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

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INTRODUCTION

- Approximately 50% to 60% of patients with major depressive disorder (MDD) do not obtain an adequate response following their first antidepressant treatment[1]
- Severe depression, defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥35, may negatively impact functional outcomes[2]
- Antidepressant tolerance/tachyphylaxis (AT), defined as initial response to antidepressant treatment followed by relapse while on the same dose, may be a poor prognostic indicator for response to subsequent antidepressant treatment[3]
- Esmethadone (REL-1017) has demonstrated promise as a safe and well-tolerated oral, once-daily, uncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist with potential efficacy as adjunctive treatment of MDD[4-6]

AIM

- To evaluate the efficacy, safety, and tolerability of REL-1017 as an adjunctive treatment in patients with MDD, in a subgroup with AT (independently assessed at screening, prior to randomization), and in a subgroup with severe depression

METHODS

Study Design:

- A Phase 3, double-blind, randomized, placebo-controlled trial of oral once-daily adjunctive REL-1017 was conducted in adult outpatients with MDD and inadequate response to 1 to 3 antidepressants administered at adequate therapeutic doses and for at least 8 weeks
- Patients were 18 to 65 years old and randomly assigned to receive REL-1017 (75 mg loading dose on Day 1 and then 25 mg/day thereafter) or placebo for 28 days
- During screening and prior to randomization, patients' prior antidepressant treatment response followed by relapse (AT) was independently assessed by clinicians from the Massachusetts General Hospital Clinical Trials Network and Institute (MGH CTNI) using the MGH Antidepressant Treatment Response Questionnaire (ATRQ)[7]

Endpoint Measurements:

- The primary efficacy endpoint was the absolute change from baseline to Day 28 in the MADRS total score

Data Analysis:

- Prespecified populations for efficacy analyses included:
  - Intent-to-treat (ITT) population: all randomized patients, irrespective of protocol deviations (PDs) or discontinuation
  - Per-protocol (PP) population: patients who completed treatment with no major PDs impacting efficacy assessments
- In this study, the ITT population was the same as the full analysis set (FAS) and the safety set (SS); all randomized patients also received at least 1 dose of study drug
- Prespecified subgroup analyses were performed in females and in patients ≥50 years of age
- Additional post hoc analyses were performed in:
  - PP AT subgroup: patients with AT from the PP population
  - PP MADRS ≥35 subgroup: patients with a MADRS total score ≥35 at baseline, which was categorized as severe depression, from the PP population
- Data for the primary efficacy endpoint were analyzed using mean difference (MD) in MADRS total score

DISCLOSURES

Drs. Pappagallo and Manfredi contributed equally. This work was funded by Relmada Therapeutics, Inc. Drs. De Martin, Guidetti, Alimonti, Mattarei, and Comai are employed by or have received compensation from companies or institutions that received funding from Relmada Therapeutics, Inc. Dr. Fava is a consultant to Relmada on behalf of Massachusetts General Hospital and did not receive any personal compensation. Drs. Stahl, Pani, Gorodetzky, Vocci, Sapienza, Kosten, Folli, Manfredi, Pappagallo, and Inturrisi have received consultant fees from Relmada Therapeutics, Inc. Drs. O'Gorman, Kroeger, Champasa, and Traversa are employees of Relmada Therapeutics, Inc. Drs. De Martin and Mattarei have received grant support from MGGM LLC and consultant fees from Neuroarbor LLC. Drs. Guidetti and Comai have received consultant fees from MGGM LLC. Drs. Inturrisi and Manfredi are co-inventors of technology related to esmethadone.

RESULTS

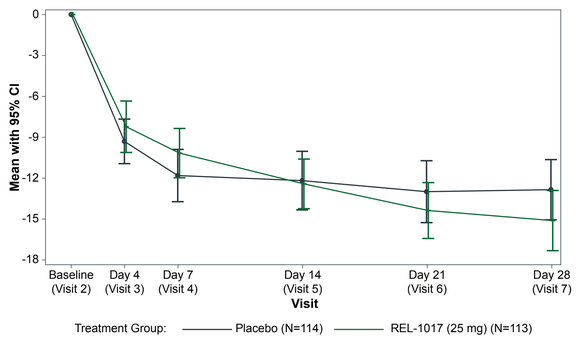

Figure 1. MADRS total score change from baseline, ITT (N=227). At Day 28, the MD between REL-1017 (N=113) and placebo (N=114) was 2.3 (*P*=0.1537; effect size=0.21).

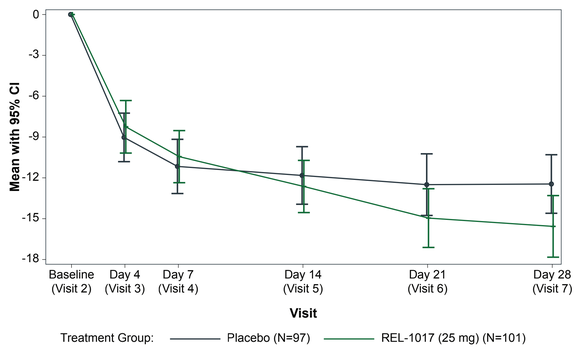

Figure 2. MADRS total score change from baseline, PP (N=198). At Day 28, the MD between REL-1017 (N=101) and placebo (N=97) was 3.1 (*P*=0.0510; effect size=0.29).

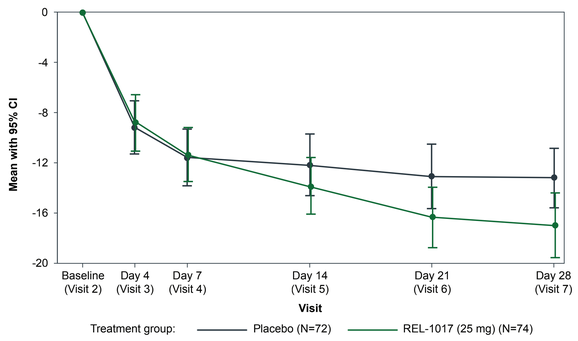

Figure 3. MADRS total score change from baseline, PP females (N=146). At Day 28, the MD between REL-1017 (N=74) and placebo (N=72) was 3.8 (*P*=0.0417; effect size=0.36).

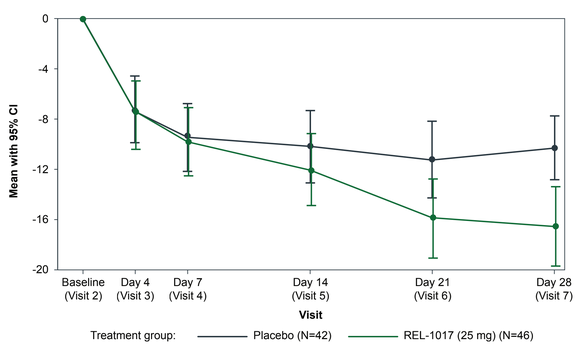

Figure 4. MADRS total score change from baseline, PP ≥50 years of age (N=88). At Day 28, the MD between REL-1017 (N=46) and placebo (N=42) was 6.3 (*P*=0.0043; effect size=0.64).

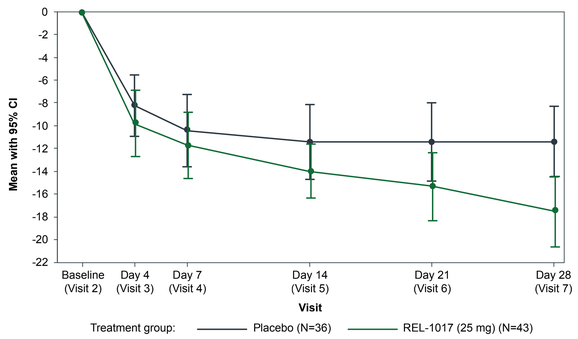

Figure 5. MADRS total score change from baseline, PP AT (N=79). At Day 28, the MD between REL-1017 (N=43) and placebo (N=36) was 6.1 (*P*=0.0101; effect size=0.62).

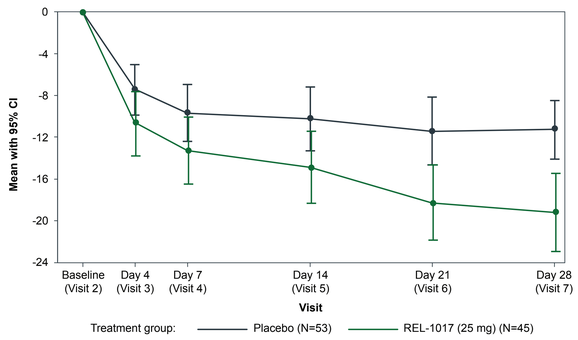

Figure 6. MADRS total score change from baseline, PP MADRS ≥35 (N=98). At Day 28, the MD between REL-1017 (N=45) and placebo (N=53) was 7.9 (*P*=0.0015; effect size=0.68).

Table 1. MADRS total score change from baseline at Day 28.

MADRS total score change from baseline at Day 28	ITT (N=227)	PP (N=198)	PP females (N=146)	PP ≥50 years of age (N=88)	PP AT (N=79)	PP MADRS ≥35 (N=98)
Placebo mean (SD)	12.9 (10.4)	12.5 (9.9)	13.1 (9.7)	10.3 (8.5)	11.4 (9.0)	11.3 (10.1)
REL-1017 mean (SD)	15.1 (11.3)	15.6 (11.2)	16.9 (11.3)	16.5 (10.8)	17.5 (10.4)	19.2 (13.0)
REL-1017 vs placebo MD (SD)	2.3 (10.9)	3.1 (10.6)	3.8 (10.6)	6.3 (9.7)	6.1 (9.8)	7.9 (11.6)
P value	0.1537	0.0510	0.0417	0.0043	0.0101	0.0015
Effect size	0.21	0.29	0.36	0.64	0.62	0.68

- In the ITT population, there was a trend toward significance for the primary endpoint (*P*=0.1537)
- In the PP population, the MD between REL-1017 and placebo in MADRS total score change from baseline at Day 28 was 3.1 (*P*=0.0510)
- In the PP population, prespecified subgroup analyses showed statistically significant effects in females (*P*=0.0417) and in patients ≥50 years of age (*P*=0.0043)
- In the PP AT subgroup, there was a statistically significant MD of 6.1 (*P*=0.0101) for REL-1017 vs placebo in MADRS total score change from baseline at Day 28
- In the PP MADRS ≥35 subgroup, there was a statistically significant MD of 7.9 (*P*=0.0015) for REL-1017 vs placebo in MADRS total score change from baseline at Day 28

Table 2. Treatment-emergent adverse events (TEAEs), safety set (N=227).

Variable	Placebo (N=114)		REL-1017 25 mg (N=113)		All patients (N=227)	
	N	%	N	%	N	%
Patients with ≥1 TEAE*	61	53.5	55	48.7	116	51.1
Patients with ≥1 treatment-related TEAE	28	24.6	30	26.5	58	25.6
Patients with ≥1 serious treatment-related TEAE	0	0	0	0	0	0
Patients with TEAE leading to withdrawal of study drug	5	4.4	2	1.8	7	3.1
TEAEs occurring in 5% or more of patients per treatment arm						
Headache	9	7.9	13	11.5	22	9.7
COVID-19	10	8.8	6	5.3	16	7.0
Upper respiratory tract infection	6	5.3	8	7.1	14	6.2
Nausea	5	4.4	8	7.1	13	5.7
Diarrhea	7	6.1	5	4.4	12	5.3
Constipation	7	6.1	3	2.7	10	4.4
Dizziness	2	1.8	7	6.2	9	4.0

*TEAE is defined as an adverse event that starts or worsens at any time after initiation of study drug.

- Adverse events (AEs) were primarily mild or moderate and transient
- There were no treatment-related serious AEs

There were no indications of withdrawal or opioid abuse (data available at the poster "No Indication of Abuse or Withdrawal Potential With Esmethadone (REL-1017): Results From Two Phase 3 Randomized Placebo-Controlled Trials in Patients With Major Depressive Disorder").

Twenty-nine patients in the ITT population were excluded from the PP population (17 placebo and 12 REL-1017).

- Eighteen (12 placebo and 6 REL-1017) did not complete treatment
- Ten (4 placebo and 6 REL-1017) experienced major protocol deviations
- One patient (placebo) did not complete treatment and experienced a major protocol deviation

Table 3. Baseline demographic characteristics, safety set (N=227).

Demographics	Safety set (N=227) N (%)
Years of age, mean (SD)	43.5 (14.6)
MADRS total score, mean (SD)	35 (4.8)
Body mass index (kg/m^2), mean (SD)	26.026 (3.035)
Sex	
Male	58 (25.6)
Female	169 (74.4)
Race	
Asian	13 (5.7)
Black/African American	30 (13.2)
White	175 (77.1)
Multiracial	6 (2.6)
Other	3 (1.3)
Ethnicity	
Hispanic or Latino	52 (22.9)
Not Hispanic or Latino	164 (72.2)
Not reported	9 (4.0)
Unknown	2 (0.9)

CONCLUSIONS

- **The efficacy of REL-1017 was considerably more favorable in the prespecified PP analysis compared to the ITT analysis**
  - Although discrepancies in outcomes between ITT and PP populations are typically related to adherence,[8] in this study, differences were not the result of tolerability and safety adverse events affecting treatment compliance
  - "Professional patients" who do not have MDD[9] may especially flatten the response to a potential antidepressant with no detectable psychoactive effects. We hypothesize that the ITT population may have contained a higher proportion of "professional patients" and patients with transient reactive depression (perhaps related to COVID-19 pandemic stress) who were poorly motivated to complete treatment and assessments
  - The more favorable prespecified efficacy outcomes observed in females and in subjects ≥50 years of age could suggest heightened REL-1017 effectiveness in these populations. Alternatively, these subgroups may have reduced likelihood of including "professional patients"; professional patients are more likely to be younger males[10]
- **Favorable outcomes were observed in post hoc analyses of PP AT and MADRS ≥35 subgroups**
  - The MDD history in the AT subgroup may have been better substantiated due to the careful assessment performed by the independent group of specialized MGH CTNI clinicians and the use of the validated MGH ATRQ screening tool. The MGH ATRQ selection of AT patients may have aided in screening out "professional patients" and patients with transient reactive depression, leading to a lower proportion of such patients in the AT subgroup
  - The favorable efficacy outcomes observed in the AT subgroup also raise the interesting hypothesis that REL-1017 may have efficacy toward mitigating antidepressant tolerance, with a mechanism that is potentially mediated via NMDAR uncompetitive antagonism
  - The ≥35 baseline MADRS subgroup may have included a lower proportion of "professional patients" and patients with transient reactive depression
- **REL-1017 may be a safe and effective adjunctive treatment for patients with MDD, including patients with severe MDD or at higher risk for treatment failure because of AT, with an AE profile that is likely to compare favorably to currently available adjunctive MDD treatments**
- **In MDD trials assessing drugs with favorable adverse event profiles, the PP analysis may provide a superior measure for evaluating efficacy compared to the ITT analysis**

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