Inhaled Mebufotenin (GH001) for Adult Patients With Postpartum Depression:

A Phase 2a Open-Label Clinical Trial

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Abstract

Objective: Postpartum depression (PPD) is a debilitating mood disorder with peripartum onset. Current treatment options are limited in PPD. GH001 is a synthetic inhalation formulation of the psychoactive molecule mebufotenin (5-MeO-DMT). This trial investigated the preliminary efficacy and safety of GH001 in adult females with PPD.

Methods: This phase 2a, proof-of-concept, open-label trial enrolled women aged 18–45 years (March 2023 to August 2024) with a Mini-International Neuropsychiatric Interview–confirmed diagnosis of major depressive disorder with peripartum onset. Patients had Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≥28 at baseline. GH001 was administered as an individualized dosing regimen of up to 3 escalating doses (6, 12, and 18 mg) on day 1. The primary end point was the change in MADRS total score from baseline to day 8. Secondary end points included antidepressant response (≥50% reduction), remission (MADRS total score ≤10), and safety and tolerability of GH001.

Results: Ten patients were enrolled. Mean baseline MADRS total score was 36.7 (SD = 4.8). Mean MADRS total score change from baseline to day 8 was −35.4 points (SD = 5.5; $P < .0001$). All patients achieved response and were in remission on day 8, which was first observed 2 hours after their final dose on day 1. Inhalation of GH001 was well tolerated, and no serious adverse events (AEs) were reported. All treatment-emergent AEs were mild or moderate, with headache as the most frequently reported AE.

Conclusion: GH001 demonstrated rapid and significant improvements in depressive symptoms and remission of PPD with an acceptable safety profile and parallel improvements across secondary end points.

Trial Registration: ClinicalTrials.gov identifier: NCT05804708; EudraCT identifier: 2021-006879-42

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Postpartum (or peripartum) depression (PPD) is a common peripartum complication that can have serious consequences for the well-being of the mother and the long-term development of the child.[1,2] Epidemiologic studies estimate the global prevalence rate of PPD to be as high as 20%, with up to 30% of diagnosed patients still experiencing symptoms 2 years after giving birth.[3–5] PPD is associated with numerous short- and long-term negative outcomes for the mother, child, and the entire family, especially if treatment is delayed and/or insufficient.[6–8] Typical antidepressive treatments (eg, selective serotonin reuptake inhibitors [SSRIs]) have a slow onset of action, low remission rates, and chronic or long-lasting side effects that can lead to discontinuation.[9,10] Zuranolone, the only treatment for PPD approved by the US Food and Drug Administration (FDA), demonstrates rapid-acting antidepressant effects over a 14-day treatment course; however, clinical use remains low as compared to serotonergic antidepressants.[10–13]

Mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) is a potent psychoactive molecule that acts as a nonselective serotonin agonist with higher affinity for the 5-HT_{1A} receptor subtype versus the

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Clinical Points

- Inhaled mebufotenin (GH001) administered as a single-day individualized dosing regimen demonstrated rapid and significant reductions in depressive symptoms in patients with postpartum depression, with 100% remission by Day 8.
- GH001 was well tolerated, with no serious adverse events, no sedative effects, and same-day discharge for all patients, supporting the feasibility of this treatment approach in clinical settings.
- Preliminary breastmilk pharmacokinetic data suggest that mebufotenin and its metabolites are rapidly eliminated, supporting a treatment strategy requiring only a brief interruption of breastfeeding around dosing.

5-HT_{2A} subtype and a short half-life in plasma.[14,15] Early-phase clinical trials of mebufotenin administered via pulmonary inhalation (GH001) demonstrated acceptable safety and tolerability, with an ultrarapid onset of antidepressive effects in patients with treatment-resistant depression (TRD).[16,17] This is the first clinical trial of mebufotenin in adult, female patients with PPD, investigating its potential antidepressant effects, safety, and impact on maternal functioning and behavior.

METHODS

Trial Oversight

The clinical trial screened patients from 3 sites in the United Kingdom and the Netherlands and enrolled patients from 1 site in the United Kingdom between March 2023 and August 2024. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice and ethical principles of the Declaration of Helsinki.[18] The regulatory authority and research ethics committee for each trial site approved the protocol before patient enrollment. All patients provided their written informed consent after being fully informed about the purpose of the trial and after procedure(s) and possible side effects were fully explained. The sponsor (GH Research, Dublin, Ireland) designed and funded the trial and supported medical writing assistance for drafting the manuscript under direction from the authors.

Patients

This phase 2a, proof-of-concept, single-arm, open-label trial enrolled female outpatients aged 18–45 years who met the Mini-International Neuropsychiatric Interview[19] (v 7.0.2) diagnostic criteria for major depressive disorder with peripartum onset, were >4 weeks postpartum at dosing and ≤12 months postpartum at screening, and had a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≥28, reflecting moderate-to-severe depressive symptoms. Antidepressants, antipsychotics, psychedelics, dissociatives, and any medication with monoamine oxidase inhibitor activity were prohibited during the trial period and within 2 weeks (or 5 half-lives prior to baseline, whichever was longer). Any decision to discontinue medication was made by patients and investigators, based on clinical judgment, with involvement of patients' physicians or psychiatrists; no medication was discontinued for the sole purpose of allowing patients to participate in the trial. Any tapering/washout schedule was performed per clinical practice, with support from research site staff. Initiation or modification of psychotherapy during the trial was prohibited. Patients either had to have ceased lactating at screening or, if still lactating or actively breastfeeding, must have agreed to temporarily cease breastfeeding from just prior to dosing through 24 hours after the last dose. Additional details including the full inclusion and exclusion criteria are provided in the Supplementary Appendix.

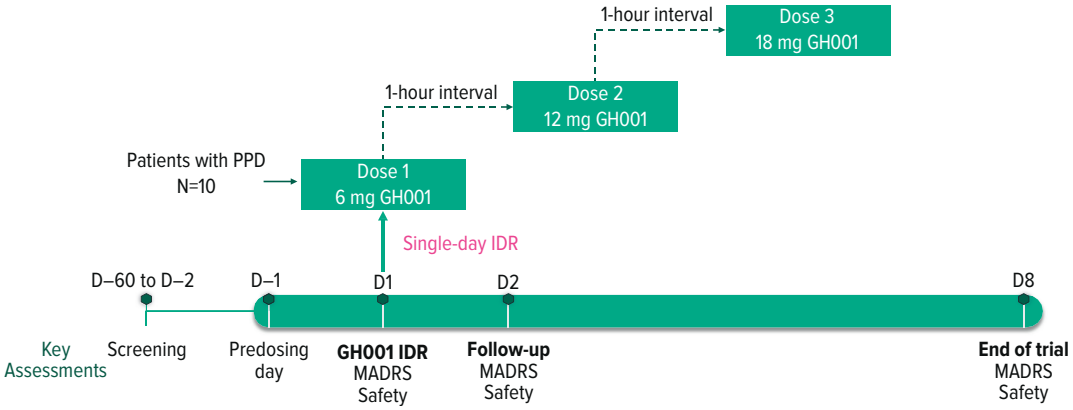
Trial Visits

The trial consisted of a screening period; a day 1 visit where eligibility was reconfirmed; a day 1 visit where patients received the study drug, GH001; a day 2 follow-up visit; and the end of trial visit on day 8. The 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, as per recent FDA recommendations.[20] On the same day of dosing (day 1), patients were discharged once all trial assessments were completed and once they were deemed discharge-ready as assessed using a proprietary assessment, the Clinical Assessment of Discharge Readiness (CADR), administered by a health care professional.

Study Drug

GH001, an inhalation formulation of synthetic mebufotenin, was administered using the Volcano Medic 2 Vaporization System (Storz & Bickel, Germany). The system vaporizes the formulation to produce an aerosol, which is collected in a detachable balloon for inhalation by the patient. Prior to GH001 administration, patients were trained in the inhalation technique and were prepared for the potential psychoactive effects of the study drug by the trial physician. Patients received GH001 as an individualized dosing regimen (IDR) of up to 3 escalating doses (6, 12, and 18 mg) on a single day with a 1-hour interval between doses (Figure 1). A second or third dose was administered if the previous dose was well tolerated according to the trial

Figure 1.
Design of the Clinical Trial



Abbreviations: D = day, IDR = individualized dosing regimen, MADRS = Montgomery-Asberg Depression Rating Scale, PPD = postpartum depression.

physician's judgment (based on vital signs and adverse events [AEs]) and if the patient did not achieve an intense psychoactive effect (peak experience [PE], defined as a mean score of ≥75 on the Peak Experience Scale [PES])[21] following the previous dose; further details are provided in the Supplementary Appendix.

Assessments

The primary end point was mean change in severity of depressive symptoms assessed by MADRS[22] total score from baseline to day 8. Secondary efficacy end points included mean change from baseline in MADRS total score at 2 hours after the final dose of the IDR and on day 2; proportion of patients in remission (MADRS total score ≤10); proportion of patients with treatment response (≥50% reduction from baseline MADRS total score); overall disease severity assessed by change from baseline to day 8 on the Clinical Global Impression–Severity (CGI-S) scale[23]; and maternal functioning and behavior by change from baseline to day 8 in Barkin Index of Maternal Functioning (BIMF)[24] total score and functional area scores.

Safety and tolerability were assessed throughout the trial as secondary end points and included the following parameters: incidence of treatment-emergent adverse events (TEAEs) classified according to the Medical Dictionary for Regulatory Activities (MedDRA), version 27.1; vital signs, electrocardiogram, spirometry, standard safety laboratory analyses (hematology, biochemistry, urinalysis), sedation as assessed by the Modified Observer's Assessment of Alertness and Sedation (MOAA/S),[25] psychiatric symptoms as assessed by the Brief Psychiatric Rating Scale (BPRS),[26] dissociative symptoms assessed by the Clinician Administered Dissociative States Scale (CADSS),[27] suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS),[28] cognitive effects assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB),[29] and discharge readiness on day 1 assessed using the CADR. Psychoactive effects of the study drug were assessed by the proprietary PES,[21] the Challenging Experience Questionnaire (CEQ),[30] and the Mystical Experience Questionnaire 30-item version (MEQ30),[31] as well as the duration of the psychoactive effects. As an exploratory end point, concentrations of mebufotenin, its psychoactive metabolite bufotenine, and its terminal nonpsychoactive metabolite 5-methoxyindole-3-acetic acid (5-MIAA) were measured in breast milk of lactating patients using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The assigned lower limit of quantification for LC-MS/MS was 0.025 ng/mL. Further details including timing of all assessments can be found in the Supplementary Appendix.

Statistical Methodology

For the primary end point, a *P* value was calculated using a 1-sample *t*-test with a 1-sided significance level of $\alpha = .025$. The trial was originally powered to include 15 patients; with 10 patients, the trial remained adequately powered to detect a clinically meaningful difference. Secondary and exploratory end points were reported using descriptive statistics. The trial was registered on ClinicalTrials.gov (NCT05804708) and EudraCT (2021-006879-42).

RESULTS

Patients

From March 2023 to August 2024, the trial enrolled 10 patients diagnosed with PPD with a mean (SD) age of

Table 1.

Baseline Demographic and Clinical Characteristics of Study Patients[a]

Characteristic	Value (N=10)
Female sex, n (%)	10 (100.0)
Age, y	31.6 (5.19)
Ethnicity, n (%)	
Hispanic or Latino	1 (10.0)
Not Hispanic or Latino	9 (90.0)
Race, n (%)	
Black or African American	1 (10.0)
White	9 (90.0)
BMI, kg/m²	27.6 (6.62)
Parity	2 (0.9)
Current depressive episode	
Duration of current episode, weeks	30.9 (12.93)
Received pharmacotherapy for the current episode, n (%)[b]	1 (10.0)
Received psychotherapy for the current episode, n (%)	0
Received brain stimulation intervention for the current episode, n (%)	0
Prior depressive episode(s)	
No. of prior depressive episodes	1.3 (1.25)
Received pharmacotherapy for prior MDE(s), n (%)	6 (60.0)
Received brain stimulation for prior MDE(s), n (%)	0
Family history	
Presence of depression in immediate family, n (%)	3 (30.0)
Presence of alcohol/substance abuse in immediate family, n (%)	3 (30.0)
Disease characteristics	
MADRS total score	36.7 (4.79)
CGI-S rating	4.8 (0.79)
BIMF total score	68.8 (15.6)
BPRS total score	41.0 (8.34)

[a]Values are expressed as mean (SD) unless otherwise specified.
[b]The period up to 30 days prior to screening.
Abbreviations: BIMF = Barkin Index of Maternal Functioning, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impression–Severity, MADRS = Montgomery–Asberg Depression Rating Scale, MDE = major depressive episode.

31.6 (5.2) years. The mean (SD) duration of their current depressive episode was 30.9 (12.9) weeks, and the mean (SD) parity was 2 (0.9). One patient (10.0%) had received pharmacotherapy for the current depressive episode, and 6 patients (60.0%) had received pharmacotherapy for prior major depressive episodes. The mean (SD) baseline MADRS total score was 36.7 (4.8; n = 10), baseline CGI-S was 4.8 (0.79; n = 10), and baseline BIMF total score was 68.8 (15.6; n = 8) out of a possible total score of 120, indicating a significant degree of functional impairment.[24] Additional details of the patient population are outlined in Table 1. All patients completed the trial, with GH001 IDR dosed as follows: 6 mg (n = 1), 6 + 12 mg (n = 7), 6 + 12 + 18 mg (n = 2) (Supplementary Table 3).

Efficacy

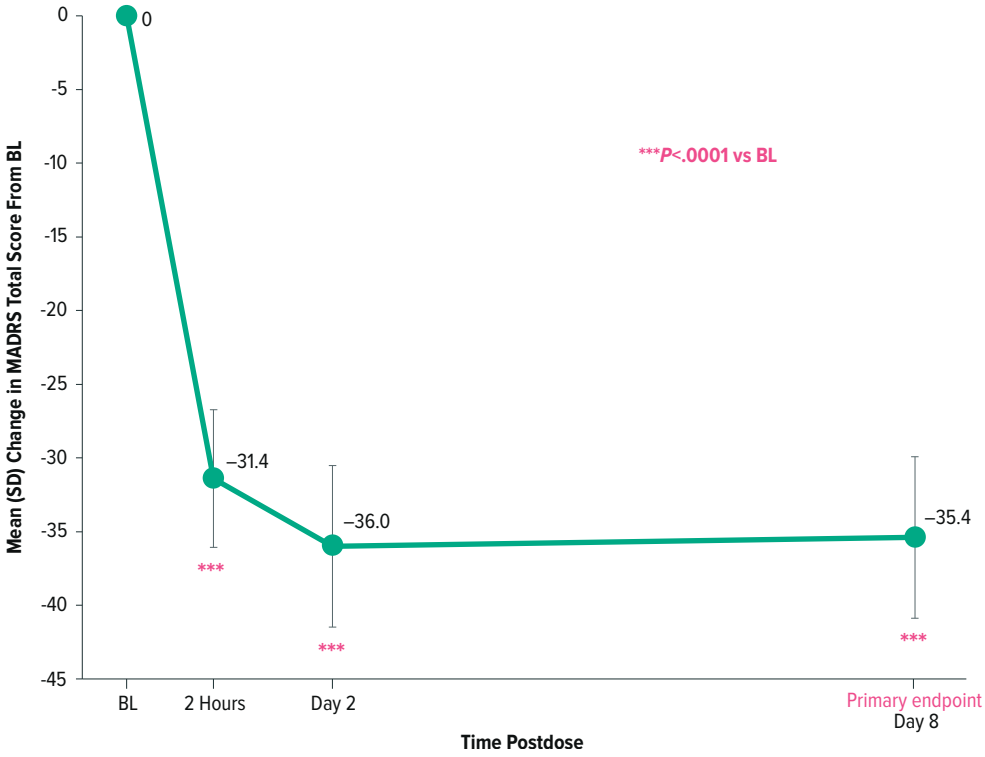
The primary end point was achieved, with a significant mean (95% CI) reduction from baseline to day 8 of −35.4 points (−39.32 to −31.48) in MADRS total score with GH001 treatment ($P < .0001$), corresponding to an approximate 96% relative reduction from baseline. Significant reductions in MADRS total score were also observed at 2 hours postdose and on day 2 ($P < .0001$ for both time points; Figure 2). All 10 patients demonstrated large and consistent reductions in MADRS total score at 2 hours postdose, on day 2, and on day 8 (Figure 3). All patients (100%) achieved both response and remission at day 8, as well as at 2 hours postdose and on day 2. All patients had a reduction in the illness severity measured by the CGI-S, with mean (SD) change in score from baseline to 2 hours postdose, day 2, and day 8 of −3.7 (0.82), −3.8 (0.79), and −3.8 (0.83), respectively. At day 8, BIMF total score increased by a mean (SD) of 34.1 (16.10) points (n=8), an approximate 56% improvement. Increases from baseline were observed on day 8 across most BIMF functional areas (Supplementary Table 4).

Psychoactive Effects

Assessed by the PES, 7 of 10 patients (70.0%) achieved a PE. No consistent effects were noted for the CEQ or the MEQ30. The clinician-reported duration of

Figure 2.

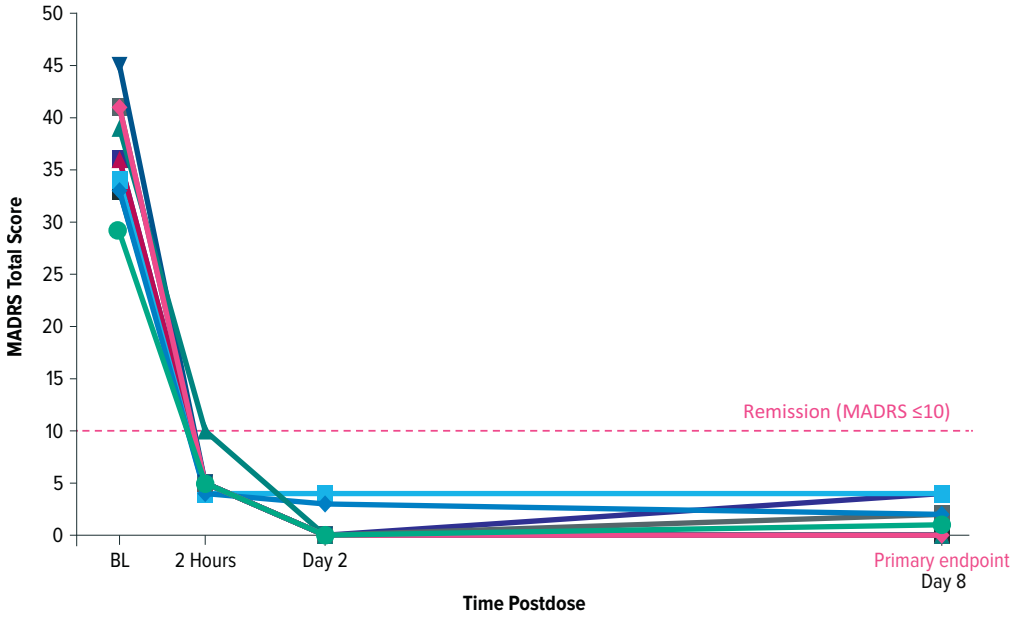
Mean Change From Baseline in MADRS Total Score



Abbreviations: BL = baseline, MADRS = Montgomery-Asberg Depression Rating Scale, PPD = postpartum depression.

Figure 3.

MADRS Total Scores for Individual Patients



Abbreviations: BL = baseline, MADRS = Montgomery-Asberg Depression Rating Scale, PPD = postpartum depression.

Table 2.
Treatment-Emergent Adverse Events

Event	Patients, n (%)	Events
Any TEAE	8 (80.0)	13
6 mg (n = 1)	1 (100)	1
6 + 12 mg (n = 7)	6 (85.7)	11
6 + 12 + 18 mg (n = 2)	1 (50.0)	1
Drug-related TEAEs[a]	7 (70.0)	11
Serious TEAEs	0	0
TEAE leading to discontinuation of study drug	0	0
TEAE leading to early termination from the trial	0	0
Deaths	0	0
Maximum severity of TEAEs		
Mild	7 (70.0)	12
Moderate	1 (10.0)	1
Severe	0	0
MedDRA system organ class, preferred term		
Nervous system disorders	**6 (60.0)**	**8**
Headache	5 (50.0)	5
Dizziness	1 (10.0)	1
Dysgeusia	1 (10.0)	1
Paresthesia	1 (10.0)	1
Gastrointestinal disorders	**4 (40.0)**	**4**
Abdominal pain	1 (10.0)	1
Diarrhea	1 (10.0)	1
Nausea	1 (10.0)	1
Vomiting	1 (10.0)	1
Cardiac disorders	**1 (10.0)**	**1**
Tachycardia	1 (10.0)	1

[a]Any event with a definite, probable, or possible relationship to the study drug was considered drug-related.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.

psychoactive effects following GH001 administration showed no clear dose response, with median (range) individual dose durations of 22.0 (5–62), 25.0 (7–37), and 25.0 (10–40) minutes after the 6-, 12-, and 18-mg doses, respectively.

Safety

Thirteen TEAEs were observed in 8 of 10 patients (80.0%), and were mostly mild in severity (87.5%); only 1 patient reported a TEAE with moderate severity (Table 2). Headache was the most reported TEAE (5/10 patients); all other TEAEs occurred in a single patient each. No TEAEs of flashbacks, serious TEAEs, or severe TEAEs were reported, and no patients withdrew from the trial. There was no apparent dose-response relationship with TEAEs; AEs were distributed across dose levels without a clear pattern (Table 2).

Assessment of psychiatric and psychotic symptoms with the BPRS showed a mean (SD) reduction in BPRS total score from baseline to day 8 of −23.7 (8.34), bringing the day 8 score of 18.1 (0.33) close to the 18-point minimal score of the BPRS. There were no notable or consistent changes from baseline values in clinical laboratory assessments of hematology, chemistry, or urinalysis, and no individual patient had abnormal clinically significant (CS) shifts in any laboratory measurement. Similarly, assessments of vital signs showed no CS changes, and there were no clearly identifiable trends in respiratory rate, SpO_2, body temperature, spirometry, or body weight. As in other trials with psychedelics,[32–35] transient increases in blood pressure and heart rate were observed after administration of GH001, spontaneously returning to baseline within 20–60 minutes after dosing. Assessed after the psychoactive effects had subsided, there was no worsening of clinician-rated assessments (CADSS and MOAA/S) and no consistent evidence of a GH001-mediated impairment in performance on CANTAB tasks. The proportion of patients reporting suicidal ideation per the C-SSRS was reduced from 3 patients (30.0%) at baseline to none (0%) at discharge (day 1), day 2, and day 8; no patients reported suicidal behavior or nonsuicidal self-injurious behavior at any of the scheduled C-SSRS assessments. Using the CADR, all patients were deemed ready for discharge within the dosing day.

Exploratory Breast Milk Analysis

Of the lactating patients (n = 4), 3 received GH001 6+12 mg and 1 received GH001 6 + 12 + 18 mg as part of the IDR. Mebufotenin levels in breast milk ranged from 0.24 to 3.11 ng/mL at 1 hour postdose, declining to below the limit of quantification (BLQ, 0.025 ng/mL) to 0.04 ng/mL ~8 hours postdose; all levels were BLQ on days 2 and 8. Bufotenin was BLQ in breast milk at all time points. 5-MIAA levels ranged from 13.9 to 28.5 ng/mL at 1 hour, declining to BLQ to 0.90 ng/mL at ~8 hours and BLQ on day 8.

DISCUSSION

In this phase 2a, proof-of-concept, open-label trial evaluating the antidepressant effects and safety of GH001 in a group of patients with moderate and severe PPD (mean baseline MADRS >34), the primary end point was met. A significant mean reduction of 35.4 points in MADRS total score (corresponding to an approximate 96% reduction in symptom severity) was found from baseline to day 8, with clinically meaningful effects observed as early as 2 hours postdose and all patients achieving remission, which was maintained through the final assessment on day 8. While cross-study comparisons must be interpreted cautiously, these findings indicate a time to response that is considerably faster than what has been reported for the approved treatment zuranolone and the previously approved but now withdrawn brexanolone.[11–13,36,37] The MADRS reduction observed here (−35.4 points) compares favorably with that reported in the brexanolone proof-of-concept randomized controlled trial in PPD

(−28.0 points at 60 hours; n = 10).[36] Antidepressant efficacy has also been observed with GH001 in TRD, where a placebo-adjusted MADRS reduction of −15.5 points (Cohen's $d = 2.0$) was demonstrated in a phase 2b trial,[38] and in bipolar II disorder with a current major depressive episode, where a MADRS reduction of −16.8 points was observed in a phase 2a open-label trial.[39]

Further strengthening the validity of the observed antidepressant effects, parallel improvements were seen in the CGI-S and BPRS scales, with broad improvement across the assessed psychopathological symptoms of the BPRS. On the BIMF scale, GH001 was associated with a 56% improvement on the overall score, with improvements across multiple domains of self-reported maternal functioning, predominantly psychological well-being. GH001 administered via inhalation further demonstrated a favorable safety profile without sedative effects and with same-day discharge from the clinic. The inhalation was well tolerated, and no serious TEAEs were reported. Preliminary results of the pharmacokinetic analysis of breast milk in this trial support a treatment strategy with only a brief interruption of breastfeeding around GH001 dosing. Mebufotenin and its metabolite 5-MIAA were transiently present in breast milk and were both rapidly eliminated by ~10 hours postdose. Bufotenin was not detected in any breast milk sample.

The pharmacologic profile of GH001 differs from that of currently available treatments for PPD. SSRIs, the established first-line treatment, have an onset of action of 4–6 weeks with side effects including headache, nausea, somnolence, and sexual dysfunction which can impact adherence.[10] Zuranolone, an orally formulated γ-aminobutyric acid-A receptor modulator, requires a 14-day dosing schedule with onset over several days.[11–13] Common side effects include somnolence, dizziness, and fatigue, with driving restrictions for 12 hours after each dose.[40] This trial applied diligent assessment of such effects using specific scales for sedation and posttreatment drowsiness (MOAA/S and CADR) and dissociation (CADSS) and found no signs of adverse effects after the psychoactive effects had subsided, with all patients being discharge-ready shortly after receiving the last dose of study drug and no negative effects on cognitive function. Psychotherapeutic interventions are commonly employed in trials for psychoactive molecules and may increase expectancy and performance biases.[20] Psychotherapeutic interventions were not included in the trial design and thus did not contribute to observed treatment benefits with GH001. When designing the trial, there was a focus on patient safety, securing a patient population without significant psychiatric comorbidity, not presently receiving antidepressant treatment, and with the availability of a person to act as a caregiver for the child while the patient took part in the trial. These strict requirements limited the recruitment of patients, so while the trial originally planned to include 15 patients, enrolment was stopped early due to recruitment challenges.

Certain limitations of this trial must be acknowledged including the enrolment of a small number of patients (N = 10), its relatively short follow-up of 1 week, the lack of a control arm, and no blinding. These factors may limit the ability to attribute changes in depressive symptoms exclusively to the investigational treatment. The predominantly White (90%) population, and the fact that 9/10 patients were not receiving pharmacotherapy for their current depressive episode, may further limit the generalizability of these findings to broader, more diverse PPD populations including those on concurrent antidepressant treatment. Additionally, while the magnitude and rapidity of symptom reduction with GH001 are noteworthy, comparisons with other medications for PPD must be made cautiously due to differences in trial populations, methodologies (ie, placebo-controlled trial vs open-label trial), and outcome measures. Mechanistically, mebufotenin is pharmacologically distinct from SSRIs and zuranolone, acting as a direct, nonselective serotonin receptor agonist with preferential 5-HT_{1A} affinity that engages glutamatergic signaling and rapid neuroplasticity, potentially accounting for the rapid onset of antidepressant effects.[41] The ultra-short duration of psychoactive effects enables the single-day IDR to be administered during a single supervised visit with same-day discharge, which may support administration in an outpatient setting.

The American Psychiatric Association recommends initiating or continuing pharmacotherapy for patients with PPD, especially those with severe illness, using the minimally effective dose and considering breastfeeding safety.[42] Should these findings be replicated in larger, placebo-controlled trials, GH001's rapid onset, short half-life, and favorable safety profile would fit well into the existing PPD management recommendations. Emerging data from a 6-month open-label extension of a phase 2b trial in TRD suggest that intermittent retreatment with GH001, rather than continuous maintenance pharmacotherapy, may be sufficient to sustain remission; whether a similar approach is applicable in PPD will require investigation in future trials. Given the preliminary improvements in maternal functioning, future research should evaluate GH001's impact on the mother-infant relationship.

In conclusion, GH001 administered as a single-day IDR in adult female patients with PPD was well tolerated with an acceptable safety profile, with large improvements in depressive symptoms and maternal functioning up to 7 days posttreatment. These results support further investigations of the longer-term efficacy and safety of GH001 in PPD. Future randomized,

placebo-controlled trials with longer follow-up periods will be essential to validate the preliminary findings presented here.

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Supplementary Material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Inhaled Mebufotenin (GH001) for Adult Patients with Postpartum Depression: A Phase 2a Open-Label Clinical Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Materials

Supplementary Methods

Prohibited Treatments and Washout

- Monoamine oxidase inhibitor (MAOIs): Patients were required to avoid concomitant administration or presence in the blood of MAOIs, including plant derived MAOIs (such as harmala alkaloids in Ayahuasca or Syrian Rue). Patients were not permitted to use any medication with MAOI activity (such as isocarboxazide, phenelzine, selegiline or tranylcypromine, linezolid, or methylene blue) within 14 days or 5 half-lives (whichever is longer) prior to the first administration and until the end of the trial.
- Serotonergic drugs: Concomitant administration of other agents which, directly or indirectly, act agonistically on serotonergic systems (such as selective serotonin reuptake inhibitors [SSRIs] such as paroxetine or citalopram, a serotonin-norepinephrine reuptake inhibitor [SNRI] such as venlafaxine or duloxetine, L-tryptophan, serotonin [5-HT] or St. John's wort) were prohibited within 14 days or 5 half-lives (whichever was longer, 5 weeks in the case of fluoxetine) prior to the first administration and until the end of the trial.
- Tricyclic antidepressants (TCAs): TCAs such as amitriptyline or imipramine were also contraindicated within 14 days or 5 half-lives (whichever was longer) prior to the first administration and until the end of the trial.
- Psychoactive medication: As a precautionary measure, patients were not permitted to receive psychoactive medication at a defined interval (based on medication half-life) before the dosing day, on the dosing day, and until the end of the trial.
- Dietary supplements: Plant-based or herbal dietary supplements were prohibited.
- Over-the-counter (OTC) medications: OTC medications were not allowed in the 2 weeks prior to the first GH001 administration and until the end of the trial, with the exception of oral

contraceptives, up to 4000 mg paracetamol or 1200 mg ibuprofen per day for a maximum of 3 days and vitamins ad libitum.

Peak Experience Scale

GH001 was administered on a single day as an individualized dosing regimen (IDR). The IDR is based on the Peak Experience Scale (PES)[1], and the administration of a higher dose level is guided by evaluating whether the patient achieved a peak experience (PE) at the previously administered dose. The GH001 IDR comprised of up to three increasing doses of GH001 (6, 12, and 18 mg, administered via the Volcano Medic 2 Vaporization System); if the first dose was well tolerated and no PE was achieved at the first dose level (6 mg), a second higher dose (12 mg) was administered; if the second dose was well tolerated and no PE was achieved with the second higher dose, a third dose (18 mg) was administered.

The achievement of the PE was evaluated using a proprietary questionnaire (the PES) that was completed by the patient once the psychoactive effects had subsided. The PES was developed specifically for the GH001 program and consists of three visual analog scales, each ranging from 0 to 100, summarized as a total average score. The specific three-item features of an intense experience after GH001 administration, i.e., its overall intensity (item one), any feelings of loss of control, to capture the prominent feature of ego dissolution (item two), and its profoundness, to capture how deep and meaningful the experience was (item three). A mean score of ≥75 on the PES has been selected as the threshold determining whether a patient achieved a PE following dosing with GH001, after which no further dose escalation in the GH001 IDR is done.

Supplementary Table 1. Eligibility Criteria

Inclusion Criteria	
Patients were eligible for the trial if all the following criteria were met, unless they fulfilled one or more of the exclusion criteria:	
1	Understands the nature of the clinical trial and has provided signed and dated written informed consent in accordance with local regulations before the conduct of any trial-related procedures.
2	Is female and in the age range between 18 and 45 years (inclusive) at screening.
3	Has a BMI in the range of 18.5 and 40 kg/m^2 (inclusive) at screening.
4	Meets the trial criteria for PPD as assessed by a trial psychiatrist or registered clinical psychologist:

	Diagnosis of Major Depressive Disorder without psychotic features, confirmed by the MINI (v7.0.2), with peri-partum onset that began no earlier than gestation and no later than the first 4 weeks postpartum, and is > 4 weeks postpartum at dosing and ≤12 months postpartum at screening.
	Has a MADRS total score of equal to or greater than 28 at screening and pre-dose on Day 1.
5	Must have either ceased lactating at screening; or, if still lactating or actively breast feeding at screening, must agree to temporarily cease breastfeeding their infant(s) from just prior to receiving study drug on Day 1 through 24 hours post last dose, and to pump and discard all breastmilk during those 24 hours as needed, but need to include a pump/discard at 2.5 hours post last dose and 24 hours post last dose prior to reinitiating breastfeeding.
6	Patients of child-bearing potential must agree to remain completely abstinent (complete avoidance of heterosexual intercourse) or use a highly effective (failure rate <1%), medically accepted contraceptive method for 30 days prior to dosing and for 90 days after GH001 dosing. Highly effective contraception methods include, but are not limited to: bilateral tubal ligation/occlusion, hormone contraceptives that inhibit ovulation, or intrauterine device (including hormone-releasing intrauterine device/systems). Patients must have a negative pregnancy test at screening and on the pre-test day (Day -1).
7	The investigator, after consultation with the patient's GP and/or treating psychiatrist, deems it acceptable, and patient is willing, to delay start of other antidepressant or antianxiety medication until after the end of the trial at Day 8, and patient agrees to keep any psychotherapy unchanged from 7 days prior to dosing on Day 1 until the end of the trial at Day 8.
8	Is able to inhale three liters of air from the test balloon within a single breath at screening and on the pre-test day (Day -1) and prior to first dose (Day 1). An incentive spirometer will be given to patients following screening. They will be encouraged to practice deep inhalations prior to the first dose on the test day (Day 1). Patients failing the test inhalation at screening may have the test inhalation repeated within 14 days of the original screening date.
9	Has a GP or treating psychiatrist and gives permission to contact those physicians for the purpose of discussing medication use, discontinuation, or medication re-initiation or other medical aspects relating to the trial participation and provides their contact details.
10	Is willing and able to comply with all requirements and rules of the trial.
11	Is willing and able to nominate a trusted caregiver that is willing to live with the patient and infant for the duration of the patient's participation in the trial and that is available to take full responsibility for the care and attention (e.g., feeding, changing, etc.) of their infant(s) for the entirety of the test day (Day 1) and for 7 days post last dose, and that is present at screening, provides contact details and consents to being contacted by study staff during the duration of the study. Note: It is expected the mother will continue routine care of their infant(s), but a trusted caregiver must be available as support during the trial period.
Exclusion Criteria	
Patients who met any of the following criteria prior to the first dose of study drug were not eligible for enrollment into the trial:	
1	Has, based on history, psychiatric assessment, and evaluation of the MINI, a current or prior diagnosis of bipolar disorder, a manic or hypomanic episode, a psychotic disorder, MDD or other mood disorder with psychotic features, obsessive compulsive disorder, PTSD, autism spectrum disorder, borderline personality disorder, schizophrenia, delusional disorder, paranoid personality disorder, schizoaffective disorder, clinically significant intellectual disability, or any other psychiatric comorbidity that renders the patient unsuitable for the trial according to the investigator's judgment.
2	Has one or more first or second degree relatives with a current or prior diagnosis of bipolar disorder, psychotic disorder or other mood disorder (including MDD) with psychotic features.
3	Current pregnancy resulting in termination, still-birth, pre-term delivery (before week complete gestational week 37), need for intensive care therapy of mother or intensive care therapy of child of duration >72 hours, or adoption of child away from patient.
4	Has clinically significant premenstrual syndrome or premenstrual dysphoric disorder that renders the patient unsuitable for the study according to the investigator's judgment.
5	Has significant suicide risk as defined by (a) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, during the screening period, or at Baseline; or (b) suicidal behaviors within the past year; or (c) clinical assessment of significant suicidal risk during clinical interview; or (d) non-suicidal self-injury within the past.

6	Has had an inadequate response to an adequate course of electroconvulsive therapy, vagal nerve stimulation, repetitive Transcranial Magnetic or Electrical Stimulation, or deep brain stimulation in the current episode of depression as assessed using the ATHF-SF.
7	Has taken anti-depressive medication (e.g., a SSRI such as paroxetine, fluoxetine (including in combination with olanzapine) or citalopram, a SNRI such as venlafaxine or duloxetine, a TCA such as amitriptyline or imipramine, an antipsychotic such as quetiapine, lithium, an atypical antidepressant such as bupropion or vortioxetine, a NMDA receptor antagonist such as esketamine, a MAOI such as isocarboxazide, phenelzine, selegiline or tranylcypromine within 14 days or 5 half-lives (whichever is longer) prior to dosing (exception: within the last 5 weeks in the case of fluoxetine). Cessation of such medication for the sole purpose of inclusion in this trial is not allowed.
8	Has taken any medication with MAOI activity such as isocarboxazide, phenelzine, selegiline or tranylcypromine, linezolid or methylene blue within 14 days or 5 half-lives (whichever is longer) prior to dosing.
9	Has taken opioids (e.g., oxycodone), or stimulants (e.g., amphetamine) within the last 7 days prior to dosing (or 5 half-lives, whichever is longer).
10	Is taking a total daily dose of benzodiazepines greater than the equivalent of 6 mg/day of lorazepam at screening.
11	Has taken sedatives (e.g., benzodiazepines or non-benzodiazepine sleeping medication [e.g., zolpidem, zaleplon]) within 12 hours prior to dosing.
12	Has taken synthetic or naturally occurring cannabinoids within 7 days prior to dosing.
13	Has taken ayahuasca, kambó, yopo, ibogaine, psilocybin, LSD, mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]), DMT, Syrian Rue, ketamine, esketamine, Salvia divinorum or other psychedelic agents or mixtures or dissociative in their synthetic or naturally occurring form within 14 days prior to dosing.
14	Has used synthetic, plant-based, or herbal dietary supplements with known MAOI or antidepressant activity within 14 days prior to dosing.
15	Has received any investigational medication within the last 6 weeks prior to dosing.
16	Has previously experienced a significant adverse reaction to a hallucinogenic or psychedelic drug (e.g., psilocybin, Psilocybe spp. mushrooms, mebufotenin, DMT, ayahuasca, LSD, mescaline) according to the investigator's judgment.
17	Has known allergies or hypersensitivity or any other contraindication to mebufotenin or has diagnosed or suspected genetic monoamine oxidase deficiency or reduced activity, or has one or more immediate family members with diagnosed or suspected genetic monoamine oxidase deficiency or reduced activity (e.g., Norrie disease or Brunner syndrome).
18	Has any current or past clinically significant condition (e.g., severe infection, severe pulmonary disease, uncontrolled hypertension, new onset of hypertensive disorders of pregnancy during pregnancy or in the postnatal period that have not resolved at screening [e.g., gestational hypertension, pre-eclampsia/eclampsia, superimposed pre-eclampsia], uncontrolled diabetes, severe cardiovascular disease, severe hepatic or renal failure, severe brain disorder [including seizure disorder, stroke, dementia, degenerative neurologic diseases, meningitis, encephalitis, and head injury with loss of consciousness]) that may interfere with the interpretation of the trial results, constitutes a health risk for the patient, or that otherwise renders the patient unsuitable for the trial according to the investigator's judgment.
19	Takes any medication or other substance that renders the patient unsuitable for the trial according to the investigator's judgment.
20	Has a clinically significant abnormality in physical examination, vital signs, ECG, or clinical laboratory parameters which renders the patient unsuitable for the trial according to the investigator's judgment.
21	Has a QT interval corrected using Fridericia's formula (QTcF) $\geq$ 470 ms during screening or before dose administration, or history of additional risk factors for torsades des pointes (e.g., heart failure, family history of Long QT Syndrome, or the use of concomitant medications that prolong the QT/QTc interval).
22	Has abnormal thyroid function at screening. Patients that are on thyroid medications are eligible when they are euthyroid at screening.
23	Patient who has a positive pregnancy test at screening or on the pre-test day (Day -1), is pregnant, or plans to become pregnant during the course of the trial and up to 90 days after GH001 dosing.
24	Patients with DSM-5 alcohol use disorder (excluding tobacco and caffeine use disorders) within 6 months prior to screening.

25	If a smoker, is unwilling or unable to abstain from cigarette smoking or vaping on the day of study drug administration (nicotine replacement therapy is permitted).
26	Shows positive alcohol breath test on the pre-test day (Day -1) or on Day 1 prior to the first administration of GH001.
27	Shows a positive drug urine test at screening, on the pre-test day (Day -1) or on Day 1 prior to the first administration of GH001. Patients with a positive drug test at screening may have the test repeated once at a later date. This determination, and the reason for permitting a repeat test, must be recorded in the patient's source documents. A positive repeat drug test or a positive pre administration test is exclusionary. If the urine screen tests positive for benzodiazepines, and the patient took allowed benzodiazepines within the permitted time period as outlined in the exclusion criteria, this will not constitute a screen failure. Details of the benzodiazepine taken, including dose and timing shall be recorded in the source documents.
28	A positive Coronavirus Disease 2019 (COVID-19) test during the screening, on the pre-test day (Day -1) or on Day 1 as confirmed by an antigen or polymerase chain reaction (PCR) test. Patients with a positive test result for COVID-19 during the screening period or on the scheduled trial dosing day may be rescreened, or attend their rescheduled Day -1/Day 1 visit, a minimum of 5 days after initially testing positive, with/without a negative COVID-19 test result, provided that they are clinically recovered, and at the discretion of the investigator.

Abbreviations: AFHF-SF = Antidepressant Treatment History Form: Short Form; BMI = Body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; DMT = N,N-dimethyltryptamine; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; ECG = Electrocardiogram; GP = General practitioner; LSD = Lysergic acid diethylamide; MADRS = Montgomery–Åsberg Depression Rating Scale; MAOI = Monoamine oxidase inhibitor; MDD = Major depressive disorder; MINI = Mini-International Neuropsychiatric Interview; NMDA = N-methyl-D-aspartate; PPD = Postpartum depression; PTSD = Post-traumatic stress disorder; SNRI = Serotonin and norepinephrine reuptake inhibitor; SSRI = Selective serotonin reuptake inhibitor; TCA = Tricyclic antidepressant.

Supplementary Table 2. Schedule of Assessments

Assessment	Description	Schedule
Efficacy		
MADRS[2]	10-item clinician-rated scale; symptoms are rated on a 7-point scale from 0 (no symptoms) to 6 (severe symptoms); overall scoring range: 0–60, with higher scores indicating more severe depression; administered using the structured interview guide for the MADRS.	Baseline, Day 1 (2 hours post-last IDR dose), Day 2, Day 8
CGI-S[3]	Single 7-point scale from 1 (normal) to 7 (extremely ill); the CGI-S assessment was conducted after the MADRS assessment; administered by a psychiatrist or registered clinical psychologist with adequate experience with patients with MDD.	Baseline, Day 1 (2 hours post-last IDR dose), Day 2, Day 8
BIMF[4]	20-item self-reported patient centered tool assessing postpartum maternal functioning, which was designed to measure functioning in the year after childbirth; each item is rated on a 7-point scale from 0-6 as follows: 0. Strongly disagree; 1. Disagree, 2. Somewhat disagree; 3. Neutral; 4. Somewhat agree; 5. Agree; 6. Strongly agree; total score range: 0-120, with higher scores indicating greater severity of functional impairment.	Baseline Day 8

Assessment	Description	Schedule
Safety		
TEAEs	AEs were coded using Medical Dictionary of Regulatory Activity (Version 26.0).	Baseline, Day 1, Day 2, Day 8
Vital signs	Vital signs were measured pre-dose (before first IDR dose only), after any PsE had fully subsided, and 60 minutes after each IDR dose; heart rate and SpO_2 were monitored continuously during the acute psychoactive phase; measurements were recorded at 5, 10, 15, 20, 25, and 30 minutes after each IDR dose.	Baseline, Day 1 (after each IDR dose and at discharge), Day 2, Day 8
ECG	Standard 12-lead electrocardiogram; variables included heart rate, RR, QT, PR, and QRS intervals and QT interval corrected using Fridericia's formula.	Baseline, Day 1 (at discharge), Day 2, Day 8
Clinical laboratory tests	Included hematology, clinical chemistry, thyroid function test, and urine samples for laboratory safety and to assess for drugs of abuse or alcohol.	Baseline and Day 8
Spirometry	Pulmonary function test; measures FVC, FEV_1, FEV_1/FVC ratio.	Baseline, Day 1 (post-each IDR dose and at discharge), Day 2, Day 8
MOAA/S[5]	6-point scale assessing level of sedation, with a score of 5 ("responds readily to name spoken in normal tone") to 0 ("no response after painful trapezius squeeze"); administered by a physician.	Baseline, Day 1 (after each IDR dose, 60 minutes after final dose, and at discharge)
BPRS[6]	18-item clinician-rated scale assessing psychiatric symptoms; items rated on a 7-point Likert scale from 1 (not present) to 7 (extremely severe); total score range: 18–126, higher scores indicate greater severity; covers areas like anxiety, depression, hostility, hallucinations, disorientation; administered via semi-structured interview by trained clinicians.	Baseline, Day 1 (at discharge), Day 2, Day 8
C-SSRS[7]	Detailed questionnaire assessing suicidal behavior and ideation, with five questions addressing each; administered by a psychiatrist or licensed clinical psychologist; baseline/screening version was used at screening; Since Last Visit was used at other time points.	Baseline, Day 1 (at discharge), Day 2, Day 8
CADSS[8]	19-item subjective scale administered by a psychiatrist or licensed clinical psychologist; each item scored 0 (not at all) to 4 (extremely; total score: 0–76) based on the patient's described experience	Baseline, Day 1 (at discharge), Day 2, Day 8
CADR	Proprietary structured discharge assessment administered by a physician to ensure that the patient was without hallucinations and that any AEs had subsided.	Day 1 (at discharge)
Cognitive assessments[9]	Cognition was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The test order in CANTAB is VRM (immediate recall), RVP, SWM, DSST, and VRM (delayed recall).	Baseline, Day 1 (at discharge), Day 2, Day 8
Psychoactive Effects		
PES[1]	Three visual analog scales (0–100) for assessing intensity, feeling of loss of control, and profoundness during a psychoactive experience; PES score was the average of the three scale scores; a mean score of 75 or greater was the threshold for determining that a patient achieved a Peak Experience.	Day 1 (after each IDR dose)

Assessment	Description	Schedule
MEQ30[10]	30-item questionnaire comprising four factors: mystical, positive mood, transcendence of time and space, and ineffability; each item is rated on a 6-point scale from 0 (none, not at all) to 5 (extreme, more than ever before in my life and stronger than 4); total score is calculated as the average of all non-missing item scores for a scoring range of 0–5.	Day 1 (after each IDR dose)
CEQ[11]	26-item tool comprising 7 factors (grief, fear, death, insanity, isolation, physical distress, and paranoia); each item is scored from 0 (none, not at all) to 5 (extreme, more than ever before in my life); total score was calculated as the average of transformed item scores for a scoring range of 0–5.	Day 1 (after each IDR dose)
Duration of PsE	Physician evaluation.	Day 1 (after each IDR dose)
Pharmacokinetics		
Breastmilk sampling	To assess the level of mebufotenin and its metabolites bufotenin and 5-MIAA in breastmilk samples.	Baseline, Day 1 (<2.5 hours post-dose), Day 2, Day 8

Abbreviations: BIMF = Barkin Index of Maternal Functioning; BPRS = Brief Psychiatric Rating Scale; CADR = Clinical Assessment of Discharge Readiness; CADSS = Clinician Administered Dissociative States Scale; CEQ = Challenging Experience Questionnaire; CGI-S = Clinical Global Impression Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; DSST = Digit symbol substitution test; ECG = Electrocardiogram; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; HAM-D-17 = Hamilton Rating Scale for Depression; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; MEQ30 = Mystical Experience Questionnaire (30-item); MDD = Major depressive disorder; MOAA/S = Modified Observer's Assessment of Alertness and Sedation scale; PES = Peak Experience Scale; PR = Pulse rate; PsE = Psychoactive effects; RR = Respiratory rate; RVP = Rapid visual information processing; SpO_2 = Oxygen saturation; SWM = Spatial working memory; TEAE = Treatment-emergent adverse events; VRM = Verbal recognition memory.

Supplementary Results

Supplementary Table 3. Patient Disposition

Parameter, n (%)	**GH001 (N = 10)**
Patient Screening, n	
Screened	24
Screening failed	14
Reason for screening failure	
Failed to meet eligibility criteria	10
Out of window screening	2
Withdrawal by patient	1
Lost to follow-up	1
Patients receiving IDR doses	
Dose 1 (6 mg)	1 (10.0)
Dose 2 (6 + 12 mg)	7 (70.0)
Dose 3 (6 + 12 + 18 mg)	2 (20.0)

Supplementary Table 4: Summary of Barkin Index of Maternal Functioning at Baseline and Day 8

	Score Range	Baseline		Day 8	
		n	Mean (SD)	n	Mean (SD)
Total Score	0-120	9	69.7 (14.8)	9	100.7 (10.6)
Self care	0-18	9	6.9 (2.1)	9	12.1 (4.6)
Infant care	0-18	9	11.2 (0.7)	9	11.2 (1.0)
Mother-child interaction	0-18	9	10.6 (3.5)	9	15.8 (1.4)
Psychological well-being	0-18	9	31.7 (7.9)	9	49.0 (7.2)
Social support	0-18	9	10.2 (4.2)	9	15.4 (2.1)
Management	0-12	9	20.2 (6.5)	9	29.2 (4.2)
Adjustment	0-18	9	5.8 (2.2)	9	9.9 (1.5)

Abbreviations: SD = Standard deviation.

Supplementary References

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