Clotilde Guidetti 1; Luca Pani 2,3,4; Giulia Serra 1; Marco Pappagallo 3; Maurizio Fava 5; Paolo Manfredi 3

1) Child and Adolescent Psychiatry Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
2) Department of Psychiatry & Behavioral Sciences, University of Miami, School of Medicine, Miami, FL, USA
3) Relmada Therapeutics, New York, NY, USA
4) Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
5) Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Title: Case report: REL-1017 reduces abnormal Clinician Administered Dissociative States Scale scores in patients with major depressive disorder

Background: Dissociative symptoms may be found in a subset of patients with Major Depressive Disorders (MDD). The Clinician-Administered Dissociative States Scale (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. The total CADSS score is derived by adding the score for each of the 23 items. A score of 4 or more on the CADSS is considered abnormal and clinically meaningful. Uncompetitive N-Methyl-D-aspartic acid receptor (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. **Methods:** This retrospective case series describes a subset of patients from a double-blind, randomized, placebo-controlled, in-patient 7-day, phase 2 trial of oral, once daily, 25 mg (75 mg loading dose on Day 1, first dose) and 50 mg REL-1017 (100 mg loading dose on Day 1, first dose) as adjunctive treatment for major depressive disorder (MDD). This subset of patients was selected based on abnormal CADSS score at baseline, pre-treatment with the study drug. As part of REL-1017 safety evaluation, the CADSS was administered at four timepoints to all study patients: 1) 30-60 minutes pre-treatment at baseline on Day 1; 2) 2 hours post-treatment on Day 1 (after first dose of study drug); 3) 2 hours post-treatment on Day 7 (after last dose); 4) prior to discharge on Day 9 (2 days after last dose). **Results:** Among the 62 randomized patients, four patients had a CADSS score of at least 4 on Day 1 before study drug administration (2 patients in the 25 mg arm (CADSS score 22 and 4); 1 patient in the 50 mg arm (CADSS score 35); 1 patient in the placebo arm (CADSS score 6). Among these 4 patients, starting on Day 1, 2 hours post-treatment, the 2 subjects in the 25 mg subgroup (75 mg loading dose) and 1 subject in the 50 mg subgroup (100 mg loading dose) showed a clinically meaningful decrease in their CADSS score, while the single patient in the placebo group showed no change. CADSS scores on Day 1 pre-treatment, Day 1 post-treatment, Day 7 post last treatment 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 two patients in the 25 mg REL-1017 subgroup, the single patient in the 50 mg REL-1017 subgroup, and the single patient in the placebo group, respectively. **Conclusions:** These retrospective case report data potentially signal that REL-1017 may determine rapid and sustained improvement in patients with MDD and concurrent clinically meaningful dissociative symptoms assessed by a CADSS score of 4 or above. Ongoing Phase 3 trials with REL-1017 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.

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