REL-1017 (esmethadone; d-methadone) as Adjunctive Treatment in Patients with Major Depressive Disorder: A Phase 2a Double-Blind Randomized Trial

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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 major depressive disorder (MDD) and inadequate response to standard antidepressants[1].
- REL-1017 (esmethadone; d-methadone) 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]

OBJECTIVE

- 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

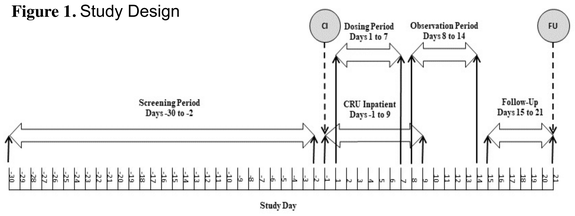
Study Design
- Double-blind, placebo-controlled, 3-arm, 7-day inpatient clinical trial in which patients were randomized in a 1:1:1 ratio to placebo or 25 or 50 mg REL-1017 orally once daily for 7 days and followed up to day 21 (**Figure 1**)
- REL-1017 treatment groups received an oral loading dose 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

Safety Assessments
- The safety analysis set (SAS) population was used for all analyses of safety endpoints and included all randomized patients who received any trial treatment (REL-1017 or placebo).

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

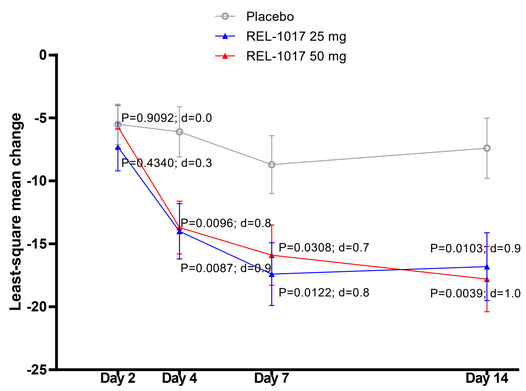
Characteristics	Placebo (N=22)	REL-1017 25 mg (N=19)	REL-1017 50 mg (N=21)	All Patients (N=62)
Age, years [a]	49.7 ± 11.1	49.4 ± 12.4	48.6 ± 10.9	49.2 ± 11.3
Male, n (%)	11 (50.0%)	11 (57.9%)	12 (57.1%)	34 (54.8%)
Hispanic/Latino ethicity, n (%)	1 (4.5%)	1 (5.3%)	0 (0%)	2 (3.2%)
Race, n (%)				
Asian	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

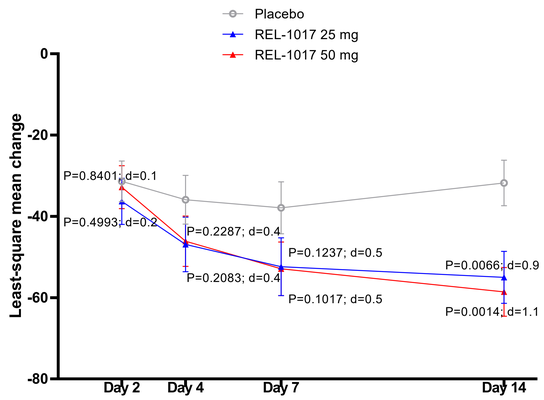
- We observed significant improvements in MADRS total score both with 25 and 50 mg REL-1017 compared to placebo at Day 4. This improvement was sustained at Days 7 and 14 (**Figure 2**).
- A significant improvement in the SDQ score was observed with both 25 and 50 mg REL-1017 as compared to placebo at Day 14 (**Figure 3**).
- Consistently, we observed a significant improvement in the CGI-S score with both 25 and 50 mg REL-1017 as compared to placebo at Days 7 and 14 (**Figure 4**).
- Finally, a significant improvement in the CGI-I score was also observed with both 25 and 50 mg REL-1017 vs. placebo at Day 4. The improvement was sustained at Days 7 and 14 (**Figure 5**).

Figure 2. Change from baseline for MADRS total score



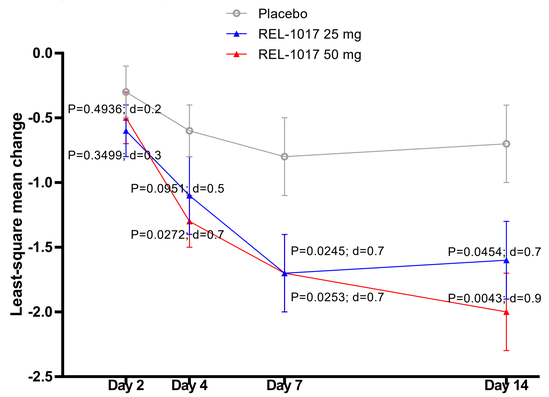
P-values were statistical test significance between treatment and placebo on days 4,7 and 14

Figure 3. Change from baseline for the SDQ score



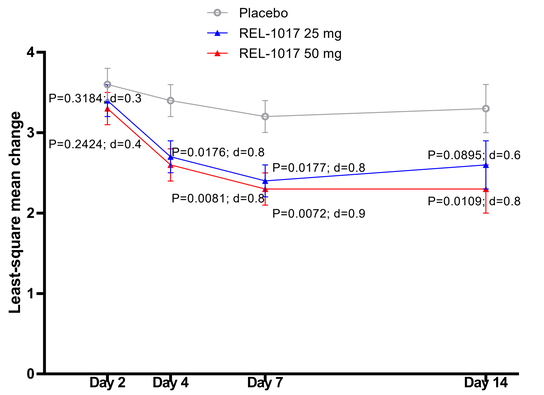
P-values were statistical test significance between treatment and placebo on day 14

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



P-values were statistical test significance between treatment and placebo on days 4, 7 and 14

Figure 5. Change from baseline for the CGI-I score



P-values were statistical test significance between treatment and placebo on days 4, 7 and 14

Table 2. Treatment emergent adverse events by preferred term (SAS Population)

Variable	Placebo (N=22)		REL-1017 25mg (N=19)		REL-1017 50mg (N=21)		All Patients (N=62)	
	n	%	n	%	n	%	n	%
Patients with a serious AE	0	0	0	0	0	0	0	0
Patients with a severe TEAE	0	0	0	0	0	0	0	0
Patients with at least 1 AE	12	54.5	9	47.4	15	71.4	36	58.1
TEAEs occurring in 3 or more patients								
Constipation	3	13.6	1	5.3	3	14.3	7	11.3
Nausea	2	9.1	1	5.3	2	9.5	5	8.1
Diarrhea	3	13.6	0	0	0	0	3	4.8
Headache	3	13.6	2	10.5	3	14.3	8	12.9
Somnolence	2	9.1	1	5.3	1	4.8	4	6.5
Dizziness	1	4.5	1	5.3	1	4.8	3	4.8
Back Pain	0	0	1	5.3	2	9.5	3	4.8

Safety Assessment

- There were no serious adverse events and no treatment-emergent adverse events that resulted in treatment discontinuation or discontinuation from the trial.
- Only mild and moderate transient adverse events were reported. Adverse effects were reported by 12 (54.5%) patients in the placebo group, 9 (47.4%) patients in the REL-1017 25 mg group, and 15 (71.4%) patients in the REL-1017 50 mg group **(Table 2).**
- The most common adverse effect that occurred in at least 5% of all patients were headache, constipation, and nausea **(Table 2).**
- Importantly, patients experienced no evidence of dissociative effects, no opioid-like euphoric effects and no withdrawal symptomatology and no psychotomimetic or suicidal tendencies (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 very favorable safety and tolerability profiles in patients with MDD.
- On the last assessment day (Day 14), the MADRS primary efficacy endpoint showed effect sizes of 0.9 and 1 for the 25 and 50 mg groups, respectively
- This study confirmed the Phase 1 study findings of REL-1017's excellent safety and tolerability.
- REL-1017 has the potential to be best in class among rapid acting antidepressant NMDAR channel blockers.

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DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. and performed by Syneos Health at 10 centers in the US. Drs. Fava, Stahl, Pani, Folli, Mangano, Vitolo, Pappagallo, Inturrisi, and Manfredi are paid consultants of Relmada Therapeutics. Drs. Wessel, De Somer, Caron, and Traversa are current or former employees of Relmada Therapeutics. Drs. Gilbert, Mehta and Kearney are current or former employees or consultants of Syneos Health. Drs Guidetti, Gentilucci, Bettini, Mattarei, and De Martin are employed or have received fees from companies or Universities that have received payments or grants from Relmada. Drs. Inturrisi and Manfredi are inventors on esmethadone patents and other patents and patent applications.

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