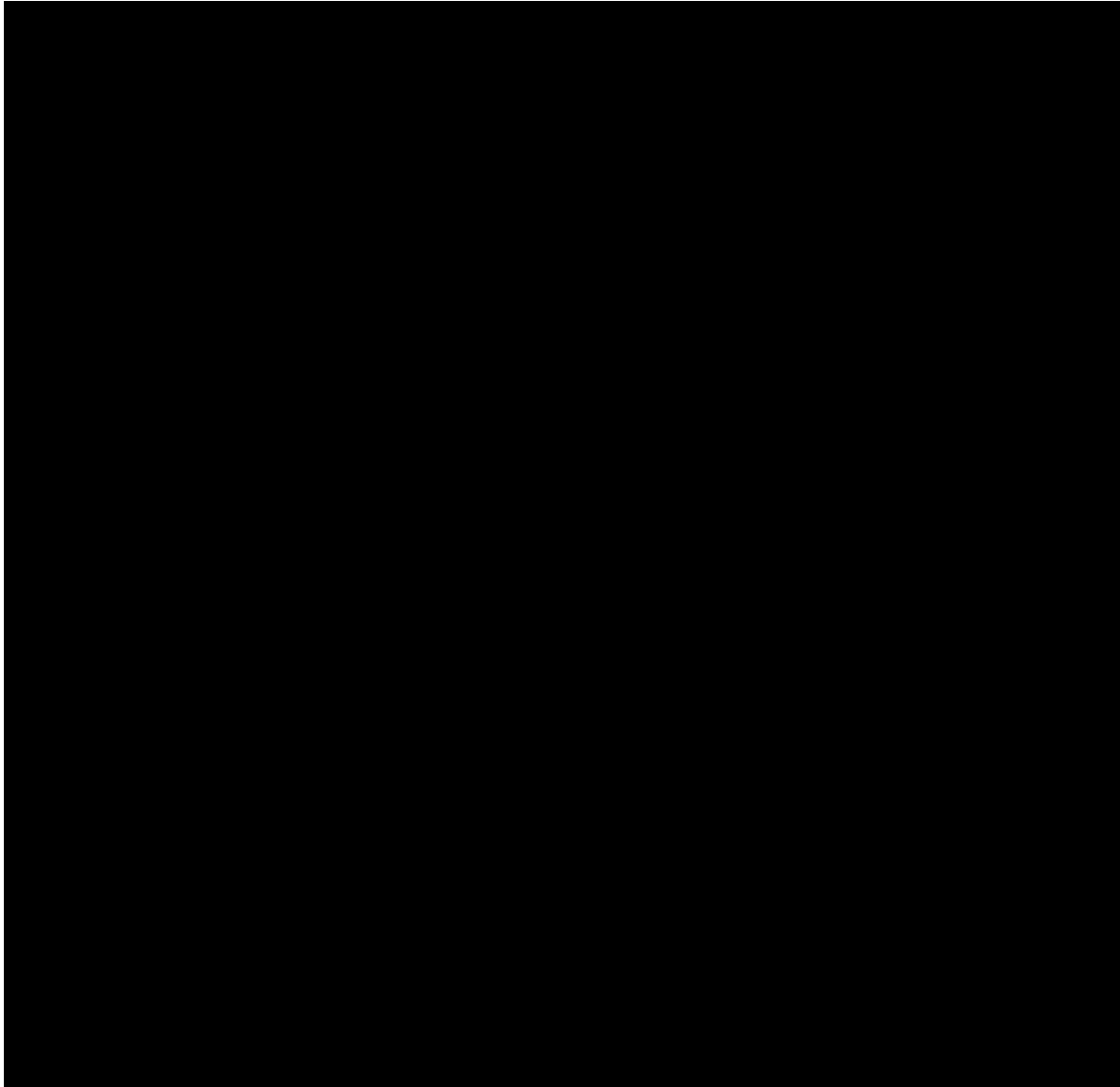
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#### **14.0**                      **LITERATURE CITED**

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