Safety and Efficacy of GH001 in Treatment-Resistant Depression: Results from a Phase 2b, Double-Blind, Randomized, Controlled Trial

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Abstract Background: Treatment-resistant depression (TRD) affects approximately 30% of patients treated for major depressive disorder (MDD) and is associated with higher rates of comorbidity, hospitalization, mortality, suicide, and poorer quality of life compared to MDD patients who are more responsive to treatment. Current therapies for TRD are limited and there is a great unmet need for treatments that offer rapid and sustained effects. Mebufotenin acts as a non-selective serotonin (5-HT) agonist with highest affinity for the 5-HT1A receptor subtype. Early phase trials in patients with TRD suggest that GH001, which is a synthetic form of mebufotenin for pulmonary inhalation, may have the potential to induce ultra-rapid improvement in depressive symptoms. The aim of this placebo-controlled trial was to investigate the safety and efficacy of GH001 in patients with TRD.

Methods: This Phase 2b multicenter trial planned to assess the efficacy and safety of GH001 in 80 patients with TRD. The trial consisted of two parts: Part 1, fully described here, was a randomized, double-blind (DB), placebo-controlled trial with follow up to 7 days post-dose. Patients were randomized in a 1:1 ratio to receive GH001 or placebo. Part 2 is an ongoing 6-month open-label extension (OLE), where up to five GH001 retreatments may be administered, depending on the patient's clinical status.
In Part 1, patients were randomized to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo on a single day. There was a 1-hour interval between doses. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability of the previous dose. As in previously conducted GH001 trials, this trial was conducted under the supervision of physicians, nurses, and other qualified healthcare professionals, but without any planned psychotherapeutic intervention before, during, or after dosing. The primary endpoint of Part 1 of this trial was mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to Day 8, assessed

by a rater without knowledge of the treatment condition.

Results: A total of 81 patients with TRD were enrolled in Part 1 with 40 patients randomized to receive GH001 IDR and 41 patients to receive placebo IDR. Change in MADRS total score from baseline to Day 8 was significantly greater with GH001 than with placebo (difference of least square means=-15.5; SE=1.7); likewise, statistically significant reductions were observed in the GH001 group at 2 hours postdose and on Day 2. Remission (MADRS total score ≤10) was achieved in 57.5% of patients treated with GH001 on Day 8 compared with 0% in the placebo group (P<0.0001). Inhalation of GH001 was well tolerated and no serious adverse events were reported. All treatment-emergent adverse events were mild or moderate with no severe adverse events. Preliminary results from 54 patients who have completed the ongoing OLE indicate that GH001 can maintain long-term remission from TRD with 77.8% of patients (n=42) in remission at 6 months. This is achieved with relatively infrequent treatment visits and rapid reduction in MADRS after each GH001 re-treatment. No serious adverse events have been reported in the OLE to date.

Conclusion: In this randomized trial, GH001 demonstrated significant improvements in depressive symptoms with an acceptable safety profile, supporting the potential of GH001 as a novel, rapid-acting treatment for TRD.

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