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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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

Background: Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor uncompetitive antagonist and antidepressant candidate with promising safety, tolerability, and efficacy results from Phase 1 and 2 trials.

Methods: A Phase 3, randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of oral once-daily adjunctive REL-1017 in patients with major depressive disorder (MDD) and inadequate response to standard antidepressants. Patients were aged 18 to 65 years and experiencing a major depressive episode despite ongoing treatment with a standard antidepressant. Patients were randomly assigned to receive 75 mg REL-1017 (loading dose) or placebo on Day 1, followed by 25 mg REL-1017 or placebo from Day 2 to Day 28. The primary efficacy endpoint was change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Day 28. The full analysis set (FAS) comprised all randomized and dosed patients. The per-protocol set (PPS) comprised patients completing the 28-day treatment without major protocol deviations that impacted efficacy assessments.

Results: In the PPS (N=198: 101 REL-1017; 97 placebo), the change in MADRS total score from baseline was 15.6 for REL-1017 and 12.5 for placebo, with a mean difference (MD) of 3.1 (p=0.051; effect size=0.29). Application of a mixed-effect model with repeated measures (MMRM) produced consistent results (least square MD=2.94; p=0.0565; effect size=0.28). In the FAS (N=227: 113 REL-1017; 114 placebo), there was a trend toward significance for the primary endpoint (MD=2.3; p=0.1537; effect size=0.21) and a statistically significant difference in response rate (patients with ≥50% decrease in MADRS score compared to baseline: 39.8% REL-1017 versus 27.2% placebo; p=0.0438; odds ratio=1.77).
In the PPS, prespecified subgroup analyses showed statistically significant effects in females (N=146; MD=3.8; p=0.0417; effect size=0.36) and in patients >50 years of age (N=88; MD=6.3; p=0.0043; effect size=0.64).
Adverse events (AEs) were mild or moderate and transient. There were no treatment-related serious AEs. There were no indications of withdrawal or opioid abuse. Seven patients experienced AEs leading to discontinuation of the study drug (5 placebo and 2 REL-1017). Among the 29 patients in the FAS excluded from the PPS (17 placebo and 12 REL-1017), 19 (13 placebo and 6 REL-1017) did not complete treatment, and 11 (5 placebo and 6 REL-1017) had major protocol deviations (1 patient did not complete treatment and had a major protocol deviation).

Conclusions: The efficacy results of this trial support pursuing regulatory approval and confirm the favorable tolerability and safety results from Phase 1 and 2 studies. Efficacy results were more favorable in the PPS analysis compared to the FAS analysis. This difference was not caused by AEs impacting trial adherence. We hypothesize that the FAS may have included a higher number of inappropriately diagnosed patients (eg, "professional patients" and subjects with transient reactive depression, perhaps related to the stress of the COVID-19 pandemic) who were less motivated to complete treatment and comply with assessments, thereby explaining the more favorable results seen in the PPS compared to the FAS. PPS analyses may be better suited for evaluating drug efficacy compared to FAS in MDD trials assessing drugs with a favorable side effect profile.

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BACKGROUND

- Esmethadone (REL-1017) is an N-methyl-D-aspartate receptor (NMDAR) uncompetitive antagonist and antidepressant candidate with promising pharmacokinetic, safety, tolerability, and efficacy results from Phase 1 and 2 trials[1,2]
- REL-1017 has no detectable psychoactive effects in healthy subjects,[1] in patients with major depressive disorder (MDD),[2] and in experienced recreational substance users[3]

OBJECTIVE

- To examine the efficacy and safety of REL-1017 in a Phase 3, randomized, double-blind, placebo-controlled trial in patients with MDD and inadequate response to standard antidepressants (NCT04688164)

METHODS

Study Design:
- A Phase 3, randomized, double-blind, placebo-controlled trial of oral once-daily adjunctive REL-1017 was conducted in patients with MDD and inadequate response to standard antidepressants
- Patients were aged 18 to 65 years and experiencing a major depressive episode despite ongoing treatment with an adequate course of a standard antidepressant
- Patients were randomly assigned to receive 75 mg REL-1017 (loading dose) or placebo on Day 1, followed by 25 mg REL-1017 or placebo from Day 2 to Day 28

Endpoint Measurements:
- The primary efficacy endpoint was defined as the absolute change from baseline to Day 28 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score
- One of the key secondary endpoints was response rate, defined as patients with ≥50% decrease in MADRS total score compared to baseline at Day 28

Data Analysis:
The following prespecified analysis sets were included:
- Full analysis set (FAS): all randomized and dosed patients
- Per-protocol set (PPS): patients completing the 28-day treatment without major protocol deviations that impacted efficacy assessments
- Safety set: all randomized patients who received any dose of study drug
- Subgroups of sex (male, female) and age (<50 years of age, ≥50 years of age)

Data for the primary endpoint were analyzed using mean difference (MD) in MADRS total score and using a mixed-effect model with repeated measures (MMRM) with consideration of repeated assessments of the MADRS total score and with the independent variables of treatment, visit, the interaction of treatment and visit, and the baseline MADRS total score.

Data for response rate for the FAS population were analyzed using a chi-square test (2-sided with α=0.05).

RESULTS

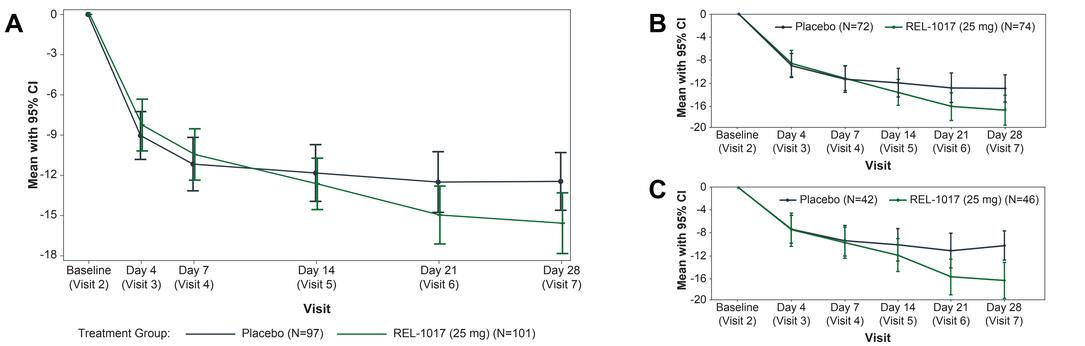

Figure 1. MADRS total score change from baseline, PPS (N=198). A. At Day 28, the MD between REL-1017 (N=101) and placebo (N=97) was 3.1 (*P*=0.051; effect size=0.29). **B.** At Day 28, the MD between REL-1017 and placebo in females (N=146) was 3.8 (*P*=0.0417; effect size=0.36). **C.** At Day 28, the MD between REL-1017 and placebo in patients ≥50 years of age (N=88) was 6.3 (*P*=0.0043; effect size=0.64).

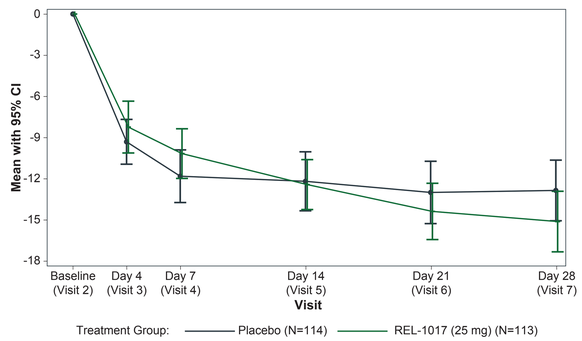

Figure 2. MADRS total score change from baseline, FAS (N=227). At Day 28, the MD between REL-1017 (N=113) and placebo (N=114) was 2.3 (*P*=0.1537; effect size=0.21).

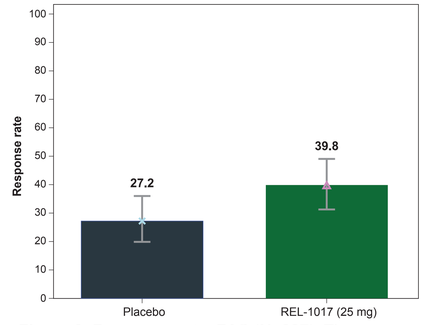

Figure 3. Response rate, FAS (N=227). The response rate at Day 28 was 39.8% for REL-1017 and 27.2% for placebo (*P*=0.0438; odds ratio=1.77).

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

MADRS total score change from baseline at Day 28	PPS (N=198)	FAS (N=227)
Placebo mean (SD)	12.5 (9.9)	12.9 (10.4)
REL-1017 mean (SD)	15.6 (11.2)	15.1 (11.3)
REL-1017 vs placebo MD (SD)	3.1 (10.6)	2.3 (10.9)
P-value	0.051	0.1537
Effect size	0.29	0.21
Placebo LS mean (SE)	12.69 (1.1)	13.37 (1.09)
REL-1017 LS mean (SE)	15.63 (1.06)	15.1 (1.05)
REL-1017 vs placebo least square MD (LSMD) (SE)	2.94 (1.53)	1.74 (1.52)
P-value, MMRM	0.0565	0.2547
Effect size	0.28	0.16

- In the PPS, the MD between REL-1017 and placebo in MADRS total score change from baseline at Day 28 was 3.1 (*P*=0.051); MMRM application produced consistent results (LSMD=2.94; *P*=0.0565)
- In the PPS, prespecified subgroup analyses showed statistically significant effects in females (*P*=0.0417) and in patients ≥50 years of age (*P*=0.0043)
- In the FAS, there was a trend toward significance for the primary endpoint (*P*=0.1537) and a statistically significant difference in response rate (*P*=0.0438)

CONCLUSIONS

- **Efficacy results were more favorable in the PPS analysis compared to the FAS analysis. While discrepancies in outcomes between FAS and PPS are generally due to adherence,[4] in this case, this difference was not attributable to adverse events impacting trial adherence**
- **We hypothesize that the FAS may have included a higher proportion of "professional patients" and patients with transient reactive depression (perhaps related to COVID-19 pandemic stress) who were less 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.[5] The results of the analyses of REL-1017 in the PPS and in subgroups less likely to include "professional patients" support its development as adjunctive treatment of MDD**
- **PPS analyses may be better suited for evaluating drug efficacy compared to FAS in MDD trials assessing drugs with a favorable side effect profile. Professional patients without MDD may flatten the response to potentially effective antidepressant candidates,[6] especially when testing drugs with no detectable psychoactive effects. Prespecified subgroup subanalyses may add insight to efficacy evaluations of novel antidepressant candidates**

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
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

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

- Adverse events were predominantly mild or moderate and transient
- There were no treatment-related serious adverse events

There were no indications of withdrawal or opioid abuse (data available at poster "No Indication of Abuse Potential and Absence of Withdrawal Signs and Symptoms From Esmethadone (REL-1017): Results From a Phase 3 Randomized Controlled Trial in Patients With Major Depressive Disorder").

Among the 29 patients in the FAS excluded from the PPS (17 placebo and 12 REL-1017), 19 (13 placebo and 6 REL-1017) did not complete treatment, and 11 (5 placebo and 6 REL-1017) had major protocol deviations (1 patient did not complete treatment and had 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)
Unknown	2 (0.9)

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DISCLOSURES

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