Subanalysis of Subjective Cognitive Measures From a Phase 2, Double-Blind, Randomized Trial of REL-1017 in Patients With Major Depressive Disorder

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ABSTRACT

Objective: Improvement of cognitive function in patients with major depressive disorder (MDD) is an important treatment outcome. REL-1017 (esmethadone HCl) is a novel *N*-methyl-D-aspartate receptor (NMDAR) channel blocker and a potentially rapidly acting antidepressant. The objective of this study was to define the effects of REL-1017 on subjective cognitive measures in patients with MDD.

Methods: Post hoc analysis was conducted of subjective cognitive measures from the Montgomery-Asberg Depression Rating Scale (MADRS) and the Symptoms of Depression Questionnaire (SDQ) from a randomized, double-blind, placebo-controlled, Phase 2a study. The study, designed to assess the safety, tolerability, and efficacy of 2 dosages (25 mg and 50 mg) of REL-1017 as an adjunctive treatment in patients with MDD unresponsive to standard antidepressants, included 62 patients. We analyzed subjective cognitive measures derived from the MADRS and SDQ scales at baseline and up to day 14, 7 days after the last dose of study drug. We developed 2 composite indexes that included subjective cognitive measures selected from the MADRS and SDQ.

Results: The subanalysis of single measures and the 2 composite indexes derived from the MADRS and SDQ measures showed clinically meaningful and statistically significant improvements in cognitive function ($P < .05$).

Conclusions: In a Phase 2a clinical trial, REL-1017 improved subjective measures of cognitive impairment, in addition to improving total MADRS and SDQ scores. These results need to be confirmed in larger and longer studies in MDD that include objective measures of cognitive function. Phase 3 studies of REL-1017 for MDD are currently underway.

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Major depressive disorder (MDD) is a prevalent, chronic, and highly disabling multidimensional psychiatric disorder representing a growing public health issue. MDD is the second leading cause of disability and chronic disease burden in the United States, among all medical conditions, as measured by "disability-adjusted life years."[1] By 2030, MDD is projected to become the leading cause of global disease burden according to the World Health Organization (WHO).[2] Data from the National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III) show that the 12-month prevalence and the lifetime prevalence of MDD were 10.4% and 20.6%, respectively, with most patients experiencing moderate (6 to 7 symptoms) or severe (8 to 9 symptoms) depression associated with comorbidity and functional impairment.[3]

MDD is a heterogeneous condition with a broad constellation of symptoms including cognitive/motivational, anxiety/irritability, and sleep domains, all of which heavily impact quality of life and global functioning. Many studies[4] have shown that cognitive dysfunction is an important predictor of occupational and social functional impairment in adults with MDD. The importance of rapidly improving MDD functional outcomes, including cognitive measures, is increasingly recognized because the improvement of subjective cognitive impairment may be as important as the improvement of mood for patients with MDD.[5]

Up to 50%–60% of MDD patients do not achieve adequate response following the first antidepressant treatment.[6] Moreover, the response to antidepressants is delayed by 4 to 8 weeks after initiation.[7] Atypical antipsychotics are US Food and Drug Administration (FDA)–approved as adjunctive treatment of MDD for those patients with inadequate response to antidepressants, although they have modest efficacy and neurologic and metabolic side effects.[8]

N-methyl-D-aspartate receptor (NMDAR) channel blockers are emerging as a new drug class with potentially rapid and effective antidepressant activity.[9,10] Esketamine was recently approved by the FDA as an adjunctive treatment for MDD in patients with treatment-resistant depression, having been shown to be efficacious in MDD in a recent meta-analysis.[11] Due to poor oral absorption, esketamine is

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Clinical Points

- The efficacy of REL-1017 in treating cognitive symptoms could be related to the neural plasticity mechanism of action with potential disease-modifying effect rather than symptomatic treatment, especially when used early after the onset of MDD.
- Residual cognitive symptoms have been identified as a predictor of poor outcomes when treating depression; accurate measuring of cognitive function may be considered a sign rather than a symptom and may provide the most accurate measurement of severity of MDD and response to treatment.
- A combination of esmethadone with cognitive-behavioral psychotherapy may help patients with MDD experiencing cognitive symptoms feel better.

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administered intranasally. Furthermore, esketamine causes temporary dissociative side effects and changes in blood pressure, requiring monitoring after administration.[12] The uncompetitive NMDAR blockers, memantine and the dextromethorphan-quinidine combination, have been approved by the FDA to treat Alzheimer's disease and pseudobulbar affect, respectively. Dextromethorphan, another uncompetitive NMDAR channel blocker, in combination with bupropion, is in clinical development for the treatment of MDD.[13]

REL-1017 (esmethadone HCl, d-methadone HCl, dextromethadone HCl, (+)-methadone) is the opioid-inactive dextro-isomer of racemic methadone and a novel NMDAR channel blocker, with a preference for GluN1-GluN2D NMDAR subtypes.[14,15] NMDARs are known to have a central role in directing neural plasticity.[16,17] Impaired neural plasticity due to dysregulation of NMDARs has been implicated in a multiplicity of neuropsychiatric disorders and may play an important role in MDD.[18] REL-1017 demonstrated rapid antidepressant-like effects in animal models of depressed behavior, including the forced swim test, the novelty-suppressed feeding test, the female-urine sniffing test, and the chronic unpredictable stress paradigm, with efficacy equivalent to ketamine.[19,20] REL-1017 increased plasma levels of brain-derived neurotrophic factor (BDNF) in humans[21] and induced neural plasticity in experimental models of depression via BDNF-dependent mechanisms.[20] REL-1017 showed favorable safety, tolerability, and pharmacokinetic (PK) profiles in Phase 1 studies.[22,23] Recently, it has been shown that REL-1017 is not neurotoxic on the central nervous system[24] and does not cause withdrawal and dependence symptoms in rats.[25] REL-1017 produced rapid, robust, and sustained antidepressant efficacy in a Phase 2 clinical trial in the absence of opioid or psychotomimetic effects.[26] REL-1017 is currently undergoing testing in Phase 3 trials for MDD (ClinicalTrials.gov identifiers: NCT04688164, NCT05081167, NCT04855747). This subanalysis examined the potential effects of REL-1017 on subjective cognitive function.

METHODS

Study Design and Patients

We performed a post hoc subanalysis of subjective cognitive measures obtained from a double-blind, placebo-controlled, inpatient, 7-day treatment, 3-arm, Phase 2a trial (ClinicalTrials.gov identifier: NCT03051256).[26] The safety, tolerability, and efficacy of 2 dosages of REL-1017 (25 mg or 50 mg/d once a day) as adjunctive treatment were examined in patients with MDD unresponsive to serotonergic antidepressants.

Assessments

The efficacy measures used in this study were select items from the Montgomery-Asberg Depression Rating Scale (MADRS) and the Symptoms of Depression Questionnaire (SDQ), respectively, which were the first and one of the secondary endpoints of the Phase 2 trial. The MADRS is a clinician-reported instrument frequently used to measure outcome in antidepressant efficacy studies.[27] This 10-item scale evaluates core symptoms of depression, scored from 0 (symptom not present or normal) to 6 (severe or continuous presence of the symptom). A higher MADRS score indicates more severe depression. The overall score ranges from 0 to 60 with scores above 34 indicating severe depression. The SDQ is a 44-item self-report scale intended to capture the broad heterogeneity of symptoms of MDD.[28] The SDQ items can be analyzed as a total score and can also be subdivided into 5 subscales. Subscale 1 measures common dimensions of depressive symptoms including lassitude, energy, mood, and cognitive and social functioning. Subscale 2 measures anxiety, anger, irritability, and agitation. Subscale 3 includes items on suicide, self-harm, and worthlessness. Subscales 4 and 5 measure physiologic features of depression, namely sleep difficulties and changes in appetite/weight, respectively. Each item is rated on a 6-point scale. Each item is rated based on a subject's perception of what is normal for the individual (score = 2), what is better than normal (score = 1), and what is worse than normal (scores = 3–6).

The MADRS and SDQ were administered predose on day 1 (at baseline) and on day 2, postdose on day 4 and on day 7 within 3 hours of dosing, and on day 14 (end of observation period). The MADRS was administered according to the Structured Interview Guide for the MADRS.[29] Clinician-rated cognitive symptoms were assessed from item 6 of the MADRS, which measures subjective concentration difficulties. Patient-reported subjective cognitive symptoms were assessed using 8 SDQ items: item 16 (wakefulness), item 22 (slowed down feeling), item 35 (ability to focus/sustain attention), item 36 (ability to remember/recall information), item 37 (ability to find words), item 38 (sharpness/mental acuity), item 39 (ability to make decisions), and item 42 (ability to work/study/function at home), which are all included in SDQ subscale 1.

As an additional analysis of measures of overall subjective cognitive function, we also developed 2 SDQ/MADRS Composite Cognitive Indexes. To make the 2 measures

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comparable between each other, we converted the MADRS and SDQ score data (collected singularly from every person in each reporting day) following these rules: CI = (MADRS +1) * (100/7) CI = (SDQ −1) * (100/5).

Tables 1 and 2 compare the 2 scales with the corresponding index values. The conversion aims at making the 2 scales comparable to synthesize a larger amount of data in a single composite index. The Composite Cognitive Index 1 is the equally weighted mean of the cognitive item scores from the 8 SDQ items and item 6 from MADRS. The Composite Cognitive Index 2 is computed by applying a 0.5 weight to the single MADRS question values and 0.5 weight to the mean values of the 8 SDQ items.

Statistical Analysis

Statistical analyses were performed using MATLAB software, version R2019. The change from baseline of the single cognitive items of the MADRS and the SDQ scores and of the Composite Cognitive Indexes 1 and 2 on day 14 was compared for placebo versus REL-1017 active treatment groups, 25 mg and 50 mg (analyzed separately and combined), using a mixed model analysis as described by Fava et al.[26] The likelihood-based method applied was the mixed-effect model repeated measures with fixed-effect terms for treatment, visit (day 2, day 4, day 7, day 14), and the interaction between treatment and visit. The least square (LS) mean difference (between REL-1017 and placebo) was provided along with the P value for testing the null hypothesis and the Cohen's effect size (calculated based on the LS mean differences and the pooled standard deviations). An inferential statistical analysis was applied to each treatment group (REL-1017 25 mg group, N = 16; REL-1017 50 mg group, N = 18) and to the combined active treatment sample (N = 34: REL-1017 25 mg group, N = 16 + REL-1017 50 mg group N = 18).

RESULTS

Several measures indicated marked difference in the subjective cognitive measures between patients treated with REL-1017 versus placebo. These changes were consistently in the direction of less severe cognitive symptoms in patients treated with REL-1017 on day 14, 7 days after treatment discontinuation. Statistically significant differences in the change from baseline were observed on day 14 for patients in the REL-1017 25 mg group compared to the placebo group on "concentration difficulties" (item 6 of the MADRS, P = .03, Table 3, Figure 1 panel A), "ability to focus/sustain attention" (item 35 of the SDQ, P = .02, Table 3, Figure 1 panel D), "ability to remember/find words" (item 37 of the SDQ, P = .04, Table 3, Figure 1 panel F), "sharpness/mental acuity" (item 38 of the SDQ, P = .03, Table 3, Figure 1 panel G), and the Composite Cognitive Index 1 and 2 (P = .01, Table 4, Figure 2A and P = .008, Table 2, Figure 2B, respectively).

REL-1017 50 mg was found to be superior to placebo for improving cognitive symptoms on day 14 as rated with the MADRS item 6 "concentration difficulties" (P = .03, Figure

Table 1. Montgomery-Asberg Depression Rating Scale (MADRS) Conversion Table

MADRS	Composite Index
0	14,285
1	28,57
2	42,857
3	57,143
4	71,429
5	85,714
6	100

Table 2. Symptoms of Depression Questionnaire (SDQ) Conversion Table

SDQ	Composite Index
1	0
2	20
3	40
4	60
5	80
6	100

1 Panel A), with all the cognitive items of the SDQ (items 16, 22, 35–39, 42; Table 3; Figure 1 panels B–I), and with the Composite Cognitive Index 1 and 2 (P = .0008, Table 4, Figure 2A and P = .001, Table 4, Figure 2B, respectively).

Also in the combined REL-1017 25 mg + 50 mg group, REL1017 was found to be superior to placebo for improving cognitive symptoms as rated with the MADRS item 6 "concentration difficulties" (P = .01, Figure 1 Panel A), with all the cognitive items of the SDQ (items 16, 22, 35–39, 42; Table 3 and Figure 1 panels B–I), and with the Composite Cognitive Index 1 and 2 (P = .0009, Table 4, Figure 2A and P = .0006, Table 4, Figure 2B, respectively).

Moreover, as previously reported,[26] there were clinically meaningful and statistically significant improvements on total MADRS score starting on day 4 in both REL-1017 treatment groups, and the improvement continued through day 7 and day 14, 7 days after study drug discontinuation. For the SDQ total score and subscales 1, 2, and 4, clinically meaningful and statistically significant improvements were shown on day 14 in both REL-1017 groups, as described in detail by Fava and colleagues.[26]

DISCUSSION

The mechanism of action of NMDAR uncompetitive antagonists in MDD may be related to the restoration of glutamatergic neural plasticity. Because of the relevance of cognitive symptomatology in patients with MDD, we performed a post hoc analysis of select MADRS and SDQ items that may inform on the effects of the novel uncompetitive NMDAR antagonist REL-1017 on subjective measures of cognitive function.

Emerging data on impaired neural plasticity as the potential pathophysiologic basis for MDD[18,30] and the use of glutamatergic modulators for the treatment of MDD,[9] taken together with the established pivotal role of NMDARs in neural plasticity,[16,17] underscore the importance of assessing

Table 3. Least Square Mean Change From Baseline to Day 14 for REL-1017 (25 mg/d, 50 mg/d, and 25 mg/d + 50 mg/d groups) Compared With Placebo Group for the Selected MADRS and SDQ Cognitive Items

	Treatment Group	N	Least Square Mean Difference	P value	Effect Size
			Day 14		
MADRS item 6	Placebo	20			
	REL-1017 25 mg	16	−1.2	.030585	0.93086
	REL-1017 50 mg	18	−1.1167	.037433	0.64502
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−1.1559	.012929	0.75833
SDQ item 16	Placebo	20			
	REL-1017 25 mg	16	−0.875	.088525	0.5487
	REL-1017 50 mg	18	−0.97222	.051758	0.68368
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.92647	.03161	0.61989
SDQ item 22	Placebo	20			
	REL-1017 25 mg	16	−0.575	.10818	0.62064
	REL-1017 50 mg	18	−1.4222	.00011625	1.2997
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−1.0235	.0016381	0.97095
SDQ item 35	Placebo	20			
	REL-1017 25 mg	16	−0.9	.022684	0.78291
	REL-1017 50 mg	18	−1.2056	.0020484	1.1179
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−1.0618	.0016883	0.9587
SDQ item 36	Placebo	20			
	REL-1017 25 mg	16	−0.275	.52057	0.21329
	REL-1017 50 mg	18	−0.87222	.039037	0.69896
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.59118	.10637	0.46334
SDQ item 37	Placebo	20			
	REL-1017 25 mg	16	−0.8125	.04797	0.69711
	REL-1017 50 mg	18	−0.94444	.018579	0.77416
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.88235	.010858	0.74362
SDQ item 38	Placebo	20			
	REL-1017 25 mg	16	−0.7875	.033654	0.80092
	REL-1017 50 mg	18	−0.85	.018535	0.77116
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.82059	.0085499	0.78997
SDQ item 39	Placebo	20			
	REL-1017 25 mg	16	−0.675	.10478	0.53532
	REL-1017 50 mg	18	−1.1889	.0041341	1.0716
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.94706	.0082958	0.7947
SDQ item 42	Placebo	20			
	REL-1017 25 mg	16	−0.8	.088666	0.59226
	REL-1017 50 mg	18	−1.0222	.026219	0.79594
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−0.9175	.02063	0.70333

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire.

cognitive domains in MDD. This subanalysis of MADRS and SDQ data suggests that the rapid, robust, and sustained therapeutic effects of REL-1017 for MDD are not limited to improving mood but extend to subjective cognitive domains. These improvements in subjective cognitive measures support the postulated mechanism of action for REL-1017 as a promising rapid-acting antidepressant candidate that may restore impaired neural plasticity in patients with MDD and may signal disease-modifying potential for REL-1017 and other uncompetitive NMDAR channel blockers effective for MDD. Additionally, MDD symptomatology improvements extending to cognitive, motivational, anxiety, irritability, and sleep function as shown by our subanalysis and Fava and colleagues[26] may have meaningful implications for patient

quality of life and functioning, including working and social abilities, with a potentially positive socioeconomic impact. A better definition of the different areas of impairment may improve our understanding of the mechanism of disease of MDD and its impact on patient quality of life and function and the development of targeted interventions.

Among the domains affected in depression, cognition is an extremely important dimension related to loss of human capital. Cognitive impairment has been reported to affect function independent of mood symptoms and has been correlated with functional impairments. A significant percentage of patients successfully achieving conventional symptomatic remission do not return to premorbid functioning and experience decreases in working abilities

Figure 1. Least Square Mean Change From Baseline From Day 2 Through Day 14 for REL-1017 (25 mg/d, 50 mg/d, and 25 mg/d + 50 mg/d groups) Compared With Placebo Group for (A) MADRS Item 6, (B) SDQ Item 16, (C) SDQ Item 22, (D) SDQ Item 35, (E) SDQ Item 36, (F) SDQ Item 37, (G) SDQ Item 38, (H) SDQ Item 39, and (I) SDQ Item 42
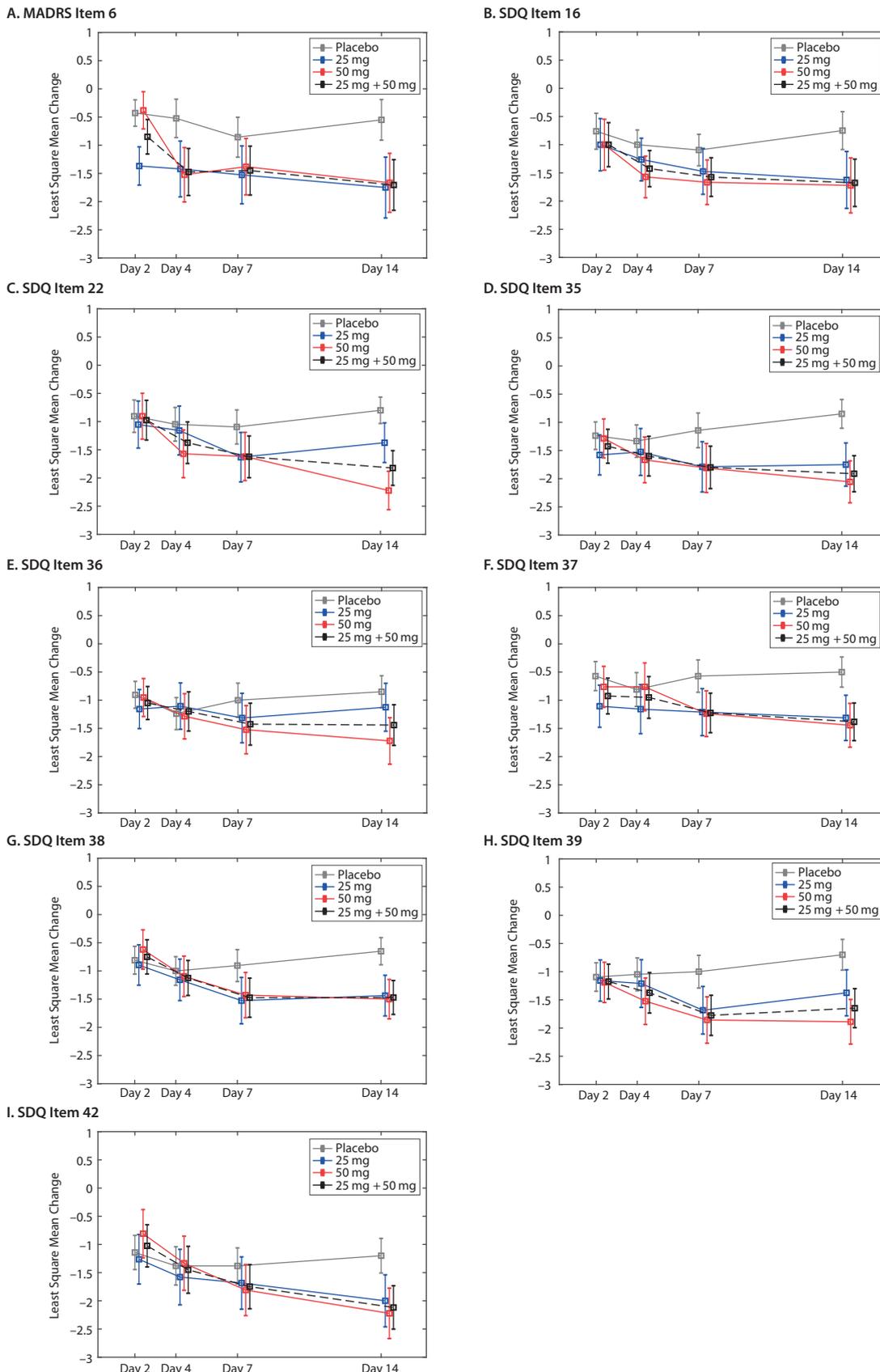
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire.

Table 4. Least Square Mean Change From Baseline to Day 14 for REL-1017 (25 mg/d, 50 mg/d, and 25 mg/d + 50 mg/d groups) Compared With Placebo Group for the Composite Cognitive Index 1[a] and Composite Cognitive Index 2[b]

			Day 14		
	Treatment Group	N	Least Square Mean Difference	P value	Effect Size
Composite Cognitive Index 1	Placebo	20			
	REL-1017 25 mg	16	−14.71	.018284	0.86289
	REL-1017 50 mg	18	−20.612	.00089908	1.1525
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−17.835	.00090287	1.0213
Composite Cognitive Index 2	Placebo	20			
	REL-1017 25 mg	16	−15.775	.0081705	1.0731
	REL-1017 50 mg	18	−18.573	.0015456	1.0171
	Combined active treatment groups (REL-1017 25 mg + REL-1017 50 mg)	34	−17.256	.00068677	1.0417

[a]Mean (MADRS item 6) (SDQ items 16, 22, 35, 36, 37, 38, 39, 42).
[b]0.5 (MADRS item 6) + 0.5 (SDQ item 16, 22, 35, 36, 37, 38, 39, 42).
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire.

Figure 2. Least Square Mean Change From Baseline From Day 2 Through Day 14 for REL-1017 (25 mg/d, 50 mg/d, and 25 mg/d + 50 mg/d groups) Compared With Placebo Group for the (A) Composite Cognitive Index 1[a] and (B) Composite Cognitive Index 2[b]

A. Composite Cognitive Index 1
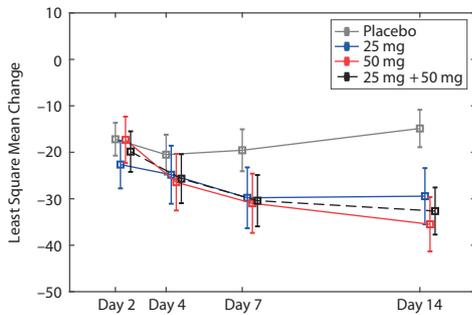
B. Composite Cognitive Index 2
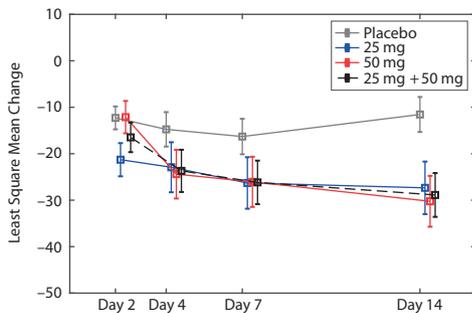
[a]Mean (MADRS item 6) (SDQ items 16, 22, 35, 36, 37, 38, 39, 42).
[b]0.5 (MADRS item 6) + 0.5 (SDQ items 16, 22, 35, 36, 37, 38, 39, 42).
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SDQ = Symptoms of Depression Questionnaire.

and productivity.[31] Clinical presentation of MDD, as defined by the *DSM-5*, includes cognitive impairment as a criterion item of a major depressive episode (MDE).[32] Domain-specific cognitive deficits in learning and memory, executive function, processing speed, and attention and concentration are highly replicated findings in patients with MDD presenting with an MDE.[33] It is important to note that improvements in mood may not translate into functional recovery.[34]

When treating MDD, cognitive impairments may persist during periods of symptomatic improvement, suggesting a lack of direct correlation between emotional and functional improvement.[31] The persistence of cognitive impairments after remission of depressive symptoms has been shown to contribute to the failure in achieving full functional recovery in MDD.[34,35] While efficacy testing of antidepressant drugs has generally focused on mood symptoms, emerging evidence indicates that a substantial percentage of patients may continue to exhibit clinically significant cognitive deficits that impact functional capacity despite remission of mood symptoms.[4,36] The inherent disconnect between mood and functional improvements indicates that antidepressants should ideally also target functionally relevant domains in addition to mood symptoms to provide a successful long-term remission and a global functional recovery in MDD.

The effect of antidepressant therapies on cognitive function remains controversial. Originally, selective serotonin reuptake inhibitors (SSRIs) did not appear to cause cognitive impairment in contrast to tricyclic antidepressants,[37] but there is conflicting evidence regarding this side effect, and many patients complain of concentration and memory impairment during their course of therapy with SSRIs.[38] A study reported that patients with obsessive-compulsive disorder and MDD, which were treated with SSRIs, experienced statistically significant memory loss after 8 weeks of treatment.[39]

To date, only 2 antidepressants (ie, duloxetine and vortioxetine) have demonstrated clinically relevant effects on cognitive dysfunction in MDD.[35] Vortioxetine has shown clinically relevant improvements in cognitive dysfunction, independent of mood symptoms, in adults aged 18–65 years with MDD.[40] Some studies have also shown a procognitive effect of duloxetine in patients with MDD, which may be secondary to the improvement in depressive symptoms.[41–43] Additionally, some findings suggest that ketamine treatment may exert beneficial effects on measures of executive functioning in patients with treatment-resistant depression. It is a testable hypothesis that the antisuicide effects of

ketamine may be in part mediated by improvements in executive function (eg, impulsivity).[44] There is a need to improve measurements and targeting of cognitive dysfunction and overall performance in occupational and functional domains. We analyzed item 6 from the MADRS, which is the one item that is most closely related to subjective cognitive function. This additional MADRS analysis is consistent with the conclusion of the SDQ-1 subscale, suggesting that REL-1017 may induce subjective cognitive improvement.

Finally, therapeutic results that are sustained after treatment discontinuation may signal neural plasticity-related effects that are potentially disease-modifying effects.[26] The goal of treatment in MDD is rapid and full functional recovery. Early assessment of MDD patients with standardized tools that evaluate a multiplicity of symptomatic domains and early treatment with drugs that potentially address these same domains may lead to improved functional outcomes.[4,45] Integration of emotional assessment with assessments of cognitive/motivational domains may improve our understanding of the pathophysiology of MDD and the potentially wide spectrum of efficacy of NMDAR antagonists, beyond the improvement of mood.

This study has several limitations. First, cognitive function was not assessed with objective neuropsychological tests of executive function, processing speed, attention, and learning and memory, but with subjective cognitive measures. Therefore, further research looking at objective measures of cognitive performance would be helpful to obtain definitive results regarding the efficacy of therapeutics for cognitive impairment in MDD. Other limitations include a short-term follow-up (up to 2 weeks) and a limited sample size. These results need to be replicated in larger and longer Phase 3 studies, which are currently underway and also include objective measures of cognitive function.

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