Case Report: REL-1017 Reduces Abnormal Clinician Administered Dissociative States Scale Scores in Patients with Major Depressive Disorder

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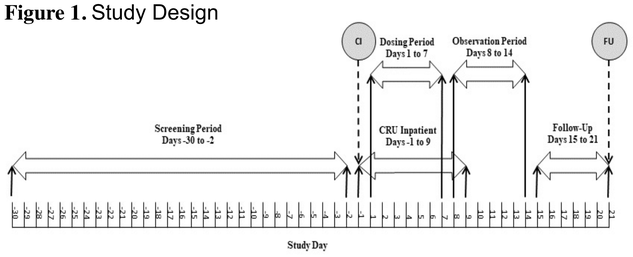
INTRODUCTION

- Dissociative symptoms may be seen in a subset of patients with Major Depressive Disorders (MDD).
- Uncompetitive NMDAR channel blockers have been proposed as a treatment for Post-Traumatic Stress Disorder (PTSD).
- REL-1017 is a novel low potency NMDAR channel blocker currently in Phase 3 studies for MDD.[1]

OBJECTIVE

To describe a case report series of patients with MDD and concurrent clinically meaningful abnormal dissociative symptoms from a double-blind, randomized, placebo-controlled, in-patient 7-day, phase 2 trial of 25mg and 50mg REL-1017 as adjunctive treatment for major depressive disorder (MDD).

Figure 1. Study Design



METHODS

- The subset of patients was selected retrospectively on the basis of an abnormal pre-treatment score on the Clinician Administered Dissociative States Scale (CADSS)[2].
- As part of the REL-1017 safety evaluation, the CADSS was administered to all study patients at 30 to 60 minutes pre-dose at baseline (Day 1), 2 hours post-dose on Day 1 (after first dose), 2 hours post-dose on Day 7 (after last dose), and prior to discharge on Day 9.

MEASURES

- The CADSS is a 23-item scale for the measurement of present-state dissociative symptoms with good inter-rater reliability and construct validity that can discriminate patients with dissociative disorders.
- Each item was scored on a 5-point Likert scale: 0= not at all, 1= slightly, 2=moderately, 3= considerably, 4= extremely.
- The total CADSS score is derived by adding the score for each of the 23 items (Table 1).
- A score of 4 or more on the CADSS total score is considered abnormal and clinically meaningful.
- The CADSS is subdivided into 4 subscales: sub-1 assesses symptoms of gaps in memory not due to ordinary forgetting (amnesia); sub-2 assesses out of body experiences and other distortions of the sense of one's own body (depersonalization); sub-3 assesses distortions in visual perception, such as seeing things as if they are in a tunnel or seeing things in black and white (derealization); sub-4 assesses single dissociative symptoms (items 20,21,22,23).

RESULTS

- Overall, there were no statistically significant changes from baseline in CADSS least square means vs placebo following administration of the study drug, indicating no meaningful dissociative effects from REL-1017.
- Among the 62 randomized patients, 4 patients (2 patients in the 25 mg arm (CADSS score 22 and 4), 1 patient in the 50 mg arm (CADSS score 35), and 1 patient in the placebo arm (CADSS score 6) were found to have a CADSS score of at least 4 on Day 1 before study drug administration (Day 1 pre-dose). Among these 4 patients, starting on Day 1, the 2 subjects in the 25 mg subgroup and 1 subject in the 50 mg subgroup showed a clinically meaningful decrease in dissociative symptoms after the first oral administration of REL-1017, while the single patient in the placebo group showed no change in the dissociative symptoms.
- CADSS scores on Day 1 pre-dose, Day 1 post-dose, Day 7 post last dose, and on Day 9 prior to discharge were 22-2-6-0; 4-0-0-0; 35-14-9-0, and 6-6-n/a-n/a, for the 2 patients treated with 25 mg REL-1017, the single patient treated with 50 mg REL-1017, and the single patient treated with placebo, respectively (Table 2).

Table 1. Items of CADSS Scale and Subscales

CADSS	Items	Sub-1	Sub-2	Sub-3	Sub-4
		Amnesia	Depersonalization	Derealization	Single Items
1	Do things seem to be moving in slow motion?			X	
2	Do things seem to be unreal to you, as if you are in a dream?			X	
3	Do you have some experience that separates you from what is happening?		X		
4	Do you feel as if you are looking at things from outside your body?		X		
5	Do you feel as if you are watching the situation as an observer or spectator?		X		
6	Do you feel disconnected from your own body?		X		
7	Does your sense of your own body feel changed?		X		
8	Do people seem motionless/dead/mechanical?			X	
9	Do objects look different than you would expect?			X	
10	Do colors seem diminished in intensity?			X	
11	Do you see things as if you were in a tunnel?			X	
12	Does this interview seem to take longer than you would have expected?			X	
13	Do things seem to be happening very quickly, as if there is a lifetime in a moment?			X	
14	Do things happen that you later cannot account for?	X			
15	Do you space out, or in some way or another lose track of what is going on?	X			
16	Do sounds almost disappear or become stronger than you would have expected?			X	
17	Do things seem to be very real as if there is a special sense of clarity?			X	
18	Does it seem as if you are looking at the world through a fog?			X	
19	Do colors seem brighter than expected?			X	
20	Do you feel confused on who you really are?				X
21	Do you feel that parts of yourself do not fit together?				X
22	Do you have gaps in your memory?				X
23	Do you feel like you have more than one identity?				X

Table 2. CADSS Score for Subjects at Evaluation Points

Subject	CADSS Score On Day 1 pre-dose	CADSS Score On Day 1 post-dose	CADSS Score On Day 7 post last dose	CADSS Score On Day 9
Subject 003-004 **25mg**	22 (items 14,5,6,1,17,20,21,22,23)	2	6	0
Subject 005-006 **25mg**	4 (items 15,12)	0	0	0
Subject 003-003 **50mg**	35 (items 14,15,3,4,5,6,7,1,2,8,9,10,11,12,18,20,21,22,23)	14	9	0
Subject 003-001 **Placebo**	6 (items 5,6,8,11,22)	6	n/a	n/a

CONCLUSIONS

- These retrospective data potentially signal that REL-1017 may determine a rapid and sustained improvement in dissociative symptoms in patients with MDD and concurrent clinically meaningful abnormal dissociative symptoms assessed by a CADSS score of 4 or above.
- Ongoing Phase 3 trials with oral 25 mg REL-1017 once daily for 28 days are expected to enroll a total of 1200 outpatients with MDD.
- These studies will potentially generate additional data that may support the initiation of controlled studies with REL-1017 for the treatment of PTSD .

DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. Drs. Fava, Pani, Folli, Pappagallo, and Manfredi are paid consultants of Relmada Therapeutics. Drs. Guidetti, Serra, and De Martin 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.

REFERENCES

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