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Results of a Phase 2a Clinical Trial of Inhaled Mebufotenin (GH001) in Patients with Bipolar II Disorder and a Current Major Depressive Episode

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Background

- Bipolar II disorder (BDII) is a chronic psychiatric disorder characterized by alternating episodes of hypomania and major depressive episodes (MDE), imposing high burdens of illness on individuals[1]
- The estimated lifetime prevalence rate of BDII is between 0.4 and 5%[2,3]
- Current treatments for depressive symptoms in patients with BDII remain limited, offering insufficient efficacy and tolerability highlighting the need for new therapeutic approaches[4]
- Mebufotenin (5-MeO-DMT) is a rapid acting psychoactive molecule that acts as a non-selective serotonin agonist with highest affinity for the 5-HT_{1A} receptor subtype[5]
- GH001, a synthetic form of mebufotenin for pulmonary inhalation, has been well tolerated in early-stage trials and has shown potential to induce rapid remission of depressive symptoms in patients with treatment-resistant depression (TRD)[6,7]
- The trial presented here is the first in which mebufotenin was administered to patients diagnosed with BDII and a current MDE

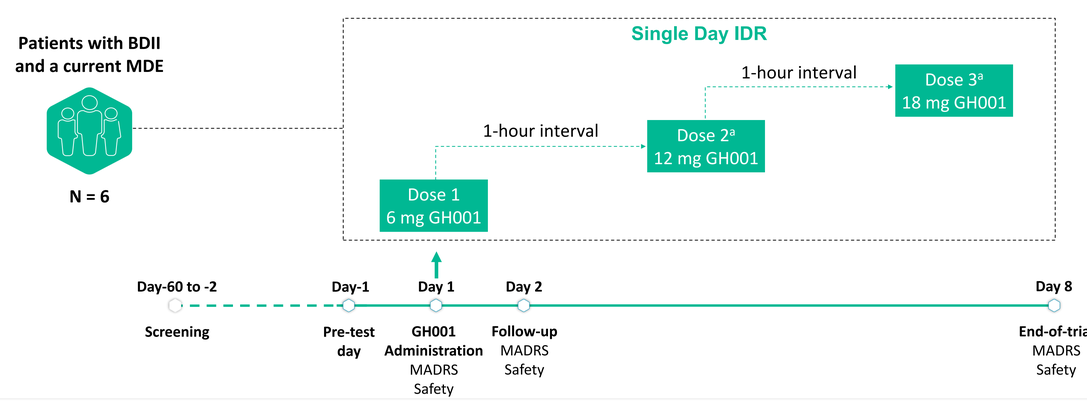
Objective

- To investigate the safety and antidepressant effects of GH001 in adult patients with BDII and a current MDE

Methods

- This Phase 2a, proof-of-concept, open-label trial (NCT05839509) enrolled patients aged 18-64 years who met Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria for BDII with a current MDE
- Patients were required to have a Montgomery–Åsberg Depression Rating Scale (MADRS) total score of ≥24 and a Young Mania Rating Scale (YMRS) total score of ≤8 at baseline and prior to dosing on Day 1
- Patients were not permitted to receive any antidepressant medications within 7 days or 5 half-lives, whichever was longer, prior to dosing. Lithium use within 6 months prior to dosing was not permitted, if applicable
- 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)
- 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
- Secondary endpoints included response (≥50% reduction from baseline in MADRS total score), remission (MADRS total score ≤10), Clinical Global Impression-Severity (CGI-S) scale, Bipolar Depression Rating Scale (BDRS), and safety and tolerability

Figure 1. Clinical Trial Design



[a]A second or third dose was administered if the previous dose was well tolerated according to the trial physician's judgement (based on vital signs and adverse events) and if the patient did not achieve an intense psychoactive effect (peak experience; defined as a mean score of ≥75 on the Peak Experience Scale) following the previous dose. Abbreviations: BDII = Bipolar II disorder; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode.

Results

Disposition and Demographics

- A total of six patients with BDII and a current MDE were enrolled in this trial. Patient disposition and demographics are presented in Table 1

Table 1. Patient Disposition and Baseline Characteristics

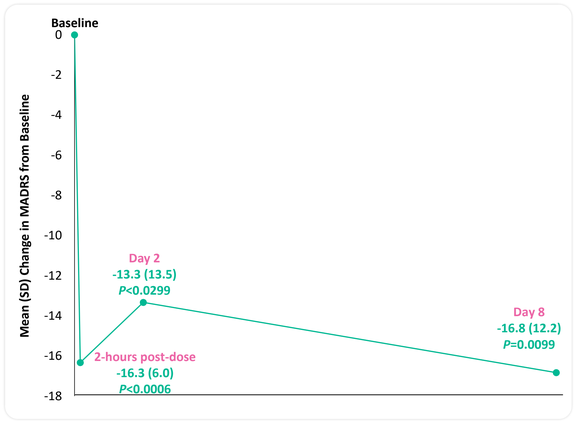
	N=6
Completed trial, n (%)	6 (100)
Discontinued, n (%)	0
Number of previous MDE, mean (SD)	14.0 (12.4)
Duration of current MDE (weeks), mean (SD)	20.8 (22.7)
MADRS total score at baseline, mean (SD)	32.0 (5.1)
Demographics	
Female, n (%)	4 (66.7)
Age (years), mean (SD)	44.2 (9.3)
Height (cm), mean (SD)	174.7 (10.1)
Weight (kg), mean (SD)	76.1 (18.6)
BMI (kg/m^2), mean (SD)	24.8 (5.0)
Race, White, n (%)	6 (100)

Abbreviations: BMI = Body mass index; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; SD = Standard deviation.

Efficacy

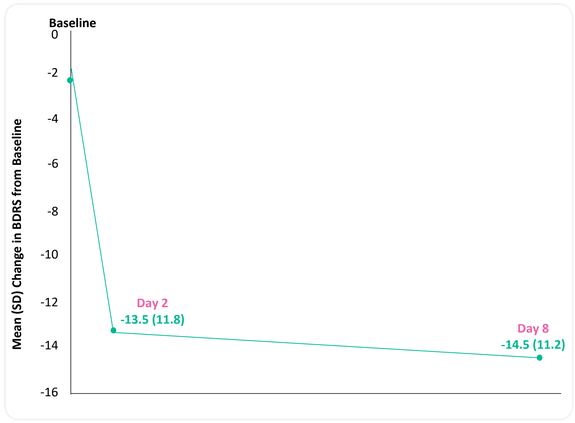
- The primary endpoint was achieved, with a significant reduction from baseline to Day 8 in mean (standard deviation [SD]) MADRS total score of −16.8 (12.2) (*P*=0.0099; Figure 2)
- Significant reductions in mean (SD) MADRS total score were also observed at 2-hours post-dose (–16.3 [6.0]) and Day 2 (–13.3 [13.5]; Figure 2)
- One-third (33.3%) of patients responded and were in remission on Day 8
- The rapid reduction in the severity of depressive symptoms as assessed by the MADRS, were mirrored in the CGI-S and the BDRS
  - A mean (SD) reduction of –2.5 (1.5) on the CGI-S and –14.5 (11.2) on the BDRS were observed from baseline to Day 8 (Figure 3)

Figure 2. Mean Change in MADRS Total Score From Baseline in Patients With BDII and a Current MDE



Abbreviations: BDII = Bipolar II disorder; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; SD = Standard deviation.

Figure 3. Mean Change in BDRS Total Score From Baseline in Patients With BDII and a Current MDE



Abbreviations: BDII = Bipolar II disorder; BL = Baseline; BDRS = Bipolar Depression Rating Scale; MDE = Major depressive episode; SD = Standard deviation.

Safety

- Treatment-emergent adverse events (TEAEs) were observed in 5/6 patients (83.3%) and were mostly mild in severity (87.5%) with two moderate and one severe events
- Headache (50%), nausea (33.3%) and anxiety (33.3%) were the most frequently reported TEAEs; all other TEAEs occurred in a single patient each
- One severe event of anxiety was reported which subsided within 24 hours; no TEAEs of flashbacks were reported
- There were no treatment-emergent serious adverse events (SAEs), and no patient withdrew from the trial
- There were no clinically significant changes in spirometry after inhalation of GH001
- There was a clinically significant reduction in mean (SD) Brief Psychiatric Rating Scale from baseline to Day 8 (−15.7 [12.0]). There was no clinically relevant worsening of other clinician-rated assessments (based on the Clinical Assessment of Discharge Readiness, Columbia-Suicide Severity Rating Scale, and Modified Observer's Assessment of Alertness and Sedation scales) and all patients were deemed ready for discharge within the same day of dosing
- Following dosing with GH001, YMRS scores remained low and stable, decreasing from 2.2 at baseline to 1.0 by Day 8 (−1.2 [SD=1.5]), indicating no emergence of manic symptoms
- The safety profile observed in this trial was consistent with other completed trials investigating GH001 in TRD and postpartum depression

Table 2. Summary of Safety in Patients with BDII and a Current MDE

	Event #	n (%)
Any TEAE	**18**	**5 (83.3)**
Mild	15	5 (83.3)
Moderate	2	2 (33.3)
Severe	1	1 (16.7)
Treatment-related TEAEs	18	5 (83.3)
Treatment-emergent SAE	0	0
TEAEs by Preferred Term		
Headache	4	3 (50.0)
Nausea	6	2 (33.3)
Anxiety	2	2 (33.3)
Paresthesia	1	1 (16.7)
Agitation	1	1 (16.7)
Hypoaesthesia oral	1	1 (16.7)
Neck pain	1	1 (16.7)
Fatigue	1	1 (16.7)
Cough	1	1 (16.7)

Abbreviations: BDII = Bipolar type II; MDE = Major depressive episode; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

Conclusions

- In this trial evaluating the safety and antidepressant effects of GH001 in patients with BDII and a current MDE, the primary endpoint was met: a significant reduction from baseline in MADRS total score was observed on Day 8
- Significant reductions in MADRS total scores were also observed at 2-hours post-dose, supporting the rapid onset of antidepressant effects of GH001
- GH001 administered via inhalation demonstrated a favorable safety profile and was well tolerated in patients with BDII and a current MDE; no treatment-related SAEs were reported

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