SUMMARY OF TRIAL RESULTS

Trial PROTOCOL: GH001-BD-202

A Phase 2 Clinical Trial of GH001 in Patients with Bipolar II Disorder and a Current Major Depressive Episode

Name of investigational product:	GH001
EudraCT number:	2021-006861-39
Clinicaltials.gov number:	NCT05839509
Indication studied:	Bipolar disorder type II and a current major depressive episode
Development phase of trial:	Phase 2a
First patient enrolled:	06 April 2023
Last patient completed:	02 July 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 trial: A Phase 2 Clinical Trial of GH001 in Patients with BDII and a Current Major Depressive Episode

Trial center(s): The trial was conducted at seven investigational sites across Germany, The Netherlands, and the United Kingdom

Publications (reference): None

Studied period (years):	**Phase of development:**
Date first patient enrolled: 06 April 2023 Date last patient completed: 02 July 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 patients with bipolar disorder type II (BDII) and a current major depressive episode (MDE).

Secondary: To determine the following after a single-day IDR of 6, 12, and 18 mg GH001 in patients with BDII and a current MDE:

- The effects on depressive symptoms and global clinical status
- The safety and tolerability
- The intensity and duration of the psychoactive effects (PsE)

Methodology:

This was a multi-center, prospective, open-label, non-randomized, single arm, Phase 2a trial.

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 six 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: Six patients

Diagnosis and main criteria for inclusion:

The population for this trial was male and female patients between 18 and 64 years (inclusive) who met the trial criteria for BDII and were experiencing a MDE, as assessed by a trial psychiatrist or registered clinical psychologist:

a. Met the DSM-5 diagnostic criteria for BDII with a current MDE confirmed by the Mini-International Neuropsychiatric Interview v7.0.2.

b. Had a MADRS total score of ≥24 at screening and prior to first dose on Day 1.

Test product, doses, and mode of administration:

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.
- Change from baseline in Bipolar Depression Rating Scale (BDRS) on Day 2 and 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.
  - The incidence of adverse events (AEs) of mania or hypomania (as assessed using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria for mania/hypomania).
  - Change from baseline in Young Mania Rating Scale (YMRS) assessed as part of the discharge evaluation on Day 1, and on Day 2 and Day 8.
  - 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.

Statistical methods:

Trial Populations:

The full analysis set (FAS) included all enrolled 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 enrolled patients who received at least one dose of study drug.

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 α=0.025. Remission was defined as patients with total MADRS score ≤10. Responders were defined as patients with ≥50% reduction in total MADRS score compared to baseline.

Other Efficacy Measures

The secondary endpoints utilizing the MADRS, CGI-S, and BDRS scales were conducted 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 BDRS and total BDRS 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.

Results

Demographics:

Overall, the six patients enrolled in this trial were White (100%) and not Hispanic or Latino (100%), with an overall mean (SD) and median (range) age of 44.2 (9.28) and 42.5 (32 to 57) years, respectively. All patients had an ongoing MDE with an overall median (range) duration of 12.0 (5 to 54) weeks for the four patients for whom this was reported.

Disposition:

All six 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. Two of the patients enrolled received only the initial dose of 6 mg, one patient received both the 6 mg and 12 mg doses, and three patients received all three doses(6 mg, 12 mg, and 18 mg).

Efficacy:

The primary efficacy endpoint of change from baseline in MADRS assessed at Day 8 was evaluated in six 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 -16.8 (12.2; $P<0.0099$), corresponding to a relative mean change of -51.8%.

Assessment of secondary efficacy endpoints demonstrated:

- At 2 hours post-dose and on Day 2, the mean (SD) change in MADRS total score from baseline was -16.3 (6.0) and -13.3 (13.5), respectively.
- Based on the defined MADRS criteria, two (33.3%) of the enrolled patients were considered responders (≥50% reduction from baseline) and two (33.3%) were in remission (MADRS total score ≤10) at Day 8; the two patients who achieved response and the two patients who achieved remission were the same patients.
- 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 -1.8 (1.3), -1.7 (2.2), and -2.5 (1.5), respectively.
- A reduction in the BDRS total score was observed in all six patients following GH001 administration, with mean (SD) change from baseline at Day 2, and Day 8 of -13.5 (11.8), and 14.5 (11.2), respectively.

Attainment of a PE using the PES:

- In total, 5/6 patients (83.3%) achieved a PE: two patients achieved a PE after the 6 mg dose, one patient achieved a PE after the 6-12 mg doses, and two patients achieved a PE after the 6-12-18 mg doses. The patient who didn't achieve a PE received all three doses.
- The mean (SD) PES total score after the last IDR dose and the mean (SD) maximum PES total score achieved during the IDR was 82.95 (16.95) and 83.83 (14.88), respectively.

CEQ:

- Overall, no consistent CEQ trends were noted with the IDR.

MEQ30:

- There was no clear dose-related trend for the MEQ30.

Duration of PsE:

- By total GH001 dose, the median (range) duration was 35.0 (14 to 56), 22.0 (22 to 22), and 42.0 (40 to 51) minutes after the 6, 6-12, and 6-12-18 mg doses, respectively.

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 BDII and a current MDE. There were no treatment-emergent 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, 18 TEAEs occurred in five patients (83.3%), the most common of which were nausea (six events in two patients [33.3%]), headache (four events in three patients [50%]) and anxiety (two events reported

in two patients [33.3%]). All other TEAEs occurred as a single event. TEAEs were categorized as mild (15 events), moderate (two events), or severe (one event) and all events were considered treatment-related by the investigator.

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 results of the C-SSRS showed no increase in the incidence of suicidal ideation. Assessment of psychiatric and psychotic symptoms with the BPRS and YMRS showed a decrease in psychiatric/psychotic and manic symptoms at all time points, respectively. No or minimal observations of dissociative symptoms were noted as measured by the CADSS. Similarly, there was no overall trend in the MOAA/S scores. 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 patients with BDII and a current MDE was well-tolerated with an acceptable safety profile, with patients reporting improvement in symptoms of depression up to 7 days following treatment. Overall, these results support further investigations into the efficacy and safety of GH001 treatment of patients with BDII.