NCT02670551

**Study ID**: RGH-MD-54

**Title:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Fixed-Dose Clinical Trial Evaluating The Efficacy, Safety And Tolerability Of Cariprazine In Patients With Bipolar I Depression

**Protocol Amendment 2 Date:** 17-Feb-2016

## 1.0 TITLE PAGE

**Forest Laboratories, LLC, an Allergan Affiliate**
**Harborside Financial Center, Plaza V**
**Jersey City, NJ 07311**

# A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER, FIXED-DOSE CLINICAL TRIAL EVALUATING THE EFFICACY, SAFETY AND TOLERABILITY OF CARIPRAZINE IN PATIENTS WITH BIPOLAR I DEPRESSION

RGH-MD-54

**IND #77,726**

**Original Protocol Date**: 12 Nov 2015

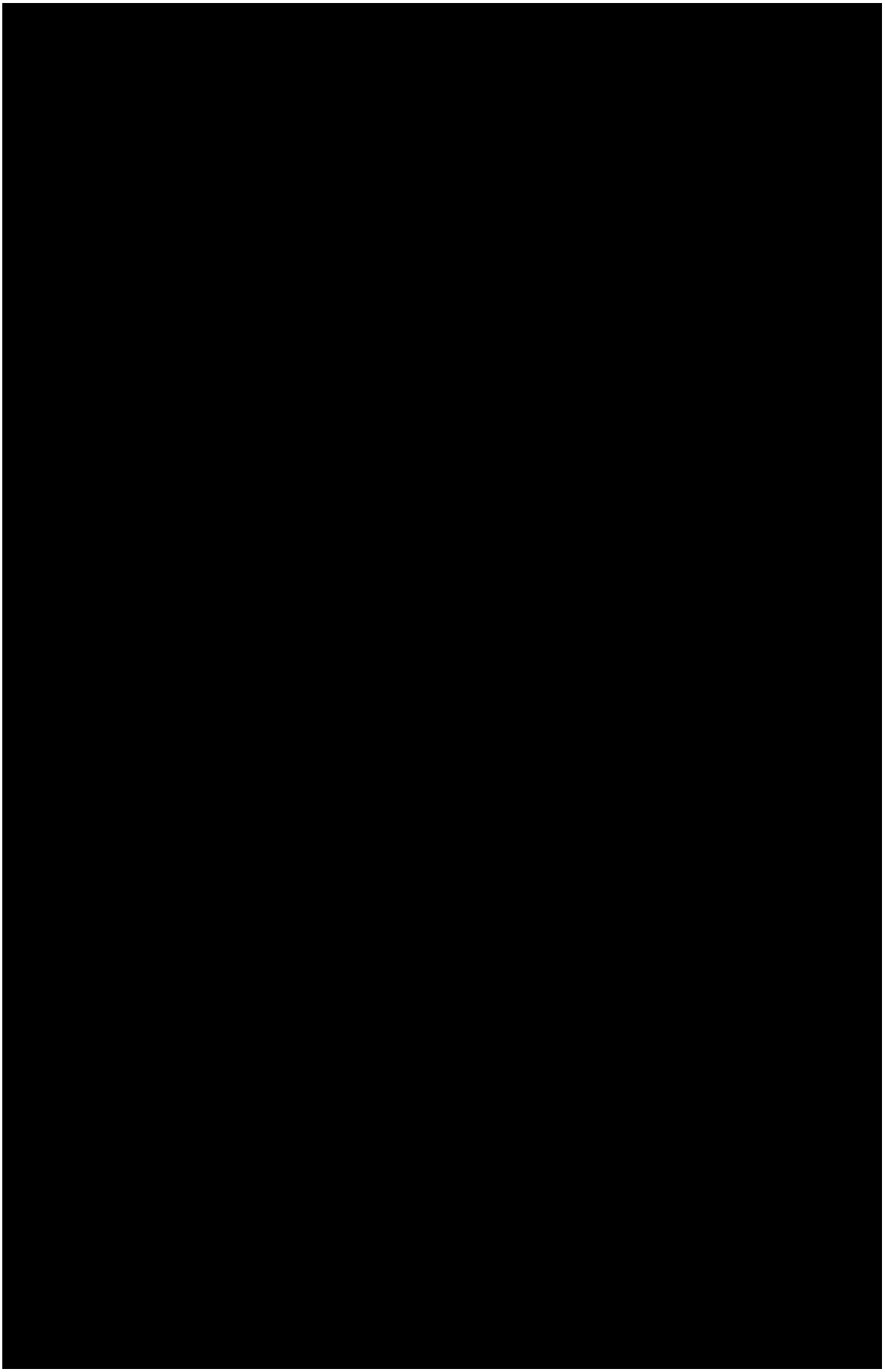
**Amendment #1 Date:** 02 Feb 2016

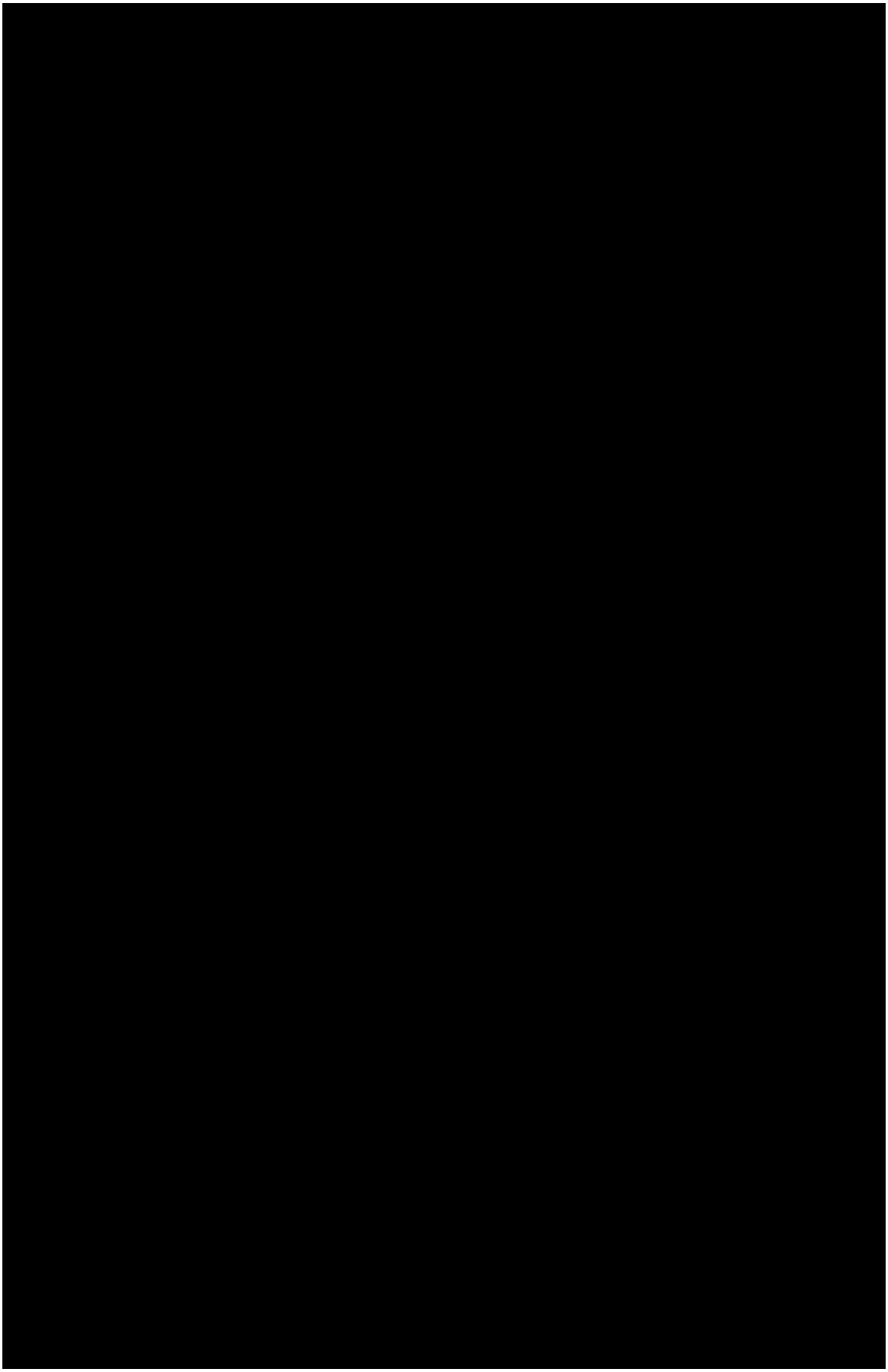
**Amendment #2 Date:** 17 Feb 2016

## 2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS

| CLINICAL STUDY SYNOPSIS: Study RGH-MD-54 | |
|---|---|
| **Title of Study** | A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Fixed-Dose Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Cariprazine in Patients with Bipolar I Depression |
| **Study Centers (Country)** | Approximately 85 study centers (United States, non-United States) |
| **Development Phase** | 3 |
| **Objective** | To evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3.0 mg/day relative to placebo in patients with bipolar I depression |
| **Methodology** | Multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study |
| **Number of Patients** | 480 planned (approximately 160 per treatment group) |
| **Diagnosis and Main Criteria for Inclusion** | Male and female outpatients who are 18 to 65 years of age, meet *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for bipolar I disorder without psychotic features confirmed by the administration of the Mini International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks and not exceeding 12 months in duration, a minimum score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD-17), a minimum score of 2 on item 1 of the HAMD-17, and a minimum score of 4 on the Clinical Global Impressions-Severity Scale (CGI-S) at Visit 1. |
| **Test Product, Dosage, and Mode of Administration** | Cariprazine 1.5 mg/day and 3.0 mg/day capsules, oral administration |
| **Duration of Treatment** | A no-drug screening period of approximately 7-14 days, followed by 6 weeks of double-blind treatment and a 1-week, no investigational product safety follow-up period. |
| **Reference Therapy, Dosage, and Mode of Administration** | Matching placebo capsules, oral administration |
| **Criteria for Evaluation** | |
| **Primary Outcome Measure** | Montgomery-Åsberg Depression Rating Scale (MADRS) |
| **Secondary Outcome Measure** | CGI-S |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| | |
|---|---|
| **Statistical Methods** | The primary efficacy parameter will be the change from baseline to Week 6 in MADRS total score. The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline value and baseline by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores.<br>The secondary efficacy parameter will be the change from baseline to Week 6 in CGI-S score. The secondary efficacy parameter will be analyzed using an MMRM as used for the primary analysis.<br>Matched parallel gatekeeping procedure will be used to control the overall type I error rate for multiple comparisons of the 2 cariprazine dose groups (1.5 mg/day or 3.0 mg/day) with placebo at Week 6 for the primary and secondary efficacy parameters. Statistical significance will be determined by comparing the adjusted p-values to $\alpha = 0.050$.<br>[redacted] |





## 3.0 OVERALL TABLE OF CONTENTS

## 3.1 LIST OF IN-TEXT FIGURES

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## 3.2 LIST OF IN-TEXT TABLES

**Page**

## 4.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| AIMS | Abnormal Involuntary Movement Scale |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BARS | Barnes Akathisia Rating Scale |
| β-hCG | β-human chorionic gonadotropin |
| BMI | body mass index |
| BP | blood pressure |
| CFR | Code of Federal Regulations |
| CGI-S | Clinical Global Impressions–Severity |
| C-SSRS | Columbia–Suicide Severity Rating Scale |
| DHHS | Department of Health and Human Services |
| DSM-5 | *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition |
| ECG | electrocardiogram, electrocardiographic |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EPS | extrapyramidal symptom |
| ET | early termination |
| FDA | Food and Drug Administration |
| FR | Federal Register |
| GCP | good clinical practice |
| HAM-A | Hamilton Rating Scale for Anxiety |
| HAMD-17 | 17-item Hamilton Depression Rating Scale |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |

| | |
|---|---|
| ICF | informed consent form |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug (application) |
| IRB | Institutional Review Board |
| ITT | intent to treat |
| IxRS | Interactive Voice/Interactive Web Response System |
| [redacted] | [redacted] |
| MADRS | Montgomery-Åsberg Depression Rating Scale |
| MMRM | mixed-effects model for repeated measures |
| NA | not applicable |
| NDA | New Drug Application |
| PCS | potentially clinically significant |
| PI | principal investigator |
| PID | patient identification |
| PRN | as needed (*pro re nata*) |
| QIDS-$SR_{16}$ | Quick Inventory of Depressive Symptomatology – Self-Report |
| QTc | QT interval correct for heart rate |
| QTcB | QT interval corrected for heart rate using the Bazett formula |
| QTcF | QT interval corrected for heart rate using the Fridericia formula |
| RSM | Regional Site Manager |
| SAE | serious adverse event |
| SAS | Simpson-Angus Scale |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| YMRS | Young Mania Rating Scale |

# 5.0 ETHICAL CONSIDERATIONS

This clinical study is designed to comply with the International Conference on Harmonisation (ICH) Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and Good Clinical Practice (GCP) (ICH E6; 62 FR 25692, 09 May 1997).

## 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 the Sponsor, along with a roster of IRB members or the US Department of Health and Human Services (DHHS) 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 Code of Federal Regulations (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 site will require approval from an IEC and government agency. During the course of the study, the Sponsor 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 site 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

The study will be conducted in full compliance with US Food and Drug Administration (FDA) guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR § 312.120.

## 5.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA (Health Insurance Portability and Accountability Act of 1996) authorization (in compliance with 21 CFR, Parts 50 and 312), data protection consent (Europe only), or other written documentation in accordance with the relevant country and local privacy requirements (where applicable) before participating in any study-related procedures.

Each patient will read and sign an instrument of informed consent and the HIPAA authorization form (in countries where applicable), data protection consent (Europe only), or other written documentation in accordance with the relevant country and local privacy requirements (where applicable) after having had an opportunity to discuss them with the principal investigator (PI) before signing; each patient will be made aware that he or she may withdraw from the study at any time.

The informed consent statement contains all the elements of informed consent listed in Appendix I of the protocol; the HIPAA authorization contains all the core elements and mandatory statements as defined in the CFR. Signed copies of the ICF and the HIPAA authorization form or other locally applicable form will be given to the patient, and both documents will be placed in the PI's study files. A unique patient identification (PID) number will be assigned according to Section 9.4.3 at the time the patient signs the ICF.

## 6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 85 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 informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

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

The following information can be found on FDA Form 1572 and/or study contacts page and/or Trial Master File: Name and contact information of sponsor study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

## 7.0 INTRODUCTION

Bipolar disorder is a complex, chronic illness causing dramatic mood swings and unusual shifts in energy and behavior, ultimately resulting in functional impairments. It manifests itself as alterations in mood and energy from euphoria and excitability (mania or hypomania) to depression and psychomotor retardation (Goodwin and Jamison, 1990) and is associated with significant morbidity and mortality. Bipolar disorder in the United States affects 5.7 million adults or about 2.6% of the population 18 years and older in any given year (Kessler et al, 2005) and has a considerable economic effect on our society (Wyatt and Henter, 1995). In the year 2000, this disorder ranked as the seventh leading cause of worldwide nonfatal disease burden (World Health Organization, 2001). Suicide rates within this population are among the highest of all psychiatric illnesses (Muller-Oerlinghausen et al, 2002).

The depressive phase of bipolar disorder causes significantly more morbidity and mortality than the manic or hypomanic phase. Patients with bipolar disorder experience depressive symptoms much more frequently than manic or hypomanic symptoms (Hlastala et al, 1997; Judd et al, 2002, 2003; Keller et al, 1986; Post, 2005; Post et al, 2003). In addition, compared with bipolar mania, bipolar depression is associated with an increased risk of suicide and psychosocial impairment (Altshuler et al, 2002; Calabrese et al, 2003, 2004; Dilsaver et al, 1997; Leverich et al, 2003; MacQueen et al, 2001).

Although there is a substantial burden associated with bipolar depression, the treatment of this phase of bipolar disorder has not been as widely studied as the treatment of bipolar mania, and pharmacotherapeutic options are limited. At present, only Seroquel (quetiapine), Seroquel XR (quetiapine XR), Symbyax (olanzapine and fluoxetine), and Latuda (lurasidone HCl) are approved by the FDA for the treatment of patients with bipolar depression. Other common pharmacotherapies include lithium, anticonvulsants (eg, valproate, lamotrigine), antidepressants, atypical antipsychotics, or combinations of these.

Treatment needs are not completely met by the currently available therapies; and only a low percentage of patients persistently benefit from them. A significant percentage of patients do not fully respond to the currently available treatments and continue to experience subthreshold symptoms and even relapse. Side effects commonly associated with the currently available treatments for bipolar depression include tremors, psychomotor slowing, cognitive impairment, exacerbation of agitation, nephrotoxicity, altered thyroid function, and sexual dysfunction. Atypical antipsychotics in particular have been associated with an increased risk of metabolic side effects, including body weight gain, dyslipidemia, glucose intolerance, and type 2 diabetes. The use of antidepressants has been shown to increase the risk of switching to the manic phase. More effective therapies with improved side effect profiles are still needed to enhance outcomes in these patients without the possibility of inducing mania or rapid cycling.

Dysfunction in dopamine (DA) neurotransmission has been implicated in the pathophysiology of bipolar disorder. Several lines of evidence suggest that the manic phase is associated with increased DA neurotransmission and the depressive phase with decreased DA neurotransmission. It has been hypothesized that the cyclical nature of bipolar disorder is due to alterations between these hyper- and hypodopaminergic states (Berk et al, 2007). The contributions of individual $D_2$-like receptor subtypes ($D_2$, $D_3$, $D_4$) to bipolar disorder are not fully established. However, there is increasing evidence that $D_3$ receptors may play an important role in depression. Evidence for this has been derived mainly from studies in mice with a targeted disruption of $D_3$ receptors ($D_3$(-/-) mice). These animals are more resistant to stressful procedures, display anxiolytic-like behavior, and are more sensitive to antidepressants in behavioral models compared with the wild-type littermates (Leggio et al, 2008; Steiner et al, 1997). A compound with a "DA system stabilizing" effect and with preferable $D_3$ receptor functional antagonist properties may prove to be most beneficial for the treatment of all the phases of bipolar disorder including bipolar depression. RGH-188 (cariprazine) exhibits these characteristics.

Cariprazine is an orally active and potent dopamine $D_3$-preferring $D_3$/$D_2$ receptor partial agonist discovered by Gedeon Richter Plc., Budapest, Hungary, and currently in development by Forest Laboratories, LLC (an Allergan Affiliate), and Gedeon Richter Plc, for the treatment of schizophrenia, acute bipolar mania, bipolar depression, and as adjunctive treatment for major depressive disorder. In September 2015, cariprazine (VRAYLAR™) was approved in the United States for the treatment of schizophrenia, at doses of 1.5 to 6 mg/day, and for the acute treatment of manic or mixed episodes associated with bipolar I disorder, at doses of 3 to 6 mg/day.

The chemical name of the hydrochloride salt of cariprazine is trans-N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl}-N',N'-dimethylurea hydrochloride. Its molecular formula is $C_{21}H_{32}Cl_2N_4O$ HCl; its molecular weight is 463.87. Two main metabolites, desmethyl and didesmethyl cariprazine, have been identified. The receptor binding profile of both these metabolites is similar to that of the parent compound.

A unique feature of cariprazine is that it binds with significantly higher affinity to $D_3$ than to $D_2$ receptors. Its affinity for $D_3$ receptors is approximately 1 order of magnitude greater than that for $D_2$ receptors. Similar to aripiprazole, but unlike other atypical antipsychotics, cariprazine acts as a "DA system stabilizer." Cariprazine displays partial agonist as well as antagonist activity on biosynthesis- (and release-) modulating presynaptic $D_2$ receptors and has preferential dopaminergic actions in the limbic regions. However, cariprazine is more potent than aripiprazole, and the degree of its apparent partial agonist activity is greater.

Cariprazine also has considerable affinity for, and is a partial agonist and antagonist at, the serotonin 5-$HT_{1A}$ and 5-$HT_{2B}$ receptors, respectively. Antidepressant-like and/or anxiolytic-like effects of cariprazine may also be mediated through these receptors. Cariprazine has low potency at other receptor sites, such as the 5-$HT_{2C}$, histamine $H_1$, and adrenergic receptor sites.

Cariprazine was evaluated in patients with bipolar depression in 2 multicenter, randomized, double-blind, placebo-controlled studies (Study RGH-MD-52 [2011] and Study RGH-MD-56 [2014]).

Study RGH-MD-52 was 11 weeks in duration: a no-drug washout period of up to 1 week, 8 weeks of double-blind treatment, and 2 weeks of safety follow-up with treatment as determined by the PI. This was a fixed-flexible dose study. A total of 227 Bipolar I and II patients were randomized to 1 of 3 treatment groups and received at least 1 dose of the investigational product: placebo (n = 77), cariprazine low dose (0.25-0.75 mg/day, n = 75) and cariprazine high dose (1.5-3.0 mg/day, n = 75). The dose was fixed for first 4 weeks of double-blind treatment; all patients received the lower of the dose range (1 capsule; placebo, cariprazine 0.25 mg/day, or cariprazine 1.5 mg/day). At the end of Week 4, the dose could be increased to 2 capsules if response was not adequate (< 40% reduction in Montgomery-Åsberg Depression Rating Scale [MADRS] score from baseline) and there were no significant tolerability issues as judged by the Investigator. Approximately 76% of the patients completed the study: 78% in the placebo group, 84% in the cariprazine low-dose group, and 65% in the cariprazine high-dose group. More patients discontinued for adverse events (AEs) in the cariprazine high-dose group (9.3%) than in the placebo group (2.6%) and cariprazine low-dose group (4.0%). The average patient age was 39 years, and approximately 64% were female. The 3 treatment groups were balanced with respect to demographics and baseline characteristics. For the primary efficacy parameter, the change from baseline to the end of Week 8 in the MADRS total score using mixed-effects model for repeated measures (MMRM), the overall p-value was not statistically significant. Numerical improvement was seen in the cariprazine high-dose group relative to the placebo group up to end of week 6. Similar results were seen for other efficacy parameters. SAEs were reported in 6 patients (2 patients in the placebo group, 2 patients in the cariprazine low-dose group, and 2 patients in the cariprazine high-dose group). Treatment-emergent adverse events (TEAEs) reported in at least 10% of patients in any treatment group included insomnia, akathisia, headache, dry mouth, nausea, upper respiratory tract infection and diarrhea. Of these, insomnia, akathisia, dry mouth, nausea and diarrhea were reported more frequently in the cariprazine-treated patients.

Study RGH-MD-56 was 11 weeks in duration and comprised up to 14 days of screening followed by 8 weeks of double-blind treatment and 1 week of safety follow-up. A total of 584 bipolar I patients were randomized to 1 of 4 treatment groups and 578 patients received at least 1 dose of the investigational product: placebo (n = 145), cariprazine 0.75 mg/day (n = 141), cariprazine 1.5 mg/day (n = 146), cariprazine 3 mg/day (n = 146). Overall, 72.5% of the patients completed the study: 72.4% in the placebo group, 73.0% in the cariprazine 0.75 mg/day group, 80.1% in the cariprazine 1.5 mg/day group, and 64.4% in the cariprazine 3 mg/day group. The average patient age was 42 years, and approximately 62% were female. For both the primary and secondary efficacy parameters, change from baseline in MADRS total score and Clinical Global Impressions-Severity (CGI-S) score at Week 6, statistically significant improvement was demonstrated for the cariprazine 1.5 mg dose relative to placebo. Nominally significant improvement was shown for cariprazine 3 mg, which did not remain statistically significant after adjusting for multiplicity. No statistically significant treatment effect was shown for the 0.75 mg dose at Week 6. A post-hoc analysis of patients who completed the full 8 weeks of treatment (completer population) in Study RGH-MD-56 demonstrated similar reductions from baseline relative to placebo in MADRS total score for the cariprazine 1.5 and 3 mg/day groups at Week 6 and Week 8. Cariprazine was generally well-tolerated. No deaths were reported during the study. Serious adverse events were reported for 5 patients (3.4%) in the placebo group, 1 patient (0.7%) in the cariprazine 0.75 mg group, and 2 patients (1.4%) each in the cariprazine 1.5 mg and 3 mg treatment groups. Adverse events that led to discontinuation were reported in similar proportions of patients across the placebo (10.3%) and cariprazine (8.2%-11.6%) treatment groups. The most common AEs that led to discontinuation were akathisia, agitation, anxiety, and depression. Overall, TEAEs were reported for 55% of patients in the placebo treatment group and 57%-62% of patients in the cariprazine treatment groups. Akathisia and irritability were the only TEAEs reported for ≥ 5% of patients in any cariprazine treatment group and at an incidence at least twice that of the placebo group.

Based upon these data, the current study is designed to prospectively confirm the efficacy of a fixed-dose regimen of cariprazine 1.5 mg/day or 3 mg/day compared to placebo for treatment of the depressive episode in patients with bipolar I disorder. The safety and tolerability of the fixed-dose regimens will be evaluated.

A description of the chemistry, pharmacology, toxicology, pharmacokinetics, and clinical results of cariprazine is provided in the Investigator's Brochure (RGH-188 [cariprazine], 2015).

## 8.0 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3.0 mg/day relative to placebo in patients with bipolar I depression.

# 9.0 INVESTIGATIONAL PLAN

## 9.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This clinical study will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in adult patients with a *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5; American Psychiatric Association, 2013) diagnosis of Bipolar I disorder who are currently experiencing a major depressive episode.

The study will be conducted in outpatients (i.e., non-hospitalized) and will consist of approximately 7 to 14 days of screening and washout followed by 6 weeks of double-blind treatment and a 1-week safety follow-up period. At the end of the screening period, patients meeting the eligibility criteria for this study will be randomized (1:1:1) to 1 of 3 treatment groups (placebo, cariprazine 1.5 mg/day, cariprazine 3 mg/day). The study is designed to enroll outpatients, but as per local clinical practice, patients may be hospitalized for up to 7 days during the screening period or during the first week of treatment with double-blind investigational product. Further need for hospitalization will require consultation with the Study Physician. A total of 480 patients are planned to be randomized in this study.

Patients who complete 6 weeks of double-blind treatment or who prematurely discontinue before completing 6 weeks of double-blind treatment will be followed for 1 more week (safety follow-up period). During the safety follow-up period, patients may be started on a standard treatment as determined by the PI. No investigational product will be administered during the safety follow-up period.

[redacted]

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

The double-blind design was adopted to minimize systematic bias resulting from the Investigator or the patient knowing the treatment being administered. Randomization is expected to minimize patient selection bias and increase baseline comparability among the treatment groups. The doses of cariprazine under study were chosen on the basis of experience from the RGH-MD-52 and RGH-MD-56 studies (see Section 7.0), as well as experience in the cariprazine development program in healthy volunteers and patients with other indications and other atypical antipsychotics for the treatment of bipolar depression. The use of a placebo control is critical to the study to allow discrimination of patient outcomes caused by the individual dose levels of cariprazine from outcomes caused by other factors (e.g., the observer or patient expectations, the natural progression of the disease, the conditions of being in a study).

No double-blind down-taper has been included as cessation of cariprazine at doses comparable to those under study has not given rise to appreciable discontinuation symptoms.

## 9.3 SELECTION OF STUDY POPULATION

### 9.3.1 Inclusion Criteria

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

**Inclusion criteria to be assessed at Visit 1 (Screening)**

1. Written informed consent, signed, obtained from the patient before the initiation of any study-specific procedures

2. Male or female patients 18 to 65 years of age, inclusive

3. Currently meet the DSM-5 criteria for bipolar I disorder without psychotic features confirmed by the administration of the Mini International Neuropsychiatric Interview (MINI), with a current major depressive episode of at least 4 weeks and not exceeding 12 months in duration

4. Currently treated as an outpatient at the time of enrollment

5. A verified previous manic or mixed episode. Verification must include one of the following sources:

    a. Treatment of mania with an anti-manic agent (eg, lithium or divalproate) or antipsychotic medication with an approved indication for mania

    b. Hospital records/Medical records

    c. Patient report corroborated by caretaker or previous or current treating clinician

6. 17-item Hamilton Depression Rating Scale (HAMD-17) total score ≥ 20

7. HAMD-17 item 1 score ≥ 2

8. CGI-S score ≥ 4

9. Negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test (women of childbearing potential only)

10. Normal physical examination, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal findings that are judged not clinically significant by the PI

**Inclusion criteria to be assessed at Visit 2 (Baseline)**

11. Continue to meet Visit 1 inclusion criteria

### 9.3.2 Exclusion Criteria

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

**Exclusion criteria to be assessed at Visit 1 (Screening)**

***Psychiatric Criteria***

1. Young Mania Rating Scale (YMRS) total score > 12
2. Four or more episodes of a mood disturbance (depression, mania, hypomania, or mixed state) within the 12 months before Visit 1
3. Any current axis 1 psychiatric diagnosis other than bipolar disorder with the exception of specific phobias
4. History of meeting DSM-5 criteria for:
    - Dementia, amnesic, or other cognitive disorder
    - Schizophrenia, schizoaffective, or other psychotic disorder
    - Mental retardation
5. DSM-5–based diagnosis of borderline or antisocial personality disorder or other axis II disorder of sufficient severity to interfere with participation in this study
6. History of meeting DSM-5 criteria for substance-related disorders (excluding caffeine-related and tobacco-related disorders) within the 6 months before Visit 1
7. Positive result on blood alcohol test or urine drug screen for any prohibited medication. Exception:
    - patients with a positive cannabinoid on entry may be retested before randomization. If the patient remains positive, the patient is no longer eligible
    - patients positive for opiates on entry, discussion with Study Physician is required.

[redacted]

[redacted]

***Treatment-Related Criteria:***

14. Electroconvulsive therapy in the 3 months before Visit 1

15. Previous lack of response to electroconvulsive therapy

16. Treatment with a depot antipsychotic drug within 6 months prior to Visit 1

17. Treatment with clozapine in a dose of > 50 mg/day in the past 2 years

[redacted]

19. Previous treatment with vagus nerve stimulation or transcranial magnetic stimulation within 6 months before Visit 1

20. Prior participation with any clinical trials, involving experimental or investigational drugs, within 6 months before Visit 1 or during the study

21. Initiation or termination of psychotherapy for depression within the 3 months preceding Visit 1, or plans to initiate, terminate, or change such therapy during the course of the study.

22. Initiation or termination of phototherapy within the 2 weeks before screening, or plans to initiate same during the course of the study

***Other Medical Criteria:***

23. [redacted]

24. Female patients who meet the following criteria:

    - Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study

[redacted]

[redacted]

30. Gastric bypass or any condition that would be expected to affect drug absorption (lap band procedures are acceptable if there is no problem with absorption)

[redacted]

32. Known history of cataracts or retinal detachment

33. Known human immunodeficiency virus infection

[redacted]

***Other Criteria:***

38. Employee, or immediate relative of an employee, of the Sponsor, any of its affiliates or partners, or the study center

[redacted]

### 9.3.3 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the protocol. Patients can be prematurely discontinued from the study for one of the following reasons:

- Screen Failure (Failure to meet inclusion/exclusion criteria)
- Withdrawal of consent
- Adverse event
- Lack of Efficacy
- Protocol violation
- Non-compliance with Study Drug
- Lost to follow-up
- Study terminated by Sponsor
- Site terminated by Sponsor
- Other

A patient completing Visits 1 through 6 will be considered a completer. All randomized patients who prematurely discontinue from the study, regardless of the 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 Visit 6/ET). All investigational products dispensed at earlier visits that had not been previously collected should be collected at the final visit. Patients refusing to come in for a final visit must be requested in writing, with a registered letter, to come in for an ET visit and to return any unused investigational product. A copy of the letter, together with the source documentation, will be kept by the Investigator. The reasons for premature discontinuation from the study will be reflected on the study termination record of the eCRF.

Patients with Visit 6/ET more than 4 days after the last dose of double-blind investigational product will be administered safety assessments only.

### 9.3.4 Patient Replacement Procedures

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

## 9.4 TREATMENTS

### 9.4.1 Treatments Administered

Investigational product in the form of capsules packaged in blister packs will be provided by the Sponsor. No investigational product will be administered during the screening period or the safety follow-up period. For the 6-week double-blind treatment period, patients will be supplied with identically appearing capsules of either cariprazine or placebo.

### 9.4.2 Identity of Investigational Product(s)

Investigational product will be supplied in blister packs containing 10 capsules and will be labeled with the protocol number, the visit number/space to write visit number, storage information, warning language (viz, "Caution: New Drug—Limited by Federal Law to Investigational Use"), and instructions to take the capsules once daily as directed, and the medication identification number. Investigational product labels will be country specific. Immediately before dispensing the investigational product, the Investigator will write the patient's initials, site number, and date on the label.

All investigational products will be provided by the Sponsor, or designees, to the study centers. Investigational product must be stored in an appropriate secure area (e.g., a locked cabinet in a locked room) at controlled room temperature [redacted] with excursions permitted between [redacted]) and must be protected from light, heat, and moisture.

The Investigator is responsible for recording the receipt and use of all investigational products supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused investigational products must be returned; and, whenever investigational products are returned, unit counts must be performed. All investigational products must be accounted for. At the end of the study, or upon drug expiration, any unused investigational product must be returned to the Sponsor or Sponsor's designee.

### 9.4.3 Method of Assigning Patients to Treatment Groups

[redacted]

Each study center will be provided with investigational products. An interactive voice/interactive Web response system (IxRS) will be used during the study to monitor enrollment and medication allocation. If the patient meets the randomization criteria, the study center will contact the IxRS at end of Visit 2 to randomize the patient. IxRS will randomize the patient to the appropriate treatment arm (placebo, cariprazine 1.5 mg/day, or cariprazine 3.0 mg/day) and determine the investigational product number to be assigned to the patient based on the randomization.

### 9.4.4 Selection of Dosages in the Study

The doses of cariprazine selected for this study were based on the results from 2 completed studies in patients with bipolar depression (RGH-MD-52 and RGH-MD-56), as well as experience in the cariprazine development program in healthy volunteers and patients with other indications and other atypical antipsychotics for the treatment of bipolar depression. Study RGH-MD-52 indicated numerically better results for the high-dose cariprazine group (1.5-3.0 mg/day) relative to placebo up to end of Week 6. In the cariprazine low-dose group (0.25-0.75 mg/day), better efficacy was observed following a dose increase, and tolerability was not compromised. Thus, cariprazine 0.75, 1.5, and 3.0 mg/day were selected for further evaluation in Study RGH-MD-56.

In Study RGH-MD-56, for both the primary and secondary efficacy parameters, change from baseline in MADRS total score and CGI-S score at Week 6, statistically significant improvement was demonstrated for the cariprazine 1.5 mg dose relative to placebo. Nominally significant improvement was shown for cariprazine 3 mg, which did not remain statistically significant after adjusting for multiplicity. No statistically significant treatment effect was shown for the 0.75 mg dose at Week 6. A post-hoc analysis of patients who completed the full 8 weeks of treatment (completer population) in Study RGH-MD-56 demonstrated similar reductions from baseline relative to placebo in MADRS total score for the cariprazine 1.5 and 3 mg/day groups at Week 6 and Week 8.

The primary efficacy results and the post-hoc completers analysis in Study RGH-MD-56 led to the selection of the cariprazine 1.5 and 3 mg/day doses for further evaluation in this study. A dose higher than 3 mg/day was not chosen because of concerns related to the potential for higher extrapyramidal symptom rates with increasing cariprazine dose.

A fixed-dose regimen allows for unambiguous evaluation of safety and efficacy of individual doses.

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

All investigational products will be dispensed in blister packs. Each blister pack will contain 10 capsules arranged in 10 columns and 1 row, adequate for the 7 days of the week plus 3 extra days. The configuration of the blister packs is provided in Table 9.4.5–1.

At Visit 2, patients who continue to meet all eligibility criteria will be assigned a randomization number and dispensed a corresponding blister pack of double-blind investigational product for the first week of double-blind treatment. Patients will be instructed to take 1 capsule daily, in order from left to right of the blister pack, beginning on the evening of Visit 2 or the morning after Visit 2

At Visit 3 (end of week 1 of double-blind treatment) patients will be dispensed 1 blister pack. At Visits 4 and 5 (end of week 2 and end of week 4 of double-blind treatment), patients will be dispensed 2 blister packs.

All patients randomized to cariprazine dose groups will receive cariprazine 1.5 mg/day for 2 weeks, from Day 1 through Day 14. For patients randomized to the cariprazine 3.0 mg/day group, the dose will be increased to 3.0 mg/day on Day 15.

Drug holidays (up to a maximum of 3 consecutive days) are allowed if there are tolerability problems at the discretion of the Investigator. Patients unable to tolerate the fixed dose of the investigational product or patients off drug for 4 or more consecutive days will be prematurely discontinued from the study.

All investigational products will be taken orally as a single daily dose at approximately the same time of day (morning or evening). The dosing time can be switched if there are tolerability problems. Any switch must allow at least 24 hours between 2 consecutive doses and must be documented in the eCRF.

At each visit, patients will be instructed to return all unused investigational product.

**Table 9.4.5–1. Blister Card Configuration and Dosing Regimen**

| | *Visit 2 Days 1-7 + 3 extra days* | *Visit 3 Days 8-14 + 3 extra days* | *Visit 4 Days 15-28 + 6 extra days* | *Visit 5 Days 29-42 + 6 extra days* |
|---|---|---|---|---|
| ***Treatment group: placebo*** | | | | |
| Row 1 | 0 mg | 0 mg | 0 mg | 0 mg |
| ***Treatment group: cariprazine 1.5 mg/day*** | | | | |
| Row 1 | 1.5 mg | 1.5 mg | 1.5 mg | 1.5 mg |
| ***Treatment group: cariprazine 3.0 mg/day*** | | | | |
| Row 1 | 1.5 mg | 1.5 mg | 3.0 mg | 3.0 mg |

Note: At Visit 2 and Visit 3 patients will be dispensed 1 blister pack. At Visit 4 and Visit 5, patients will be dispensed 2 blister packs. Each blister pack will contain 10 capsules, adequate for 7 days plus 3 extra days.

### 9.4.6 Blinding

The study will be conducted as a double-blind investigation. A list of patient randomization codes will be generated by the Sponsor's Statistical Programming, and implemented by the IxRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

### 9.4.7 Unblinding

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

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

In an emergency, the Investigator can obtain the treatment assignment of any patient at his or her study site through the IxRS. In an emergency, the Investigator will access the IxRS to break the blind.

The unblinding of bioanalytical representatives is to be carried out in a secure manner following the Sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

### 9.4.8 Prior and Concomitant Therapy

A complete list of drugs that are allowed and not allowed as concomitant medications for either episodic or long-term use is provided in Appendix III. Throughout the duration of this study, additional psychotropic medications, including psychostimulants, are not allowed, with some notable exceptions listed below. Psychotropic medications include the following: antipsychotics, antidepressants (including monoamine oxidase-B inhibitors), stimulants, anticonvulsants/mood stabilizers, sedatives/hypnotics/anxiolytics, dopamine releasing drugs or dopamine agonists, and psychotropic drugs not otherwise specified (including herbal products).

Patients will be asked to abstain from drinking alcohol during the study. Patients who have been taking stable doses of benzodiazepines (up to 2 mg/day) for at least 1 month before randomization can continue use. Medically appropriate episodic use (up to 3 days) of narcotic analgesics for acute medical indications (i.e., tooth extraction) is allowed during the study.

Medication history, including the use of psychotropic medication and of any other medication, will be recorded at Visit 1 (Screening). Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

***For insomnia the following will be allowed. It should not be prescribed prophylactically.***

- Zolpidem (maximum of 10 mg/day)
- Zolpidem extended release (maximum of 12.5 mg/day)
- Zaleplon (maximum of 20 mg/day)
- Eszopiclone (maximum of 3 mg/day)
- Zopiclone (maximum of 7.5 mg/day)
- Chloral hydrate (maximum of 1000 mg/day) may be used acutely with approval from Study Physician)

These medications must be administered before bedtime as recommended in their prescribing information. The medication must be documented on the concomitant medications page of the eCRF. No such medication is permitted within 8 hours of psychiatric or neurological assessments.

***For <u>EPSs or akathisia</u>:***

For EPSs or akathisia that emerge or worsen during the study, the following rescue medications will be allowed; however, each of the 3 EPS scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson Angus Scale [SAS]) should first be performed (unless a medical urgency [eg, dystonia, severe akathisia, etc] requires otherwise) to support the decision to administer the medications:

- Benztropine (up to 4 mg/day orally or up to 2 mg/day if given parenterally) or equivalent (eg, trihexyphenidyl up to 6 mg/day in divided doses)
- Diphenhydramine (up to 50 mg/day) for EPS
- Propranolol for the treatment of akathisia. Daily dose of propranolol depends on heart rate and BP (up to 160 mg/day)

The medication listed above should not be used prophylactically. The need for continued use of these medications should be regularly assessed by the PI and documented appropriately. The EPSs must be documented on the AE page of the eCRF, and the medication on the concomitant medications page of the eCRF.

Injectable agents are not allowed, except for the treatment of an acute dystonic reaction if deemed necessary.

***Rescue medications for agitation, restlessness, and hostility:***

Episodic use of lorazepam up to 2 mg/day (or equivalent) and for up to 3 consecutive days at a time is allowed for agitation, restlessness, and hostility.

The agitation, restlessness, or hostility must be documented on the AE and/or the medical history page of the eCRF. The medication use must be documented on the rescue medication page of the eCRF. Efficacy assessments should not be performed within 8 hours of administration of lorazepam or equivalent benzodiazepine or within 24 hours of administration of diazepam.

### 9.4.9 Monitoring Treatment Compliance

Investigational product compliance will be monitored by counting the number of capsules dispensed and the number returned by the patient. Before new investigational product is dispensed at any visit, every effort will be made to collect all unused investigational product. If a patient demonstrates poor compliance at any time during the study (< 80% or > 120% measured by pill counts), then they should be discontinued from the study.

## 9.5 EFFICACY AND SAFETY VARIABLES

### 9.5.1 Diagnostic and Efficacy Assessments

#### *9.5.1.1 Diagnostic Assessment*

***Mini International Neuropsychiatric Interview (Version 7.0.0, 01 Jan 2014)***

The MINI (Version 7.0.0, 01 Jan 2014) is a clinician-rated diagnostic assessment that will be considered a source document in this study. The interview will be administered by the PI or Sub-Investigator who is a psychiatrist or a doctoral-level clinical psychologist or who has extensive professional training and experience in the diagnosis of mental illness.

#### *9.5.1.2 Primary Efficacy Assessment*

***Montgomery-Åsberg Depression Rating Scale***
The MADRS (Montgomery and Åsberg, 1979) is a 10-item, clinician-rated scale that evaluates the patient's depressive symptomatology during the past week. Patients are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each item will be scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity. This scale will be administered by a trained rater with adequate experience in the assessment of the patient's depressive symptomatology using the MADRS.

#### *9.5.1.3 Secondary Efficacy Assessment*

***Clinical Global Impressions–Severity***
The CGI-S (Guy, 1976) is a clinician-rated scale that measures the overall severity of a patient's illness in comparison with the severity of other patients the physician has observed. The patient is rated on a scale from 1 to 7 with 1 indicating a "normal state" and 7 indicating "among the most extremely ill patients." The CGI-S will be administered by the PI or a Sub-Investigator with extensive professional training and experience in assessing mental illness.

[redacted]

#### *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 was reported from the time the patient signed the ICF until 30 days after the final protocol-defined study visit or, if the final visit does not occur, the last known dose of investigational product, 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 site 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

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; i.e.:**

- 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, i.e.:**

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

#### *9.5.2.3 Severity Assessment*

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

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

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

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

#### *9.5.2.4 Serious Adverse Events*

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

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

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

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

Preplanned hospitalizations (e.g., elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) or routine (i.e. required) country-specific hospitalization during washout 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 site 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 (i.e., is it an SAE?), as well as the severity and casual relationship
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

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

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

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

The Sponsor is required to inform worldwide regulatory authorities of SAEs and Ocular Events of Special Interest that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE and Ocular Events of Special Interest that occur after informed consent is obtained.

The following serious and non-serious adverse events (ie, Ocular Events of Special Interest) require a 15-day alert report:

- cataract, lens, or lenticular abnormality or change, opacity, opacification or opalescence
- blindness, night blindness, visual acuity or vision decrease, abnormality or change, visual acuity test abnormality or change
- retinal, macular, or optic nerve degeneration, abnormality or change; retinal pigment epithelium detachment, abnormality or change
- color vision decrease, abnormality or change

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study site personnel must report the event to the Sponsor's Global Drug Safety department on the SAE Form for Clinical Trials.

Within 24 hours of learning of any non-serious Ocular Event of Special Interest, the study site personnel must report the event on the Ocular Event Reporting Form. Serious Ocular Events should be reported on the SAE Form for Clinical Trials.

In addition to completing the appropriate form, the Sponsor's Study Safety 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 site must transmit the SAE Form for Clinical Trials or the Ocular Event of Special Interest form to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials or the Ocular Event of Special Interest form, completed with all available details, must still be faxed within 24 hours of knowledge of the event at the study site.

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 and Ocular Events of Special Interest are to be followed by the study staff until resolution or until the SAE or Ocular Event of Special Interest is deemed stable. ***The Sponsor may contact the study site to solicit additional information or follow up on the event.***

Fax the SAE Form for Clinical Trials to the Sponsor:

SAE Form fax number:
[redacted]

The Medical Emergency Phone number is provided in Regulatory Binder contact list.

#### *9.5.2.7 Reporting of Pregnancies Occurring During the Study*

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

The pregnancy must be followed to term and the outcome reported by completing a follow-up a Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (e.g., 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 (e.g., hospitalization) indicated in addition to the Pregnancy Form.

[redacted]

[redacted]

### 9.5.3 Investigational Product Concentration Measurements

Blood samples will be collected by a qualified phlebotomist via venipuncture using lavender-top Vacutainer tubes containing potassium $K_2$EDTA as the anticoagulant. A 2-mL tube will be used to collect the samples for determination of the plasma concentrations of cariprazine and its metabolites.

Four blood samples (2 mL each) will be collected at Visit 4 (Week 2), Visit 5 (Week 4), Visit 6/ET (Week 6), and Visit 7 (Week 7). Samples may be collected at any time during the visit. The date and time of plasma sampling will be recorded in the eCRF along with the date and approximate time of the previous 3 doses of investigational product. Every effort should be made to collect PK samples for each patient. However, if for reasons of safety or patient refusal, blood sampling is not possible, the PK sample can be skipped.

All Vacutainer and plasma collection tubes must be prechilled in an ice bath before use.

The clock times of all blood draws will be recorded for each patient. All Vacutainer and polypropylene tubes will be labeled at the study center with a code number that corresponds to the PID number, visit number, date, and blood draw time. The central laboratory will supply the labels with code numbers, blood Vacutainer tubes, and the polypropylene tubes. Other laboratory supplies are the responsibility of the Investigator.

Samples must be centrifuged for plasma harvesting within 30 minutes of blood draw.

For details on blood sample collection, plasma separation, storage, and shipment, see the instructions from the central laboratory (Central Laboratory Manual).

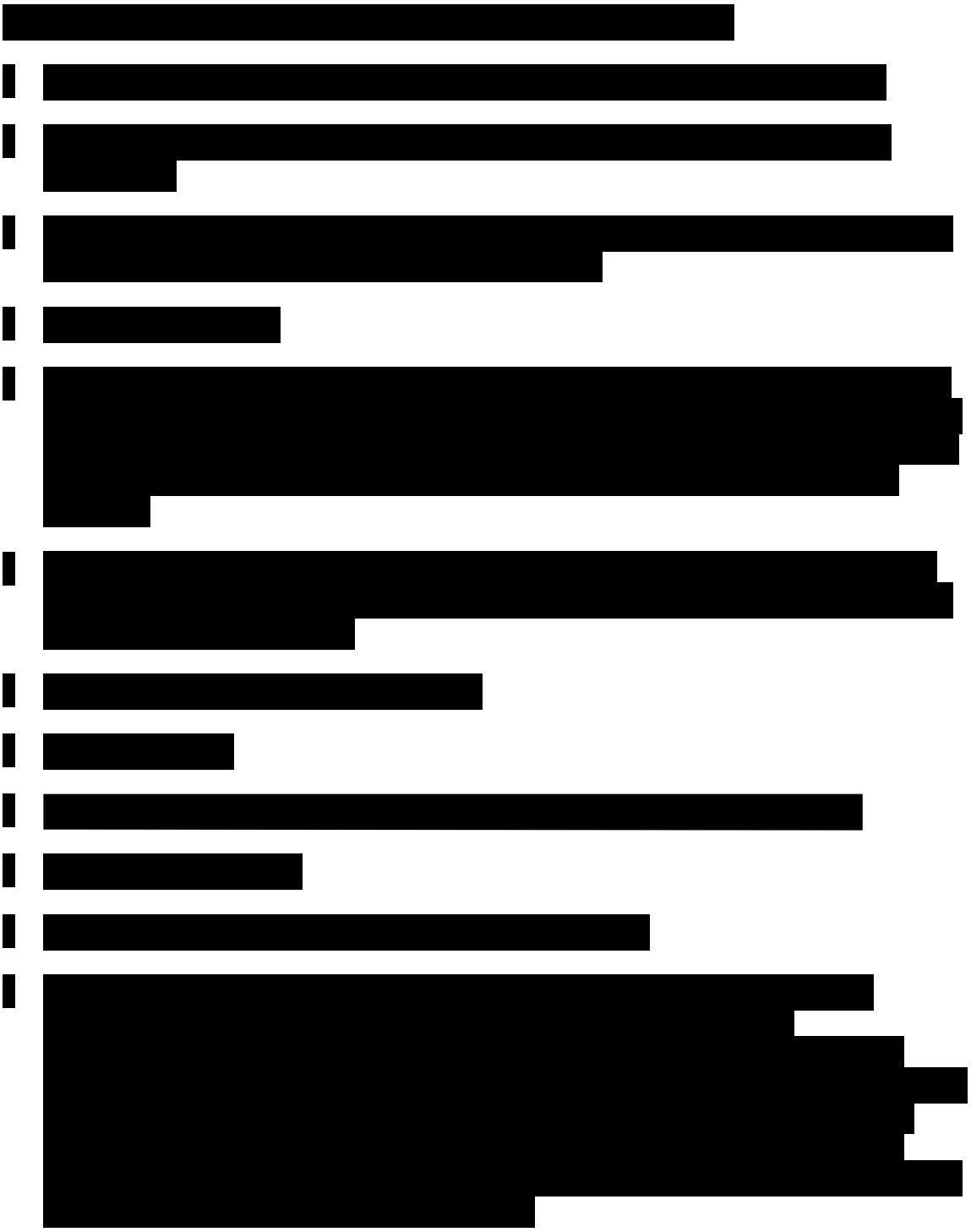
### 9.5.4 Health Economic and Outcomes Research Assessments

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.

[redacted]



[redacted]

[redacted]

## 9.6 DATA QUALITY ASSURANCE

### 9.6.1 Data Monitoring

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

### 9.6.2 Data Recording and Documentation

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

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

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

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, laboratory reports, patient diaries, regulatory documents, etc.) 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 the Sponsor, 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.

#### *9.7.1.1 Screened Population*

The Screened Population will consist of all patients who signed informed consent and received a PID number.

#### *9.7.1.2 Randomized Population*

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

#### *9.7.1.3 Safety Population*

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

#### *9.7.1.4 Intent-to-Treat Population*

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

### 9.7.2 Patient Disposition

The number and percentage of patients in 3 of the study populations (Randomized, Safety, and ITT) will be summarized by treatment group and study center; the Screened Population will be summarized overall only by study center.

Screen-failure patients (ie, patients screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population. The number and percentage of patients who completed the double-blind treatment period, and of patients who prematurely discontinued during the same period and who entered the safety follow-up period will be presented for each treatment group and pooled across treatment groups for the Randomized Population. Patients are considered to have entered the safety follow-up period if they had Visit 7 (Week 7). The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the eCRFs will be summarized (number and percentage) by treatment group for the Randomized Population.

### 9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (e.g., age, race, ethnicity, sex, weight, height, BMI) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations.

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

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Population. Multiple medication use by a patient will only be counted once.

### 9.7.4 Extent of Exposure and Treatment Compliance

#### *9.7.4.1 Extent of Exposure*

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

#### *9.7.4.2 Measurement of Treatment Compliance*

Dosing compliance for a specified period is defined as the total number of capsules actually taken by a patient during that period divided by the number of capsules that were expected to be taken during the same period multiplied by 100. The total number of capsules actually taken during a specific period is calculated as the number of days in that period multiplied by the number of capsules taken each day during that period. The number of capsules expected to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day. Descriptive statistics for investigational product compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the whole double-blind treatment period of the study for the Safety Population.

### 9.7.5 Efficacy Analyses

All efficacy analyses will be based on the ITT Population, unless stated otherwise. The baseline for each specific efficacy endpoint is defined as the value recorded at Visit 2/Week 0. If this value is not available, the last available value before the first dose of double-blind investigational product will be used as the baseline value. Efficacy results will be considered to be statistically significant after consideration of the multiplicity-control strategy for controlling the Type I error at 0.05 level; details are described in Section 9.7.5.2. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical hypothesis tests will be performed at the 2-sided 5% significance level for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For efficacy analyses in which study center is a factor, a small center will be defined as a center with fewer than 2 patients in at least 1 treatment group in the ITT Population. Small centers will be pooled to form pseudo-centers so that each treatment group includes at least 2 ITT patients within the center. Pooling will be done within each country 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 number to the smallest center number. The pooling process starts with the largest small center from the top, which will be pooled with the smallest from the bottom until a non-small center is formed. The process will be repeated using the small centers left out after the first pass. If any centers are left out at the end of the process, they will be pooled with the smallest pseudo-center. If there is more than 1 smallest pseudo-center, the pseudo-center with the smallest center number 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 more than 1 smallest non-small center, the one with the smallest center number will be selected.

These pseudo-centers will be used for all efficacy analyses when the model is adjusted for study center.

[redacted]

#### *9.7.5.1 Primary Efficacy Parameters*

The primary efficacy parameter will be the change from baseline to Week 6 in MADRS total score. The primary analysis will be performed using a MMRM with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline value and baseline by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values.

[redacted]

[redacted]

### *9.7.5.2 Secondary Efficacy Parameters*

The secondary efficacy parameter will be change from baseline to Week 6 in CGI-S score. The secondary efficacy parameter will be analyzed using an MMRM with treatment group, study center, visit, and treatment group–by-visit interaction as fixed effects and the baseline CGI-S score and baseline CGI-S score–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 will be used to estimate denominator degrees of freedom.

To control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6 for the primary and secondary efficacy parameters, the parallel gatekeeping procedure will be implemented (Chen et al, 2005). The 4 null hypotheses will be grouped into 2 families denoted by F1 and F2, with F1 consisting of 2 null hypotheses for comparisons of the 2 active doses versus placebo in change from baseline to Week 6 in MADRS total score, and F2 consisting of 2 null hypotheses for comparisons of the 2 active doses versus placebo in change from baseline to Week 6 in CGI-S score. Family F1 will serve as the parallel gatekeeper for F2. The matched gatekeeping procedure utilizes the special logical relationship between the primary and the secondary parameters to enhance the power of statistical testing. The secondary efficacy parameter will be tested at a specific dose only if the corresponding primary efficacy parameter is statistically significant. The Simes test will be used to derive the local p-values for the interaction hypotheses. The adjusted p-values for the 4 elementary hypotheses will be calculated based on the closed testing principle. Statistical significance will be determined by comparing the adjusted p-values to $\alpha = 0.050$.

[redacted]

[redacted]

[redacted]

#### *9.7.6.6 Investigational Product Plasma Concentration Parameters*

Plasma samples will be analyzed for the concentrations of cariprazine and its desmethyl and didesmethyl metabolites using a validated bioanalytical method. A population PK approach will be used to estimate individual-level drug-exposure parameters (i.e., steady-state area-under-the-curve (AUC), steady-state maximum concentration [Cmax], steady-state minimum concentration [Cmin]) for each of the 3 analytes. This will be performed via the use of appropriate nonlinear mixed-effects modeling software. The effects of demographics/covariates (eg, gender, body weight, height, concomitant medications) on the pharmacokinetics of the 3 analytes will be evaluated. The relationship, if any, between effectiveness and drug-exposure parameters will be explored.

### 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

The primary efficacy endpoint is the change from baseline at Week 6 in MADRS total score. The secondary endpoint is the change from baseline at Week 6 in CGI-S score. For the comparison of the primary endpoint, the sample size of 160 subjects per arm will provide approximately 82% statistical power to show statistically significantly higher effect in each dose of cariprazine versus placebo. The study has statistical power of 90% to show at least one of the two cariprazine doses is statistically significantly more efficacious than placebo in the primary endpoint. These calculations assumed an effect size of 0.36 (treatment group difference relative to SD). For a given successful (statistically significant) dose versus placebo with respect to the primary endpoint, its probability in detecting an effect size of 0.36 as statistically significant versus placebo with respect to the secondary endpoint is 88%. All statistical powers presented in this section were calculated adjusting for multiple comparisons using matched parallel gatekeeping procedure with the family-wise Type I error rate being controlled at a 0.05 level (2-sided). The dropout rate is assumed to be 22% at Week 6. Within-person correlation for both primary and secondary endpoints is assumed to be 0.6, as well as correlation between the two endpoints (primary and secondary) to be 0.6. Assumptions of effect sizes, correlation coefficients, and drop-out rate are based on RGH-MD-56 study.

### 9.7.10 Computer Methods

Statistical analyses will be performed using version 9.1.3 (or newer) of SAS on a UNIX operating system.

## 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 the Sponsor. 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 the Sponsor. 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. 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 the Sponsor.

## 9.9 PROTOCOL DEVIATIONS AND VIOLATIONS

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

Protocol deviations must be reported to the Sponsor either verbally or electronically within 5 working days from the day of discovery.

A *protocol violation* is a form of protocol deviation that has a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data.

Protocol violations must be reported to the Sponsor within 24 hours, if possible. The IRB/IEC must be notified within the time period dictated by the IRB/IEC associated with this study.

# 10.0 STUDY SPONSORSHIP

## 10.1 STUDY TERMINATION

The Sponsor 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 the Sponsor. 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 the Sponsor, and will follow Sponsor procedures on publications.

# 11.0 INVESTIGATOR OBLIGATIONS

## 11.1 DOCUMENTATION

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

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

## 11.2 PERFORMANCE

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

## 11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigators listed on Form FDA 1572 (or equivalent). The investigational products must be stored in a secured place and must be locked. At study initiation, a Sponsor representative, will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor will provide a mechanism to document receipt and accountability of investigational product. All unused investigational products must be returned to the Sponsor. It is the Investigator's responsibility to ensure that patients return their investigational product.

## 11.4 CASE REPORT FORMS

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

## 11.5 RETENTION AND REVIEW OF RECORDS

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

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor 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 the Sponsor 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. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

## 11.6 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and PID number. Patients' names are not to be transmitted to the Sponsor. 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 (RGH-MD-54 Amendment #2, dated 17 Feb 2016) and with all applicable government regulations and good clinical practice guidance.

_____ _____/_____/_____
Investigator's Signature Date

_____
Investigator's Name

# 13.0 APPENDICES

## APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. 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; the Sponsor; 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 consent (e.g., "I agree to participate . . .")
- A place for the patient's signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

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

## APPENDIX II. CONTACT INFORMATION

Contact information for sponsor personnel is maintained in the ***Regulatory*** Binder.

## APPENDIX III. CONCOMITANT MEDICATIONS

| Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Analgesics | Y | Y | Nonnarcotic analgesics are allowed. Medically appropriate episodic use of narcotic analgesics for acute medical indications limited to 3 days for an episode is allowed |
| Anesthetics | | | |
| General | N | N | If procedures requiring general anesthesia are to occur/have occurred, please contact the Sponsor Medical Director to report the medical condition(s) |
| Local | Y | N | — |
| Anorexics | N | N | — |
| Antacids | Y | Y | — |
| Antiacne agents | Y | Y | Topical agents only, including topical antibiotics. Isotretinoin (Accutane) is **not** allowed |
| Antianginal agents | Y | Y | — |
| Antiarrhythmics and other cardiac agents | N | Y | Only class II agents (eg, propranolol), class IV agents (eg, diltiazem, verapamil), and digoxin are allowed. Dosage must be stable for 1 month before screening. Adenosine, parasympatholytics (atropine) and sympathomimetics (epinephrine, dopamine) are **not** allowed. |
| Antiasthma agents | Y | Y | Systemic steroids are not allowed; inhaled steroids at approved dosages are allowed |
| Antibiotics | Y | N | Linezolid (Zyvox) and Isoniazid are **not** allowed**.** Clarithromycin, telithromycin, chloramphenicol, rifampicin and rifabutin are **not** allowed. |
| Anticonvulsants | N | N | |
| Anticoagulants | N | N | Warfarin (Coumadin) is **not** allowed |
| Anticonvulsants | N | N | — |
| Antidepressants | N | N | — |
| Antidiarrheal agents | Y | N | Only loperamide (Imodium), bismuth subsalicylate (Pepto-Bismol), and kaolin preparations are allowed |

| Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Antiemetics/Antinauseants | Y | N | Antidopaminergic agents (such as metoclopramide and phenothiazines), domperidone, scopolamine, 5-HT3 receptor antagonists (eg, ondansetron) and sedating (H1) antihistamines are not allowed. Phosphoric acid preparations (Emetrol, Emecheck), bismuth subsalicylate (Pepto-Bismol), and cola syrup are allowed. |
| Antifungal agents | | | |
| Systemic | N | N | — |
| Topical | Y | Y | — |
| Antihistamines | Y | Y | Sedating (H1) antihistamines are not allowed. Only Allegra (fexofenadine), Zyrtec (cetirizine), Xyzal (levocetirizine), Claritin (loratadine), and Clarinex (desloratadine) are allowed for episodic or chronic use. Combination products containing the word nighttime or some synonym routinely include a sedating antihistamine and are not allowed (see Cough/cold Preparations for combination products). Terfenadine is not allowed. |
| Antihypertensives | N | Y | Diupres (chlorothiazide and reserpine), clonidine (Catapres), guanabenz (Wytensin), guanfacine (Tenex), guanethidine (Ismelin), methyldopa (Aldomet), direct vasodilators (hydralazine, minoxidil), sodium nitroprusside, nitroglycerin, and diazoxide are not allowed. For all others (β-blockers, calcium channel blockers, ACE inhibitors, etc) the medication and dosage should be stable for 1 month before screening |
| Anti-impotence medications | Y | Y | — |
| Anti-inflammatory drugs | Y | Y | Indomethacin and systemic corticosteroids are not allowed |
| Antimigraine | Y | N | Triptans allowed. Ergotamine or ergot derivatives are not allowed. Narcotics, antidepressants, and anticonvulsants are not allowed |
| Antineoplastics | N | N | — |

| **Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications** | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Antiobesity drugs/appetite suppressants | N | N | — |
| Antiplatelet agents | N | Y | Aspirin (maximum dosage of 325mg/day) and clopidogrel (Plavix) are allowed |
| Antipsoriatic treatments | Y | Y | Acitretin (Soriatane) is not allowed |
| Antiparkinsonian drugs | N | N | Dopamine-releasing drugs, dopamine agonists, amantadine, levodopa, and monoamine oxidase–B inhibitors are not allowed. For extrapyramidal symptoms, diphenhydramine (50 mg/day) and benztropine (up to 4 mg/day or up to 2 mg/day, if given parenterally) are allowed (see Section 9.4.8). Propranolol may also be used for treatment of akathisia |
| Antipsychotics | N | N | — |
| Antismoking medications | N | N | Varenicline (Chantix) is not allowed.<br>Nicotine replacement therapies are allowed |
| Antiviral agents | Y | Y | The following agents are allowed: acyclovir, famciclovir, valacyclovir, penciclovir, docosanol, trifluridine, and vidarabine. Amantadine and rimantadine are not allowed. Interferons are not allowed |
| Anxiolytics | Y | N | Lorazepam or its equivalent benzodiazepine may be prescribed ***as rescue medication*** for agitation, restlessness**,** or hostility. ***Episodic use of lorazepam up to 2 mg/day (or equivalent) and for up to 3 consecutive days at a time is allowed for agitation, restlessness, and hostility***.<br>Lorazepam or other benzodiazepines may not be used in the 8 hours before any behavioral assessments. Diazepam may not be used in the 24 hours before any behavioral assessments. |

| Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Cough/cold preparations | Y | N | Cough preparations containing dextromethorphan or narcotics are not allowed. Decongestant preparations containing pseudoephedrine or phenylpropanolamine are not allowed. Phenylephrine nasal sprays are allowed for brief medically appropriate use for up to 5 days (also see Antihistamines) |
| Diuretics | N | Y | Medication and dosage must be stable for 1 month before screening |
| Drugs used to treat constipation | Y | N* | *Bulk laxatives, emollient laxatives are allowed<br>Episodic use of stimulant laxatives containing senna, bisacodyl, and anthraquinone derivatives is allowed. Osmotic laxatives such as oral magnesium hydroxide (milk of magnesia), oral sodium citrate and sodium biphosphate are allowed. Hyperosmotic laxatives such as sorbitol, lactulose, and polyethylene glycol are not allowed |
| Gastrointestinal:<br>H2-blockers/<br>proton pump inhibitors/<br>prokinetic agents | Y | Y | Cimetidine (Tagamet) is not allowed.<br>Metoclopramide and cisapride are not allowed |
| Hormones | N | Y | Thyroid hormone replacement is allowed. Therapeutic use in psychiatric disorders (eg, T3 augmentation therapy) is not allowed. Dosage of thyroid medication must be stable for 1 month before screening.<br>Systemic contraceptives (oral contraceptives of estrogen and progestin combinations, contraceptive implants such as Depo-Provera and Norplant, or transdermally delivered contraceptives such as Ortho Evra) are allowed but must be stable for 1 month before screening |
| Hormone suppressants | N | Y | Only Proscar (finasteride) and Avodart (dutasteride) are allowed. Dosage must be stable for 3 months before screening |

| Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Hypoglycemic agents | N | Y | Oral hypoglycemic agents are allowed, except the strong CYP3A inducers pioglitazone and troglitazone are not allowed. Chronic use of insulin is allowed. Consult Study Physician for episodic use of insulin. Dosage must be stable for 1 month before screening |
| Hypolipidemics | N | Y | Statins (lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin), fibrates (gemfibrozil, fenofibrate), and ezetimibe are allowed. Dosage must be stable for 1 month before screening. The Study Physician must be consulted for combined use of hypolipidemic agents. Bile sequestrants are not allowed. Niacin and niacinamide may be allowed if patient has taken these agents chronically ≥ 12 months |
| Mood stabilizers | N | N | — |
| Muscle relaxants | N | N | — |
| Psychotropic drugs not otherwise specified (including herbal products) | N | N | No drugs with psychomotor effects or with anxiolytic, stimulant, antipsychotic, or sedative properties are allowed. Herbal/dietary products and supplements with potential psychoactive actions including St. John's wort, kava kava, SAMe, valerian root, DHEA, tyrosine, and 5-HTP are not allowed |
| Sedatives/hypnotics | Y | Y | Zolpidem extended release (maximum of 12.5 mg/day), zolpidem (maximum of 10 mg/day), zaleplon (maximum of 20 mg/day), chloral hydrate (maximum of 1000 mg/day), and eszopiclone (maximum of 3 mg/day) are allowed for sleep. Sedatives/hypnotics may not be used in the 8 hours before any behavioral assessments |
| Steroids | | | |
| Systemic | N | N | — |
| Topical | Y | Y | — |
| Inhalant | Y | Y | — |
| Intra-articular | Y | NA | — |

| **Medications Allowed (Y) and Medications Not Allowed (N) as Concomitant Medications** | | | |
|---|---|---|---|
| ***Drug Class*** | ***Frequency of Use*** | | ***Restrictions*** |
| | ***Episodic (PRN)*** | ***Chronic*** | |
| Stimulants | N | N | Oral or transdermal methylphenidate, amphetamine products or prodrugs, pseudoephedrine, modafinil (Provigil), and armodafinil (Nuvigil) are not allowed |
| Vaccines | Y | NA | — |

N = not allowed; NA = not applicable; PRN = as needed; Y = yes, allowed

## APPENDIX IV. MONTGOMERY-ÅSBERG DEPRESSION RATING SCALE

### Montgomery Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

*Item List*

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

*1. Apparent Sadness*

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.

1

2 Looks dispirited but does brighten up without difficulty.

3

4 Appears sad and unhappy most of the time.

5

6 Looks miserable all the time. Extremely despondent.

*2. Reported sadness*

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.

1

2 Sad or low but brightens up without difficulty.

3

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5

6 Continuous or unvarying sadness, misery or despondency.

*3. Inner tension*

Representing feeling of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.

1

2 Occasional feelings of edginess and ill-defined discomfort.

3

4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.

5

6 Unrelenting dread or anguish. Overwhelming panic.

*4. Reduced sleep*

Representing the experience of reduced duration or depth of sleep compared with the subject's own normal pattern when well.

0 Sleeps as usual.
1

2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.

3

4 Sleep reduced or broken by at least two hours.

5

6 Less than two or three hours sleep.

*5. Reduced appetite*

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.

1

2 Slightly reduced appetite.

3

4 No appetite. Food is tasteless.

5

6 Needs persuasion to eat at all.

*6. Concentration difficulties*

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.

1

2 Occasional difficulties in collecting one's thoughts.

3

4 Difficulties in concentration and sustaining thought which reduces ability to read or hold a conversation.

5

6 Unable to read or converse without great difficulty.

*7. Lassitude*

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.

1

2 Difficulties in starting activities.

3

4 Difficulties in starting simple routine activities which are carried out with effort.

5

6 Complete lassitude. Unable to do anything without help.

*8. Inability to feel*

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.

1

2 Reduced ability to enjoy usual interests.

3

4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

5

6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

*9. Pessimistic thoughts*

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.

1

2 Fluctuating ideas of failure, self-reproach or self-depreciation.

3

4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.

5

6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

*10. Suicidal thoughts*

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

3

4 Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.

5

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

[redacted]

[redacted]

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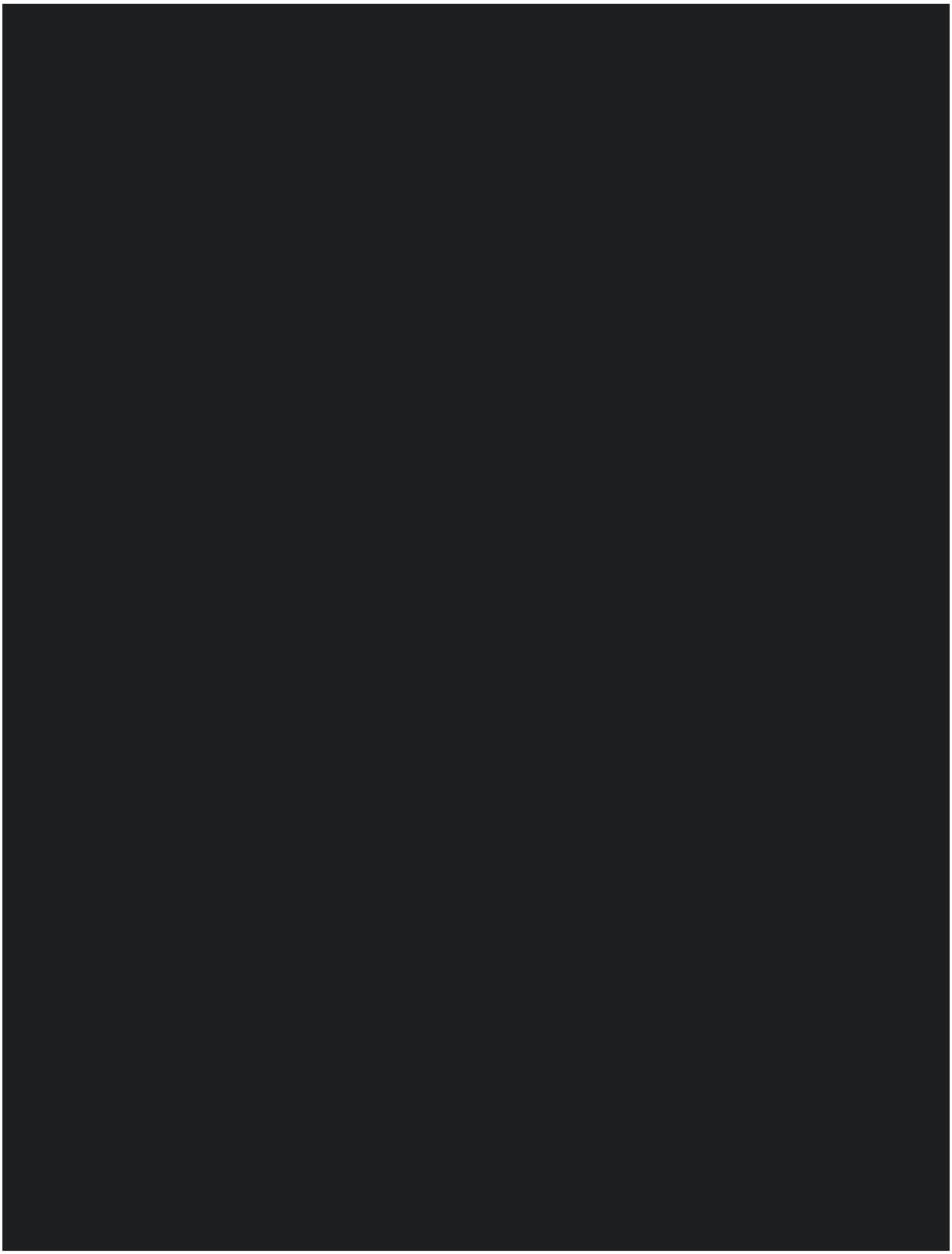
[redacted]



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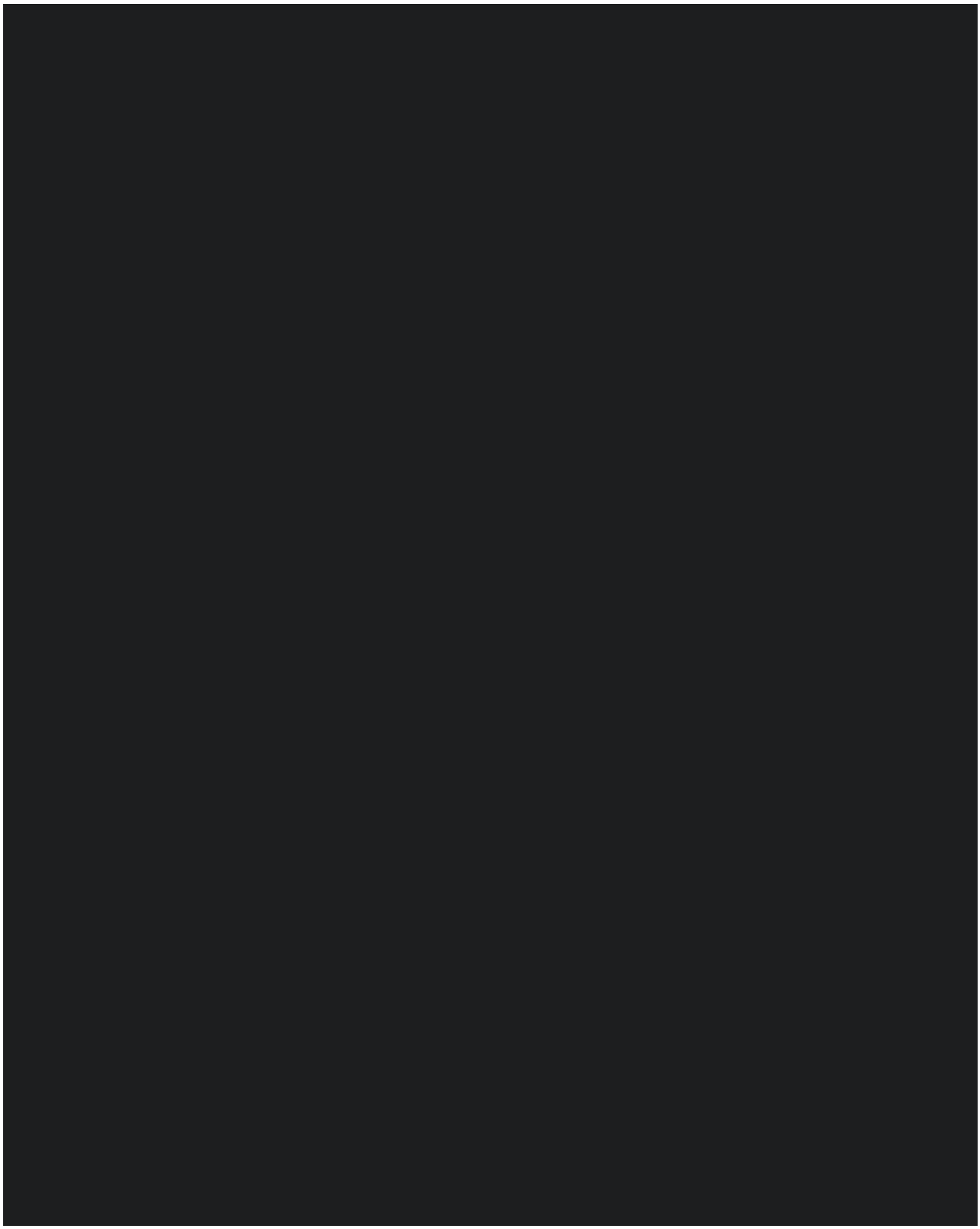


## APPENDIX VII. CLINICAL GLOBAL IMPRESSIONS–SEVERITY

**SEVERITY OF ILLNESS**

Considering your total clinical experience with this population, how mentally ill is the patient at this time?

Check one:

1 = Normal, not at all ill

2 = Borderline ill

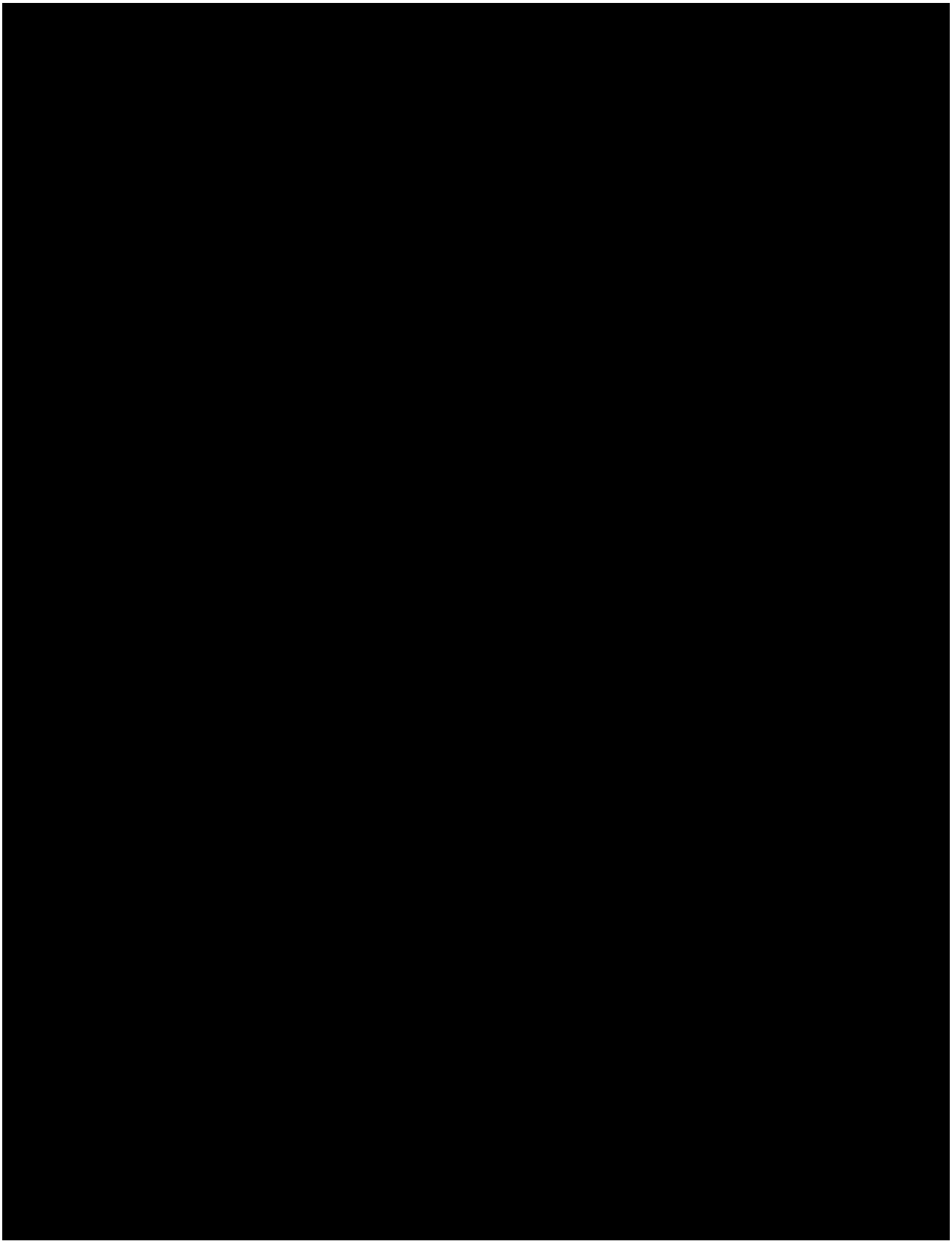
3 = Mildly ill

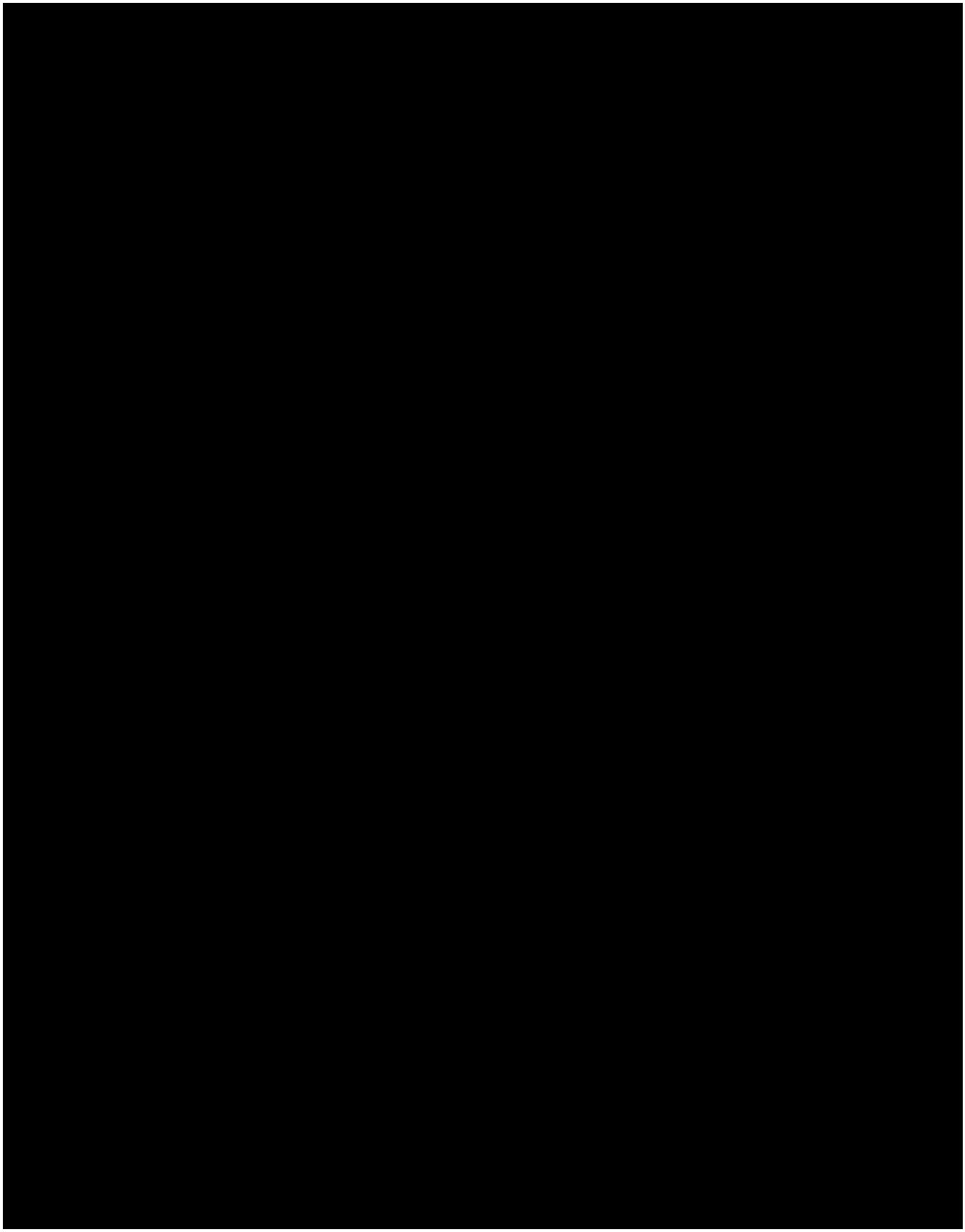
4 = Moderately ill

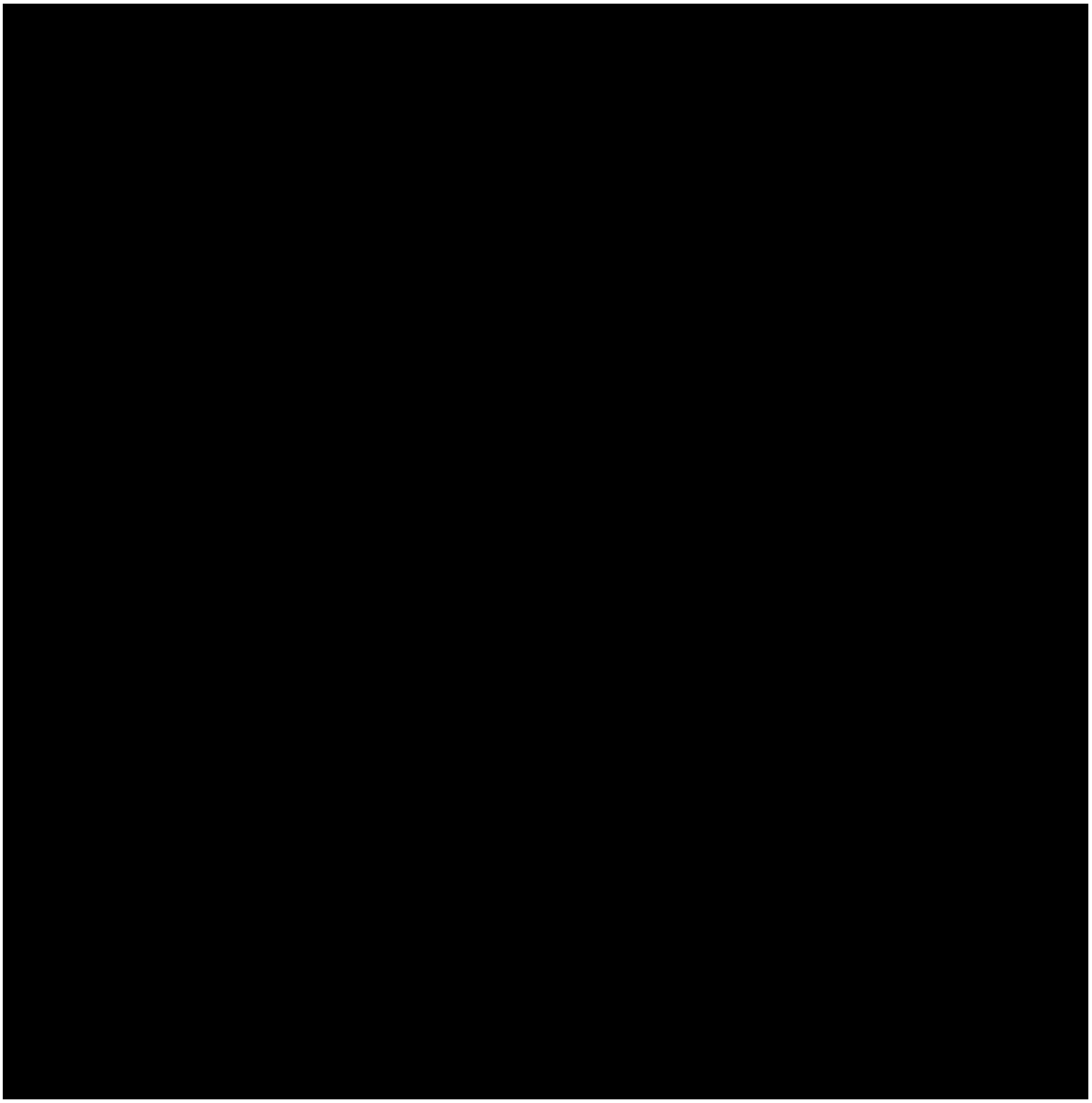
5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients







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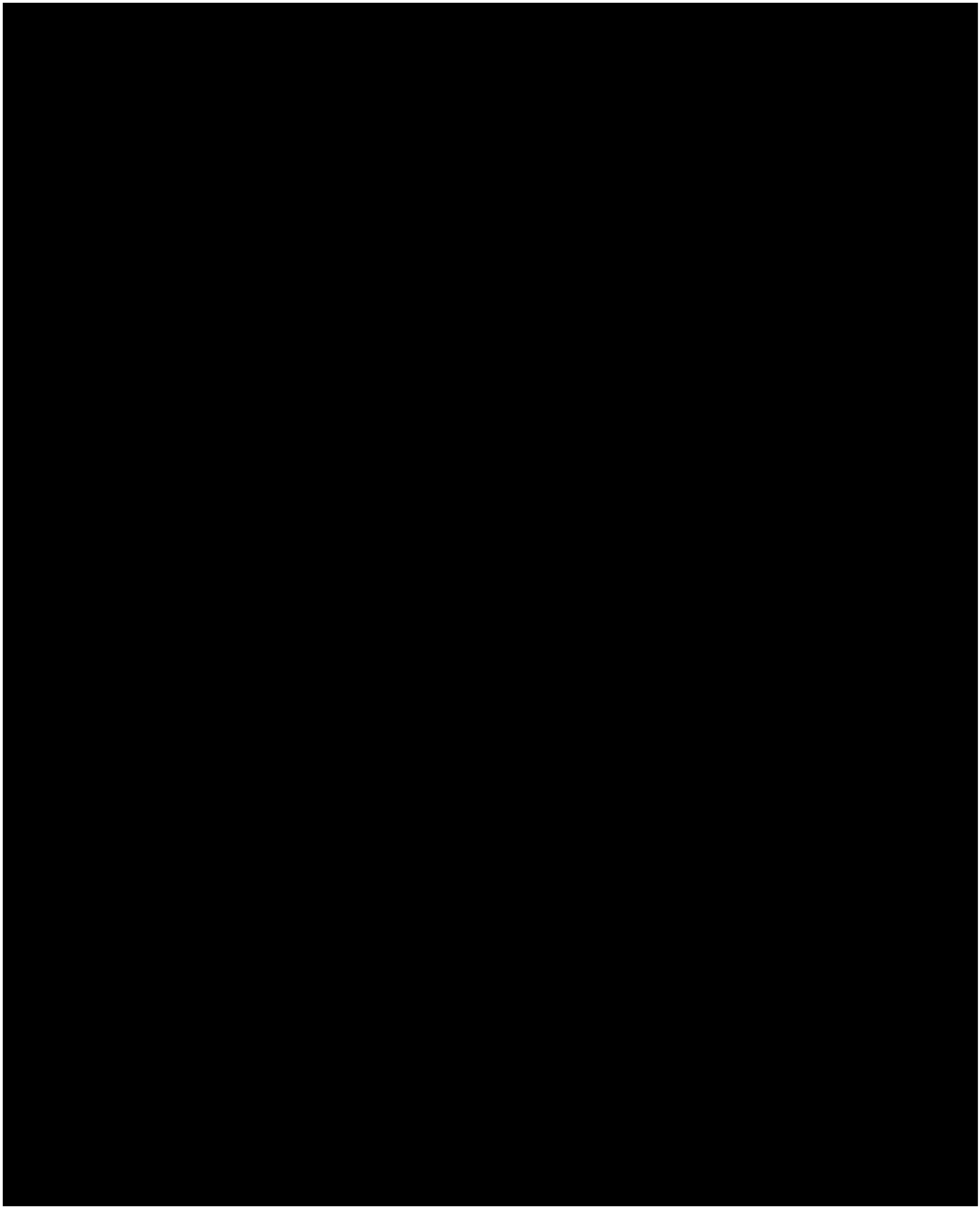

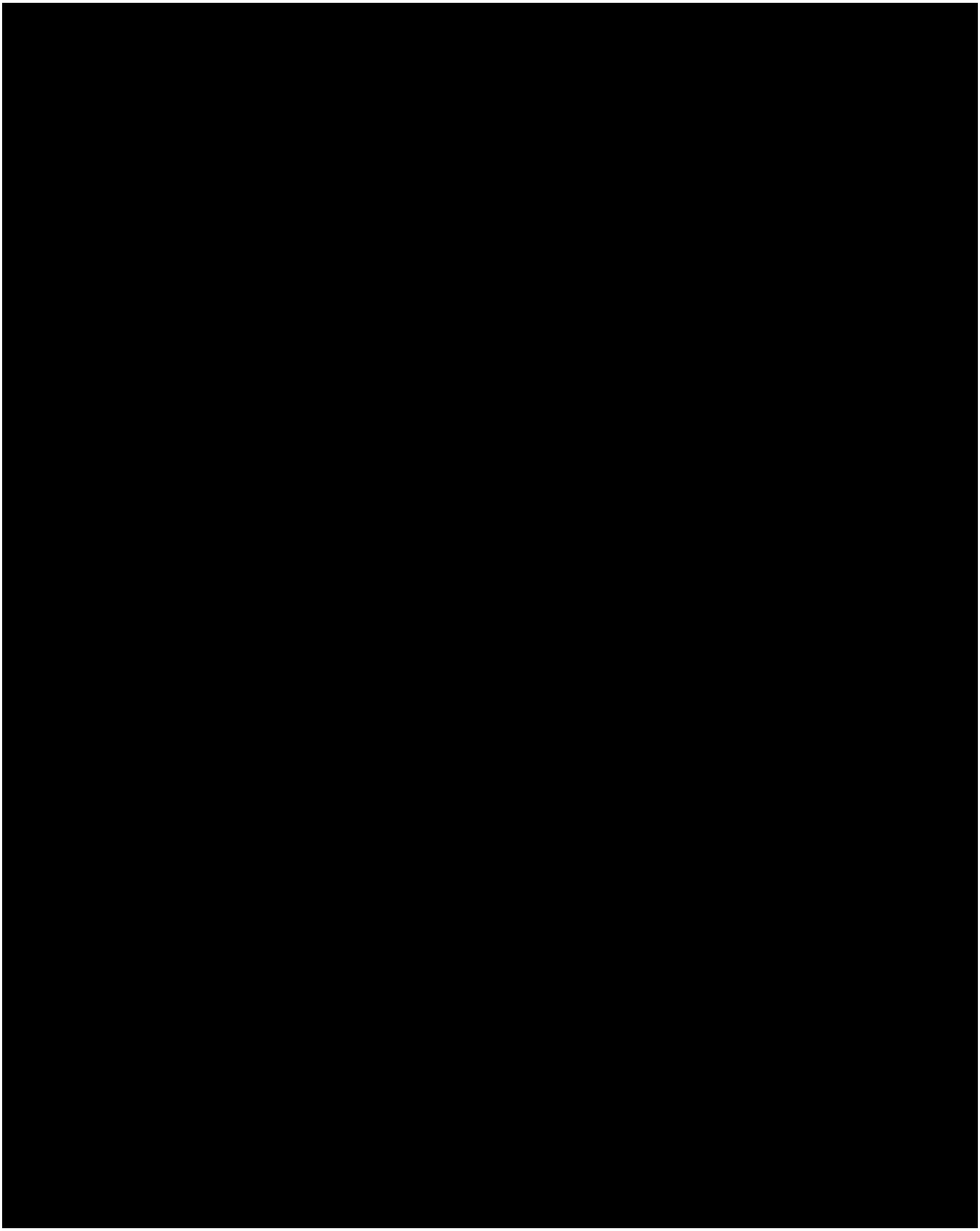

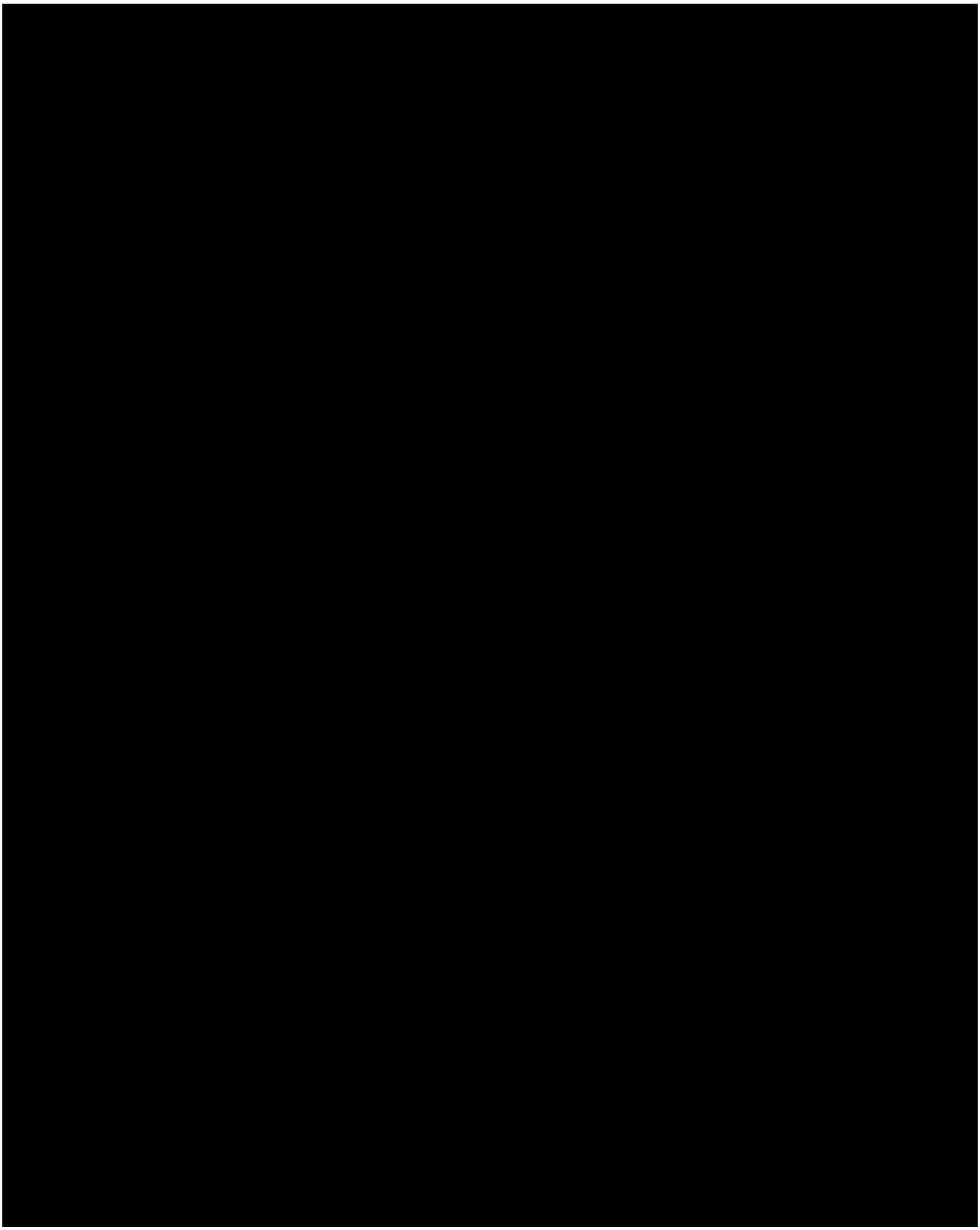

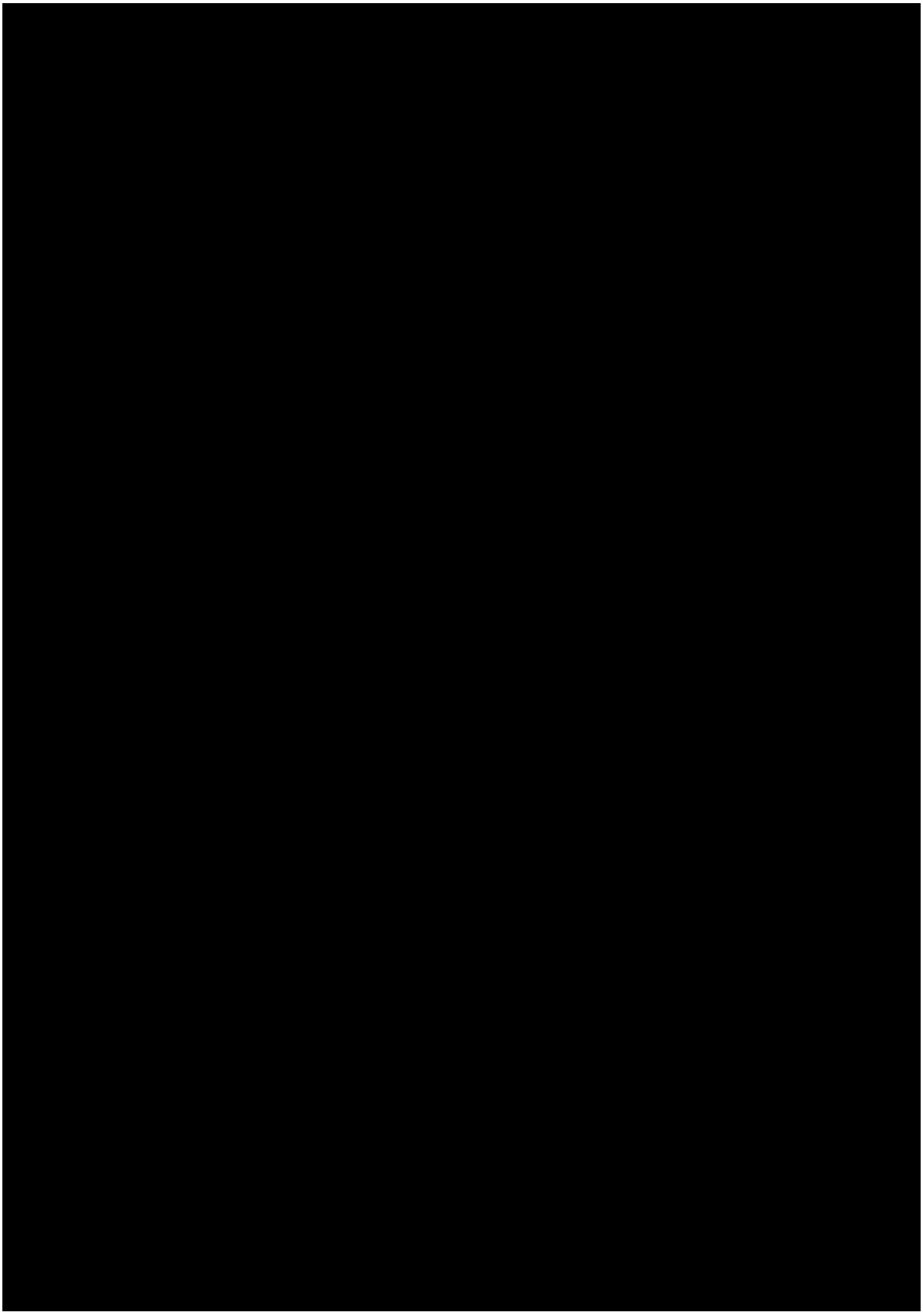

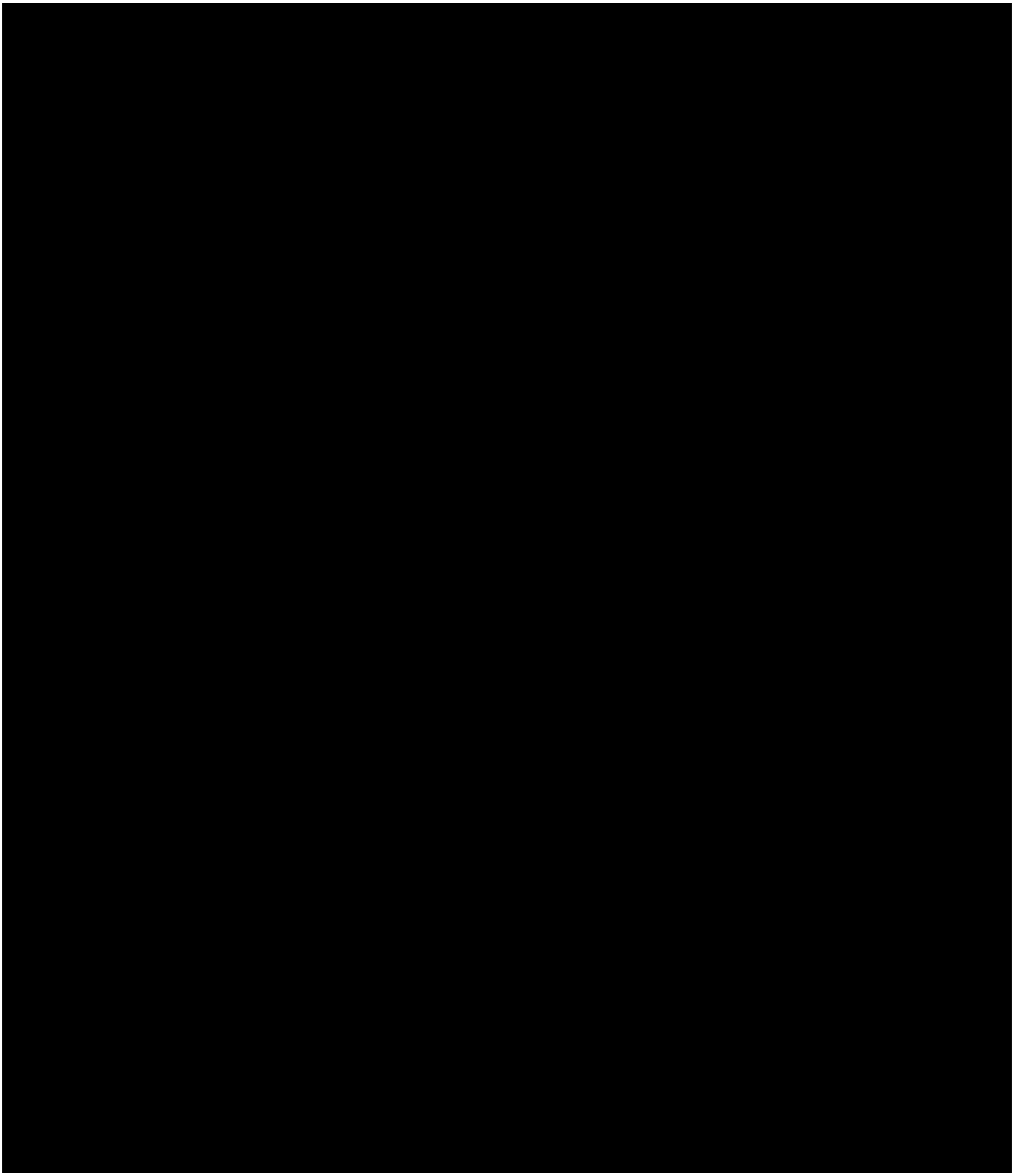

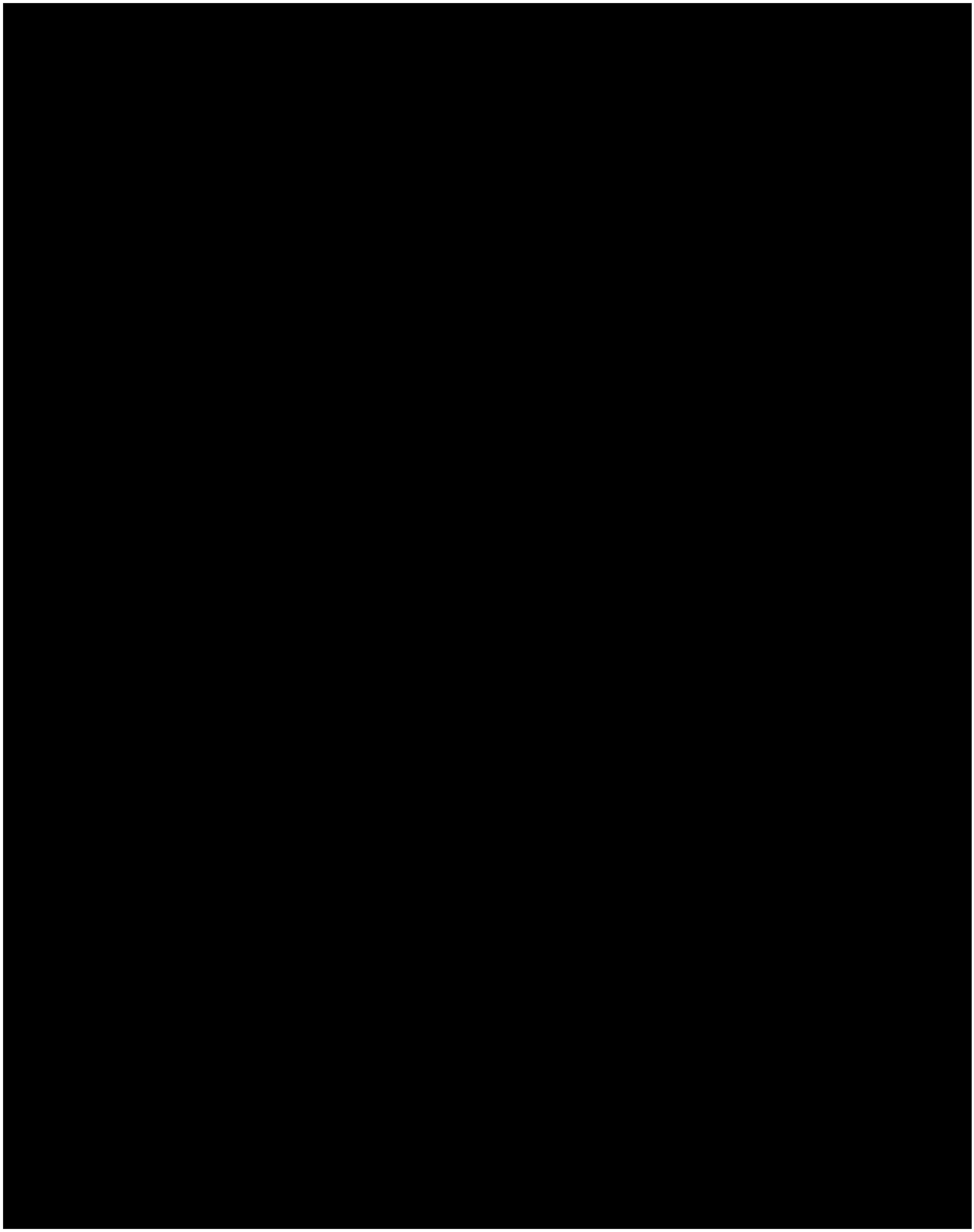

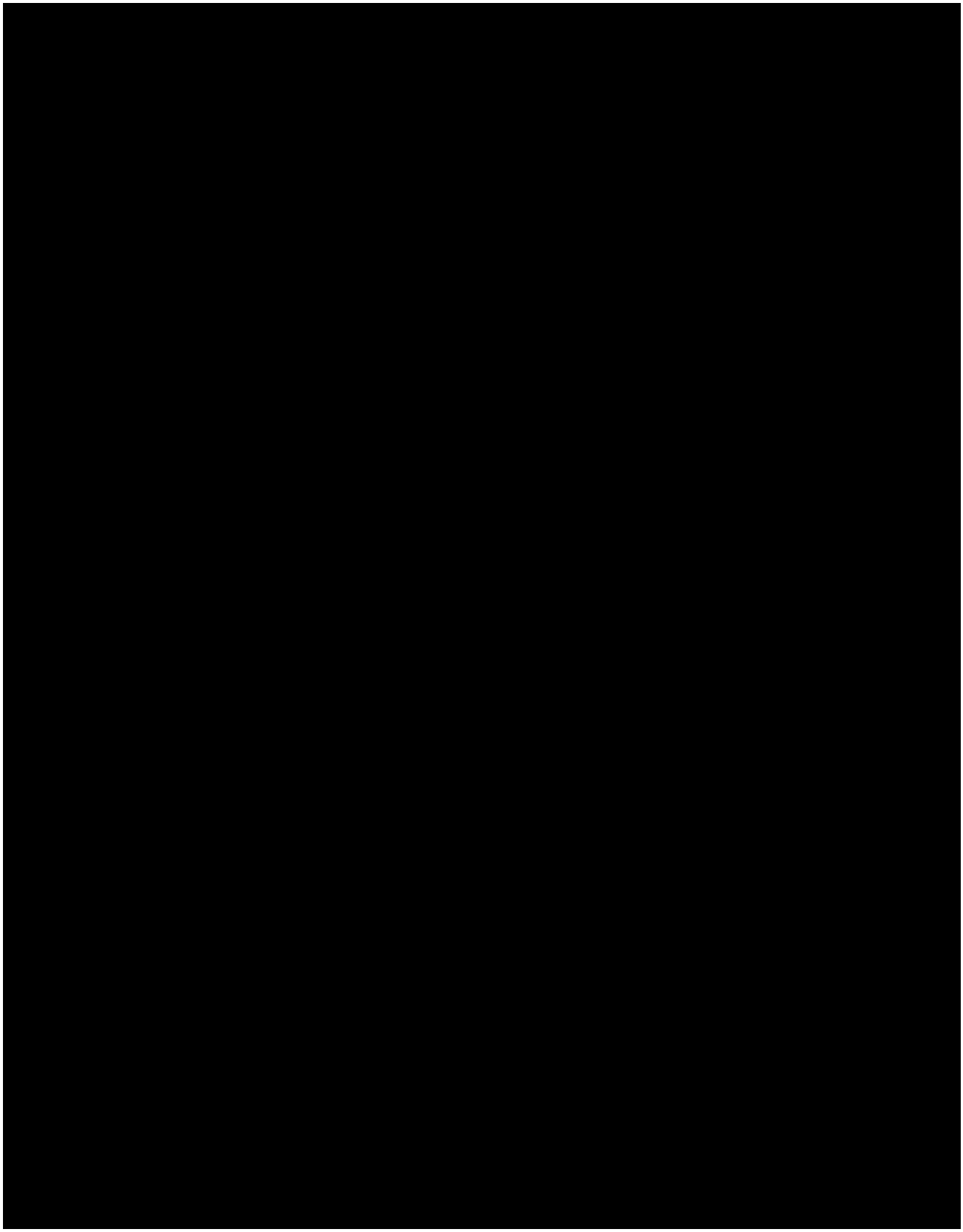

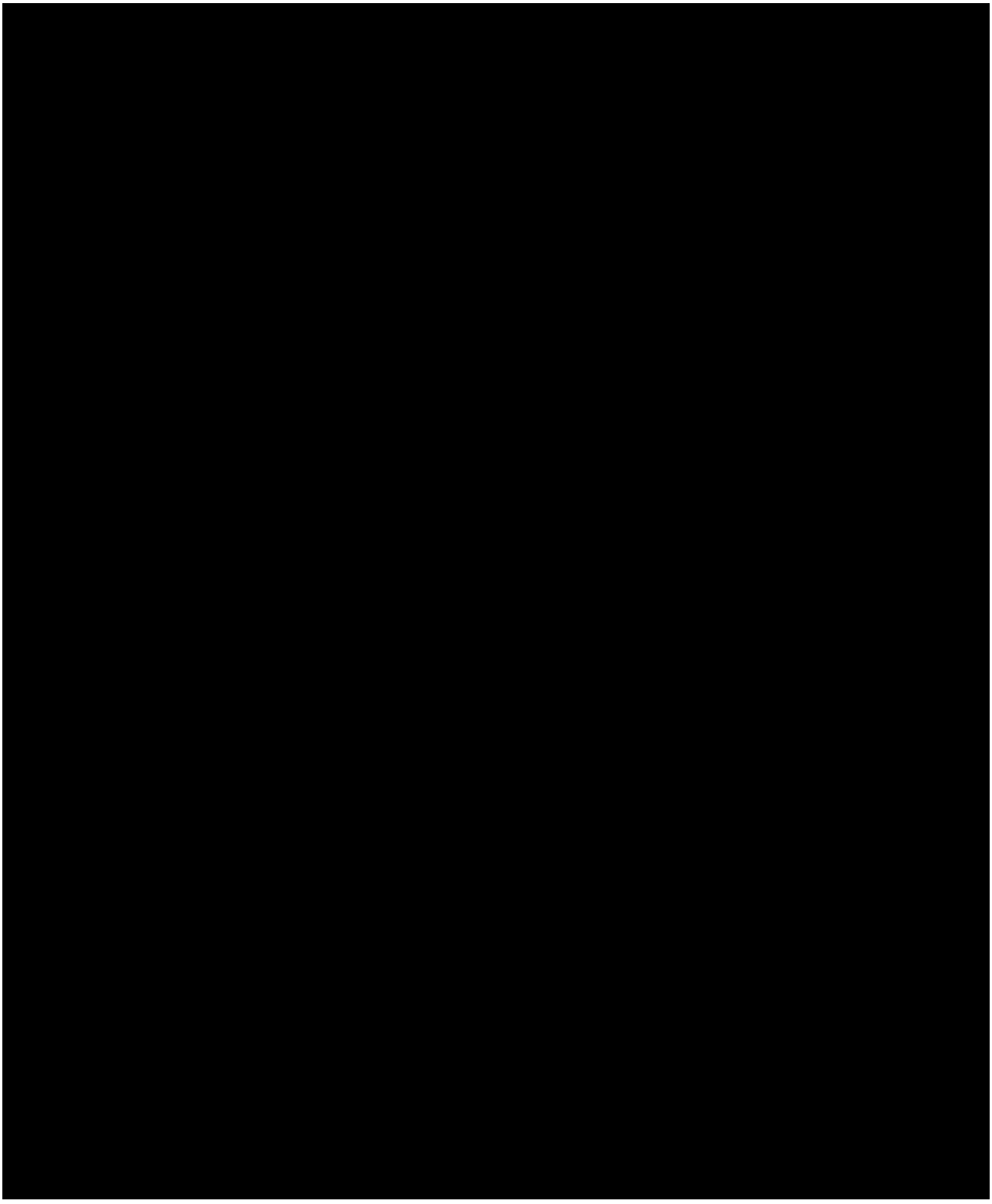

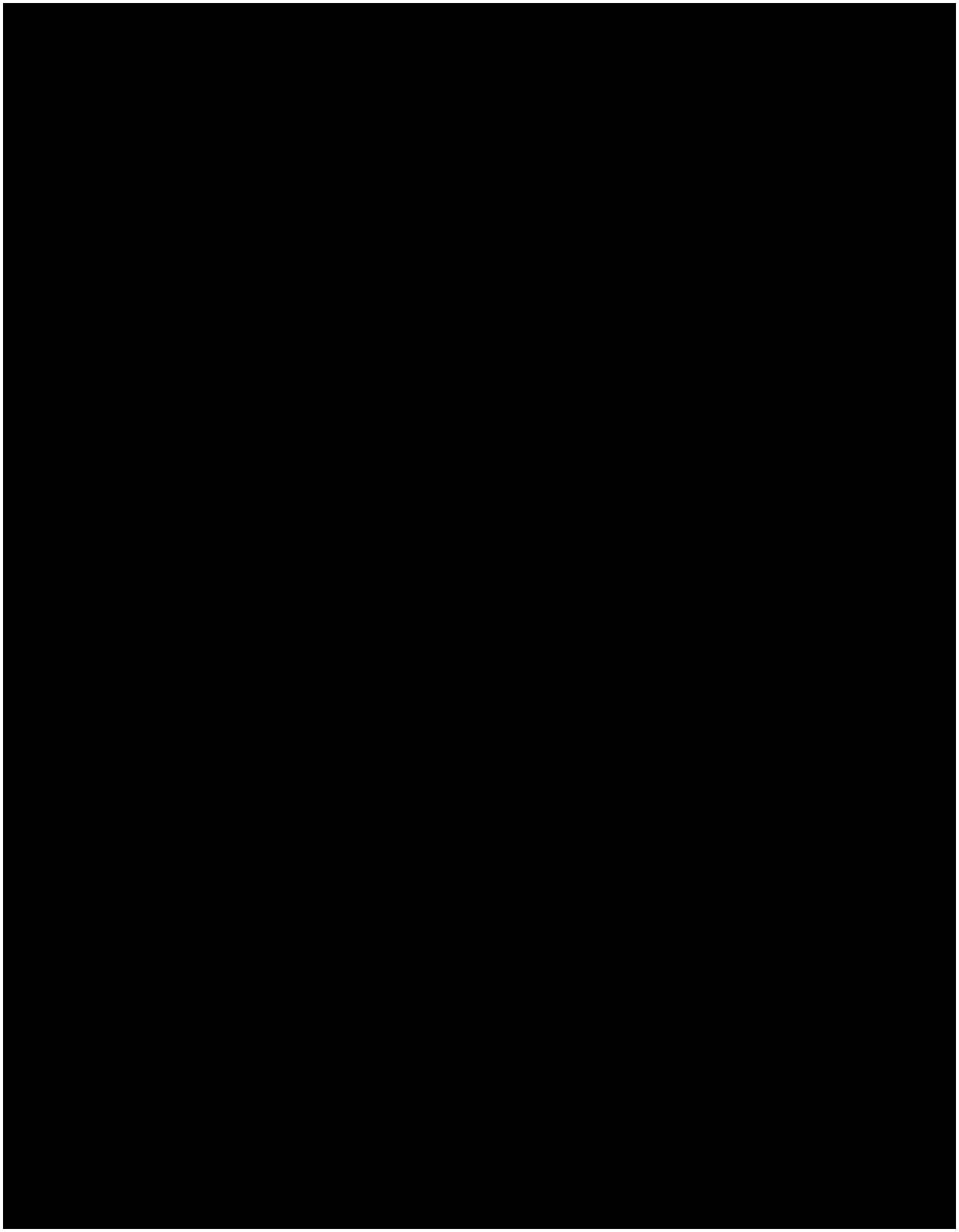

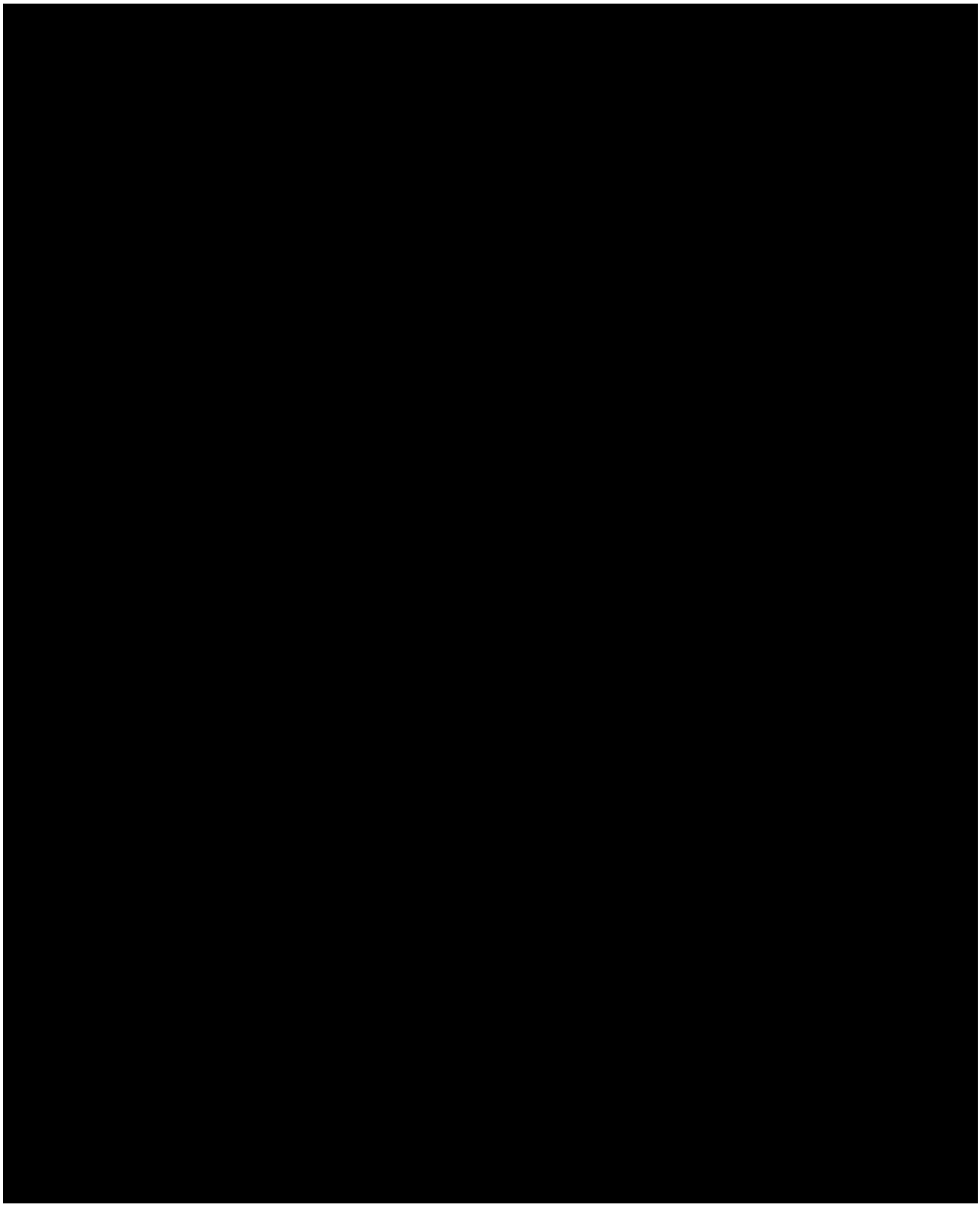

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# SUMMARY OF CHANGES TO PROTOCOL

# RGH-MD-54, A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER, FIXED-DOSE CLINICAL TRIAL EVALUATING THE EFFICACY, SAFETY AND TOLERABILITY OF CARIPRAZINE IN PATIENTS WITH BIPOLAR I DEPRESSION

**Amendment #2, 17 Feb 2016**

**IND #77, 726**

**Original Protocol Date:** 12 Nov 2015

**Protocol Amendment #1:** 02 Feb 2016

## 1.0 INTRODUCTION

Amendment #2 specifies the following change to RGH-MD-54 Protocol Amendment #1, dated 02 Feb 2016:

[redacted]

The page and protocol section numbers in the headings of this amendment are those of the previous version of the protocol.

## 2.0 GLOBAL CHANGES

The following changes have been made globally to the protocol:

- None

## 3.0 SECTIONS DELETED

The following sections have been removed from the protocol:

- None

## 4.0 SECTIONS ADDED

- None

## 5.0 REVISIONS

[redacted]