Efficacy and Safety of Esmethadone (REL-1017) in Patients With Major Depressive Disorder and Inadequate Response to Standard Antidepressants: Findings From Two Early-Terminated Phase 3 Trials

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Background

Up to 50% of patients with MDD do not respond to first-line therapy. Available adjunctive antidepressants have delayed onset and metabolic, cardiovascular, neurological and sexual side effects.

Objective

To evaluate the efficacy and safety of esmethadone (REL-1017), a novel, safe and well-tolerated, rapid-acting adjunctive antidepressant in development for patients with MDD and inadequate response to first-line therapy.

Methods

We present results from two prematurely terminated Phase 3 randomized, double-blind, placebo-controlled trials: REL-1017-302 (NCT04855747) and REL-1017-304 (NCT06011577). Participants received esmethadone (75 mg on Day 1, followed by 25 mg daily) or matching placebo for 28 days.

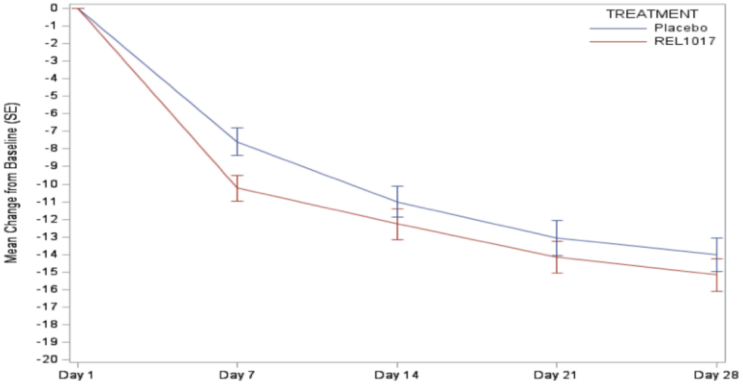
Results

Neither trial met the primary endpoint (MADRS CFB at Day 28). Study REL-1017-302 (N=236): esmethadone showed statistically significant rapid antidepressant efficacy at Day-7 (prespecified key secondary endpoint) [MADRS meßan difference (MD): 2.52 points, p=0.0290; Cohen's effect size (ES): 0.29]. However, statistical significance was lost at later timepoints due to greater-than-expected improvement in the placebo arm. Study REL-1017-304 (N=27) showed a similar trend for rapid antidepressant efficacy at Day-7 (MADRS MD: 3.8 points) but did not achieve statistical significance due to the small sample size. Pooled data (N=263) confirmed Day-7 significance (Day 7 p= 0.0127; ES-0.32) (Table 1; Figure 1). Prespecified MMRM and per protocol analyses were supportive of Day-7 rapid antidepressant effects. Consistent with prior trials, totaling over 1000 participants exposed to REL-1017, treatment emergent adverse events (TEAE) were mostly mild or moderate, with no serious adverse events (SAE), no meaningful opioid effects or dissociative effects, no metabolic, neurological, cardiovascular, or sexual side effects.

Table 1 and Figure 1

Pooled studies 302+304: MADRS Change from Baseline (ITT population)

MADRS Change		Treatment		REL-1017 vs Placebo	Effect Size (Cohen's d)	p-value (Student's t test)
		Placebo (N=130)	REL-1017 (N=133)			
7 Days	N	123	128			
	Mean (SD)	-7.6 (8.62)	-10.2 (8.14)	-2.65 (8.38)	0.32	0.0127
14 Days	N	123	124			
	Mean (SD)	-11.0 (9.74)	-12.3 (9.78)	-1.25 (9.76)	0.13	0.3152
21 Days	N	119	122			
	Mean (SD)	-13.1 (10.77)	-14.2 (9.98)	-1.10 (10.37)	0.11	0.4128
28 Days	N	122	126			
	Mean (SD)	-14.0 (10.35)	-15.2 (10.43)	-1.16 (10.39)	0.11	0.3809



Conclusions

With the limitations of early study termination, Day-7 statistically significant antidepressant effects and favorable safety results support the development of esmethadone as a once-daily, oral, rapid-acting, safe and well-tolerated adjunctive antidepressant. Notably, despite loss of statistical significance after the Day-7 timepoint, patients in the REL-1017 arm continued to improve at all subsequent timepoints, signaling that the Day-7 antidepressant effects were sustained.

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Disclosures: Drs. Comai, De Martin, Fava, Folli, Gentilucci, Gorodetzky, Guidetti, Inturrisi, Kosten, Mattarei, Manfredi, Pani, Pappagallo, Rizzo, Sapienza, Vocci received compensation from Relmada Therapeutics and or companies or institutions that received funding from Relmada Therapeutics, Inc. (former developer of REL-1017) and or MGGM Therapeutics, a New York corporation providing drug development services. Dr. Fava is a consultant to Relmada on behalf of Massachusetts General Hospital and did not receive any personal compensation. Drs. Manfredi and Inturrisi are co-inventor and co-owners of technology related to. esmethadone. Levomecor Inc., a Delaware corporation, is the current sponsor of the REL-1017 program and is the sponsor for REL-1017 development activities performed by MGGM Therapeutics. Dr. Manfredi is CEO of Levomecor and Scientific Advisor of MGGM. Dr Gentilucci is CEO of MGGM. Andrea Varalli, a consultant for MGGM, provided graphic design services. World Congress of Psychiatry, Prague (CZ) October 4-8, 2025