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GH001 vs Placebo in Patients With Treatment-Resistant Depression
A Randomized Clinical Trial

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IMPORTANCE Few pharmacotherapies are approved for treatment-resistant depression, and many patients do not achieve remission following treatment with those therapies.

OBJECTIVE To examine the efficacy and safety of single-day treatment with a synthetic formulation of inhaled mebufotenin (GH001) vs placebo in patients with treatment-resistant depression.

DESIGN, SETTING, AND PARTICIPANTS This was a 7-day, randomized, double-blind, placebo-controlled phase 2b trial with a 6-month open-label extension phase conducted at 16 sites in Europe from May 2023 to March 2025. Adult patients aged 18 to 64 years with treatment-resistant depression, defined as nonresponse to 2 to 5 oral antidepressant treatments, with current episode duration of up to 2 years were included. Of 128 assessed for eligibility, 81 were randomized and completed the placebo-controlled period of the trial.

INTERVENTIONS Patients were randomly assigned 1:1 to receive an individualized dosing regimen of up to 3 escalating doses of GH001 (6, 12, and 18 mg) or a placebo individualized dosing regimen on a single day (day 1).

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the change from baseline to day 8 in Montgomery-Åsberg Depression Rating Scale total score (range, 0-60; higher scores indicate greater severity of depression), comparing GH001 with placebo. Secondary end points included remission (Montgomery-Åsberg Depression Rating Scale score ≤10) at day 8.

RESULTS Among the 81 patients randomized to GH001 (n = 40) or placebo (n = 41), the mean (SD) age was 41.6 (11.4) years and 43.9 (10.9) years and 24 (60.0%) and 22 (53.7%) were female, respectively. Change in Montgomery-Åsberg Depression Rating Scale score from baseline to day 8 was significantly greater for GH001 vs placebo (least squares mean difference [SE], −15.5 [1.7]; $P < .001$; effect size, −2.0). Day 8 remission rates were 23/40 (57.5%) with GH001 and 0/41 (0%) with placebo. No severe or serious adverse events were reported in the placebo-controlled period.

CONCLUSIONS AND RELEVANCE In this study, an individualized dosing regimen of inhaled GH001 resulted in significant improvements in depression symptoms relative to placebo and was well tolerated, supporting its potential as a novel, rapid-acting treatment for treatment-resistant depression.

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Visual Abstract

Supplemental content

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Fewer than half of patients with major depressive disorder treated with standard antidepressants achieve remission.[1,2] Failure to show improvement following at least 2 adequate trials of antidepressant medications is defined as treatment-resistant depression (TRD).[3-5] TRD is associated with profound impairment in functioning, often leading to substantial economic burden to health care systems.[6-9] Few treatments are currently approved for TRD in the US.[10] Thus, there is a great unmet need for safe, effective pharmacotherapies offering rapid and sustained remission of TRD.

A growing body of evidence indicates that psychedelics (eg, psilocybin, *N,N*-dimethyltryptamine [DMT], and mebufotenin [5-MeO-DMT]) may provide rapid symptom reduction in patients with TRD.[11-13] Mebufotenin is a rapid-acting psychoactive molecule that acts as a nonselective serotonin (5-HT) agonist with high affinity for the 5-HT_{1A} receptor subtype.[14,15] A preliminary assessment of the antidepressant activity of GH001, a synthetic inhaled formulation of mebufotenin, was conducted in an early-phase clinical trial of TRD (mean change from baseline in Montgomery-Åsberg Depression Rating Scale [MADRS] total score at day 8: −21.0).[13] GH001 was well tolerated in that trial[13] and in trials in healthy volunteers.[16]

This randomized clinical trial for mebufotenin assessed the efficacy, safety, and tolerability of an individualized dosing regimen (IDR) of GH001 compared with placebo IDR in treating depression symptoms in patients with TRD.

Key Points

Question Does single-day treatment with inhaled mebufotenin (GH001) using an individualized dosing regimen reduce symptoms of depression in patients with treatment-resistant depression?

Findings In this randomized, double-blind phase 2b trial among 81 patients, GH001 treatment significantly reduced Montgomery-Åsberg Depression Rating Scale scores from baseline to day 8 vs placebo. Patients treated with GH001 experienced significantly greater remission than those receiving placebo.

Meaning Significant improvements in depression symptoms observed after GH001 vs placebo treatment support its potential as a novel, rapid-acting treatment for treatment-resistant depression.

Methods

Trial Oversight

This phase 2b clinical trial was conducted from May 2023 to March 2025 at 16 European sites, per International Council for Harmonisation Good Clinical Practice guidelines and ethical principles derived from the Declaration of Helsinki.[17] The independent ethics committee for each trial site approved the protocol before patient enrollment. All patients provided written informed consent. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients

Eligible patients were adults aged 18 to 64 years who met *DSM-5* criteria for major depressive disorder, confirmed by the Mini-International Neuropsychiatric Interview version 7.0.2,[18] and had TRD per the regulatory framework established by the US Food and Drug Administration[5] (current episode duration ≤2 years, nonresponse to ≥2 and ≤5 oral antidepressant treatments after ≥6 weeks, using the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]). Eligible patients had screening and baseline scores of ≥20 on the 17-item Hamilton Depression Rating Scale[19] (HAM-D-17) (eTable 1 in Supplement 2). The current major depressive episode was validated using the Massachusetts General Hospital-Structured Assessment for Evaluation of Risk (MGH-SAFER) criteria interview.[20]

Antidepressants, antipsychotics, and medications with monoamine oxidase inhibitor activity were prohibited during the trial and within 2 weeks prior to baseline. The decision to discontinue medication was made by patients and investigators, based on clinical judgement, with involvement of patients' physicians or psychiatrists; no medication was discontinued for the sole purpose of trial participation. Tapering and washout were conducted at investigators' discretion per normal practice. Initiation or modification of psychotherapy during the trial was also prohibited (see the protocol in Supplement 1).

Study Design

The trial included a 7-day, double-blind, placebo-controlled period (part 1) and a 6-month open-label extension (OLE) (part 2; eFigure 1 in Supplement 2). In part 1, patients and all site staff involved in administration of the study treatment, efficacy and safety assessments, and patient care during the trial were blinded to treatment assignment (ie, included in the term *double-blind*).

On day 1 of part 1, eligible patients were randomly assigned 1:1 to GH001 or placebo. After completion of baseline assessments, study drug was administered using an IDR in which patients received up to 3 escalating doses of GH001 (6, 12, and 18 mg) or a placebo IDR on a single day with a 1-hour interval between doses. Based on experience in early GH001 trials, an IDR was used to optimize therapeutic benefit to patients with TRD. A second or third dose of GH001 or placebo was administered if the previous dose was well tolerated according to the trial physician's judgement (based on vital signs and adverse events [AEs]) and if the patient did not achieve an intense psychoactive effect (peak experience; defined as a mean score of 75 or higher on the Peak Experience Scale[21] [see the protocol in Supplement 1]) following the previous dose. The study drug was administered via inhalation after vaporization using the Volcano Medic 2 Vaporization System (Storz & Bickel). As part of the informed consent process, and again prior to dosing, patients were informed of the potential psychoactive effects of the study drug.

Day 1 efficacy assessments were conducted 2 hours after the final IDR dose; safety was assessed after each dose and at discharge according to the assessment schedule in eTable 2 in Supplement 2. Follow-up efficacy and safety assessments were conducted on day 2 (telephone) and day 8 (in-person visit).

Following completion of part 1, all patients from the GH001 and placebo groups were automatically enrolled in the 6-month OLE, during which they were eligible for up to 5 GH001 IDR treatments. OLE treatments were administered based on MADRS score criteria (eFigure 1 in Supplement 2), with the goals of achieving and maintaining remission and evaluating long-term safety. Assessments in both parts were conducted using the same procedures.

For this report, outcomes of patients in remission on day 8 of part 1 are described across the 6-month OLE to permit assessment of durability of response after 1 GH001 single-day IDR treatment. Time to first retreatment, number of retreatments received in part 2, and remission rate at 6 months are reported. A detailed description of part 2, including reproducibility of psychoactive effects, tolerability of repeated dosing, and outcomes of those who switched from placebo to GH001 will be reported subsequently.

This trial was conducted under the supervision of qualified health care professionals, providing psychological support per standard of care, but without any planned psychotherapeutic intervention before, during, or after dosing. Patients remained under supervision with medical support available until they were determined to be discharge ready. Preparation of GH001 and placebo for administration and criteria for dose escalation per the IDR are described in the protocol in Supplement 1.

Efficacy End Points

The primary efficacy end point was change in MADRS total score (range, 0-60; higher scores indicate greater severity of depression) from baseline to day 8 vs placebo. Secondary efficacy end points included proportions of patients in remission (MADRS score ≤10) or with treatment response (≥50% reduction from baseline MADRS score) and change from baseline to day 8 in Hamilton Rating Scale for Anxiety (HAM-A),[22] Clinical Global Impression–Severity (CGI-S),[23] and Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)[24] scores. To reduce the risk of functional unblinding, MADRS assessments were administered remotely by blinded independent raters who were not involved in MGH-SAFER or HAM-D-17 screening, administration of GH001, assessment of psychoactive effects, collection of safety data, or care of the patient. Because GH001 potentially could be associated with transient AEs related to psychoactive effects, MADRS raters could not access or review patient safety records. Trial team members received training to mitigate unblinding.

Safety End Points

Safety and tolerability end points included incidence of treatment-emergent AEs (TEAEs), AEs of special interest, serious AEs, and AEs leading to discontinuation. TEAEs were classified according to the *Medical Dictionary for Regulatory Activities* version 26.0. Additional safety assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS), Modified Observer's Assessment of Alertness and Sedation Scale (MOAA/S), Clinician-Administered Dissociative States Scale (CADSS), and the Clinical Assessment of Discharge Readiness (CADR), are described in eTable 2 in Supplement 2.

Psychoactive Effects

Psychoactive effects were assessed using the Peak Experience Scale,[21] 30-item Mystical Experience Questionnaire,[25] and Challenging Experience Questionnaire.[26] Results are reported in the eTables 6-8 in Supplement 2.

Statistical Analysis

A total sample size of 71 patients was estimated to provide 90% power (1-sided α = .05) to detect a between-group difference of 7 points in mean change from baseline in MADRS score at day 8, assuming an SD of 10, based on previous findings.[13] Eighty patients were targeted for randomization, assuming a drop-out rate of approximately 10%.

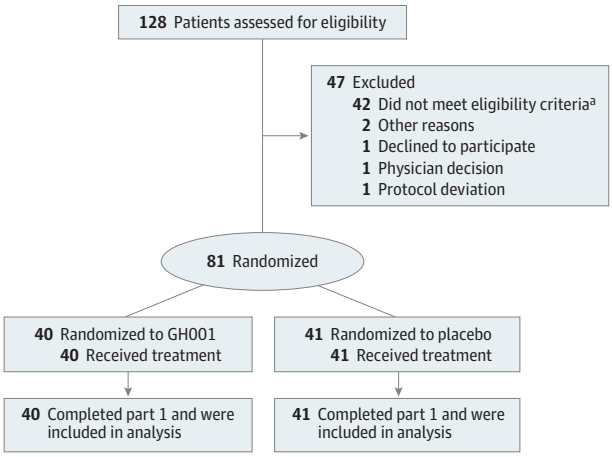
Efficacy and safety analyses included all randomized patients who received at least 1 dose of the study drug. Change in primary endpoint was analyzed by analysis of covariance with treatment and baseline MADRS score in the model; effect size (Cohen *d*) was calculated. Treatment effect was estimated with a 2-sided 95.18% CI, adjusted using an α-spending approach[27] because an interim analysis was conducted (see the protocol in Supplement 1) with a 2-sided *P* value. Continuous secondary efficacy measures were analyzed by analysis of covariance with treatment and baseline outcome value in the model (without alpha adjustment). Dichotomous efficacy measures were analyzed using Mantel-Haenszel tests (treatment by outcome variable) and 2-sided 90% CIs. Number needed to treat for remission was calculated. Secondary efficacy measures were considered descriptive and analyzed without adjustment for multiple comparisons. Additional statistical methods are included in the eMethods in Supplement 2.

Results

Patient Disposition and Treatment Exposure

Eighty-one patients were enrolled and randomized to treatment (GH001, n = 40; placebo, n = 41); all patients completed part 1 (**Figure 1**). In the GH001 group, the mean (SD) age was 41.6 (11.4) years; 24 (60.0%) were female and 16 (40.0%) were male. In the placebo group, the mean (SD) age was 43.9 (10.9) years; 22 (53.7%) were female and 19 (46.3%) were male. Baseline demographic and clinical characteristics were comparable in GH001 and placebo groups (**Table 1**; eTable 3 in Supplement 2). Among patients randomized to a single-day GH001 IDR, 9 of 40 (22.5%) received one 6-mg dose, 21 of 40 (52.5%) received 6- and 12-mg doses, and 10 of 40 (25.0%) received 6-, 12-, and 18-mg doses. The IDR was administered with a 1-hour interval between doses. The median duration of psychoactive effect ranged from 9.0 to 14.0 minutes for 6-, 12-, and 18-mg GH001 doses (Table 1). All patients assigned to placebo IDR received 3 placebo doses. Although no placebo-treated patients had a peak experience, all 41 had a maximum Peak Experience Scale score greater than 0 (median [range] duration of psychoactive effect, 0 [0-15] minutes).

Figure 1. Patient Flow Diagram



[a]Reasons for failure to meet eligibility criteria are listed in eTable 4 in Supplement 2.

Part 1 Efficacy

Least squares mean (SE) change in MADRS score from baseline to day 8 was −15.2 (1.2) for patients treated with GH001 (n = 40) and 0.3 (1.2) for patients treated with placebo (n = 41). The least squares mean difference (SE) was −15.5 (1.7; $P < .001$; Cohen d, −2.0) (**Figure 2**). At day 8, 23 of 40 (57.5%) GH001-treated patients and 0 of 41 placebo-treated patients were in remission (MADRS score ≤10; number needed to treat = 2), and 24 of 40 (60.0%) and 0 of 41, respectively, were responders (≥50% reduction from baseline in MADRS score; number needed to treat = 2). Significant mean improvements from baseline in HAM-A total score, CGI-S score, and Q-LES-Q-SF total score were observed for GH001 vs placebo at day 8 (**Figure 3**). A post hoc analysis of CGI-S at baseline and day 8 indicated a reduction in severity of illness overall (eFigure 2 in Supplement 2).

Part 1 Safety

TEAEs occurred in 29 of 40 (72.5%) GH001-treated patients and 3 of 41 (7.3%) placebo-treated patients. The most common TEAEs in GH001-treated patients were nausea (17 patients [42.5%]), salivary hypersecretion (8 patients [20.0%]), paraesthesia (8 patients [20.0%]), dysgeusia (3 patients [7.5%]), and headache (3 patients [7.5%]); of those, only headache was reported in the placebo group (1 patient [2.4%]) (**Table 2**); all TEAEs reported in the GH001 group were mild or moderate in severity. AEs of special interest reported in GH001-treated patients included memory impairment and affect lability (2 patients [5.0%] each) and agitation, anxiety, confusional state, euphoric mood, visual hallucination, and somnolence (1 patient [2.5%] each). No severe or serious TEAEs or TEAEs of flashbacks were reported in either treatment group. No patients discontinued GH001 or placebo because of TEAEs.

In the GH001 group, suicidal ideation was reported by 7 of 40 (17.5%) patients at baseline and 4 of 40 (10.0%) at day 8. No GH001-treated patients developed new-onset suicidal ideation between baseline and day 8. In the placebo group, 5 of 41 (12.2%) patients reported suicidal ideation both at baseline and at day 8, 2 (4.9%) reported suicidal ideation at baseline but not day 8, and 2 (4.9%) patients without baseline suicidal ideation reported it at day 8. C-SSRS scores and MADRS suicidality item scores at baseline and day 8 are summarized in eFigures 3 and 4 in Supplement 2. No suicidal behaviors were reported in GH001- or placebo-treated patients at baseline or on any scheduled C-SSRS assessments.

On the MOAA/S, all but 1 patient scored 5 (responds readily to name spoken in normal tone) after psychoactive effects had subsided; the remaining patient (total dose, GH001 6 mg) scored 4 after dosing but scored 5 at discharge. All patients but 1 (total dose, GH001 6 mg; 97.5%) were considered discharge-ready at 1 hour postdose; the remaining patient requested to

Table 1. Demographic and Baseline Clinical Characteristics and Exposure

	GH001 (n = 40)	Placebo (n = 41)
Characteristics		
Age, mean (SD), y	41.6 (11.4)	43.9 (10.9)
Sex, No. (%)		
Female	24 (60.0)	22 (53.7)
Male	16 (40.0)	19 (46.3)
Race, White, No. (%)	40 (100)	41 (100)
BMI, mean (SD)	24.8 (4.3)	27.5 (6.3)
Previously used any psychedelic (lifetime), No. (%)	4 (10.0)	5 (12.2)
HAM-D-17 total score, mean (SD)[a]	24.9 (2.6)	24.6 (2.3)
MADRS total score, mean (SD)[b]	29.0 (5.4)	28.2 (4.6)
No. of MDEs, mean (SD)	(2.1 (1.4)	2.0 (1.1)
≥3 MDEs, No. (%)	14 (35.0)	13 (31.7)
Time since first depressive episode, mean (SD), y	11.3 (9.7)	12.2 (8.4)
Duration of current MDE, mean (SD), wk	50.8 (28.3)	63.3 (106.9)
Exposure		
Patients receiving total IDR dose(s), No. (%)[c]		
1 dose (6 mg GH001 or 1 placebo dose)	9 (22.5)	0 (0)
2 doses (6, 12 mg GH001 or 2 placebo doses)	21 (52.5)	0 (0)
3 doses (6, 12, 18 mg GH001 or 3 placebo doses)	10 (25.0)	41 (100)
Median (range) duration of psychoactive effects, min[d]		
6 mg (or first placebo dose)	9.0 (2-35)	0 (0-15)
12 mg (or second placebo dose)	14.0 (4-50)	0 (0-5)
18 mg (or third placebo dose)	11.5 (8-50)	0 (0-7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IDR, individualized dosing regimen; HAM-D-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode.

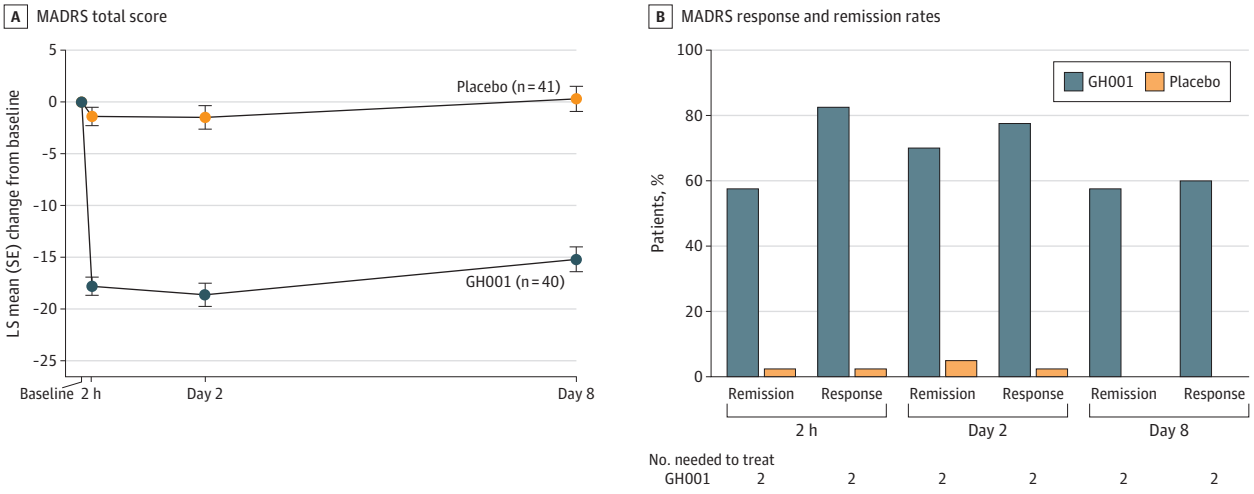
[a] HAM-D-17 total score range, 0-52; higher scores indicate greater severity of depression.

[b] MADRS total range, 0-60; higher scores indicate greater severity of depression.

[c] For patients in the GH001 and placebo groups, up to 3 doses of GH001 or placebo were administered.

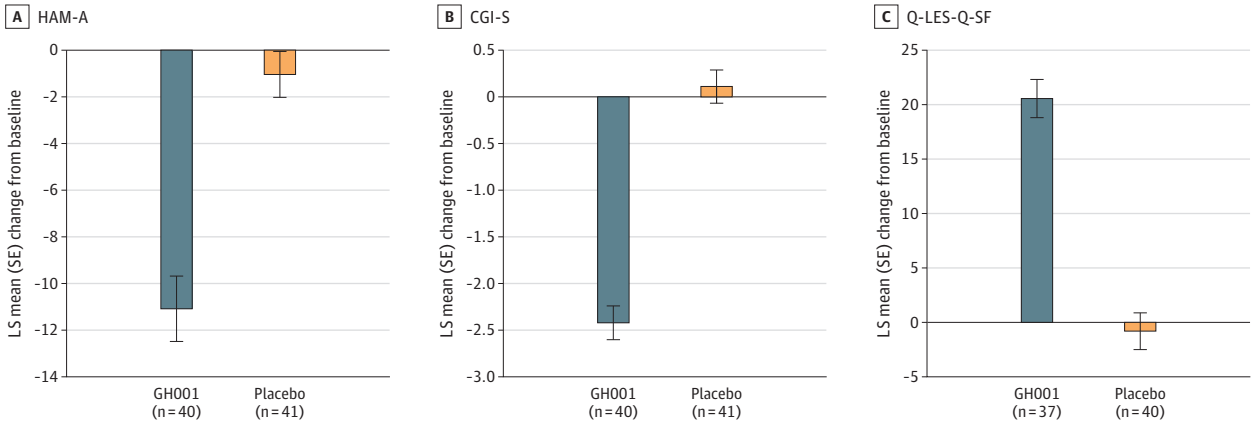
[d] Includes all patients who received respective dose of GH001 or placebo, irrespective of total dose.

Figure 2. Dot Plot and Bar Graph Showing Efficacy in Part 1



A, Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (primary end point) (least squares [LS] mean difference vs placebo: −15.5; $P < .001$; effect size: Cohen *d*, −2.0). B, MADRS response (≥50% reduction from baseline) and remission (total score ≤10) rates; number needed to treat for remission and for response.

Figure 3. Bar Graphs Showing Secondary Efficacy End Points



Change from baseline in (A) Hamilton Rating Scale for Anxiety (HAM-A) total score (least squares [LS] mean difference, −10.0; 95% CI, −12.4 to −7.7); (B) Clinical Global Impression–Severity (CGI-S) score (LS mean difference, −2.5; 95% CI, −3.0 to −2.1); (C) Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) total score (LS mean difference, 21.4; 95% CI, 17.3 to 25.4).

rest at site and was discharged at 3 hours postdose. No clinically significant changes were observed in CADSS scores (1 hour postdose, after psychoactive effects had subsided), and Brief Psychiatric Rating Scale Positive Symptoms scores indicated no evidence of treatment-emergent positive symptoms.

No clinically significant changes in vital signs, spirometry, clinical laboratory tests, or 12-lead electrocardiograms were observed following dosing in part 1. Vital sign measurements during study drug administration are reported in Supplement 2.

Initial Part 2 Results

Following trial completion and unblinding of treatment allocation, it was revealed that all 23 patients entering the OLE (part 2) in remission had received active GH001 during part 1. Across the 6-month follow-up of individuals who were in remission on day 8 of in part 1, 3 patients (13%) remained in remission and received no additional treatment. Among the 20 patients who met retreatment criteria during part 2, time to first retreatment was 6 weeks (range: 2-12 weeks); 5 patients received 1 to 2 retreatments, and 15 received 3 to 4 retreatments. At the final assessment, mean (SD) MADRS score for the 23 participants who were in remission on day 8 of part 1 was 7.2 (6.5). Overall, 20 of 23 (87.0%) of the patients who remitted in part 1 were in remission at the completion of the 6-month part 2. Dosing characteristics and tolerability indices during part 2 were virtually identical to those reported during part 1; GH001 was well tolerated, and there were no serious treatment-related AEs over 6 months. No evidence of tolerance to GH001

Table 2. Treatment-Emergent Adverse Events During Part 1

	Patients, No. (%)	
Treatment-emergent adverse event	GH001 (n = 40)	Placebo (n = 41)
Any adverse event	29 (72.5)	3 (7.3)
Adverse events by maximum severity		
Mild	14 (35.0)	2 (4.9)
Moderate	15 (37.5)	1 (2.4)
Severe	0	0
Treatment-related adverse events	29 (72.5)	1 (2.4)
Serious adverse events	0	0
Adverse events leading to death	0	0
Adverse events leading to discontinuation	0	0
Adverse events occurring in ≥5% of patients in either group		
Nausea	17 (42.5)	0
Salivary hypersecretion	8 (20.0)	0
Paresthesia	8 (20.0)	0
Dysgeusia	3 (7.5)	0
Headache	3 (7.5)	1 (2.4)
Memory impairment	2 (5.0)	0
Fatigue	2 (5.0)	0
Affect lability	2 (5.0)	0

therapeutic effects was observed. No treatment-emergent events of suicidal intent or suicidal behavior occurred during follow-up. A detailed analysis of part 2, including OLE treatment outcomes of patients who received placebo in part 1, will be presented in a subsequent report.

Discussion

In the randomized, double-blind, placebo-controlled period, patients with TRD receiving a single GH001 IDR (up to 3 doses: 6, 12, and 18 mg) achieved rapid reductions in symptoms of depression. Improvements in MADRS score were statistically significant and clinically meaningful,[28] with least squares mean difference of −15.5 between GH001 and placebo groups at day 8 (effect size, −2.0). GH001 treatment also resulted in large improvements in symptoms of anxiety, global illness severity, and patient-reported quality of life vs placebo at day 8. The magnitude of improvement in MADRS score 1 week after double-blind GH001 dosing compares favorably with results from trials in TRD of olanzapine/fluoxetine, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor plus intranasal esketamine, esketamine monotherapy, electroconvulsive therapy, or repetitive transcranial magnetic stimulation.[29-35] Pooled effect sizes of 0.26 and 0.667 have been reported at various time points in meta-analyses of 5 studies of olanzapine/fluoxetine (vs an antidepressant)[36] and 4 intranasal esketamine studies (vs baseline),[37] respectively. However, direct comparisons are challenging given differences in patient characteristics, trial durations, and designs. Moreover, most patients who experienced remission after the first GH001 IDR needed further treatments to maintain improvements over 6 months.

GH001 was well tolerated in part 1; all TEAEs were mild or moderate in severity, and there were no serious AEs, deaths, or discontinuations because of AEs. The observed scoring ranges for GH001- and placebo-treated patients on the Challenging Experience Questionnaire (eTable 7 in Supplement 2) suggest that the psychoactive experience was well tolerated in most patients. There was no evidence of treatment-emergent worsening of suicidal ideation, treatment-emergent suicidal intent or behavior, psychotic symptoms, or dissociation at discharge. Part 1 results indicate GH001, administered as an IDR of up to 3 doses in 1 day, is associated with rapid improvement in symptoms of depression and an acceptable safety profile. Initial results from the OLE suggest that GH001 achieved long-term remission in patients with TRD over a 6-month period, with infrequent dosing. The favorable safety and tolerability profile, including short duration of psychoactive effects and rapid discharge readiness, further supports its suitability for clinical use.

Use of the MGH-SAFER criteria interview, developed to increase clinical trial quality, strengthened this trial by improving diagnostic validity.[20] Additional strengths include the comparably low rate of previous exposure to psychedelics, and robust findings in a difficult-to-treat population. Notably, psychotherapeutic interventions, which are commonly employed in trials for psychoactive drugs and may increase expectancy, functional unblinding, and performance biases,[38] were not included in the trial design and thus did not contribute to observed treatment benefits with GH001.

Limitations

Several limitations of this trial warrant consideration. First, GH001 produces characteristic psychoactive effects that are inherently difficult to conceal from patients and health care providers. These effects may have biased patients and staff who observed treatment administration, possibly amplifying perceived benefit or suppressing response when no psychoactive effects were experienced. To mitigate potential functional unblinding, the trial was designed in accordance with regulatory guidance available at the time of initiation: efficacy assessments were conducted remotely by independent raters who were fully blinded to treatment allocation and who had no involvement in patient screening, study drug administration, safety monitoring, or patient care. Future studies of GH001 should include formal assessment of blinding integrity. Second, although our trial's enrollment criteria aligned with current TRD regulatory standards, relatively few patients had extensive histories of treatment resistance or prolonged, chronic illness courses. In subsequent research, it will be important to include patients with more advanced levels of treatment resistance and longer-standing symptoms. Additionally, while the sample size was adequate to meet the objectives of a phase 2b trial, it did not permit robust subgroup analyses of relevant clinical and sociodemographic factors. Although the overall trial duration was 6 months, the short duration of the double-blind period makes direct comparison with other TRD trial results difficult. Initial OLE findings of part 2 indicate that most patients achieved sustained remission with relatively infrequent GH001 treatments.

Conclusions

In the randomized, double-blind part 1 of this phase 2b trial in patients with TRD, a single-day GH001 IDR was well tolerated and resulted in rapid, large, and significant reductions in the primary endpoint (MADRS) and all secondary outcome measures. During the 6-month OLE, most patients who benefitted from GH001 in part 1 were in remission with infrequent treatments. Future research will explore the longer-term efficacy and safety of GH001.

ARTICLE INFORMATION

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