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 in healthy volunteers and patients with TRD, with a rapid reduction in the severity of depressive episodes[6,7]
- The trial presented here is the first in which mebufotenin was administered to patients diagnosed with BDII and a current MDE

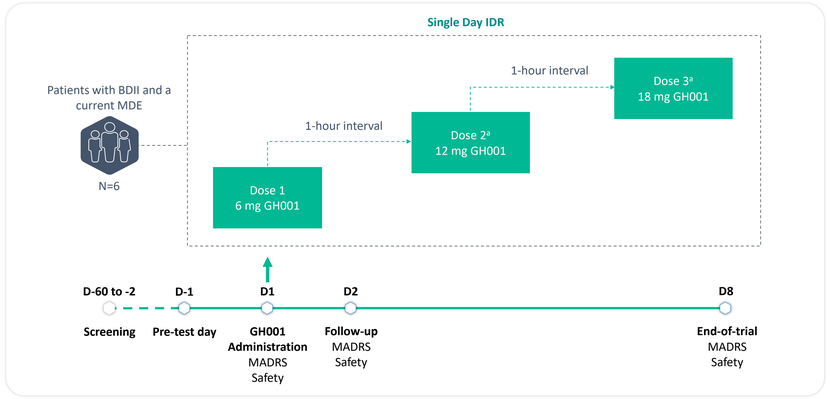
Objective

- 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 (including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants) 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
- Other efficacy endpoints assessed included response (≥50% reduction from baseline in MADRS total score), remission (MADRS total score ≤10) , Clinical Global Impression-Severity (CGI-S) scale, and Bipolar Depression Rating Scale (BDRS)
- Safety and tolerability were assessed throughout the trial as secondary endpoints and included the following parameters: treatment-emergent adverse events (TEAEs), manic symptoms assessed by YMRS, 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), suicidality as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Discharge readiness was assessed by the Clinical Assessment of Discharge Readiness (CADR)

Figure 1. Clinical Trial Design



[a]The criteria for administration of the second and third doses in the IDR were based on the patient's subjectively reported psychoactive effects, and the safety and tolerability at the previous dose level according to the trial physician's judgement.
Abbreviations: BDII = Bipolar II disorder; D = Day; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode.

Results

Disposition and Demographics

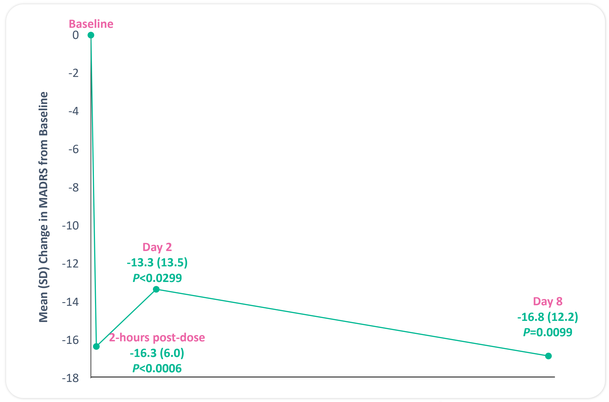
- A total of six patients with BDII and a current MDE were enrolled in this trial. Patient disposition and demographics are presented in Table 1

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 (1.00)

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

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

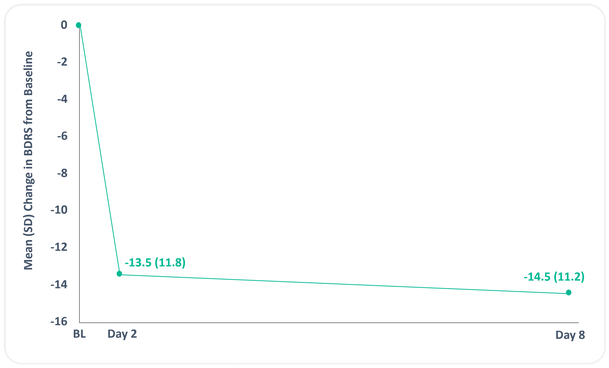


Abbreviations: BDII = Bipolar II disorder; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; SD = Standard deviation.

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) which corresponds to a reduction of 52.5% (*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 showed response to treatment on Day 8, with a remission rate of 33.3% at 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 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

- 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 serious TEAEs, 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) BPRS from baseline to Day 8 (−15.7 [12.0])
- 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
- 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

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
Death	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

References

1. American Psychiatric Association, DSM-5 Task Force. (2013).
2. Merikangas KR, et al. *Arch Gen Psychiatry*, 2011;68(3):241-251.
3. Benazzi F. *CNS Drugs*, 2007;21(9):727-40.
4. Aaronson ST, et al. *JAMA Psych*. 2024;81(6):555-562.
5. Halberstadt AL, et al. *Psychopharmacology*. 2012;221:709-718.
6. Reckweg J, et al. *Front Pharmacol*. 2021;12:760671.
7. Reckweg JT, et al. *Front Psychiatry*. 2023;14:1133414.

Acknowledgments

This trial was sponsored by GH Research. The sponsor would like to thank the participants in the trial. The sponsor would also like to thank the investigators who conducted this trial. Under the guidance of authors, medical writing and editorial support were provided by Brian Brennan, PhD of GH Research Ireland Limited.

Disclosures

PR and MDL: Nothing to disclose. **MB:** Advisor to Alfred E. Tiefenbacher GmbH Co. KG, COMPASS Pathfinder Ltd., GH Research, MedEd-Link Inc., Janssen Global Services, LLC, Livanova, Mindforce Game Lab AB, and Novartis. Received lecture fees from MedTrix GmbH and Streamedup GmbH. **CBS:** Consultant to and shareholder of GH Research. **FD:** Consultant to GH Research. **AR:** Honoraria for lectures and/or advisory boards – AbbVie, Boehringer Ingelheim, Cyclerion, Compass, GH Research, Janssen, LivaNova, Medice, MSD, Newron, Sage/Biogen, and Shire/Takeda. Research grants – Medice and Janssen. **MET:** Grants – Acadia, Alkermes, Axsome, Intra-Cellular Therapies, Janssen, National Institute of Mental Health, Otsuka, Patient-Centered Outcomes Research Institute (PCORI), and Takeda. Advisory Boards – Autobahn Therapeutics, Axsome, Clexio Biosciences, Gerson Lehrman Group, GH Research, Lundbeck, Janssen, Johnson & Johnson, Luye Pharma, Merck, Object Pharma, Otsuka, Pfizer, Sage, Seelos Therapeutics, Sunovion, and Takeda. Royalties – American Psychiatric Association Foundation, Guilford Publications, Herald House, Wolters Kluwer, and W W Norton & Company. **KK, POG, VV:** Employee and stock option holder of GH Research. **BTB:** Consultant – National Health and Medical Research Council (Australia). Honoraria – Angelini, AstraZeneca, Biogen, BMS, Boehringer Ingelheim, Johnson & Johnson, LivaNova, Lundbeck, Medscape, Otsuka, Pfizer, Roche, Servier, Sumitomo Pharma, Sunovion, Teva, Viatris, and Wyeth. Advisory boards – Biogen, Boehringer Ingelheim, Janssen-Cilag, LivaNova, Lundbeck, Medscape, Novartis, GH Research, Otsuka, and Teva. Research grants from private industries or nonprofit funds – AstraZeneca, BMBF (Germany), BMG (Germany), DFG (Germany), ERA PerMed, Fay Fuller Foundation, Horizon Europe (European Union), James & Diana Ramsay Foundation (Adelaide), Johnson & Johnson, Lundbeck, La Marató de TV3, National Health and Medical Research Council (Australia), Sanofi-Synthélabo, and Wellcome Trust (UK).

Presented at the 27th Annual Conference of the International Society for Bipolar Disorders | Chiba, Japan | September 17-19, 2025