CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of REL-1017 for Treatment of Major Depressive Disorder (The RELIANCE-I Study)

Protocol Number: **REL-1017-301**

NCT Number:	NCT04688164
Name of Investigational Product:	REL-1017
Phase of Development:	3
Indication:	Major Depressive Disorder
Sponsor:	Relmada Therapeutics Inc.
Document Date:	December 01 2022

Certain information within this protocol has been redacted to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Names, addresses, and other personally identifiable information
- Proprietary information, such as scales or coding systems, which are considered confidential information.
- Other information as needed to protect the trade secret and/or confidential information of Relmada Therapeutics

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Protocol Number: **REL-1017-301**

[redacted]	[redacted]
Name of Investigational Product:	REL-1017
Phase of Development:	3
Indication:	[redacted]
Sponsor:	Relmada Therapeutics, Inc. 2222 Ponce de Leon Blvd, Floor 3 Coral Gables, FL 33134
	[redacted]
Protocol Version:	[redacted]
Amendment Version:	[redacted]
Protocol Date:	December 01 2022

PROTOCOL APPROVAL SIGNATURES

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Protocol Version [redacted]

Amendment Version [redacted]

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

[redacted]
Relmada Therapeutics

_____
Signature

_____
Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

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

I agree, as an Investigator conducting this study:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

<Name>
<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

1 SYNOPSIS

Title of Study	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of REL-1017 for Treatment of Major Depressive Disorder (The RELIANCE-I Study)
Sponsor	Relmada Therapeutics, Inc. (Relmada)
Investigators/Study Sites	Approximately [redacted] planned in the United States
Phase of Development	3

Objectives	**Endpoints**
Primary	
To evaluate the therapeutic efficacy of REL-1017 in subjects with inadequate response to ongoing antidepressant therapy (ADT)compared to placebo at Day 28 on the Montgomery-Åsberg Depression Rating Scale (MADRS10) total score	Absolute change from Baseline to Day 28 of the MADRS10 total score in REL-1017 compared to placebo in subjects with inadequate response to ongoing ADT
Key Secondary	
Key Secondary Efficacy Objectives To evaluate the therapeutic efficacy of REL-1017 for treatment of Major Depressive Disorder (MDD) in subjects with inadequate response to ongoing ADT compared to placebo in the following measurements: • Clinical Global Impression of Severity (CGI-S) score at Day 28 • MADRS10 score at Day 7 • MADRS10 remission rate (total score ≤10) at Day 28 • MADRS10 response rate (improvement ≥50% compared with total Baseline score) at Day 28	Key Secondary Efficacy Endpoints • Absolute change from Baseline to Day 28 of the CGI-S score • Absolute change from Baseline to Day 7 of the MADRS10 total score • MADRS10 remission rate (total score ≤10) at Day 28 • MADRS10 response rate (improvement ≥50% compared with total Baseline score) at Day 28
[redacted]	• [redacted]

Objectives	Endpoints
[redacted]	[redacted]
Withdrawal	
Withdrawal Objectives • To evaluate signs and symptoms of withdrawal in approximately the first 200 participants who complete the 28-day double-blind treatment period, during 14 days after last dosing.	Withdrawal Endpoints Signs and symptoms of withdrawal in approximately the first 200 completers of the 28-day double-blind treatment period during 14 days after last dosing: • Change from Day 28 until Day 42 in Clinical Opiate Withdrawal Scale (COWS) score • Change from Day 28 until Day 42 in Subjective Opiate Withdrawal Scale (SOWS) score • Change from Day 28 until Day 42 in Physician Withdrawal Checklist (PWC-20) score [redacted]

Objectives	Endpoints
	[redacted]
Safety	
Safety and Tolerability Objectives • To evaluate safety and tolerability of REL-1017 • [redacted]	Safety Endpoints • Treatment-emergent adverse events (TEAEs) [redacted] • Vital signs and weight • Physical examination • Clinical laboratory parameters (chemistry, hematology, and urinalysis) • C-SSRS [redacted]
Pharmacokinetic	
Pharmacokinetic Objectives • To evaluate pharmacokinetics (PK) of REL-1017 and potential metabolites	Pharmacokinetic Endpoints • Estimation of REL-1017 PK profile (maximum observed plasma concentration [C_{max}], trough concentration [C_{trough}], and apparent terminal elimination half-life at steady state [$t_{1/2}$] based on sparse PK sampling

Study Design	This is an outpatient, 2-arm, Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of REL-1017 at 25 mg once daily (QD) for treatment of MDD in subjects with inadequate response to ongoing ADT
Investigational Product/Reference Product	REL-1017 in 25 mg and matching placebo
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

	Participants will be asked to stay on a stable dosing regimen of the current antidepressant therapy (ADT) between Day 1 and Day 28, while exposed to REL-1017 or matching placebo. Dosing with REL-1017 should take place once daily at the same time as the first-line ADT is taken. [redacted]
Study Population and Duration of Participation	Adult participants (aged 18 to 65 years, inclusive) diagnosed with MDD (based on Structured Clinical Interview for DSM-5 [SCID-5] for MDD, matching Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]), who are currently in a major depressive episode (MDE), [redacted] and with a substantiated inadequate response to 1 to 3 courses of a valid course of an approved antidepressant in the current MDE, ie, to an approved dose and duration (minimum 6 weeks) of a marketed ADT treatment course [redacted] The maximum duration of the MDE must not exceed 36 months. [redacted] [redacted] After signing of the informed consent form (ICF), each participant will undergo an up to 30-day Screening period and a 28-day randomized double-blind placebo-controlled period, for a total of approximately 58 days of study participation. For approximately the first 200 completers of the 28-day dosing with study drug, a 14-day safety follow-up period will be added, extending the time of study participation to approximately 72 days. All participants who complete the 28-day treatment period will be offered the opportunity to enroll in a 1 year open-label study under its separate study protocol.
Planned Sample Size	The REL-1017-301 study is designed to achieve 90% power, with an overall two-tailed α-level of 0.05. [redacted]

	[redacted]
Inclusion Criteria	To enroll in the clinical study, participants must meet the following inclusion criteria: 1. Must be able to read, speak, and understand English or Spanish and must provide written informed consent prior to the initiation of any protocol-specific procedures. 2. Male or female participant, aged 18 to 65 years, inclusive. 3. [redacted] 4. Participant is willing and able to commit to meet all study requirements, adhere to both approved ADT and study drug regimen, and complete all assessments and all scheduled visits, per Investigator judgment. 5. Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception from Screening and for at least 2 months after the last study drug administration. For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include vasectomy or male condom for participants, plus an additional method of contraception for their female partners. Highly effective methods of contraception are those which 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 (eg, oral, patch, or injectable) • A double-barrier protection method (eg, condom, sponge, or vaginal diaphragm with spermicide cream, foam, or gel) • Abstinence from heterosexual intercourse is accepted if this is the participant's usual lifestyle and must be continued until at least 2 months after the last dose of study drug. Women who are not of childbearing potential must be congenitally or surgically sterile (hysterectomy and/or bilateral

	oophorectomy/salpingo-oophorectomy, as determined by the participant'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 follicle-stimulating hormone (FSH) level ≥40 mIU/mL as confirmation. 6. Diagnosed with MDD as defined by the Diagnostic and Statistical Manual, Fifth Edition (DSM-5), and confirmed by the SCID-5 MDD. 7. Hamilton Depression Rating Scale-17 (HAMD17) score [redacted] at Screening and independently confirmed by SAFER assessment. [redacted] 9. Diagnosed with a current MDE lasting from 8 weeks to 36 months as defined by the DSM-5 and confirmed by the SCID-5 MDD, as well as independent confirmation of HAMD17 score, SAFER/ATRQ, and contextual appropriateness to be a participant in this study, after evaluation by an MGH-CTNI clinician. 10. Treated for at least 6 weeks prior to Screening and stabilized for at least 6 weeks prior to Baseline on an approved dosing regimen of ADT (eg, selective serotonin reuptake inhibitor [SSRI], serotonin and norepinephrine reuptake inhibitor [SNRI], bupropion (a norepinephrine–dopamine reuptake inhibitor [NDRI] and nicotinic receptor antagonist) 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. Maximal doses and recommended doses for each ADT are at the discretion of the Investigator and Medical Monitor, except for citalopram and escitalopram [redacted]
Exclusion Criteria	1. History or presence of clinically significant abnormality as assessed by physical examination, medical history, 12-lead ECG, vital signs, or laboratory values, which in the opinion of the Investigator would jeopardize the safety of the participant or the validity of the study

	results, including established QT prolongation, long QT syndrome, torsades de pointes, bradyarrhythmia, ventricular tachycardia, uncompensated heart failure (greater than New York Heart Association [NYHA] Class 1 congestive heart failure [CHF]), uncontrolled hypokalemia, or uncontrolled hypomagnesemia. 2. More than class 2 angina pectoris or a myocardial infarction (MI) or acute coronary syndrome within the past 3 months. 3. Any medical, psychiatric condition, or social context that, in the opinion of the investigator, is likely to unfavorably alter the risk-benefit of subject participation, to interfere with protocol compliance, or to confound safety or efficacy assessments. 4. Have any significant illness, of any nature, including possible Coronavirus-SARS-2 related fever and symptoms, requiring hospitalization, emergency treatment, or isolation (quarantine) within 4 weeks prior to Screening or during the Screening period, and as determined by the Investigator. 5. History or first degree relative with history of unexplained sudden death or long QT syndrome. 6. Triplicate 12-lead ECG with average QTcF (QT interval with Fridericia's correction) ≥450 msec and/or a QRS interval ≥120 msec at Screening. 7. Current or recent uncontrolled orthostasis or orthostatic hypotension necessitating treatment. 8. Poorly controlled diabetes as defined by a glycosylated hemoglobin (HbA1c) >7.5%, despite standard care. 9. Any use of long-term prescribed opioids (ie, >120 days in a 6-month period) within 6 months prior to Screening or any recreational use of opioids. [redacted] 12. Use of any anxiolytic, antipsychotic, anticonvulsant/antiepileptic, mood stabilizer, or stimulant medication(s) within 30 days prior to Baseline. Note: Participant should be medically stable, the medication was appropriately tapered and participant has no withdrawal symptoms. 13. Use of St. John's Wort, [Hypericum Perforatum]) within 30 days prior to Baseline. 14. Participated in a ketamine, esketamine, dextromethorphan or any other NMDAR-antagonist study, or who received esketamine at any time. 15. Received ketamine, memantine, and/or dextromethorphan treatment within 30 days prior to Screening. 16. History of allergy or hypersensitivity to methadone or related drugs. 17. Receiving new-onset psychotherapy (individual, group, marriage, or family therapy) within 2 months prior to Screening, or planning to start psychotherapy at any time during participation in the study. 18. Any lifetime experience of electroconvulsive therapy (ECT) and/or vagus nerve stimulation (VNS), or any other type of physical brain stimulation. 19. Received repetitive transcranial magnetic stimulation (rTMS) less than 6-months prior to the Screening visit.

	20. Any current and primary psychiatric disorder (ie, a condition that is the primary focus of distress and/or treatment other than MDD), as defined by the DSM-5 and confirmed by psychiatric history and/or examination by the Investigator. 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. 21. Participants who, in the Investigator's judgment, are at significant risk for suicide. A participant with a C-SSRS ideation score of 4 or 5 within the last 6 months or any suicide attempt within the past year of either Screening or Baseline must be excluded. 22. Any lifetime history of bipolar I or II disorder, psychosis and/or mania as defined by the DSM-5 and confirmed by psychiatric history and/or examination by the Investigator. 23. Comorbid moderate to heavy alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. [redacted] 24. A positive result on the urine drug/alcohol screen within 30 days prior to Baseline (Day 1). At Investigator discretion, a retest is permitted. 25. [redacted]
[redacted]	[redacted]

	[redacted]
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 (FAS):** Participants who are randomized and dosed, irrespective of any deviation from the protocol or premature discontinuation. Participants will be analyzed according to randomized treatment. The FAS will be used as primary population for analyses of efficacy estimands and endpoints. **Per-Protocol Set:** Valid completer, ie, participants who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. This set will be analyzed according to the treatment actually received. **Safety Set:** All randomized participants who received any dose of study drug. The treatment group assignment in this population will be according to the treatment received. This population will be used for the analysis of safety. **Pharmacokinetic (PK) Set:** All participants who received at least one dose of REL-1017 and have at least one PK concentration measured.
