Rapid and Sustained Antidepressant Effects of REL-1017 (esmethadone) as an Adjunctive Treatment for Major Depressive Disorder: A Phase 2 Trial

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ABSTRACT

Background: N-methyl-D-aspartate receptor (NMDAR) channel blockers are a new drug class with potentially rapid and effective antidepressant activity. REL-1017 (esmethadone HCl) blocks the NMDAR with no meaningful opioid or psychotomimetic effects. This trial investigated the effects of REL-1017 as adjunctive treatment in patients with major depressive disorder (MDD) who failed 1 to 3 courses of standard antidepressant treatments (SAT) in the current major depressive episode (MDE).

Methods: This Phase 2, multicenter, randomized, double-blind, placebo-controlled 3-arm trial assessed the safety, tolerability, pharmacokinetics (PK) and efficacy of oral REL-1017 once daily as adjunctive therapy in patients with MDD. Patients were 18-65 year old adults with inadequate responses to 1-3 SATs in the current MDE. Patients were randomized in a 1:1:1 ratio to either placebo (n=22), or 25 mg REL-1017 (n=19) or 50 mg QD REL-1017 50 mg (n=21) orally QD. Patients in the REL-1017 groups received a single oral loading dose of 75 mg (25 mg group) or 100 mg (50 mg group) on Day 1. On Days 2-7, inpatient treatment continued with placebo, 25 mg or 50 mg and patients were then discharged on Day 9 with follow up visits on Days 14 and 21. Efficacy was assessed with the Montgomery-Asberg Depression Rating Scale (MADRS), Symptoms of Depression Questionnaire (SDQ) and Clinical Global Impression (CGI) scales at Days 2, 4, 7, and 14. Safety scales included the 4-Item Positive Symptom Rating Scale (4-PSRS) for psychotomimetic symptoms, Clinician-Administered Dissociative States Scale (CADSS) for dissociative symptoms, Clinical Opiate Withdrawal Scale (COWS) for withdrawal signs and symptoms and Columbia Suicide Severity Rating Scale (C-SSRS) for suicidality. The PK samples were collected on Days 1-9 and 14.

Results: All 62 randomized patients [$\bar{x}$ age = 49.2 years, $\bar{x}$ baseline Hamilton Depression Rating Scale-17 (HAM-D-17) score = 25.3, $\bar{x}$ baseline MADRS score = 34.0] were evaluated. Statistically significant improvements with REL 1017 25 and 50 mg vs. placebo were observed on the MADRS, CGI-S, CGI-I, and SDQ. Statistically significant improvement on the MADRS appeared on Day 4 in both REL-1017 dose groups and was sustained through Day 7 (last dose) and Day 14 (7 days after the last dose) with $p \leq 0.0308$ and effect sizes from 0.7 to 1.0. Similar findings emerged from the CGI scales. Adverse event (AE) profiles were similar with placebo and REL-1017 groups. AEs were transient and mild or moderate, and no serious AEs occurred. There were no dissociative or psychotomimetic effects, opioid effects and no signs pr symptoms of withdrawal upon abrupt discontinuation.

Conclusion: Oral REL-1017 showed robust, rapid, and sustained antidepressant effects and favorable safety, tolerability, and PK profiles in patients with MDD. This study confirms the favorable safety, tolerability, and PK profile seen with REL-1017 in Phase 1 studies. REL-1017 has the potential to be best in class among effective, rapid-onset, safe, and well-tolerated NMDAR channel blocker antidepressants.

INTRODUCTION

- N-methyl-D-aspartate receptor (NMDAR) channel blockers such as ketamine and esketamine are emerging as a new drug class with potentially rapid and effective antidepressant activity in patients with MDD and inadequate response to SATs.[1]
- REL-1017 (esmethadone) is a low affinity, low potency NMDAR channel blocker. It binds to the MK-801 site of the NMDAR with low micromolar IC_{50} value.[2]
- Esmethadone has antidepressant-like activity in all tested models of depression via mToR and BDNF dependent pathways. [3, 4]
- Esmethadone has 20-fold lower affinity for mu opioid receptors (MORs) compared to other NMDARs and does not contribute in a clinically meaningful way to the opioid effects of racemic methadone.[5, 6]
- Esmethadone has favorable tolerability, safety, and pharmacokinetic profiles and does not produce meaningful opioid or psychotomimetic effects.[7]

OBJECTIVES

- To assess the safety, tolerability, and efficacy of oral REL-1017 once daily as adjunctive therapy in patients with MDD

METHODS

Patient Selection
- Adults ages 18-65 year with MDD; Hamilton Depression Rating Scale (HAMD-17) score ≥19
- Current depressive episode lasting at least 8 weeks
- Inadequate response to antidepressants in the current episode

Study Design
- Double-blind, placebo-controlled 3-arm 7-day inpatient clinical trial in which patients were randomized in a 1:1:1 ratio to placebo or 25 or 50 mg REL-1017 orally once daily for 7 days and followed up to day 21 (**Figure 1**)
- REL-1017 treatment groups received an oral loading dose of 75 mg (25 mg group) or 100 mg (50 mg group) on Day 1
- On Days 2-7, REL-1017 treatment groups received 25 or 50 mg
- Efficacy assessed using multiple scales on days 2, 4, 7, and 14

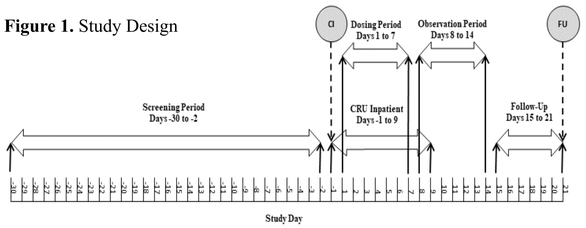
Efficacy Assessments
- Montgomery-Asberg Depression Rating Scale (MADRS) - 10 questions on a scale from 0-60
- Symptoms of Depression Questionnaire (SDQ) – 44 questions
- Clinical Global Impression – Improvement (CGI-I) and Severity (CGI-S) scales – scored from 1 to 7

METHODS

Safety Assessments
- 4-Item Positive Symptom Rating Scale (4-PSRS) for psychotomimetic symptoms
- Clinician-Administered Dissociative States Scale (CADSS) for dissociative symptoms
- Clinical Opiate Withdrawal Scale (COWS) for withdrawal signs and symptoms
- Columbia Suicide Severity Rating Scale (C-SSRS) for suicidality

Data Analysis
- Assessments were least squares (LS) mean standard error (SE) change from baseline to Days 7 and 14 for the intent-to-treat (ITT) population
- Data was analyzed with mixed model for repeated measures

Figure 1. Study Design



RESULTS

Table 1. Baseline characteristics of randomized patients per group

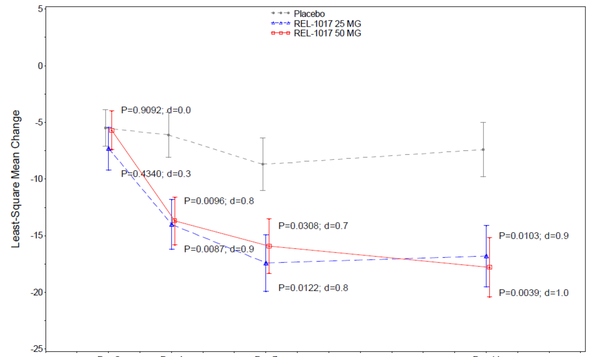
Characteristics	Placebo (N=22)	REL-1017 25 mg (N=19)	REL-1017 50 mg (N=21)	All Patients (N=62)
Age, years [a]	49.7 ± 11.1	49.4 ± 12.4	48.6 ± 10.9	49.2 ± 11.3
Male, n (%)	11 (50.0%)	11 (57.9%)	12 (57.1%)	34 (54.8%)
Not Hispanic/Latino, n (%)	21 (95.5%)	18 (94.7%)	21 (100%)	60 (96.8%)
Race, n (%)				
Asian	0	0	1 (4.8%)	1 (1.6%)
Black or African American	13 (59.1%)	13 (68.4%)	13 (61.9%)	39 (62.9%)
Caucasian	9 (40.9%)	6 (31.6%)	7 (33.3%)	22 (35.5%)
Body Mass Index, kg/m^2 [a]	29.0 ± 4.3	27.7 ± 3.3	27.7 ± 5.0	28.2 ± 4.3
HAM-D-17 Score [a]	25.6 ± 3.5	25.1 ± 3.5	25.0 ± 3.8	25.3 ± 3.6

[a] **mean ± standard deviation**

Efficacy Results
- Significant improvement in the MADRS total score was observed with 25 and 50 mg REL-1017 vs. placebo at Day 4. The improvement was sustained at Days 7 and 14 (**Figure 2**)
- Significant improvement in the SDQ score was observed with 25 and 50 mg REL-1017 vs. placebo at Day 14 (**Figure 3**)
- Significant improvement in the CGI-S score was observed with 25 and 50 mg REL-1017 vs. placebo at Days 7 and 14 (**Figure 4**)
- Significant improvement in the CGI-I score was observed with 25 and 50 mg REL-1017 vs. placebo at Day 4. The improvement was sustained at Days 7 and 14 (data not shown)

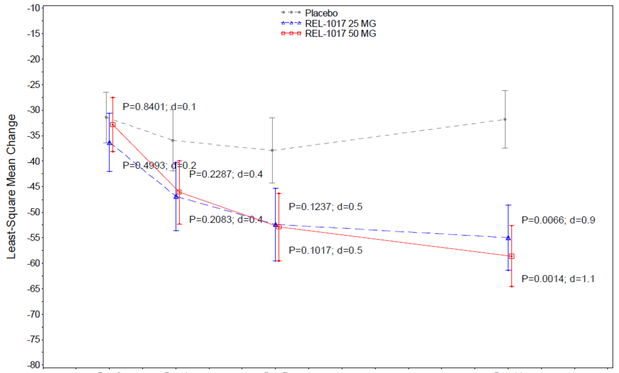
RESULTS

Figure 2. Change from baseline for MADRS total score



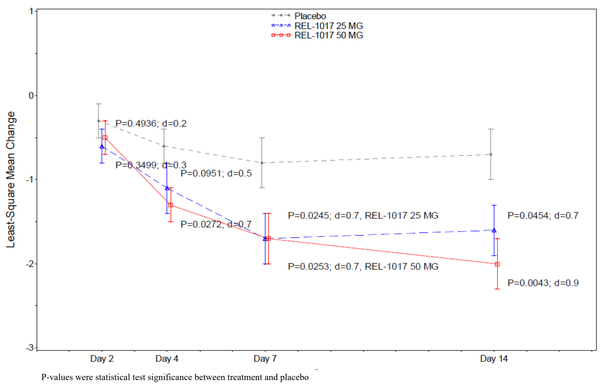
P-values were statistical test significance between treatment and placebo

Figure 3. Change from baseline for the SDQ score



P-values were statistical test significance between treatment and placebo

Figure 4. Change from baseline for the CGI-S total score

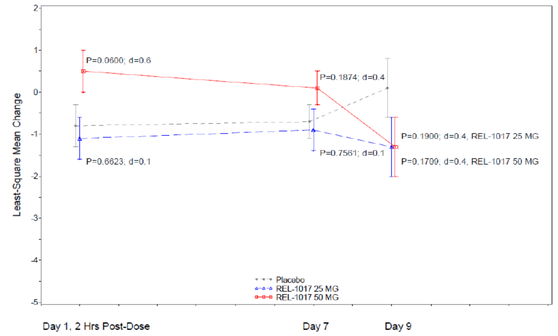


P-values were statistical test significance between treatment and placebo

DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. Drs. Fava, Stahl, Pappagallo, Inturrisi and Manfredi are paid consultants for Relmada Therapeutics. Drs. Inturrisi and Manfredi are inventors on esmethadone patents and other patents and patent applications.

Figure 5. Change from baseline from Day 1 to 9 for the CADSS



P-values were statistical test significance between treatment and placebo

Figure 6. Change from baseline from Day 8 to 14 for the COWS

P-values were statistical test significance between treatment and placebo

Safety Results
- Patients experienced no evidence of dissociative or opioid withdrawal **(Figures 5 and 6)**
- Furthermore, no psychotomimetic or suicidal effects were observed (data not shown)
- Only mild and moderate adverse events were reported, no serious adverse events (data not shown)

CONCLUSIONS

- This Phase 2a randomized, double-blind, placebo-controlled clinical trial showed that oral daily 25 and 50 mg REL-1017 had robust, rapid, and sustained antidepressant effects and favorable safety and tolerability profiles in patients with MDD
- Effect sizes were 0.5 or higher at all timepoints for efficacy assessments
- This study confirmed the Phase 1 study findings of REL-1017's safety and tolerability
- REL-1017 has the potential to be best in class among effective, rapid-onset, safe, and well-tolerated NMDAR channel blocker antidepressants

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