Robust Antidepressant Efficacy of the Novel 5-HT2A Receptor Agonist GM-2505 in a Double Blind, Randomized, Controlled Phase 2a Trial in Patients with Mdd

Submission ID 3005961

Submission Type Pharmaceutical Pipeline

Topic Depressive Disorders

Status Submitted

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SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract GM-2505 is a novel 5-hydroxytryptamine2A (5-HT2A) receptor agonist and serotonin (5-HT) releaser with a short half-life and duration of psychotropic effects. It is currently being investigated for the treatment of major depressive disorder (MDD) and other neuropsychiatric disorders. Described here are the results of a randomized, double-blind, active-controlled Phase 2a trial of GM-2505 in 40 male and female patients with recurrent MDD. All participants were antidepressant-free for at least 6 weeks prior to screening and remained off antidepressant medication throughout the trial. All patients were administered two intravenous doses of GM-2505 with a 2-week interval between dosing. In Arm 1, half of the patients initially received a low dose on Day 1 as active control, which produced measurable, but minimal, psychotropic effects in healthy volunteers (HVs). In Arm 2, the other half received a moderate dose on Day 1, which exerted robust psychedelic effects in HVs. On Day 15, all patients received a high dose, which induced maximal psychedelic effects in HVs. The patients were monitored for safety and antidepressant responses through Day 29, with a priori timepoints for comparing MADRS change from baseline scores at Day 14 and Day 29. This allowed for initial examination of dose-response for efficacy, safety, PK, and PD. Statistically significant decreases in MADRS scores were observed in both study arms and decreases were always greater for Arm 2, which received two robustly psychedelic doses. At Day 14, there was an effect size of ~1.0 for a between-subjects comparison of the least square mean change from baseline in MADRS scores for Arm 2 treated with the moderate dose compared to Arm 1 treated with the active control low dose. At Day 29, two weeks following the high dose, MADRS scores further significantly decreased in both arms based on a within-subject comparison of Day 29 to Day 14 and the MADRS change from baseline in Arm 2 was significantly greater than in Arm 1 based on a between-subjects comparison. Further, there were robust categorical MADRS response and remission rates indicating that both the moderate and high doses were efficacious. The superior response in Arm 2 also suggests that a regimen of two robustly psychedelic doses, administered two weeks apart, produces greater efficacy than a single robust psychedelic dose. There were no serious adverse events (SAEs) and the treatment emergent adverse events (TEAE)

profile was similar to that in HVs. There were no patients with suicidal ideation and a plan/intent. GM-2505 induced expected transient increases in systolic and diastolic blood pressure and pulse rate. In conclusion, GM-2505 is a promising, best-in-class 5-HT2A receptor agonist with the potential to safely and effectively treat patients with MDD, offering a novel and transformative approach to depression treatment.

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