Esmethadone (REL-1017) improves cognition in patients with severe major depressive disorder and inadequate response to standard antidepressants: a post hoc analysis from a phase 3 randomized controlled trial

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BACKGROUND

- Subjective cognitive impairment is a key symptom of major depressive disorder (MDD) [1]
- Esmethadone (REL-1017)) is a promising novel N-methyl-D-aspartate (NMDA) receptor uncompetitive antagonist under development for the adjunctive treatment of MDD in patients with inadequate response to first line antidepressants [2,3]
- REL-1017 improved subjective cognitive impairment when administered as adjunctive treatment to patients with MDD in a Phase 2 trial [3]
- In a recently completed Phase 3 study (NCT04688164), esmethadone did not meet the primary efficacy endpoint at Day 28 for mean change from baseline in MADRS.[4] However, post-hoc analyses in the subgroup of patients with severe depression (baseline MADRS ≥35) showed efficacy [4]

AIM

- This study aimed at investigating the effects of REL-1017 on subjective cognitive measures in the subgroup of severely depressed patients unresponsive to standard antidepressants enrolled in a Phase 3 adjunctive MDD study

METHODS

Study Design

- Outpatients 18-65 years of age with MDD confirmed by *DSM-5* criteria were randomly assigned to daily adjunctive oral esmethadone (75mg on day 1, followed by 25mg daily on days 2 through 28) or placebo for 28 days
- Subjects were in the midst of a major depressive episode (MDE) of at least moderate intensity lasting 8 weeks to 36 months and had inadequate response (MADRS total score ≥24 at screening) to 1-3 antidepressants of adequate dose and duration documented in the MGH ATRQ assessment and passed the MGH CTNI SAFER interview (remote visit)
- This study presents post hoc analyses of MADRS and SDQ items measuring subjective cognitive measures in the subgroup of patients with severe depression (baseline MADRS ≥35)
- Patients with severe depression and recorded assessments both at baseline and at Day 28 (primary endpoint) were included in post-hoc mean difference (MD) analyses. All patients with severe depression were included in mixed model of repeated measures (MMRM) analyses

MEASURES

- Single items from the MADRS directly (item 6) and indirectly (items 3,4,7,8) related to subjective cognitive symptoms
- Items from the Symptoms of Depression Questionnaire (SDQ) related to subjective cognitive symptoms (items 16, 22, 35, 36, 37, 38, 39, 42). The analysis of these 8 SDQ items followed a previously described methodology (SDQ cognition) [3]

REFERENCES

1. Cognitive function following a major depressive episode: a systematic review and meta-analysis. Semkovska, Maria et al. The Lancet Psychiatry, Volume 6, Issue 10, 851 – 861
2. Fava M, Stahl SM, De Martin S, Mattarei A, Bettini E, Comai S, Alimonti A, Bifari F, Pani L, Folli F, Guidetti C, Furlan A, Sgrignani J, Locatelli P, Cavalli A, O'Gorman C, Traversa S, Inturrisi CE, Pappagallo M, Manfredi PL. Esmethadone-HCl (REL-1017): a promising rapid antidepressant. Eur Arch Psychiatry Clin Neurosci. 2023 Oct;273(7):1463-1476
3. Guidetti C, Serra G, Pani L, Pappagallo M, Maglio G, Martin S, Mattarei A, Folli F, Manfredi PL, Fava M. Subanalysis of Subjective Cognitive Measures From a Phase 2, Double-Blind, Randomized Trial of REL-1017 in Patients With Major Depressive Disorder. Prim Care Companion CNS Disord. 2023 Feb 14;25(1):22m03267
4. Fava M, Stahl SM, Pani L, De Martin S, Cutler AJ, Maletic V, Gorodetzky CW, Vocci FJ, Sapienza FL, Kosten TR, Kröger C, Champasa P, O'Gorman C, Guidetti C, Alimonti A, Comai S, Mattarei A, Folli F, Bushnell D, Traversa S, Inturrisi CE, Manfredi PL, Pappagallo M. 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. J Clin Psychiatry. 2024 Jun 17;85(3):24m15265

DISCLOSURES

This work was funded by Relmada Therapeutics, Inc. Drs. De Martin, Guidetti, 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. Pani, Manfredi, Pappagallo, have received consultant fees from Relmada Therapeutics. Drs Papakostas, Apicella and Ortiz have no relevant conflict of interest.

RESULTS

- A total of 227 patients were randomized. Among these, 112 had severe depression (baseline MADRS ≥35)
- Statistically significant differences in change from baseline (CFB) were observed at day 28 for patients in the REL-1017 group (N=48) compared to placebo (N=51) on "concentration difficulties" (item 6 of the MADRS, **Table 1, Figure 2**). The analysis of 8 SDQ items related to cognition showed clinically meaningful and statistically significant improvements (**Table 1, Figure 1**). Other MADRS items potentially related to cognition ("inner tension", "reduced sleep", "lassitude" and "inability to feel") showed statistically significant improvements (**Table 2, Figure 2**)
- Consistent results were seen in MMRM analysis (**Table 3**)

Table 1. Post-hoc analyses in the subgroup of patients with severe depression (baseline MADRS ≥35): Mean Difference (MD) change from baseline (CFB) for placebo and REL-1017) in MADRS item 6 and in the SDQ Cognition (items: 16, 22, 35, 36, 37, 38, 39, 42).

		Day 28			
Treatment Group	**N**	**CFB Mean (SD)**	**Mean Difference (SE)**	**P Value**	**Effect Size (ES)**
MADRS Item 6 "Concentration Difficulties"					
Placebo	51	-1.1 (1.5)			
Rel-1017	48	-1.8 (1.7)	-0.7 (1.6)	**0.038**	0.42
SDQ Cognition					
Placebo	37	-6.2 (6.8)			
Rel-1017	32	-9.8 (7.5)	-3.6 (1.7)	**0.043**	0.49

Table 2. Mean Difference (MD) change from baseline (CFB) for placebo and for REL-1017 in MADRS items indirectly related to cognition (items 3,4,7,8).

		Day 28			
Treatment Group	**N**	**CFB Mean (SD)**	**Mean Difference (SE)**	**P Value**	**Effect Size (ES)**
MADRS Item 3 "Inner Tension"					
Placebo	51	-1.0 (1.1)			
Rel-1017	48	-1.8 (1.9)	-0.8 (1.5)	**0.009**	0.53
MADRS Item 4 "Reduced Sleep"					
Placebo	51	-0.8 (1.7)			
Rel-1017	48	-1.6 (1.8)	-0.9 (1.7)	**0.014**	0.50
MADRS Item 7 "Lassitude"					
Placebo	51	-1.3 (1.8)			
Rel-1017	48	-2.3 (1.9)	-1.0 (1.8)	**0.005**	0.57
MADRS Item 8 "Inability to feel"					
Placebo	51	-1.3 (1.5)			
Rel-1017	48	-2.3 (1.9)	-1.0 (1.7)	**0.005**	0.58

CONCLUSIONS

Novel treatments shown to restore impaired neural plasticity in experimental models of depressive-like behavior may be especially effective for relieving subjective cognitive impairment in patients with MDD. These post-hoc Phase 3 results in patients with severe depression suggest potential efficacy of REL-1017 for the relief of subjective cognitive impairment, as observed in a prior study.[3] These findings support the potential of REL-1017 in addressing cognitive impairment in patients with severe MDD. Larger studies may be needed to confirm the efficacy of REL-1017 on relieving subjective cognitive symptoms in patients with severe MDD and to further explore its long-term impact on overall functioning.

Figure 1.

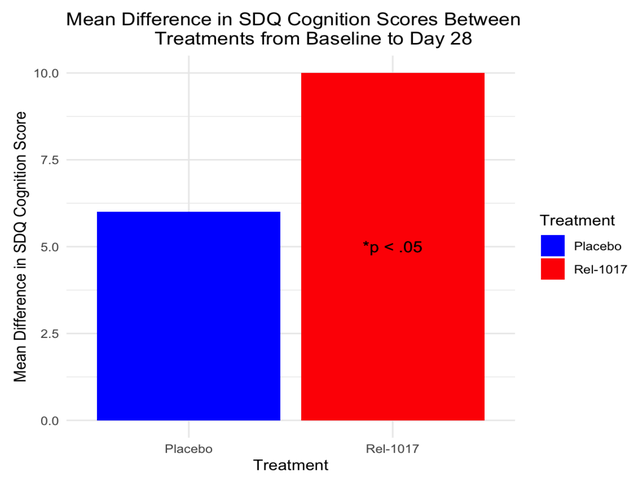

Figure 2.

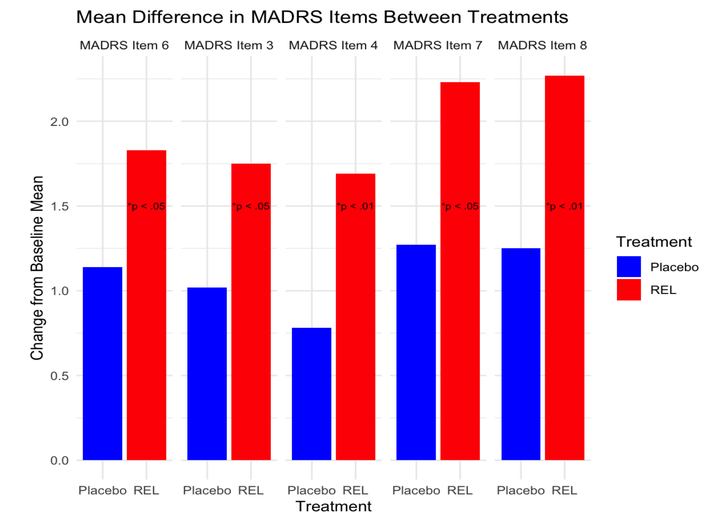

Table 3. Mixed Model Repeated Measures (MMRM) for placebo and for esmethadone (REL-1017) in MADRS items: post-hoc analyses in the subgroup of patients with severe depression (baseline MADRS ≥35)

		Day 28				
Treatment Group	**N**	**LS Mean (SE)**	**95% CI**	**LS Mean Difference (SE)**	**P Value**	**Effect Size**
MADRS Item 6 "Concentration Difficulties"						
Placebo	51	-1.09 (0.21)	(-1.51, -0.66)			
Rel-1017	48	-1.87 (0.23)	(-2.32, -1.42)	-0.78 (0.31)	**0.014**	0.50
MADRS Item 3 "Inner Tension"						
Placebo	51	-1.01 (0.20)	(-1.40, -0.62)			
Rel-1017	48	-1.65 (0.21)	(-2.06, -1.24)	-0.64 (0.29)	**0.028**	0.45
MADRS Item 4 "Reduced Sleep"						
Placebo	51	-0.84 (0.21)	(-1.26, -0.43)			
Rel-1017	48	-1.50 (0.22)	(-1.93, -1.06)	-0.65 (0.31)	**0.035**	0.43
MADRS Item 7 "Lassitude"						
Placebo	51	-1.35 (0.23)	(-1.81, -0.89)			
Rel-1017	48	-2.23 (0.25)	(-2.81, -1.83)	-0.97 (0.34)	**0.005**	0.56
MADRS Item 8 "Inability to feel"						
Placebo	51	-1.26 (0.23)	(-1.73, -0.80)			
Rel-1017	48	-2.22 (0.25)	(-2.71, -1.73)	-0.96 (0.34)	**0.005**	0.56

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