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Supplementary Material

Article Title: Efficacy and Safety of Esmethadone (REL-1017) in Patients with Major Depressive Disorder and Inadequate Response to Standard Antidepressants: A Phase 3 Randomized Controlled Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Material

Appendix 1
Screening and Rater Review Process

A SAFER interview will be conducted off-site during the screening period and eligibility will be assessed based on the inclusion/exclusion criteria by the investigator and verified by an MGH-CTNI-certified clinician who will interview the participants using the HAMD17, SAFER/ATRQ, and eligibility criteria per the study protocol.
The SAFER interview assesses depression in a real-world setting and confirms that the participant's illness is a specific state and excludes participants with any symptoms that are nonspecific or not readily assessable.

The ATRQ is administered at screening by a certified rater, the MGH-CTNI-certified clinician as part of the SAFER Interview. 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).

Appendix 2
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. Body mass index (BMI) between 18.0 and 30.0 kg/m^2, at screening.
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 ≥19 at screening and independently confirmed by 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 score of ≥24.
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, SSRI, SNRI, or bupropion (a 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.

    Note: Discontinuation of any of the listed ADT must occur at least 6 weeks prior to baseline.

    Note: Participants taking trazodone and/or bupropion as secondary ADT are permitted.

    Note: A dosing 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. An appropriate and valid participant in the study, after independent MGH-CTNI SAFER/ATRQ assessment of the participant'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 (Criteria: **S**tate versus trait; **A**ssessability; **F**ace validity; **E**cological validity; and **R**ule of three Ps [pervasive, persistent, and pathological]).

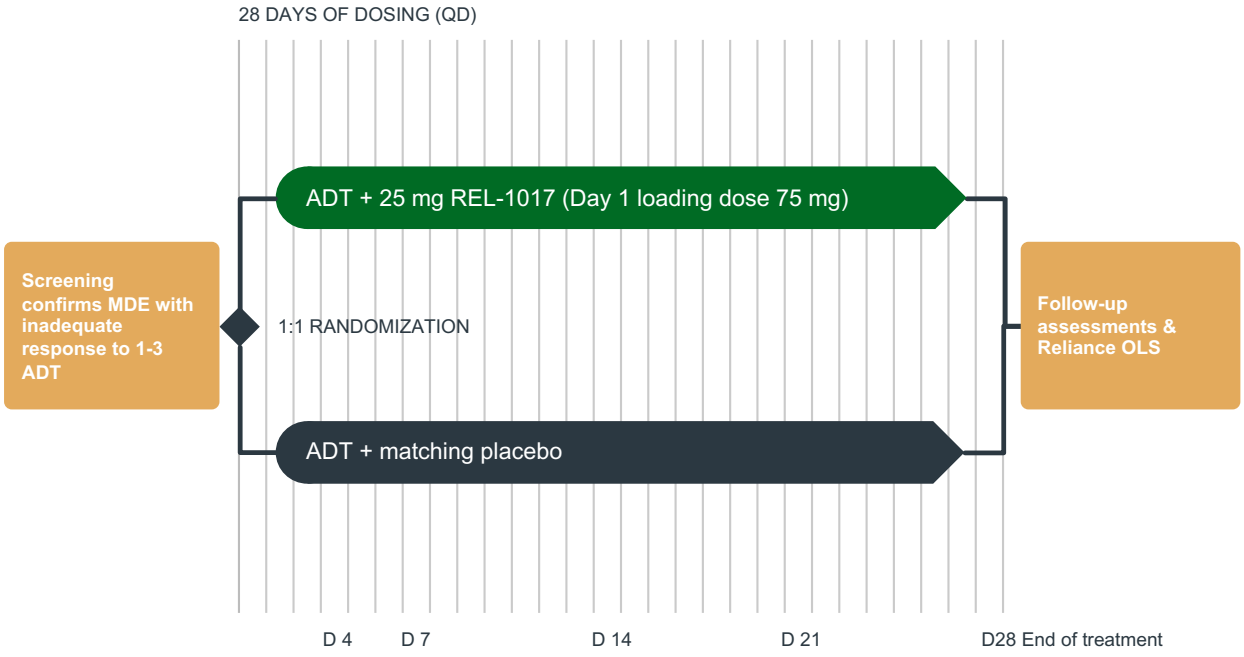
Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline 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 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 NYHA Class 1 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 SARS-COV-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 ≥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.
10. More than 3 doses of opioids within 30 days prior to baseline.
11. Any use of benzodiazepines within 30 days prior to baseline and/or more than 3 doses of antipsychotics, when used for non-psychiatric indications, within 30 days prior to Bbseline.
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. Heavy drinking is defined as an average of 3 or more drinks per day, in the last month.
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. HAMD17 score <19 at Baseline or an increase in absolute value of >40% or a decrease in absolute value of >20% on the HAMD17 score between screening and baseline as conducted by the certified site rater.
26. Evidence of clinically significant hepatic or renal impairment, including an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (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 medical monitor), or clinically significant abnormal endocrine laboratory values (including clinically significant abnormal thyroid parameters, ie, thyroid stimulating hormone [TSH] < 0.9 x LLN or > 1.25 x ULN.
27. Diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and in situ melanoma) within 4 years prior to screening.
28. Any planned elective surgery requiring general anesthesia.
29. Participant has had gastric bypass surgery or has had any procedures or disorders that interfere with gastrointestinal transit or absorption.
30. Participated in a clinical study with an investigational medication in the past 6 months, or participated in more than 2 clinical studies with investigational medications in the past 2 years.
31. Females who are currently lactating.

Supplementary Figure 1. Study Design



Supplementary Table 1. Time from Discontinuation of Prohibited Medications, Supplements, and Other Substances or Therapies

Prohibited Medications, Supplements, and Other Substances or Therapies	Minimum Time from Discontinuation to Screening[a]
Ketamine, esketamine, dextromethorphan, or any other NMDAR-antagonist administered as part of a clinical study	Lifetime
Esketamine	Lifetime
Electroconvulsive therapy (ECT) and/or vagus nerve stimulation (VNS) or any other type of physical brain stimulation	Lifetime
Repetitive transcranial magnetic stimulation (rTMS)	180 days
Long-term opiate use (i.e. >120 days)	180 days
New-onset psychotherapy	60 days
Ketamine, memantine and/or dextromethorphan	30 days

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

Prohibited Medications, Supplements, and Other Substances or Therapies	Minimum Time from Discontinuation to Baseline[a]
Anxiolytic drugs	30 days
Antipsychotic drugs	30 days
Anticonvulsants/Antiepileptic drugs	30 days
Mood stabilizers (including lithium and valproic acid)	30 days
Stimulants (including amphetamines)	30 days
More than 3 doses of opioids	30 days
Any doses of benzodiazepines	30 days
St. John's Wort	30 days

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

Supplementary Table 2. MMRM Analysis for Intent-To-Treat, Per Protocol, and Post-Hoc Severe Depression Population for Mean Change from Baseline to Day 28.

	Placebo	Esmethadone	LS Mean Difference (esmethadone – placebo)
Intent to Treat	N=114	N=113	
Baseline, mean (SD)	35.3 (4.3)	34.7 (5.2)	
LS Mean (SE)	-13.37 (1.09)	-15.10 (1.05)	-1.74 (1.52)
95% CI	-15.52, -11.22	-17.18, -13.02	-4.74, 1.26
p-value			0.255
Effect size			-0.16
Per Protocol	N=97	N=103	
Baseline, mean (SD)	35.1 (4.4)	34.6 (5.3)	
LS Mean (SE)	-12.69 (1.10)	-15.63(1.06)	-2.94 (1.53)
95% CI	-14.87, -10.51	-17.73, -13.54	-5.96, 0.08
p-value			0.057
Effect size			-0.28
Severe Depression (MADRS 10 ≥35)			
Intent to Treat	N=61	N=51	
Baseline, mean (SD)	38.3 (2.9)	39.4 (3.3)	
LS Mean (SE)	-11.83 (1.58)	-17.87 (1.70)	-6.04 (2.33)
95% CI	-14.97, 8.70	-21.24, 14.50	-10.65, -1.42
p-value			0.011
Effect size			-0.51
Per Protocol	N=53	N=45	
Baseline, mean (SD)	38.2 (3.0)	39.4 (3.4)	
LS Mean (SE)	-11.56 (1.58)	-18.81 (1.69)	-7.25 (2.32)
95% CI	-14.69, -8.43	-22.17, -15.45	-11.87, -2.64
p-value			0.002
Effect size			-0.64