Protocol Title: A Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety of REL-1017 as a Treatment of Major Depressive Disorder (RELIANCE-OLS)

Protocol Number: **REL-1017-310**

NCT Number	NCT04855760
Name of Investigational Product:	REL-1017
Phase of Development:	3
Indication:	Major Depressive Disorder
Sponsor:	Relmada Therapeutics Inc.
Protocol Date:	March 04 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

CLINICAL STUDY PROTOCOL

A Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety of REL-1017 as a Treatment of Major Depressive Disorder (RELIANCE-OLS)

Protocol Number: **REL-1017-310**

[redacted]

Name of Investigational Product:	[redacted] REL-1017
Phase of Development:	3
Indication:	Major Depressive Disorder
Sponsor:	[redacted] [redacted] Relmada Therapeutics, Inc. 2222 Ponce de Leon Blvd, Floor 3 Coral Gables, FL 33134 [redacted] [redacted]
Protocol Version:	4.0
Amendment Version:	3.0
Protocol Date:	04-Mar-2022

-CONFIDENTIAL-

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety of REL-1017 as a Treatment of Major Depressive Disorder (RELIANCE-OLS)

Protocol Number: REL-1017-310

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, Inc.

_____

Signature

_____

Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety of REL-1017 as a Treatment of Major Depressive Disorder (RELIANCE-OLS)

Protocol Number: REL-1017-310

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 participants 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/her financial ties with the Sponsor. Relmada Therapeutics, Inc., will obtain and disclose any relevant information in this regard solely for complying with regulatory requirements.

Hence, I:

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

<Name>
<Title>

_____
Investigator Signature

_____
Date (DD-Mmm-YYYY)

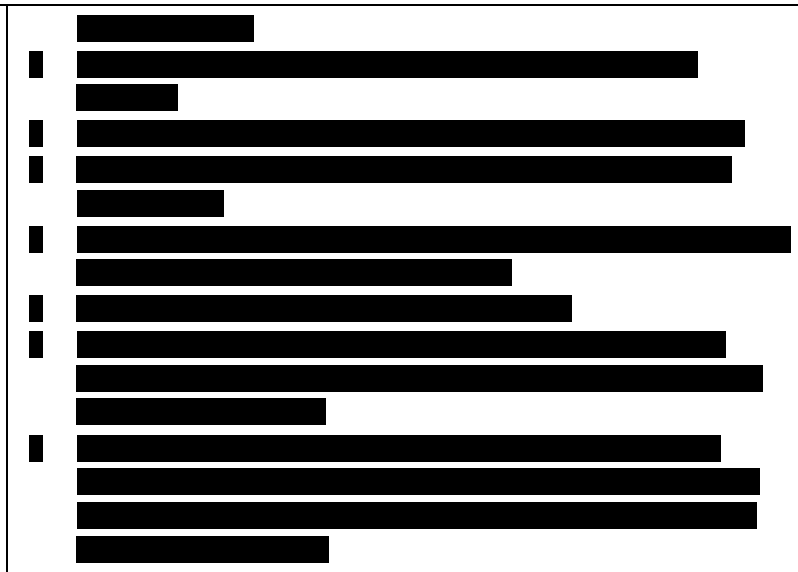
_____
Institution

1 SYNOPSIS

Title of Study	A Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety of REL-1017 as a Treatment of Major Depressive Disorder (RELIANCE-OLS)
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 long-term safety and tolerability of REL-1017 as adjunctive treatment to an approved antidepressant therapy (ADT) and as a monotherapy.	• Treatment-emergent adverse events (TEAEs)
Secondary	
To evaluate the long-term safety of REL-1017 as adjunctive treatment to an approved ADT and as a monotherapy.	• Evaluate the effects on the electrocardiogram (ECG), including heart rate, pulse rate (PR), QRS, and QT interval with Fridericia's correction (QTcF) intervals • Vital signs and weight • Physical examination • Clinical laboratory parameters (chemistry, hematology, and urinalysis) • Columbia-Suicide Severity Rating Scale (C-SSRS) • Clinician-Administered Dissociative States Scale (CADSS) • [redacted]
Exploratory	

To evaluate the impact and long-term durability of REL-1017 as an adjunctive treatment to an approved ADT and as a monotherapy over a 1-year period on depression, [redacted]	• The Montgomery-Åsberg Depression scale (MADRS10)
	  ○ Absolute value and change from Baseline of MADRS10 total score
	  ○ Remission rate (total score ≤10)
	  ○ Response rate (improvement ≥50% compared with total Baseline score)
	  ○ Time course of changes from Baseline
	• Clinical Global Impression of Severity (CGI-S) score
	• Hamilton Anxiety Rating Scale (HAM-A) total score
	• Symptoms of Depression Questionnaire (SDQ) total score
	• Sheehan Disability Scale (SDS) domain score
	• Clinical Global Impression of Improvement (CGI-I) score
	• [redacted]

	
Pharmacokinetics (*De novo* participants only)	
To evaluate pharmacokinetics (PK) of REL-1017 and potential metabolites	• REL-1017 concentration at 2.5 hours after first dose and at subsequent timepoints

Study Design	This is a 1-year open-label study (OLS) following the randomized double-blind placebo-controlled Phase 3 studies. *De novo* participants (adjunctive ADT or monotherapy) who have not been part of prior Phase 3 studies with REL-1017 may also be enrolled. Participants in the OLS from REL-1017-301 or REL-1017-302 will continue to take their prescribed ADT plus REL-1017. Participants from REL-1017-303 will continue to refrain from use of concomitant ADT. All participants who complete the REL-1017 Phase 3 studies without any safety issues that would preclude participation in this OLS (according to the Investigator) are eligible.
Investigational Product/Reference Product	REL-1017 25 mg tablets
Study Drug, Dose Schedule, and Mode of Administration	REL-1017 25 mg tablets once daily (QD) for oral administration (PO) for up to 1 year. Participants enrolling from REL-1017-301 or REL-1017-302 will be asked to stay on a stable dosing regimen of their current ADT for the duration of their participation in the study while exposed to REL-1017. Participants enrolling from REL-1017-303 will be asked to continue refraining from use of concomitant ADT. Dosing of REL-1017 will take place once daily, preferably at the same time as the first-line ADT is taken for adjunct therapy participants. The following loading dose schedule will be used for *de novo* participants only:

	Day 1 – loading dose: • Three REL-1017 25 mg tablets (75 mg total) administered at the clinical study site Day 2 to Day 365 – maintenance dose: • One REL-1017 25 mg tablet QD
Study Population and Duration of Participation	All participants who complete the REL-1017 Phase 3 studies without any safety issues that would preclude participation in this OLS (according to the Investigator) are eligible. To achieve an adequate number of participants who will complete 6 months and 12 months of the study, respectively, REL-1017-310 may enroll de novo participants who have not been part of prior Phase 3 studies with REL-1017. *De novo* participants will undergo Screening assessments for eligibility to participate in this study. All participants will be enrolled for up to 13 months consisting of 12 months of treatment and a 1-month post-treatment follow-up visit.
Planned Sample Size	To evaluate overall safety of REL-1017, the sample size for the OLS aims to achieve at least 300 participants completing 6 months and at least 100 participants completing 12 months of the study. [redacted]
Inclusion Criteria **(*de novo* participants only)**	REL-1017-310 *de novo* participants will undergo Screening assessments and must meet all the following inclusion criteria to participate in this study. 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, age 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 (as applicable) 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: o Intrauterine device (IUD) o Bilateral tubal ligation, bilateral salpingectomy, or bilateral tubal occlusive procedure o 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 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 Structured Clinical Interview for DSM-5 Disorders (SCID-5). 7. Hamilton Depression Rating Scale-17 (HAMD17) [redacted] at Screening and independently confirmed by **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological] (SAFER) assessment. 8. At Baseline, before definitive admission and randomization of the participant, the MADRS10 scale will be administered and the participant must show a MADRS10 [redacted] 9. Diagnosed with a current major depressive episode (MDE) lasting from 8 weeks to 36 months as defined by the DSM-5 and confirmed by the SCID-5 for MDD, as well as independent confirmation of the HAMD17 score, [redacted] For *de novo* participants enrolling for REL-1017 adjunctive therapy: 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 medications (e.g., 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 during the Screening period and for the entire study duration, [redacted] Note: Discontinuation of any of the listed ADT must occur at

	least 6 weeks prior to Baseline. [redacted] Note: An electronic dosing diary (eDiary) will be used beginning at Screening to document the stability of background antidepressant(s); only participants reporting a minimum of 80% adherence during Screening will be randomized. 11. [redacted] For *de novo* participants enrolling for REL-1017 monotherapy: 12. [redacted]
Exclusion Criteria **(*de novo* participants only)**	REL-1017-310 *de novo* participants will undergo Screening assessments. Individuals meeting any of the following criteria are ineligible to participate in this study. 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, Medical Monitor, or Sponsor designee 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, Medical Monitor, or Sponsor designee 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related fever or other 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 ≥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. [redacted] 10. [redacted] 12. [redacted] 13. [redacted] 15. History of allergy or hypersensitivity to methadone or related drugs. 16. [redacted] 17. 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. 18. 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. 19. Comorbid moderate to heavy alcohol or substance use disorder, as defined by DSM-5, at Screening or within the 12 months prior to Screening. Heavy drinking is defined as an average of 3 or more drinks per day, in the last month. 20. A positive result on the urine drug/alcohol screen within 30 days prior to Baseline (Day 1). At Investigator discretion, in consultation with the Medical Monitor, a retest is permitted. 21. [redacted]

	[redacted] 22. Evidence of clinically significant hepatic or 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), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × upper limit of normal (ULN), bilirubin >1.5 × ULN (participants with history of Gilbert's syndrome diagnosis may be included if approved by the Medical Monitor), or endocrine laboratory values (including clinically significant thyroid parameters, i.e., thyroid stimulating hormone [TSH] < 0.9 x lower limit of normal [LLN] or > 1.25 x ULN). 23. Diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within 4 years prior to Screening. 24. Any planned elective surgery requiring general anesthesia. 25. [redacted] 27. Females who are currently lactating. For *de novo* participants enrolling for REL-1017 monotherapy: 28. Use of any antidepressant medication within 30 days prior to Screening.
Study Procedures	All participants completing a REL-1017 Phase 3 study will be offered the opportunity to enroll in the REL-1017-310 OLS. All continuing participants will be required to sign an informed consent form (ICF) before participating in the REL-1017-310 study. *De novo* participants will sign an informed consent, and enter a formal Screening period, with a Participant identification number assigned, and an outpatient Screening Visit conducted during which the participant will undergo an interview and medical assessments to determine eligibility for study participation. Participants who meet all Screening entry criteria will have the Baseline (Day 1) visit scheduled. [redacted].

Statistical Data Analysis	**Study analysis populations,** defined as follows: **Screened/Enrolled Set:** The Screened/Enrolled Set will include all participants who signed an informed consent. **Full Analysis Set (FAS)**: All participants who received at least 1 dose of study drug in the OLS and had at least 1 post-Baseline efficacy assessment, irrespective of any deviation from the protocol or premature discontinuation. The FAS will be used for analysis of efficacy. **Safety Set**: All participants who received at least 1 dose of study drug in the OLS. This population will be used for the analysis of safety. **Safety data analysis** Descriptive statistics of the safety and efficacy of the participants in the OLS will be presented based on the prior double-blind treatment groups: Double-blind placebo, double-blind REL-1017, *de novo*. In general, the Baseline for each assessment will be the last value collected prior to the first open-label dose. Summaries of efficacy results will be presented for the FAS, and summaries of safety results will be presented for the Safety Set; all will be summarized by the treatment groups "REL-1017 in double-blind study," "placebo in double-blind study," "*de novo*," "pooled placebo and *de novo*," and "overall". Continuous safety and tolerability assessments (e.g., vital signs, weight, BMI, body temperature, ECG parameters, and laboratory parameters) will be summarized using descriptive statistics for values for each visit, and additionally for change from Baseline of OLS. The time course of absolute values and change from Baseline will be presented in descriptive statistics and figures. Categorical safety data (e.g., categorical laboratory parameters, ECG overall evaluation, QT/QTcF categories) and central tendency effects will be presented by number and percentage of participants in the respective category for each visit. The number and percentage of participants with TEAEs, serious adverse events (SAEs), AEs associated with discontinuation, and TEAEs by severity and relationship to study treatment will be summarized by system

	organ class and preferred term, using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All summaries of TEAEs will be provided for the TEAEs in OLS (i.e., AEs that started or worsened in severity after first dose in the OLS). Comorbidities and comedications will be summarized in count and frequency tables**.** **Exploratory Efficacy variables** Continuous efficacy variables will be reported using descriptive statistics for values for each visit, and additionally for change from Baseline of OLS. The time course of absolute values and change from Baseline will be presented in figures. Categorical efficacy data will be presented by number and percentage of participants in the respective category for each visit.