SUMMARY OF TRIAL RESULTS

Trial PROTOCOL: GH001-PPD-203

A Phase 2 Clinical Trial of GH001 in Patients with Postpartum Depression

Name of investigational product:	GH001
EudraCT number:	2021-006879-42
Clinicaltials.gov number:	NCT05804708
Indication studied:	Postpartum depression
Development phase of trial:	Phase 2a
First patient enrolled:	02 March 2023
Last patient completed:	02 August 2024
Name of sponsor:	GH Research Ireland Limited

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Guideline E6(R2) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) and ISO 14155:2020.

Name of Sponsor/Company: GH Research Limited

Name of finished product: GH001

Name of active ingredient: Mebufotenin (5-methoxy-*N,N*-dimethyltryptamine [5-MeO-DMT])

Title of study: A Phase 2 Clinical Trial of GH001 in Patients with Postpartum Depression

Study center(s): The trial was conducted at five investigational sites in the Netherlands and United Kingdom.

Publications (reference): None

Studied period (years):	**Phase of development:**
Date first patient enrolled: 02 March 2023 Date last patient completed: 02 August 2024	Phase 2a

Objectives:

Primary: To determine the onset and 7-day durability of anti-depressive effects of a single-day individualized dosing regimen (IDR) of 6, 12, and 18 mg GH001 in adult, female patients with postpartum depression (PPD).

Secondary: To determine the following after a single-day IDR of 6, 12, and 18 mg GH001 in adult female patients with PPD:

- Anti-depressive effects
- Effects on maternal behavior
- Safety and tolerability
- Intensity and duration of psychoactive effects (PsE)

Exploratory: To determine the amount of mebufotenin and its metabolites (bufotenin and 5-methoxyindole-3-acetic acid [5-MIAA]) in breastmilk, blood, and urine following administration of a single-day IDR of 6, 12, and 18 mg GH001 in adult, female patients with PPD.

Methodology:

This was a multi-center, prospective, open-label, non-randomized, single arm, Phase 2a trial to determine the safety and efficacy of GH001 in female patients with PPD.

The trial consisted of a screening period of up to 60 days (Day -60 to Day -2), a Day -1 visit where assessments were performed and eligibility was reconfirmed, a Day 1 visit where patients received a single-day IDR of GH001 via inhalation after vaporization and underwent trial assessments, a Day 2 follow-up visit, and the end of trial visit on Day 8.

GH001 was administered using the Volcano Medic 2 Vaporization System (Storz & Bickel, Germany). Prior to GH001 administration, patients were trained on the inhalation technique and were prepared for the potential PsE. Patients remained under medical supervision from their arrival at the trial site on Day 1 until discharge. Patients were discharged once all trial assessments were completed, and once they were deemed discharge-ready per the Clinical Assessment of Discharge Readiness (CADR).

GH001 was administered as an IDR on Day 1 where up to three doses of GH001 (6, 12, and 18 mg) were administered to patients via inhalation within a single day, with a recommended interval of 1 hour between doses as follows:

- All patients received an initial dose of 6 mg GH001.
- The second dose (12 mg) was administered based on the patient's subjectively reported psychoactive effects, and the safety and tolerability level of the first dose (6 mg) according to the trial physician's judgement.
- Similarly, a third dose (18 mg) was administered based on the patient's subjectively reported psychoactive effects, and the safety and tolerability level of the second dose (12 mg) according to the trial physician's judgement.

This trial was stopped early by the Sponsor after the treatment of 10 patients due to challenges associated with patient recruitment. As outlined in the protocol and the statistical analysis plan (SAP), 15 patients were planned to be enrolled. The Sponsor also concluded that a sufficient number of patients had completed the trial to demonstrate proof of concept in this patient population.

Number of patients (planned and analyzed):

Planned: 15 patients

Enrolled/Analyzed: 10 patients

Diagnosis and main criteria for inclusion:

The population for this study was female patients between 18 and 45 years (inclusive) who met the trial criteria for PPD as assessed by a study psychiatrist:

a. Diagnosis of major depressive disorder (MDD) without psychotic features, confirmed by the Mini-International Neuropsychiatric Interview (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.

b. Had a Montgomery–Åsberg Depression Rating Scale (MADRS) total score of ≥28 at screening and pre-dose on Day 1.

Test product, dose and mode of administration, batch number:

Test product: GH001, an inhalation formulation of synthetic mebufotenin (5-MeO-DMT).

Doses: GH001 was administered as an IDR consisting of up to three increasing doses of GH001 (6, 12, and 18 mg) on a single day.

Mode of administration: Inhalation after vaporization using the Volcano Medic 2 Vaporization System.

Duration of treatment:

Up to three doses of study drug administered as an IDR on a single dosing day, with a 1-hour interval between doses.

Criteria for evaluation:

The primary efficacy endpoint was the change from baseline in MADRS assessed at Day 8.

Secondary endpoints included the following:

- Anti-depressive effects:
  - The proportion of patients in remission (MADRS ≤10) at 2 hours after the final dosing on Day 1, and at Day 2 and Day 8.
  - Change from baseline in MADRS assessed at 2 hours after the final dosing on Day 1, and at Day 2.
  - The proportion of responders (≥50% reduction from baseline in MADRS total score) at 2 hours after the final dosing on Day 1, and at Day 2 and Day 8.
  - Change from baseline in Clinical Global Impression – Severity scale (CGI-S) at 2 hours after final dosing on Day 1, and at Day 2 and Day 8.
- Maternal behavior: the change from baseline in the Barkin Index of Maternal Functioning (BIMF) total and sub-scale scores to Day 8
- Safety and tolerability:
  - Reporting of treatment-emergent adverse events (TEAEs)
  - Clinically significant changes from baseline in electrocardiogram (ECG), vital signs, safety laboratory assessments and spirometry assessments.
  - Assessment of sedation (Modified Observer's Assessment of Alertness and Sedation scale [MOAA/S]) following each dose (when the PsE had subsided and 60 minutes after each dosing) and as part of the discharge evaluation on Day 1.
  - Change from baseline in Clinician Administered Dissociative States Scale (CADSS) assessed as part of the discharge evaluation on Day 1 and at Day 2 and Day 8.
  - Assessment of patient discharge readiness at discharge on Day 1 using the CADR.
  - Change from baseline in Brief Psychiatric Rating Scale (BPRS) assessed as part of the discharge evaluation on Day 1, and at Day 2 and Day 8.
  - Change from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) assessed as part of the discharge evaluation on Day 1, and at Day 2 and Day 8.
- The PsE experienced by the patients as reported 30 to 60 minutes after each dose (when the PsE had subsided), as assessed by:
  - Peak experience (PE) scale (PES) to assess the achievement of a PE (PES total score ≥75)
  - Challenging Experience Questionnaire (CEQ)
  - Mystical Experience Questionnaire (MEQ30)

- The duration of the PsE: defined as the time from dosing to the time when the PsE subsided (investigator-scored), completed 30 to 60 minutes after each dosing.

Exploratory endpoints included the following:

- The amount of mebufotenin, bufotenin, and 5-MIAA measured in breastmilk obtained on Day -1, 1 hour, and 2.5 hours after last dosing, in the evening of Day 1, and on Day 2 and Day 8.
- The amount of mebufotenin, bufotenin, and 5-MIAA measured in blood obtained on Day -1, 1 hour, and 2.5 hours after last dosing, and on Day 2 and Day 8.
- The amount of mebufotenin, bufotenin, and 5-MIAA measured in urine obtained on Day -1, 2.5 hours after last dosing, in the evening of Day 1, and on Day 2 and Day 8.

Statistical methods:

Study Populations:

- The full analysis set (FAS) included all randomized patients who received at least one dose of study drug and had at least one post dose assessment for efficacy endpoint.
- The per protocol (PP) analysis set included all patients in the FAS who had completed the IDR as PP and had no major protocol deviation that was liable to bias the evaluation of the main primary efficacy endpoint.
- The safety analysis set included all randomized patients who received at least one dose of study drug.
- The serum pharmacokinetics (PK) set included all patients who received at least one dose of study drug and had at least one measurable serum concentration.
- The breastmilk PK set included all patients who received at least one dose of study drug and provided at least one measurable breastmilk sample.
- The urine PK set included all patients who received at least one dose of study drug and provided at least one measurable urine sample.

Primary Efficacy Analyses:

The primary endpoint was the change in MADRS total score from baseline to Day 8 analyzed in the FAS. There are ten individual items included in the MADRS questionnaire. Each item yields a score of 0 to 6 and the score of all ten items are summed as the total score (ranging from 0 to 60). Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) were summarized for the total score (per MADRS item for each timepoint), the absolute change from baseline, and the relative change from baseline.

Only the absolute and relative change from baseline to Day 8 in MADRS were analyzed by a one-sample t-test with a one-sided significance level of $\alpha=0.025$. Remission was defined as patients with total MADRS score ≤ 10. Responders were defined as patients with $\geq 50\%$ reduction in total MADRS score compared to baseline.

Other Efficacy Measures

The secondary endpoints utilizing the MADRS, CGI-S, and BIMF scales were conducted primarily with the FAS.

CGI-S scores were reported using descriptive statistics at each timepoint. Change from baseline was also reported at each timepoint. The score of individual items of BIMF and total BIMF score were also reported using descriptive statistics.

Psychoactive Effects

The FAS was used to perform all PsE analyses. All data were listed, and, for the assessments of PES, CEQ, and MEQ30, summarized with descriptive statistics.

Safety Analyses:

All safety assessments were listed and where appropriate, summarized with descriptive statistics.

Pharmacokinetics Analysis:

The serum PK set, breastmilk PK set, and urine PK set were used to perform all PK analysis.

Concentrations and PK parameters for mebufotenin, bufotenin, and 5-MIAA were listed individually and summarized using descriptive statistics. For the purposes of summarizing and plotting concentration-time data, concentration value(s) below the lower limit of quantification (LLOQ) were assigned a value of zero if the time point is prior to treatment, otherwise these were assigned as LLOQ/2.

Results

Demographics:

Overall, the 10 patients enrolled in this trial were predominantly White and not Hispanic or Latino (90.0%), with an overall mean (SD) and median (range) age of 31.6 (5.19) and 32.5 (22 to 38) years, respectively. All patients had an ongoing PPD episode with an overall median (range) duration of 30.0 (14 to 51) weeks.

Disposition:

All 10 patients enrolled in the trial received at least one dose of GH001, had at least one post-dose efficacy assessment, and were included in the FAS and safety set. One patient received only a single dose (6 mg) of the IDR, seven patients received two doses (6 and 12 mg) of the IDR, and two patients received all three doses (6, 12, and 18 mg) of the IDR.

Efficacy:

The primary efficacy endpoint of change from baseline in MADRS assessed at Day 8 was evaluated in 10 patients after a single-day IDR of GH001 on Day 1. At Day 8, MADRS total score was significantly reduced from baseline, with a mean (SD) change of -35.4 (5.48; $P<0.0001$), corresponding to a relative mean change of -96.3%. These data demonstrate the anti-depressive effects of GH001 were maintained for up to 7 days post-dose.

Assessment of secondary efficacy endpoints demonstrated:

- The onset of antidepressant effects of GH001 was rapid, with a mean (SD) change in MADRS total score of -31.4 (4.67) observed 2 hours post-dose, which decreased further at Day 2 to values similar to the primary endpoint (mean [SD] change of -36.0 [5.48]).
- All patients were considered clinical responders (≥50% reduction in MADRS total score from baseline) and were in remission (MADRS total score ≤10) at all timepoints evaluated (2 hours postdose, Day 2, and Day 8).

- All patients had a reduction in the severity of depressive symptoms measured through the CGI-S, with mean (SD) change in score from baseline to 2 hours post-dose, Day 2, and Day 8 of -3.7 (0.82), -3.8 (0.79), and -3.8 (0.83), respectively.
- Maternal well-being and function improved based on an approximately 44% increase in mean (SD) BIMF total score from 69.7 (14.82) at baseline to 100 (10.64) at Day 8 (out of a possible maximum of 120).

Attainment of a PE using the PES:

- In total, seven of 10 patients (70.0%) achieved a PE at their maximum individual dose level: one (10.0%) after the 6 mg dose and six (60.0%) after the 6-12 mg doses.
- The mean (SD) PES total score after the last administered IDR dose was 82.3 (18.4), which was also the mean maximum PES total score achieved after any dose during the IDR. In general, PES total score was highest following the second GH001 administration (12 mg dose) in the IDR, with median (range) scores per individual dose of 35.5 (1 to 96.3), 85.7 (41.7 to 100), and 55.0 (41.7 to 68.3) after the 6, 12, and 18 mg doses, respectively.

CEQ:

- Overall, no consistent CEQ trends were noted with the IDR. A small decreasing trend was noted per total GH001 dose, which was not apparent per individual dose.

MEQ30:

- A complete mystical experience was reported by one patient (10.0%) after the 12 mg dose.
- No consistent trend was noted for the MEQ30, except for a small decreasing trend in total score by total GH001 dose, which was not apparent per individual dose.

Duration of PsE:

- Overall, the clinician-reported duration of PsE was relatively consistent following GH001 administration, with median (range) individual dose durations of 22.0 (5 to 62), 25.0 (7 to 37), and 25.0 (10 to 40) minutes after the 6, 12, and 18 mg doses, respectively.
- The maximum duration of PsE was 62 minutes in one patient (10.0%) following the 6 mg dose, with all other patients having durations of PsE between 5 and 40 minutes.

Safety:

Overall, the results from this trial indicate that GH001 administration as an IDR of up to three escalating doses (6, 12, and 18 mg) via inhalation using the Volcano Medic 2 Vaporization System has an acceptable safety profile and is well tolerated in patients with PPD. There were no severe TEAEs, serious adverse events (SAEs), deaths, premature discontinuations of GH001 due to TEAEs, or withdrawals from the trial following any administration of GH001 as an IDR.

In total, 13 TEAEs occurred in eight patients (80.0%), the most common of which was headache (five events in five patients [50.0%]). All other TEAEs occurred as a single event. All reported TEAEs were mild (12 events in seven patients [70.0%]) or moderate (one event in one patient [10.0%]), with the majority considered treatment-related adverse events (11/13 events).

There were no notable or consistent changes from baseline values in clinical laboratory assessments of hematology, chemistry, or urinalysis, and no individual patient had shifts to abnormal clinically

significant in any laboratory measurement. Similarly, assessments of vital signs showed no clinically significant changes and there were no clearly identifiable trends in blood pressure, respiratory rate, SpO_2, body temperature, or body weight. Transient increases in heart rate were observed after administration of GH001 and spontaneously returned to baseline. Overall, no other clinically significant vital sign findings were reported.

Clinician-rated assessments indicated that GH001 has a favorable safety profile. The proportion of patients reporting suicidal ideation per the C-SSRS was reduced from three patients (30.0%) at baseline to none at discharge (Day 1), Day 2, and Day 8. Assessment of psychiatric and psychotic symptoms with the BPRS showed a mean (SD) reduction in total BPRS score from baseline to Day 8 of -23.7 (8.34), representing the minimum possible rating. Treatment with GH001 did not result in a dissociative state or sedation once PsE had subsided, as measured by the CADSS and MOAA/S, respectively. All patients were deemed to be discharge-ready as assessed by the CADR on Day 1.

Overall conclusion

GH001 administered as a single-day IDR in adult female patients with PPD was well-tolerated with an acceptable safety profile, with patients reporting improvement in symptoms of depression and maternal function up to 7 days following treatment. Overall, these results support further investigations into the efficacy and safety of GH001 treatment of female patients with PPD.