Effect of Percentage of Life-Years From the Start of Major Depressive Disorder on the Therapeutic Response to REL-1017

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Background: Chronicity of depression has not proven to be a reliable predictor of response to standard antidepressant treatments (SATs) or response to placebo. However, early improvements after treatment are generally associated with better outcomes and earlier and more severe first episodes of depression may play a role in the prognosis of MDD. NMDAR channel blockers are emerging as a promising novel treatment for MDD. The mechanism of action of NMDAR channel blockers is related to BDNF and mTor-dependent neural plasticity. REL-1017 (dextromethadone) is a novel safe and well tolerated NMDAR channel blocker that increases BDNF in humans. In a recent Phase 2 study, REL-1017 showed rapid, robust, and sustained therapeutic effects in patients with MDD. We investigated whether REL-1017 may be more effective in MDD patients with a lower percentage of life-years from the start of MDD.

Methods: We reviewed historical data on the start date of MDD from a Phase 2a study of REL-1017 as adjunctive treatment in patients with MDD who failed 1-3 adequate SATs. The percentage of life-years spent from the start of MDD was calculated by computing the number of years from the start date of MDD recorded in the REL-1017 database divided by age and multiplied by 100. Patients were then divided as below and above the median value. The MADRS change from baseline (CFB) was compared between REL-1017 and placebo groups by Student' t test for unpaired data.

Results: The median percentage of life years from the start date of MDD for the 62 randomized patients was 23%. At 25 mg and 50 mg doses, patients below the median percentage of life-years were significantly more responsive to REL-1017 vs. placebo. In contrast, among patients above the median percentage of life-years, the response to REL-1017 vs. placebo was not statistically significant.

Conclusion: In this of a Phase 2 trial, 25 and 50 mg doses of REL-1017 were significantly effective vs. placebo in reducing MADRS scores below the median (23%) for percentage of life-years from the start of MDD. When the same data were analyzed for patients above the median (23%) for percentage of life-years, results did not reach statistical significance at either REL-1017 dose. This differential therapeutic effect related to chronicity of MDD has not been previously reported for monoaminergic drugs, atypical antidepressants or ketamine. The differential therapeutic effects of REL-1017 when administered earlier compared to later in the course of MDD may signal potential disease modifying effects related to neural plasticity. If these preliminary findings are confirmed in a planned Phase 3 trial, REL-1017 could become first line treatment for patients with recent onset of MDD. In the context of MDD clinical trials, a careful analysis of patients above or below the median for years of life from the start of MDD may signal treatments with potentially disease modifying effects.

References [3 required]

De Martin S, Vitolo O, Bernstein G, Alimonti A, et al. The NMDAR Antagonist Dextromethadone Increases Plasma BDNF Levels in Healthy Volunteers Undergoing a 14-Day In-Patient Phase 1 Study. ACNP 57th Annual Meeting: Poster Session II. Neuropsychopharmacol. 2018;43:228–382.
Fogaça MV, Fukumoto K, Franklin T, Liu RJ, Duman CH, Vitolo OV, Duman RS. N-Methyl-D-aspartate receptor antagonist d-methadone produces rapid, mTORC1-dependent antidepressant effects. Neuropsychopharmacology. 2019;44(13):2230-8.
Papakostas GI, Fava M. Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. Dialogues Clin Neurosci. 2008;10(4):439-451.