

A Phase 2a Double-Blind Randomized Trial of REL-1017 in Patients with Major Depressive Disorder: Analysis of Subscales from the Symptoms of Depression Questionnaire

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INTRODUCTION

- Major Depressive Disorder (MDD) is the second leading cause of disability and chronic disease burden in the United States, among all medical conditions¹.
- REL-1017 (esmethadone HCl; d-methadone HCl), is a novel N-methyl-D-aspartate receptor (NMDAR) channel blocker and potential rapid antidepressant currently in Phase 3 development².
- The importance of improving functional outcomes in MDD is increasingly recognized. The Symptoms of Depression Questionnaire (SDQ) (Table 1) was developed to capture the heterogeneity of symptoms of MDD³.

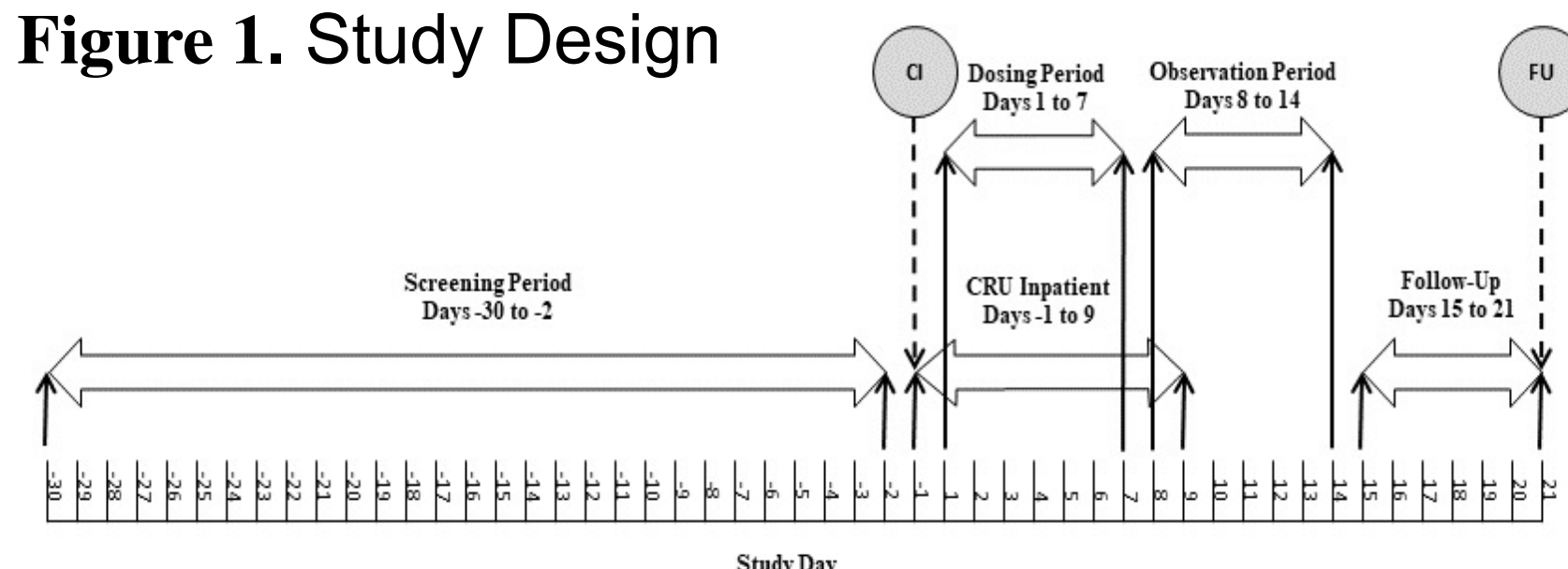
OBJECTIVE

- To determine the effect of REL-1017 on SDQ total score and SDQ subscale scores (Table 1) in order to better characterize the functional implications of its therapeutic potential.

METHODS

- Analysis of SDQ data from a double-blind, placebo-controlled, inpatient, two-dose, 25 and 50 mg, three-arm, 1:1:1, randomized, Phase 2a trial conducted at 10 centers in the United States².

Figure 1. Study Design



MEASURES

- The total SDQ consists of 44 items (Table 1) that can be analyzed as total score and can also be subdivided into 5 subscales (Table 1): lassitude, mood, cognitive/social functioning (SDQ-1); anxiety, agitation, anger, and irritability (SDQ-2); desire to be dead (SDQ-3); disruptions in sleep quality (SDQ-4); changes in appetite and weight (SDQ-5)³.
- Each item is rated on a 6-point scale, on the basis of a patient's perception of what is normal (score 2), what is better than normal (score=1), and what is worse than normal (scores=3 to 6).

DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. Drs. Fava, Folli, Pappagallo, Pani, and Manfredi are paid consultants of Relmada Therapeutics. Drs. Guidetti, Serra, De Martin, Mattarei are employed or have received fees from companies or Universities that have received payments or grants from Relmada. Dr. Manfredi is an inventor on esmethadone patents and other patents and patent applications.

Table 1. Items of SDQ Scale and Subscales

SDQ Items	SDQ-1	SDQ-2	SDQ-3	SDQ-4	SDQ-5
	Lassitude Cognition	Anxiety	Desire to be dead	Sleep quality	Appetite Weight
1 How has your mood been over the past week?			x		
2 How responsive has your mood been over the past week?	X				
3 How has your affect (or how you display your mood to the external world) been over the past week?	X				
4 How prone to tears have you been over the past week?		X			
5 How reactive have you been to positive things/events over the past week?	X				
6 How reactive have you been to negative things/events over the past week?		X			
7 How has your motivation/interest/enthusiasm been over the past week?	X				
8 How sensitive (e.g., thin-skinned) have you been to rejection/criticism over the past week?		X			
9 How optimistic have you been over the past week?			X		
10 How has your outlook on life been over the past week?			X		
11 How has your outlook on suicide been over the past week?			X		
12 How has your outlook on harming your body been over the past week?			X		
13 How has your ability to fall asleep been over the past week?				X	
14 How has your ability to stay asleep in the middle of the night been over the past week?				X	
15 How has your ability to stay asleep around the time before waking up been over the past week?				X	
16 How has your wakefulness/alertness been over the past week?	X				
17 How sleepy during the day have you been over the past week?	X				
18 How much have you been oversleeping at night over the past week?	X				
19 How much have you been oversleeping during the day over the past week?	X				
20 How has your energy been over the past week?	X				
21 How heavy (in arms or legs) have you felt over the past week?		X			
22 How slowed down have you felt over the past week?	X				
23 How agitated have you felt over the past week?		X			
24 How irritable have you been over the past week?		X			
25 Have you had anger attacks (suddenly feeling very angry and like exploding with anger) over the past week?		X			
26 How anxious/worried have you felt over the past week?		X			
27 Have you had panic attacks over the past week?		X			
28 How has your appetite been over the past week?				X	
29 Have you lost weight over the past week?				X	
30 Has your appetite been excessive over the past week?				X	
31 Have you gained weight over the past week?				X	
32 Have you had tachycardia/palpitations over the past week?	X				
33 Have you had pains or aches over the past week?		X			
34 Have you had gastrointestinal (stomach or bowel) symptoms over the past week?		X			
35 How has your ability to focus/sustain attention been over the past week?	X				
36 How has your ability to remember/recall information been over the past week?	X				
37 How has your ability to find words been over the past week?	X				
38 How has your sharpness/mental acuity been over the past week?	X				
39 How has your ability to make decisions been over the past week?	X				
40 How has your sexual functioning been over the past week?	X				
41 How has your social functioning been over the past week?	X				
42 How has your ability to work/study/function at home been over the past week?	X				
43 How guilty have you felt over the past week?		X			
44 How worthless have you felt over the past week?			X		

CONCLUSIONS

- In patients with MDD, aside for improving the overall CFB compared to placebo in SDQ and MADRS total scores (Fig. 2), adjunctive treatment with both tested doses of REL-1017 resulted in clinically meaningful and statistically significant improvements in cognitive/motivational, anxiety/irritability, and sleep specific SDQ subscales (Table 2).
- The rapid, robust, and sustained efficacy of REL-1017 for MDD is not limited to improving mood (Fig. 3 MADRS CFB), but potentially extends to cognitive, motivational, anxiety, irritability and sleep function (Table 2), with potentially meaningful implications for the patients' working and social abilities and potential downstream positive socioeconomic impact.
- These encouraging results in multiple areas affected by MDD may signal disease modifying effects of esmethadone that may potentially offer advantages over symptomatic treatments limited to mood improvement, as seen with currently available antidepressant treatments.
- As expected for a trial that excluded patients at suicidal risk, SDQ-3 (desire to be dead), did not show improvement. SDQ-5 (changes in appetite and weight), did not show changes possibly due to short treatment course and the variability of these two parameters in MDD.

RESULTS

- A total of 62 adult male and female patients (18 to 65 years of age) diagnosed with MDD participated in the trial. Treatment with REL-1017 resulted in rapid, robust, and sustained efficacy as adjunctive treatment in MDD with favorable tolerability, safety, and PK profiles.
- On Day 14, last day of efficacy measurement, the difference from placebo of the LS mean (90% CI) for REL-1017 25 mg and REL-1017 50 mg groups, respectively, showed improvement for both tested doses on SDQ total score [-23.2; p=0.0066 (effect size: 0.9); -26.8 p=0.0014 (effect size: 1.1) (Figure 2).
- Additionally, for SDQ subscales, REL-1017 25 mg and REL-1017 50 mg groups, respectively showed significant improvement as compared to placebo in 3 subscales: SDQ-1 [-13.9; p=0.0025 (effect size: 1.0); -15; p=0.0009 (effect size: 1.1)], SDQ-2 [-4.6; p=0.0398 (effect size: 0.7); -7.2; p=0.0012 (effect size: 1.1)] and SDQ-4 [-2.7; p=0.0055 (effect size: 1.0); -2.8; p=0.0029 (effect size: 1.0)]. There were no significant differences between the treated groups and placebo in SDQ-3 and SDQ-5 subscales (Table 2)

Figure 2. Change from baseline for SDQ total score

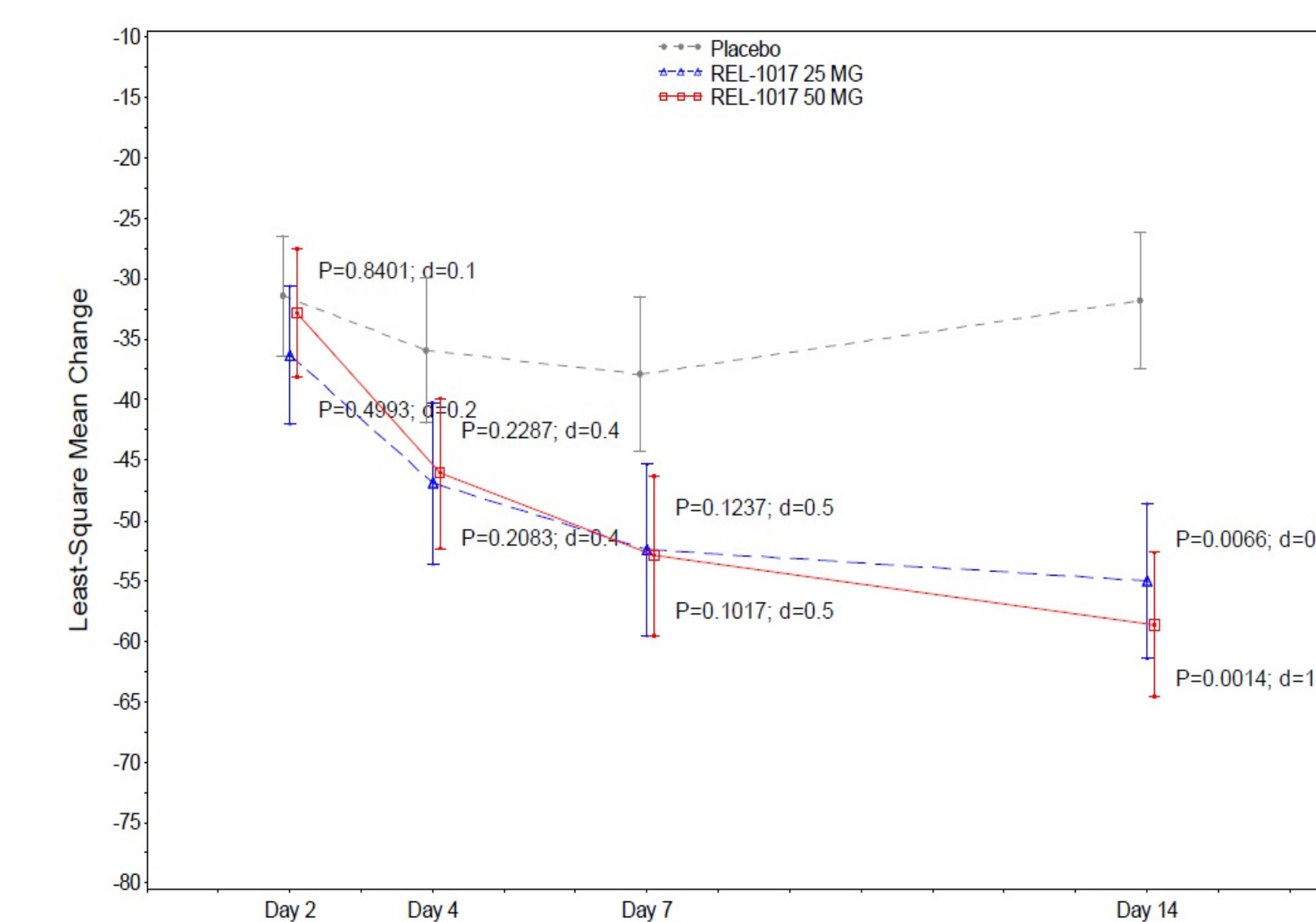


Figure 3. Change from baseline for MADRS total score

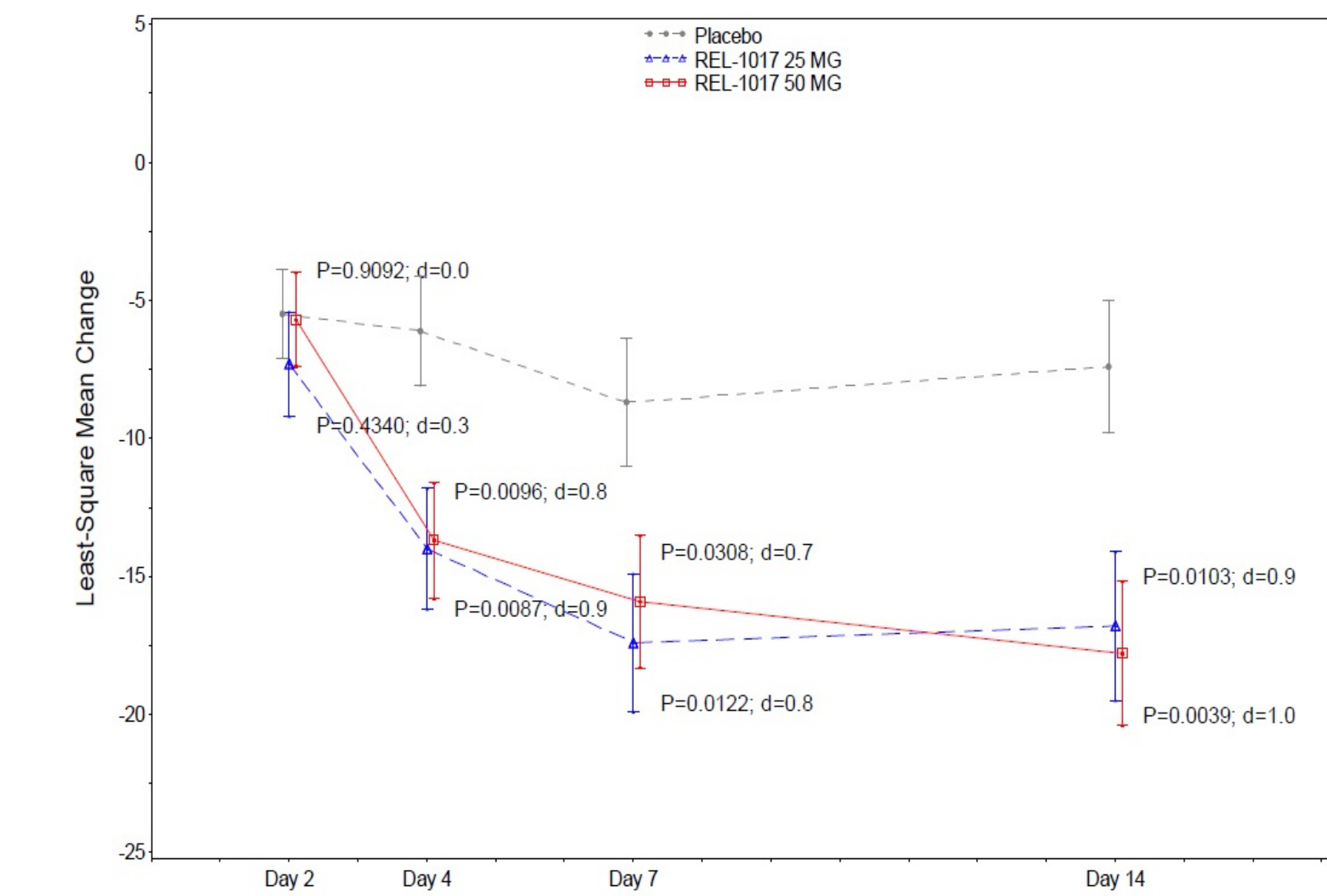


Table 2. Analysis of SDQ-5 subscales from Baseline to EOP (Day 14)

SDQ Subscale	Treatment Group	N	LS Mean (SE)	Difference of LS Mean: REL-1017 vs Placebo (90% CI)	P-value	Effect Size (90% CI)
Lassitude, mood, cognitive/social functioning (SDQ-1)	Placebo	20	-14.6 (3.0)			
	REL-1017 25 mg	16	-28.6 (3.5)	-13.9 (-21.3, -6.6)	0.0025	1.0 (0.5, 1.6)
	REL-1017 50 mg	18	-29.6 (3.2)	-15.0 (-22.1, -7.8)	0.0009	1.1 (0.6, 1.7)
Anxiety, agitation, anger, and irritability (SDQ-2)	Placebo	20	-8.9 (1.5)			
	REL-1017 25 mg	16	-13.4 (1.7)	-4.6 (-8.2, -0.9)	0.0398	0.7 (0.1, 1.2)
	REL-1017 50 mg	18	-16.0 (1.6)	-7.2 (-10.7, -3.7)	0.0012	1.1 (0.6, 1.6)
Desire to be dead (SDQ-3)	Placebo	20	-4.2 (0.8)			
	REL-1017 25 mg	16	-6.2 (1.0)	-2.0 (-4.1, 0.1)	0.1088	0.5 (0.0, 1.1)
	REL-1017 50 mg	18	-5.8 (0.9)	-1.7 (-3.7, 0.3)	0.1725	0.4 (0.0, 1.0)
Disruptions in sleep quality (SDQ-4)	Placebo	20	-2.5 (0.6)			
	REL-1017 25 mg	16	-5.3 (0.7)	-2.7 (-4.3, -1.1)	0.0055	1.0 (0.4, 1.6)
	REL-1017 50 mg	18	-5.3 (0.7)	-2.8 (-4.3, -1.3)	0.0029	1.0 (0.5, 1.6)
Changes in appetite & weight (SDQ-5)	Placebo	20	-1.9 (0.4)			
	REL-1017 25 mg	16	-1.7 (0.5)	0.2 (-0.8, 1.2)	0.7272	0.1 (0.0, 0.7)
	REL-1017 50 mg	18	-1.7 (0.4)	0.2 (-0.8, 1.2)	0.7472	0.1 (0.0, 0.6)

REFERENCES

- Vos T, Barber RM, Bell B, et al: Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study Lancet 2015; 386(9995):743–800.
- Fava M, Stahl S, Pani L, De Martin S et al: REL-1017 (esmethadone) as Adjunctive Treatment in Patients with Major Depressive Disorder: a Phase 2a Double-Blind Randomized Trial. In press.
- Pedrelli P, Blais MA, Alpert JE, Shelton RC, Walker RS, Fava M: Reliability and Validity of the Symptoms of Depression Questionnaire (SDQ). CNS Spectrums 2014; 19(6):535–46.

