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CLINICAL STUDY PROTOCOL

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial of REL-1017 as an Adjunctive Treatment for Major Depressive Disorder (RELIGHT)

Protocol Number: **REL-1017-304**

IND Number:	133345
Name of Investigational Product:	REL-1017
Phase of Development:	3
Indication:	Major Depressive Disorder
Sponsor:	Paul Greene, PhD SVP Clinical Operations Relmada Therapeutics, Inc. 2222 Ponce de Leon Blvd, Floor 3 Coral Gables, FL 33134 Tel: 786-629-1376 Email: pgreene@relmada.com
Protocol Version:	4.0 (Amendment 3)
Protocol Date:	10 Jul 2024

-CONFIDENTIAL-
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PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial of REL-1017 as an Adjunctive Treatment for Major Depressive Disorder (RELIGHT)

Protocol Number: REL-1017-304

Protocol Version 4.0 Amendment 3

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

Paul Greene, PhD
SVP Clinical Operations
Relmada Therapeutics

DocuSigned by:
Paul Greene
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Signature

7/10/2024

Date (DD-Mmm-YYYY)

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Trial of REL-1017 as an Adjunctive Treatment for Major Depressive Disorder (RELIGHT)

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Protocol Version 4.0 Amendment 3

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2):

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)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the study 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, 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 or her financial ties with the Sponsor. Relmada Therapeutics, Inc., will obtain and disclose any relevant information in this regard solely to comply with regulatory requirements.

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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.

Investigator Name	Investigator Signature
Investigator Title	Date (DD-Mmm-YYYY)
Institution	

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1 SYNOPSIS

Title of Study	A Randomized, Double-Blind, Placebo-Controlled Trial of REL-1017 as an Adjunctive Treatment for Major Depressive Disorder (RELIGHT)
Sponsor	Relmada Therapeutics, Inc. (Relmada)
Product Name/Number	Esmethadone hydrochloride/REL-1017
Protocol Number	REL-1017-304
Investigators/Study Sites	Approximately 80 study sites in North America
Phase of Development	3
Primary Endpoint	The primary efficacy endpoint is the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from Baseline to Day 28 for REL-1017 as compared to placebo in the Total Population.
Key Secondary Endpoints	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Total Population in the following measurements: • MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Day 28, REL-1017, as compared to placebo • MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Day 28, REL-1017, as compared to placebo • Change from Baseline (CFB) to Day 7 in the MADRS total score for REL-1017, as compared to placebo • CFB to Day 28 in the Clinical Global Impression of Severity (CGI-S) score, REL-1017, as compared to placebo
Key Secondary Endpoints in the Sub- Population with Baseline MADRS ≥ 35	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Sub- Population with Baseline MADRS ≥ 35 in the following measurements: • CFB to Day 28 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score for REL-1017 as compared to placebo • MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Day 28, REL-1017, as compared to placebo • MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Day 28, REL-1017, as compared to placebo • CFB to Day 7 in the MADRS total score for REL-1017, as compared to placebo • CFB to Day 28 in the Clinical Global Impression of Severity (CGI-S) score, REL-1017, as compared to placebo

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Exploratory Endpoints	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Total Population and in the Sub- Population with Baseline MADRS ≥ 35 in the following measurements: • QIDS-SR-16 (16-item Quick Inventory of Depressive Symptomatology – Self Report) CFB • Sheehan Disability Scale (SDS) total and domain scores CFB • Q-LES-Q-SF (Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form) CFB • HAM-A (Hamilton Anxiety Rating Scale) CFB • DSST (Digit Symbol Substitution Test) CFB • Patient Global Impression of Improvement (PGI-I), absolute score • Clinical Global Impression of Improvement (CGI-I), absolute score
Safety Endpoints	• Adverse events (AE) recording • Discontinuation due to AEs • Incidence of treatment-emergent adverse events (TEAEs) • Vital signs and weight CFB • Physical examination CFB • Clinical laboratory parameters (chemistry, hematology, and urinalysis) CFB • Columbia Suicide Severity Rating Scale (C-SSRS) CFB
Study Design	The REL-1017-304 study is a 2-arm, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of REL-1017 at 25 mg QD for MDD in subjects with inadequate response to ADT. During the study, subjects currently receiving ADT (i.e., a marketed ADT treatment course at the approved dosing regimen), who experience an inadequate therapeutic response, will be stratified according to MADRS score at Baseline, then randomized in a 1:1 ratio to REL-1017 or placebo, and receive treatment for 28 days. The primary efficacy analysis will be based on the Day 28 assessment of the primary and secondary efficacy endpoints in the Total Population). At Baseline subjects will be stratified according to depression severity: • Baseline MADRS score <35 (moderate depression) • Baseline MADRS score ≥35 (severe depression) Subjects in each group will subsequently be randomized 1:1 to REL-1017 or placebo

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BMI=body mass index; D=day; MADRS=Montgomery-Åsberg Depression Rating Scale 10 item-questionnaire; MDE=major depressive episode; QD=once daily in the morning; SAFER=State versus Trait; Assessability; Face Validity; Ecological Validity; and Rule of Three Ps (Pervasive, Persistent, and Pathological)

Screening Period

After signing the ICF, an identification number will be assigned to the subject via the EDC/IRT system. Prior to randomization, all subjects will enter an up to 30-day screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT), with a current major depressive episode of at least 8 weeks in duration. They must have had an inadequate response (<50% symptom reduction) to an adequate trial of 1-3 antidepressant therapies (ADT) (as determined by administering the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [ATRQ]) in their current Major Depressive Episode (MDE).

Subjects who are deemed eligible by the Principal Investigator and the Medical Monitor will undergo the SAFER/ATRQ/MADRS interview by clinicians at the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI). Eligibility for enrollment will also be assessed by an independent medical adjudicator, who is a clinical psychiatrist, to ensure appropriate diagnosis and clinical presentation.

To ensure that appropriate subjects are entered into the study, MGH-CTNI-certified clinician will independently assess each subject using the SAFER interview, MADRS, and the MGH-ATRQ. The interview will be performed remotely; an MGH-CTNI clinician will contact the subject at his or her home or another off-site location after receiving notification from the study site. Sites will then be notified of the results of the interview. Only subjects whose eligibility is confirmed by the SAFER/ATRQ/MADRS interview and the independent clinical adjudicator/Medical Monitor will be allowed to proceed in the study.

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	Treatment Period Randomization Subjects who successfully complete Screening, and who continue to meet all entry criteria, will be stratified at the baseline visit (Baseline) by depression severity into two groups, one of moderately depressed subjects (Baseline MADRS <35) and the other, i.e., of severely depressed subjects (Baseline MADRS ≥35); subjects within each group will be randomly assigned to receive either REL-1017 or placebo in a 1:1 ratio for 4 weeks The randomization schedule will be computer-generated using a permuted block algorithm separately for moderately depressed subjects (Baseline MADRS <35) and of severely depressed subjects (Baseline MADRS ≥35). **Assessments and Visits** Study visits will occur at Screening (Visit 1), Baseline (Day 1, Visit 2), and on Days 7, 14, 21, 28 and 35 (Visits 3-7). The Schedule of Assessments details the study procedures and assessments to be performed during study visits. A safety follow-up visit (Visit 7: End of Study (EOS)) will occur one week after the end of treatment visit (Visit 6: End of Treatment (EOT)). Subjects who prematurely discontinue the study will be asked to complete an Early Termination (ET) visit, equivalent to Visit 6. Assessments include those for safety, MADRS, CGI-S, CGI-I and PGI-I, SDS, Q-LES-Q-SF, and QIDS-SR-16. Blood samples for pharmacokinetics (PK) analysis will be collected on Day 1 at pre-dose, Day 7 at post-dose and on Day 28 at post-dose in-clinic visits, to measure concentrations of REL-1017 and/or metabolites. Clinical laboratory tests will be conducted at Screening and Day 1 and at subsequent in-clinic visits according to Table 1. Compliance will be defined as the attainment of concentrations consistent with expected steady-state concentrations. Compliance will also be assessed at the 80-120% level by counting the number of tablets dispensed and returned. Noncompliant subjects based on the number of tablets may be subject to early termination from the study.
Investigational Product/Reference Product	REL-1017 in 25 mg tablets and matching placebo tablets
Study Drug, Dose Schedule, and Mode of Administration	REL-1017 in a 25 mg tablet for oral administration by mouth (PO) The following dose schedule will be used in the study: Day 1 – loading dose: • Three REL-1017 25 mg tablets (75 mg total) administered at the clinical study site • Three matching placebo tablets administered at the clinical study site Day 2 to Day 28 – maintenance dose: • One REL-1017 25 mg tablet QD • One matching placebo tablet QD Subjects will be asked to stay on a stable dosing regimen of their current

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	background antidepressant therapy (ADT) between Day 1 and Day 35 while receiving REL-1017 or matching placebo between Day 1 and Day 28. The study drug should be taken once daily in the morning, and at the same time the subject takes her/his current ADT, when appropriate. Dosing with study drug should take place once daily in the morning on empty stomach.
Study Duration	Up to 65 days: 30-day screening, followed by 4 weeks of double-blind treatment, and followed by a 1-week safety follow-up visit.
Planned Sample Size	REL-1017-304 is designed to achieve 90% power, with an overall two-tailed α-level of 0.05. Based on the results of studies REL-1017 301, REL-1017-202, and ketamine studies (Su 2017), an effect size assumption of 0.33 Cohen's ($d = \Delta / \sigma$) in the main estimand of the primary efficacy endpoint, representing the absolute change from Baseline to Day 28 in MADRS total score was used. This adaptive, sample size re-estimation design has an initially planned net sample size of 340 (170 per arm) complete cases. One interim analysis is planned when approximately 75% of the initially planned Total Population have completed Day 28 assessments or have discontinued early. At this interim analysis, if the observed conditional power for the primary endpoint is between 10% and 90%, the Total Population sample size may be increased up to a maximum of 510 complete cases in order to increase conditional power up to 90%. Considering an early study termination rate of approximately 5%, the required initially planned Total Population sample size is 340 (with up to a maximum of 510) participants. This interim analysis design and Total Population sample size were computed via simulations using the software East® v6.5 (Cytel Inc.). In order to ensure a Total Population sample size of 340 (or up to 510).
Inclusion Criteria	To enroll in the clinical study, subjects must meet the following inclusion criteria: 1. Provide written informed consent to participate in the study, are able to understand the procedures and study requirements, and agree to abide by study restrictions and return for the scheduled study assessments. 2. Male or female outpatients, 18-65 years of age, inclusive. 3. Currently meet DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT, with a current major depressive episode of at least 8 weeks and not exceeding 24 months in duration at Screening (Visit 1). The confirmed diagnosis of MDD must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician or other qualified healthcare professional. Patient-reported MDD is not sufficient for inclusion in the study. 4. MADRS score ≥24 at Screening (Visit 1) and Baseline (Visit 2). 5. An appropriate and valid subject in the study, after independent MGH-CTNI SAFER/ATRQ assessment of the subject's MDD condition to confirm the diagnosis of MDD, as well as the inadequate response to 1 to 3 valid courses of treatment with an antidepressant medication in the current Major Depressive Episode (MDE), defined as <50% improvement with an antidepressant medication at doses listed on the SAFER and ATRQ Interview Forms. 6. Treated and stabilized at same dose for at least 6 weeks prior to Screening, experiencing <50% improvement on an approved dosing regimen of one ADT during the current MDE, and committed to remaining on the same

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	stable dosing regimen for the Screening period and for the entire study, at or above the minimally adequate dose in the ATRQ. Documentation of stable and ongoing ADT must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician or other qualified healthcare professional. 7. Normal physical examination findings and clinical lab test results from Screening (Visit 1) or abnormal results that are judged not clinically significant by the investigator. 8. Body Mass Index (BMI) between 18 and 35 kg/m^2, inclusive. 9. If female and of childbearing potential, has a negative urine pregnancy test at Screening (Visit 1) and Baseline (Visit 2), is practicing adequate methods of birth control (i.e., oral or parenteral contraceptives, intrauterine device, condoms, spermicides), and is not currently pregnant or breastfeeding nor plans to become pregnant during the course of the study. a. Abstinence from heterosexual intercourse is acceptable if aligns with subject's preferred and usual lifestyle. b. Female subjects taking hormonal contraceptives or using intrauterine devices must have been doing so for at least 1 month prior to Screening and as per instructions in product labelling. c. Female subjects may be enrolled without a negative urine pregnancy test if they are surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy) or at least 2 years post-menopausal. d. Male subjects and their female sexual partners should use an acceptable method of birth control during the study.
Exclusion Criteria	**Psychiatric Exclusion Criteria** 1. History of: a. Any depressive episode with psychotic or catatonic features. b. Any manic or hypomanic episode whether due to bipolar I or II illness, or medication/substance-induced. c. Bipolar Depression d. Schizophrenia, schizoaffective disorder, or other psychotic illness. e. Obsessive Compulsive Disorder active within 12 months of Screening (Visit 1). f. Panic disorder, with or without agoraphobia active within 12 months of Screening (Visit 1). g. Any anxiety disorder which has been the primary focus of clinical care rendering MDD secondary to anxiety within 6 months prior to screening. h. Post-traumatic Stress Disorder active within 12 months of Screening (Visit 1). i. Personality Disorders: Borderline, Antisocial, Paranoid or Schizotypal of sufficient severity that they may interfere with study participation. j. Alcohol use disorder or substance use disorder (excluding nicotine and caffeine) active within 12 months of Screening (Visit 1). 2. MADRS improvement of >20% or worsening of >40% between Screening (Visit 1) and Baseline (Visit 2). 3. Psychiatric hospitalization during the current major depressive episode.

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4. Risk of Suicide deemed clinically significant based on:
    a. Patient Interview (Investigator Judgment)
    b. C-SSRS information gathered at Screening (Visit 1) or Baseline (Visit 2) (e.g., A subject answers "Yes" to question 4 or 5 of the C-SSRS ideation and the most recent episode occurred within the current major depressive episode.
    c. MADRS item 10 score ≥5 at Screening (Visit 1) or Baseline (Visit 2).
    d. Suicidal attempt within the current depressive episode or within the last year prior to Screening.
5. Any current and primary psychiatric disorder (i.e., a condition that is the primary focus of distress and/or treatment other than MDD), as defined by the DSM-5. These disorders include, but are not limited to, any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive-compulsive disorder, intellectual disability, or pervasive developmental disorder.

Medication/Treatment Exclusion Criteria

6. 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 and the Medical Monitor would jeopardize the safety of the subject or the validity of the study results, including established QT prolongation, long QT syndrome, torsades de pointes, bradyarrhythmia, ventricular tachycardia, or uncompensated heart failure (greater than New York Heart Association [NYHA] Class 1 congestive heart failure [CHF]), uncontrolled hypokalemia, or uncontrolled hypomagnesemia
7. More than class 2 angina pectoris or a myocardial infarction (MI) or acute coronary syndrome within the past 3 months.
8. History of long QT or first degree relative with history of unexplained sudden death or long QT syndrome.
9. 12-lead ECG with QTcF (QT interval with Fridericia's correction) ≥450 msec at Screening.
10. Current or recent uncontrolled orthostasis or orthostatic hypotension necessitating treatment.
11. Poorly controlled diabetes as defined by a glycosylated hemoglobin (HbA1c) >7.5%, despite standard care. Subjects with HbA1c >7.5% may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
12. Any long-term use (i.e., >120 days in a 6-month period) of prescribed opioids or controlled substances within 6 months, prior to Screening – as verified by appropriate medical records, Prescription Monitoring Program (PMP) or alternative verified documentation as requested by Medical Monitor or delegate – or any recreational use of opioids or controlled substances.
13. Having received any and/or requires ongoing treatment with any prohibited medications, supplements, or herbal products listed in Appendix A per the applicable timeline.
14. History of allergy or hypersensitivity to methadone or related drugs.
15. Enrolled in a clinical trial in the last 5 months prior to screening, or previously enrolled at any time in a clinical trial for an indication that

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conflicts with a primary diagnosis of MDD as determined by the Medical Monitor. These studies include, but are not limited to, those targeted at any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive-compulsive disorder, intellectual disability, or pervasive developmental disorder.

Other Medical Exclusion Criteria

16. Any current or past medical, psychiatric condition, or social context that, in the opinion of the Investigator, Medical Monitor or independent adjudicator, is likely to unfavorably alter the risk-benefit of the subject participation, to interfere with protocol compliance, or to confound safety or efficacy assessments. This includes, but is not limited to, diseases of the following systems: hematologic, oncologic, endocrine, cardiovascular, renal, hepatic, respiratory, gastrointestinal, infectious, neurologic and psychiatric.
17. History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs; conditions increasing the risk of seizures such as stroke, head injury, tumor or central nervous system (CNS) infection, arteriovenous malformation, neuroleptic malignant syndrome/serotonin syndrome; or clinically significant metabolic disorders (hypoglycemia, hyponatremia, severe hepatic impairment, renal impairment, and hypoxia).
18. Positive breath alcohol test or urine drug screen (UDS) for any prohibited medications or drugs of abuse (cocaine, marijuana, phencyclidine, opioids, amphetamines or other agents) within 30 days prior to and/or at Baseline (Visit 2). A positive result for a psychoactive drug not previously disclosed will result in screen failure. Retesting is permitted at the discretion of the Principal Investigator and the Medical Monitor. Please consult with the Medical Monitor in the case of a positive result for benzodiazepines or other disclosed medications that have been approved by the Medical Monitor.
19. Exclusion Criterion 19 was removed in protocol v3.0.
20. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase, and/or alanine aminotransferase) results >2.0 x the upper limit of normal (ULN) and Creatine Phosphokinase (CPK) >2.0 × ULN, or clinically significant abnormal endocrine laboratory values. Subjects with excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
21. Evidence of clinically significant renal impairment, including an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2009 calculation). Subjects with excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
22. Patients with clinically significant high BP may be accepted in the study per the judgment of the investigator if they subsequently have acceptable BP levels on retesting at least 30 minutes apart.
23. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no dosage change for at least one month prior to Screening (Visit 1). Serum thyroid stimulating hormone (TSH) must be >0.75 x lower limit of normal (LLN) and <1.25 x ULN. Subjects with

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	excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested. 24. Participant has had gastric bypass surgery or has had any procedure or disorders that would interfere with gastrointestinal transit or absorption. 25. History of allergy, hypersensitivity, or intolerance to opiates (e.g., methadone, codeine) or related drugs.
Statistical Data Analysis	Study analysis populations will be defined as follows: **Screened/Enrolled Set:** The Screened/Enrolled Set will include all participants who signed an informed consent. **Randomized Set:** The Randomized Set will include all randomized participants and will be used for the presentation of participants in all listings. **Full Analysis Set - Total Population (FAS Total):** Participants who are randomized and dosed, irrespective of any deviation from the protocol or premature discontinuation. Participants will be analyzed according to randomized treatment. **Per-Protocol Set – Total Population (PPS Total):** Valid completers, i.e., participants who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. Per-Protocol membership must be determined prior to database lock and treatment unblinding. This set will be analyzed according to the treatment actually received. **Full Analysis Set - Sub-Population with Baseline MADRS ≥ 35-(FAS MADRS ≥ 35):** Participants with severe depression (Baseline MADRS ≥35) who are randomized and dosed, irrespective of any deviation from the protocol or premature discontinuation. Participants will be analyzed according to randomized treatment. . **Per-Protocol Set – Sub-Population with Baseline MADRS ≥ 35 (PPS MADRS ≥ 35):** Valid per protocol completers with severe depression, i.e., participants with Baseline MADRS ≥35 who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. Per-Protocol membership must be determined prior to database lock and treatment unblinding. This set will be analyzed according to the treatment actually received. **Safety Population:** The Safety Population will be the primary safety analysis population and will include all subjects who receive at least one dose of the study drug. **Primary Efficacy Analysis:** The primary efficacy endpoint will be the change from Baseline in the MADRS total score at Day 28 (EOT), for REL-1017 as compared to placebo in the Total Population .The changes from Baseline in MADRS total score will be analyzed using a Mixed Model with Repeated Measures (MMRM). This model will include

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	Treatment, Visit, Treatment-by-Visit interaction and the number of failed prior treatments (1 or more than 1) as fixed effects, baseline value as a covariate, and Visit as the repeated effect. The estimated means for each arm as well as the estimated treatment effect (REL-1017-Placebo), along with the 95% confidence intervals for the treatment effect, will be presented for each visit. The primary estimand will be estimated as the difference between treatment means (MMRM least-squares) at the Day 28 visit (Visit 6). **Safety Analysis:** Adverse events will be coded by the system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) reporting system. TEAEs are those that occur following the start of treatment with double-blinded study drug through follow-up (7 days after the last dose), and SAEs that occur following the start of treatment with double-blinded study drug through 30 days after the last dose. The number and percentages of subjects with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{tau}	area under the plasma concentration-time curve from time 0 until the dosing interval of 24 hours ($AUC_{0\text{-}24}$)
BDNF	brain-derived neurotrophic factor
b-HCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure (systolic and diastolic)
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CHF	congestive heart failure
CHW	Cui-Hung-Wang
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance/bioavailable fraction absorbed
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
COVID-19	novel coronavirus 2019
C_{ss}	steady-state concentration
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough concentration
CTNI	Clinical Trials Network and Institute
CYP	cytochrome
DEA	US Drug Enforcement Administration
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
eCRF	electronic case report form
ECT	electroconvulsive therapy
EDC	electronic data capture
EDP	end of dosing period
EDTA	ethylene diamine tetra-acetic acid
eGFR	estimated glomerular filtration rate
EOS	end of study

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EOT	end of treatment
ER	emergency room
FAS	full analysis set
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAM-A	Hamilton Anxiety Rating Scale
HAMD17	Hamilton Depression Rating Scale
HbA1c	glycosylated hemoglobin
HCl	hydrochloride
HIV	human immunodeficiency virus
HR	heart rate
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
LLN	lower limited of normal
LS	least-square means
MAD	multiple ascending dose
MADRS	Montgomery-Åsberg Depression Rating Scale 10 item-questionnaire
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
MI	myocardial infarction
MMRM	mixed-effect model repeated measure
mTORC1	mammalian target of rapamycin complex 1
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NMDAR	N-methyl-D-aspartate receptor
NSDUH	National Survey on Drug Use and Health
NYHA	New York Heart Association
PCP	Phencyclidine
PCRS	Placebo-Control Reminder Script
PK	pharmacokinetic(s)

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PO	by mouth
POC	proof of concept
PRN	pro re nata (when necessary)
QD	quaque die (once daily)
QHS	quaque hora somni (every night at bedtime)
QIDS-SR-16	Quick Inventory of Depressive Symptomatology (16-Item)
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
REL-1017	esmethadone hydrochloride
Relmada	Relmada Therapeutics, Inc.
RR	respiratory rate
RNA	ribonucleic acid
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
SCID-5	Structured Clinical Interview for DSM-5 Disorders
SDS	Sheehan Disability Scale
SIGH-A	Structured Interview Guide for the HAMA
SIGH-D	Structured Interview Guide for the HAMD17
SIGMA	Structured Interview Guide for the MADRS
SNRI	serotonin and norepinephrine reuptake inhibitor
SOC	system organ class
SOP	standard operating procedure
SSR	sample size reestimation
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration
TdP	torsade de pointes
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VAST-D	US Department of Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes
VNS	vagus nerve stimulation
WHODrug	World Health Organization Drug Dictionary

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WOCBP	women of childbearing potential

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4 INTRODUCTION

4.1 BACKGROUND ON MAJOR DEPRESSIVE DISORDER

Major Depressive Disorder (MDD) is a widely prevalent, serious, and life-threatening health condition. It is the most common mental disorder and is a major cause of disability across the world. In 1994, it was estimated that approximately 1.5 million disability-adjusted life years were lost in developed countries as a result of depression (British Psychological Society & The Royal College of Psychiatrists 2010).

Prevalence data from the 2017 National Survey on Drug Use and Health (NSDUH) show that an estimated 17.3 million adults in the United States (US) had at least one major depressive episode (MDE) in their lifetime (7.1% of all US adults). An estimated 11 million US adults aged 18 years or older experienced at least one MDE with severe functional impairment (4.5% of all US adults). Of adults with a MDE, 63.8% had severe functional impairment(National Institute of Mental Health 2017). Approximately 70% of patients do not fully remit symptomatically after a full valid course of antidepressant monotherapy (Trivedi 2006), and up to 85% of patients will relapse at least once (Hardeveld 2010).

The rates of response and remission are shown to decrease, and the odds of relapse increase with each successive switch or augmentation of currently marketed antidepressants. This observation is documented in the reports from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and the US Department of Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) studies (Rush 2006; Gaynes 2009; Sinyor 2010; Gaynes 2012; Rush 2012). John Rush reports that in the STAR*D study, Quick Inventory of Depressive Symptomatology (16-Item) (QIDS-SR-16) remission rates were 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively. The overall cumulative remission rate was 67%. Overall, those who required more treatment steps had higher relapse rates during the naturalistic follow-up period in the STAR*D study. In addition, lower relapse rates were found among subjects who were in remission at follow-up entry than for those who were not after the first 3 treatment steps (Rush 2006; Trivedi 2006; Sinyor 2010; Gaynes 2012; Rush 2012).

Patients are diagnosed with depression based on Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. Once the diagnosis of MDD is confirmed, it is crucial to assess and monitor the severity of MDD. The Montgomery-Åsberg Depression Rating Scale (MADRS) is a highly reliable and sensitive measure of depression severity (Montgomery 1979), with a total score ranging from 0 to 60. The grading of depression severity on the MADRS, based on the total score, is generally accepted as follows: Normal: 0-6; Mild: 7-19; Moderate: 20-34; Severe: 35-60. Approximately 46% of people with mild depressive symptoms and 88% of people with severe depressive symptoms reported difficulty with work, home or social activities related to their symptoms (Pratt 2014). Severe MDD is associated with a higher risk of suicidal ideation and attempts compared to moderate depression (Beck 1989). Two-thirds of suicides occur in

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people with depression, and the risk of suicide in the most severely ill is up to 20 times that in the general population (Isometsa 2014). Compared to moderate MDD, severe MDD is more likely to interfere with the ability to function in everyday life, including work, social activities, and relationships (Kessler 2006), and interferes with functional outcomes (Herrmann 1998). Individuals with severe depression might experience longer depressive episodes and have a higher risk of recurrent episodes compared to those with moderate depression (Monroe 2011). Severe depression carries a higher level of social withdrawal, isolation, and stigma, which can further exacerbate the condition (Paykel 2003). Severe MDD may be less responsive to standard first-line treatments (Rush 2006). The biological underpinnings of depression might differ based on severity; neuroimaging studies have shown distinct patterns of brain activity and structure in patients with more severe depression (Frodl 2013; Javaheripour 2021). While no biomarker consistently improves the accuracy of MDD diagnosis, DSM-5 includes symptom severity as a diagnostic criterion. As mentioned earlier, MADRS score of 35 or more indicates severe depression, enhancing diagnostic accuracy. Patients with severe depression are likely to be a more uniform group, and uniformity may be a desirable feature for evaluating novel MDD therapies, such as uncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonists. In trials of SSRIs, drug–placebo differences in antidepressant efficacy are relatively small even for severely depressed patients and the relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication (Kirsch 2008). In contrast, the uncompetitive NMDAR antagonist ketamine showed significant efficacy in patients with more severe depression, but not in patients with milder depression (Su 2017). Using positron emission tomography (PET) and a radioligand specific for the synaptic vesicle protein 2A (SV2A), this index of axon terminal density was found to be inversely associated with depression severity: lower SV2A was seen only in patients with severe depression (Holmes 2019). Consistently, patients with lower SV2A density and severe depression exhibited increased SV2A density and reduction in depression severity 24 hours after ketamine treatment (Holmes 2022).

Antidepressant treatment responses for uncompetitive NMDAR antagonists increase with the severity of baseline MDD (Su 2017; Fava 2023). In contrast, in trials of serotonergic drugs, while response in the placebo arm was decreased in patients with severe depression, as expected, response in the treatment arm was not increased (Kirsch 2008). Therefore, the increased response in the treatment arm in patients with severe depression may be a unique feature of NMDAR antagonist antidepressants, not shared by serotonergic drugs.

The noted differences in responses to NMDAR uncompetitive antagonists in patients with severe depression signal a distinct MOA compared to the MOA of serotonergic drugs.

While post-hoc analyses carry the risk of Type 1 statistical error, the meaningful and statistically significant results achieved with REL-1017 in the population of patients with severe depression are aligned with results of studies with other NMDAR antagonists (Su 2017), suggesting class-specific efficacy in the severe population for uncompetitive NMDAR antagonist antidepressants,

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in contrast with results seen with serotonergic drugs (Kirsch 2008). Patients with severe depression may suffer from a disorder with a different pathophysiology compared to patients with milder symptomatology (Frodl 2013; Su 2017; Javaheripour 2021; Holmes 2022) and therefore may uniquely respond to drugs targeting restoration of impaired neural plasticity as a specific pathophysiological mechanism for MDD (Stahl 2022).

4.2 BACKGROUND ON INVESTIGATIONAL PRODUCT

Relmada Therapeutics, Inc. (Relmada) is developing REL-1017, an orally available formulation of esmethadone hydrochloride (HCl), for the treatment of MDD.

REL-1017 is a novel NMDAR antagonist being investigated as treatment for MDD. REL-1017 is believed to work via pathways that are markedly different from most currently approved drugs.

NMDARs are known to have a role in depression, as well as in normal physiological functions. REL-1017 shows preferential blocking of specific NMDAR subtypes (GluN2D) that may be of particular importance in MDD (Stahl 2022). With this mechanism, REL-1017 is being evaluated to determine whether it can provide antidepressant effects without psychotomimetic effects or other cognitive side effects seen with esketamine and without metabolic and neurological side effects seen with monoaminergic antidepressants.

REL-1017 is designated as esmethadone (USAN). It is the dextro-(the dextrorotary) isomer of its racemic methadone. As described by the US Drug Enforcement Administration (DEA), the opioid effects of racemic methadone are due to its levorotary-isomer, while the dextrorotary-isomer lacks significant respiratory depressant action and addiction liability (DEA 2019). In addition to having a preference for specific NMDAR subtypes, REL-1017 has been shown to increase plasma levels of brain-derived neurotrophic factor (BDNF) in humans (De Martin 2018) and potentially induce neural plasticity in experimental models of depression (Fogaça 2019).

Nonclinical studies have demonstrated antidepressant-like activity of REL-1017 in animal models of depressed behavior, including the forced swim test (Hanania 2020), the novelty suppressed feeding test, the female urine sniffing test, and the chronic unpredictable stress paradigm with equivalent efficacy to ketamine (Fogaça 2019; IB 2022).

For information on the clinical studies, see Section 4.2.1 through Section 4.2.6.

Relmada's current development of REL-1017 in MDD is focused on adjunctive treatment.

In the Phase 2 proof of concept (POC) study, REL-1017-202, REL-1017 demonstrated statistically significant improvements in symptoms of depression as an adjunctive treatment in individuals with MDD who experienced an inadequate response in 1 to 3 adequate ADTs during their current MDE.

In this Phase 2 study, subjects in both the REL-1017 25 mg and 50 mg treatment groups experienced statistically significant improvement of their depression, assessed on the MADRS,

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in comparison to subjects on placebo. REL-1017 was safe and well-tolerated in this study. Adverse events were mild to moderate in grade. There were no serious adverse events. There was no evidence of either treatment-induced psychotomimetic and dissociative AEs or withdrawal signs and symptoms upon treatment discontinuation (Fava 2022).

In a Phase 3 study of REL-1017 as adjunctive treatment in patients with inadequate response to standard ADT (REL-1017-301), REL 1017 did not meet the primary efficacy endpoint in the ITT analysis. However, the statistically significant difference in response rate and the prespecified supportive PP analysis suggest meaningful treatment effects. Post-hoc analyses in patients with severe MDD (Baseline MADRS ≥35) showed statistically significant efficacy with robust effect size (Fava 2023).

In a Phase 3 study of REL-1017 as monotherapy (REL-1017-303) REL-1017 failed to separate from placebo on the primary efficacy outcome of change from baseline in the MADRS total score at Week 4.

REL-1017 did not induce the opioid effects typically observed with opioid agonist drugs (Bernstein 2019; Fava 2022; Shram 2022; Fava 2023; Shram 2023). In addition REL 1017 does not elicit signs and symptoms of withdrawal after discontinuation (Shram 2023).

In the completed Phase 3 studies there were no AEs related to QTc prolongation and there were no signals for meaningful metabolic, neurological or sexual side effects.

Also, in the completed Phase 1-3 studies, REL-1017 did not show any signal for psychotomimetic symptoms, such as dissociative symptoms, hallucinations, paranoid delusions, or confusion, typically observed with other NMDAR antagonists, including ketamine and dextromethorphan.

4.2.1 Clinical Studies

Relmada has completed two Phase 1 studies, a single-ascending dose study (SAD) (REL-1017-111) and a multiple-ascending dose study (REL1017-112, multiple ascending doses (MAD)), to investigate the safety, tolerability, and pharmacokinetics (PK) of REL-1017 in healthy volunteers. Relmada has also completed a Phase 2 study (REL-1017-202) and a Phase 3 study (REL-1017-301) to investigate the dose-exposure, safety, tolerability, and efficacy of REL-1017 in adjunctive therapy of subjects with MDD in an MDE experiencing an inadequate response to a first-line SSRI or SNRI antidepressant. Relmada also completed a Phase 3 study (REL-1017-303) which evaluated the safety and efficacy of REL-1017 as compared to placebo as a monotherapy for MDD.

Results of these 5 studies are presented below; further details and other recently completed REL-1017 studies are presented in the current IB.

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4.2.2 Results from Study REL-1017-111

This was a Phase 1a SAD double-blind, randomized, placebo-controlled, safety, and PK study in healthy subjects with sequential cohorts of 7 subjects (2 sentinel subjects, followed by exposure to an additional 5 subjects at each dose level of REL-1017 (oral administration) with ascending dose arms from 5 mg to 200 mg. PK parameters were calculated for all dose levels, although some individual results had to be excluded due to emesis or statistical analysis criteria (Bernstein 2019).

Pharmacogenomics analysis was performed for subjects exhibiting either fast or slow metabolism of REL-1017. Overall, there were minimal subjective pharmacodynamics (PD) effects of REL-1017 up to 150 mg, as assessed by the Bond-Lader visual analog scale (VAS).

The overall conclusions from the REL-1017-111 study are as follows:

- The maximum tolerated dose for oral REL-1017 in healthy opiate-naïve subjects was determined to be 150 mg, and the dose-limiting toxicity was nausea and vomiting.
- PK analysis revealed high variability of the REL-1017 parameters, including maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 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, with no statistical significance. In general, there were no specific trends observed for T_{max} or $t_{½}$ of REL-1017.
- The objective measure of PD effects, pupillometry, showed a dose-response with a modest increase in pupil constriction in higher-dose groups.
- The study drug appeared to be safe. No indication of respiratory depression or clinically significant QTcF prolongation was reported.
- For tolerability, nausea and vomiting became potential AEs with higher doses.

4.2.3 Results from Study REL-1017-112

This was a Phase 1b MAD double-blind, randomized, placebo-controlled study safety, tolerability, and PK study in healthy subjects. Eight subjects were randomized into 3 arms: 25 mg, 50 mg, and 75 mg REL-1017. In each arm, 2 subjects were dosed with placebo in cranberry juice and 6 subjects with a powder formulation of REL-1017 in cranberry juice with an identical appearance and taste. Doses were administered from Day 1 to Day 10 (Bernstein 2019).

Overall conclusions from the REL-1017-112 study were:

- 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 0 until the dosing interval of 24 hours (AUC_{tau}) values also demonstrated about a 3-fold

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accumulation over the 10-day dosing period. No dose dependency was seen in this parameter.

- Steady-state was achieved by Day 7 for the 25 mg and 50 mg REL-1017 dose levels and by Day 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 steady-state concentration (C_{ss}).
- Despite the confirmed overall dose proportionality in the 2 completed PK studies, the comparison of concentration and exposure between the 50 mg (n=6) and 75 mg REL-1017 (n=5) 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-dose of REL-1017 appeared to be safe, with no indication of respiratory depression or opioid withdrawal. Dose proportional QTcF prolongation was observed, with a placebo-adjusted increase from baseline of 10-12 msec with a steady-state 25 mg once daily (QD) dosing.

4.2.4 Results from Phase 2 Study REL-1017-202

Study REL-1017-202 was a Phase 2a, inpatient, 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 subjects diagnosed with MDD. The subjects were adults with MDD diagnosed with a current MDE who had experienced an inadequate response to 1 to 3 courses of treatment with an adequate dose and duration of antidepressant medication, as defined by the Antidepressant Treatment Response Questionnaire (ATRQ). The study was conducted inpatient at 10 study sites in the United States. A total of 62 subjects were randomized in the study: 19 subjects to the REL-1017 25 mg treatment group, 21 subjects to the REL-1017 50 mg treatment group, and 22 subjects to the placebo group.

The overall conclusions from clinical Study REL-1017-202 were the following:

- The mean change from Baseline in the total MADRS score for the Intent-to-Treat (ITT) population showed a clinically and statistically significant improvement from Baseline to the end of the dosing period (EDP, on Day 7) in both active REL-1017 25 mg and 50 mg arms (-16.8 [standard deviation (SD): 11.3] and -16.6 [SD: 9.8], respectively) versus the placebo control arm (-8.8 [SD: 12.5]), while taking a constant dose of first-line antidepressant treatment. The statistically significant improvement in MADRS was sustained at Day 14, the last MADRS measurement day.

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- No events were serious or severe, and no subjects experienced treatment-emergent AEs (TEAEs) on the loading- or maintenance doses. None led to study drug discontinuation or discontinuation from the study. No subject died during the study.
- TEAEs counts were in the low single digits in all treatment arms. The TEAEs in the gastrointestinal disorders system organ class (SOC) were constipation, nausea, and diarrhea. The TEAEs in the nervous system disorders SOC were headache, somnolence, and dizziness.
- No TEAEs related to respiratory function were reported. The respiratory rate did not vary between treatment arms.
- No treatment-related effect on vital signs was observed.
- There were no clinically meaningful instances of QTcF prolongation.
- The Clinical Opiate Withdrawal Scale (COWS) mean scores from Day 7 to Day 14 were indistinguishable between placebo and the REL-1017 treatment arms, indicating an absence of opioid-type withdrawal symptoms.
- There was no distinction between placebo control and the REL-1017 treatment arms in the Clinician-Administered Dissociative States Scale (CADSS) score at any time point. No psychotomimetic or dissociative symptoms were observed in any subject.

4.2.5 Results from Phase 3 Study REL-1017-301

Study REL-1017-301 was a Phase 3, outpatient, multicenter, randomized, double-blind, placebo-controlled, 2-arm study to assess the efficacy and safety of REL-1017 as adjunctive therapy in adult subjects with MDD experiencing inadequate response to ongoing ADT treatment. A total of 227 subjects were randomized in the study: 113 subjects to the REL-1017 25 mg treatment group and 114 to the placebo group.

REL 1017 did not meet the primary efficacy endpoint in the ITT analysis, however, the statistically significant difference in response rate and the prespecified supportive PP analysis suggest meaningful treatment effects. Post-hoc disease-severity population enriched design in patients with severe MDD (Baseline MADRS ≥35) showed statistically significant efficacy with robust effect size.

In the ITT population analysis (n=227), the raw mean CFB was -15.1 [standard deviation (SD) 11.3] for esmethadone (n=113) and -12.9 (SD 10.4) for placebo (n=114), with a raw mean difference (MD) of 2.3, which was not statistically significant (p=0.154; Cohen's effect size (ES) 0.21). In the PP population analysis (n=198) the raw mean CFB was -15.6 (SD 11.2) for esmethadone (n=101) and -12.5 (SD 9.9) for placebo (n=97), with a MD of 3.1, (p=0.051, ES: 0.29). Post-hoc analyses in patients with severe MDD (Baseline MADRS ≥35): ITT (n=112): MMRM mean difference 6.0; p=0.0109, ES=0.51; PP (n=98): MMRM mean difference 7.3; p=0.0024, ES=0.64). Adverse events (AEs) were predominantly mild or moderate and transient, with no significant differences between groups (Fava 2023).

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REL-1017 was safe and generally well-tolerated with no opioid-like effects, no withdrawal effects, and no psychotomimetic effects.

4.2.6 Results from Phase 3 Study REL-1017-303

Study REL-1017-303 was a Phase 3, outpatient, multicenter, randomized, double-blind, placebo-controlled, 2-arm study to assess the efficacy and safety of REL-1017 as a monotherapy in the treatment of MDD. Subjects were adults with a diagnosis of MDD currently experiencing a MDE. A total of 232 subjects were randomized in the study: 116 subjects to the REL-1017 25 mg treatment group and 116 to the placebo group.

REL-1017 demonstrated a non-significant improvement compared to placebo on the primary efficacy endpoint of change in the MADRS total score from Baseline at Week 4; -14.8 points for REL-1017 and –13.9 points for placebo; p=0.85).

REL-1017 was safe and generally well-tolerated with no opioid-like effects, no withdrawal effects, and no psychotomimetic effects.

4.3 STUDY RATIONALE FOR CONDUCTING STUDY REL-1017-304

Relmada intends to further evaluate REL-1017 for the adjunctive treatment of MDD given the positive findings from the Phase 2 study (Fava 2022) and the Phase 3 study (Fava 2023). Post-hoc analyses in patients with severe MDD (Baseline MADRS ≥35) showed statistically significant efficacy with robust effect size.

Preclinical and clinical data suggest that NMDAR antagonists such as ketamine and esmethadone modulate neural plasticity and increase prefrontal connectivity, thereby potentially reversing MDD. The antidepressant-like effects of REL-1017 may be BDNF-dependent (Fogaça 2019; De Martin 2021). Antidepressant treatment responses for REL-1017 and other uncompetitive NMDAR antagonists increase with the severity of baseline MDD (Su 2017; Fava 2023). In contrast, in trials of serotonergic drugs, the response in the placebo arm is decreased in patients with severe depression, as expected, while the response to treatment is not increased (Kirsch 2008).

The better responses to NMDAR uncompetitive antagonists in patients with severe depression signal a distinct MOA compared to the MOA of serotonergic drugs and indicate that patients with severe depression may uniquely respond to REL-1017 (Su 2017).

The preclinical and previous clinical experience with REL-1017 provided the basis for the initiation of the Phase 2 REL-1017-202 study which established the evaluation of the efficacy and safety of REL-1017 at 25 mg and 50 mg to MDD patients in the clinic setting. In this study, subjects with MDD, diagnosed with a current MDE and experiencing an inadequate response to 1 to 3 courses of ADT, were randomized 1:1:1 to treatment with ADT plus placebo, or ADT plus REL-1017 at 25 mg or 50 mg for 7 days of daily dosing. The results of this study demonstrated robust, rapid and sustained statistically significant antidepressant effects of REL-1017 when administered together with standard ADT that resulted in an improvement in the MADRS score

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by more than 16 points at Day 7 and as early as Day 4 and sustained to Day 14. The demonstrated PD effect did not appear to be enhanced on 50 mg QD. Therefore, the proposed dose selected for the planned REL-1017-304 study is 25 mg daily.

This study, REL-1017-304, will extend the findings from the Phase 2 study in a larger study population of outpatients, to evaluate the effect of REL-1017 during 28 days of daily dosing. Demonstration of the sustained efficacy of treatment for 4 weeks of therapy is clinically representative of long-term management of MDD as a chronic condition. Because REL-1017 is proposed for the treatment of patients diagnosed with MDD, the subjects for the REL-1017-304 study 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 adequate dose and duration (as defined by the ATRQ). These subjects are stratified according to the severity of the disorder and then are randomized in a 1:1 ratio to REL-1017 in the active treatment arm or to placebo in the placebo arm. This population will provide the opportunity to compare the safety and efficacy effects of 4 weeks of treatment with REL-1017 compared with placebo in subjects with MDD and ongoing ADT with inadequate response.

4.4 STUDY ENDPOINTS

Primary Endpoint	The primary efficacy endpoint is the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from Baseline to end-of-treatment (Day 28) for REL-1017 compared to placebo in the Total Population.
Key Secondary Endpoints	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Total Population in the following measurements: • MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Day 28, REL-1017, as compared to placebo • MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Day 28, REL-1017, as compared to placebo • Change from Baseline to Week 1 in the MADRS total score for REL-1017, as compared to placebo • Change from Baseline to Day 28 in the Clinical Global Impression of Severity (CGI-S) score, REL-1017, as compared to placebo
Key Secondary Endpoints in the Sub- Population with Baseline MADRS ≥ 35	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Sub- Population with Baseline MADRS ≥ 35 in the following measurements: • Change from Baseline in MADRS total score from Baseline to Day 28 for REL-1017, as compared to placebo • MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Day 28, REL-1017, as compared to placebo

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	• MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Day 28, REL-1017 as compared to placebo • Change from Baseline to Day 7 in the MADRS total score for REL-1017, as compared to placebo • Change from Baseline to Day 28 in the Clinical Global Impression of Severity (CGI-S) score, REL-1017, as compared to placebo
Exploratory Endpoints	To evaluate the therapeutic efficacy of REL-1017 compared to placebo in the Total Population and in the Sub- Population with Baseline MADRS ≥ 35 in the following measurements: • QIDS-SR-16 (16-item Quick Inventory of Depressive Symptomatology – Self Report) CFB • Sheehan Disability Scale (SDS) total and domain scores CFB • Q-LES-Q-SF (Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form) CFB • HAM-A (Hamilton Anxiety Rating Scale) CFB • DSST (Digit Symbol Substitution Test) CFB • Patient Global Impression of Improvement (PGI-I), absolute score • Clinical Global Impression of Improvement (CGI-I), absolute score
Safety Endpoints	• Adverse events (AE) recording • Discontinuation due to AEs • Incidence of treatment-emergent adverse events (TEAEs) • Vital signs and weight CFB • Physical examination CFB • Clinical laboratory parameters (chemistry, hematology, and urinalysis) CFB • C-SSRS CFB

4.5 BIOMARKER, PHARMACOGENOMIC (DNA), AND EXPRESSION (RNA) EVALUATIONS

Although there currently is no biomarker for MDD, the assessment of biomarkers and their potential relationship to treatment groups and therapeutic efficacy will be explored. Blood samples will be collected to measure genetic and protein markers, including, but not limited to, BDNF allelic variants and plasma levels, as well as exploratory metabolite characterization. The timing of each assessment is detailed in the Schedule of Assessments (Table 1).

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5 INVESTIGATIONAL PLAN

5.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

The REL-1017-304 study is a 2-arm, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of REL-1017 at 25 mg QD for MDD in subjects with inadequate response to ADT. During the study subjects currently receiving ADT (i.e., a marketed ADT treatment course at the approved dosing regimen), who experience an inadequate therapeutic response, will be stratified according to MADRS score at Baseline, randomized in a 1:1 ratio to REL-1017 or placebo , and receive treatment for 28 days. The primary efficacy analysis will be based on the Day 28 assessment of the primary and secondary efficacy endpoints in the Total Population.

The overall duration of the study, including Screening and intervention period, will be approximately 65 days per subject: a 30-day screening period, 4 weeks of double-blind treatment, and a 1-week safety follow-up visit.

A total of approximately 340 subjects are estimated to be included in the trial to obtain the Total Population . Subjects will be stratified according to depression severity based on MADRS score at Baseline MADRS <35 (moderate depression) or Baseline MADRS ≥35 (severe depression) and randomized in a 1:1 ratio to the active REL-1017 25 mg QD arm (n=170) or matching placebo arm (n=170)for each of the two groups. Enrollment will complete only after at least 340 subjects are randomized within the Total Population.

The study design is presented in Figure 1.

Screening Period

After signing the ICF, an identification number will be assigned to the subject via the EDC/IRT system. Prior to randomization, all subjects will enter an up to 30-day screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version (SCID-5-CT), with a current major depressive episode of at least 8 weeks in duration. They must have had an inadequate response (<50% symptom reduction) to an adequate trial of 1-3 antidepressant therapies (ADT) (as determined by administering the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [ATRQ]) in their current Major Depressive Episode (MDE).

Subjects who are deemed eligible by the Principal Investigator will undergo the SAFER/ATRQ/MADRS interview by clinicians at the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI). Eligibility for enrollment will also be assessed by an independent medical adjudicator, who is a clinical psychiatrist, to ensure appropriate diagnosis and clinical presentation.

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To ensure that appropriate subjects are entered into the study, a MGH-CTNI-certified clinician will independently assess each subject using the SAFER interview, and the MGH-ATRQ. The interview will be performed remotely; an MGH-CTNI clinician will contact the subject at his or her home or another off-site location after receiving notification from the study site. Sites will then be notified of the results of the interview. Only subjects whose eligibility is confirmed by the SAFER/ATRQ/MADRS interview and the independent clinical adjudicator/Medical Monitor will be allowed to proceed in the study.

Treatment Period

Randomization

Subjects who successfully complete Screening, and who continue to meet all entry criteria, will be stratified at the baseline visit (Baseline) by depression severity into two groups, one of moderately depressed subjects (Baseline MADRS <35) and the other, i.e., the severely depressed subjects (Baseline MADRS ≥35); subjects within each group will be randomly assigned to receive either REL-1017 or placebo in a 1:1 ratio for 4 weeks. The randomization schedule will be computer-generated using a permuted block algorithm separately for moderately depressed subjects (Baseline MADRS <35) and of severely depressed subjects (Baseline MADRS ≥35).

Assessments and Visits

Study visits will occur at Screening (Visit 1), Baseline (Day 1, Visit 2), and on Days 7, 14, 21, 28 and 35 (Visits 3-7). The Schedule of Assessments details the study procedures and assessments to be performed during study visits. A safety follow-up visit (Visit 7: End of Study [EOS]) will occur one week after the end of treatment visit (Visit 6: End of Treatment (EOT)). Subjects who prematurely discontinue the study will be asked to complete an Early Termination (ET) visit, equivalent to Visit 6 .

Assessments include those for safety, MADRS, CGI-S, CGI-I and PGI-I, SDS, Q-LES-Q-SF, and QIDS-SR-16.

Blood samples for pharmacokinetics (PK) analysis will be collected on Day 1 at pre-dose, Day 7 at post-dose and on Day 28 at post-dose in-clinic visits, to measure concentrations of REL-1017 and/or metabolites. Clinical laboratory tests will be conducted at Screening and Baseline (Day 1) and at subsequent in-clinic visits according to Table 1. Compliance will be defined as the attainment of concentrations consistent with expected steady-state concentrations. Compliance will also be assessed at the 80-120% level by counting the number of tablets dispensed and returned. Noncompliant subjects, based on the number of tablets, may be subject to early termination from the study

Active REL-1017 and matching placebo treatment arms will take the study drug according to the following schedule:

Day 1 – loading dose:

- Three REL-1017 25 mg tablets (75 mg total) administered at the clinical study site
- Three matching placebo tablets administered at the clinical study site

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Day 2 to Day 28 – maintenance dose:

- One REL-1017 25 mg tablet QD
- One matching placebo tablet QD

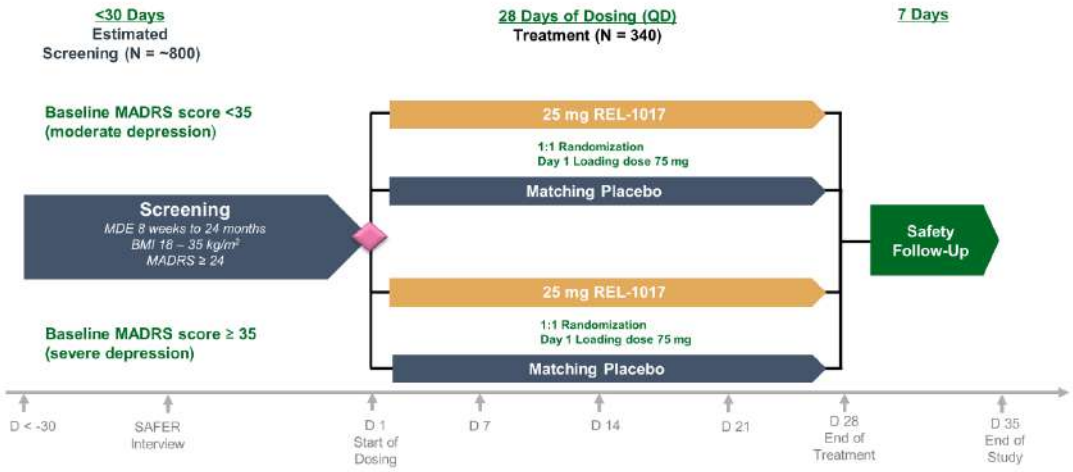
Subjects will be asked to stay on a stable dosing regimen of the same, current ADT during the 30-day Screening period, between Day 1 and Day 28, while receiving REL-1017 or matching placebo. The study drug should be taken once daily in the morning, and at the same time the subject takes her/his current ADT, when appropriate. On clinic days, this would be approximately 2 hours prior to the in-clinic visit. Dosing with study drug should take place once daily in the morning on empty stomach.

A total of approximately 340 subjects are estimated to be included in the trial.. Subjects will be stratified according to depression severity based on MADRS score at Baseline < 35 (moderate depression) or ≥35 (severe depression) and randomized in a 1:1 ratio to the active REL-1017 25 mg QD arm or matching placebo arm for each of the two groups. Enrollment will complete only after at least 340 subjects are randomized within the Total Population.

An unblinded interim analysis for sample size re-estimation (IA-SSR) based on the calculation of the conditional power (Mehta 2011) and adopting the Cui-Hung-Wang (CHW) paradigm (Cui 1999), could result in an increase of total sample size of up to 50%.

Subjects may be offered the opportunity to enroll in an expanded access program (EAP).

Figure 1: Study Design



Abbreviations: BMI=body mass index; D=day; MADRS=Montgomery-Åsberg Depression Rating Scale 10 item-questionnaire; MDE=major depressive episode; QD=once daily in the morning; SAFER=State versus Trait; Assessability; Face Validity; Ecological Validity; and Rule of Three Ps (Pervasive, Persistent, and Pathological)

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5.2 DISCUSSION OF STUDY DESIGN

This is an outpatient study to be conducted at approximately 80 sites in North America.

Enrolling in the study will be adults diagnosed with MDD (based on Structured Clinical Interview for DSM-5 Disorders [SCID-5] for MDD, matching Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]), who are currently in an MDE, and with a substantiated inadequate response to 1 to 3 courses of treatment of an ADT course per the ATRQ during the current MDE for at least 8 weeks prior to Screening and stabilized 6 weeks prior to Baseline, independently confirmed by SAFER interview, and commitment to remain on the same stable dosing regimen (as confirmed by assessment of an independent clinician using the ATRQ).

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6 SELECTION OF STUDY POPULATION

6.1 INCLUSION CRITERIA

To enroll in the clinical study, subjects must meet the following inclusion criteria:

1. Provide written informed consent to participate in the study, are able to understand the procedures and study requirements and agree to abide by study restrictions and return for the scheduled study assessments.
2. Male or female outpatients, 18-65 years of age, inclusive
3. Currently meet DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT, with a current major depressive episode of at least 8 weeks and not exceeding 24 months in duration at Screening (Visit 1). The confirmed diagnosis of MDD must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician or other qualified healthcare professional. Patient-reported MDD is not sufficient for inclusion in the study.
4. MADRS score ≥24 at Screening (Visit 1) and Baseline (Visit 2).
5. An appropriate and valid subject in the study, after independent MGH-CTNI SAFER/ATRQ assessment of the subject's MDD condition to confirm the diagnosis of MDD, as well as the inadequate response to 1 to 3 valid courses of treatment with an antidepressant medication in the current MDE, defined as <50% improvement with an antidepressant medication at doses listed on the SAFER and ATRQ Interview Forms.
6. Treated and stabilized at same dose for at least 6 weeks prior to Screening, experiencing <50% improvement on an approved dosing regimen of one ADT during the current MDE, and committed to remaining on the same stable dosing regimen for the Screening period and for the entire study, at or above the minimally adequate dose in the ATRQ. Documentation of stable and ongoing ADT must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician or other qualified healthcare professional.
7. Normal physical examination findings and clinical lab test results from Screening (Visit 1) or abnormal results that are judged not clinically significant by the investigator.
8. Body Mass Index (BMI) between 18 and 35 kg/m^2, inclusive.
9. If female and of childbearing potential, has a negative urine pregnancy test at Screening (Visit 1) and Baseline (Visit 2), is practicing adequate methods of birth control (i.e., oral or parenteral contraceptives, intrauterine device, condoms, spermicides), and is not currently pregnant or breastfeeding nor plans to become pregnant during the course of the study.
    a. Abstinence from heterosexual intercourse is acceptable if aligns with subject's preferred and usual lifestyle.
    b. Female subjects taking hormonal contraceptives or using intrauterine devices must have been doing so for at least 1 month prior to Screening and as per instructions in product labelling.

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c. Female subjects may be enrolled without a negative urine pregnancy test if they are surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy) or at least 2 years post-menopausal.
d. Male subjects and their female sexual partners should use an acceptable method of birth control during the study.

6.2 EXCLUSION CRITERIA

Individuals meeting any of the following criteria at Screening or Baseline are ineligible to participate in this study:

Psychiatric Exclusion Criteria

1. History of:
    a. Any depressive episode with psychotic or catatonic features.
    b. Any manic or hypomanic episode whether due to bipolar I or II illness, or medication/substance-induced.
    c. Bipolar Depression
    d. Schizophrenia, schizoaffective disorder, or other psychotic illness.
    e. Obsessive Compulsive Disorder active within 12 months of Screening (Visit 1).
    f. Panic disorder, with or without agoraphobia active within 12 months of Screening (Visit 1).
    g. Any anxiety disorder which has been the primary focus of clinical care rendering MDD secondary to anxiety within 6 months prior to screening.
    h. Post-traumatic Stress Disorder active within 12 months of Screening (Visit 1).
    i. Personality Disorders: Borderline, Antisocial, Paranoid or Schizotypal of sufficient severity that they may interfere with study participation.
    j. Alcohol use disorder or substance use disorder (excluding nicotine and caffeine) active within 12 months of Screening (Visit 1).
2. MADRS improvement of >20% or worsening of >40% between Screening (Visit 1) and Baseline (Visit 2).
3. Psychiatric hospitalization during the current major depressive episode.
4. Risk of Suicide deemed clinically significant based on:
    a. Patient Interview (Investigator Judgment)
    b. CSSR-S information gathered at Screening (Visit 1) or Baseline (Visit 2) (e.g., A subject answers “Yes” to question 4 or 5 of the C-SSRS ideation and the most recent episode occurred within the current major depressive episode.
    c. MADRS item 10 score ≥5 at Screening (Visit 1) or Baseline (Visit 2).
    d. Suicidal attempt within the current depressive episode or within the last year prior to Screening.
5. Any current and primary psychiatric disorder (i.e., a condition that is the primary focus of distress and/or treatment other than MDD), as defined by the DSM-5. These disorders include, but are not limited to, any psychotic disorder, post-traumatic stress disorder,

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borderline personality disorder, antisocial personality disorder, obsessive-compulsive disorder, intellectual disability, or pervasive developmental disorder.

Medication/Treatment Exclusion Criteria

6. 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 and the Medical Monitor would jeopardize the safety of the subject or the validity of the study results, including established QT prolongation, long QT syndrome, torsades de pointes, bradyarrhythmia, ventricular tachycardia, or uncompensated heart failure (greater than New York Heart Association [NYHA] Class 1 congestive heart failure [CHF]), uncontrolled hypokalemia, or uncontrolled hypomagnesemia
7. More than class 2 angina pectoris or a myocardial infarction (MI) or acute coronary syndrome within the past 3 months.
8. History of long QT or first degree relative with history of unexplained sudden death or long QT syndrome.
9. 12-lead ECG with QTcF (QT interval with Fridericia's correction) ≥450 msec at Screening.
10. Current or recent uncontrolled orthostasis or orthostatic hypotension necessitating treatment.
11. Poorly controlled diabetes as defined by a glycosylated hemoglobin (HbA1c) >7.5%, despite standard care. Subjects with HbA1c >7.5% may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
12. Any long-term use (i.e., >120 days in a 6-month period) of prescribed opioids or controlled substances within 6 months, prior to Screening – as verified by appropriate medical records, Prescription Monitoring Program (PMP) or alternative verified documentation as requested by Medical Monitor or delegate – or any recreational use of opioids or controlled substances.
13. Having received and/or requires ongoing treatment with any prohibited medications, supplements, or herbal products listed in Appendix A per the applicable timeline.
14. History of allergy or hypersensitivity to methadone or related drugs.
15. Enrolled in a clinical trial in the last 5 months prior to screening, or previously enrolled at any time in a clinical trial for an indication that conflicts with a primary diagnosis of MDD as determined by the Medical Monitor. These studies include, but are not limited to, those targeted at any psychotic disorder, post-traumatic stress disorder, borderline personality disorder, antisocial personality disorder, obsessive-compulsive disorder, intellectual disability, or pervasive developmental disorder.

Other Medical Exclusion Criteria

16. Any current or past medical, psychiatric condition, or social context that, in the opinion of the investigator, Medical Monitor or independent adjudicator, is likely to unfavorably

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alter the risk-benefit of the subject participation, to interfere with protocol compliance, or to confound safety or efficacy assessments. This includes, but is not limited to, diseases of the following systems: hematologic, oncologic, endocrine, cardiovascular, renal, hepatic, respiratory, gastrointestinal, infectious, neurologic and psychiatric.

17. History of seizure disorder; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates or antiepileptic drugs; conditions increasing the risk of seizures such as stroke, head injury, tumor or CNS infection, arteriovenous malformation, neuroleptic malignant syndrome/serotonin syndrome; or clinically significant metabolic disorders (hypoglycemia, hyponatremia, severe hepatic impairment, renal impairment, and hypoxia).
18. Positive breath alcohol test or urine drug screen (UDS) for any prohibited medications or drugs of abuse (cocaine, marijuana, phencyclidine, opioids, amphetamines, or other agents within 30 days prior to and/or at Baseline (Visit 2). A positive result for a psychoactive drug not previously disclosed will result in screen failure. Retesting is permitted at the discretion of the Principal Investigator and the Medical Monitor. Please consult with the Medical Monitor in the case of a positive result for benzodiazepines or other disclosed medications that have been approved by the Medical Monitor.
19. Exclusion Criterion 19 removed in protocol v3.0.
20. Screening liver enzyme test (e.g., bilirubin, aspartate aminotransferase, and/or alanine aminotransferase) results >2.0 x the upper limit of normal (ULN) and Creatine Phosphokinase (CPK) >2.0 × ULN, or clinically significant abnormal endocrine laboratory values. Subjects with excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
21. Evidence of clinically significant renal impairment, including an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2009 calculation). Subjects with excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
22. Patients with clinically significant high BP may be accepted in the study per the judgment of the investigator if they subsequently have acceptable BP levels on retesting at least 30 minutes apart.
23. Hypo- or hyperthyroidism, unless stabilized on appropriate pharmacotherapy with no dosage change for at least one month prior to Screening (Visit 1). Serum thyroid stimulating hormone (TSH) must be >0.75 x lower limit of normal (LLN) and <1.25 x ULN. Subjects with excursions from the above allowed normal ranges may continue in the study if approved by the Relmada Medical Monitor after discussion with the Principal Investigator. Re-testing might be suggested.
24. Participant has had gastric bypass surgery or has had any procedure or disorders that interfere with gastrointestinal transit or absorption.

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25. History of allergy, hypersensitivity, or intolerance to opiates (e.g., methadone, codeine) or related drugs.

6.3 RESCREENING

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore are not randomized (screen failures), may be rescreened once, at the discretion of and with written permission from, the Medical Monitor, with the exception of subjects presenting with alcohol or drug abuse or previously undisclosed psychoactive drugs; subjects excluded because of QTc prolongation, unless they were receiving a QT-prolonging drug which has subsequently been discontinued; those who had hypokalemia or hypomagnesemia which has been corrected for a minimum of 14 days; or those screen failed by the independent medical adjudicator/Medical Monitor or who failed the CTNI interview.

6.4 STUDY WITHDRAWAL AND REMOVAL OF SUBJECTS

If a subject discontinues study treatment and/or is withdrawn from the study for any reason, the date and the reason for study treatment discontinuation or study withdrawal must be recorded on the electronic case report form (eCRF).

Subjects may be discontinued from the study for any reason. Subjects who are discontinued from study drug treatment (e.g., because of an AE) prior to study completion (Day 28) will be followed up until 7 days after the last dose of study drug (End of Study [EOS]) to complete the required assessments as indicated in the Schedule of Assessments (Table 1). Study drug discontinuation reasons may include:

- Occurrence of intolerable AE, as assessed by the Investigator or designee.
- Clinically significant abnormality on vital signs, ECGs, clinical laboratory tests, or physical examination evaluations, as assessed by the Investigator or designee.
- QTcF > 500 msec or an increase from Baseline > 60 msec (including on the local ECG machine interpretation). Triplicate ECGs will be conducted. If the triplicate ECG, as assessed by an appropriately trained expert (the ECG Core Lab or a cardiac electrophysiologist) verifies that the QTcF interval is > 500 msec or that the increase from Baseline is > 60 msec from Baseline (Day 1 pre-dose), the study drug will be stopped, and causality will be investigated.
- Non-compliance with protocol study requirements and restrictions.
- Administrative reasons (e.g., Sponsor decision).
- Major violation of the protocol.
- Investigator decision.
- It is in the best interest of the subject.

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- Use of a concomitant medication that, in the opinion of the Investigator or designee, would interfere with the study procedures or data integrity or compromise the safety of the subject.

Subjects will be considered terminated from the study for the following:

- Withdrawal of consent
- Lost to follow-up
- Death

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with GCP. This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

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7 TREATMENT

7.1 STUDY DRUG ADMINISTRATION

Active REL-1017 in 25 mg tablets or matching placebo tablets will be provided at the clinical study site in bottles containing a supply of 15 tablets. The investigational drug will be dispensed at Baseline (Day 1), on Day 7, Day 14, and Day 21, for QD oral administration by mouth (PO) with or without food according to the following schedule:

Day 1 (Baseline) – loading dose:

- REL-1017 arm: Three (3) 25 mg tablets (75 mg total) administered at the clinical study site
- Placebo arm: Three (3) matching tablets administered at the clinical study site

Day 2 to Day 28:

- REL-1017 arm: One (1) 25 mg tablet QD
- Placebo arm: One (1) matching tablet QD

Dosing should take place QD before meals at the same time as the first-line ADT is taken. On clinic days, this would be approximately 2 hours prior to in-clinic visit.

The study drug should be taken once daily in the morning, and at the same time the subject takes his/her current ADT, where appropriate. On clinic days, this would be approximately 2 hours prior to the in-clinic visit. Dosing with study drug should take place once daily in the morning on empty stomach.

Required Antidepressant Therapy:

Subjects will continue to take the same stable dose of the single approved ADT medication, for which the subject has had an inadequate response, from Screening throughout the course of the study to the End of Study Visit (Day 35), with no dosing changes nor the addition of new ADT medications.

7.2 STUDY DRUG IDENTIFICATION

7.2.1 Packaging and Labeling

Each bottle 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
- Recommended storage conditions of drug
- Bottle number
- Lot number of the drug

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- Name and address of the Sponsor
- Protocol code or study number
- Quantity of drug per bottle

7.2.2 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. Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture to the location of delivery.

Upon receipt by the study site, the study drug 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 study drug was received in acceptable condition. Once inspected, the study drug will be stored in a restricted access, secured area with access limited to authorized research site staff, under physical conditions consistent with the study drug's specific requirements. After study drug is dispensed to subjects, the remaining study drug will be returned to storage in a restricted access, secured area under physical conditions consistent with the study drug's specific requirements, in full compliance with US DEA regulations on storage and inventory control, dispensing and drug accounting.

The research site's pharmacist or delegate is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study, according to applicable regulations. All bottles of dispensed study drug that have been provided to the subjects will be returned to the pharmacy, and any unused study drug will be recorded. Dispensed study drug tablets that have not been used will not be relabeled or reassigned for use by other subjects. Re-dispensing of study drug to the same subject is allowed. Study drug that has been dispensed, but not used, will be stored and disposed of according to the Sponsor's instructions.

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

7.2.3 Dispensing

Details regarding the administration of the study drug will be outlined in the pharmacy manual. Only eligible subjects will receive the study drug. Only authorized research site staff may supply or administer the study drug.

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7.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Subjects will be stratified at Baseline based on Baseline MADRS score < 35 (moderate depression) and Baseline MADRS score ≥35 (severe depression). Within each population, blocked randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject 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 subject will be assigned a unique identification number during the Screening process. This number will be used to identify the subject throughout the study. Once an identification number is assigned, it cannot be reassigned to any other subject.

The randomization will be a blocked randomization; the random treatment assignment code used in the Interactive Response Technology (IRT) platform will be prepared by an unblinded randomization statistician.

7.4 SELECTION OF DOSING REGIMEN

Since extensive clinical experience is available for racemic methadone and some clinical experience is available for esmethadone (Isbell 1948; Fraser 1962; Olsen 1977; Moryl 2016), the initial 25-mg daily dose was selected based on the comparative characteristics of racemic methadone and available data with REL-1017 in healthy subjects (Bernstein 2019) as well as the evidence from the Phase 2 study (Fava 2022) and safety data summarized in the updated IB. The leading dose was selected based on Phase 1 PK data to allow reaching steady-state during the first day of treatment.

In Phase 1 studies of REL-1017 the 150 mg dose was safe (Bernstein 2019; Shram 2022). Due to differences in the pharmacologic activity of the methadone enantiomers and based on the body of evidence summarized in the updated Investigator Brochure (IB), opioid-related AEs observed with racemic methadone are not anticipated to occur with the administration of esmethadone. As described by the US DEA, the opioid effects of racemic methadone are due to its levo-isomer, while the dextro-isomer lacks significant respiratory depressant action and addiction liability (DEA 2019).

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.

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To reach steady-state quickly for REL-1017 25 mg and REL-1017 50 mg treatment arms in Study REL-1017-202, a loading dose on Day 1 was administered. In the 25 mg REL-1017 tablet arm, a loading dose of 75 mg was taken at the study site on Day 1, followed by a 25 mg REL-1017 tablet QD on Days 2 to 8. In the 50 mg REL-1017 tablet arm, a loading dose of 100 mg REL-1017 was taken at the study site on Day 1, followed by a 50 mg REL-1017 tablet QD on Days 2 to 8.

PK/PD modeling, based on the demonstrated AUC_{tau} of REL-1017 in preclinical and clinical studies and on the AUC_{tau} of ketamine at doses that provide antidepressant efficacy, supports the conclusion that REL-1017 at 25 mg and 50 mg QD were predicted to be the optimal safe, well-tolerated and equally effective doses. In the current study, an initial daily dose of 25 mg was selected on the basis of the equivalent PD observed in the REL-1017-202 study at the 25 mg and 50 mg dosing levels.

7.5 TREATMENT PERIOD

Subjects will take a loading dose of REL-1017 75 mg (3 tablets) or matching placebo at Baseline (Day 1) and a maintenance dose of REL-1017 25 mg (1 tablet QD) or matching placebo thereafter during the 28-day treatment period.

7.6 CODE BREAKING

The compliance auditor(s) who verify conformity to study procedures and the unblinded statisticians who generate the code will have access to the blind. Under normal circumstances, the blind will not be broken until all subjects 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 subject. Individual code breaks will result in the withdrawal of the subject from the study. The date, time, and reason for the unblinding will be documented in the source documents.

7.7 ACCOUNTABILITY AND COMPLIANCE

The pharmacist or other designated individual will maintain records of study treatment delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study subjects.

At each visit after initiation of treatment, study site personnel will record compliance of the subject with the assigned regimen. Subjects will be instructed to bring their bottles containing

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unused tablets back for inspection at each study visit. Subjects are to be reminded of the importance of compliance, with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Investigators will maintain records that adequately document that the subjects were provided with the correct bottle of tablets and reconcile the products received from the drug dispensing center. Study drug will not be returned to the Sponsor until accountability and reconciliation have been fully conducted by the site monitor.

Study drug bottles must be returned at each visit, and tablet counts will be recorded to assess compliance. Non-compliance is defined as taking less than 80% or more than 120% of study drug during any outpatient evaluation period (visit to visit). Discontinuation for non-compliance is at the Investigator's discretion and is to be recorded on the eCRF.

7.8 PRIOR AND CONCOMITANT MEDICATIONS AND THERAPIES

All medications taken and therapies received within 6 months prior to Screening must be noted on the eCRF. Medications taken and therapies received related to the primary indication (MDD) within the 5 years prior to Screening will also be recorded on the eCRF. The reported concomitant medications and/or therapies will be reviewed and evaluated by the Investigator to determine if they affect a subject's eligibility or continued participation in the study.

Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the eCRF.

After the Baseline visit, medication to treat minor treatment-emergent illness(es) is generally permitted; however, therapies discussed in the next section are expressly prohibited throughout the study.

7.9 PROHIBITED AND/OR RESTRICTED COMEDICATIONS AND THERAPIES

Prohibited and/or restricted medications or therapies are provided in Appendix A. Restricted comedication management is the responsibility of the Investigator, exercising good clinical judgment in the interest of the subject's health and contextual considerations.

Decisions regarding comedication must be made by the Investigator or prescribing physician in accordance with the guidance provided in comedication management (Section 15) and to the best clinical judgment of the Investigator, in consultation with the Medical Monitor. Initiation of any new comedication during the study is not permitted unless a medical necessity requires a therapeutic decision made according to the best clinical judgment of the Investigator, prescribing

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physician, and Medical Monitor. Specifically, a QT-prolonging drug should not be started by a subject during the study, except with the Medical Monitor's agreement.

The Investigators and their designees are obliged to ensure the well-being of all subjects during this study. If medical intervention is required during the study, no medication or treatment will be withheld from a subject, and the Investigator will ensure proper documentation is kept in the source documentation. Due to each subject's clinical condition being unique, there is no specific rescue plan or rescue therapy recommended. 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.

7.10 CONTRACEPTIVE PRECAUTIONS

For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include vasectomy or male condom for subjects, 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 subject has childbearing potential, and the subject will be advised to use medically acceptable birth control methods. Abstinence from heterosexual intercourse is accepted if this is the subject's usual lifestyle and must be continued until at least 2 months after the last dose of study drug.

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

WOCBP (women of childbearing potential; not surgically sterilized and between menarche and 1 year post-menopause) must agree to use at least 1 highly effective method of contraception from Screening through at least 2 months after the last study drug administration. Women who are not of childbearing potential must be congenitally or surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by the subject's medical history) or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least 1 year without another cause and a confirmatory FSH level ≥40 mIU/mL.

Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and 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)
- Abstinence from heterosexual intercourse is accepted if this is the subject's usual lifestyle and must be continued until at least 2 months after the last dose of study drug.

Women who are lactating are prohibited from participating in the study.

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

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8 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Sections 9 and 10 provide details regarding efficacy assessments and safety assessments, respectively, and Section 10.5 specifies laboratory assessment samples to be obtained.

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Table 1: Schedule of Assessments

Visit	1	2	3	4	5	6	7
	Screening	Baseline				EOT/ET	EOS
Week	Up to -4	0	1	2	3	4	5
Assessment Day	Up to -30	1	7 (+2)	14 (+2)	21 (+2)	28 (+2)	35 (+2)
Informed Consent	X						
Subject Registry	X						
Medical and Psychiatric History	X						
Demographics and Height	X						
Inclusion/Exclusion Review	X	X					
Physical Examination[a]	X	X				X	
Weight and BMI	X	X				X	X
Concomitant Medications/Therapies	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X
ECG[c]	X	X	X			X	
LABORATORY TESTING							
Hematology	X	X				X	X
Biochemistry	X	X				X	X
Urinalysis (Dipstick)[d]	X	X				X	X
Hepatitis B, Hepatitis C, and HIV	X						
TSH	X						
Drug Screen (urine)[e]	X	X		X		X	X
Breath Alcohol[f]	X	X					
Serum FSH Test for All Females	X						
Urine Pregnancy Test for WOCBP[g]	X	X	X	X	X	X	
Serum Pregnancy Test (B-HCG)[g]	X						
Blood Sample for DNA Extraction[h]		X					
PK Blood Sampling[i]		X	X			X	
ASSESSMENTS							
SAFER Interview[j]	X						
SCID-5 MDD	X						
ATRQ	X						
PCRS[k]		X	X	X	X	X	
MADRS	X	X	X	X	X	X	
CGI-S (Severity)[l]	X	X	X	X	X	X	
CGI-I (Improvement)			X	X	X	X	
PGI-I (Improvement)			X	X	X	X	

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QIDS-SR-16	X	X	X	X	X	X	
HAM-A	X	X				X	
SDS	X	X	X	X	X	X	
Q-LES-Q-SF		X	X	X	X	X	
DSST		X				X	
C-SSRS[m]	X	X	X	X	X	X	X
DOSING							
Randomization		X					
Study Drug Dispensing		X	X	X	X		
Study Drug Return/Compliance/Accountability[n]			X	X	X	X	
Adverse Events (AEs)	X	X	X	X	X	X	X

Abbreviations: ADT: antidepressant therapy; AE = adverse event; ATRQ = Antidepressant Treatment Response Questionnaire; b-HCG = beta-human chorionic gonadotropin; BMI = body mass index; BP = blood pressure; CGI-I = Clinical Global Impression of Improvement; CGI-S: Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HAM-A = Hamilton Anxiety Rating Scale; HAMD17 = Hamilton Depression Rating Scale; HIV = human immunodeficiency virus; HR = heart rate; MADRS = Montgomery-Åsberg Depression Rating Scale 10; MDD = major depressive disorder; PCRS = Placebo-Control Reminder Script; PK = pharmacokinetics; RR = respiratory rate; SAFER = State versus trait; Assessability; Face Validity; Ecological Validity; and Rule of Three Ps (Pervasive, Persistent, and Pathological; SCID-5-MDD = Structured Clinical Interview for DSM-5 Disorders; SDS = Sheehan Disability Scale; SOP = Standard Operating Procedure; TSH = thyroid stimulating hormone

Note: Procedures performed after the assessment scales should follow from least invasive to more invasive. The following order is recommended: all assessment scales, vital signs, ECGs and lastly PK blood draw.

a. Focused physical examination at Baseline (Day 1) and EOT (Day 28) will be limited to the following body systems: general appearance, gastrointestinal/abdominal, cardiovascular/heart, respiratory/lungs, neurological, musculoskeletal, and any other assessments required to evaluate AEs. Additional physical examinations can be performed at the discretion of the Investigator.

b. Vital signs include body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measured after the subject has been resting in a supine or semi-supine position for at least 3 minutes.

c. Screening ECG will be collected singularly (vs triplicate). One set of triplicate ECGs will be taken at Baseline (Day 1) pre-dose and one set of triplicate ECGs will be taken at Day 7. On Day 28, subjects will have post-dose one set of triplicate ECG performed, after completed efficacy assessments. All study ECGs should be conducted in a supine position (resting for at least 10 minutes). Subjects taking strong inhibitors of CYP3A4 should have triplicate ECGs performed additionally at Visits 4, 5, and 7 (refer to Section 10.4)[x]

d. Urinalysis will be taken by dipstick and reviewed locally for abnormalities. If there is an out of range value, a urine sample should be sent to the central lab for a Urine Microscopy. At Baseline, urine drug screening will be performed locally on-site.

e. Urine drug screen tests will be for tetrahydrocannabinol, opiates (including oxycodone), amphetamines, cocaine, and benzodiazepines. The UDS will be collected and sent to the central lab at the Screening Visit (including any screening retests), Day 14, Day 28 (EOT), and Day 42 (EOS). **At Baseline, urine**

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drug screening will be performed locally on-site.

f. Subjects should abstain from alcohol for 24 hours prior to each study visit. Breath alcohol testing will be performed at Screening and Baseline (Day 1). If there is any doubt or concern regarding alcohol use, research site staff may request a breath alcohol test at subsequent visits during the study.

g. An on-site urine pregnancy test will be performed at each study visit for WOCBP. A serum pregnancy test (b-HCG) will be performed at Screening in addition to an onsite urine pregnancy test. During the study, a repeat serum pregnancy test will be performed if a subject's urine pregnancy test result is positive.

h. A whole blood sample for DNA isolation will be collected from all subjects who sign the Pharmacogenetic Testing Informed Consent for potential pharmacogenetic analysis of genes that may affect the PK of REL-1017. This analysis will be restricted to the evaluation of genes that may be involved in the PK of REL-1017 (e.g., drug metabolism, disposition, elimination). One 4 mL whole blood sample for DNA isolation will be collected on Baseline (Day 1) from each subject. 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 confidentiality. The samples will be retained while research on REL-1017 continues.

i. PK blood samples will be taken on Days 1 (immediately following the ECG recording and pre-dose), 7 (post-dose and within 10 minutes of ECG) and 28 (post-dose and within 10 minutes of ECG). Subjects taking strong inhibitors of CYP3A4 should have PK blood samples taken additionally at Visits 4, 5, and 7 (refer to Section 10.4)[x]

j. The SAFER interview should be scheduled with MGH-CTNI (per instructions in the MGH-CTNI manual) to take place in the screening period. MGH-CTNI clinicians will administer the SAFER Interview, MADRS and ATRQ as independent confirmation of inclusion criteria.

k. The PCRS is read by the MADRS Rater to <u>each</u> subject <u>immediately before</u> administering the MADRS.

l. CGI-S is performed at Baseline prior to the first administration of study drug.

m. At Screening, the C-SSRS Baseline/Screening version is administered to subjects. At subsequent visits, the C-SSRS Since Last Visit version is administered to subjects.

n. Site personnel will record compliance of the participant's assigned regimen. Study drug bottles containing unused tablets must be returned at each visit and tablet counts will be recorded.

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8.1 INFORMED CONSENT

Before performing any study-related procedures, the Investigator (or designee) will obtain signed informed consent from the subject.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number.

8.2 RATER QUALIFICATION

The 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.

8.3 PLACEBO-CONTROL REMINDER SCRIPT (PCRS)

The Placebo-Control Reminder Script (PCRS) © (Cohen 2021) educates clinical study subjects on key causes of the placebo and nocebo effects, namely the tempering of subject study expectations, reminding subjects what a placebo is and how that relates to their reporting of symptoms and potential side effects, and explaining how interactions with research site staff differ from their experience with previous providers. To do this, the PCRS informs subjects that they are to be honest about their symptoms, site staff have no expectations of symptom improvement or worsening and will not be disappointed if they feel better, worse or the same, and asks participants to explain in their own words its content to ensure comprehension. Per the instructions on the PCRS, the MADRS rater will read the script verbatim immediately before administering this scale. The PCRS is read to EACH subject at EACH Visit immediately before administrating the MADRS, as listed on the Schedule of Events (Table 1) typically taking about 3 minutes to read. The PCRS has been empirically found to significantly manage (reduce) the placebo and nocebo effects (Cohen 2021).

8.4 ORDER OF ASSESSMENTS

8.4.1 Visit 1 (Screening)

All subjects agreeing to participate in the study must give informed consent by signing the ICF before any study-related procedures are performed. Screening begins after ICF has been signed and dated by the subject and the Investigator or other appropriate site staff. The duration of the Screening will depend on each individual subject and may last up to 30 days.

The following procedures should be performed in order after the ICF is reviewed and signed:

1. Assign subject number via the EDC/IRT system.
2. Register the subject in the subject registry(ies).

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3. Standardized assessments to include: MADRS (which should be the first assessment completed), SCID-5 MDD, ATRQ, CGI-S, QIDS-SR-16, HAM-A, SDS and C-SSRS.
4. Collection of urine sample for urinalysis and drug screen analysis.
5. Breath alcohol test.
6. Collection of medical and psychiatric history, concomitant medications and demographic information. Physical examination, ECG and pulse oximetry need to be performed, and height, weight, BMI and vital signs recorded.
7. Blood sample collection to obtain hematology, biochemistry, hepatitis B and C, HIV, TSH and FSH data. A serum pregnancy test (b-HCG) is performed at screening for females of childbearing potential.

Subjects that meet all eligibility and inclusion and no exclusion criteria, will undergo Visit 2 (Baseline).

During the Screening Period, subjects who are deemed eligible by the Principal Investigator and the Medical Monitor will undergo the SAFER/ATRQ/MADRS interview by clinicians at the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI). Eligibility for enrollment will also be assessed by an independent medical adjudicator, who is a clinical psychiatrist, to ensure appropriate diagnosis and clinical presentation.

To ensure that appropriate subjects are entered into the study, MGH-CTNI-certified clinician will independently assess each subject using the SAFER interview, MADRS and the MGH-ATRQ. The interview will be performed remotely; an MGH-CTNI clinician will contact the subject at his or her home or another off-site location after receiving notification from the study site. Sites will then be notified of the results of the interview. Only subjects whose eligibility is confirmed by the SAFER/ATRQ/ MADRS interview and the independent clinical adjudicator/Medical Monitor will be allowed to proceed in the study.

8.4.2 Visit 2 (Baseline, Day 1)

Subjects continuing to meet all eligibility and inclusion criteria and no exclusion criteria, will be stratified according to depression severity (MADRS score <35 and MADRS score ≥35) and randomized within each group at Baseline to start the study treatment.

1. Read the Placebo-Control Reminder Script (PCRS) to the subject.
2. Assessment scales including MADRS (which should be the first assessment completed), CGI-S, QIDS-SR-16, HAM-A, SDS, Q-LES-Q-SF, DSST and C-SSRS.
3. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
4. One set of triplicate ECGs taken pre-dose.
5. PK blood sample pre-dose.
6. Laboratory tests, consisting of: blood sample for hematology and biochemistry analysis, optional blood sample for DNA extraction for the analysis of genes that may affect the PK

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of REL-1017, urine sample for urinalysis, drug screening (performed locally on-site) and pregnancy test (for WOCBP), and breath alcohol test (on-site).
7. Physical examination, limited to general appearance and examination of gastrointestinal/abdominal, cardiovascular/heart, respiratory/lungs, neurological, musculoskeletal, and other assessments that might be required to evaluate AEs. Weight and BMI need to be recorded as well.
8. Perform final confirmation subject meets all inclusion criteria and no exclusion criteria.
9. Randomization and drug dispensation; subject takes loading dose on-site.
10. Record changes to concomitant medications and/or AEs to be reported.

8.4.3 Visit 3 (Day 7; +2-day window)

At Visit 3 (Day 7), subjects should return to the study site and the following assessments completed in the order specified below:

1. Read the Placebo-Control Reminder Script (PCRS) to the subject.
2. MADRS (which should be the first assessment completed), CGI-S, CGI-I, PGI-I, QIDS-SR-16, SDS, Q-LES-Q-SF and C-SSRS.
3. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
4. One set of triplicate ECGs.
5. PK blood sample post-dose and within 10 minutes of ECG.
6. Study Drug bottle from the previous visit must be returned and unused tablets count recorded. Further details specified in Section 7.8. Study drug should be dispensed/re-dispensed as necessary.
7. Record changes to concomitant medication and/or AEs.
8. Urine sample collected for pregnancy test (for WOCBP).

8.4.4 Visit 4 (Day 14; + 2-day window)

At Visit 4 (Day 14), subjects should return to the study site and the following assessments completed in the specified order below:

1. Read the Placebo-Control Reminder Script (PCRS) to the subject.
2. MADRS (which should be the first assessment completed), CGI-S, CGI-I, PGI-I, QIDS-SR-16, SDS, Q-LES-Q-SF and C-SSRS.
3. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
4. Study Drug bottle from the previous visit must be returned and unused tablets count recorded. Study drug should be dispensed/re-dispensed as necessary.
5. Record changes to concomitant medication and/or AEs.
6. Urine sample collected for pregnancy test (for WOCBP)
7. Urine sample for drug screening (on-site testing)

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8.4.5 Visit 5 (Day 21; + 2-day window)

At Visit 5 (Day 21), subjects should return to the study site and the following assessments completed in the order specified below:

1. Read the Placebo-Control Reminder Script (PCRS) to the subject.
2. MADRS (which should be the first assessment completed), CGI-S, CGI-I, PGI-I, QIDS-SR-16, SDS, Q-LES-Q-SF and C-SSRS.
3. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
4. Study Drug bottle from the previous visit must be returned and unused tablets count recorded. Study drug should be dispensed/re-dispensed as necessary.
5. Record changes to concomitant medication and/or AEs.
6. Urine sample collected for pregnancy test (for WOCBP).

8.4.6 Visit 6 (Day 28; + 2-day window; EOT/ET)

Subjects who have received their last dose of study drug and completed the study should return to the site for the EOT visit (Day 28). The following assessments should be completed in the order specified below:

1. Read the Placebo-Control Reminder Script (PCRS) to the subject.
2. MADRS (which should be the first assessment completed), CGI-S, CGI-I, PGI-I, QIDS-SR-16, HAM-A, SDS, Q-LES-Q-SF, DSST and C-SSRS.
3. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
4. One set of triplicate ECG post-dose.
5. PK blood extraction post-dose and within 10 minutes of ECG.
6. Study Drug bottle from the previous visit must be returned and unused tablets count recorded.
7. Physical examination, limited to general appearance and examination of gastrointestinal/abdominal, cardiovascular/heart, respiratory/lungs, neurological, musculoskeletal, and other assessments that might be required to evaluate AEs. Weight and BMI need to be recorded as well.
8. Record changes to concomitant medications and/or AEs.
9. Laboratory tests, consisting of: blood sample for hematology and biochemistry analysis, urine sample for urinalysis, drug screening and pregnancy test (for WOCBP).

8.4.7 Visit 7 (Day 35 + 2-day window EOS)

Seven days after EOT visit, subjects undergo the EOS visit (Day 35), where follow-up safety, tolerability and withdrawal symptom assessments are performed. For subjects who discontinue or withdraw from study prior to the EOT visit, these assessments will be completed 7 days after the last dose of study drug. At EOS, the following assessments should be completed:

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1. C-SSRS assessment scale.
2. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
3. Weight and BMI collection.
4. Record changes to concomitant medications and/or AEs.
5. Laboratory tests, consisting of: blood sample for hematology and biochemistry analysis, urine sample for urinalysis, drug screening.

8.4.8 Early Termination (ET)

Subjects that desire to withdraw from the study or are withdrawn by the Investigator (e.g.. Due to continuing non-compliance or safety concerns) will be given instructions to complete safety follow-up visit. Subjects who discontinue study drug prior to Day 28 will have the Early Termination assessments conducted at the time of study drug discontinuation. Every reasonable effort will be made to follow up with subjects one week later to complete the End of Study assessments. Documentation of early termination/ withdrawal will be completed at the site and subject will be marked as early termination into EDC as well upon completion of the ET visit.

At early termination visit, assessments should be conducted according to Visit 6.

8.5 ENTRY CRITERIA MEASUREMENTS

8.5.1 Structured Clinical Interview for DSM-5

The SCID-5 for MDD is a semi-structured interview guide to ensure consistency with the DSM-5 diagnostic classification. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria.

8.5.2 SAFER Interview

Subjects who are deemed eligible by the Principal Investigator and the Medical Monitor will undergo the remote SAFER/ATRQ interview by clinicians at the Massachusetts General Hospital Clinical Trials Network and Institute (MGH-CTNI). Eligibility for enrollment will also be assessed by an independent medical adjudicator, who is a clinical psychiatrist, to ensure appropriate diagnosis and clinical presentation.

The SAFER interview assesses depression in a real-world setting and confirms that the subject’s illness is a specific state and excludes subjects with any symptoms that are nonspecific or not readily assessable.

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8.5.3 Antidepressant Treatment Response Questionnaire (ATRQ)

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) (Chandler 2010).

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9 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing. For assessment scales performed at each visit, MADRS must be the first assessment performed by the rater at the site. Subsequent assessments, following MADRS, can be conducted in any order as determined by the investigator's discretion. The following order of assessments is recommended, from the least to the most invasive procedure: all assessment scales, vital signs, ECGs and lastly PK blood draw.

9.1 PRIMARY EFFICACY ASSESSMENT AND STRATIFICATION SCALE

9.1.1 Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item questionnaire with each item scored between 0 and 6, resulting in a total score between 0 and 60, with scores above 34 indicating severe depression. Higher MADRS scores indicate more severe depression. The questionnaire is most frequently used in clinical studies to measure outcomes in antidepressant efficacy studies. This scale exhibits construct validity (internal homogeneity) and concurrent validity relative to the HAMD17 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. The MADRS must be administered using the Structured Interview Guide for the MADRS (SIGMA). The MADRS will be administered at Screening and Baseline by a certified rater, in addition to during the SAFER interview in the screening period by an MGH-CTNI independent clinician. (Montgomery 1979; Williams 2008).

9.2 SECONDARY EFFICACY ASSESSMENT

9.2.1 Clinical Global Impression of Severity (CGI-S)

The CGI-S measures the severity of the disease using a 7-point Likert scale ranging from 1=normal, not at all ill to 7=among the most extremely ill subjects (Busner 2007).

9.2.2 Hamilton Anxiety Depression Scale (HAM-A)

The HAM-A will be measured at Screening and at the end of study outlined in Table 1 by a certified site rater using the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A).

The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental

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agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each of the 14 items is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0 to 56, where <17 total points indicates mild severity, 18 to 24 total points indicates mild to moderate severity, and 25 to 30 total points indicates moderate to severe.

9.2.3 Sheehan Disability Scale (SDS)

The SDS is a brief, 5-item self-report tool that assesses functional impairment in work/school, social life, and family life.

Work/school, social life, and family life/home responsibilities are each scored, individually, on a scale of 0 to 10.

Higher scores are associated with significant functional impairment (e.g., scores ≥5 on any of the 3 domains). (Sheehan DV 1983)

9.2.4 Clinical Global Impression of Improvement (CGI-I)

The CGI-I measures the improvement since the start of study treatment of the subjects using a 7-point Likert scale ranging from 1=very much improved to 7= very much worse.

CGI-I will be measured at post-dose at all visit time points outlined in Table 1.

9.2.5 Digit Symbol Substitution Test (DSST)

The DSST will be conducted via paper version only and completed at the site visit. The DSST evaluation may not be performed if subjects are unable to attend the site visit. The DSST was developed as an experimental tool to assess cognitive dysfunction. It measures processing speed and attention. The DSST, a symbol-digit pair exercise, requires subjects to match as many symbols with numbers as possible within a fixed time frame. Previous studies reported patients with MDD were associated with levels of executive dysfunction and impairment (Jaeger 2018).

9.2.6 Quick Inventory of Depressive Symptomatology – Self Report

The QIDS-16-SR is a 16-item assessment completed by the subject to determine depressive symptom severity.

9.2.7 Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form

The Q-LES-Q-SF is a 14-item assessment by subject to determine life satisfaction based on domains of activity: physical health, feelings, work, household duties, school/course work, leisure time activities, and social relations. Each item uses a 5-point scale for a maximum of 70 points. Higher scores indicate higher life satisfaction.

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10 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, SAEs, and clinical laboratory results [routine hematology and biochemistry]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 1).

10.1 MEDICAL AND PSYCHIATRIC HISTORY

Medical and psychiatric history will be recorded at Screening. Documentation of psychiatric history, including MDD diagnosis, and medical history (medical and pharmacy records or alternative verified documentation as requested by the study Medical Monitor or delegate) must be available and present in the source documents. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses, up to and including 5 years before Screening. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing (Day 1) are to be regarded as concomitant. Medical history will include alcohol consumption, substance use, and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 10.6. All changes not present at Baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include year of birth, age, sex at birth, race, and ethnicity, height, weight, and BMI.

10.2 VITAL SIGNS

Vital signs (body temperature, pulse oximetry, respiratory rate, heart rate, and systolic and diastolic blood pressure (BP) measurements) will be evaluated at the visits outlined in Table 1. All vital signs will be measured after the subject has been resting in a supine or semi-supine position for at least 3 minutes. BP measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, RR, or heart rate (HR) measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

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10.3 PHYSICAL EXAMINATION

A complete physical examination (general appearance; head, eyes, ears, nose and throat; cardiovascular/heart; respiratory/lungs; gastrointestinal/abdominal; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) will be performed at Screening as outlined in Table 1. At subsequent visits, a focused physical examination will be conducted, limited to include the following body systems: general appearance, gastrointestinal/abdominal, cardiovascular/heart, respiratory/lungs, neurological, musculoskeletal, and any other assessments required to evaluate AEs. Physical examinations and any additional physical examinations will be performed by a physician or an appropriately qualified practitioner as delegated at the discretion of the Investigator.

Body weight (without shoes) and BMI will be recorded at Screening, Day 1, EOT (Day 28), and at EOS. Height (without shoes) will be recorded at Screening only.

Clinically significant findings prior to dosing will be recorded on the medical history eCRF. During the study, any clinically significant change from Screening will be documented as an AE on the AE eCRF. Clinically significant is defined as any variation in physical examination finding that has medical relevance and may result in an alteration in medical care.

10.4 ELECTROCARDIOGRAMS

A single 12-lead, resting ECG will be obtained at Screening (Table 1).

At Baseline (Day 1), pre-dose, but after Scale Assessments and Patient Reported Outcomes (PROs), one set of triplicate ECGs will be taken, each ECG at least 30 seconds apart. On Day 7, approximately 2-3 hours, if possible, after the subject has dosed at home, one set of triplicate ECGs will be taken, each ECG at least 30 seconds apart.

On Day 28, subjects will have post-dose one set of triplicate ECGs performed after efficacy assessments have been completed. Note: The post-dose ECGs should be aligned with the PK time points. The time of the subject's last reported dose prior to ECG should be captured in the source documents and eCRF.

Subjects taking strong inhibitors of CYP3A4 should have additional triplicate ECGs performed at Visits 4, 5, and 7 so that weekly ECGs are collected in subjects taking these medications (i.e., ceritinib, clarithromycin, cobicistat, idelalisib, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, telithromycin, and voriconazole) as increases in esmethadone exposure have been reported.

Subjects will be required to lie quietly in a supine position with minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other subjects) for at least 10 minutes prior to each ECG collection.

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ECGs will be performed by the site team member and data interpretation will be done by a Core ECG Laboratory. The core laboratory analysis will constitute the primary ECG dataset for the study. The QTcF analysis will be based on the mean values of the triplicate ECG.

At Screening, the central reader will examine the ECG trace for signs of cardiac disease that could exclude the subject from the study, as defined in the exclusion criteria. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the source documentation. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

If a subject has a QTcF >500 msec or an increase from Baseline >60 msec (including on the local ECG machine interpretation), triplicate ECGs will be conducted after approximately 30 minutes. If the triplicate ECG, as assessed by an appropriately trained expert (the ECG Core Lab or a cardiac electrophysiologist) verifies that the QTcF interval is >500 msec or that the increase from Baseline is >60 msec from Baseline (Day 1 pre-dose) that is not due to a significant increase in the QRS duration, the study drug will be stopped and causality will be investigated.

10.5 LABORATORY ASSESSMENTS

Clinical laboratory tests (chemistry, hematology, and urinalysis) will be conducted at Screening, Baseline (Day 1), and at subsequent visits as shown in the Schedule of Assessments (Table 1) and below Table 2, 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.

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).

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Table 2 List of Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis (Dipstick)* (onsite)
hemoglobin hematocrit erythrocytes platelets leukocytes with differential (including eosinophils, neutrophils, basophils, lymphocytes and monocytes)	eGFR (screening only) HbA1c (Screening only) creatinine total bilirubin (and fractionation of bilirubin >ULN) albumin blood urea nitrogen total protein alkaline phosphatase creatine phosphokinase aspartate aminotransferase alanine aminotransferase glucose sodium potassium magnesium calcium chloride phosphate bicarbonate TSH (Screening only)	pH specific gravity protein glucose ketones bilirubin occult blood nitrite urobilinogen leukocyte esterase * Reflex microscopy when indicated
FSH and pregnancy testing: A serum FSH test will be conducted for all females at Screening. A urine pregnancy test, and serum pregnancy test (b-HCG) will be conducted on all WOCBP at Screening. Negative pregnancy test results are required for enrollment in the study; a negative urine pregnancy test will be required at Baseline (Day 1) for confirmation. Additional confirmatory pregnancy tests will be administered at all subsequent study visits as shown in Table 1. During the study, a repeat serum pregnancy test will be performed if a subject's urine pregnancy test result is positive.		
Urine drug and alcohol screen: Drug and alcohol abuse testing will be performed according to the assessment schedule. Screening for drugs will include: tetrahydrocannabinol, opiates (including oxycodone), amphetamines, cocaine, and benzodiazepines. **NOTE**: At Baseline, urine drug screening will be performed locally on-site and the following drugs will be tested: amphetamine, barbiturates, buprenorphine, benzodiazepines, cocaine, methadone metabolite, methamphetamine, ecstasy, methadone, opiates, oxycodone, phencyclidine, tricyclic antidepressants, tetrahydrocannabinol.		
Serologic testing for hepatitis B surface antigens, hepatitis C antibodies, and HIV antibody testing will be performed at the Screening visit.		

10.5.1 Viral Screen

Serology tests will be used to screen for hepatitis B, hepatitis C, and HIV at Screening. Subjects positive for hepatitis B, hepatitis C, and/or HIV will be eligible for the study based on Investigator discretion. Positive results will be managed according to local regulatory requirements and the site's SOPs.

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10.5.2 Breath Alcohol Test

Breath alcohol testing will be performed at Screening and Baseline (Day 1). If there is any doubt or concern regarding alcohol use, research site staff may request a breath test for alcohol measures at subsequent visits during the study. Subjects should abstain from alcohol for 24 hours prior to all site visits.

10.6 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 from signing of the informed consent and throughout the study except in the case of screen-failed subjects in which only Serious Adverse Events will be collected. AEs will be elicited using a non-leading question at every visit from Screening through EOS (Day 42).

All measures required for the management of AEs will be recorded in the source documentation.

10.6.1 Adverse Event Definition

An AE is any untoward medical occurrence in a study subject 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 its relationship to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the study drug(s) was given (e.g., during the time from discontinuation of prohibited medications).

Preexisting conditions, diseases, or disorders are not considered AEs unless there is a change in severity, frequency, or quality.

10.6.2 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

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appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an ER 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, severity, or frequency in the risk information set out in the IB or on the label of the drug.

10.6.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (e.g., from chemistry, hematology, or urinalysis) or other abnormal assessments (e.g., from vital signs, ECGs, C-SSRS) judged as clinically significant by the Investigator or designee will be recorded as AEs or SAEs if they meet the definitions provided in Section 10.6.1 and Section 10.6.2. 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.

10.7 EVALUATION OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

10.7.1 Classification of Adverse Event Severity

The Investigator or designee is responsible for making an assessment as to the seriousness, severity, causality, and outcome of an AE. Severity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) accessible at: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.

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- Grade 5 Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.7.2 Classification of Adverse Event Causality

Classification of AE intensity will be performed using the CTCAE v5.0. If there is insufficient information to determine severity, the AE must still be reported.

For each recorded AE or SAE, the Investigator or designee must assess the causality based on the following criteria (Table 3) to determine the relationship between the AE and study drug.

Table 3 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.
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.

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Classification	Definition
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 dyskinesia). • Follows a known pattern of response to the suspected study drug.
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.

10.7.3 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 4.

Table 4 Classification of Adverse Event Outcomes

Classification	Definition
Fatal	The study 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., 30 days after the last dose of study drug), 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.

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10.8 REPORTING PROCEDURES

10.8.1 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 subject will be reported to Sponsor, by the Investigator or designee within **24 hours** of learning of the event.

The contact information for the pharmacovigilance team is as follows:

Email:	relmadapv@primevigilance.com; PVsafety@relmada.com; medical@relmada.com

Relmada 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 Sponsor, where required) must report these events to the appropriate IRB/IEC that approved the protocol (unless otherwise required and documented by the IRB/IEC).

All additional follow-up evaluations for SAEs will be reported to Sponsor within 24 hours of knowledge using the contact information above.

10.8.2 Any Adverse Event

Regardless of seriousness, severity, or presumed relationship to study drug, all AEs will be recorded in the source documentation and assessed using CTCAE v5.0.

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 severity 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.

10.8.3 Pregnancy

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

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

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10.9 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All unresolved AEs will be followed for up to a minimum of 30 days after the subject's final dose of study drug on Day 28 unless the Investigator's judgment dictates otherwise, the event has resolved or stabilized before Day 28, or the subject 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., subject or health care practitioner refuses to provide additional information, the subject 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 subjects that occur after the follow-up period. However, if the Investigator or designee learns of any AE or SAE at any time after a subject has been discharged from the study and the event is considered as reasonably related to the study drug, the Investigator will notify Sponsor.

10.10 OTHER MEASUREMENTS/ASSESSMENTS

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

The C-SSRS Baseline/Screening version will be assessed at Screening, and the C-SSRS Since Last Visit version will be administered at Baseline (Day 1) and at subsequent visits as shown in Table 1.

The C-SSRS is routinely used to quantify the severity of suicidal ideation and behavior. Both the ideation and behavior components 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 6 "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 (Posner 2011).

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The C-SSRS will be administered to study subjects during the course of the study and results will be reviewed throughout the conduct of the study by the Principal Investigator/delegated Investigator at each site, Medical Monitor, and the Independent Data Monitoring Committee (DMC). The DMC will monitor the trend in relative risk of suicide in the active group versus placebo and will make recommendations to the Sponsor on the appropriate course of actions to be taken regarding individual subjects and/or the clinical trial.

Site staff are trained and certified on the administration of the C-SSRS, which includes safety follow-up and action when suicidal ideation is communicated by subject to site staff as per local site policy (this may include a 24-hour emergency contact number for subjects or their family members/friends, calling 911 or the 988 Suicide and Life Crisis Lifeline, or referring the subject to the emergency room). If an upward trend in suicide score for any subject is observed during the course of treatment, the PI or delegated Investigator will assess and take appropriate measures, which may include withdrawing from the study, further evaluation or clinical management, and/or hospitalization as appropriate.

10.11 PHARMACOKINETIC ASSESSMENTS

Standard PK assessments, appropriate for a Phase 3 study, have been included as outlined in Section 11.1.

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11 PHARMACOKINETICS

11.1 PHARMACOKINETIC SAMPLING

Venous blood samples will be collected at Baseline (Day 1) and as outlined below to determine the plasma concentrations of REL-1017 (Table 1):

- On Day 1, PK sample will be obtained at pre-dose.
- On Day 7, PK sample post-dose will be obtained.
- On Day 28, PK sample post-dose will be obtained.

Note: PK sample will be collected within 10 minutes after the ECG at the applicable visit and time point (Day 1, Day 7, and Day 28).

Plasma samples will be collected, processed, and shipped according to the site's SOPs and instructions from the Sponsor or the bioanalytical laboratory.

The plasma samples will be analyzed by the bioanalytical laboratory using validated methods. Plasma samples may also be used for exploratory bioanalytical method development and/or metabolite(s) characterization.

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

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

11.2 PHARMACOGENETIC ANALYSIS

At Baseline (Day 1) of dosing, a blood sample for DNA isolation will be collected from all subjects who sign the Pharmacogenetic Testing Informed Consent for potential pharmacogenetic analysis of genes that may affect the PK or efficacy of REL-1017. This analysis would be restricted to the evaluation of genes that may be involved in the PK of REL-1017 (e.g., drug metabolism, disposition, elimination) or BDNF physiology.

One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each subject into an appropriately labeled ethylene diamine tetra-acetic acid (EDTA) tube. 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 confidentiality. The samples will be retained while research on REL-1017 continues, but not longer than 20 years.

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12 STATISTICAL ANALYSIS

12.1 STATISTICAL AND ANALYTICAL PLANS

This section provides general approaches for statistical analysis. They may be changed due to regulatory agencies feedback. Complete details of the statistical analyses to be performed will be documented in a Statistical Analysis Plan (SAP) that will be finalized prior to unblinding the study data. The SAP will include more details of the analysis populations, summary strategies, and any amendments to the proposed analyses, if necessary. Any changes to the final SAP will be outlined in the final clinical study report.

12.2 ANALYSIS POPULATIONS

Study analysis populations will be defined as follows:

Screened/Enrolled Set: The Screened/Enrolled Set will include all participants who signed an informed consent.

Randomized Set: The Randomized Set will include all randomized participants and will be used for the presentation of participants in all listings.

Full Analysis Set - Total Population (FAS Total): Participants who are randomized and dosed, irrespective of any deviation from the protocol or premature discontinuation. Participants will be analyzed according to randomized treatment.

Per-Protocol Set – Total Population (PPS Total): Valid completers, i.e., participants who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. Per-Protocol membership must be determined prior to database lock and treatment unblinding. This set will be analyzed according to the treatment actually received.

Full Analysis Set - Sub-Population with Baseline MADRS ≥ 35 (FAS MADRS ≥ 35): Participants with severe depression (Baseline MADRS ≥35) who are randomized and dosed, irrespective of any deviation from the protocol or premature discontinuation. Participants will be analyzed according to randomized treatment. .

Per-Protocol Set – Sub-Population with Baseline MADRS ≥ 35 (PPS MADRS ≥ 35): Valid per protocol completers with severe depression, i.e., participants with Baseline MADRS ≥35 who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. Per-Protocol membership must be determined prior to database lock and treatment unblinding. This set will be analyzed according to the treatment actually received.

Safety Population: The Safety Population will be the primary safety analysis population and

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will include all subjects who receive at least one dose of the study drug.

Populations for Exploratory Analyses

Exploratory analyses will be performed in the subset of participants with moderate depression (Baseline MADRS <35). Analyses will be performed within the corresponding intention-to-treat and per-protocol subsets.

12.3 DETERMINATION OF SAMPLE SIZE

Based on the results of studies REL-1017-301, REL-1017-202, and intravenous ketamine (Su 2017), a conservative effect size of 0.33 Cohen's ($d = \Delta / \sigma$) was assumed for the main estimand of the primary efficacy endpoint (change from Baseline to Day 28 in MADRS total score).

The study incorporates an adaptive sample size re-estimation (SSR) design with an initially planned sample size of 340 total patients in the Total Population. A fixed sample size design with this planned sample size will have a power of 90% for an effect size of 0.33 assuming a dropout rate of 5%. The planned interim analysis (taking place when approximately 255, i.e., 75% of initially planned patients in the Total Population, are evaluable or have dropped out) may result in an increase of up to 50% of the planned sample size in the Total Population if the conditional power at the interim is between 10% and 90%. Incorporating the SSR results in the power of the study increasing to 90% for an effect size of 0.33.

In order to ensure the Total Population sample size of 340 subjects (or up to 510 subjects with SSR).

Sample size calculations and design of the interim analysis were performed (via simulation) with the software package East® v6.5 (Cytel Inc.).

Cui-Hung-Wang (CHW) Interim Analysis for Sample Size Re-Estimation (IA-SSR):

An IA-SSR adopting the Cui-Hung-Wang paradigm (Cui 1999) is planned for assessing the conditional power of the analysis of the estimand of the primary efficacy analysis and to reassess the Total Population sample size in accordance with the decision rules specified in the Statistical Analysis Plan (SAP) and Data Monitoring Committee (DMC) Charter.

The IA will be performed by an independent, unblinded, firewalled DMC when approximately, 255 participants, i.e., about 75% of the initially planned participants in the Total Population have completed their 28-day assessments in the study or discontinued early.

Based on the conditional power and sample size re-estimation results, the DMC may recommend the following options at the IA, according to the effective DMC's Charter:

- Continue the study unmodified if conditional power is <10% or >90%

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- Continue the study with sample size increase (up to 50% of initially planned sample size in the Total Population) if conditional power is between 10% and 90%

The IA-SSR will be performed by an independent, unblinded, firewalled statistical team supporting an independent, unblinded, and firewalled DMC in charge of continuous supervision of safety and tolerability, as well as reviewing and interpreting the results of the efficacy IA and making a recommendation based on prespecified decision rules and the effective DMC Charter.

The interim analysis for sample size re-estimation was simulated using East® v6.5 (Cytel Inc.) which may also be used to perform the interim analysis calculations for the sample size re-estimation.

Further details are provided in the SAP and DMC Charter.

Weighted Test-Statistic and Updated Point and Confidence Estimates:

In case of a sample size increase after the IA:

- The data up to the time point of the IA and the data observed thereafter will be combined using the weighted CHW test-statistics in the final analysis
- The resulting updated point estimates and confidence interval estimates will be calculated using the formula presented by Lawrence and Hung (Lawrence 2003).

12.4 MISSING DATA

A mixed-effect model repeated measure (MMRM) approach based on missing at-random assumptions will be used to address missing efficacy data that are not covered by the main estimands of primary efficacy.

To investigate the robustness of the results with regards to missing values in the main estimand of the primary efficacy endpoint, the primary endpoint will be analyzed via multiple imputation methods. To further assess the robustness, tipping point analyses for the primary endpoint will be performed. Details on the handling of missing data and missing values imputation for further estimands and endpoints will be provided in the SAP.

12.5 PRIMARY ENDPOINT ESTIMAND

The primary efficacy endpoint is the absolute change from Baseline on Day 28 of the MADRS total scores in subjects on ADT plus REL-1017 or matching placebo.

The main estimand for the primary efficacy endpoint is defined as follows:

- Total Population: All randomized participants as defined by the study inclusion/exclusion criteria who are randomized and dosed
- Variable: Change from Baseline to Day 28 in the MADRS total scores (Visit 6)
- Intercurrent events (ICE)

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1. Study or treatment discontinuation
    a. Due to lack of efficacy
    b. Due to adverse event related to study medication
    c. Due to adverse event unrelated to study medication
    d. Due to other reasons
2. Treatment with prohibited medication
3. Death
    a. Related to MDD
    b. Unrelated to MDD

- ICE strategy
    - ICE 1a, 1b, 2: A hypothetical strategy will be applied assuming that patients after the ICE follow the course of patients receiving placebo.
    - ICE 1c, 1d, 3b: A hypothetical strategy will be applied assuming that patients after the ICE follow the course of the arm they were randomized to.
    - ICE 3a: A composite strategy will be applied by imputing values after the ICE with the worst possible MADRS score (=60).
- Population-level summary: Difference of the change from Baseline to Day 28 in MADRS scores between REL-1017 treatment group versus placebo estimated by MMRM.

Additional estimands of interest for the primary efficacy analysis will be provided in the SAP.

12.6 EFFICACY ESTIMAND ANALYSIS

Main estimands are defined for the primary efficacy variable:

- Absolute change from Baseline to Day 28 of the MADRS total score in the Total Population

and for the following 4 key secondary efficacy variables in hierarchical rank order of the hypothesis testing procedure:

- MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Day 28, REL-1017 as compared to placebo
- MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Day 28, REL-1017 as compared to placebo
- Change from Baseline (CFB) to Week 1 in the MADRS total score for REL-1017 as compared to placebo
- Change from Baseline to Day 28 in the Clinical Global Impression of Severity (CGI-S) score, REL-1017 as compared to placebo

Confirmatory testing will be performed only for these main estimands, whereby the testing of the key secondary estimands will follow the ordered hierarchical approach.

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The primary statistical analysis of all confirmatory tested estimands will be performed on the Total Population using the mixed-effect model repeated measure (MMRM) analysis. For the main primary estimand, the changes from baseline in MADRS total score will be analyzed using a Mixed Model with Repeated Measures (MMRM). This model will include Treatment, Visit, Treatment-by-Visit interaction and the number of failed prior treatments (1 or more than 1) as fixed effects, Baseline value as a covariate, and Visit as the repeated effect. The estimated means for each arm as well as the estimated treatment effect (REL-1017 – Placebo) along with the 95% confidence intervals for the treatment effect will be presented for each visit. The primary estimand will be estimated as the difference between treatment means (MMRM least-squares) at the Day 28 visit (Visit 6).

As a sensitivity analysis for all estimands, the MMRM analysis will be performed using a range of missing value imputations. For the main estimand of the primary efficacy, a tipping point analysis will be applied to investigate the robustness of the analysis results. Supportive analyses based on the Per-Protocol Population will be provided.

12.6.1 Correlation Between Biomarkers and Therapeutic Efficacy

Assessment of selected biomarkers and their potential relationship to treatment groups and therapeutic efficacy as measured via MADRS total score may be explored using correlation analyses and graphical presentation. Blood samples will be collected to measure genetic and protein markers including, but not limited to, BDNF allelic variants and plasma levels.

12.7 PRESPECIFIED SUBGROUP ANALYSES

Subgroup analyses include antidepressant tachyphylaxis-tolerance; treatment-resistant depression; race, gender (female/male); age (> 50 and ≤ 50); BMI < 30 or ≥ 30; subjects with no prior participation in clinical trials or subjects with prior participation; time since MDD diagnosis above and below ten years. Additional post-hoc analyses may be performed as appropriate. As an exploratory endpoint we will analyze efficacy in the moderate depression patients (Baseline MADRS <35).

12.8 ANALYSIS OF SAFETY ASSESSMENTS

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

12.8.1 Adverse Events

The number and percentage of subjects with TEAEs, SAEs, and AEs leading to study treatment discontinuation, and additionally TEAEs by maximum severity and relationship to study treatment will be summarized by SOC, preferred term, and treatment.

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Summary tables of AEs during and after the treatment with time-adjusted count- and incidence rates will be presented.

AEs involving potential abuse will be categorized in tabular form and will include time of onset and duration of the event, dose of drug taken, severity and outcome. If available, PK values for each individual subject who experienced these AEs will be provided to understand if there is a temporal correlation between drug plasma levels and AEs.

12.8.2 Other Safety Analyses

Descriptive statistics for vital signs, weight, and body temperature will be calculated and presented for each time point by treatment (absolute values and change from Baseline). Summary tables will present actual values and the change from Baseline.

The ECG analysis, including possible evaluation of a potential exposure-response relationship or a population PK/QTc model will be detailed in a separate ECG Analysis Statistical Analysis Plan.

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 Baseline). Descriptive statistics and the number of subjects with laboratory test results below, within, and above normal ranges will be tabulated by visit. Biomarkers and genetic markers will also be summarized by treatment group. Pregnancy test results, drug abuse screen results, breath alcohol data, Hepatitis B, Hepatitis C, HIV assessments, viral screen data, and TSH will be listed only.

The C-SSRS data which is a validated standard assessment instrument of suicidal ideation severity, including suicidal ideation intensity, suicidal behavior, non-suicidal self-injury behavior, and lethality, will be summarized by treatment group and visit. Additionally, a summary of subjects answering Yes to questions of C-SSRS form grouped by any question, combinations of questions, and by each individual question will be provided by treatment group.

12.9 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics and Baseline characteristics (age, sex, race, ethnicity, body weight, height, body temperature, and BMI) will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum for continuous variables and the proportion of subjects for categorical variables) for the Safety population. No formal statistical comparison between the groups will be performed.

The number of subjects in each of the treatment groups will be presented, in addition to the number of subjects who complete each visit. The reasons for all post-randomization study drug discontinuations or study terminations will be tabulated and grouped by treatment group and all

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subjects combined. All deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment will be described.

Medical history and psychiatric history will be coded using MedDRA. Medical history and psychiatric history will be listed, including onset of MDD and onset of current MDE. Physical examination abnormalities will be listed.

Prior and concomitant medications will be coded using WHODrug Dictionary. Prior and concomitant medications will be listed. Concomitant medication will be summarized by treatment. Comorbidities and comedications will be summarized by treatment.

All depression-associated comedication before, during, and after the randomized exposure period will be listed.

12.10 INTERIM ANALYSIS

One interim analysis for sample size re-estimation (IA-SSR) with a potential to increase the sample size based on the conditional power is planned, adopting the Cui-Hung-Wang paradigm (Cui 1999). This IA-SSR of the Total Population will be performed when approximately 255 subjects, about 75% of the initially planned subjects in this group have completed their Day 28 assessments in the study or discontinued early. The IA-SSR will be performed according to the effective SAP, by an independent, unblinded, firewalled statistical team. The conditional power at the IA-SSR will be calculated based on the observed treatment effect in the primary endpoint analysis in the Total Population. Based on the conditional power and sample size re-estimation results, the firewalled statistical team may recommend the following options at the IA:

- Continue the study with unmodified sample size if the conditional power is <10% or >90%.
- Continue the study with increased sample size (up to a maximum sample size in the Total Population of 510 subjects) if the conditional power is between 10% and 90%.

The study cannot be terminated to claim treatment efficacy at the IA-SSR.

Weighted Test-Statistic and Updated Point and Confidence Estimates:

In case of a sample size increase after the IA:

- The data up to the time point of the IA and the data observed thereafter will be combined using the weighted CHW test-statistics in the final analysis
- The resulting updated point estimates and confidence interval estimates will be calculated using the formula presented by Lawrence and Hung (Lawrence 2003).

Further details will be provided in the SAP. The effective SAP will be submitted to the FDA before the IA-SSR is performed.

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12.11 ANALYSIS OF PHARMACOKINETICS

PK analyses will be detailed in the SAP.

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13 STUDY MANAGEMENT

13.1 REGULATORY GUIDELINES

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

13.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The Investigator will ensure that this protocol is reviewed and approved by the IRB/IEC. The IRB/IEC will also review and approve the site's ICF and any other written information provided to the subject, including any advertisements used for subject recruitment. Prior to the enrollment of subjects, the Investigator or designee will forward copies of the IRB/IEC 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/IEC reviews and approves these amended documents. IRB/IEC approval of an amended ICF must be obtained before new subjects consent to take part in the study using the amended form. Copies of the IRB/IEC approval of the amended study documentation and the approved materials will be forwarded to the Sponsor as soon as available.

13.2.1 Informed Consent

At Screening, the Investigator or designee will inform the subject of all aspects pertaining to the individual's participation in the study.

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

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13.3 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/IEC. 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/IEC.

13.4 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.

13.5 SUBJECT IDENTIFIERS

To ensure subject anonymity and to limit disclosure, subjects will be assigned a unique identification number after signing the ICF at their first assessment. This identifier will be cross-referenced in the subject's chart. The identifier will not contain any potentially identifiable information.

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

13.6 PURPOSE OF COLLECTING PERSONAL INFORMATION AND USE

The purpose of collecting personal information from subjects (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.

13.6.1 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/IEC; the FDA, and other regulatory agencies may inspect subject medical records related to the study to check the validity and accuracy of the data gathered in this study. Medical records (with subject initials and/or date of birth only) may be copied. The confidentiality of subject records will be maintained except where the release of information is required by law.

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With the agreement of the subject, the Investigator may inform the subject'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 individual's participation in the study. The subject has the right to request access to and request corrections to his or her medical record.

The Sponsor ensures that any authorized third-party that performs services on behalf of the Sponsor acts in a manner consistent with the confidentiality information outlined in this Protocol and ICF. While every effort will be made to protect the privacy of subject information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect subject privacy.

13.6.2 Release of Subject Information

The results of this study will be reported in such a manner that subjects 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 subject names.

13.6.3 Consent for Collection, Access, Use, and Disclosure of Subject Information

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

13.7 STUDY MONITORING

13.7.1 Quality Control

Relmada 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, Relmada'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 Relmada's SOPs and such considerations as the study objectives and/or endpoints, purpose of the study, study design complexity, and enrollment rate.

13.7.2 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

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site, as required. The extent, nature, and frequency of 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 with 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 subjects 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 subject identification number, 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 subject's completion, discontinuation from treatment, or withdrawal from the study, including the reason, if appropriate.

As study drug is blinded when received at the site, no monitor that visits the site to review the pharmacy records will be unblinded to treatment allocations.

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 13.12.

13.7.3 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 CRFs will be collected from

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the study site at the termination of the study after all monitoring visits and data queries are completed.

13.8 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 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.

13.9 DATA HANDLING

Any data to be recorded directly on the eCRFs will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 13.10.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which data are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system. Access to the database is available to only authorized users via the study's web site, where a user's unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the database. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

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13.10 SOURCE DOCUMENTS

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of study-related monitoring, audits, review by IRB/IECs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

13.11 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/IEC promptly and provide the study subjects 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.

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13.12 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 subjects
- Identification number code list, Screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Copies of eCRFs and of documentation of corrections for all subjects
- Study drug accountability records
- All other source documents (e.g., 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.

13.13 PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

13.13.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IRBs/IECs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

13.13.2 Protocol Deviations

Should a protocol deviation impacting protocol assessments or procedures, subject safety or dosing occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting

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of protocol deviations to the IRB/IEC will be conducted in accordance with mandates of applicable regulatory authorities.

13.14 ETHICAL CONSIDERATIONS

The Investigator will conduct the study in accordance with 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.

IRBs/IECs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

13.15 FINANCING AND INSURANCE

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

13.16 PUBLICATION POLICY/DISCLOSURE OF DATA

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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15 COMEDICATIONS TO BE USED WITH CAUTION

15.1 QT

Based on clinical data from Phase 1 and Phase 2 studies, multiple doses up to 10 days of REL-1017 appeared to be safe. These same studies have shown dose-dependent but not clinically meaningful QTcF prolongation. Concomitant use of drugs that cause QTcF prolongation but are not known to cause torsade de pointes (TdP) is permitted with caution at the discretion of the Investigator and with approval of the Medical Monitor if subjects are not excluded based on QTcF at Screening. Concomitant medications known to cause TdP are excluded. In REL-1017-304, frequent ECG safety monitoring will be conducted as outlined in the Schedule of Assessments (Table 1).

Please refer to the following comprehensive online database for comedications' QT/TdP risk assessment.

QTcF and TdP risk assessment database: https://www.crediblemeds.org/

A QT prolongation and TdP risk assessment is provided interactively in the medication field on the website.

Citation: Woosley RL, Heise CW, Gallo T, Tate J, Woosley D, Romero KA. Website: www.CredibleMeds.org, QTdrugs List. Accessed 17 May 2023. AZCERT, Inc. 1457 E. Desert Garden Dr., Tucson, AZ 85718

15.2 DRUG-DRUG INTERACTIONS

Clinically significant CYP 450 drug-drug interaction data.

In vitro studies using recombinant CYP enzyme testing indicate that REL-1017 is metabolized by multiple enzymes. However, the only clinically relevant inhibition was observed with CYP2D6. Additionally, REL-1017 was found to be a pan-cytochrome inducer in human hepatocytes (Relmada data on file).

Concomitant use of CYP2D6 substrates with a narrow therapeutic window is permitted with caution. Subjects who are using CYP2D6 substrates that may have narrow therapeutic window should be monitored closely as some subjects may experience a greater exposure in the presence of REL-1017 (perpetrator effect).

Concomitant use of strong clinical inducers of P450-mediated metabolism is permitted with caution. Subjects who are using substrates of for P450-mediated metabolism that may have a narrow therapeutic window should be monitored closely as some subjects may experience a lower exposure of the concomitant medication(s) medications in the presence of REL-1017

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(perpetrator effect). REL-1017 is metabolized via multiple metabolic pathways, so concomitant use of REL-1017 with other medications is less likely to cause a clinically relevant effect on REL-1017 concentration (victim effect).

Decisions regarding comedication must be made by the Investigator or prescribing physician in accordance with the guidance provided in comedication management in this protocol, and to the best clinical judgment of the Investigator and Study Medical Monitor.

Websites with comprehensive and up-to-date information include:

FDA: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Indiana University: https://drug-interactions.medicine.iu.edu/MainTable.aspx
All entries in the on-line table are color-coded for the degree of sensitivity to the specific CYPs.

Citation: Food and Drug Administration (FDA): Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Last updated 22 August 2022. Accessed 17 May 2023.

Citation: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. Date of last update unknown. Accessed 17 May 2023.

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APPENDIX A: Prohibited medications, supplements or therapy

Medication, supplement or therapy	**Timeframe for prohibition[a]**
Electroconvulsive therapy (ECT) and/or vagus nerve stimulation (VNS) or any other type of physical brain stimulation	Lifetime and for duration of study
Ketamine and/or esketamine	60 days prior to Baseline and for duration of study
Repetitive transcranial magnetic stimulation (rTMS)	6 months prior to Screening and for duration of study
Opiates	
Long-term opiate use (i.e. >120 days)	6 months prior to Screening
More than 3 doses of opioids	30 days prior to Baseline
Any opioid use	For duration of study
Initiation or termination of phototherapy	30 days prior to Baseline and for duration of study
Initiation or termination of psychotherapy	60 days prior to Screening and for duration of study
Memantine and/or dextromethorphan (in combination with quinidine [Neudexta®] or bupropion [Auvelity®])	30 days prior to Screening and for duration of study
Anxiolytic drugs including Benzodiazepines	PRN use 30 days prior to Baseline and for duration of study
Antipsychotic drugs	PRN use 30 days prior to Baseline and for duration of study
Anticonvulsants/Antiepileptic drugs	PRN use 30 days prior to Baseline and for duration of study
Mood stabilizers	PRN use 30 days prior to Baseline and for duration of study
Stimulants	PRN use 30 days prior to Baseline and for duration of study
St. John's Wort	PRN use 30 days prior to Baseline and for duration of study
Marijuana	For duration of study

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

Use of sleeping aids and hypnotics (as needed or stable dose) may be permitted after discussion with and approval by the Medical Monitor.