Clinical Study Protocol REL-1017-202

A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study to Assess the Safety, Tolerability, PK Profile, and Symptom Response of a 7-Day Dosing with REL-1017 25 mg QD and 50 mg QD as Adjunctive Therapy in the Treatment of Patients Diagnosed with Major Depressive Disorder

Protocol Amendment 5, Version: 6.0, 07-Mar-2019

Short Title	Safety, Tolerability, PK Profile, and Symptom Response of a 7-Day Dosing with 25 mg QD and 50 mg QD of REL-1017 in MDD
Protocol Number	REL-1017-202
Syneos Health Project Number	1008945
Phase	Phase 2a
Sponsor	Sergio Traversa Chief Executive Officer Relmada Therapeutics 880 Third Avenue, 12th Floor New York, NY 10022 Work: 212-547-9591 st@relmada.com
Test Product	REL-1017 (d-Methadone) 25 mg and 50 mg
Dose/Route of Administration	REL-1017 25 mg or 50 mg powder dissolved in 100 mL Ocean Spray® Diet Cranberry Juice administered orally
Medical Monitor	Morgan Kearney, MD Syneos Health, Inc. 3201 Beechleaf Court, Suite 600 Raleigh, NC, USA 27604 24-Hr Contact Phone Numbers: Office: 919-257-6801 Mobile: 919-397-0174

Protocol Date	13-Dec-2016 (Version 1.0)
Amendment 1	19-Jan-2017 (Version 2.1)
Amendment 2	29-Jan-2018 (Version: 3.0)
Amendment 3	05-Apr-2018 (Version 4.0)
Amendment 4	19-Nov-2018 (Version 5.0)
Amendment 5	07-Mar-2019 (Version 6.0)

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PROTOCOL SYNOPSIS

Title of Study:	Protocol REL-1017-202: A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study to Assess the Safety, Tolerability, PK Profile, and Symptom Response of a 7-Day Dosing with REL-1017 25 mg QD and 50 mg QD as Adjunctive Therapy in the Treatment of Patients Diagnosed with Major Depressive Disorder
Sponsor:	Relmada Therapeutics, Inc. (Relmada)
Phase of Development:	Phase 2a
Clinical Study Objectives:	Primary Objective: • To assess the safety and tolerability of 25 mg and 50 mg of REL-1017 (d-methadone) compared to Placebo as adjunctive treatment in patients with major depressive disorder (MDD) Secondary Objectives: • To characterize the pharmacokinetic (PK) profile of 25 mg and 50 mg of REL-1017 (d-methadone) as adjunctive treatment in patients with MDD • To explore the efficacy of 25 mg and 50 mg of REL-1017 (d-methadone) as adjunctive treatment in patients with MDD
Endpoints:	Safety and Tolerability: The following assessments will be conducted to measure safety and tolerability throughout the study: • Adverse Events (AEs) • Vital Signs • Weight • Physical Examination • Clinical Laboratory Parameters (chemistry, hematology, and urinalysis) • Electrocardiogram (ECG) parameters • Columbia-Suicide Severity Rating Scale (C-SSRS) • Clinician Administered Dissociative States Scale (CADSS) • Clinical Opiate Withdrawal Scale (COWS) • 4-Item Positive Symptom Rating Scale (PSRS)

Endpoints (Continued):	Pharmacokinetics: The PK profile of REL-1017 25 mg and 50 mg will be evaluated on Day 1 through Day 7, Day 8, Day 9, and Day 14 where the data allow: • Maximum observed plasma concentration (C_{max}) • Time to maximum observed plasma concentration (T_{max}) • Area under the plasma concentration-time curve from time zero until the dosing interval of 24 hours (AUC_{tau}) • Area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-}last}$) on Day 7 • Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$) • Apparent termination elimination rate constant (λ_z) • Apparent terminal elimination half-life ($t_{½}$) • Attainment of steady state • Steady state clearance (C_{SS}/F) • Volume of distribution at steady state (V_{SS}/F) • Accumulation ratios based on minimum observed plasma concentration (C_{min}), C_{max}, and AUC_{tau} Efficacy: The following assessments will be conducted to evaluate efficacy: • Change from Baseline (Day 1) to the End of the Dosing Period (EDP, Day 7) on the Montgomery-Asberg Depression Rating Scale (MADRS) • Change from Baseline (Day 1) to EDP (Day 7) on the Symptoms of Depression Questionnaire (SDQ) • Change from Baseline (Day 1) to EDP (Day 7) on the Clinical Global Impressions of Severity (CGI-S) scale. • Change from Baseline (Day 2) to EDP (Day 7) on The Clinical Global Impressions of Improvement (CGI-I) scale will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14. The timing of each assessment is detailed in the Time and Events Schedule (Table 1).
Study Design:	A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study to Assess the Safety, Tolerability, PK Profile, and Symptom Response of a 7-Day Dosing with REL-1017 25 mg QD and 50 mg QD as Adjunctive Therapy in the Treatment of Patients Diagnosed with MDD
Investigational Product:	REL-1017 (d-Methadone) 25 mg, 50 mg, 75 mg and 100 mg Powder Formulation

Study Drug, Dose Schedule, and Mode of Administration:	REL-1017 consists of d-methadone hydrochloride (HCl) in a powder formulation. The following doses will be used in the study: • REL-1017 75 mg QD Day 1, 25 mg REL-1017 QD Day 2-7 • REL-1017 100 mg QD Day 1, 50 mg REL-1017 QD Day 2-7 • Placebo (Ocean Spray® Diet Cranberry Juice) REL-1017 will be provided as a powder and prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing. Patients will continue to take the same, stabilized antidepressant medication that they were taking at Screening throughout the course of the study, and the supply of medication during the confined study period will be arranged and assured by the Investigator. An unblinded pharmacist will assign study drug to patients according to randomized treatment codes provided by the Interactive Web Response System (IWRS). The randomization code used in the IWRS will be prepared by a statistician who is not working as a statistician on the study in any other capacity. The study drug solution or Placebo will be prepared within 3 hours of administration in blinded containers, and then will be dispensed to blinded study staff for administration to the patients. After drinking the 100 mL of study drug, 25 mL of non-carbonated water will be added to the study drug container and gently swirled. The patient will drink this rinse volume followed by 125 mL of non-carbonated water to drink immediately thereafter. All dosing must be completed within 5 minutes. Dosing will take place once daily in the morning after an overnight fast of at least 8 hours.
Study Population and Duration of Participation	Adult patients with MDD who are diagnosed with a current major depressive episode (MDE) and who have experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration (as defined by the Antidepressant Treatment Response Questionnaire [ATRQ]) of an antidepressant medication for the current episode will be randomized to study drug in a 1:1:1 ratio. Approximately 120 patients will be screened, and approximately 60 qualified patients will be randomized to study drug in a 1:1:1 ratio (approximately 20 patients per arm). Each patient will participate for up to 51 days (30 days Screening, 7 days treatment, and 14 days of observation and follow-up).
Sample Size Considerations:	As this is a Phase 2a study, formal sample size calculations are not applicable. The study will not be powered for signal detection.

Inclusion Criteria:	To enroll in the clinical study, patients must meet the following inclusion criteria: 1. Males and females between 18 and 65 years of age, inclusive. 2. Diagnosed with recurrent MDD as defined by the Diagnostic and Statistical Manual, Fifth Edition (DSM-5), and confirmed by the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI). 3. Diagnosed with a current MDE lasting 8 weeks to 36 months as defined by the DSM-5 and confirmed by the MINI. 4. Treated with an adequate dosage of a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or bupropion during the current MDE for at least 8 weeks prior to Screening with the same, adequate dosage for the last 4 weeks. Minimum adequate doses are defined in the ATRQ. The maximum dose allowed for paroxetine is 40 mg QD, for fluoxetine is 60 mg QD, and for sertraline is 200 mg QD. 5. Have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication in the current episode, defined as <50% improvement with an antidepressant medication at doses listed on the SAFER Interview (Criteria: **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological). 6. Hamilton Depression Rating Scale-17 (HAM-D-17) ≥19 at Screening and Check-in (Day -1). 7. Body Mass Index (BMI) between 18.0 and 35.0 kg/m^2, inclusive, and a minimum weight of 50.0 kg. 8. Per the Investigator's judgment, able to meet all study requirements, including the confined/inpatient portion of the study, adherence with both approved antidepressant therapy and study drug regimen, and completion of all assessments and all scheduled visits. 9. Male and female patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in the protocol, from Screening and for at least 2 months after the last study drug administration. Female patients must have a negative pregnancy test, and must not be lactating. 10. Must be able to read, speak, and understand English and must provide written informed consent prior to the initiation of any protocol-specific procedures.

Exclusion Criteria:	1. History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator would jeopardize the safety of the patient or the validity of the study results, including torsades de pointes, any bradyarrhythmias, or uncompensated heart failure. 2. Chronic use of prescribed opioids (i.e., >120 days in a 6-month period) up to 6 months prior to Screening or any recreational use of opioids. 3. Evidence of clinically significant hepatic or renal impairment, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN), bilirubin >1 x ULN, or endocrine laboratory values (including clinically significant thyroid parameters, i.e., thyroid stimulating hormone [TSH], triiodothyronine [T3], and thyroxine [T4]). 4. History or family history of sudden unexplained death or long QT syndrome (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle). 5. An average QTcF ≥450 msec or an average QRS interval ≥120 msec from the 12-lead ECGs performed at Screening. 6. History of clinically diagnosed hypotension requiring treatment. 7. History or presence of any condition in which an opioid is contraindicated (e.g., significant respiratory depression, acute or severe bronchial asthma or hypercarbia, bronchitis, or has/is suspected of having paralytic ileus). 8. No more than 3 prescribed doses of an opioid within the 6 months prior to Screening and no use at all within the last month. 9. Use of an antipsychotic, anticonvulsant, or mood stabilizer, regardless of indication, within the 3 months prior to Screening. 10. History of allergy or hypersensitivity to methadone or related drugs (e.g., opioids). 11. Positive test for hepatitis B or human immunodeficiency virus (HIV). Patients with a positive hepatitis C test may be considered for inclusion with approval from the Medical Monitor. 12. Any current and primary psychiatric disorder, as defined as a condition that is the primary focus of distress and/or treatment, other than MDD. 13. Any lifetime history of bipolar I or II disorder, any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive compulsive disorder, eating disorder, intellectual disability, or pervasive developmental disorder.

Exclusion Criteria (Continued):	14. History in the past 12 months of a primary diagnosis of anxiety disorder or panic disorder not related to the current MDE. 15. Current diagnosis of alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. Patients with the following diagnoses within the past 12 months, however, may be included at the Investigator's discretion: mild alcohol use disorder, mild cannabis use disorder, and any severity tobacco use disorder. 16. A confirmed positive result on the urine drug/alcohol screen at Screening or Check-in. If the urine drug/alcohol screen is positive at Screening, retesting or rescreening may be scheduled with prior approval from the Medical Monitor. 17. Patients who, in the Investigator's judgment, are at significant risk for suicide. A patient with a C-SSRS ideation score of 4 or 5 within the last 6 months or any suicide attempt within the past year must be excluded, as should a patient with an ideation score of 4 or 5 or any suicide attempt at the Check-in or Baseline Visit. 18. Patients with a 20% improvement between Screening and Check-in (Day -1) on the HAM-D-17. 19. Patients who did not safely discontinue prohibited medications. 20. Patients receiving new onset psychotherapy (individual, group, marriage, or family therapy) within 2 months prior to Screening or plans to start at any time during participation in the study. 21. Patients who have received electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or vagus nerve stimulation (VNS) or who have participated in a ketamine study within the last 6 months. 22. Patients with any clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, chronic pain, or gastrointestinal disorder. Medical conditions that are minor or well-controlled may be permitted if they will not increase the safety risk to the patient or compromise interpretation of the safety or efficacy endpoints. 23. Patients taking fluvoxamine or St. John's Wort. 24. Patients who have participated in a clinical study with an investigational medication in the past 6 months, or who have participated in more than 4 clinical studies with investigational medications in the past 2 years.

Procedures:	Screening: After the Informed Consent Form (ICF) is signed, a Screening number will be assigned to the patient, and an outpatient Screening Visit will be conducted during which the patient will undergo an interview and medical assessments to determine eligibility for study participation. Patients who meet all the screening entry criteria will be scheduled for admission to the clinical research unit (CRU). The patient's eligibility assessment will be reviewed by an external medical team based on key protocol inclusion and exclusion criteria to promote appropriate patient enrollment and data quality. Sites should submit specific Screening information (detailed in the in the Massachusetts General Hospital Clinical Trials Network and Institute [MGH CTNI] manual) within 72 hours after the Screening Visit for review by the external medical team prior to proceeding to Check-in. Subjects who are deemed eligible by the Principal Investigator and confirmed by the Medical Monitor will undergo the SAFER Interview by clinicians at the MGH CTNI. To ensure that appropriate subjects are entered into the study, a remote interview will be conducted by MGH CTNI raters. The assessments administered will be the SAFER Interview, which will include the HAM-D17, and the MGH ATRQ. The interview will be performed remotely by the MGH CTNI rater, and the subject will be contacted at his or her home or other off-site location after the Screening Visit, during which call the above assessments will be performed. Sites will be notified of the results within 24 hours of the interview. Only subjects whose eligibility will be confirmed by the SAFER Interview will be allowed to proceed in the study. Check-in (Day -1): Inpatient admission may occur up to 30 days after the Screening Visit as soon as it is determined that patients meet all screening criteria. Upon Check-in, patients will undergo further medical and psychiatric Screening according to the Time and Events Schedule (Table 1) to ensure they continue to qualify for participation in the study. Baseline (Day 1): Assessments will be conducted according to the Time and Events Schedule (Table 1). The Baseline criteria checklist must be completed on Day 1, prior to randomization, to determine if the patient is still eligible for participation in the study. Any patient who does not meet full Screening and Baseline entry criteria must be discontinued from the study and will be considered a screen failure. Patients who meet full Screening and Baseline entry criteria will be randomized and assigned a Patient Identification (ID) Number.

Procedures (Continued):	Dosing Period (Day 1 to Day 7):

	The dosing period will begin on Day 1 and continue through the last dose of study drug on Day 7 (EDP). Study drug will be administered in the morning. The patient's prescribed antidepressant will be administered by site personnel while the patient is confined to the study unit. Assessments during the dosing period will include measures of safety and tolerability, PK, and efficacy. For patients who discontinue study drug prior to Day 7, all EDP assessments should be completed according to the Time and Events Schedule (Table 1), provided informed consent has not been withdrawn. 24-Hour Post-Dose Assessments (Day 8): On Day 8, patients will be evaluated 24 hours after the final dose of study drug on Day 7 according to the Time and Events Schedule (Table 1). Discharge (Day 9): Following the last dose of study drug, each patient (including those who discontinue from the study drug prior to Day 7) is to remain in the inpatient facility for at least 2 additional days of safety and efficacy monitoring. The assessments to be conducted prior to Discharge are listed in the Time and Events Schedule (Table 1). Outpatient Observation Period (Day 10 to Day 14): The End of the Observation Period (EOP) will occur on Day 14 when the EOP interview will be conducted in person to assess psychiatric symptoms and safety endpoints, including medical conditions, new medications, and newly emergent AEs as listed in the Time and Events Schedule (Table 1). Samples will be drawn for PK analysis. For patients who discontinue study drug prior to Day 7, the EOP interview will occur 7 days after their last dose of study drug. (The window for the EOP visit is ± 3 days.) Follow-Up Period (Day 15 to Day 21): Follow-up interviews will be conducted with all patients (including those who discontinue from the study drug prior to Day 7) 14 days after their last dose of study drug. (The visit window is ± 3 days). In the Follow-Up interview (Day 21), C-SSRS, AEs, and concomitant medications will be recorded (Table 1). This interview may be conducted by telephone. During the Follow-Up Period, safety evaluations should be conducted, at the discretion of the Investigator, to evaluate any unresolved abnormal treatment-emergent findings.

Procedures (Continued):	Safety: Adverse events will be listed and summarized by treatment group. All AEs reported in this study will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 or higher. The overall incidences of AEs and serious AEs (SAEs) in system-organ-class and preferred term will be tabulated by treatment group. In addition, incidence rates (frequencies and percentages) will be broken down by intensities and relationship to treatment with REL-1017. Changes from Check-in (Day -1) in vital signs, ECGs, weight, body temperature, and clinical laboratory tests will be derived by treatment group. Any clinically significant abnormalities will be followed until resolution or stabilization.
Statistical Data Analysis:	Safety: Safety and tolerability parameters will be listed by treatment and patient and displayed in summary tables using descriptive statistics. The number and percentage of patients with treatment-emergent AEs will be summarized by system organ-class, preferred term, and treatment and for each treatment by maximum severity and relationship to study treatment. Descriptive statistics for vital signs, weight, and oral body temperature will be calculated and presented for each time point by treatment (absolute values and change from Baseline). Absolute values, change from Check-in (Day -1) in 12-lead ECG results and QT/QTcF categories will be summarized using descriptive statistics; frequencies (numbers and percentages) will be calculated for the overall evaluation by scheduled time and treatment. Laboratory data will be summarized by the type of laboratory test and scheduled visit. Descriptive statistics will be calculated and presented for each time point by treatment (absolute values and change from Check-in [Day -1]). Descriptive statistics and the number of patients with laboratory test results below, within, and above normal ranges will be tabulated by scheduled time. Medical history and physical examination abnormalities will be listed. Concomitant medication data will also be listed. Pharmacokinetics: The pharmacokinetic (PK) parameters for REL-1017 determined by non-compartmental analysis will be summarized. Graphs of the concentration (original and log transformed) versus time will be generated. Descriptive statistics, including number of patients, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum will be calculated by time point for REL-1017 25 mg and 50 mg.

Statistical Data Analysis (Continued):	Pharmacokinetics (Continued): Concentrations below the limit of quantification (BLQ) will be set to zero for the generation of summary statistics for concentrations and the generation of mean concentration time plots. For the calculation of the PK parameters, concentration-time data will be treated as follows: BLQ concentrations prior to the first quantifiable concentration will be set to zero; BLQ concentrations after the first quantifiable concentration will be treated as missing; and pre-dose sampling times relative to dosing will be set to zero. Descriptive statistics, including number of patients, mean, SD, geometric mean, geometric CV, minimum, maximum, and median will be calculated for all REL-1017 PK parameters except T_{max} or $t_{½}$. The Tmax data will be summarized with number of patients, minimum, maximum, and median. The $t_{½}$ data will be summarized with number of patients, mean, SD, minimum, maximum, and median. Efficacy: The depressive symptom changes associated with 7 days of daily dosing with REL-1017 25 mg and 50 mg will be measured using the MADRS, SDQ, and CGI-S. The MADRS, SDQ, and CGI-S will be conducted pre-dose at Baseline (Day 1) and on Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and at EOP (Day 14). The CGI-I will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14. The change from Baseline in each parameter on Day 7 will be compared among treatment groups (Placebo, REL-1017 25 mg, and REL-1017 50 mg) using a MMRM (Mixed Model of Repeated Measurement) with treatment group, stratification (concomitant antidepressant drug) factor, visit (Day 2, Day 4, and Day 7), interaction between treatment and visit as independent variables, and Baseline endpoint as a covariate. Least square (LS) means with standard errors (SEs), differences in LS means with standard errors (SEs), 90% confidence intervals (Cis) for the difference in LS means, and corresponding P-values will be presented. Actual values, absolute change, and percent change from Baseline will be summarized by treatment and all visits. The assumptions of normality may be evaluated using the Shapiro-Wilks test. If the assumptions of normality are not satisfied, the ranked change and ranked Baseline may replace the change and Baseline in the above mixed model as a sensitivity analysis.

Table 1 Time and Events Schedule

Visit	Screening	Check-In	Baseline						EDP		Discharge	EOP	FU
Assessment Day[a]	-30 to -2	-1	1[a]	2	3	4	5	6	7	8	9	14	21
Informed Consent	X												
Medical History	X	X										X[b]	X[b]
Psychiatric History	X												
Medication History	X												
Demographics and Height	X												
Inclusion/Exclusion Review	X	X											
MINI	X												
ATRQ	X	X											
HAM-D-17	X	X											
SAFER Interview	X												
Physical Examination	X	X							X		X		
Vital Signs and Pulse Oximetry[c]	X	X	X	X	X	X	X	X	X	X	X	X	
Weight and Oral Body Temperature	X	X							X			X	
BMI	X												
ECG[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology/Biochemistry/Urinalysis[e]	X	X	X[e]						X[e]			X	
Hepatitis B, Hepatitis C, and HIV	X												
Thyroid Panel - TSH, T3, and T4	X												
Drug Screen (urine)[f]	X	X											
Breath Alcohol[g]	X	X										X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X						X	X	X	X
Study Restrictions Review[h]	X												

Visit	Screening	Check-In	Baseline						EDP		Discharge	EOP	FU
Assessment Day[a]	-30 to -2	-1	1[a]	2	3	4	5	6	7	8	9	14	21
Inpatient Unit Confinement		X	X	X	X	X	X	X	X	X	X		
Concomitant Medications[i]		X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for DNA Extraction[j]			X										
MADRS[k]			X	X		X			X			X	
SDQ[k]			X	X		X			X			X	
CGI-S[k]			X	X		X			X			X	
CGI-I[k]				X		X			X			X	
CADSS[l]			X						X		X		
4-Item PSRS[l]			X						X		X		
Randomization			X										
PK Blood Sampling[m]			X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test for Females	X	X										X	X
Serum FSH Test for Females	X												
Study Drug Dosing QD			X	X	X	X	X	X	X				
COWS										X	X	X	
Telephone Follow-Up Call													X

Abbreviations: 4-Item PSRS = 4-Item Positive Symptom Rating Scale; AE = adverse event; ATRQ = Antidepressant Treatment Response Questionnaire; BMI = Body Mass Index; BP = Blood Pressure;; CADSS = Clinician Administered Dissociative States Scale; CGI-I = Clinical Global Impressions of Improvement; CGI-S = Clinical Global Impressions of Severity; COWS = Clinical Opiate Withdrawal Scale; CRU = Clinical Research Unit; C-SSRS = Columbia-Suicide Severity Rating Scale; CTNI = Clinical Trials Network and Institute; DNA = deoxyribonucleic acid; ECG = Electrocardiogram; EDP = End of the Dosing Period; EOP = End of the Observation Period (Day 14 ± 3 days); FSH = follicle stimulating hormone; FU = Follow-Up Visit (Day 21 ± 3 days); HAM-D-17 = Hamilton Rating Scale for Depression; HIV = Human Immunodeficiency Virus; HR = Heart Rate; MADRS = Montgomery-Asberg Depression Rating Scale; MGH = Massachusetts General Hospital; MINI = Mini International Neuropsychiatric Interview, Version 7.0.2; PK = Pharmacokinetics; QD = Quaque Die (Once Daily); RR = Respiratory Rate; SOP = Standard Operating Procedure; SDQ = Symptoms of Depression Questionnaire; SAFER = State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps [pervasive, persistent, and pathological).

[a] All Baseline/Day 1 assessments and activities will be done pre-dose, unless otherwise specified.

[b] Review of Medical History for Status of Intercurrent Illnesses.

[c] Vital signs include blood pressure (BP), heart rate (HR), pulse oximetry, and respiratory rate (RR) measured after the patient has been resting in a supine or semi- supine position for at least 3 minutes. Measurement of orthostatic BP should follow measurement of supine or semi-supine BP with patients asked to

stand for 3 minutes before measurement of orthostatic BP. From Day 2 through Day 7, vital signs will be measured once before the dose of study drug. Vital signs will be measured once on Day 8, Day 9 prior to Discharge and Day 14.

[d] On Day 1 and Day 2, an ECG will be done 1 hour pre-dose and 2 hours, 4 hours, 6 hours, and 8 hours post-dose. From Day 3 through EDP (Day 7), an ECG will be done 2 hours after the dose of study drug. An ECG will also be done on Day 8, prior to Discharge on Day 9, and at EOP (Day 14).

[e] Testosterone levels will be assayed for male patients on Day 1 and Day 7.

[f] Urine drug screen tests for tetrahydrocannabinol, opiates (including oxycodone), amphetamines, cocaine, and benzodiazepines.

[g] Patients will be asked to abstain from alcohol for 24 hours prior to Screening, 24 hours prior to Check-in to the CRU, while in the CRU, and 24 hours prior to the Day 14 visit.

[h] Sites should submit specific Screening information (detailed in the MGH CTNI manual) within 72 hours after the Screening Visit for review by the external medical team prior to proceeding to Check-in.

[i] The patient's prescribed antidepressant will be administered by site personnel while the patient is confined to the study unit.

[j] A whole blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes that may affect the PK of d-methadone. Pharmacogenetic analysis will be performed only in cases where patients exhibit abnormal PK results. This analysis will be restricted to the evaluation of genes that may be involved in the PK of d-methadone (e.g., drug metabolism, disposition, elimination). One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each patient. Samples will be collected and shipped according to the site's standard operating procedures (SOPs) and instructions from the Sponsor and/or pharmacogenetic laboratory. The samples will be stored in a secure space with adequate measures to protect patient confidentiality. The samples will be retained while research on d-methadone (REL-1017) continues, but not longer than 20 years.

[k] MADRS, SDQ, and CGI-S will be conducted pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14. The CGI-I will be conducted at pre-dose on Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14.

[l] 4-Item PSRS and CADSS will be measured at 30 to 60 minutes pre-dose on Day 1, 2 hours post-dose on Day 1, 2 hours post-dose on Day 7, and prior to Discharge on Day 9.

[m] A safety catheter will be placed before dosing on Day 1 until the 12-hour post-dose sample has been collected in case a rescue medication is required. PK sampling will be done on Day 1 at 1 hour pre-dose and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose. On Day 2 through Day 7, sampling will be done 1 hour pre-dose. On Day 8, sampling will be done approximately 24 hours after the last dose of study drug (on Day 7). On Day 9, sampling will be done approximately 48 hours after the last dose (on Day 7). Sampling will also be done on Day 14 at 7 days (± 3 days) (approximately 168 hours) after the last dose of study drug (on Day 7).

SPONSOR APPROVAL PAGE

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Version: 6.0
Date: 07-Mar-2019

Relmada Therapeutics, Inc.

07 March 2019

Ottavio V. Vitolo, MD, MMSc
SVP, Head of R&D and Chief Medical Officer
Relmada Therapeutics, Inc.

Date

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study to Assess the Safety, Tolerability, PK Profile, and Symptom Response of a 7-Day Dosing with REL-1017 25 mg QD and 50 mg QD as Adjunctive Therapy in the Treatment of Patients Diagnosed with Major Depressive Disorder

I agree, as an Investigator conducting this study:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided, reviewed, and approved by Relmada Therapeutics, Inc.
- Not to implement any deviations from or changes to this protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard to the patients/subjects or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the current Investigator's Brochure or equivalent document provided by Relmada Therapeutics, Inc.
- That I am aware of, and will comply with, Good Clinical Practice (GCP) and all applicable regulatory requirements, including the regulations governing the use of controlled substances.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug and that they are qualified to perform their study-related duties and functions as described in this protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the qualified Investigator's ownership interest in the Sponsor or the study drug and more generally about his/her financial ties with the Sponsor. Relmada Therapeutics, Inc., will obtain and disclose any relevant information in this regard solely for complying with regulatory requirements.

Hence, I:

- Agree to supply Relmada Therapeutics, Inc., with all information regarding ownership interest and financial ties with Relmada Therapeutics, Inc. (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study; and
- Agree that Relmada Therapeutics, Inc., may disclose this information about such ownership interests and financial ties to regulatory authorities.

Principal Investigator's Name (please print)	Signature	Date (dd-mmm-yyyy)

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ACRONYMS AND ABBREVIATIONS

4-Item PSRS	4-Item Positive Symptom Rating Scale
ADT	Antidepressant Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AMPA	α-Amino-3-Hydroxy-5-Methylisoxazolepropionate
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATRQ	Antidepressant Treatment Response Questionnaire
AUC	Area under the Plasma Concentration-Time Curve
$AUC_{0\text{-}inf}$	Area under the Plasma Concentration-Time Curve from Time Zero to Infinity
$AUC_{0\text{-}last}$	Area under the Plasma Concentration-Time Curve from Time Zero until the Last Quantifiable Time Point
AUC_{tau}	Area under the Plasma Concentration-Time Curve from Time Zero until the Dosing Interval of 24 Hours ($AUC_{0\text{-}24}$)
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure (Systolic and Diastolic)
BPM	Beats per minute
CADSS	Clinician Administered Dissociative States Scale
CGI	Clinical Global Impressions
CGI-S	Clinical Global Impressions of Severity
CGI-I	Clinical Global Impressions of Improvement
CGS-19755	Selfotel, NMDA Receptor Antagonist
CL/F	Apparent Clearance/Bioavailable Fraction Absorbed
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRU	Clinical Research Unit
C_{SS}	Concentration at Steady State
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{SS}/F	Steady State Clearance
CTNI	Clinical Trials Network and Institute
CV	Coefficient of Variation
CYP	Cytochrome
DNA	Deoxyribonucleic Acid

DSM-5	Diagnostic and Statistical Manual, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EDP	End of the Dosing Period (Day 7)
EDTA	Ethylene Diamine Tetra-acetic Acid
EOP	End of the Observation Period (Day 14)
EW	Early Withdrawal
FDA	United States Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GluR1	Glutamate Receptor 1
HAM-D-17	Hamilton Depression Rating Scale
HCl	Hydrochloride
hERG	Human Ether-A-Go-Go-Related Gene
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IKr	Delayed Rectifier Current Channel
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
K_i	Thermodynamic Inhibition Constant
λz	Apparent Termination Elimination Rate Constant
LD_{50}	Half Maximum Lethal Dose
LS	Least Square Means
MAD	Multiple Ascending Dose
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities (Version 16.0 or Higher)
MGH	Massachusetts General Hospital
mGlu2/3	Metabotropic Glutamate (mGlu) Receptors

MINI	Mini International Neuropsychiatric Interview, Version 7.0.2
MK-801	Dizocilpine, NMDA Receptor Antagonist
MTD	Maximum Tolerated Dose
mTORC1	Rapamycin Complex 1
NMDA	N-methyl-D-aspartate
PD	Pharmacodynamic(s)
PFC	Prefrontal Cortex
PK	Pharmacokinetic(s)
PSD95	Postsynaptic Density Protein 95
QD	Quaque Die (Once Daily)
QT	Measure of the Time between the Start of the Q Wave and the End of the T Wave in the Heart's Electrical Cycle
QTc	Corrected QT
QTcF	QT Interval with Fridericia's Correction
RBC	Red Blood Cell (Count)
REL-1017	d-Methadone (Dextromethadone) Hydrochloride
Relmada	Relmada Therapeutics, Inc.
RR	Respiratory Rate
rTMS	Repetitive Transcranial Magnetic Stimulation
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAFER	State versus Trait; Assessability; Face Validity; Ecological Validity; and Rule of Three Ps (Pervasive, Persistent, and Pathological)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDQ	Symptoms of Depression Questionnaire
SIGH-D	Structured Interview Guide for the HAM-D-17
SIGMA	Structured Interview Guide for the MADRS
SMS	Scheduled Measurement System
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
Syneos Health	Syneos Health, Inc. (formerly INC Research, Inc. [Contract Research Organization])
$t_{½}$	Apparent Terminal Elimination Half-Life
T3	Triiodothyronine
T4	Thyroxine
T_{max}	Time to Maximum Observed Plasma Concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

VAS	Visual Analogue Scale
VNS	Vagus Nerve Stimulation
V_{SS}/F	Volume of Distribution at Steady State
WBC	White Blood Cell (Count)
WHO	World Health Organization

1 STUDY BACKGROUND

Among mental and behavioral disorders, unipolar depression is by far the most common with 12-month global prevalence rates averaging approximately 5.5%.[1] The global burden of disease for patients with major depressive disorder (MDD) is ranked as second only to chronic lower back pain, and is associated with an estimated 54,700 years lived with disability per 1000 persons.[2] Of note, the World Health Organization (WHO) predicts that by 2030 unipolar depressive disorder will account for 6.2% of the total disability adjusted life years lost due to all diseases worldwide. Approximately 70% of patients do not fully remit symptomatically after a full course of monotherapy antidepressant treatment,[3] and up to 85% of patients will relapse at least once.[4]

Other disadvantages of available treatments include the slow onset of action and side effects that compromise patient compliance,[5] all of which translate to a clear unmet need for medications that can enhance the efficacy of existing antidepressants, regardless of whether they are efficacious alone. It is hypothesized that augmenting established antidepressant therapies (ADTs) with medications that modulate alternate neurotransmitter systems may enhance the efficacy of current treatment and increase the likelihood of response. To date, three second generation antipsychotics (aripiprazole, quetiapine extended release, and brexpiprazole) have been approved as adjunctive therapy to antidepressants for the treatment of MDD, but no adjunctive medication from an alternate pharmacological class is currently approved by the United States Food and Drug Administration (FDA).

d-Methadone (dextromethadone) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that binds to the dizocilpine (MK-801) binding site of the receptor with an affinity comparable to that of well-established NMDA receptor antagonists.[6] In experimental studies, d-methadone was found to block morphine tolerance and NMDA-induced hyperalgesia. In the rat formalin test, d-methadone was also found to be anti-nociceptive,[7] which was not blocked by naloxone and was the result of NMDA receptor antagonistic activity.

There have been a limited number of studies evaluating the d-methadone stereoisomer. The predominant use of d-methadone is in the racemic form of methadone (referred to as racemic methadone in this protocol), which is a 50/50 mix of l-methadone and d-methadone. Although both d-methadone and l-methadone bind to the MK-801–labeled, non-competitive site of the NMDA receptor,[5] only l-methadone binds to opioid receptors with high affinity.[8] Unlike d-methadone in racemic methadone, l-methadone is primarily responsible for opioid effects. Therefore, treatment with d-methadone at doses equivalent to the racemic methadone is expected to result in NMDA antagonism with fewer expected clinical opioid effects.

The drug substance, d-methadone hydrochloride (HCl), is manufactured by Mallinckrodt Pharmaceuticals, St. Louis, MO. Relmada Therapeutics, Inc., (Relmada) is developing REL-1017, a formulation of d-methadone HCl that is administered orally.

Relmada has conducted clinical studies to identify the dose levels of d-methadone that have little

to no opioid effects and that are expected to possess NMDA antagonistic properties for the evaluation of oral REL-1017 in the treatment of MDD and neuropathic pain conditions. Initial Phase 1 single ascending dose (SAD)[9] and multiple ascending dose (MAD)[10] clinical studies of REL-1017 were designed to evaluate the safety and tolerance of the pure d-methadone isomer in healthy opioid-naïve subjects and identify a safe and potentially effective dose range in this population. These studies showed that REL-1017 was safe and well tolerated at single oral doses up to 150 mg (maximum tolerated dose [MTD]) in healthy opioid-naïve subjects. In addition, there were no events of respiratory depression or QT prolongation (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) at all doses tested up to 200 mg.

In the multiple ascending dose (MAD) study, C_{max} demonstrated a progressive increase from one dose to the next due to drug accumulation. The area under the plasma concentration-time curve from time zero until the dosing interval of 24 hours (AUC_{0-24}) (AUC_{tau}) values also demonstrated a large accumulation over the 10 days of dosing. Steady state was achieved by dose 7 for the 25 mg and 50 mg REL-1017 dose levels and by dose 6 for the 75-mg dose level.

Dose proportionality between the 25 mg, 50 mg, and 75 mg dose levels was demonstrated for the single-dose parameters C_{max} and AUC_{tau} and for steady state parameters C_{max}, AUC_{tau}, and concentration at steady state (C_{ss}). Despite the confirmed dose proportionality, the comparison of concentration and exposure between the 50 mg and 75 mg REL-1017 treatment groups demonstrated only slight differences. The subjective pharmacodynamic (PD) effects of REL-1017, as assessed by the Bond-Lader Visual Analogue Scale (VAS), were minimal. The objective measure of PD effects, pupillometry, showed a dose response for the 75 mg REL-1017 group. The multiple doses of REL-1017 administered in this study appeared to be safe with no indication of respiratory depression, clinically significant QT interval with Fridericia's correction (QTcF) prolongation, or opioid withdrawal.

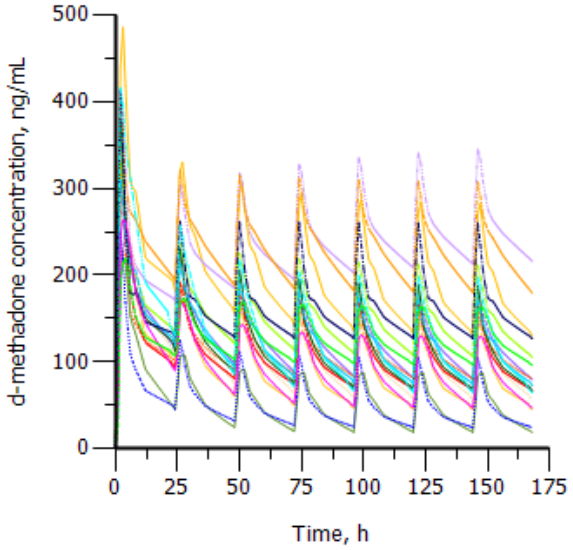
The safety and pharmacokinetic (PK) data from these initial studies were used to select the doses of REL-1017 that will be evaluated in this study, REL-1017-202. Additionally, the preclinical data for the forced swim test in rats were used to identify efficacious doses for MDD. On the forced swim test, d-methadone at the dose of 10 mg/kg shows equivalent antidepressant activity on the parameter "Frequency of behavior – Immobility" as that of ketamine at the dose of 10 mg/kg. The 20 and 40 mg/kg d-methadone subcutaneous doses decreased immobility even further, but their effects were not significantly different from each other.

The human efficacious AUC for ketamine is 635 ng*hr/mL with the ratio 6.5 to the AUC exhibiting efficacy in the mouse forced swim test.[11] Comparison of rat PK data and PK data in healthy human volunteers using the conversion ratio for ketamine and other anti-depressant drugs provided information about d-methadone exposure in humans to target. The predicted AUC_{tau} for d-methadone antidepressant activity in humans with the 10 mg/kg dose is in the range of 4000 to 5000 ng*hr/mL and 10,000 to 13,500 ng*hr/mL, based on the ketamine and other anti-depressant equivalent conversion ratio of 6.5 or 17.88, respectively. The AUC_{tau} was approximately 4500 ng*hr/mL (range of 2000 to 7000 ng*hr/mL) after the oral administration of

25 mg d-methadone in healthy subjects and was approximately 10,000 ng*hr/mL (range of 4000 to 17,000 ng*hr/mL) after the oral administration of 50 mg d-methadone. This approach, despite its limitations, supports that the dose range selected for this study should demonstrate antidepressant activity in the targeted population.

The nonparametric superimposition of data from the d-methadone MAD study in healthy volunteers was used to model different dosing regimens using loading doses of 25, 50, 75, and 100 mg with a maintenance dose of 25 mg. The extrapolations demonstrated that the best combination to reach steady state sooner was a 75 mg loading dose followed by daily doses of 25 mg and 100 mg loading doses followed by daily doses of 50 mg. The loading dose of >75 mg was shown to be safe both as a single dose and multiple doses in healthy volunteers (Figure 1).

Figure 1: Non-parametric Superimposition PK Profile for Once Daily Loading Dose of 75 mg and Maintenance Doses of 25 mg for 6 Days



The intent of this study is to assess the safety and tolerance of daily dosing for 7 days with 2 dose strengths of the pure REL-1017 isomer as adjunctive therapy in adult patients with MDD who are diagnosed with a current major depressive episode (MDE) and who have experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration (as defined by the ATRQ) of an antidepressant medication for the current episode; these patients will be randomized to study drug in a 1:1:1 ratio.

1.1 Pre-Clinical Data

1.1.1 In Vitro

The NMDA receptor binding properties of d-methadone have been characterized and compared to other NMDA receptor antagonists.[6,12] Racemic methadone and its d- and l-isomers exhibit low micromolar affinities for the [^{3}H]MK-801–labeled non-competitive site of the NMDA receptor in

both rat forebrain and spinal cord synaptic membranes. The thermodynamic inhibition constant (K_i) values and displacement curves are similar to dextromethorphan, an established NMDA receptor antagonist. They lack affinity at the [^{3}H]CGS-19755 (selfotel)–labeled competitive site of the NMDA receptor.[13] Therefore, racemic methadone and its d- and l-isomers differ from morphine, hydromorphone, and naltrexone in that they have non-competitive antagonist activity at the NMDA receptor.

The affinity of racemic methadone as well as its pure stereoisomers for various subtypes of NMDA receptor channels expressed in *Xenopus* oocytes[14] demonstrates that the affinities for channel subtypes vary between the d- and l-isomer. The clinical relevance of these preferences is unknown.

The literature demonstrates a high affinity of d-methadone for the NMDA receptor, which provides the basis for its antinociceptive effects via a central glutamatergic system. At the same time, in vitro data demonstrate that the affinity of d-methadone for the mu1, mu2, and delta opioid receptors is 10 to 30 times lower compared to l-methadone.[8,13]

In vitro studies on the binding of d-methadone to the cardiac potassium channel human ether-a-go-go-related gene (hERG) and inhibition of the delayed rectifier current channel (IKr) are used to predict the possibility of corrected QT (QTc) prolongation and other cardiac issues. The Fridericia formula will be used for QTc. d-Methadone inhibits the hERG current in oocyte models to the same extent as l-methadone, although at lower concentrations. The half maximal inhibitory concentration (IC_{50}) of d- and l-methadone was 0.10±0.01 and 0.27±0.01 mM, respectively.[15] In HEK293 cells consistently expressing hERG, the current inhibition by d-methadone was approximately 65%, while it was 40% by l-methadone. In general, l-methadone blocked I_{hERG} significantly less potently than d-methadone, whereas the racemic methadone block was intermediate. The obtained IC_{50} values were as follows: racemic methadone 3 μM; d-methadone 2 μM; l-methadone 7 μM.[16]

Based on tests with racemic methadone, positive results have been seen in multiple in vivo assays, e.g., the mouse dominant lethal assay and the mammalian spermatogonial chromosome aberration test. For additional data from in vitro studies of d-methadone, please see the Investigator's Brochure.

1.1.2 In Vivo

The in vivo studies of methadone have mostly involved the racemic mixture, which includes d- and l-methadone acting as an NMDA receptor antagonist and l-methadone acting as an opioid receptor agonist. Thus, in terms of safety and tolerance, the expected side effects of d-methadone alone could be expected to be of the same nature or less compared to racemic methadone, especially in terms of opioid-related effects. Some NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Based on racemic methadone, positive tests were seen in multiple assays (the in vivo mouse dominant lethal assay, the in vivo mammalian spermatogonial chromosome aberration test, in the

E. coli DNA repair system and Neurospora crassa and mouse lymphoma forward mutation assays). No effect on respiratory parameters was observed in guinea pigs, while the locomotor activity was comparable to that of l-methadone or racemic methadone.[17]

There were no significant differences in PK parameters when beagles were administered a single 0.25 mg/kg intravenous (IV) dose of either isomer or 0.5 mg/kg of racemic methadone.[18]

After IV administration in mice, the isomers of methadone demonstrated a slightly higher half maximum lethal dose (LD_{50}) than the racemic mix.[19]

Intrathecal infusions of d-methadone in dogs demonstrated effects such as marked hind limb or whole-body hypertonicity, paralysis, marked sedation, agitation and/or spontaneous vocalization, extreme sensitivity to light touch applied to the flank (allodynia), and/or marked ataxia at higher doses.[20,21]

In a developmental toxicity study, pregnant CD® rats (Charles River Laboratories) were given daily oral gavage administration of 0 (vehicle), 10, 20, and 40 mg/kg d-methadone hydrochloride on GD 6 through GD 17. No test article-related effects were observed on maternal survival, clinical findings, ovarian and uterine parameters (mean number of corpora lutea, implantation sites, viable fetuses/litter size, resorptions, and pre- and postimplantation loss), or macroscopic findings at any dose level evaluated. Test article-related, but non-adverse, effects on maternal body weight and/or body weight change were observed at 10, 20, and 40 mg/kg/day and on food consumption at 40 mg/kg/day. No test article-related effects were observed on fetal sex ratios; body weights; or external, visceral, or skeletal examinations.

No developmental toxicity was observed at any dose level tested. The no-observed-adverse-effect level (NOAEL) for both maternal and developmental toxicity was set to be 40 mg/kg/day. Based on a 60-kg human body weight and conversion of rat to human dose based on body surface area, the human equivalent dose (HED) was determined to be 387 mg. The dose provides approximately 15.48-fold and 7.74-fold safety margins when compared to the 25 mg and 50 mg doses of REL-1017-202. The safety margins calculations were based on the on the FDA Guidance “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[22]

The genotoxic effects of d-methadone are unknown.

1.2 Previous Human Experience

Relmada has completed two studies of the safety, tolerability, and PK of REL-1017 (d-methadone).

1.2.1 Results from Clinical Study REL-1017-111

Study REL-1017-111 was “A Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Single Ascending Doses of d-Methadone in Healthy Subjects.” It was a double-blind, randomized, placebo-controlled study in sequential arms. Safety and PK for REL-1017 (d-methadone) oral administration were determined in ascending dose arms from 5 mg to 200 mg. Pharmacokinetic parameters were calculated for all dose levels, although some individual results had to be excluded due to emesis or statistical analysis criteria.

Pharmacogenomics analysis was performed for subjects exhibiting either fast or slow metabolism of REL-1017. Overall, there were minimal subjective PD effects of REL-1017 up to 150 mg, as assessed by the Bond-Lader VAS. For additional information, please reference the Investigator's Brochure.

The overall conclusions drawn from Clinical Study REL-1017-111 were:

- The MTD for oral REL-1017 in healthy opiate-naive subjects was determined to be 150 mg.
- The PK analysis revealed high variability of the REL-1017 parameters, including C_{max}, time to maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), apparent terminal elimination half-life ($t_{½}$), and apparent clearance/bioavailable fraction absorbed (CL/F).
- Statistical models demonstrated linear proportionality of C_{max} and $AUC_{0\text{-}inf}$ versus dose, although the result was not statistically significant.
- In general, there were no specific trends observed for T_{max} or $t_{½}$ of REL-1017.
- The subjective PD effects of REL-1017 up to 150 mg were minimal.
- The objective measure of PD effects, pupillometry, showed a dose response with greater pupil constriction in the higher dose groups.
- The single doses of REL-1017 administered in this study appeared to be safe with no indication of respiratory depression or clinically significant QTcF prolongation. In terms of tolerability, nausea and vomiting become potential adverse events (AEs) with higher doses.

1.2.2 Results from Clinical Study REL-1017-112

Study REL-1017-112 was "A Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Multiple Ascending Doses of d-Methadone in Healthy Subjects." It was a double-blind, randomized, Placebo-controlled study in sequential arms. There were 8 subjects randomized into 3 arms of 25 mg, 50 mg, and 75 mg REL-1017. In each arm, 2 subjects were dosed with Placebo and 6 subjects with a powder formulation of REL-1017. Doses were administered from Day 1 to Day 10. (For additional information, please reference the Investigator's Brochure.)

The overall conclusions drawn from Clinical Study REL-1017-112 were:

- C_{max} demonstrated a progressive increase from one dose to the next due to drug accumulation. AUC_{tau} values also demonstrated a large accumulation over the 10 days of dosing.
- Steady state was achieved by Dose 7 for the 25 mg and 50 mg REL-1017 dose levels and by Dose 6 for the 75 mg dose level.
- Dose proportionality between the 25 mg, 50 mg, and 75 mg dose levels was demonstrated for the single-dose parameters C_{max} and AUC_{tau} and for steady state parameters C_{max}, AUC_{tau},

and C_{ss}.

- Despite the confirmed dose proportionality, the comparison of concentration and exposure between the 50 mg and 75 mg REL-1017 treatment groups demonstrated only slight differences.
- The subjective PD effects of REL-1017, as assessed by the Bond-Lader VAS, were minimal. The objective measure of PD effects, pupillometry, showed a dose response for the 75 mg REL-1017 group.
- The multiple doses of REL-1017 administered in this study appeared to be safe with no indication of respiratory depression, clinically significant QTcF prolongation, or opioid withdrawal.

1.3 Study Rationale

1.3.1 Role of NMDA Receptors in Neuronal Plasticity and Depression

Currently available medications have proven to be useful for the treatment of depression, but also have serious limitations. These include low response rates, a significant number of treatment-resistant patients, and time-lag for response, which emphasizes a major unmet need for more efficacious and faster-acting antidepressants. Recent studies have demonstrated that ketamine, a non-competitive glutamate-NMDA receptor antagonist, produces rapid onset (2 hours) and long-lasting (7 days) antidepressant actions in treatment-resistant patients. This rapid action, by a mechanism completely different from typical monoamine reuptake inhibitors, represents a significant finding in the field of depression.

The molecular and cellular mechanisms underlying the actions of ketamine are more complicated than simple antagonism of the NMDA receptor. NMDA receptor blockade results in a nearly immediate (30 minutes) stimulation of the mammalian target of rapamycin complex 1 (mTORC1), which underlies the rapid behavioral responses to ketamine.[22] mTORC1 has been linked to the regulation of synaptic plasticity. A role for protein synthesis-dependent plasticity in the actions of ketamine is supported by studies demonstrating that ketamine increases synaptic protein levels (postsynaptic density protein 95 [PSD95], glutamate receptor 1 [GluR1]) and synaptogenesis (spine number and function) in rat prefrontal cortex (PFC), and produces rapid antidepressant behavioral responses. Moreover, these effects of ketamine are blocked by the selective mTORC1 inhibitor rapamycin. Studies have found that metabotropic glutamate receptor (mGlu2/3) antagonists[23] and another class of rapid acting antidepressant, the muscarinic receptor antagonist scopolamine, also increases mTORC1 signaling and synaptogenesis in the PFC.[24] Other studies have demonstrated that GLYX-13, a putative NMDA receptor modulator with glycine-site partial agonist/antagonist properties, also increases mTORC1 signaling, levels of synaptic proteins, and spine-synapse number and function in the PFC.[25]

GluA1 and α-amino-3-hydroxy-5-methylisoxazolepropionate (AMPA) receptors are also implicated in the antidepressant effect of ketamine. The antidepressant actions of NMDA antagonists are blocked by pretreatment with an AMPA receptor antagonist.[23,24,25,26] These

findings represent a fundamental shift in our understanding of the mechanisms underlying the rapid actions of NMDA receptor blockade and identify several novel therapeutic targets for treatment-resistant depression.[27,28]

1.3.2 NMDA Antagonist Activity of d-Methadone

Racemic methadone, the 50/50 combination of d-methadone and l-methadone, has been in widespread use for decades and has been studied extensively. Methadone is currently approved for use in the management of severe pain, detoxification treatment of opioid addiction, and maintenance treatment of opioid addiction.

The results of a study evaluating the receptor binding profiles of methadone, its stereoisomers, and morphine suggest that d-methadone does not essentially contribute to the opioid effect of racemic methadone and that it has a 10 times lower affinity for the mu_1, mu_2, and delta receptor compared to l-methadone.[8]

In another study, racemic methadone and its stereoisomers were evaluated in competition binding assays. Racemic methadone and its d- and l-isomers exhibited low micromolar affinities for the [^{3}H]MK-801–labeled non-competitive site of the NMDA receptor in both rat forebrain and spinal cord synaptic membranes, with thermodynamic inhibition constant (K_i) values and displacement curves similar to those of dextromethorphan, an established NMDA receptor antagonist. They lacked affinity at the [^{3}H]CGS-19755–labeled competitive site of the NMDA receptor.[13]

Relmada examined the antagonist effects of racemic methadone, d-methadone, racemic ketamine, and [S]-ketamine on the electrophysiological response of human cloned NMDA NR1/NR2a and NR1/NR2b receptors expressed in HEK293 cells. The results demonstrated approximately equivalent antagonism of peak current for all compounds in the low µM range (Table 2).

Table 2 Relmada Study: Effects of Test Articles on NR1/NR2A and NR1/NR2B Glutamate Receptors Expressed in Mammalian Cells (Antagonist Mode)

	NR1/NR2A		NR1/NR2B	
	IC_{50}	Hill Slope	IC_{50}	Hill Slope
Memantine	5.00	1.08	1.46	-1.62
Racemic Ketamine	8.07	1.55	2.69	-1.01
S-(+)-Ketamine	7.56	0.86	3.28	-0.85
Racemic Methadone	11.12	0.96	9.94	-0.76
d-Methadone	13.49	1.16	11.12	-0.87

Abbreviations: IC_{50} = half maximal inhibitory concentration; ID = identification. Note: Data are on file at Relmada.

1.3.3 Effect of d-Methadone in the Forced Swim and Spontaneous Locomotor Tests

When rats are forced to swim in a small cylinder from which no escape is possible, they readily adopt a characteristic immobile posture and make no further attempts to escape except for small movements needed to prevent them from drowning. The immobility induced by the procedure can be reversed or largely decreased by a wide variety of antidepressants, suggesting that this test is sensitive to an antidepressant-like effect. However, since this test will also pick up many false positives (e.g., psychostimulants and antihistaminergics), locomotor activity was also performed to rule out hyperactivity.

All rats were exposed to a swim test ("habituation") prior to compound administration. This pre-administration swim test consisted of one 15-minute session which was followed 24 hours later by a 5-minute experimental test. Immobility, climbing, and swimming behaviors were recorded every 5 seconds for a total of 60 counts per subject.

Rats were administered vehicle, ketamine, or d-methadone on Day 1 (after habituation; 24 hours prior to the forced swim testing). The test and the analysis of the video files were performed by an observer blind to the treatment.

At all doses tested, d-methadone significantly decreased the immobility of the rats compared to the vehicle suggesting antidepressant-like activity. In addition, the effect of d-methadone (20 mg/kg and 40 mg/kg) on immobility was larger than the effect seen with ketamine (10 mg/kg). It should be noted that the effects of d-methadone (10 mg/kg, 20 mg/kg, and 40 mg/kg) in the forced swim test were not confounded by any changes in the locomotor activity of the rats.[28]

1.3.4 Rationale for Protocol REL-1017-202

In summary, preclinical and clinical data suggest that low doses of NMDA receptor antagonists such as ketamine initiate brain plasticity processes and increase prefrontal connectivity, reversing the potential effects of chronic stress and depression. The elucidation of these processes, however, has been derived from animal research. There remains a need for research with depressed human subjects to determine if these putative mechanisms of action involving the NMDA receptor and downstream pathways mediate ketamine's antidepressant effects in depressed patients.

The pre-clinical and previous clinical experience with REL-1017 (d-methadone) provided the basis for the initiation of the present study, which will extend the evaluation of the safety, tolerability, and PK of REL-1017 at 2 doses with repeated administration to humans. Since REL-1017 is proposed for use as adjunctive therapy in the treatment of patients diagnosed with MDD, the patients will be adults with MDD who are diagnosed with a current MDE and who have experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration (as defined by the Antidepressant Treatment Response Questionnaire [ATRQ]) of an antidepressant medication for the current episode will be randomized to study drug in a 1:1:1 ratio. This population will provide the opportunity to compare the safety and efficacy effects of treatment with an antidepressant plus REL-1017 versus the effects of an antidepressant alone.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is safety:

Safety objectives will assess the safety and tolerability of 25 mg and 50 mg of REL-1017 (d-methadone) compared to Placebo as adjunctive treatment in patients with MDD. The following assessments will be conducted to measure safety and tolerability throughout the study:

- AEs
- Vital signs
- Weight
- Physical examination
- Clinical laboratory parameters (chemistry, hematology, and urinalysis)
- Electrocardiogram (ECG) parameters
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Clinician Administered Dissociative States Scale (CADSS)
- Clinical Opiate Withdrawal Scale (COWS)
- 4-Item Positive Symptom Rating Scale (4-Item PSRS)

2.2 Secondary Objectives

The secondary objectives of this study are:

2.2.1 Pharmacokinetics:

The PK objective will characterize the PK profile of 25 mg and 50 mg of REL-1017 (d-methadone) as adjunctive treatment in patients with MDD. The PK profile of REL-1017 25 mg and 50 mg will be evaluated on Day 1 through Day 7, Day 8, Day 9, and Day 14 where the data allow:

- Maximum observed plasma concentration (C_{max})
- Time to maximum observed plasma concentration (T_{max})
- Area under the plasma concentration-time curve from time zero until the dosing interval of 24 hours (AUC_{tau})
- Area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-}last}$) on Day 7
- Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Apparent termination elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$)

- Attainment of steady state
- Steady state clearance (C_{SS}/F)
- Volume of distribution at steady state (V_{SS}/F)
- Accumulation ratios based on minimum observed plasma concentration (C_{min}), C_{max}, and AUC_{tau}

2.2.2 Efficacy:

The efficacy of 7 days of daily dosing with REL-1017 25 mg and 50 mg will be measured with the following efficacy endpoints:

- Change from Baseline (Day 1) to End of the Dosing Period (EDP, Day 7) on the Montgomery-Asberg Depression Rating Scale (MADRS) with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14;
- Change from Baseline (Day 1) to EDP (Day 7) on the Symptoms of Depression Questionnaire (SDQ) with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14; and,
- Change from Baseline (Day 1) to EDP (Day 7) on the Clinical Global Impressions of Severity (CGI-S) with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14.
- Evaluation of Clinical Global Impressions of Improvement (CGI-I) total score on Day 7 (post-dose), as well as CGI-I scores on Days 2 (pre-dose), 4 (post-dose), and 14.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This a Phase 2a, multicenter, randomized, double-blind, Placebo-controlled 3-arm study to assess the safety and tolerability of multiple oral doses of REL-1017 25 mg and 50 mg as adjunctive therapy in the treatment of patients diagnosed with MDD. The patients will be adults with MDD who are diagnosed with a current MDE who have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication. This population will provide the opportunity to compare the safety and efficacy of REL-1017 with SSRIs, SNRIs, or bupropion versus an antidepressant with Placebo.

The study will be conducted at approximately 10 sites in the United States.

Approximately 60 qualified patients will be randomized to 25 mg or 50 mg of REL-1017 or Placebo with approximately 20 patients per treatment group. REL-1017 will be provided as a powder and will be prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing.

An unblinded pharmacist will assign study drug patients according to randomized treatment codes provided by a statistician who is not working as a statistician on the study in any other capacity. The study drug solution will be prepared within 3 hours of administration in blinded containers, and then will be dispensed to blinded study staff for administration to the patients.

The administration of study drug must be observed by a staff member. After drinking the 100 mL of study drug, 25 mL of non-carbonated water will be added to the study drug container and gently swirled. The patient will drink this rinse volume followed by 125 mL of non-carbonated water to drink immediately thereafter. All dosing must be completed within 5 minutes.

Dosing will take place once daily in the morning after an overnight fast.

3.2 Study Procedures

The overall duration of the study will be up to 51 days per patient. All patients will be admitted to the clinical research unit (CRU) for a period of approximately 10 days during which they will receive daily doses of REL-1017 or Placebo for 7 consecutive days. The Screening Visit will assess patient eligibility to participate in the study and will occur between Day -30 and Day -2. Patients will be admitted the day prior to receiving the study drug (Day -1) and will remain in the CRU under clinical supervision for at least 48 hours after the last dose is received on Day 7. Patients will be discharged on Day 9, but return to the CRU 7 days after their last dose of study drug for follow-up evaluations. The study personnel will telephone each patient 14 days after the last dose of study drug and conduct a Follow-Up interview to assess the patient's condition.

The patient's eligibility assessment will be reviewed by an external medical team based on key protocol inclusion and exclusion criteria to promote appropriate patient enrollment and data quality. Sites should submit specific Screening information (detailed in the Massachusetts Clinical Trials Network and Institute [MGH CTNI] manual) within 72 hours after the Screening

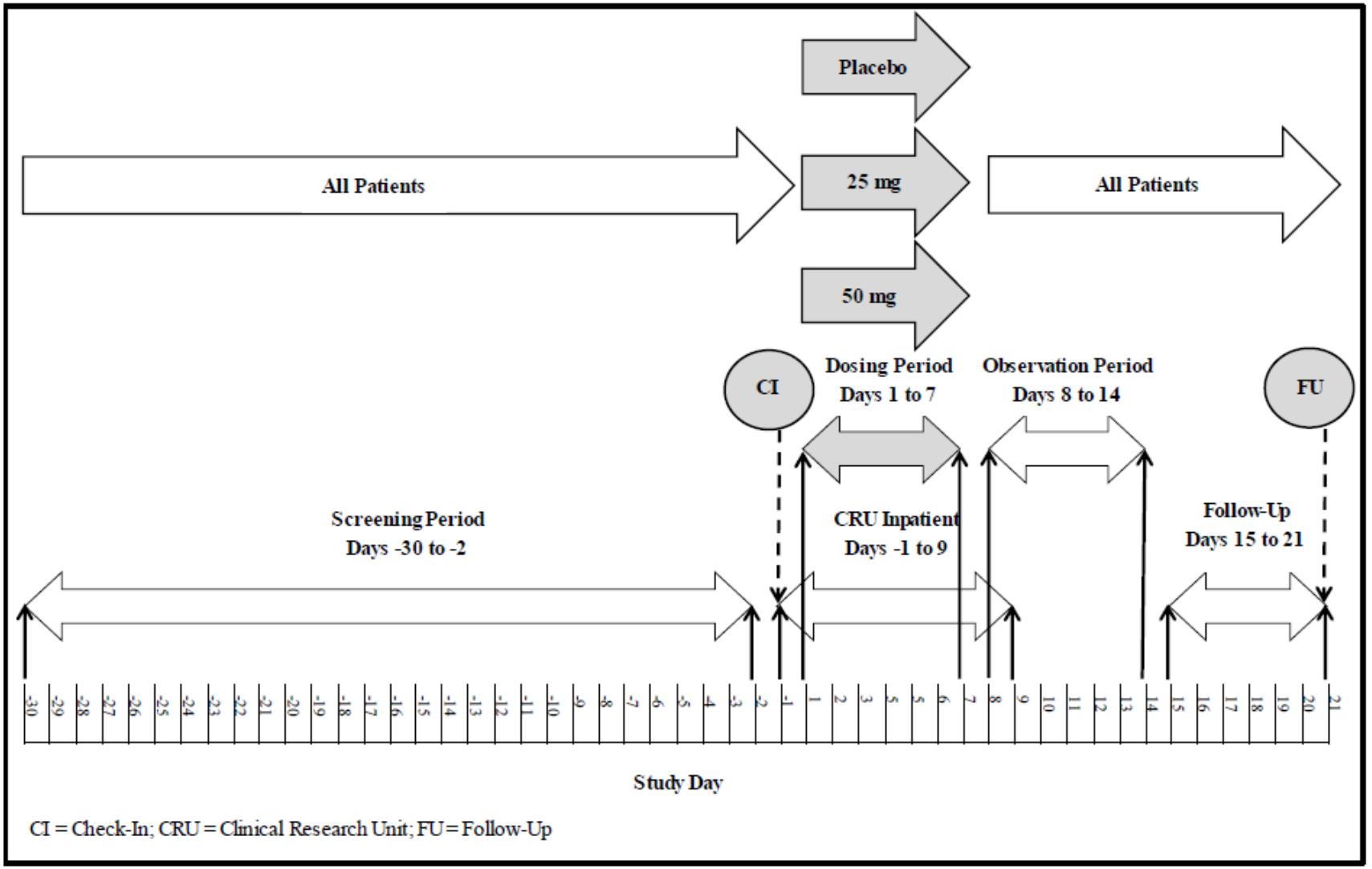
Visit for review by the external medical team prior to proceeding to Check-in. Subjects who are deemed eligible by the Principal Investigator and confirmed by the Medical Monitor will undergo the SAFER Interview[30] by clinicians at the MGH CTNI. To ensure that appropriate subjects are entered into the study, a remote interview will be conducted by MGH CTNI raters. The assessments administered will be the SAFER Interview, which will include the HAM-D17, and the MGH ATRQ. The interview will be performed remotely by the MGH CTNI rater, and the subject will be contacted at his or her home or other off-site location after the Screening Visit, during which call the above assessments will be performed. Sites will be notified of the results within 24 hours of the interview. Only subjects whose eligibility will be confirmed by the SAFER Interview will be allowed to proceed in the study.

The study design is summarized in Figure 2. Study assessments will be performed at the visits and time points outlined in the Time and Events Schedule (Table 1).

Approximately 60 qualified patients will be randomized to study drug in a 1:1:1 ratio. Arm 1 will consist of approximately 20 patients who will receive REL-1017 25 mg. Arm 2 will consist of approximately 20 patients who will receive REL-1017 50 mg. Arm 3 will consist of approximately 20 patients who will receive Placebo. REL-1017 will be provided as a powder and prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing. The study drugs will consist of the following:

- Arm 1: REL-1017 (d-methadone) 75 mg of powder in 100 mL of Ocean Spray® Diet Cranberry Juice QD on Day 1, 25 mg of powder in 100 mL Ocean Spray® Diet Cranberry Juice QD on Day 2-7.
- Arm 2: REL-1017 (d-methadone) 100 mg of powder in 100 mL of Ocean Spray® Diet Cranberry Juice QD on Day 1, 50 mg of powder in 100 mL Ocean Spray® Diet Cranberry Juice QD on Day 2-7.
- Arm 3: Placebo = 100 mL Ocean Spray® Diet Cranberry Juice.

Figure 2: Flow Chart of Study Design



3.3 Discussion of Study Design

Adult patients with MDD who are diagnosed with a current MDE and who have experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration (as defined by the ATRQ) of an antidepressant medication for the current episode will be randomized to study drug in a 1:1:1 ratio. This population will provide the opportunity to compare the safety and efficacy of REL-1017 with SSRIs, SNRIs, or bupropion versus an antidepressant with Placebo.

The randomized, double-blind, Placebo-controlled study is a scientifically valid design for an early Phase 2 study, and the Patient Identification (ID) Numbers are appropriate for the exploratory nature of this study.

The timing of the continuous monitoring and confinement are based on the clinical information of the respiratory depression and other effects as described above (see Section 1).

4 STUDY POPULATION

4.1 Number of Patients

Adult patients with MDD who are diagnosed with a current MDE and who have experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration (as defined by the ATRQ) of an antidepressant medication for the current episode will be randomized to study drug in a 1:1:1 ratio. Approximately 20 patients each will receive REL-1017 75 mg/REL-1017 25 mg, REL-1017 100 mg/REL-1017 50 mg, or Placebo.

Investigators should strive to evenly distribute the choice of ADTs at their respective sites among different ADTs. No more than 2 out of every 6 patients at an investigational site should be assigned to any 1 ADT without permission by the Medical Monitor.

Approximately 120 patients will be screened, and approximately 60 qualified patients will be randomized to study drug in a 1:1:1 ratio (approximately 20 patients per arm). Each patient will participate for up to 51 days (30 days Screening, 7 days treatment, and 14 days of observation and follow-up).

4.2 Inclusion Criteria

Patients will be considered eligible to participate in this study if each of the following inclusion criteria is satisfied at Screening:

1. Males and females between 18 and 65 years of age, inclusive.
2. Diagnosed with recurrent MDD as defined by the Diagnostic and Statistical Manual, Fifth Edition (DSM-5), and confirmed by the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI).
3. Diagnosed with a current MDE lasting 8 weeks to 36 months as defined by the DSM-5 and confirmed by the MINI.
4. Treated with an adequate dosage of a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or bupropion during the current MDE for at least 8 weeks prior to Screening with the same, adequate dosage for the last 4 weeks. Minimum adequate doses are defined in the (ATRQ). The maximum dose allowed for paroxetine is 40 mg QD, for fluoxetine is 60 mg QD, and for sertraline is 200 mg QD.
5. Have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication in the current episode, as defined as <50% improvement with an antidepressant medication at doses listed on the SAFER Interview (Criteria: **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological]).
6. Hamilton Depression Rating Scale-17 (HAM-D-17) ≥19 at Screening and Check-in (Day -1).
7. Body Mass Index (BMI) between 18.0 and 35.0 kg/m^2, inclusive, and a minimum weight of 50.0 kg.

8. Per the Investigator's judgment, able to meet all study requirements, including the confined/inpatient portion of the study, adherence with both approved ADT and study drug regimen, and completion of all assessments and all scheduled visits.
9. Male and female patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in Section 4.4.2, from Screening and for at least 2 months after the last study drug administration. Female patients must have a negative pregnancy test, and must not be lactating.
10. Must be able to read, speak, and understand English and must provide written informed consent prior to the initiation of any protocol-specific procedures.

4.3 Exclusion Criteria

Patients will not be considered eligible to participate in this study if any one of the following exclusion criteria is satisfied at Screening:

1. History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator would jeopardize the safety of the patient or the validity of the study results, including torsades de pointes, any bradyarrhythmias, or uncompensated heart failure.
2. Chronic use of prescribed opioids (i.e., >120 days in a 6-month period) up to 6 months prior to Screening or any recreational use of opioids.
3. Evidence of clinically significant hepatic or renal impairment, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 x upper limit of normal (ULN), bilirubin >1 x ULN, or endocrine laboratory values (including clinically significant thyroid parameters, i.e., thyroid stimulating hormone [TSH], triiodothyronine [T3], and thyroxine [T4]).
4. History or family history of sudden unexplained death or long QT syndrome (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle).
5. An average QTcF ≥450 msec or an average QRS interval ≥120 msec from the 12-lead ECGs performed at Screening.
6. History of clinically diagnosed hypotension requiring treatment.
7. History or presence of any condition in which an opioid is contraindicated (e.g., significant respiratory depression, acute or severe bronchial asthma or hypercarbia, bronchitis, or has/is suspected of having paralytic ileus).
8. No more than 3 prescribed doses of an opioid within the 6 months prior to Screening and no use at all within the last month.
9. Use of an antipsychotic, anticonvulsant, or mood stabilizer, regardless of indication, within the 3 months prior to Screening.

10. History of allergy or hypersensitivity to methadone or related drugs (e.g., opioids).
11. Positive test for hepatitis B or human immunodeficiency virus (HIV). Patients with a positive hepatitis C test may be considered for inclusion with approval from the Medical Monitor.
12. Any current and primary psychiatric disorder, as defined as a condition that is the primary focus of distress and/or treatment, other than MDD.
13. Any lifetime history of bipolar I or II disorder, any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive compulsive disorder, eating disorder, intellectual disability, or pervasive developmental disorder.
14. History in the past 12 months of a primary diagnosis of anxiety disorder or panic disorder not related to the current MDE.
15. Current diagnosis of alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. Patients with the following diagnoses within the past 12 months, however, may be included at the Investigator's discretion: mild alcohol use disorder, mild cannabis use disorder, and any severity tobacco use disorder.
16. A confirmed positive result on the urine drug/alcohol screen at Screening or Check-in. If the urine drug/alcohol screen is positive at Screening, retesting or rescreening may be scheduled with prior approval from the Medical Monitor.
17. Patients who, in the Investigator's judgment, are at significant risk for suicide. A patient with a Columbia-Suicide Severity Rating Scale (C-SSRS) ideation score of 4 or 5 within the last 6 months or any suicide attempt within the past year must be excluded, as should a patient with an ideation score of 4 or 5 or any suicide attempt at the Check-in or Baseline Visit.
18. Patients with a 20% improvement between Screening and Check-in (Day -1) on the HAM-D-17.
19. Patients who did not safely discontinue medications prohibited in Section 4.4.1.
20. Patients receiving new onset psychotherapy (individual, group, marriage, or family therapy) within 2 months prior to Screening or plans to start at any time during participation in the study.
21. Patients who have received electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or vagus nerve stimulation (VNS) or who have participated in a ketamine study within the last 6 months.
22. Patients with any clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, chronic pain, or gastrointestinal disorder. Medical conditions that are minor or well-controlled may be

permitted if they will not increase the safety risk to the patient or compromise interpretation of the safety or efficacy endpoints.

23. Patients taking fluvoxamine or St. John's Wort.

24. Patients who have participated in a clinical study with an investigational medication in the past 6 months, or who have participated in more than 4 clinical studies with investigational medications in the past 2 years.

4.4 Study Restrictions

4.4.1 Prohibited Medications

All patients must have discontinued all prohibited medications prior to the Screening period to meet the protocol requirements. Table 3 provides the required duration of time to discontinuation period for selected prohibited medications. All other prohibited medications should be stopped prior to Check-in at the CRU. Benzodiazepines and non-benzodiazepine sleep aids taken as scheduled medications and at stable doses not higher than that in the FDA-approved label for at least 30 days prior to the Check-in are allowed in the study. Any questions regarding these medications should be directed to the Study Medical Monitor. Initiation of these medications during the study is not allowed.

Any medication taken consistently by the patient for 30 days prior to Screening and that is not a prohibited medication may be continued during the study if appropriately documented and captured in the electronic Case Report Form (eCRF). All medications taken within 6 months prior to Screening must be noted on the eCRF.

The Investigators and their designees are obliged to ensure the well-being of all patients during this study. If medical intervention is required during the study, no medication or treatment will be withheld from a patient; and the Investigator will ensure proper documentation is kept in the eCRF. Due to each subject's clinical condition being unique, there is no specific rescue plan or rescue therapy recommended for subjects. If a subject experiences a clinical condition, the Investigator should use clinical judgment and knowledge of the subject's specific condition to institute the best treatment for that subject.

All medications taken by patients after Screening until the completion of the final Follow-Up Visit or the Early Withdrawal (EW) Visit will be documented as concomitant medications. The reported concomitant medications will be reviewed and evaluated by the Investigator to determine if they affect a patient's eligibility or continued participation in the study.

Table 3 Time from Discontinuation of Prohibited Medications, Supplements, and Other Substances

Prohibited Medications, Supplements, and Other Substances	Time from Discontinuation to Check-In[1]
Monoamine oxidase inhibitors (MAOIs)	90 days
Tricyclic antidepressants and atypical antidepressants	90 days
PRN Benzodiazepines	30 days
All other psychotropic medications except for those allowed in the study	90 days
Herbal drugs/dietary supplements for depression, anxiety, or insomnia	30 days

PRN = As Needed.

1 The Medical Monitor should be contacted for any questions regarding the potential for pharmacological interactions with concomitant medications used by patients during the study. These include off-label use of medications for depression.

The use of the following medications is prohibited during the study:

1. Antidepressants other than the approved, stable dose started prior to the study; the maximum allowed dose for paroxetine is 40 mg QD, for fluoxetine is 60 mg QD, and for sertraline is 200 mg QD.
2. Antipsychotics
3. Antiepileptic drugs
4. Benzodiazepines and hypnotics used as needed or above the approved doses
5. Stimulants
6. Opioid analgesics
7. Nutritional supplements and non-prescription based herbal preparations with central nervous system (CNS) effects
8. Barbiturates

4.4.2 Contraceptive Precautions

For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include vasectomy, or male condom for patients plus an additional method of contraception for their female partners. For vasectomized men, original documents obtained after vasectomy or a note from the family physician is required to confirm sterility. In the absence of such documents, it will be assumed that the patient is of childbearing potential, and the patient will be advised to use the medically acceptable birth control methods.

Men must also abstain from sperm donation from Screening until at least 2 months after the last study drug administration.

Females of child-bearing potential (not surgically sterilized and between menarche and 1 year

post menopause) must agree to use 2 methods of contraception through the end of the study and until at least 2 months after the last study drug administration. Surgical sterilization is defined as removal of the uterus and/or both ovaries. Acceptable forms of contraception for female patients include:

- Intrauterine device (IUD)
- Bilateral tubal ligation, bilateral salpingectomy, or bilateral tubal occlusive procedure
- Hormonal contraceptives (e.g., oral, patch, or injectable)
- A double-barrier protection method (e.g., condom, sponge, or vaginal diaphragm with spermicide cream, foam, or gel)

Women must also abstain from egg donation from Screening until at least 2 months after the last study drug administration.

4.4.3 Dietary and Other Restrictions

During the inpatient period for the study, patients will receive a standard diet. No additional food or beverages may be consumed while patients are staying in the CRU. Meals will be served at specific times after the completion of any scheduled assessments.

Aside from the inclusion and exclusion criteria listed in Section 4.2 and Section 4.3, respectively, the patient must agree to abide by each of the following restrictions for the specified time:

- Patients will be asked to abstain from alcohol for 24 hours prior to Screening, 24 hours prior to Check-in to the CRU, while in the CRU, and 24 hours prior to the Day 14 visit.
- Patients will be required to abstain from recreational drug use throughout the study, from Screening until after the Day 21 Follow-Up telephone call. Abstinence from drug use will be confirmed with urine drug screens at Screening and Check-in, and patients will be reminded to adhere to restrictions throughout the study.
- Dosing will occur in the morning following an overnight fast of at least 8 hours.
- Patients will be required to abstain from blood donation during the study and for 30 days following the last study visit. A copy of the Informed Consent Form (ICF) with the study restrictions will be provided to each patient. Patients will be reminded by phone calls prior to study visits to adhere to study restrictions as described in the ICF.
- Patients will be required to follow the ICF and the clinic code of conduct.

4.5 Patient Discontinuation/Withdrawal Criteria

Any patient who voluntarily withdraws consent or is discontinued (e.g., because of an AE) from the study prior to completion will be considered as withdrawn from the study. Patients may be discontinued from the study for any reason including any of the following circumstances:

- Occurrence of intolerable AE, as assessed by the Investigator or designee.
- Clinically significant abnormality on vital signs, electrocardiogram (ECG), clinical

laboratory, or physical examination evaluations, as assessed by the Investigator or designee.

- Subjects with a QTcF ≥500 msec or ≥60 msec above the patient's Baseline value will discontinue study medication and be re-assessed. The ECG should be repeated until values return below 500 msec, or ≥60 msec above Baseline. These findings will be reviewed by a cardiologist. Any additional intervention for the safety of the subject should be discussed with the Study Medical Monitor and Sponsor.
- ALT or AST ≥2 x ULN.
- Withdrawal of consent.
- Lost to follow-up.
- Administrative reasons (e.g., Sponsor decision).
- Major violation of the protocol.
- If in the opinion of the qualified Investigator, it is in the best interest of the patient.
- Non-compliance with study requirements and restrictions.
- Use of a concomitant medication that, in the opinion of the Investigator or designee, could interfere with the study procedures or data integrity or compromise the safety of the patient.
- Positive breath alcohol test at Check-in to the CRU.
- Termination of the study.

When an event such as a family emergency, a transient intercurrent illness (e.g., a cold) unrelated to study drug, or a remediable act of non-compliance prevents a patient from Check-in to the CRU, but the patient wishes to continue in the study, with the agreement of the Investigator, the research site staff may attempt to reschedule the Check-in and retain the patient in the study.

If a patient is prematurely discontinued from participation in the study for any reason after study drug administration, the Investigator or designee must make every effort to perform the assessments scheduled for the Day 14 visit (7 days after the last dose of study drug). The reason for withdrawal will be recorded in the eCRF and the patient's source medical record.

In the event of a patient discontinuation following dosing, PK and safety assessments may continue at the discretion of the Investigator based on the time points outlined in the Time and Events Schedule (Table 1).

Patients who are randomized, but not dosed, may be replaced. Patients who receive at least one dose of study drug, but are withdrawn prior to study completion, will not be replaced.

4.6 Rater Qualifications

Raters must demonstrate sufficient assessment experience as well as appropriate educational background and indication experience.

Raters performing the clinical assessments will require training and approval by the Sponsor designated vendor prior to rating in this study.

The vendors designated by the Sponsor will conduct rater qualification and will provide documentation about each rater's certification and/or training.

If possible, each subject will be interviewed and assessed throughout the study by the same rater.

5 STUDY DRUG INFORMATION

5.1 Study Drug Administration

The study drug will be administered as a single oral dose. Patients will receive one of the following:

Day 1 Dosing

- Arm 1: 75 mg REL-1017 powder prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing
- Arm 2: 100 mg REL-1017 powder prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing
- Arm 3: 100 mL of Ocean Spray® Diet Cranberry juice (Placebo).

Day 2-6 Dosing

- Arm 1: 25 mg REL-1017 powder prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing;
- Arm 2: 50 mg REL-1017 powder prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing; or,
- Arm 3: 100 mL of Ocean Spray® Diet Cranberry juice (Placebo).

The administration of study drug must be observed by a staff member. After drinking the 100 mL of study drug, 25 mL of non-carbonated water will be added to the study drug container and gently swirled. The patient will drink this rinse volume followed by 125 mL of non-carbonated water to drink immediately thereafter. All dosing must be completed within 5 minutes.

Dosing will take place once daily in the morning after an overnight fast (at least 8 hours).

5.2 Study Drug Identification

The investigational product, REL-1017, is composed of d-methadone HCl as a powder and prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing. The drug product will be supplied by the Sponsor. The study drug will be administered as a solution of 25 mg, 50 mg, 75 mg or 100 mg REL-1017, based on randomization prepared in Ocean Spray® Diet Cranberry Juice with a final volume of 100 mL

Patients will continue to take the same, stabilized antidepressant medication that they were taking at Screening throughout the course of the study, and the supply of medication during the confined study period will be arranged and assured by the Investigator.

An unblinded pharmacist will assign study drug to patients according to randomized treatment codes provided by the Interactive Web Response System (IWRS). The randomization code used in the IWRS will be prepared by a statistician who is not working as a statistician on the study in any other capacity. The study drug solution will be prepared within 3 hours of administration in

blinded containers, and then will be dispensed to blinded study staff for administration to the patients.

After drinking the 100 mL of study drug, 25 mL of non-carbonated water will be added to the study drug container and gently swirled. The patient will drink this rinse volume followed by 125mL of non-carbonated water to drink immediately thereafter.

All dosing must be completed within 5 minutes.

Dosing will take place once daily in the morning after an overnight fast of at least 8 hours.

5.2.1 Packaging and Labeling

Each container of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory requirements.

Clinical study drug supply labels will bear the following information:

- Statement indicating that the drug is an investigational drug.
- Name, number, or identifying mark of the drug.
- Re-test date of the drug.
- Recommended storage conditions of the drug.
- Lot number of the drug.
- Name and address of the Sponsor.
- Protocol code or study ID.
- Quantity of drug per container.

The pharmacy staff at each site will record the following information for the Ocean Spray® Diet Cranberry Juice that is used for Placebo and to dissolve the REL-1017 for administration during the clinical study:

- Type of container, e.g., plastic bottle, aluminum can.
- Size of container.
- Name and address of the manufacturer/distributor.
- Lot number.
- Expiration/use buy/sell by/best if used by date.

5.2.2 Handling, Storage, and Accountability

All study drug will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures (SOPs), and applicable regulations (*Guidelines for Temperature Control of Drug Products during Storage and Transportation, GUIDE-0069*). Appropriate storage temperature and transportation conditions will be maintained

for the study drug from the point of manufacture up to delivery of the study drug.

Upon receipt by the study site, the bulk study drugs will be promptly transferred to the appropriate environmentally controlled storage area. The research pharmacy staff will examine the shipment and temperature monitoring devices (if applicable) to verify that the bulk study drugs were received in acceptable condition. Once inspected, the bulk study drugs will be stored in a restricted access, secured area with access limited to authorized research site staff, under physical conditions consistent with the investigational product's specific requirements. After study drug is dispensed to patients, the remaining bulk study drug will be returned to storage in a restricted access, secured area under physical conditions consistent with the investigational product's specific requirements.

The research site's pharmacist or delegate is responsible for ensuring that all bulk study drug received at the site is inventoried and accounted for throughout the study, according to applicable regulations. All containers of dispensed study drug that have been provided to the patients will be returned to the pharmacy, and any volume of unused study drug will be recorded. Dispensed study drugs that have not been used will not be provided to patients again (even to the same patient), nor relabeled or reassigned for use by other patients. Study drugs that have been dispensed, but not used, will be stored and disposed of according to the Sponsor's instructions.

The contents of dispensed study drug containers will not be combined. Unused bulk study drugs and dispensed study drugs will be available for verification by the Sponsor's site monitor.

5.2.3 Dispensing

The study drug will be dissolved in Ocean Spray® Diet Cranberry Juice. Details regarding the preparation and administration of the study drug will be outlined in the pharmacy manual. The study drug solution will be prepared within 3 hours of administration. Only eligible patients participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drug.

5.3 Method of Assigning Patients to Treatment Groups

Randomization will be used to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown patient attributes (e.g., demographics and Baseline characteristics) are evenly balanced between treatment groups, and to enhance the validity of statistical comparisons between treatment groups.

Each potential patient will be assigned a unique number in the Screening process (Patient ID Number). This number will be used to identify the patient throughout the study. Patients who are randomized will be assigned a unique randomization number. Once any patient number is assigned, it cannot be reassigned to any other patient.

All randomization codes will be generated by the designated unblinded statistician at Syneos Health, Inc., (formerly INC Research, Inc.) before the start of the study. The treatment assignment for each subject will be assigned through the IWRS in a 1:1:1 ratio (REL-1017 25 mg, REL-1017 50 mg, or Placebo). Stratified randomization will be used to achieve a reasonable balance of patients taking cytochrome (CYP) 2B6 inhibitor ADTs versus patients who

take non-CYP2B6 inhibitors within the three treatment groups. A randomization list will be computer-generated for each of the two strata using random permuted blocks (first strata: patients receiving concomitant ADTs that are cytochrome CYP2B6 inhibitors: paroxetine, fluoxetine, sertraline; second strata: patients receiving concomitant ADTs that are not CYP2B6 inhibitors). The goal of stratified randomization is to end the study with a similar number of patients taking CYP2B6 inhibitors in each study treatment group (e.g., if 15 patients are randomized who are taking ADTs with CYP2B6 inhibitor activity, then approximately 5 will be in the REL-1017 25 mg group, 5 will be in the REL-1017 50 mg group, and 5 will be in the Placebo group). Stratification will allow for subgroup exploratory analyses to be interpreted more easily after the study is complete and unblinded.

If applicable, replacement patients for patients who withdraw prior to dosing will receive the same treatment allocation as those whom they replace.

5.4 Selection of Doses

Since extensive clinical experience is available for racemic methadone and some clinical experience for d-methadone,[31,32,33] the 25 mg and 50 mg doses are selected based on the comparative characteristics of racemic methadone and available data with d-methadone in healthy patients.

The following rationale was applied. In recent studies in healthy patients, an oral dose of at least 0.2 g/kg (10 mg to 20 mg) or 8 mg to 15 mg was well tolerated and provided information on the PK of individual isomers and the interaction with other CYP3A4 substrate drugs.[34] Moreover, in the study of REL-1017 alone in opiate-naive patients, a dose as high as 150 mg was tested with no severe adverse reactions. Due to differences in the pharmacologic activity of the methadone enantiomers, the same incidence and severity of opioid-related AEs observed with racemic methadone are not anticipated to occur with the administration of d-methadone.

Based on the safety data from Protocol REL-1017-111, single doses of 5 mg, 20 mg, 60 mg, 100 mg, and 150 mg of REL-1017 or Placebo were well tolerated. The results of Protocol REL-1017-112 evaluated 10 days of dosing with as high as 75 mg, and no impact on safety was observed. Regardless of the confirmed dose proportionality, the comparison of concentration and exposure between the 50 mg and 75 mg REL-1017 treatment groups demonstrated only slight differences. Consequently, 25 mg and 50 mg doses were chosen for administration in Protocol REL-1017-202 as daily doses over a period of 7 days.

To reach steady state more quickly for REL-1017 25 mg and REL-1017 75 mg dosing arms, a loading dose on Day 1 was added to each dosing arm, REL-1017 75 mg on Day 1 followed by 25 mg REL-1017 on Day 2-7; 100 mg REL-1017 on Day 1 followed by 50 mg REL-1017 on Day 2-7.

PK/PD modelling, based on the demonstrated AUC_{tau} of d-methadone in pre-clinical and clinical studies and on the AUC_{tau} of ketamine at doses that provide antidepressant efficacy, supports the conclusion that d-methadone 25 mg and 50 mg QD are the predicted efficacious doses.

5.5 Blinding and Unblinding Procedures

The REL-1017 powder will be dissolved in a strong-tasting juice/drink (Ocean Spray® Diet Cranberry Juice) to mask the taste of the d-methadone. This will help to maintain the blind. Also, patients who are randomized to receive Placebo will receive an equivalent volume of Ocean Spray® Diet Cranberry Juice.

5.6 Treatment Phase

The only persons with access to the blinding schema during the treatment phase will be the designated pharmacy personnel who are responsible for the dispensing of study drug, the compliance auditor(s) who verify conformity to study procedures, and the unblinded statisticians who generate the code. Under normal circumstances, the blind will not be broken until all patients have completed treatment. Blinded dosing information will be broken only in an emergency where knowledge of the dosing information could impact further treatment decisions or aid in the emergency treatment of a patient. Individual code breaks will result in the withdrawal of the patient from the study. The date, time, and reason for the unblinding will be documented in the appropriate section of the eCRF and in the source documents.

5.7 Treatment Compliance

Study drugs, including the patient's current ADT, will be administered under the supervision of study personnel, and treatment compliance will be verified accordingly.

6 STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Time and Events Schedule (Table 1).

The pre-dose period on Day 1 will be considered time zero. Other logistical considerations (e.g., sequence of events, assessment windows) will be outlined in study-specific procedures. Post-Screening psychiatric scales will be administered using the timeframe since the last administration of the scale.

6.1 Study Procedures

6.1.1 Screening (Day -30 to Day -2)

After the ICF is signed, a Screening number will be assigned to the patient, and an outpatient Screening Visit will be conducted during which the patient will undergo an interview and medical assessments to determine eligibility for study participation. Patients who meet all the Screening entry criteria will be scheduled for admission to the inpatient facility.

6.1.2 Check-In (Day -1)

Inpatient admission may occur up to 30 days after the Screening Visit as soon as it is determined that patients meet all Screening criteria. Upon Check-in, patients will undergo further medical and psychiatric Screening according to the Time and Events Schedule (Table 1) to ensure they continue to qualify for participation in the study. The patient's prescribed antidepressant will be administered by site personnel while the patient is confined to the study unit.

6.1.3 Baseline (Day 1)

Assessments will be conducted according to the Time and Events Schedule (Table 1). The Baseline criteria checklist must be completed on Day 1, prior to randomization, to determine if the patient is still eligible for participation in the study. Any patient who does not meet full Screening and Baseline entry criteria must be discontinued from the study and will be considered a screen failure. Patients who meet full Screening and Baseline entry criteria will be randomized and assigned a Patient ID Number.

6.1.4 Dosing Period (Day 1 to Day 7)

The dosing period will begin on Day 1 and continue through the last dose of study drug on Day 7 (End of the Dosing Period [EDP]). Study drug will be administered in the morning. Assessments during the dosing period will include measures of safety and tolerability, PK, and efficacy. For patients who discontinue study drug prior to Day 7, all EDP assessments should be completed according to the Time and Events Schedule (Table 1) provided informed consent has not been withdrawn.

6.1.5 24-Hour Post-Dose Assessments (Day 8)

On Day 8, patients will be evaluated 24 hours after the final dose of study drug on Day 7 according to the Time and Events Schedule (Table 1). Blood samples will also be drawn for PK analysis approximately 24 hours after the last dose of study drug.

6.1.6 Discharge (Day 9)

Following the last dose of study drug, each patient (including those who discontinue from the study drug prior to Day 7) is to remain in the inpatient facility for at least 2 additional days of safety and efficacy monitoring. The assessments to be conducted prior to Discharge on Day 9 are listed in the Time and Events Schedule (Table 1). Blood samples will also be drawn for PK analysis prior to Discharge on Day 9.

6.1.7 Outpatient Observation Period (Day 10 to Day 14)

The End of the Observation Period (EOP) will occur on Day 14 when the EOP interview will be conducted in person to assess psychiatric symptoms and safety endpoints, including medical conditions, new medications, and newly emergent AEs as listed in the Time and Events Schedule (Table 1). A confirmatory pregnancy test will be administered. Blood samples will also be drawn for PK analysis approximately168 hours after the last dose of study drug. For patients who discontinue study drug prior to Day 7, the EOP interview will occur 7 days after their last dose of study drug. (The window for the EOP visit is ± 3 days.)

6.1.8 Follow-Up Period (Day 15 to Day 21)

Follow-up interviews will be conducted with all patients (including those who discontinue from the study drug prior to Day 7) 14 days after their last dose of study drug. (The visit window is ± 3 days). In the Follow-Up interview (Day 21), C-SSRS, AEs, and medications will be recorded (Table 1). This interview may be conducted by telephone. A confirmatory pregnancy test will be administered if the visit is conducted at the site. During the Follow-Up Period, safety evaluations should be conducted, at the discretion of the Investigator, to evaluate any unresolved abnormal treatment-emergent findings.

6.2 Safety Assessments

Safety assessments will be performed at the time points indicated in the Time and Events Schedule (Table 1).

6.2.1 Vital Signs

Routine vital sign parameters will be measured at Screening and Check-in (Day -1), pre-dose and 1 hour post-dose on Day 1, pre-dose on Day 2 through Day 7, once on Day 8, prior to Discharge on Day 9 and on Day 14. Vital signs should be measured after the patient has been in a supine or semi-supine position for at least 3 minutes. Vital signs will include blood pressure (BP, systolic and diastolic, mmHg), heart rate (HR, pulse rate [bpm]), pulse oximetry, and respiratory rate (RR, breaths/minute). Measurement of orthostatic BP should follow measurement of supine or semi-supine BP. Patients should be asked to stand for 3 minutes before measurement of orthostatic BP. The BP cuff should be kept in place between supine and orthostatic BP measurements. Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

6.2.2 Weight and Body Temperature

Weight and oral body temperature (°C) will be recorded at Screening, Check-in (Day -1), EDP (Day 7), and EOP (Day 14).

6.2.3 Physical Examination

The physical examination, assessing the patient's overall health and physical condition, will be performed at Screening, Check-in (Day -1); Day 7 and prior to Discharge (Day 9). The patient's BMI will be calculated at Screening. Height will be recorded at Screening only.

6.2.4 12-Lead Electrocardiograms (EGCs)

12-Lead ECGs will be performed at Screening; at Check-in (Day -1); 1 hour pre-dose and 2 hours, 4 hours, 6 hours, and 8 hours post-dose on Day 1 and Day 2; daily 2 hours post-dose on Day 3 through EDP (Day 7); on Day 8; prior to Discharge on Day 9; and at EOP (Day 14). Electrocardiograms will be performed in triplicate at each time point (e.g., 3 separate 10-second ECG recordings collected at intervals of approximately 1 minute apart, but within 5 minutes).

Electrocardiograms will be performed with the electrodes positioned on the torso after the patient has been resting in a supine or semi-supine position for at least 3 minutes. The ECG will electronically measure and calculate ventricular HR and the PR, QRS, measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (QT), and QTc intervals. The Fridericia formula will be used for QTc. Triplicate ECGs will be averaged in the database for data analysis.

ECGs will be submitted electronically to central ECG reading center for evaluation of subject for entry into the study. The Investigator will make a final judgment on whether to include the subject's ECGs meets the entry criteria for the study.

At the discretion of the Investigator, a standard 12-lead ECG with conventional lead placement may be performed at any time during the study (e.g., in case potential ischemia or any cardiac abnormality is observed).

6.2.5 Clinical Laboratory Assessments

Clinical laboratory tests (chemistry, hematology, and urinalysis) will be conducted at Screening, Check-in (Day -1), EDP (Day 7), and EOP (Day 14) unless otherwise noted. Blood and urine samples will be collected, processed, and shipped according to the research site's SOPs and instructions from the safety laboratory. All laboratory safety data will be reviewed by the Investigator or designee for clinical significance.

Blood volumes required per draw, laboratory test, and study phase are available in Appendix 11.1. Additional laboratory samples may be taken at the discretion of the Investigator or designee (e.g., if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety).

6.2.5.1 Clinical Chemistry

Quantitative analysis will be performed for the following analytes: alkaline phosphatase, albumin, calcium, chloride, creatinine, random glucose, potassium, magnesium, ALT, AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase, sodium, total bilirubin, urea, and testosterone.

6.2.5.2 Hematology

A peripheral blood smear will be performed to assess blood cell morphology. Quantitative analysis will be performed for at least the following analytes: hemoglobin, hematocrit, red blood cell count (RBC), white blood cell (WBC) count, WBC differential (absolute counts), and numerical platelet count.

6.2.5.3 Urinalysis

Qualitative or quantitative analysis will be performed for the following analytes, as appropriate: specific gravity, pH, ketones, glucose, nitrite, blood, leukocyte esterase, protein, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed.

6.2.5.4 Thyroid Panel

A thyroid panel will be evaluated at Screening to identify patients with clinically significant abnormal laboratory results for TSH, T3, and T4.

6.2.5.5 Viral Screen

Serology will screen for hepatitis B, hepatitis C, and HIV at Screening. Patients with negative viral serology tests for hepatitis B and HIV will be eligible for the study. Positive hepatitis C values will be reviewed for eligibility on a case by case basis by the Medical Director. Positive results will be managed according to local regulatory requirements and the site's SOPs.

6.2.5.6 Breath Alcohol

Breath alcohol testing will be performed according to the site's SOPs at Screening, Check-in (Day -1), and Day 14. If there is any doubt or concern regarding alcohol use, research site staff may request a breath test for alcohol measures at any time during the study.

6.2.5.7 Drugs of Abuse Screen

A urine drug test will be conducted at Screening and Check-in. The urine drug screen will test for following drugs of abuse: tetrahydrocannabinol, opiates (including oxycodone), amphetamines, cocaine, and benzodiazepines.

6.2.5.8 Pregnancy Testing

A urine pregnancy test and a serum follicle stimulating hormone (FSH) test will be administered to all female patients at Screening (Day -30 to Day -2). Negative test results are required for enrollment in the study. Another negative urine pregnancy test will be required at Check-in (Day -1) for confirmation. Additional confirmatory pregnancy tests will be administered at the End of the Observation Period Visit (Day 14 ± 3 days and Follow-Up Visit (Day 21 ± 3 days).

6.2.6 Other Safety Assessments

6.2.6.1 Clinical Administered Dissociative States Scale (CADSS)

The Clinical Administered Dissociative States Scale (CADSS) will be measured at 30 to 60 minutes pre-dose on Day 1, 2 hours post-dose on Day 1, 2 hours post-dose on Day 7, and prior to Discharge on Day 9.

6.2.6.2 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be measured at Screening and Check-in (Day -1); at pre-dose on Day 1 and Day 2; and on Day 8, Day 9, EOP (Day 14) and EOS (Day 21).

6.2.6.3 The Clinical Opiate Withdrawal Scale (COWS)

The COWS will be measured on Day 8, Day 9, and EOP (Day 14).

6.2.6.4 4-Item Positive Symptom Rating Scale (4-Item PSRS)

The 4-Item PSRS will be measured at 30 to 60 minutes pre-dose at Baseline (Day 1), 2 hours post-dose on Day 1 (after first dose), 2 hours post-dose on Day 7 (EDP) (after last dose), and prior to Discharge on Day 9.

6.3 Pharmacokinetic Assessments

Venous blood samples will be collected daily from Day 1 through Day 7, Day 8, Day 9, and on Day 14 at the following time points to determine the plasma concentrations of REL-1017:

- PK sampling will be done on Day 1 at 1 hour pre-dose and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose.
- On Day 2 through Day 7, sampling will be done 1 hour pre-dose.
- On Day 8, sampling will be done approximately 24 hours after the last dose of study drug (on Day 7).
- On Day 9, sampling will be done approximately 48 hours after the last dose (on Day 7).
- On Day 14, sampling will be done approximately 168 hours after the last dose (on Day 7 ± 3 days).

A safety catheter will be placed before dosing on Day 1 until the 12-hour post-dose sample has been collected in the event a rescue medication is required.

Samples will be collected, processed, and shipped according to the site's SOPs and instructions from the Sponsor or the bioanalytical laboratory. The blood volumes required for PK sampling are available in Appendix 11.1.

The plasma samples will be analyzed by the bioanalytical laboratory using validated methods.

Plasma samples will be shipped frozen on dry ice from the research site to the bioanalytical laboratory. Samples will not be shipped without prior arrangement with the bioanalytical laboratory and notification of the Sponsor.

Drug concentration information that may unblind the study will not be reported to the study site or blinded personnel until the study has been unblinded.

6.4 Efficacy Assessments

Efficacy assessments will be performed at the time points indicated in the Time and Events Schedule (Table 1).

6.4.1 Primary Efficacy Measure

The Montgomery-Asberg Depression Rating Scale (MADRS) will be measured at pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14.

6.4.2 Secondary Efficacy Measures

6.4.2.1 Symptoms of Depression Questionnaire (SDQ)

The SDQ is a 44-item, self-report scale designed to measure the severity of symptoms across several subtypes of depression. The SDQ was developed to more fully capture the heterogeneity of symptom presentations of depressive disorders than current, widely used scales for MDD. The SDQ includes items that inquire about an extensive number of depressive symptoms beyond the ones included in other commonly used scales such as the Quick Inventory of Depression Symptomatology (QIDS).

The 44 SDQ items are rated on a 6-point scale. Each item is rated based on a subject's perception of what is normal for the individual (score = 2), what is better than normal (score = 1), and what is worse than normal (scores = 3–6).

Items reflect a broad and heterogeneous collection of depression related symptom features. For example, Factor 1 (see Appendix 11.9) measures common dimensions of depressive symptoms including lassitude, energy, mood, and cognitive, and social functioning (subscale 1). Factor 3 includes items on outlook on life, pessimism, suicide, self-harm, and worthlessness (subscale 3). Factors 4 and 5 measure physiological features of depression, namely sleep difficulties and changes in appetite/weight, respectively. Moreover, the SDQ includes several items that inquire about anxiety symptoms often present among depressed patients.[35]

6.4.2.2 Clinical Global Impressions (CGI) Scale

The CGI-S will be measured at pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14. The CGI-I will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14.

6.5 Pharmacogenetic Analysis

On Day 1 of dosing, a blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes that may affect the PK of d-methadone. Pharmacogenetic analysis may be performed in cases where patients experience abnormal PK results. This analysis would be restricted to the evaluation of genes that may be involved in the PK of d-methadone (e.g., drug metabolism, disposition, elimination).

One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each patient into an appropriately labeled ethylene diamine tetra-acetic acid (EDTA) tube. The tube will be inverted 8 to 10 times to reduce the chance of clot formation. Within 30 minutes of collection, the sample will be stored at -20°C or colder until shipped on dry ice sufficient to last during

transport. Samples will be collected and shipped according to the site's SOPs and instructions from the Sponsor and/or pharmacogenetic laboratory.

The samples will be stored in a secure space with adequate measures to protect patient confidentiality. The samples will be retained while research on d-methadone (REL-1017) continues, but not longer than 20 years.

6.6 Appropriateness of Measures

All safety and efficacy assessments have been well documented and are generally regarded as reliable, accurate, and relevant in this patient population.

6.6.1 Baseline Measurements

6.6.1.1 Mini International Neuropsychiatric Interview

The MINI, Version 7.0.2, is a widely used psychiatric structured diagnostic interview instrument that can be used to assess the effectiveness of the patient's prescribed antidepressant medication. The interview is brief and only requires "yes" or "no" answers.[36]

6.6.1.2 Antidepressant Treatment Response Questionnaire

The ATRQ examines the efficacy and adequacy of any antidepressant treatment in a step-by-step procedure. This widely accepted questionnaire evaluates improvement (0% to 100%) and adequacy (adequate duration and dose).[37]

6.6.1.3 Hamilton Depression Rating Scale (HAM-D-17)

The HAM-D-17 has proven useful for many years as a way of determining a patient's level of depression before, during, and after treatment. Many clinicians consider the HAM-D-17 to be the gold standard for evaluating the severity of a patient's depression. In Study REL-1017-202, the HAM-D-17 must be administered using the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D).[38]

6.6.2 Efficacy Measurements

6.6.2.1 Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is one of the questionnaires most frequently used in clinical studies to measure outcome in antidepressant efficacy studies. This scale exhibits construct validity (internal homogeneity) and concurrent validity relative to the HAM-D-17 and the concepts of endogenous and non-endogenous depression. The questionnaire includes questions on the following symptoms: (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. A higher MADRS score indicates severer depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60 with scores above 34 indicating severe depression. In Study REL-1017-202, the MADRS must be administered using the Structured Interview Guide for the MADRS (SIGMA).[39, 40,41]

6.6.2.2 Clinical Global Impressions (CGI) Scale

The CGI-S is a standard method used in clinical studies to quantify and track patient progress

and treatment response over time. The scale is composed of 7 ratings: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients. The score ranges from 1 to 7, and a lower CGI-S score indicates lower levels of depression.[42]

The CGI-I is a standard method used in clinical studies to quantify and track patient change over time. The scale is composed of 7 ratings: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse. The score ranges from 1 to 7, and a lower CGI-I score indicates greater improvement in symptoms.[42]

6.6.3 Other Safety Measurements

6.6.3.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is routinely used to quantify the severity of suicidal ideation and behavior. Both the ideation and behavior subscales are sensitive to change over time.

The scale identifies behaviors that may be indicative of an individual's intent to commit suicide. This measure contains six "yes" or "no" questions in which respondents are asked to indicate whether they have experienced several thoughts or feelings relating to suicide over the past month. Each question addresses a different component of the respondent's suicide ideation severity: (1) Desire to be dead; (2) Suicidal thoughts; (3) Consideration of suicide methods; (4) Formed intent to commit suicide; (5) Completed suicide plan; and (6) Initiated suicide plan. A higher score indicates a higher intensity of suicidal ideation.[43]

At the Screening Visit, the C-SSRS Baseline/Screening version will be administered. At all subsequent visits, the C-SSRS Since Last Visit version will be administered.

6.6.3.2 Clinician Administered Dissociative States Scale (CADSS)

The CADSS is an instrument for the measurement of present-state dissociative symptoms with good interrater reliability and construct validity. The CADSS can discriminate patients with dissociative disorders from healthy subjects and patients with other psychiatric disorders. The CADSS is a 23-item scale with all items administered to the subject. A higher score indicates a higher likelihood of the presence of a dissociative state. Subscales of the CADSS were developed to identify amnesia (Items 14 and 15), depersonalization (Items 3 to 7), and de realization (Items 1, 2, 8 to 13, and 16 to 19).[44]

6.6.3.3 Clinical Opiate Withdrawal Scale (COWS)

Safety assessments have been included to monitor for any opioid-related effects. The COWS is a clinician-administered instrument that rates 11 common opiate withdrawal signs or symptoms. The summed score of the 11 items can be used to assess a patient's level of opiate withdrawal and to make inferences about their level of physical dependence on opioids.[45]

6.6.3.4 4-Item Positive Symptom Rating Scale (4-Item PSRS)

The 4-Item PSRS was adapted from the Brief Psychiatric Rating Scale developed by Ventura and colleagues. It is a clinician-administered scale intended to assess the extent to which a subject is

currently experiencing positive psychotic symptoms. The scale assesses paranoia and hallucinations as well as some specific issues related to difficulty thinking and having unusual thoughts. When administering the scale, the rater enters a number for each of 4 symptom constructs with scores that range from 1 (not present) to 7 (extremely severe). Total score on the 4-Item PSRS can range from 4 to 28. [46,47]

6.6.4 Pharmacokinetic (PK) Assessments

Standard PK assessments, appropriate for an early Phase 2 study, have been included as outlined in Section 6.3.

7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator or designee and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE. Procedures for managing AEs and SAEs are detailed in the research site's SOPs.

Spontaneously reported or observed AEs will be recorded throughout the study, and AEs will be elicited using a non-leading question at every visit from Screening through the Day 21.

Follow-Up telephone call will assess the status of any AE ongoing at the time of Discharge and record any new AE that has occurred. Regardless of seriousness, intensity, or presumed relationship to the study drug, all AEs will be recorded in the source documentation from the time of first contact with the patient (e.g., Screening) until the end of the Follow-Up Period of the study (Day 21).

AEs that occur after medical Screening and prior to administration of the first dose of study drug will be recorded in the source documentation as Baseline signs and symptoms. All measures required for the management of AEs will be recorded in the source documentation.

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, regardless of relationship to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the investigational product(s) was given (e.g., during the time from discontinuation of prohibited medications).

Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

7.1.2 Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose

- Results in death,
- Is life-threatening (at the time of the event),
- 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 a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information set out in the Investigator's Brochure or on the label of the drug.

7.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (e.g., from clinical chemistry or hematology tests or urinalysis) or other abnormal assessments (e.g., from vital signs, ECGs, C-SSRS, 4-Item PSRS, CADSS, COWS) judged as clinically significant by the Investigator or designee will be recorded as AEs or SAEs if they meet the definitions provided in Section 7.1.1 and Section 7.1.2. Furthermore, abnormal laboratory findings or other abnormal assessments present at Baseline that significantly worsen following the start of the study (i.e., become clinically significant) will be reported as AEs or SAEs. However, abnormal laboratory findings present at the start of the study that do not worsen will not be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.1.4 Other Adverse Events of Interest

If other AEs of interest are observed during the study, they will be recorded in the eCRFs and analyzed as appropriate in the final clinical study report. Examples of these types of AEs would be difficulty breathing, chest pain, or clinically significant bradycardia, tachycardia, or QTcF prolongation (≥500 msec or ≥60 msec above the patient's Baseline value that continuously occurs over a period of time). At the discretion of the Investigator, ECGs or other relevant tests may be repeated for confirmation of the results.

If more than one ECG is collected, the mean of the replicate measurements will be reported. If any of the 3 individual ECG tracings has a QTcF value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from those triplicate measurements is also ≥500 msec. Changes from Baseline will be defined as the change between QTcF post-dose from the time-matched average Baseline triplicates on Baseline Day 1 (Visit 2).

The study drug will be administered under the supervision of study personnel, which should eliminate the opportunity for abuse during the course of the study. However, Investigators should take note of AEs that might suggest that the study drug has the potential for abuse. For example, the occurrence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential.

Examples of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms that may provide abuse-related information about a drug include:

- Euphoria-related terms - euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect
- Terms indicative of impaired attention, cognition, and mood - somnolence, mood disorders, and disturbances
- Dissociative/psychotic terms - psychosis, aggression, confusion, and disorientation
- Drug withdrawal syndrome

7.2 Evaluation of Adverse Events and Serious Adverse Events

The Investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality, and outcome of an AE.

7.2.1 Classification of Adverse Event Intensity

For each recorded AE or SAE, the Investigator or designee must assess the intensity based on the following criteria (Table 4). If there is insufficient information to determine intensity, the AE must still be reported.

Table 4 Classification of Adverse Event Intensity

Classification	Definition
Mild	An event 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	An event that is 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 subject.
Severe	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required.

7.2.2 Classification of Adverse Event Causality

For each recorded AE or SAE, the Investigator or designee must assess the causality based on the following criteria (Table 5) to determine the relationship between the AE and study drug.

Table 5 Classification of Adverse Event Causality

Classification	Definition
Unrelated	The AE or SAE is judged to be *clearly and incontrovertibly due only to extraneous causes* (e.g., disease, environment) and does not meet the criteria for study drug relationship listed under probable, possible, or unlikely.

Classification	Definition
Unlikely	The AE or SAE is *unlikely related* to the study drug, when the AE or SAE: • Does not follow a reasonable temporal sequence from administration of the study drug. • May readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • Does not follow a known pattern of response to the study drug. • Does not reappear or worsen when the study drug is re-administered.
Possible	The AE or SAE is *possibly related* to the study drug when the connection to the study drug appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE: • Follows a reasonable temporal sequence from administration of the study drug. • May have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
Probable	The AE or SAE is *probably related* to the study drug when the connection to study drug can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE: • Follows a reasonable temporal sequence from administration of the study drug. • Cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. • Disappears or decreases upon cessation or reduction in dose (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the study drug, yet drug relatedness clearly exists, e.g., bone marrow depression or tardive dyskinesias). • Follows a known pattern of response to the suspected study drug. • Reappears upon re-challenge.

Classification	Definition
Definite	The AE or SAE is *definitely related* to the study drug when the event: • Follows a reasonable temporal sequence from administration of the study drug. • Follows a known pattern of response to the suspected study drug. • Is confirmed by improvement on stopping and reappearance of the event on repeated exposure to the study drug. • Cannot be reasonably explained by the known characteristics of the subject's clinical state.

7.2.3 Classification of Adverse Event Outcome

For each recorded AE or SAE, the Investigator or designee must assess the outcome at the time of the last observation. The outcome of AEs or SAEs will be documented as outlined in Table 6.

Table 6 Classification of Adverse Event Outcomes

Classification	Definition
Fatal	The subject died.
Resolved	The AE or SAE has ended.
Resolved with Sequelae	The AE or SAE has ended but changes are noted from Baseline.
Unresolved	The AE has not ended. An AE outcome can only be categorized as unresolved, if the AE is: • *Ongoing* at the end of the reporting period (i.e., 14 days after the last dose of study drug on Day 7), and the Investigator deems that further follow-up is not medically required. • *Lost to follow-up* after repeated unsuccessful attempts to contact the subject. • *Ongoing and referred* to the subject's physician or a specialist for follow-up.

7.3 Reporting Procedures

7.3.1 Serious Adverse Events and Serious Unexpected Adverse Events

Any SAE, expected or unexpected, irrespective of relationship to study treatments, including death due to any cause, experienced by a study patient will be reported to Relmada, by the Investigator or designee within **24 hours** of learning of the event. Information regarding the SAE will be transmitted to Relmada by fax at 1-888-228-5672.

The contact information for the Syneos Health safety and pharmacovigilance team and for the

Medical Monitor is as follows:

Name:	Syneos Health Safety and Pharmacovigilance
Fax:	1-877-464-7787
Email:	safetyreporting@syneoshealth.com
Name:	Morgan Kearney, MD, Associate Medical Director
Address:	Syneos Health, Inc. 3201 Beechleaf Court, Suite 600 Raleigh, NC, USA 27604
Phone:	1-919-257-6801
Mobile:	1-919-397-0174
Email:	Morgan.Kearney@syneoshealth.com

Syneos Health assumes responsibility for the appropriate reporting of AEs to the regulatory authorities. All SAEs that are unlisted and associated with the use of the study drug will also be reported to all Investigators. The Investigator (or Relmada Therapeutics, Inc., where required) must report these events to the appropriate IRB that approved the protocol (unless otherwise required and documented by the IRB).

All additional follow-up evaluations for SAEs will be reported to Relmada.

7.3.2 Any Adverse Event

Regardless of seriousness, intensity, or presumed relationship to study drug, all AEs will be recorded in the source documentation. When the signs and symptoms are due to a common etiology, the diagnoses will be recorded whenever possible. In addition, the Investigator must record his or her opinion as to the intensity of the AE and whether the AE is related to the study drug. All measures required for management of the AE will be recorded in the source documentation.

7.3.3 Pregnancy

Given that the effects of the study drug on egg and sperm have not been fully elucidated, any pregnancy in the patient or partner of a patient participating in the study will be reported to Relmada within **24 hours** of learning of the event.

Follow-up information will be obtained where possible (i.e., with the consent of the patient or patient's partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

7.4 Follow-Up of Adverse Events and Serious Adverse Events

All unresolved AEs will be followed for up to a minimum of *14 days* after the patient's final dose of study drug on Day 7 unless the Investigator's judgment dictates otherwise, the event has resolved or stabilized before Day 21, or the patient is lost to follow-up.

All AEs that result in discontinuation and all SAEs will be followed until one of the following occurs:

- The event resolves.

- The event stabilizes.
- The event returns to a Baseline value, if a Baseline value is available.
- The event can be attributed to agent(s) other than the study drug or to factors unrelated to study conduct.

When it becomes unlikely that any additional information can be obtained (e.g., patient or health care practitioner refuses to provide additional information, the patient is lost to follow-up), the Investigator or designee will ensure that the follow-up includes any pertinent supplemental investigations (e.g., laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals) to elucidate the nature and/or causality of the AE or SAE.

Investigators are not obligated to actively seek AEs or SAEs in former study patients that occur after the Follow-Up Period. However, if the Investigator or designee learns of any AE or SAE at any time after a patient has been discharged from the study and the event is considered as reasonably related to the study drug, the Investigator will notify Relmada.

8 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1 Statistical and Analytical Plans

8.1.1 Analysis Populations

The study analysis populations will consist of

- Randomized population: All patients who are randomized.
- Safety population: All randomized patients who receive any study treatment (REL-1017 or Placebo).
- Pharmacokinetic population: All patients who receive REL-1017, with at least 1 post-dose blood draw to determine plasma concentration of d-methadone. Pharmacokinetic parameters will be reported for this population where available.
- Intent-to-Treat population: All randomized patients who receive any study treatment (REL-1017 or Placebo) and have a Baseline and at least 1 post-Baseline efficacy measurement (MADRS, SDQ, CGI-S, or CGI-I).

The details of patient evaluability criteria will be determined prior to study unblinding.

8.1.2 General Statistical Considerations

Complete details of the statistical analyses to be performed will be documented in a Statistical Analysis Plan (SAP) that will be completed prior to unblinding the study data. This document will include more details of the analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final clinical study report.

8.1.3 Endpoint Definitions

8.1.3.1 Primary Endpoint: Safety and Tolerability of REL-1017

The primary objective is to evaluate the safety and tolerability of 7 days of daily dosing with REL-1017 25 mg or 50 mg in patients. The following assessments will be conducted to measure safety and tolerability throughout the study:

- AEs
- Vital signs
- Weight
- Physical examination
- Clinical laboratory parameters (chemistry, hematology, and urinalysis)
- Electrocardiogram (ECG) parameters
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Clinician Administered Dissociative States Scale (CADSS)

- Clinical Opiate Withdrawal Scale (COWS)
- 4-Item Positive Symptoms Response Scale (4-Item PSRS)

8.1.3.2 Secondary Objective: Pharmacokinetic Profile of REL-1017

A secondary objective is to evaluate the PK profiles of 7 days of daily dosing with REL-1017 25 mg and 50 mg on Day 1 through Day 7, Day 8, Day 9, and Day 14 where data allow. The plasma concentration of d-methadone as a function of time will be analyzed using non-compartmental, validated software to estimate the following PK parameters:

- Maximum observed plasma concentration (C_{max})
- Time to maximum observed plasma concentration (T_{max})
- Area under the plasma concentration-time curve from time zero until the dosing interval of 24 hours (AUC_{tau})
- Area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-}last}$)
- Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)
- Apparent termination elimination rate constant (λz)
- Apparent terminal elimination half-life ($t_{½}$)
- Attainment of steady state
- Steady state clearance (C_{SS}/F)
- Volume of distribution at steady state (V_{SS}/F)
- Accumulation ratios based on minimum observed plasma concentration (C_{min}), C_{max}, and AUC_{tau}

In addition, other relevant parameters may be calculated.

8.1.3.3 Secondary Objectives: Efficacy of REL-1017

The efficacy of 7 days of daily dosing with REL-1017 25 mg and 50 mg as measured by the following efficacy endpoints:

- Change from Baseline (Day 1) to EDP (Day 7) on the MADRS with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14;
- Change from Baseline (Day 1) to EDP (Day 7) on the SDQ with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14;

- Change from Baseline (Day 1) to EDP (Day 7) on the CGI-S with measurements made pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14.
- Evaluation of CGI-I total score on Day 7 (post-dose), as well as CGI-I scores on Days 2 (pre-dose), 4 (post-dose), and 14.

8.1.4 Planned Analyses

All analyses (other than PK parameter calculations) will be performed using SAS Version 9.3 or higher, run on the Microsoft Windows Server 2003 R2 operating system. Pharmacokinetic parameter calculations will be performed using WinNonlin Version 6.3 or higher, run on the Windows XP platform or higher.

8.1.4.1 Analysis of Safety Assessments

Safety and tolerability parameters will be listed by treatment and patient and displayed in summary tables using descriptive statistics.

8.1.4.2 Adverse Events

Original terms used in the eCRFs by Investigators or designees to identify AEs will be coded using the MedDRA (Version 16.0 or higher). The number and percentage of patients with treatment-emergent AEs will be summarized by system-organ-class, preferred term, and treatment and for each treatment by maximum severity and relationship to study treatment. A treatment-emergent AE is any that is new in onset or was aggravated in severity or frequency following the first dose of study drug (Day 1), up to and including the last visit of the study (Day 21).

8.1.4.3 Other Safety Assessments

Vital signs will consist of BP (systolic and diastolic), HR, pulse oximetry, and RR. Descriptive statistics will be calculated and presented for each time point by treatment (absolute values and change from Baseline). Vital signs will be measured after the patient has been resting in a supine or semi-supine position for at least 3 minutes. Measurement of orthostatic BP should follow measurement of supine or semi-supine BP. Patients should be asked to stand for 3 minutes before measurement of orthostatic BP. The BP cuff should be kept in place between supine and orthostatic BP measurements. Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

Descriptive statistics will be calculated and presented for each time point by treatment (absolute values and change from Check-in [Day -1]) for weight and oral body temperature.

Absolute values, change from Check-in (Day -1) in 12-lead ECG results (average of triplicate assessments, where applicable), and QT/QTcF categories per FDA Guidance E14 will be summarized using descriptive statistics; frequencies (numbers and percentages) will be calculated for the overall evaluation by scheduled time and treatment. Patients must be supine for at least 3 minutes before an ECG is recorded, and they must remain supine or semi-supine and awake while the ECG is recorded. Overall interpretation and machine read intervals (HR, PR,

QRS, QT and QTcF) will be recorded on the ECG eCRF. Clinically significant ECG findings that emerge after drug treatment will be recorded on the AE eCRF.

Laboratory data will be summarized by the type of laboratory test and scheduled visit. Descriptive statistics will be calculated and presented for each time point by treatment (absolute values and change from Check-in [Day -1]). Descriptive statistics and the number of patients with laboratory test results below, within, and above normal ranges will be tabulated by scheduled time. Abnormal findings in laboratory data will be listed with a flag for clinical significance based on the Investigator judgment.

Physical examination results will be listed.

Medical history abnormalities will be coded to MedDRA terms using Version 16.0 or higher. Physical examination abnormalities will also be listed.

The original verbatim terms collected in the eCRF for concomitant medications will be coded using the WHO Drug Dictionary into drug class (Anatomical Therapeutic Chemical [ATC] level 2) and preferred term. These data will be listed.

8.1.4.4 Analysis of Pharmacokinetics

Blood samples will be collected for PK analysis on:

- Day 1 at 1 hour pre-dose (Baseline) and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose;
- Day 2 through Day 7 at 1 hour pre-dose;
- On Day 8 at 24 hours after the last dose of study drug (Day 7);
- On Day 9 at 48 hours after the last dose of study drug (Day 7) prior to Discharge from the CRU; and,
- On Day 14 at approximately 168 hours (± 3 days) after the last dose of study drug on Day 7.

The PK parameters for REL-1017 determined by non-compartmental analysis will be summarized. Graphs of the concentration (original and log transformed) versus time will be generated. Descriptive statistics, including number of patients, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum, will be calculated by time point for REL-1017 25 mg and 50 mg. Concentrations below the limit of quantification (BLQ) will be set to zero for the generation of summary statistics for concentrations and the generation of mean concentration-time plots.

For the calculation of the PK parameters, concentration-time data will be treated as follows: BLQ concentrations prior to the first quantifiable concentration will be set to zero; BLQ concentrations after the first quantifiable concentration will be treated as missing; and pre-dose sampling times relative to dosing will be set to zero. Descriptive statistics, including number of patients, mean, SD, geometric mean, geometric CV, minimum, maximum, and median will be calculated for all REL-1017 PK parameters except T_{max} or $t_{½}$. The T_{max} data will be summarized with number of patients, minimum, maximum, and median. The $t_{½}$ data will be summarized with number of patients, mean, SD, minimum, maximum, and median.

8.1.4.5 Analysis of Efficacy Assessments

The depressive symptom changes associated with 7 days of daily dosing with REL-1017 25 mg and 50 mg will be measured using the MADRS, SDQ, and CGI-S. The MADRS, SDQ, and CGI-S will be conducted pre-dose at Baseline (Day 1) and on Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and at EOP (Day 14). The CGI-I will be administered pre-dose on Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and at EOP (Day 14).

The change from Baseline in each parameter on Day 7 will be compared among treatment groups (Placebo, REL-1017 25 mg, and REL-1017 50 mg) using a mixed model of repeated measurement with treatment group, stratification (concomitant antidepressant drug) factor, visit (Day 2, Day 4, and Day 7), interaction between treatment and visit as independent variables, and Baseline endpoint as a covariate. Least square (LS) means with standard errors, differences in LS means with standard errors, 90% confidence intervals for the difference in LS means, and corresponding P-values will be presented.

Actual values, absolute change, and percent change from Baseline will be summarized by treatment and all visits.

The assumptions of normality may be evaluated using the Shapiro-Wilks test. If the assumptions of normality are not satisfied, the ranked change and ranked Baseline may replace the change and Baseline in the above mixed model as a sensitivity analysis.

8.1.5 Demographics and Other Baseline Characteristics

Demographics and Baseline characteristics (age, sex, race, ethnicity, body weight, height, oral body temperature, and BMI) will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum for continuous variables and the proportion of patients for categorical variables) for the Safety population. No formal statistical comparison between the groups will be performed. Demographics and height will be recorded at Screening only. Weight and oral body temperature will also be recorded at Check-in (Day -1), EDP (Day 7), and EOP (Day 14). In addition, BMI will be calculated at Screening.

The patient's eligibility for participation in the study will be determined with the inclusion and exclusion criteria at Screening. The inclusion and exclusion criteria will be reviewed again at Check-in (Day -1) when the patient is admitted to the CRU. The study restrictions review will also occur at Check-in (Day -1).

Patients will be confined to the CRU from Check-in (Day -1) through Discharge on Day 9. Patients will be administered study drug daily from Day 1 through Day 7.

Randomization will occur on Day 1 prior to administration of the first dose of study drug. The treatment assignment for each patient will be assigned through the IWRS in a 1:1:1 ratio (REL-1017 25 mg, REL-1017 50 mg, or Placebo), and the randomization schedule will be stratified based on patients receiving concomitant ADTs that are cytochrome (CYP) 2B6 inhibitors (e.g., paroxetine, fluoxetine) versus those who are not.

Medical history and psychiatric history will be coded into the most recent version of MedDRA available (Version 16.0 or higher). Medical history will be listed by treatment arm and patient at

Screening and Check-in (Day -1). Psychiatric history will be listed by treatment arm and patient at Screening only.

Prior and concomitant medications will be assigned a 12-digit code using the most recent version of the WHO drug codes available. Prior and concomitant medications will be listed by treatment arm and patient. Medication history (prior medications) will be listed at Screening, and concomitant medications will be listed at every visit from Check-in (Day -1) through EOP (Day 21) and summarized by treatment.

The effectiveness of the patient's prescribed antidepressant medication will be assessed using the MINI, ATRQ, and HAM-D-17. The MINI will be conducted at Screening only, while the ATRQ and HAM-D-17 will be conducted at both Screening and Check-in (Day -1).

The mental status of patients will be further evaluated with the C-SSRS, CADSS, and COWS. The C-SSRS will be conducted at Screening, Check-in (Day -1), Baseline (Day 1, first day of dosing), Day 2 (24 hours after first dose), Day 8 (24 hours after last dose), Discharge (Day 9), Day 14 (EOP), and Day 21 (Follow-up). The 4-Item PSRS will be measured at 30 to 60 minutes pre-dose at Baseline (Day 1), 2 hours post-dose on Day 1 (after first dose), 2 hours post-dose on Day 7 (EDP) (after last dose), and prior to Discharge on Day 9. The CADSS will be measured at 30 to 60 minutes pre-dose at Baseline (Day 1), 2 hours post-dose on Day 1 (after first dose), 2 hours post-dose on Day 7 (after last dose), and prior to Discharge on Day 9. The COWS will be conducted on Day 8 (24 hours after the final dose of study drug), on Day 9 (Discharge), and at EOP (Day 14).

The Investigator or designee will contact each patient by telephone on Day 21 (14 days after the last dose of study drug) to assess C-SSRS, ask about AEs and evaluate the patient's general status.

The number of patients in each of the treatment groups will be presented, in addition to the number of patients who complete each visit. The reasons for all post-randomization discontinuations will be tabulated and grouped by treatment group and all patients combined. All deviations related to study inclusion or exclusion criteria, conduct of the study, patient management, or patient assessment will be described.

8.1.6 Interim Analyses

No interim analyses are planned for this study.

8.1.7 Missing Data

A mixed model of repeated measurement based on missing at random will be used to address missing efficacy data (MADRS, SDQ, CGI-S, and CGI-I). Details on the handling of missing data and missing values imputation will be provided in the SAP.

8.2 Determination of Sample Size

As this is a Phase 2a study, formal sample size calculations are not applicable. The study will not be powered for signal detection; however, summary statistics will be calculated, and effect size calculations will be performed for efficacy measures.

The sample size of 20 patients in each of the two active treatment groups (REL-1017 25 mg and 50 mg) and 20 patients in the Placebo group was chosen to obtain reasonable evidence of safety and efficacy without exposing undue numbers of patients to the investigative product at this phase of clinical development.

9 STUDY ADMINISTRATION

9.1 Data Collection and Electronic Data Capture

The Investigator or designee will record all required patient data using the specified data collection method agreed upon by Syneos Health, Inc., and Relmada (i.e., paper source and/or the electronic data capture [EDC] system).

The study site will use a validated EDC system to enter patient data onto eCRFs. Data will be collected using the EDC system and entered into a quality controlled clinical database. Prior to the commencement of the study, items to be included in the clinical database will be determined, and suitable paper source documents will be created to ensure the appropriate collection of all required data. The clinical staff conducting the study will enter the required data onto source documents; and generally, different staff members (who have been trained to do so) will enter the data from source documents into the clinical database, although there may be some staff overlap. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel; and all data entries will be verified for accuracy and correctness.

The EDC system is optimized for manual keying and review (including review by independent monitors) and maintains a full audit trail. For patients who do not qualify for the treatment phase of the study, data collected during the Screening Visit will not be entered into the clinical database.

Clinical laboratory and PK data will be received from the laboratory as ASCII files and merged with the data from the clinical database. Scheduled Measurement System (SMS) data will be captured electronically and imported into the clinical database.

The study file and all source data will be retained at the clinical site until notification is given by the Sponsor for destruction.

9.2 Regulatory and Ethical Considerations

9.2.1 Ethical Conduct of the Study

The Investigator will conduct the study in accordance with Good Clinical Practice (GCP) and all applicable regulations, including, where applicable, the principles that have their origin in the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor's representatives and/or regulatory authority's representatives at any time.

9.2.2 Regulatory Authority Approval

In accordance with applicable local regulations, the Sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiating the study in that country or jurisdiction.

9.2.3 Ethics Approval

The Investigator will ensure that this protocol is reviewed and approved by the appropriate IRB. The IRB will also review and approve the site's ICF and any other written information provided to the patient, including any advertisements used for patient recruitment. Prior to the enrollment

of patients, the Investigator or designee will forward copies of the IRB approval and approved study documentation to the Sponsor.

If, during the study, it is necessary to amend study documentation (e.g., protocol, ICF), the Investigator or designee will be responsible for ensuring that the IRB reviews and approves these amended documents. IRB approval of an amended ICF must be obtained before new patients consent to take part in the study using the amended form. Copies of the IRB approval of the amended study documentation and the approved materials will be forwarded to the Sponsor as soon as available.

9.2.4 Patient Informed Consent

At Screening, the Investigator or designee will inform the patient or, where applicable, the patient's legally authorized representative (e.g., parent, guardian, next of kin, or other individual or body with appropriate jurisdiction) of all aspects pertaining to the patient's participation in the study.

The process for obtaining the patient's informed consent will be in accordance with all applicable regulatory requirements. The Investigator or designee and the patient or the patient's legally acceptable representative will both sign and date the ICF before the patient can participate in the study. The patient or patient's legally acceptable representative will receive a copy of the consent form, and the original form will be retained in the site study records. The patient's decision regarding participation in the study will be entirely voluntary. The Investigator or designee will emphasize to the patient or the patient's legally acceptable representative that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled.

If the ICF is amended during the study, the Investigator will follow all applicable regulatory requirements pertaining to the implementation and use of the amended ICF, including use for previously consented patients.

9.2.5 Principal Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

9.3 Privacy

The research site's Privacy Officer will provide guidance on privacy issues to the Investigator. The Investigator or designee is responsible for complying with applicable privacy regulations per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

9.3.1 Patient Identifiers

To ensure patient anonymity and to limit disclosure, patients will be assigned a unique patient Screening number after signing the ICF at their first assessment. Patients will be assigned unique

randomization numbers at the time of randomization. These patient identifiers will be cross-referenced in the patient's chart. The patient identifiers will not contain any potentially identifiable information.

A patient identifier log will be maintained, linking each patient's name to the corresponding patient identifiers. This log will be stored at the research site in a secure location.

9.3.2 Purpose of Collecting Personal Information and Use

The purpose of collecting personal information from patients (including health and medical information) during this study is for scientific research and/or as supportive evidence for drug-related submissions to regulatory authorities, in compliance with legal or regulatory requirements.

9.3.3 Access and Disclosure of Personal Information

The knowledge gained through this study is the property of Relmada Therapeutics, Inc. The Sponsor, representatives, and affiliated companies of the Sponsor; the IRB; the FDA, and other regulatory agencies may inspect patient medical records related to the study to check the validity and accuracy of the data gathered in this study. Patient medical records (with patient initials and/or date of birth only) may be copied. The confidentiality of patient records will be maintained except where the release of information is required by law.

With the agreement of the patient, the Investigator may inform the patient's primary care physician about his or her participation in the study and will forward any clinically significant findings from clinical tests such as the ECG and laboratory tests. The primary care physician may contact the Investigator for any further information regarding the patient's participation in the study. The patient has the right to request access to and request corrections of his or her medical record.

Syneos Health ensures that any authorized third party that performs services on behalf of Syneos Health acts in a manner consistent with the Syneos Health Privacy Policy. While every effort will be made to protect the privacy of patient information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect patient privacy.

9.3.4 Release of Patient Information

The results of this study will be reported in such a manner that patients will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies (e.g., the FDA) will not include patient names.

9.3.5 Consent for Collection, Access, Use and Disclosure of Patient Information

By signing the ICF, the patient consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a patient withdraws consent, some of the patient's information may still be collected, used, and disclosed by those involved in this study per applicable laws.

9.4 Study Monitoring

9.4.1 Quality Control by Syneos Health

Syneos Health performs quality control at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with this study protocol; Syneos Health's SOPs; the FDA; the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of quality control reviews will be based on Syneos Health's SOPs and such considerations as the study objectives and/or endpoints, purpose of the study, study design complexity, and enrollment rate.

9.4.2 Study Monitoring by Sponsor and/or Third Party

If applicable and in accordance with the applicable regulations, GCP, and the Sponsor's procedures, Sponsor and/or third-party monitors will periodically contact or visit the research site, as required. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor may:

- Check and assess the progress of the study.
- Review study data that have been collected.
- Conduct source document verification (for those measures that have separate source documents and assuming the source documents are compared to the eCRF).
- Identify any issues and address their resolution.
- Prepare a monitoring report.

This will be done to verify that:

- The data are authentic, accurate, and complete;
- The safety and rights of patients are being protected; and,
- The study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate the Investigator's time and/or the time of research site staff to the monitor to discuss findings and any relevant issues.

At a minimum, source documentation will be available to substantiate the Patient ID, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of AEs; administration of concomitant medication; and dates of patient completion, discontinuation from treatment, or withdrawal from the study, including the reason if appropriate.

An unblinded monitor independent of the study team will visit the sites to review the pharmacy records to ensure proper drug management during the study. The unblinded monitor will review drug receipt/dispensing/return records and study drug administration information to ensure all records are in order.

In addition to contact during the study, the monitor will also contact the site prior to the start of the study to discuss the protocol and data collection procedures with research site personnel.

At study closure, monitors will also conduct all activities as indicated in Section 9.7, Study and Site Closure.

9.4.3 Principal Investigator's Data Responsibility

The completed eCRFs will be reviewed against source documents by the monitor at each monitoring visit. If any data, signatures, or forms are missing or incorrect, the Investigator or designee will be informed and corrections will be made. Electronic Case Report Forms will be collected from the study site at the termination of the study after all monitoring visits and data queries are completed.

9.5 Data Quality Assurance

Actions to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers; the review of protocol procedures with the Investigator and associated study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. Written instructions will be provided for the collection, preparation, and shipment of blood, plasma, and urine samples. The Sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. The data will be entered into the clinical study database and verified for accuracy using the study-specific data verification plan.

9.6 Study and Site Closure

Upon completion of the study, the following activities, when applicable, will be conducted by the monitor in conjunction with the Investigator or designee, as appropriate:

- Return of all study data to the Sponsor
- Data clarifications or resolutions
- Accounting, reconciliation, and final disposition of used and unused study drugs
- Review of site study records for completeness
- Return of treatment codes to the Sponsor

In addition, the Sponsor reserves the right to suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other Investigators and/or institutions conducting the study if the study is

suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study patients with the reason for the suspension or termination.

If the study is prematurely discontinued, all study data will be returned to the Sponsor. In addition, the site will conduct final disposition of all unused study drugs in accordance with the Sponsor's procedures for the study.

Financial compensation to the Investigators and/or institutions will be in accordance with the agreement established between the Investigator and the Sponsor.

9.7 Records Retention

Following closure of the study, the Investigator will maintain a copy of all site study records in their original format in a safe and secure location in accordance with the applicable FDA regulatory requirements. Records shall be maintained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

Essential documents include:

- Signed informed consent documents for all patients
- Patient ID code list, Screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB
- Copies of eCRFs and of documentation of corrections for all patients
- Investigational product accountability records
- All other source documents (e.g., patient medical records, hospital records, laboratory records)
- All other documents as listed in Section 8 of the ICH E6 guideline for GCP (essential documents for the conduct of a clinical study)

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she will ask the Sponsor for permission to make alternative arrangements. Details of these arrangements will be documented.

10 REFERENCES

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. An Rev Public Health 2013;34:119-138.
2. Vos T, Barber RM, Bell B, et al. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743-800.
3. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163(1):28-40.
4. Hardeveld F, Spijker J, De Graaf R, et al. Prevalence and predictors of recurrence of major depressive disorder in the adult population. Acta Psychiatr Scand 2010;122(3):184-191.
5. Dupuy JM, Ostacher MJ, Huffman J, et al. A critical review of pharmacotherapy for major depressive disorder. Int J Neuropsychopharmacol 2011;14:1417-1431.
6. Ebert B, Andersen S, Krogsgaard-Larsen P. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett 1995;187(3):165-168.
7. Shimoyama N, Shimoyama M, Elliott KJ, Inturrisi CE. d-Methadone is antinociceptive in the rat formalin test. J Pharmacol Exp Ther 1997;283(2):648-652.
8. Kristensen K, Christensen CB, Christrup LL. The mu1, mu2, delta, kappa opioid receptor binding profiles of methadone stereoisomers and morphine. Life Sci 1995;56(2):45-50.
9. Relmada Therapeutics, Inc. Study REL-1017-111, "A Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Single Ascending Doses of d-Methadone in Healthy Subjects."
10. Relmada Therapeutics, Inc. Study REL-1017-112, "A Phase 1 Study to Investigate the Safety, Tolerability, and Pharmacokinetic Profile of Multiple Ascending Doses of d-Methadone in Healthy Subjects."
11. PsychoGenics, Inc. RMA003 FS Preliminary Report. "Evaluation of the Antidepressant Effects of d-Methadone in the Forced Swim Test in Rats."
12. Ebert B, Thorkildsen C, Andersen S, et al. Opioid analgesics as noncompetitive N methyl D aspartate (NMDA) antagonists. Biochem Pharmacol 1998;56(5):553-559.
13. Gorman AL, Elliott KJ, Inturrisi CE. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett 1997;223(1):5-8.
14. Callahan RJ, Au JD, Paul M, et al. Functional inhibition by methadone of N methyl D aspartate receptors expressed in Xenopus oocytes: stereospecific and subunit effects. Anesth Analg 2004;98(3):653-659.

15. Lin C, Somberg T, Molnar J, Somberg J. The effects of chiral isolates of methadone on the cardiac potassium channel IKr. Cardiology 2009;113(1):59-65.

16. Eap CB, Crettol S, Rougier JS, et al. Stereoselective block of hERG channel by (S) methadone and QT interval prolongation in CYP2B6 slow metabolizers. Clin Pharmacol Ther 2007;81(5):719-728.

17. Silverman DA, Nettleton RT, Spencer KB, et al. S-Methadone Augments R methadone induced respiratory depression in the neonatal guinea pig. Respir Physiol Neurobiol 2009;169(3):252-261.

18. Schmidt N, Brune K, Williams KM, Geisslinger G. Stereoselective pharmacokinetics of methadone in beagle dogs. Chirality 1994;6(6):492-495.

19. Scott C, Robbins EB, Chen KK. Pharmacologic comparison of the optical isomers of methadon. J Pharm Exp Ther 1948;93(3):282-286.

20. Allen JW, Horais KA, Tozier NA, Yaksh TL. Opiate pharmacology of intrathecal granulomas. Anesthesiology 2006;105(3):590-598.

21. Yaksh TL, Tozier N, Horais K, et al. Toxicology profile of N-methyl-D-aspartate antagonists delivered by intrathecal infusion in the canine model. Anesthesiology 2008;108(5):938-949.

22. FDA Guidance. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Jul 2005 (https://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf%23search=%27guidekines+for+industry+sfe+starting%27).

23. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010;329(5994):959-964.

24. Dwyer JM, Lepack AE, Duman RS. mTOR activation is required for the antidepressant effects of mGluR2/3 blockade. Int J Neuropsychopharmacol 2012;15(4):429 434.

25. Voleti B, Navarria A, Liu RJ, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. Biol Psychiatry 2013;74(10):742-749.

26. Liu, RJ, Duman C, Kato T, et al. GLYX 13 produces rapid antidepressant responses with key synaptic and behavioral effects distinct from ketamine. Neuropsychopharm 2013(Apr);38(5):729-742.

27. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: novel therapeutic targets. Science 2012;338(6103):68-72.

28. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 2016;22(3):238-249.

29. Relmada Therapeutics, Inc. Study: “Evaluation of the Antidepressant Effects of d-Methadone in the Forced Swim Test in Rats.”

30. Desseilles M, Witte J, Chang TE, et al. Massachusetts General Hospital SAFER criteria for clinical trials and research. Harv Rev Psychiatry 2013;21(5):269-274.

31. Olsen GD, Wendel HA, Livermore JD, et al. Clinical effects and pharmacokinetics of racemic methadone and its optical isomers. Clin Pharmacol Ther 1977;21(2):147-157.

32. Fraser HF, Isbell H. Human pharmacology and addictiveness of certain dextroisomers of synthetic analgesics. Bull Narc 1962;14:25-35.

33. Isbell H, Eisenman AJ. The addiction liability of some drugs of the methadon series. J Pharmacol Exp Ther 1948;93(3):305-313.

34. Boulton DW, Arnaud P, DeVane CL. A single dose of methadone inhibits cytochrome P-4503A activity in healthy volunteers as assessed by the urinary cortisol ratio. Br J Clin Pharmacol 2001;51(4):350-354.

35. Pedrelli P, Blais M, Alpert J, et al. Reliability and validity of the Symptoms of Depression Questionnaire (SDQ). CNS Spectr 2014;19(6):535-546.

36. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(S20):22-33.

37. Chandler GM, Iosifescu DV, Pollack MH, et al. RESEARCH: validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci Ther 2010;16(5):322-325.

38. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988;45(8):742-747.

39. Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). Br J Psychiatry 2008;192(1):52-58.

40. Structured Interview Guide for the MADRS. Royal College of Psychiatrists, 2011. Developed from Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Br J Psychiatry 2008;192:52-58.

41. Montgomery SA, Asberg M. A new depressions scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-389.

42. Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 2007;4(7):28-37.

43. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-1277.

44. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 1998;11(1):125-136.

45. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003;35(2):253-259.

46. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. Psychopharmacol Bull 1988;24:97-99.

47. The 4-Item Positive Symptom Rating Scale was adapted from the Expanded Version of the BPRS developed by: Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, and Shaner, *A Manual for the expanded Brief Psychiatric Rating Scale*. International Journal of Methods Psychiatry Research 1993;3:227-244.

11 APPENDICES

11.1 Amount of Blood Drawn per Study Period

	PK Sample	DNA Sample	Safety			Total
			Clinical Chemistry	Hematology	Serology	
	Blood Volume (mL) [Number of Samples]					
Approximate volume per sample (mL)	4 mL	4 mL	5 mL	4 mL	5 mL	–
Screening	0	0	5 [1]	4 [1]	5 [2]	14 [4]
Check-in			5 [1]	4 [1]	5 [1]	14 [3]
Treatment Period	4 [7]	4 [1]	5 [1]	4 [1]	5 [1]	46 [11]
Follow-up	4 [2]	0	5 [1]	4 [1]	0	17 [4]
Total						**91 mL [21]**

DNA = Deoxyribonucleic Acid; PK = Pharmacokinetic(s).

Note: Blood volumes shown in the table are approximate. Additional blood samples may be taken if needed to follow up on individual patient safety.

11.2 SAFER Interview

Table 1

The SAFER interview: Assessing depression in a real-world setting

State vs trait nature of the symptoms • Does the patient have symptoms that are present primarily during episodes of acute illness? • Does the episode constitute a measurable exacerbation of preexisting symptoms? • Does the current episode represent a clear change from previous levels of functioning?
Assessability • Does the patient have discernible symptoms that can be assessed at each visit to determine if improvement has occurred?
Face validity • Have symptoms clearly affected behavior and function in the past 4 weeks? • If recurrent, are the characteristics of the current episode similar to a previous one?
Ecological validity • Do the symptoms occur with the frequency, intensity, duration, course, and impact consistent with our knowledge of the occurrence of major depressive disorder in a real-world setting? • Is symptomatic change likely to matter to the patient's quality of life?
Rule of the 3 Ps • Are the symptoms of the depressive episode pervasive, persistent, and pathological? (See *Table 2*)

Source: Reference 6

Table 2

The SAFER criteria: Rule of the 3 Ps

Pervasive—Do the major symptoms affect the patient across multiple arenas of life (work, relationships, school, chores, etc.)?
Persistent—Do the main symptoms occur most days, most of the day during the current episode?
Pathological—Do the symptoms of the present episode interfere with functioning?

Source: Reference 6

Text Box 1
Operationalization of the SAFER Criteria
SAFER Criteria Inventory
(© Massachusetts General Hospital)

1. Persistent Symptoms:
   - ☐ Definitely (All of the patient's symptoms are present most of the day, nearly every day)
   - ☐ Possibly (Some, but not all, symptoms are present most of the day, nearly every day)
   - ☐ Unlikely (The majority of the symptoms are not present most of the day, nearly every day)
2. Pervasive Symptoms:
   - ☐ Definitely (Symptoms impact all domains and/or contexts)
   - ☐ Possibly (Symptoms impact many domains and/or contexts, but not all)
   - ☐ Unlikely (Symptoms impact a minority of domains and/or contexts)
3. Pathological Symptoms:
   - ☐ Definitely (Symptoms are disruptive and have affected behavior or function, and are distinguishable from the patient's normal functioning)
   - ☐ Possibly (Symptoms are sometimes disruptive of behavior or function, or are not reliably distinguishable from the patient's normal functioning)
   - ☐ Unlikely (Symptoms are not disruptive and have not affected the patient's behavior or function, and are not distinguishable from the patient's normal functioning)
4. State (not Trait) Symptoms:
   - ☐ Definitely (Patient can remember a time when he or she felt well.)
   - ☐ Possibly (Patient may remember a time when he or she felt better, though the depression appears to be an exacerbation of previous dysthymia or chronic depression)
   - ☐ Unlikely (The patient is chronically dysthymic or depressed with no identifiable reference point for a well period.)
5. Acute Symptoms:
   - ☐ Definitely (Patient has symptoms of depression that began or worsened during the current episode)
   - ☐ Possibly (Symptoms of depression do not appear to have begun with the current episode)
   - ☐ Unlikely (Patient does not have symptoms of depression)
6. Specificity of Symptoms:

NOTE: A situational depression may improve or worsen in response to external circumstances. Thus, symptomatic change (either improvement or worsening) may not be reliably attributed to drug treatment.

   - ☐ Definitely (Patient has MDD does not have any other condition as the primary cause of these symptoms)
   - ☐ Possibly (There is significant doubt as to whether MDD is the primary diagnosis, because patient appears to have a symptomatic condition, e.g., PTSD or GAD, that may be responsible for many or most of the symptoms)
   - ☐ Unlikely (Patient's symptoms are likely caused by something other than MDD: another medical or psychiatric diagnosis, concomitant medications, alcohol or drug abuse, external circumstances, or, the depressive episode seems highly situational and the patient may spontaneously improve with changed circumstances)

7. Valid Symptoms (Ecological and Face Validity):

Using the responses obtained from the severity scale and SAFER questions 1–6, ascertain whether:

   a) Symptoms clearly map to the primary nosological entity and occur with the frequency, intensity, duration, course, and impact consistent with our knowledge of DSM-diagnosed MDD in a real-world setting. Symptoms do not map more closely to any other condition which might be considered a primary diagnosis, e.g. PTSD.
   b) Symptoms are not exaggerated, they represent a change from baseline, and they have had real impact on behavior or level of function over at least the past 4 weeks.
   c) Symptomatic change is likely to matter to the patient's quality of life.
   d) If recurrent, the characteristics of the current episode are similar to previous episodes. (Ask the patient this question if necessary.)

   - ☐ Definitely
   - ☐ Possibly
   - ☐ Unlikely

8. Assessable Symptoms:
   - ☐ Definitely (Patient answers questions with reasonable certainty, there is good internal consistency between answers to items, and the patient rarely stumbles, seems unsure, or contradicts himself/herself)
   - ☐ Unlikely (Patient stumbles on answers, answers in non sequiturs or digresses a lot, doesn't seem sure of answers, and/or contradicts herself/himself in answering questions)

The patient's symptoms must be able to be reliably and sensitively measured with the employed rating instruments.

9. Valid Patient (meets ALL SAFER criteria for this clinical trial):
   - ☐ Yes (SAFER questions 1–4 must be scored as "Definitely" or "Possibly," and SAFER questions 5–8 must be scored as "Definitely")
   - ☐ No (The above conditions for "Yes" are not met)

A response of "Unlikely" to any of questions 1–8 means that the patient will be a SAFER fail.

11.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

11.4 Clinician Administered Dissociative States Scale (CADSS)

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

Name_____ ID_____ Date_____
Subjective Items:

1. Do things seem to be moving in slow motion?
   - 0= Not at all.
   - 1= Mild, things seem slightly slowed down, but not very noticeable.
   - 2= Moderate, things are moving about twice as slow as normally.
   - 3= Severe, things are moving so slowly that they are barely moving.
   - 4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.
2. Do things seem to be unreal to you, as if you are in a dream?
   - 0= Not at all.
   - 1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
   - 2= Moderate, things seem dreamlike, although I know I am awake.
   - 3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
   - 4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.
3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
   - 0= Not at all.
   - 1= Mild, I feel a little bit separated from what is happening, but I am basically here.
   - 2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
   - 3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
   - 4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.
4. Do you feel as if you are looking at things from outside of your body?
   - 0= Not at all.
   - 1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
   - 2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
   - 3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
   - 4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.
5. Do you feel as if you are watching the situation as an observer or a spectator?
   - 0= Not at all.
   - 1= Mild, I feel slightly detached from what is going on, but I am basically here.
   - 2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
   - 3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

this room.

4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
   - 0= Not at all.
   - 1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
   - 2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
   - 3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
   - 4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
   - 0= Not at all.
   - 1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
   - 2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
   - 3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
   - 4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
   - 0= Not at all.
   - 1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
   - 2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
   - 3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
   - 4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
   - 0= Not at all.
   - 1= Mild, things seem slightly different than normal, although it is barely perceptible.
   - 2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
   - 3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
   - 4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
    - 0= Not at all.
    - 1= Mild, things seem slightly paler than usual if I think about it.
    - 2= Moderate, colors are somewhat diminished, but still recognizable.
    - 3= Severe, colors are extremely pale, in no way as vivid as they usually are.

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
    0= Not at all.
    1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
    2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
    3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
    4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.
12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
    0= Not at all.
    1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
    2= Moderate, it seems as if this interview has gone on for at least two hours.
    3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
    4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.
13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
    0= Not at all.
    1= Mild, things are happening slightly faster than normal.
    2= Moderate, things seem to be happening at least twice as fast as normal.
    3= Severe, things seem to be happening at least 10 times faster than normal.
    4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.
14. Have there been things which have happened during this interview [assessment] that now you can't account for?
    0= Not at all.
    1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
    2= Moderate, at least once there were things which happened which now I can't account for.
    3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
    4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am confused about what has happened.
15. Have you spaced out, or in some other way lost track of what was going on during this experience?
    0= Not at all.
    1= Mild, I have had some episodes of losing track of what is going on, but I have

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a

The Clinician Administered Dissociative States Scale (CADSS)
J. Douglas Bremner, Carolyn Mazure, Frank W. Putnam

person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristics.

11.5 Clinical Opiate Withdrawal Scale (COWS)

Clinical Opiate Withdrawal Scale (COWS)

Flowsheet for measuring symptoms over a period of time during buprenorphine induction.

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal.
For example: If heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient Name: _____ Date: _____

Buprenorphine Induction: _____

Enter scores at time zero, 30 minutes after first dose, 2 hours after first dose, etc.	Times of Observation:				
Resting Pulse Rate: Record Beats per Minute					
Measured after patient is sitting or lying for one minute 0 = pulse rate 80 or below 1 = pulse rate 81-100 • 2 = pulse rate 101-120 • 4 = pulse rate greater than 120					
Sweating: Over Past 1/2 Hour not Accounted for by Room Temperature or Patient Activity					
0 = no report of chills or flushing 1 = subjective report of chills or flushing 2 = flushed or observable moistness on face • 3 = beads of sweat on brow or face • 4 = sweat streaming off face					
Restlessness Observation During Assessment					
0 = able to sit still 1 = reports difficulty sitting still, but is able to do so • 3 = frequent shifting or extraneous movements of legs/arms • 5 = Unable to sit still for more than a few seconds					
Pupil Size					
0 = pupils pinned or normal size for room light 1 = pupils possibly larger than normal for room light • 2 = pupils moderately dilated • 5 = pupils so dilated that only the rim of the iris is visible					
Bone or Joint Aches if Patient was Having Pain Previously, only the Additional Component Attributed to Opiate Withdrawal is Scored					
0 = not present 1 = mild diffuse discomfort • 2 = patient reports severe diffuse aching of joints/muscles • 4 = patient is rubbing joints or muscles and is unable to sit still because of discomfort					
Runny Nose or Tearing Not Accounted for by Cold Symptoms or Allergies					
0 = not present 1 = nasal stuffiness or unusually moist eyes • 2 = nose running or tearing • 4 = nose constantly running or tears streaming down cheeks					
GI Upset: Over Last 1/2 Hour					
0 = no GI symptoms 1 = stomach cramps 2 = nausea or loose stool • 3 = vomiting or diarrhea • 5 = multiple episodes of diarrhea or vomiting					
Tremor Observation of Outstretched Hands					
0 = no tremor 1 = tremor can be felt, but not observed • 2 = slight tremor observable • 4 = gross tremor or muscle twitching					
Yawning Observation During Assessment					
0 = no yawning 1 = yawning once or twice during assessment • 2 = yawning three or more times during assessment • 4 = yawning several times/minute					
Anxiety or Irritability					
0 = none 1 = patient reports increasing irritability or anxiousness • 2 = patient obviously irritable/anxious • 4 = patient so irritable or anxious that participation in the assessment is difficult					
Gooseflesh Skin					
0 = skin is smooth 3 = piloerection of skin can be felt or hairs standing up on arms • 5 = prominent piloerection					
Score: 5-12 = Mild 13-24 = Moderate 25-36 = Moderately Severe More than 36 = Severe Withdrawal	Total score				
	Observer's initials				

Journal of Psychoactive Drugs Volume 35 (2), April - June 2003

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

11.6 4-Item Positive Symptom Rating Scale (4-Item PSRS)

4-ITEM POSITIVE SYMPTOM RATING SCALE

4-Item Positive Symptom Rating Scale
NA = not able to be assessed, 1 = symptom not present, 6/7 = severe/extremely severe

1. Suspiciousness	NA	1	2	3	4	5	6	7
2. Unusual Thought Content	NA	1	2	3	4	5	6	7
3. Hallucinations	NA	1	2	3	4	5	6	7
4. Conceptual Disorganization	NA	1	2	3	4	5	6	7

SCORE: _____

The 4-Item Positive Symptom Rating Scale was adapted from the Expanded Version of the BPRS developed by: Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, and Shaner, *A Manual for the expanded Brief Psychiatric Rating Scale*. International Journal of Methods Psychiatry Research 1993; 3:227-244.

11.7 Antidepressant Treatment Response Questionnaire (ATRQ)

MGH ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)

(Non-Geriatric Population: 18 to 64 years of age)(Global)

Note: The minimum therapeutic dose for each antidepressant treatment in Section I is based on prescribing information, relevant literature, and consultation with expert clinicians.

Section I. Antidepressant Medications

Instructions:

1. Please **check (√)** the names of any medications that the patient has taken since the beginning of **THIS CURRENT EPISODE** of depression.
2. Please **check (√)** if the daily dosage of the medication was **equal to or greater than the minimum** therapeutic dose for at least 6 weeks.
3. Only for those taken at the minimum therapeutic dose for at least 6 weeks, indicate the amount (%) of improvement in depression that the patient reported when they felt it was working at its best.
4. If the subject initially experienced an improvement of ≥50% and then lost that response (tolerance/bradyphylaxis), that medication will not be counted towards a failed antidepressant trial.

Tricyclic Antidepressants

Generic Name	Taken during THIS current episode of depression(√)	Took at least this dose* *for at least 6 weeks*? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
doxepin		150mg/d		
clomipramine		150mg/d		
amoxapine		150mg/d		
amitriptyline		150mg/d		
maprotiline		150mg/d		
desipramine		150mg/d		
nortriptyline		75 mg/d		
doxepin		150mg/d		
trimipramine		150mg/d		
imipramine		150mg/d		
protriptyline		30mg/d		
pipofezine		150mg/d		
noxiptiline		100mg/d		

* If the dose is below the minimum dose required, a blood level that is within the therapeutic (antidepressant) range is also acceptable.

Monoamine Oxidase Inhibitors (MAOIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *for at least 6 weeks?* (√)	Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best.

				A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
isocarboxazid		30mg/d		
phenelzine		45mg/d		
tranylcypromine		30mg/d		
selegiline patch		6 mg/24 hrs		
moclobemide		300 mg/d		
pirlindole		200 mg/d		

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
fluvoxamine		50mg/d		
paroxetine		20/25mg/d		
fluoxetine		20 mg/d		
sertraline		50 mg/d		
citalopram		20mg/d		
escitalopram		10 mg/d		
vilazodone		40 mg/d		
vortioxetine		10 mg/d		

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
venlafaxine / venlafaxine XR		150 mg/d		

duloxetine		60mg/d		
desvenlafaxine		50mg/d		
milnacipran		100mg/d		
levomilnacipran		40mg/d		

Other Antidepressants

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for at least 6 weeks? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
trazodone		300mg/d		
bupropion		300mg/d		
mirtazapine		15 mg/d		
mianserin		30 mg/d		
opipramol		150 mg/d		
nefazodone		300 mg/d		
agomelatine		25 mg/d		
tianeptine		37.5 mg/d		
reboxetine		4 mg/d		

Section II. FDA-Approved Medications added to Augment /Boost Antidepressant Effect

Instructions:

1. Please **check** (√) the names of any medication you have taken to augment or boost the antidepressant effect during **THIS CURRENT EPISODE** of depression.
2. Please **check** (√) if the subject took at least this dose for at least 6 weeks in combination with an antidepressant treatment from Sect I.
3. Please indicate the name of antidepressant treatment from Section I this drug was taken with to augment /boost its antidepressant effect.
4. Please indicate the amount (%) of improvement in depression that the patient reported when they felt this combination was working at its best.

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least* 6 weeks in combination with an antidepressant treatment from Section I**? (√)		Name of Antidepressant Treatment from Section I (see above) this drug was taken with	Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on subject's feedback, indicate the amount (%) of improvement in depression he/she reported when they feel the combination was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤25%
Aripiprazole		5 mg/d			
Quetiapine		200 mg/d			
Brexpiprazole		1 mg/d			
**The antidepressant treatment from Section I must also have been taken at the minimum therapeutic dose during the 6 weeks that the medication was taken to augment/boost antidepressant effect.					

11.8 Structured Interview Guide for the Montgomery-Asberg Depression Rating Scale (SIGMA)

STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)

Janet B.W. Williams, Ph.D. and Kenneth A. Kobak, Ph.D.

INTERVIEWING GUIDELINES: The questions in bold for each item should be asked exactly as written unless the information has been previously obtained, in which case it is appropriate to restate the information for confirmation. Follow-up questions are provided for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, for use, for example, if information is unknown. Statements in ALL CAPITALS are interviewer instructions and should not be read to the subject.

RATING GUIDELINES: Ratings should be based on the subject's condition as observed in the past

week (past 7 days). As specified in the item descriptions, three of the items, Reduced Sleep, Reduced Appetite, and Inability to Feel, are rated as present only when they reflect a change from before the depression began (EUTHYMIC BASELINE). The interviewer should attempt to identify the most recent 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the subject has dysthymia, the referent should be to the last time the subject felt alright (i.e., not depressed or high) for at least a few weeks. When a clear euthymic baseline cannot be established because of chronic depressive symptoms, these three items should be rated as observed over the past 7 days instead of comparing to a previous time point.

This interview guide is based on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry*; 1979 **134:** 382-9). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, 2005 and 2008.

STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)

PT'S INITIALS: _____ PT'S ID: _____

INTERVIEWER: **TIME BEGAN SIGMA: _____ AM / PM**

_____

DATE: _ _ _ _ _ _

OVERVIEW:
I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)?
IF OUTPATIENT: Have you been working? (What kind of work do you do? Have you been able to work your normal hours?)
IF NOT WORKING OR WORKING LESS, CLARIFY WHY.

In the past week, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?) IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (How often have you had lifts in your mood this week? What things have made you feel better?) How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?) **In the past week, how have you been feeling about the future?** (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you? **ESTABLISH EUTHYMIC BASELINE: When was the last time you were well, not depressed at all, for at least 2 months?**	**1. 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.

RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS. **In the past week, do you think you have looked sad or depressed to other people?** Did anyone say you looked sad or down? **How about when you've looked in the mirror; did you look gloomy or depressed?** IF YES: How sad or depressed do you think you have looked? How much of the time over the past week do you think you have looked depressed or down? **Has it been hard for you to laugh or smile in the past week?**	**2. APPARENT SADNESS**. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, 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.

Have you felt tense or edgy in the last week? Have you felt anxious or nervous? IF YES: Can you describe what that has been like for you? How bad has it been? **What about feeling fearful that something bad is about to happen?** How much of the time have you felt (anxious/tense/OWN EQUIVALENT) over the past week? **Have you felt panicky in the past week?** IF YES: Can you describe this feeling? How often have you felt this way? IF YES TO ANY TENSION SYMPTOM: How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)	**3. INNER TENSION.** Representing feelings 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.

How has your sleeping been in the last week? (How many hours have you been sleeping, compared to usual?) **Have you had trouble falling asleep?** (How long has it been taking you to fall asleep this past week? How many nights?) **Have you been able to stay asleep through the night?** (Have you been waking up at all in the middle of the night? How long does it take you to fall back to sleep? How many nights?) **Have there been any mornings this past week when you have awakened earlier than**	**4. REDUCED SLEEP**. Representing the experience of reduced duration or depth of sleep compared to 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 2 hours. 5 – 6 – Less than 2 or 3 hours sleep.

(EUTHYMIC BASELINE)? IF UNKNOWN: Has your sleeping been restless or disturbed?	
How has your appetite been this past week? (What about compared to your usual appetite?) IF NOT REDUCED: Have you been less interested in food? (How much less?) **Does food taste as good as usual?** IF LESS: How much less? Does it have any taste at all? (Have you had to push yourself to eat or have other people had to urge you to eat?)	**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.

Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a book or on the computer? Do you need to read things over and over again? Are you able to follow movies or television?) How often has that happened in the past week? Has this caused any problems for you? **Have you had any trouble following a conversation?** (IF YES: How bad has that been? How often has that happened this past week?) NOTE: ALSO CONSIDER BEHAVIOR DURING INTERVIEW.	**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 concentration. 1 - 2 - Occasional difficulties in collecting one's thoughts. 3 – 4 – Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation. 5 – 6 – Unable to read or converse without great difficulty.

Have you had any trouble getting started at things in the past week? IF YES: What things? How bad has that been? Have you had difficulty getting started at simple routine everyday things (like getting dressed, brushing your teeth, showering)? Are you OK once you get started at things or is it still more of an effort to get something done? Has there been anything that you needed to do that you were unable to do? Have you needed help to do things? IF YES: What things? How often? Have you done everyday things more slowly than usual? IF YES: Like what, for example? How bad has that been?	**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 simple routine activities, which are carried out with effort. 5 – 6 – Complete lassitude. Unable to do anything without help.

Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How much less interested in (those things) are you now compared to (EUTHYMIC BASELINE)? **What things have you enjoyed this week?** How much did you enjoy them? **Has there been any change in your ability to feel emotions in the past week?** (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?) **Have your feelings towards family and friends changed at all since (EUTHYMIC BASELINE)?** IF YES: Do you feel less towards them than you used to?	**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.

Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way? **In the past week have you been feeling guilty about anything? What about feeling as if you have done something bad or sinful?** IF YES: What have your thoughts been? How often have you felt that way? ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM 1.	**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 unshakeable.

This past week, have you felt like life isn't worth living? (IF NO: What about feeling as if you're tired of living?) IF YES: Tell me about that. How often have you felt that way? **This week, have you thought that you would be better off dead?** IF YES: Tell me about that. How often have you felt that way? **Have you had thoughts of hurting or even killing yourself this past week?** IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)	**10. SUICIDAL THOUGHTS.** Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this 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.

TIME ENDED SIGMA:	**_____ AM / PM**
TOTAL MADRS SCALE SCORE:	_____ _____

11.9 Symptoms of Depression Questionnaire (SDQ)

SYMPTOMS OF DEPRESSION QUESTIONNAIRE (SDQ)
TO BE ADMINISTERED AT : BASELINE, DAY 7, DAY 14

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you.

Instructions: Please read each item and circle the number above the statement that you think applies to you. Some questions use the words "minimally," "moderately," "markedly," and "extremely." Minimally means that this item happens to you only rarely or that it is mild when it happens. Moderately means that this item bothers you some of the time but that it does not interfere with your life in any way. Markedly means that this item bothers you quite a bit and that it causes you some problems in your life. That is, it interferes with your ability to do certain things that are important to you such as working, taking care of your family, or enjoying time with friends. Extremely means that this problem troubles you a lot and that it interferes with your ability to do a lot of things.

1) How has your mood been over the past week?

1	2	3	4	5	6
better than normal	normal	minimally sad	moderately sad	markedly sad	extremely sad

2) How responsive has your mood been over the past week?

1	2	3	4	5	6
more than usual	normal	minimally flat	moderately flat	markedly flat	extremely flat

3) How has your affect (or how to display you mood to the external world) been over the past week?

1	2	3	4	5	6
better than normal	normal	minimally sad	moderately sad	markedly sad	extremely sad

4) How prone to tears have you been over the past week?

1	2	3	4	5	6
less than usual	normal	minimally tearful	moderately tearful	markedly tearful	extremely tearful

5) How reactive have your been to positive things/events over the past week?

1	2	3	4	5	6
more than usual	normal	minimally less reactive	moderately less reactive	markedly less reactive	not reactive at all

6) How reactive have your been to negative things/events over the past week?

1	2	3	4	5	6
less than usual	normal	minimally more reactive	moderately more reactive	markedly more reactive	extremely reactive

7) How has your motivation/interest/enthusiasm been over the past week?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

8) How sensitive (e.g., thin-skinned) have your been to rejection/criticism over the past week?

1	2	3	4	5	6

less than usual	normal	minimally more reactive	moderately more reactive	markedly more reactive	extremely reactive

9) How optimistic have your been over the past week?

1	**2**	**3**	**4**	**5**	**6**
More optimistic than usual	normal	minimally pessimistic	moderately pessimistic	markedly pessimistic	extremely pessimistic

10) How has your outlook on life been over the past week?

1	**2**	**3**	**4**	**5**	**6**
more positive than usual	normal; happy to be alive	minimally wishing to be dead	moderately wishing to be dead	markedly wishing to be dead	extremely wishing to be dead

11) How has your outlook on suicide been over the past week?

1	**2**	**3**	**4**	**5**	**6**
more against it than usual	normally not thinking about it	minimally wishing to kill yourself	moderately wishing to kill yourself	markedly wishing to kill yourself	extremely wishing to kill yourself

12) How has your outlook on harming your body been over the past week?

1	**2**	**3**	**4**	**5**	**6**
more against it than usual	normally not thinking about it	minimally wishing to harm yourself	moderately wishing to harm yourself	markedly wishing to harm yourself	extremely wishing to harm yourself

13) How has your ability to fall asleep been over the past week?

1	**2**	**3**	**4**	**5**	**6**
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

14) How has your ability to stay asleep in the middle of the night been over the past week?

1	**2**	**3**	**4**	**5**	**6**
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

15) How has your ability to stay asleep around the time before waking up been over the past week?

1	**2**	**3**	**4**	**5**	**6**
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

16) How has your wakefulness/alertness been over the past week?

1	**2**	**3**	**4**	**5**	**6**
more than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

17) How sleepy during the day have you been over the past week?

1	**2**	**3**	**4**	**5**	**6**
less than normal	not at all	minimally sleepy	moderately sleepy	markedly sleepy	extremely sleepy

18) How much have you been oversleeping at night over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally increased	moderately increased	markedly increased	extremely increased

19) How much have you been oversleeping during the day over the past week?

1	2	3	4	5	6
less than normal	normal	minimally increased	moderately increased	markedly increased	extremely increased

20) How has your energy been over the past week?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

21) How heavy (in arms or legs) have you felt over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally heavy	moderately heavy	markedly heavy	extremely heavy

22) How slowed down have you felt over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally slowed down	moderately slowed down	markedly slowed down	extremely slowed down

23) How agitated have you felt over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally agitated	moderately agitated	markedly agitated	extremely agitated

24) How irritable have you been over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally irritable	moderately irritable	markedly irritable	extremely irritable

25) Have you had anger attacks (suddenly feeling very angry and like exploding with anger) over the past week?

1	2	3	4	5	6
never	almost never	rarely	sometimes	frequently	all the time

26) How anxious/worried have you felt over the past week?

1	2	3	4	5	6
less than normal	not at all	minimally anxious	moderately anxious	markedly anxious	extremely anxious

27) Have you had panic attacks over the past week?

1	2	3	4	5	6
felt calmer than normal	not at all	rarely	sometimes	frequently	all the time

28) How has your appetite been over the past week?

1	**2**	**3**	**4**	**5**	**6**
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

29) Have you lost weight over the past week?

1	**2**	**3**	**4**	**5**	**6**
gained some weight	not at all	minimally	mildly	moderately	markedly

30) Has your appetite been excessive over the past week?

1	**2**	**3**	**4**	**5**	**6**
less	not at all	rarely	sometimes	frequently	all the time

31) Have you gained weight over the past week?

1	**2**	**3**	**4**	**5**	**6**
lost some weight	not at all	minimally	mildly	moderately	markedly

32) Have you had tachycardia/palpitations over the past week?

1	**2**	**3**	**4**	**5**	**6**
my heart rate felt slower than usual	not at all	rarely	sometimes	frequently	all the time

33) Have you had pains or aches over the past week?

1	**2**	**3**	**4**	**5**	**6**
fewer aches and pains than usual	not at all	rarely	sometimes	frequently	all the time

34) Have you had gastrointestinal (stomach or bowel) symptoms over the past week?

1	**2**	**3**	**4**	**5**	**6**
fewer symptoms than usual	not at all	rarely	sometimes	frequently	all the time

35) How has your ability to focus/sustain attention been over the past week?

1	**2**	**3**	**4**	**5**	**6**
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

36) How has your ability to remember/recall information been over the past week?

1	**2**	**3**	**4**	**5**	**6**
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

37) How has your ability to find words been over the past week?

1	**2**	**3**	**4**	**5**	**6**
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

38) How has your sharpness/mental acuity been over the past week?

1	**2**	**3**	**4**	**5**	**6**

greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

39) How has your ability to make decisions been over the past week?

1	**2**	**3**	**4**	**5**	**6**
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

40) How has your sexual functioning been over the past week?

1	**2**	**3**	**4**	**5**	**6**
better than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

41) How has your social functioning been over the past week?

1	**2**	**3**	**4**	**5**	**6**
better than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

42) How has your ability to work/study/function at home been over the past week?

1	**2**	**3**	**4**	**5**	**6**
better than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

43) How guilty have you felt over the past week?

1	**2**	**3**	**4**	**5**	**6**
less than normal	not at all	minimally guilty	moderately guilty	markedly guilty	extremely guilty

44) How worthless have you felt over the past week?

1	**2**	**3**	**4**	**5**	**6**
less than normal	not at all	minimally worthless	moderately worthless	markedly worthless	extremely worthless

SYMPTOMS OF DEPRESSION QUESTIONNAIRE (SDQ)

TO BE ADMINISTERED AT : DAY 2, DAY 4

Please answer all questions by circling the correct answer or the answer which seems the most appropriate to you.

Instructions: Please read each item and circle the number above the statement that you think applies to you. Some questions use the words “minimally,” “moderately,” “markedly,” and “extremely.” Minimally means that this item happens to you only rarely or that it is mild when it happens. Moderately means that this item bothers you some of the time but that it does not interfere with your life in any way. Markedly means that this item bothers you quite a bit and that it causes you some problems in your life. That is, it interferes with your ability to do certain things that are important to you such as working, taking care of your family, or enjoying time with friends. Extremely means that this problem troubles you a lot and that it interferes with your ability to do a lot of things.

2) How has your mood been since Baseline?

1	**2**	**3**	**4**	**5**	**6**
better than normal	normal	minimally sad	moderately sad	markedly sad	extremely sad

2) How responsive has your mood been since Baseline?

1	2	3	4	5	6
more than usual	normal	minimally flat	moderately flat	markedly flat	extremely flat

3) How has your affect (or how to display you mood to the external world) been since Baseline?

1	2	3	4	5	6
better than normal	normal	minimally sad	moderately sad	markedly sad	extremely sad

4) How prone to tears have you been since Baseline?

1	2	3	4	5	6
less than usual	normal	minimally tearful	moderately tearful	markedly tearful	extremely tearful

5) How reactive have your been to positive things/events since Baseline?

1	2	3	4	5	6
more than usual	normal	minimally less reactive	moderately less reactive	markedly less reactive	not reactive at all

6) How reactive have your been to negative things/events since Baseline?

1	2	3	4	5	6
less than usual	normal	minimally more reactive	moderately more reactive	markedly more reactive	extremely reactive

7) How has your motivation/interest/enthusiasm been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

8) How sensitive (e.g., thin-skinned) have your been to rejection/criticism since Baseline?

1	2	3	4	5	6
less than usual	normal	minimally more reactive	moderately more reactive	markedly more reactive	extremely reactive

9) How optimistic have your been since Baseline?

1	2	3	4	5	6
More optimistic than usual	normal	minimally pessimistic	moderately pessimistic	markedly pessimistic	extremely pessimistic

10) How has your outlook on life been since Baseline?

1	2	3	4	5	6
more positive than usual	normal; happy to be alive	minimally wishing to be dead	moderately wishing to be dead	markedly wishing to be dead	extremely wishing to be dead

11) How has your outlook on suicide been since Baseline?

1	2	3	4	5	6
more against it than usual	normally not thinking about it	minimally wishing to kill yourself	moderately wishing to kill yourself	markedly wishing to kill yourself	extremely wishing to kill yourself

12) How has your outlook on harming your body been since Baseline?

1	2	3	4	5	6
more against it than usual	normally not thinking about it	minimally wishing to harm yourself	moderately wishing to harm yourself	markedly wishing to harm yourself	extremely wishing to harm yourself

13) How has your ability to fall asleep been since Baseline?

1	2	3	4	5	6
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

14) How has your ability to stay asleep in the middle of the night been since Baseline?

1	2	3	4	5	6
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

15) How has your ability to stay asleep around the time before waking up been since Baseline?

1	2	3	4	5	6
easier than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

17) How has your wakefulness/alertness been since Baseline?

1	2	3	4	5	6
more than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

17) How sleepy during the day have you been since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally sleepy	moderately sleepy	markedly sleepy	extremely sleepy

18) How much have you been oversleeping at night since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally increased	moderately increased	markedly increased	extremely increased

19) How much have you been oversleeping during the day since Baseline?

1	2	3	4	5	6
less than normal	normal	minimally increased	moderately increased	markedly increased	extremely increased

20) How has your energy been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

21) How heavy (in arms or legs) have you felt since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally heavy	moderately heavy	markedly heavy	extremely heavy

22) How slowed down have you felt since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally slowed down	moderately slowed down	markedly slowed down	extremely slowed down

23) How agitated have you felt since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally agitated	moderately agitated	markedly agitated	extremely agitated

24) How irritable have you been since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally irritable	moderately irritable	markedly irritable	extremely irritable

25) Have you had anger attacks (suddenly feeling very angry and like exploding with anger) since Baseline?

1	2	3	4	5	6
never	almost never	rarely	sometimes	frequently	all the time

26) How anxious/worried have you felt since Baseline?

1	2	3	4	5	6
less than normal	not at all	minimally anxious	moderately anxious	markedly anxious	extremely anxious

27) Have you had panic attacks since Baseline?

1	2	3	4	5	6
felt calmer than normal	not at all	rarely	sometimes	frequently	all the time

28) How has your appetite been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

29) Have you lost weight since Baseline?

1	2	3	4	5	6
gained some weight	not at all	minimally	mildly	moderately	markedly

30) Has your appetite been excessive since Baseline?

1	2	3	4	5	6
less	not at all	rarely	sometimes	frequently	all the time

31) Have you gained weight since Baseline?

1	2	3	4	5	6
lost some weight	not at all	minimally	mildly	moderately	markedly

32) Have you had tachycardia/palpitations since Baseline?

1	2	3	4	5	6
my heart rate	not at all	rarely	sometimes	frequently	all the time

felt slower than usual					

33) Have you had pains or aches since Baseline?

1	2	3	4	5	6
fewer aches and pains than usual	not at all	rarely	sometimes	frequently	all the time

34) Have you had gastrointestinal (stomach or bowel) symptoms since Baseline?

1	2	3	4	5	6
fewer symptoms than usual	not at all	rarely	sometimes	frequently	all the time

35) How has your ability to focus/sustain attention been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

36) How has your ability to remember/recall information been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

37) How has your ability to find words been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

38) How has your sharpness/mental acuity been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

39) How has your ability to make decisions been since Baseline?

1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

40) How has your sexual functioning been since Baseline?

1	2	3	4	5	6
better than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

41) How has your social functioning been since Baseline?

1	2	3	4	5	6
better than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

42) How has your ability to work/study/function at home been since Baseline?

1	2	3	4	5	6
better	normal	minimally	moderately	markedly	totally

than normal		diminished	diminished	diminished	absent

43) How guilty have you felt since Baseline?

1	**2**	**3**	**4**	**5**	**6**
less than normal	not at all	minimally guilty	moderately guilty	markedly guilty	extremely guilty

44) How worthless have you felt since Baseline?

1	**2**	**3**	**4**	**5**	**6**
less than normal	not at all	minimally worthless	moderately worthless	markedly worthless	extremely worthless

11.10 Clinical Global Impressions (CGI) Scale

CGI Source Document for Baseline CGI Administration

Clinical Global Impressions of Severity (CGI-S)

Severity	
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?	☐ 1 - Normal, not at all ill ☐ 2 - Borderline mentally ill ☐ 3 - Mildly ill ☐ 4 - Moderately ill ☐ 5 - Markedly ill ☐ 6 - Severely ill ☐ 7 - Among the most extremely ill patients

CGI Source Document for Post-Baseline CGI Administrations (Days 2, 4, 7, 14)

Clinical Global Impressions of Severity (CGI-S)

Severity	
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?	☐ 1 - Normal, not at all ill ☐ 2 - Borderline mentally ill ☐ 3 - Mildly ill ☐ 4 - Moderately ill ☐ 5 - Markedly ill ☐ 6 - Severely ill ☐ 7 - Among the most extremely ill patients

Clinical Global Impressions of Improvement (CGI-I)

Improvement	
Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to his condition at admission to the project, how much has he changed?	☐ 1 - Very much improved ☐ 2 - Much improved ☐ 3 - Minimally improved ☐ 4 - No change ☐ 5 - Minimally worse ☐ 6 - Much worse ☐ 7 - Very much worse

11.11 Structured Interview Guide for the Hamilton Depression Rating Scale-17 Item (SIGH-D)

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)
17-item version

Janet B.W. Williams, Ph.D.

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

Time period. The interview questions indicate that the ratings should be based on the patient's condition in the past week.

Referent of "usual" or "normal" condition. Several of the interview questions in the HAM-D refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

This instrument provides an interview guide for both the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960). The anchor point descriptions for both scales, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). Additional designators were added in parentheses to the depression scale anchor points by Kobak, Lipsitz and Williams to further standardize ratings. A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747).

For further information contact Dr. Williams at jbw5@columbia.edu

Revised 21 February 2007.

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)

PT'S INITIALS: _____ PT'S ID: _____ **TIME BEGAN SIGH-D: _____**

INTERVIEWER: _____ **DATE: : ___/___/___**

OVERVIEW: **I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?**	
What's your mood been like this past week (compared to when you feel OK)? Have you been feeling down or depressed? IF YES: Can you describe what this feeling has been like for you? How bad is the feeling? Does the feeling lift at all if something good happens? How are you feeling about the future? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**DEPRESSED MOOD** (sadness, hopeless, helpless, worthless): 0 - absent 1 - indicated only on questioning*(occasional, mild depression)* 2 - spontaneously reported verbally *(persistent, mild to moderate depression)* 3 - communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep *(persistent, moderate to severe depression,)* 4 - VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication *(persistent, very severe depression, with extreme hopelessness or tearfulness)*

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

NOTES:

SIGH-D-17 21 Feb 07

How have you been spending your time this past week (when not at work)? Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? How much less interested in these things have you been this past week compared to when you're not depressed? How hard to do you have to push yourself to do them? Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why? About how many hours a day do you spend doing things that interest you? Is there anything you look forward to? IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? How much less productive or efficient are you compared to before you were depressed?	**WORK AND ACTIVITIES:** 0 - no difficulty 1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies *(Mild reduction in interest or pleasure; no clear impairment in functioning)* 2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities; *(Clear reduction in interest, pleasure or functioning)* 3 - decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (hospital job or hobbies) exclusive of ward chores *(Profound reduction in interest, pleasure, or functioning)* 4 - stopped working bec. of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted *(Unable to work or fulfill primary role because of illness, and total loss of interest)*
Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began? **When have you been falling asleep and waking up over the past week?**	
Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep? Have you changed the time at which you try to get to sleep since you've been depressed?	**INSOMNIA EARLY (INITIAL INSOMNIA):** 0 - no difficulty falling asleep 1 - complains of occasional difficulty falling asleep (i.e., more than 1/2 hour, *2-3 nights)* 2 - complains of nightly difficulty falling asleep *(i.e., more than ½ hour, 4 or more nights)*

SIGH-D-17 21 Feb 07

During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep? Do you wake up more than once during the night? (If yes: How long does it take for you to fall back to sleep each time?) Have you felt your sleeping has been restless or disturbed some nights? How many nights this week have you had that kind of trouble?	**INSOMNIA MIDDLE:** 0 - no difficulty 1 - complains of being restless and disturbed during the night (or *Occasional difficulty, i.e., 2-3 nights, more than ½ hr)* 2 - waking during the night - any getting out of bed (except to void) (*Often i.e., 4 or more nights of difficulty, more than ½ hr)*
What time have you been waking up in the morning for the last time, this past week? IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)? How many mornings this past week have you awakened early?	**INSOMNIA LATE (TERMINAL INSOMNIA):** 0 - no difficulty 1 - waking in early hours of morning but goes back to sleep *(occasional, i.e., 2-3 nights difficulty)* 2 - unable to fall asleep again if gets out of bed *(often, i.e., 4 or more nights difficulty)*
Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.) Has there been any change in your interest in sex (from when you were feeling OK)? IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)	**GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances): 0 - absent 1 - mild (*Somewhat less interest than usual)* 2 - severe (*A lot less interest than usual)*
How has your appetite been this past week? (What about compared to your usual appetite?) IF LESS: How much less than usual? Have you had to force yourself to eat?	**SOMATIC SYMPTOMS GASTROINTESTINAL:** 0 - none 1 - loss of appetite but eating without encouragement (*Appetite somewhat less than usual)*

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Have other people had to urge you to eat? (Have you skipped meals?)	2 - difficulty eating without urging (or *Appetite significantly less than usual)*
Have you lost any weight since this (DEPRESSION) began? IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back? IF YES: How much? **NOTE: RATE 1 TO 3 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.**	**LOSS OF WEIGHT (Rate either A or B):** A. When rating by history: 0 - no weight loss 1 - probable weight loss due to current depression 2 - definite (according to patient) weight loss due to depression 3 - not assessed B. On weekly ratings by ward staff, when actual weight changes are measured: 0 - less than 1 lb. loss in week 1 - more than 1 lb. loss in week 2 - more than 2 lb. loss in week 3 - not assessed **NOTE: AVOID CODING "3" IF POSSIBLE**
How has your energy been this past week? IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?) This week, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?) Have you felt any heaviness in your limbs, back, or head?	**SOMATIC SYMPTOMS GENERAL:** 0 - none 1 - heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatiguability. *(Somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)* 2 - any clear-cut symptoms *(Persistent, significant loss of energy or muscle aches/heaviness)*

SIGH-D-17 21 Feb 07

Have you been putting yourself down this past week, feeling you've done things wrong, or let others down? IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? IF YES: What have your thoughts been? What about things that happened a long time ago? IF UNKNOWN: How often have you thought about this the past week? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? (Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)	**FEELINGS OF GUILT:** 0 - absent 1 - self-reproach, feels he has let people down 2 - ideas of guilt or rumination over past errors or sinful deeds *(feelings of guilt, remorse or shame)* 3 - present illness is a punishment. Delusions of guilt. (severe, pervasive feelings of guilt) 4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
This past week, have you had thoughts that life is not worth living? IF YES: What about thinking you'd be better off dead? Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?	**SUICIDE:** 0 - absent 1 - feels life is not worth living 2 - wishes he were dead or any thoughts of possible death to self 3 - suicidal ideas of gesture 4 - attempts at suicide
Have you been feeling especially tense this past week? IF YES: Is this more than is normal for you? Have you been unusually argumentative or impatient? Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How often have you felt this way the past week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**ANXIETY PSYCHIC:** 0 - no difficulty 1 - subjective tension and irritability *(Mild, occasional)* 2 - worrying about minor matters (*Moderate, causes* *some distress)* 3 - apprehensive attitude apparent in face or speech (*Severe; significant impairment in functioning due* *to anxiety)* 4 - fears expressed without questioning (*Symptoms* *incapacitating)*

SIGH-D-17 21 Feb 07

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST) FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? (How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?) NOTE: DO NOT RATE SXS THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.	**ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating): 0 - not present 1 - mild *(Symptom(s) present only infrequently, no impairment, minimal distress)* 2 - moderate (*Symptom(s) more persistent, or some interference with usual activities, moderate distress)* 3 - severe *(Significant impairment in functioning)* 4 - incapacitating
In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?) Have you worried a lot that you had a specific medical illness? Do you complain much about how you feel physically? Have you seen a doctor about these problems? What did the doctor say?	**HYPOCHONDRIASIS:** 0 - not present 1 - self-absorption (bodily) (*Some inappropriate worry about his/her health OR slightly concerned despite reassurance)* 2 - preoccupation with health *(Often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance)* 3 - frequent complaints, requests for help, etc. *(Is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health)* 4 - hypochondriacal delusions
RATING BASED ON OBSERVATION DURING INTERVIEW	**INSIGHT:** 0 - acknowledges being depressed and ill OR not currently depressed 1 - acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc. 2 - denies being ill at all

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RATING BASED ON OBSERVATION DURING INTERVIEW	**AGITATION:** 0 - none 1 - fidgetiness (slight agitation or mild restlessness) 2 - playing with hands, hair, etc. (moderate to marked restlessness or agitation) 3 - moving about, can't sit still (cannot remain seated) 4 - hand-wringing, nail biting, hair-pulling, biting of lips (interview cannot be conducted; severe agitation)

RATING BASED ON OBSERVATION DURING INTERVIEW	**RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity): 0 - normal speech and thought 1 - slight retardation at interview (mild psychomotor retardation) 2 - obvious retardation at interview (moderate; some difficulty with interview, noticeable pauses and slowness of thought) 3 - interview difficult (severe psychomotor retardation; very long pauses) 4 - complete stupor (extreme retardation; interview barely possible)

TIME ENDED SIGH-D:	_____
TOTAL HAM-D SCORE:	_____

11.12 Amendment 2: Table of Changes

Section/Change	Original Text	Revised Text
Sponsor Contact Updated	Richard M. Mangano, PhD Chief Scientific Officer Relmada Therapeutics, Inc. 275 Madison Avenue, Suite 702 New York, NY, USA 10016 Work: (646) 677-3859 Cell: (484) 947-1682 rmangano@relmada.com	***Sergio Traversa*** ***Chief Executive Officer*** ***Relmada Therapeutics, Inc.*** ***275 Madison Avenue, Suite 702*** ***New York, NY, USA 10016*** ***Work: 646-677-3853*** ***st@relmada.com***
CRO name updated.	INC Research, Inc.	***Syneos Health, Inc.***
Change of Scale: QIDS-SR was replaced with SDQ in all sections referencing scales. **Section 6.4.2.1:** New Section	Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)	***Symptoms of Depression Questionnaire (SDQ)***
Introduction Added data to support dosing justification.	…evaluated in this study, REL-1017-202. The intent of this study is….	…evaluated in this study, REL-1017-202. ***Additionally, the preclinical data for forced swim test in rats were used to identify efficacious doses…*** The intent of this study is….
Sample Size: Sample size increased to 120 patients screened to randomize 20 subjects per arm **Synopsis:** Study Population and Duration of Participation **Section 3.1:** Study Design **Section 3.2:** Study Procedures **Section 4.1:** Number of Patients	Approximately 90 patients will be screened, and approximately 45 qualified patients will be randomized to study drug in a 1:1:1 ratio (approximately 15 patients per arm).	Approximately ~~**90**~~ ***120*** patients will be screened, and approximately ~~**45**~~***60*** qualified patients will be randomized to study drug in a 1:1:1 ratio (approximately ~~**15**~~ ***20*** patients per arm).

Section/Change	Original Text	Revised Text
MGH CTNI Added, Entry Review Process Updated **Synopsis** Study Procedures **Section 3.2** Study Procedures	…detailed in the Clinical Surveillance Team manual. Decisions regarding the inclusion of patients and assessment of patient safety throughout the study primarily remain at the discretion of the Investigator; however, the Sponsor or external medical team may request exclusion or discontinuation of a patient based on the entry criteria or patient safety.	…detailed in the ~~Clinical Surveillance Team~~ Massachusetts General Hospital ***Clinical Trials Network and Institute [MGH CTNI]***manual. ….***Subjects who are deemed eligible by the Principal Investigator and confirmed by the Medical Monitor will undergo the SAFER Interview by clinicians at the Clinical Trials Network Institute. Only subjects whose eligibility will be confirmed by the SAFER Interview will be allowed to proceed in the study*** ~~Decisions regarding the inclusion of patients and assessment of patient safety throughout the study primarily remain at the discretion of the Investigator; however, the Sponsor or external medical team may request exclusion or discontinuation of a patient based on the entry criteria or patient safety.~~
Clarifying Definition of Current Episode **Synopsis** Study Population and Duration of Participation **Section 1.3.4:** Rationale for Protocol REL-1017-202 **Section 3.3:** Discussion of Study Design	Adult patients with MDD with a current MDE who have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication have been chosen for this study.	Adult patients with MDD ***who are diagnosed*** with a current ***major depressive episode*** (MDE) ***and*** who have experienced an inadequate response to 1 to 3 courses of treatment with an ***adequate dose and duration (as defined by the ATRQ) of an*** antidepressant medication ***for the current episode*** will be randomized to study drug in a 1:1:1 ratio. ~~have been chosen for this study~~.

Section/Change	Original Text	Revised Text
<u>Loading Dose:</u> Loading dose of 75 mg REL-1017 added for initial dosing of Arm 1 REL-1017 25 mg. A dose of 100 mg REL-1017 added for initial dose of Arm 2, 50 mg REL-1017. **Section 5.1** Study Drug Administration	Patients will receive one of the following: • 25 mg of REL-1017… • 50 mg of REL-1017… • 100 mL of Ocean Spray® Diet Cranberry juice (Placebo).	Patients will receive one of the following: ***<u>Day 1</u>*** • ***Arm 1: 75 mg of REL-1017 provided as a powder and prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing;*** • ***Arm 2: 100 mg of REL-1017 provided as a powder and prepared as a solution with Ocean Spray® Diet Cranberry Juice on site to obtain a final volume of 100 mL for dosing;*** • ***Arm 3: 100 mL of Ocean Spray® Diet Cranberry juice (Placebo).*** ***<u>Day 2-6</u>*** • ***Arm 1:*** 25 mg of REL-1017… • ***Arm 2:*** 50 mg of REL-1017… • ***Arm 3:*** 100 mL of Ocean Spray® Diet Cranberry juice (Placebo).
<u>Loading Dose:</u> 75 mg REL-1017 added for initial dosing of Arm 1 REL-1017 25 mg. A dose of 100 mg REL-1017 added for initial dose of Arm 2, 50 mg REL-1017. **<u>Synopsis</u>** Study Drug, Dose Schedule, and Mode of Administration	The following doses will be used in the study: • REL-1017 25 mg • REL-1017 50 mg Placebo • Ocean Spray® Diet Cranberry Juice)	The following doses will be used in the study: • REL-1017 ***75 mg QD Day 1***, 25 mg ***REL-1017 QD Day 2-7*** • REL-1017 ***100 mg QD Day 1,*** 50 mg ***REL-1017 QD Day 2-7*** • Placebo (Ocean Spray® Diet Cranberry Juice)

Section/Change	Original Text	Revised Text
Loading Dose: 75 mg REL-1017 added for initial dosing of Arm 1 REL-1017 25 mg. A dose of 100 mg REL-1017 added for initial dose of Arm 2, 50 mg REL-1017. **Section 5.4:** Selection of Doses	Not Applicable	***To reach steady state more quickly for REL-1017 25 mg and REL-1017 75 mg dosing arms, a loading dose on Day 1 was added to each dosing arm, REL-1017 75 mg on Day 1 followed by REL-1017 25 mg on Day 2-7 and REL-1017 100 mg on Day 1 followed by REL-1017 50 mg on Day 2-7.***
Inclusion Criterion #1: Modification to allow enrollment of females >1 year postmenopausal. **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	Males between 18 and 65 years of age, inclusive.	Males between 18 and 65 years of age, inclusive***; and females between 18 and 65 years of age, who are >1 year postmenopausal***.
Inclusion Criterion #3: Duration of diagnosis of MDE requirements at study entry changed from 12 months to 36 months. **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	Diagnosed with a current MDE lasting 8 weeks to 12 months as defined by the DSM-5 and confirmed by the MINI.	Diagnosed with a current MDE lasting 8 weeks to ~~12~~ **36** months as defined by the DSM-5 and confirmed by the MINI.

Section/Change	Original Text	Revised Text
Inclusion Criterion #4: Updated duration of current MDD drug treatment from 6 weeks to 8 weeks. **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	Treated with an adequate dosage of a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or bupropion during the current MDE for at least 6 weeks prior to Screening with the same, adequate dosage for the last 4 weeks. Minimum adequate doses are defined in the Antidepressant Treatment Response Questionnaire (ATRQ).	Treated with an adequate dosage of a selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or bupropion during the current MDE for at least ~~6~~ **8** weeks prior to Screening with the same, adequate dosage for the last 4 weeks. Minimum adequate doses are defined in the ~~***Antidepressant Treatment Response Questionnaire***~~ (~~ATRQ~~).
Inclusion Criterion #5: Adjustment of inclusion criteria with the addition of SAFER **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	#5 Have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication in the current episode, as defined as <50% improvement with an antidepressant medication at doses listed on the ATRQ.	#5 Have experienced an inadequate response to 1 to 3 courses of treatment with an antidepressant medication in the current episode, as defined as <50% improvement with an antidepressant medication at doses listed on the~~ ATRQ~~ ***SAFER Interview (Criteria: State versus trait; Assessability; Face validity; Ecological validity; and Rule of three Ps [pervasive, persistent, and pathological).***
Inclusion Criterion #6: Adjustment of inclusion criteria for Ham-D **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	#6 Hamilton Depression Rating Scale-17 (HAM-D-17) ≥**22** at Screening and Check-in (Day -1) with a score of ≥2 on Questionnaire Item 1**.**	#6 Hamilton Depression Rating Scale-17 (HAM-D-17) ≥~~22~~**19** at Screening and Check-in (Day -1) ~~***with a score of ≥2 on Questionnaire Item 1***~~.
Inclusion Criterion #10: Modification to require ability to read and understand English **Synopsis:** Inclusion Criteria **Section 4.2:** Inclusion Criteria	Must be able to read, speak, and understand the local language and must provide written informed consent prior to the initiation of any protocol-specific procedures.	Must be able to read, speak, and understand ~~***the local language***~~***English*** and must provide written informed consent prior to the initiation of any protocol-specific procedures.
Exclusion Criteria NEW:	Not Applicable	***Any 12-lead ECG with repeated demonstration of QTc***

Section/Change	Original Text	Revised Text
ECG exclusion added **Synopsis:** Exclusion Criteria **Section 4.3:** Exclusion Criteria		***≥450 msec or a QRS interval ≥120 msec at Screening.***
Exclusion Criterion #13: Clarified depressive disorder **Synopsis:** Exclusion Criteria **Section 4.3:** Exclusion Criteria	Any lifetime history of bipolar I or II disorder, persistent depressive disorder, any psychotic disorder… developmental disorder	Any lifetime history of bipolar I or II disorder, ~~***persistent depressive disorder,***~~ any psychotic disorder… developmental disorder
Objectives: Added measurements for evaluation of Safety Objectives **Synopsis** Objectives **Section 2.2.1:** Primary Objectives	To will assess the safety and tolerability of 25 mg and 50 mg of REL-1017 (d-methadone) compared to Placebo as adjunctive treatment in patients with major depressive disorder (MDD).	***Safety objectives will*** assess the safety and tolerability of 25 mg and 50 mg of REL-1017 (d-methadone) compared to Placebo as adjunctive treatment in patients with major depressive disorder (MDD). ***The following assessments will be conducted to measure safety and tolerability throughout the study:*** • ***AEs*** • ***Vital signs*** • ***Weight*** • ***Physical examination*** • ***Clinical laboratory parameters (chemistry, hematology, and urinalysis)*** • ***Electrocardiogram (ECG) parameters*** • ***Columbia-Suicide Severity Rating Scale (C-SSRS)*** • ***Clinician Administered Dissociative States Scale (CADSS)*** • ***Clinical Opiate Withdrawal Scale (COWS)*** • ***Brief Psychiatric Rating Scale – Positive Symptoms Subscale (BPRS-Positive)***
Objectives: Added measurements for evaluation of PK Objectives	**Not Applicable**	***The PK profile of REL-1017 25 mg and 50 mg following a loading dose of 75 mg will be evaluated on Day 1 through***

Section/Change	Original Text	Revised Text
Synopsis Objectives **Section 2.2:** Secondary Objectives		***Day 7, Day 8, Day 9, and Day 14 where the data allow:*** • ***Maximum observed plasma concentration (C_{max})*** • ***Time to maximum observed plasma concentration (T_{max})*** • ***Area under the plasma concentration-time curve from time zero until the dosing interval of 24 hours (AUC_{tau})*** • ***Area under the plasma concentration-time curve from time zero until the last quantifiable time point ($AUC_{0\text{-}last}$) on Day 7*** • ***Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$)*** • ***Apparent termination elimination rate constant (λ_z)*** • ***Apparent terminal elimination half-life ($t_{½}$)*** • ***Attainment of steady state*** • ***Steady state clearance (C_{SS}/F)*** • ***Volume of distribution at steady state (V_{SS}/F)*** • ***Accumulation ratios based on minimum observed plasma concentration (C_{min}), C_{max}, and AUC_{tau}***

Section/Change	Original Text	Revised Text
Objectives: Added measurements for evaluation of Efficacy Objectives **Synopsis** Objectives **Section 2.2.2:** Secondary Objectives	To explore the efficacy of 25 mg and 50 mg of REL-1017 (d-methadone) as adjunctive treatment in patients with MDD	***The efficacy objective is*** to explore the efficacy of 25 mg and 50 mg of REL-1017 (d-methadone) as adjunctive treatment in patients with MDD. ***The following assessments will be conducted to evaluate efficacy:*** • ***Change from Baseline (Day 1) to the End of the Dosing Period (EDP, Day 7) on the Montgomery-Asberg Depression Rating Scale (MADRS)*** • ***Change from Baseline (Day 1) to EDP (Day 7) on the Symptoms of Depression Questionnaire (SDQ)*** • ***Change from Baseline (Day 1) to EDP (Day 7) on the Clinical Global Impressions of Severity (CGI-S)*** • ~~***Change from Baseline (Day 1) to all other relevant visits on the MADRS, SDQ, and CGI-S.***~~
Prohibited Medications: Allowance of chronic and use of hypnotics during the study **Section 4.4.1:** Prohibited Medications	Non-benzodiazepine sleep aids may be continued in the study, but no more than 3 times per week, at the doses listed in Table 3; and…. **Prohibited…** **Med — Washout Period** MAOIs — 14 Days TCA/Atypical — 7 Days Benzodiazepine — 7 Days Psychotropic…. — 7 Days Herbal... — 8 Days	Non-benzodiazepine sleep aids may be continued in the study, ~~***but no more than 3 times per week***~~, at the doses listed in Table 3; and…. **Prohibited…** **Med — Washout Period** MAOIs — 3 Months TCA/Atypical — 3 Months Benzodiazepine — 1 Month Psychotropic…. — 3 Months Herbal... — 1 Month

Section/Change	Original Text	Revised Text
Rater Qualifications: Section **4.6** added	Not Applicable	***4.6 Rater Qualifications*** ***Raters must demonstrate sufficient assessment experience as well as appropriate educational background and indication experience.*** ***Raters performing the clinical assessments will require training and approval by the Sponsor designated vendor prior to rating in this study.*** ***The vendors designated by the Sponsor will conduct rater qualification and will provide written and signed documentation about each rater's certification and/or training.*** ***If possible, each subject will be interviewed and assessed throughout the study by the same rater.***
Section 6: **Study Procedures and Assessments**	The pre-dose period on Day 1 will be considered time zero. Other logistical considerations (e.g., sequence of events, assessment windows) will be outlined in study-specific procedures.	The pre-dose period on Day 1 will be considered time zero. Other logistical considerations (e.g., sequence of events, assessment windows) will be outlined in study-specific procedures. ***Post-Screening psychiatric scales will be administered using the timeframe since the last administration of the scale.***
Follow-up Assessments Added C-SSRS **Synopsis:** Procedures **Section 6.1.8:** Follow-Up: Added C-SSRS	In the Follow-Up interview (Day 21), only, AEs and medications will be recorded (Table 1).	In the Follow-Up interview (Day 21), ***~~only~~ C-SSRS,*** AEs and medications will be recorded (Table 1).

Section/Change	Original Text	Revised Text
Central ECGs: Added central ECG readings to the protocol. **Section 6.2.4:** 12-Lead Electrocardiograms	Not Applicable	***ECGs will be submitted electronically to central ECG reading center for evaluation of subject for entry into the study. The Investigator will make a final judgment on whether to include the subject's ECGs meets the entry criteria for the study.***
ECG Clarification: Clarification of ECG capture and reading.	Not Applicable	***If more than one ECG is collected, the mean of the replicate measurements will be reported. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from those triplicate measurements are also ≥500 msec. Changes from Baseline will be defined as the change between QTc post-dose from the time-matched average Baseline triplicates on Baseline Day 1 (V2).***

Section/Change	Original Text	Revised Text
Table 1 **Section 6.2.5.8:** **Pregnancy Testing**	N.A.	***A urine pregnancy test and a serum follicle stimulating hormone (FSH) test will be administered to all female patients at Screening (Day 30 to Day 2). Negative test results are required for enrollment in the study. Another negative urine pregnancy test will be required at Check in (Day 1) for confirmation.***
Section 7.1.4: Other Adverse Events of Interest	Addition of text	***The study drug will be administered under the supervision of study personnel, which should eliminate the opportunity for abuse during the course of the study. However, Investigators should take note of AEs that might suggest that the study drug has the potential for abuse. For example, the occurrence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential.*** ***Examples of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms that may provide abuse-related information about a drug include:*** • ***Euphoria-related terms - euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect***

Section/Change	Original Text	Revised Text
		• ***Terms indicative of impaired attention, cognition, and mood - somnolence, mood disorders, and disturbances*** • ***Dissociative/psychotic terms - psychosis, aggression, confusion, and disorientation*** ***Drug withdrawal syndrome***
Appendices: Rating scales added	Not Applicable	Appendices 11.2-11.9

Additional changes were made that were administrative or grammatical in nature.

11.13 Amendment 3: Table of Changes

Section/Change	Original Text	Revised Text
Exclusion Criterion #1: Addition of safety criteria **Synopsis:** Exclusion Criterion #1 **Section 4.3:** Exclusion Criterion #1	**Exclusion Criterion #1:** History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator would jeopardize the safety of the patient or the validity of the study results.	**Exclusion Criterion #1:** History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator would jeopardize the safety of the patient or the validity of the study results*, including torsades de pointes, any bradyarrhythmias, or uncompensated heart failure.*
Exclusion Criterion #4: Made Synopsis and Sect. 4.2 consistent	**Exclusion Criterion #4:** History or family history of sudden unexplained death or long QT syndrome (measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle).	**Exclusion Criterion #4:** Added text: History or family history of sudden unexplained death or long QT syndrome *(measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle).*
Inclusion Criterion #9: Synopsis:	**Inclusion Criterion #9:** Synopsis:	**Inclusion Criterion #9:** Synopsis:

Section/Change	Original Text	Revised Text
Removed reference to protocol section (Synopsis is a stand-along document)	Male patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in section 4.4.2, from Screening and for at least 2 months after the last study drug administration.	Male patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in *the protocol*, from Screening and for at least 2 months after the last study drug administration.
Exclusion Criteria #15 Section 4.3: Made consistent with Synopsis Exclusion Criteria #15	**Exclusion Criteria #15** Section 4.3: Current diagnosis of alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening.	**Exclusion Criteria #15** Section 4.3: Added text: Current diagnosis of alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. *Patients with the following diagnoses within the past 12 months, however, may be included at the Investigator's discretion: mild alcohol use disorder, mild cannabis use disorder, and any severity tobacco use disorder.*
Revision of "Washout Period" **Exclusion Criterion #19:** Synopsis Section 4.3: **Section 4.4.1:** Prohibited Medications **Table 3:** Title Column Header **Section 7.1.1:** Adverse Events	**Exclusion Criterion #19:** **Synopsis:** Patients taking medications prohibited in Section 4.4.1 of the protocol who are unable to safely complete the specified Washout Period. **Section 4.3:** Patients taking medications prohibited in Section 4.4.1 of the protocol who are unable to safely complete the specified Washout Period. **Section 4.4.1:** All patients must agree to discontinue all prohibited medications during the Screening period to meet the protocol-specified Washout Periods. Table 3 provides the required duration of washout for selected prohibited medications.	**Exclusion Criterion #19:** **Synopsis:** *Patients who did not safely discontinue prohibited medications.* **Section 4.3:** *Patients who did not safely discontinue medications prohibited in Section 4.4.1.* **Section 4.4.1:** All patients *must have* discontinued all prohibited medications *prior to* the Screening period to meet the protocol *requirements.* Table 3 provides the required *duration of time to discontinuation period* for selected prohibited medications. *Addition of text*: *All medications taken within 6 months prior to Screening must be noted on the*

Section/Change	Original Text	Revised Text
	Table 3 Title: Duration of Washout for Selected Medications, Supplements, and Other Substances **Table 3 Column Header**: Washout Period Prior to Check-In **Section 7.1.1: Adverse Events** During the study, an AE can also occur outside the time that the investigational product(s) was given (e.g., during a Washout Period).	*eCRF.* **Table 3 Title:** *Time from Discontinuation of* Selected Medications, Supplements, and Other Substances **Table 3 Column Header**: *Time from Discontinuation to Check-In* **Section 7.1.1: Adverse Events** During the study, an AE can also occur outside the time that the investigational product(s) was given (e.g., during the *time from discontinuation* of prohibited medications).
Exclusion Criterion #23 and 24: Section 4.3: Reversed order to be consistent with Synopsis	#23: Patients who have participated in a clinical study with an investigational medication in the past 6 months, or who have participated in more than 4 clinical studies with investigational medications in the past 2 years. #24: Patients taking fluvoxamine or St. John's Wort.	#23: Patients taking fluvoxamine or St. John's Wort. #24: Patients who have participated in a clinical study with an investigational medication in the past 6 months, or who have participated in more than 4 clinical studies with investigational medications in the past 2 years.
Section 4.4.1: Prohibited Medications: Revision of benzodiazepine guidance	**Section 4.4.1:** Non-benzodiazepine sleep aids may be continued in the study at the doses listed in Table 3; and initiation of these medications during the study is not allowed except that a wash-in period of at least 21 days with a steady dose is allowed during Screening for people coming off benzodiazepines.	**Section 4.4.1:** *Benzodiazepines and non-benzodiazepine sleep aids taken as scheduled medications and at stable doses not higher than the FDA-approved label for at least 30 days prior to the Check-in are allowed in the study. Any questions regarding these medications should be directed to the Study Medical Monitor. Initiation of these medications during the study is not allowed.*

Section/Change	Original Text	Revised Text
Section 4.4.1: Prohibited Medications: Addition of safety guidance to investigator	**Section 4.4.1:** Not Applicable	**Section 4.4.1:** Addition of: *Due to each subject's clinical condition being unique, there is no specific rescue plan or rescue therapy recommended for subjects. If a subject experiences a clinical condition, the Investigator should use clinical judgment and knowledge of the subject's specific condition to institute the best treatment for that subject.*
Section 4.4.1: Table 3	**Section 4.4.1, Table 3:** **Prohibited Medications, Supplements, and Other Substances** MAOIs 3 Months 14 Days TCA/Atypical 3 Months 7 Days Benzodiazepine 1 Month 7 Days Psychotropic…3 Months 7 Days Herbal... 1 Month 8 Days Footnote: Not Applicable	**Section 4.4.1, Table 3:** ***Time From Discontinuation to Check-in*** MAOIs *90 days* TCA/Atypical *90 days* *PRN* Benzodiazepine *30 days* Psychotropic…. *90 days* Herbal... *30 days* Added to the footnote: *These include off-label use of medications for depression.* Added to footnote: *PRN = As needed.*
Section 4.5: Patient Discontinuation/ Withdrawal Criteria	**Section 4.5:** Not Applicable	**Section 4.5:** Added bullet: *Subjects with a QTc ≥500 msec or ≥60 msec above the patient's Baseline value will discontinue study medication and be re-assessed. The ECG should be repeated until values return below 500 msec, or ≥60 msec above Baseline. These findings will be reviewed by a cardiologist. Any additional intervention for the safety of the subject should be discussed with the Study Medical Monitor and Sponsor.*

Section/Change	Original Text	Revised Text
Section 4.6: Rater Qualifications	**Section 4.6:** The vendors designated by the Sponsor will conduct rater qualification and will provide written and signed documentation about each rater's certification and/or training.	**Section 4.6:** The vendors designated by the Sponsor will conduct rater qualification and will *provide documentation* about each rater's certification and/or training.
Section 6.2.5.1: Clinical Chemistry: Addition of magnesium	**Section 6.2.5.1:** Quantitative analysis will be performed for the following analytes: alkaline phosphatase, albumin, calcium, chloride, creatinine, random glucose, potassium, ALT, AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase, sodium, total bilirubin, urea, and testosterone.	**Section 6.2.5.1:** Quantitative analysis will be performed for the following analytes: alkaline phosphatase, albumin, calcium, chloride, creatinine, random glucose, potassium, *magnesium,* ALT, AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase, sodium, total bilirubin, urea, and testosterone.
Section 6.6.3.2: CADSS correction	**Section 6.6.3.2:** The CADSS is a 27-item scale with 19 items that are rated by the subject, and 8 items that are scored by an observer.	**Section 6.6.3.2:** The CADSS is a *23*-item scale with *all* items *administered to* the subject.
Change of Scale: References to the CGI, CGI-S and CGI-I were modified in all sections referencing the scales. **Synopsis:** Endpoints, Statistical Data Analysis, Table 1, footnote "k," and Abbreviations **Section 2.2.2** Efficacy **Section 6.4.2.2** Clinical Global Impressions **Section 6.6.2.2**	**Synopsis:** Efficacy Endpoint: Change from Baseline (Day 1) to EDP (Day 7) on the Clinical Global Impressions of Severity (CGI-S) Statistical Data Analysis: Not Applicable **Section 2.2.2** Not Applicable **Section 6.4.2.2** Clinical Global Impressions of Severity **Section 6.6.2.2** Clinical Global Impressions of Severity (CGI-S) The score ranges from 1 to 7,	**Synopsis:** Efficacy Endpoint: *The Clinical Global Impressions of Improvement (CGI-I) scale will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14.* Added bullet: *Change from Baseline (Day 1) to EDP (Day 7) on the Clinical Global Impressions of Severity (CGI-S) scale will be measured at pre-dose on Day 1 and Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and on Day 14.* Table 1, footnote "k" and

Section/Change	Original Text	Revised Text
Clinical Global Impressions of Severity (CGI-S) **Section 8.1.1:** Analysis Populations **Section 8.1.3.3:** Secondary Objectives: Efficacy of REL-1017 **Section 8.1.4.5:** Analysis of Efficacy Assessments **Section 8.1.7:** Missing Data **Acronyms and Abbreviations:** **Appendix 11.9:**	and a lower CGI-S score indicates an increased response to therapy in the treatment of depression. **Section 8.1.1:** Not Applicable **Section 8.1.3.3:** Not Applicable **Section 8.1.4.5:** Not Applicable **Section 8.1.7:** Not Applicable **Acronyms and Abbreviations:** Not Applicable **Appendix 11.9** Replaced CGI-S scale with CGI (Severity and Improvement) scale	Abbreviations modified to reflect this change. Added to Statistical Data Analysis: *The CGI-I will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14.* **Section 2.2.2** Addition of bullet: *Evaluation of Clinical Global Impressions of Improvement (CGI-I) total score on Day 7 (post-dose), as well as CGI-I scores on Days 2 (pre-dose), 4 (post-dose), and 14.* **Section 6.4.2.2** *Clinical Global Impressions (CGI) Scale* Added text: *The CGI-I will be measured at pre-dose on Day 2, post-dose on Day 4 and Day 7 within 3 hours of dosing, and on Day 14.* **Section 6.6.2.2** *Clinical Global Impressions (CGI) Scale* The score ranges from 1 to 7, and a lower CGI-S score indicates *lower levels of depression*. Addition of CGI-I text: *The CGI-I is a standard method used in clinical studies to quantify and track patient change over time. The scale is composed of 7 ratings: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse. The score ranges from 1 to 7, and a lower CGI-*I *score indicates greater improvement in symptoms.*[42] **Section 8.1.1:** Addition of: *or CGI-I*

Section/Change	Original Text	Revised Text
		Section 8.1.3.3: Addition of: *Evaluation of CGI-I total score on Day 7 (post-dose), as well as CGI-I scores on Days 2 (pre-dose), 4 (post-dose), and 14.* **Section 8.1.4.5:** Addition of: *The CGI-I will be administered pre-dose on Day 2; post-dose on Day 4 and Day 7 within 3 hours of dosing; and at EOP (Day 14).* **Section 8.1.7:** Addition of: *and CGI-I.* **Acronyms and Abbreviations:** Addition of: *CGI: Clinical Global Impressions* *CGI-I: Clinical Global Impressions of Improvement* **Appendix *11.10*** *CGI of Severity and Improvement scale*
Change of Scale: BPRS – Positive Symptoms Subscale (BPRS) was replaced with the 4-Item PSRS in all sections referencing scales. **Synopsis:** Endpoints, Table 1, footnotes "l" and Abbreviations **Section 2.1, Primary Objectives:** BPRS-Positive Symptoms Subscale **Section 6.2.6.4:** BPRS-Positive Symptoms Subscale **Section 6.6.3.4:** BPRS-Positive Symptoms Subscale	**Synopsis:** Endpoints, Table 1, footnotes "l" and Abbreviations: Brief Psychiatric Rating Scale - Positive Symptoms Subscale (BPRS-Positive) **Section 2.1, Primary Objectives:** Brief Psychiatric Rating Scale - Positive Symptoms Subscale (BPRS-Positive) **Section 6.2.6.4:** Brief Psychiatric Rating Scale - Positive Symptoms Subscale (BPRS-Positive) **Section 6.6.3.4:** Brief Psychiatric Rating Scale - Positive Symptoms Subscale (BPRS-Positive) Text deleted: The BPRS-Positive can be used	**Synopsis:** Endpoints, Table 1, footnotes "l" and Abbreviations: *4-Item Positive Symptoms Rating Scale (4-Item PSRS)* **Section 2.1,Primary Objectives:** *4-Item Positive Symptoms Rating Scale (4-Item PSRS)* **Section 6.2.6.4:** *4-Item Positive Symptoms Rating Scale (4-Item PSRS)* **Section 6.6.3.4:** *4-Item Positive Symptoms Rating Scale (4-Item PSRS)* Text added: *The 4-Item PSRS was adapted from the Brief Psychiatric Rating Scale developed by Ventura and colleagues. It is a clinician-administered scale intended to assess the extent to which a*

Section/Change	Original Text	Revised Text
Section 7.1.3: Clinical Lab Abnormalities and Other Abnormalities Assessments **Section 8.1.3.1:** Primary Endpoint: Safety and Tolerability of REL-1017: BPRS-Positive Symptoms Subscale **Section 8.1.5:** Demographics and Other Baseline Characteristics **Section 10:** Reference #45 **Appendix 11.6:** **Acronyms and Abbreviations**	to evaluate persons having or suspected of having schizophrenia or other psychotic disorder.[39] The BPRS-Positive assesses the level of 18 symptom constructs such as hostility, suspiciousness, hallucination, and grandiosity. It is based on the clinician's interview with the patient and observations of the patient's behavior over the previous 2 to 3 days. The rater enters a number for each symptom construct that ranges from 1 (not present) to 7 (extremely severe). The positive symptoms subscale includes 4 items. **Section 7.1.3:** Clinical Laboratory Abnormalities and Other Abnormal Assessments: BPRS-Positive **Section 8.1.3.1:** Primary Endpoint: Safety and Tolerability of REL-1017: BPRS-Positive **Section 8.1.5:** Demographics and Other Baseline Characteristics: BPRS-Positive **Section 10:** Reference #45: Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, and Shaner, *A Manual for the expanded Brief Psychiatric Rating Scale*. International Journal of Methods Psychiatry Research 1993; 3:227-244. **Appendix 11.6:** BPRS-Positive Symptoms Subscale **Acronyms and Abbreviations:**	*subject is currently experiencing positive psychotic symptoms. The scale assesses paranoia and hallucinations as well as some specific issues related to difficulty thinking and having unusual thoughts. When administering the scale, the rater enters a number for each of 4 symptom constructs with scores that range from 1 (not present) to 7 (extremely severe). Total score on the PSRS can range from 4 to 28.* **Section 7.1.3:** Clinical Laboratory Abnormalities and Other Abnormal Assessments: *4-Item PSRS* **Section 8.1.3.1:** Primary Endpoint: Safety and Tolerability of REL-1017: *4-Item Positive Symptoms Rating Scale (4-Item PSRS)* **Section 8.1.5:** Demographics and Other Baseline Characteristics: *4-Item PSRS* **Section 10:** Reference #*46*: Added text: *The 4-Item Positive Symptom Rating Scale was adapted from the Expanded Version of the BPRS developed by:* Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, and Shaner, *A Manual for the expanded Brief Psychiatric Rating Scale*. International Journal of Methods Psychiatry Research 1993; 3:227-244. **Appendix 11.6:** *4-Item Positive Symptom Rating Scale (4-Item PSRS)* **Acronyms and Abbreviations:** *4-Item PSRS: 4-Item Positive*

Section/Change	Original Text	Revised Text
	BPRS-Positive: Brief Psychiatric Rating Scale - Positive Symptoms Subscale	*Symptoms Rating Scale*
Appendix 11.7 Added scale: Antidepressant Treatment Response Questionnaire (ATRQ)	**Appendix 11.7** Not Applicable	**Appendix 11.7** Added: *Appendix 11.7 Antidepressant Treatment Response Questionnaire (ATRQ)* All Appendix numbering adjusted with inclusion of new Appendix.
Appendix 11.8: Symptoms of Depression Questionnaire (SDQ): All questions (1-44): scale timeframe changed	**Appendix 11.8:** "… over the past week?"	**Appendix *11.9*:** "… *since Baseline*?"
SAFER Interview administration schedule modified **Synopsis:** Procedures Table 1 **Section 3.2:** Study Procedures	**Synopsis and Section 3.2:** Procedures: The interview will be performed remotely by the MGH CTNI rater, and the subject will be contacted at his or her home or other off-site location between the Screening and Baseline visits, during which call the above assessments will be performed. Table 1: SAFER Interview at Screening and Check-In	**Synopsis and Section 3.2** Procedures: The interview will be performed remotely by the MGH CTNI rater, and the subject will be contacted at his or her home or other off-site location *after the Screening Visit*, during which call the above assessments will be performed. Table 1: SAFER Interview at *Screening* (deleted "at Check-in").
Section 10: References: SIGMA (2011) scale added	Not Applicable	Addition of reference to SIGMA scale version 2011: *Structured Interview Guide for the MADRS. Royal College of Psychiatrists, 2011. Developed from Williams JBW, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Asberg Depression Rating Scale (SIGMA). Br J Psychiatry 2008;192:52-58.* All reference numbering adjusted

Section/Change	Original Text	Revised Text
		with inclusion of new reference.

Additional changes were made that were administrative or grammatical in nature.

11.14 Amendment 4: Table of Changes

Section/Change	Original Text	Revised Text
Inclusion Criterion #1 (Synopsis and Section 4.2): Addition of women of childbearing potential	**Inclusion Criterion #1:** Males between 18 and 65 years of age, inclusive; and females between 18 and 65 years of age, inclusive, who are >1 year postmenopausal.	**Inclusion Criterion #1:** Males ***and females*** between 18 and 65 years of age, inclusive~~;~~ ~~**and females between 18 and 65 years of age, inclusive, who are >1 year postmenopausal.**~~
Inclusion Criterion #9 (Synopsis and Section 4.2: Addition of women of child-bearing potential	**Inclusion Criterion #9:** Male patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in Section 4.4.2, from Screening and for at least 2 months after the last study drug administration.	**Inclusion Criterion #9:** Male ***and female*** patients of reproductive potential must be using and willing to continue using medically acceptable contraception, as specified in Section 4.4.2, from Screening and for at least 2 months after the last study drug administration. ***Female patients must have a negative pregnancy test, and must not be breastfeeding.***
Exclusion Criterion #5 (Synopsis and Section 4.2): Revision of ECG criterion: QTc changed to QTcF **Synopsis:** Statistical Data Analysis: Safety **Section 1.1.1** **Section 1.2.1** **Section 4.5** **Section 7.1.4** **Section 8.1.4.3**	**Exclusion Criterion #5 (Synopsis and Section 4.2):** Any 12-lead ECG with repeated demonstration of corrected QT ≥450 msec or a QRS interval ≥120 msec at Screening. **Synopsis:** Statistical Data Analysis: Safety: Absolute values, change from Check-in (Day -1) in 12-lead ECG results and QT/QTc categories … **Section 1.1.1** Not Applicable **Section 1.2.1:** The single doses of REL-1017 administered in this study appeared to be safe with no indication of respiratory depression or clinically significant QTc prolongation. **Section 4.5:** Subjects with a QTc ≥500 msec or ≥60 msec above the patient's	**Exclusion Criterion #5 (Synopsis and Section 4.2:** ~~Any 12-lead ECG with repeated demonstration of corrected QT ≥450 msec or a QRS interval ≥120 msec at Screening.~~ ***An average QTcF ≥450 msec or an average QRS interval ≥120 msec from the 12-lead ECGs performed at Screening.*** **Synopsis:** Statistical Data Analysis: Safety: Absolute values, change from Check-in (Day -1) in 12-lead ECG results and QT/QTc***F*** categories **Section 1.1.1:** Added: ***The Fridericia formula will be used for QTc.*** **Section 1.2.1:** The single doses of REL-1017 administered in this study appeared to be safe with no indication of respiratory depression or clinically significant QTc***F*** prolongation.

Section/Change	Original Text	Revised Text
	Baseline value … **Section 7.1.4:** If any of the 3 individual ECG tracings has a QTc value ≥500 msec, … Changes from Baseline will be defined as the change between QTc post-dose … **Section 8.1.4.3:** Absolute values, change from Check-in (Day -1) in 12-lead ECG results (average of triplicate assessments, where applicable), and QT/QTc categories … Overall interpretation and machine read intervals (HR, PR, QRS, QT and QTc) …	**Section 4.5:** Subjects with a QTc***F*** ≥500 msec or ≥60 msec above the patient's Baseline value … **Section 7.1.4:** If any of the 3 individual ECG tracings has a QTc***F*** value ≥500 msec, … Changes from Baseline will be defined as the change between QTc***F*** post-dose … **Section 8.1.4.3:** Absolute values, change from Check-in (Day -1) in 12-lead ECG results (average of triplicate assessments, where applicable), and QT/QTc***F*** categories … Overall interpretation and machine read intervals (HR, PR, QRS, QT and QTc***F***) …
Synopsis Table 1: Time and Events Schedule Added urine pregnancy test at EOP and FU Visits	**Synopsis Table 1:** Added urine pregnancy test at EOP and FU Visits	**Synopsis Table 1:** Added: "***X***" in the row "Urine Pregnancy Test for Females" in columns "EOP" and "FU" Visits.
1.1.2: In Vivo: Addition of pre-clinical toxicology data	**1.1.2: In Vivo:** Not Applicable	**1.1.2: In Vivo:** Added**:** ***In a developmental toxicity study, pregnant CD® rats (Charles River Laboratories) were given daily oral gavage administration of 0 (vehicle), 10, 20, and 40 mg/kg d-methadone hydrochloride on GD 6 through GD 17. No test article-related effects were observed on maternal survival, clinical findings, ovarian and uterine parameters (mean number of corpora lutea, implantation sites, viable fetuses/litter size, resorptions,***

Section/Change	Original Text	Revised Text
		and pre- and postimplantation loss), or macroscopic findings at any dose level evaluated. Test article-related, but non-adverse, effects on maternal body weight and/or body weight change were observed at 10, 20, and 40 mg/kg/day and on food consumption at 40 mg/kg/day. No test article-related effects were observed on fetal sex ratios; body weights; or external, visceral, or skeletal examinations. ***No developmental toxicity was observed at any dose level tested. The no-observed-adverse-effect level (NOAEL) for both maternal and developmental toxicity was set to be 40 mg/kg/day. Based on a 60-kg human body weight and conversion of rat to human dose based on body surface area, the human equivalent dose (HED) was determined to be 387 mg. The dose provides approximately 15.48-fold and 7.74-fold safety margins when compared to the 25 mg and 50 mg doses of REL-1017-202). The safety margins calculations were based on the on the FDA Guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (Error! Reference source not found.).***

Section/Change	Original Text	Revised Text
4.4.2: Contraceptive Precautions: Revision to precautions for male patients, and addition of contraceptive precautions for female patients	**4.4.2 Contraceptive Precautions:** For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include true abstinence, vasectomy, or male condom for patients plus an additional method of contraception for their female partners.	**4.4.2 Contraceptive Precautions:** For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include ~~true abstinence,~~ vasectomy, or male condom for patients plus an additional method of contraception for their female partners. ***Abstinence from heterosexual intercourse is accepted if this is your usual lifestyle and must be continued until at least 2 months after the last dose of study drug.*** Added: ***Females of child-bearing potential (not surgically sterilized and between menarche and 1 year post menopause) must agree to use contraception through the end of the study and until at least 2 months after the last study drug administration. Surgical sterilization is defined as removal of the uterus and/or both ovaries. Acceptable forms of contraception for female patients include:*** • ***Intrauterine device (IUD)*** • ***Bilateral tubal ligation, bilateral salpingectomy or bilateral tubal occlusive procedure*** • ***Hormonal contraceptives (e.g., oral, patch, or injectable)*** • ***A double-barrier protection method (e.g., condom, sponge, or vaginal diaphragm with spermicide***

Section/Change	Original Text	Revised Text
		cream, foam, or gel) • ***Abstinence from heterosexual intercourse is accepted if this is your usual lifestyle and must be continued until at least 2 months after the last dose of study drug.*** ***Women must also abstain from egg donation from Screening until at least 2 months after the last study drug administration.***
6.1.7 Outpatient Observation Period (Day 10 to Day 14): Pregnancy test added.	**6.1.7 Outpatient Observation Period (Day 10 to Day 14):** Not Applicable	**6.1.7 Outpatient Observation Period (Day 10 to Day 14):** Added: ***A confirmatory pregnancy test will be administered.***
6.1.8 Follow-Up Period (Day 15 to Day 21): Pregnancy test added	**6.1.8 Follow-Up Period (Day 15 to Day 21):** Not Applicable	**6.1.8 Follow-Up Period (Day 15 to Day 21):** Added: ***A confirmatory pregnancy test will be administered if the visit is conducted at the site.***
Section 6.2.5.8: Pregnancy Testing: Pregnancy tests added.	**Section 6.2.5.8: Pregnancy Testing:** Not Applicable	**Section 6.2.5.8: Pregnancy Testing:** Added: ***Additional confirmatory pregnancy tests will be administered at the End of the Observation Period Visit (Day 14 ± 3 days and Follow-Up Visit (Day 21 ± 3 days).***

Section/Change	Original Text	Revised Text
Section 7.3.3: **Pregnancy** Revised due to the inclusion of women of childbearing potential	**Section 7.3.3:** Given that the effects of the study drug on sperm have not been fully elucidated, any pregnancy in the partner of a patient participating in the study will be reported to Relmada within 24 hours of learning of the event. Follow-up information will be obtained where possible (i.e., with the consent of the patient's partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.	**Section 7.3.3:** Given that the effects of the study drug on ***egg and*** sperm have not been fully elucidated, any pregnancy in the ***patient or*** partner of a patient participating in the study will be reported to Relmada within 24 hours of learning of the event. Follow-up information will be obtained where possible (i.e., with the consent of the ***patient or*** patient's partner) regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.
Section 10: **References:** Addition of FDA guidance reference	**Section 10: References:** Not Applicable	**Section 10: References:** Added: ***FDA Guidance, "Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers"; Jul 2005.***

Additional changes were made that were administrative or grammatical in nature.

11.15 Amendment 5: Table of Changes

Section/Change	Original Text	Revised Text
Page 2, Sponsor address: Updated sponsor address	**Page 2, Sponsor address:** 750 Third Avenue, 9th Floor New York, NY, USA 10017 Work: 212-572-9606	**Page 2, Sponsor address:** *880 Third Avenue, 12th Floor* *New York, NY 10022* *Work: 212-547-9591*
Synopsis and Section 4.2: Inclusion Criteria #9: Revised "breastfeeding" to "lactating" for clarity.	**Inclusion Criteria #9:** … Female patients must have a negative pregnancy test, and must not be breastfeeding.	**Inclusion Criteria #9:** … Female patients must have a negative pregnancy test, and must not be *lactating.*
Section 4.4.2: **Contraceptive Precautions** • Two methods of contraception added • Abstinence removed from 1st	**Section 4.4.2:** Females of child-bearing potential (not surgically sterilized and between menarche and 1 year post menopause) must agree to use contraception through the end of the study …	**Section 4.4.2:** Females of child-bearing potential (not surgically sterilized and between menarche and 1 year post menopause) must agree to use *2 methods of* contraception through the end of the study …

and 4th paragraphs.	Abstinence from heterosexual intercourse is accepted if this is your usual lifestyle and must be continued until at least 2 months after the last dose of study drug.	~~Abstinence from heterosexual intercourse is accepted if this is your usual lifestyle and must be continued until at least 2 months after the last dose of study drug.~~
Section 7.1.8: **Serious Adverse Events and Serious Unexpected Adverse Events** Safety reporting email address updated	**Section 7.1.8:** INCDrugSafety@increasearch.com	**Section 7.1.8:** *safetyreporting@syneoshealth.com*

Additional changes were made that were administrative or grammatical in nature.