Results of a Phase 2a Clinical Trial of Inhaled Mebufotenin (GH001) in Patients With Postpartum Depression

Claus Bo Svendsen,[1]* Emilio Arbe,[2] Sem E. Cohen,[3] Kristina M. Deligiannidis,[4] William Gann,[5] Sarah Keady,[1] Rachael MacIsaac,[1] Stuart Ratcliffe,[2] David R. Rubinow,[6] Dan Tully,[5] Velichka Valcheva,[1] Jasper B. Zantvoord,[3] Martin Johnson[2]

[1]GH Research, Dublin, Ireland; [2]St. Pancras Clinical Research, London, United Kingdom; [3]Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [4]Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, New York, United States; [5]Department of Psychiatry, Sheffield Health and Social Care NHS Foundation Trust, Sheffield, United Kingdom; [6]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina, United States

*Presenting Author: Claus Bo Svendsen; cbs@ghres.com

Background

- Postpartum depression (PPD) is a common perinatal 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%,[3] with up to 13% of diagnosed patients still experiencing symptoms two years after giving birth[4]
- Current treatment options for PPD have slow onset of action, low remission rates, and/or high treatment burden[5]; therefore, novel treatment methods are needed
- Mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) is a potent psychedelic drug that acts as a non-selective serotonin agonist with highest affinity for the 5-HT_{1A} receptor subtype[6]
- Early-phase clinical trials of mebufotenin administered via pulmonary inhalation (GH001) demonstrated that GH001 has an acceptable safety profile and is well tolerated, with an ultra-rapid onset of therapeutic benefits[7,8]
- The trial presented here is the first in which mebufotenin was administered to patients diagnosed with PPD

Objective

- To investigate the potential antidepressant effects and safety of GH001 in adult, female patients with PPD

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Disclosures

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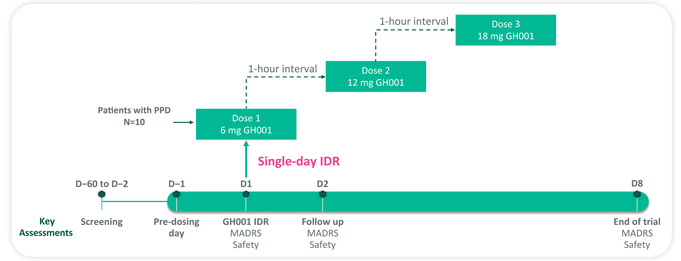
Methods

- This Phase 2a, proof-of-concept, open-label trial (NCT05804708) enrolled women aged 18–45 years who met the Mini-International Neuropsychiatric Interview diagnostic criteria for major depressive disorder with peripartum onset and who had outpatient status
- Patients were required to have received no other antidepressant therapy for 14 days prior to dosing and have a Montgomery–Åsberg Depression Rating Scale (MADRS) total score of ≥28, reflecting moderate to severe depressive symptoms
- Patients must have either 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
- Patients were administered an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) with a 1-hour interval between doses on a single day (Figure 1)
- Criteria for administration of the second and third doses as part of the IDR were based on patients' subjectively reported psychoactive effects and the safety and tolerability at the previous dose level
- This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard of care, but without any planned psychotherapeutic intervention before, during, or after dosing
- The primary endpoint was change in MADRS total score from baseline to Day 8; change from baseline in MADRS total score at 2 hours and Day 2 postdose and MADRS remission (MADRS total score ≤10) were assessed as secondary endpoints
- Safety and tolerability were assessed throughout the trial as secondary endpoints and included the following parameters: treatment-emergent adverse events (TEAEs), sedation as assessed by the Modified Observer's Assessment of Alertness and Sedation (MOAA/S), psychiatric symptoms as assessed by the Brief Psychiatric Rating Scale (BPRS), and suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Discharge readiness was assessed by the Clinical Assessment of Discharge Readiness (CADR)
- *P* values were calculated using one-sample *t* tests with a one-sided significance level of α=0.025, and the study was adequately powered to detect a clinically meaningful difference

Figure 1. Clinical Trial Design



D = Day; IDR = Individualized dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale; PPD = Postpartum depression.

Results

- This trial enrolled 10 patients diagnosed with PPD with a mean (SD) age of 32 (5.2) years
- The mean (SD) duration of the current depressive episode was 30.9 (12.9) weeks, and the mean (SD) parity was 2 (0.94)
- One patient (10.0%) had received pharmacotherapy for the current depressive episode, and six patients (60.0%) had received pharmacotherapy for prior major depressive episodes
- The mean (SD) baseline MADRS total score was 36.7 (4.8)

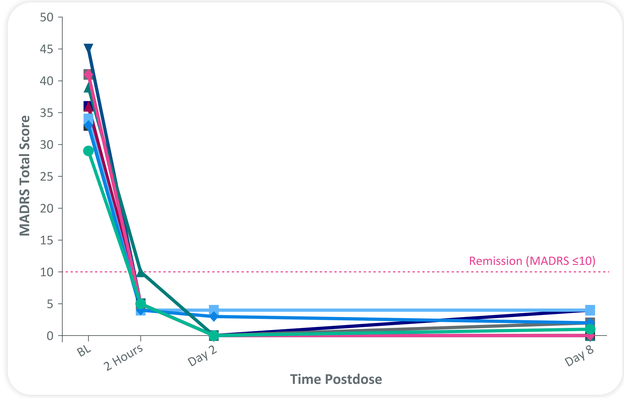
Efficacy

- The primary endpoint was achieved, with a significant reduction from baseline to Day 8 of −35.4 points (96.3%) in MADRS total score with GH001 treatment (*P*<0.0001; Figure 2)
- Significant reductions in MADRS total score were also observed at 2 hours postdose and on Day 2 (*P*<0.0001 for both time points)
- All 10 patients demonstrated nearly identical and consistent reductions in MADRS total score at 2 hours postdose, on Day 2, and Day 8 (Figure 3)
- All patients (100%) achieved remission at Day 8, as well as at 2 hours postdose and on Day 2

Figure 2. Mean Change in MADRS Total Score From Baseline in Patients With PPD Treated With GH001

BL = Baseline; MADRS = Montgomery-Åsberg Depression Rating Scale; PPD = Postpartum depression; SD, standard deviation.

Figure 3. MADRS Total Scores for Individual Patients With PPD Treated With GH001



BL = Baseline; MADRS = Montgomery-Åsberg Depression Rating Scale; PPD = Postpartum depression.

Safety

- TEAEs were observed in 8/10 patients (80.0%) and were mostly mild in severity (87.5%); only one patient reported a TEAE as moderate in severity
- Headache was the most commonly reported TEAE (5/10 patients); all other TEAEs occurred in a single patient each
- No TEAEs of flashbacks were reported
- There were no serious TEAEs or severe TEAEs, and no patient withdrew from the trial
- There was a clinically significant reduction in BPRS from baseline to Day 8 (−23.7)
- There was no clinically relevant worsening of other clinician-rated assessments (based on the CADR, C-SSRS, and MOAA/S scales)
- Based on the CADR, all patients were deemed ready for discharge within the same day of dosing

Table 1. Summary of Safety in Patients With PPD Treated With GH001 (N=10)

	Patients, n (%)
Any TEAE	8 (80.0)
Mild	7 (87.5)
Moderate	1 (12.5)
Severe	0
Treatment-related TEAEs	7 (70.0)
Serious TEAE	0
Death	0
TEAEs by Preferred Term	
Headache	5 (50.0)
Abdominal pain	1 (10.0)
Nausea	1 (10.0)
Vomiting	1 (10.0)
Diarrhea	1 (10.0)
Dizziness	1 (10.0)
Dysgeusia	1 (10.0)
Tachycardia	1 (10.0)
Paresthesia	1 (10.0)

PPD = Postpartum depression; TEAE = Treatment-emergent adverse event.

Conclusions

- In this trial evaluating the safety and antidepressant effects of GH001 in patients with PPD, the primary endpoint was met: a significant reduction from baseline in MADRS total score was observed on Day 8 postdose
- Significant reductions in MADRS total score were observed by 2 hours postdose, confirming an ultra-rapid antidepressant effect of GH001
- GH001 administered via inhalation demonstrated a favorable safety profile and was well tolerated in patients with PPD; no serious TEAEs were reported