Results from Early-Stage Trials of Inhaled Mebufotenin (GH001) in Healthy Volunteers and Patients with Treatment-Resistant Depression

Kelly Doolin[1], Velichka Valcheva[1], Claus Bo Svendsen[1], Padraig O'Grady[1], Michael E. Thase[2,3], Johannes T. Reckweg[4], Johannes G. Ramaekers[4]

[1]GH Research, Dublin, Ireland. [2]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. [3]Corporal Michael J Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA.
[4]Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands.

Background

- GH001 is a synthetic formulation of the serotonergic psychoactive drug mebufotenin administered via pulmonary inhalation that induces psychoactive effects with an ultra-rapid onset (within seconds) and short duration (generally <30 mins)[1,2]
- Mebufotenin acts as a potent agonist on serotonin (5-hydroxytryptamine [5-HT])$_{1A}$ and 5-HT$_{2A}$ receptors, with higher affinity for the 5-HT$_{1A}$ receptor subtype
- Early-stage clinical trials of various psychoactive molecules have shown promising safety and efficacy results in patients diagnosed with mental disorders[3]

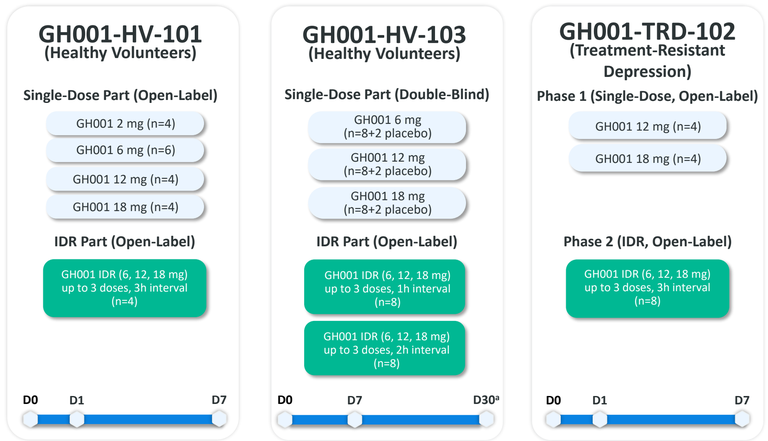
Objective

- To present the findings from three early-phase trials of GH001 in healthy volunteers and patients with treatment-resistant depression (TRD)

Methods

- Early-stage trials of GH001 enrolled 78 participants in two Phase 1 trials in healthy volunteers (HVs; n=68 [GH001, n=62; placebo, n=6]) and one Phase 1/2 trial in patients with TRD (n=16)
- GH001 was administered via the Volcano Medic (2) Vaporization System as single doses (2, 6, 12, 18 mg) or as an individualized dosing regimen (IDR) whereby up to three escalating doses (6, 12, 18 mg) were administered within a single day at intervals of 1-3 hours
- 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

Figure 1: Schematic of Early-Stage Clinical Trials of GH001



Abbreviations: D = Day; h = Hour; IDR = Individualized dosing regimen.
[a] Day 30 was a follow-up visit by telephone call.

Results

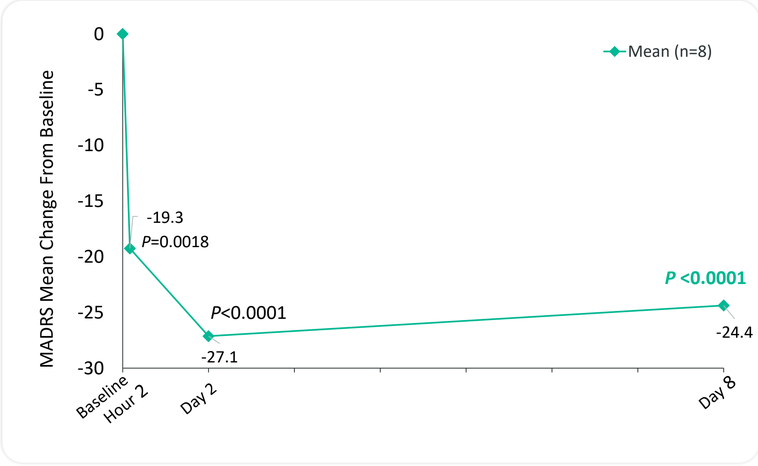
Efficacy Results

- In patients with TRD, mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score was -24.4 at Day 8 in patients administered an IDR of GH001 (n=8; Figure 2) compared to -21.0 and -12.5 in patients administered single doses of 12 and 18 mg of GH001 at Day 8, respectively (n=4 per group)
- Remission (MADRS total score ≤10) at Day 8 was greater in patients administered an IDR of GH001 (7/8 patients [87.5%]) compared to patients administered a single dose of 12 or 18 mg of GH001 (2/4 [50%] and 1/4 [25%], respectively)

Safety Results

- Inhalation of GH001 was well tolerated across the three trials including healthy volunteers and patients with TRD (Table 1)
- No severe or serious adverse events were reported and most TEAEs were mild in severity
- No noteworthy changes in vital signs were observed; transient increases in heart rate and blood pressure shortly after GH001 administration were not clinically significant
- Safety assessments, including laboratory analyses, psychological safety scales, and electrocardiogram showed no clinically significant changes
- No clinically significant changes in the Columbia-Suicide Severity Rating Scale (C-SSRS) were observed following administration of GH001
- Cognitive performance assessments indicated that GH001 does not impact memory or cognition at any dose levels acutely (2-3 hours postdose) or after 7 days, supporting the neuropsychological safety of GH001

Figure 2: MADRS Mean Change from Baseline in TRD Patients Administered GH001 IDR



Abbreviations: MADRS = Montgomery–Åsberg Depression Rating Scale.

Table 1: Summary of Safety Results Across Three Early-Stage Trials

	Total Population (N=78)
Number (%) of participants with ≥1 TEAE	50 (64.1)
Total number of TEAEs	105
Severity of TEAEs (no. of events)	
Mild	97
Moderate	8
Severe	0
Total number of treatment-related TEAEs	80
Number (%) of participants with ≥1 TEAE leading to trial/drug withdrawal	0 (0)
Number (%) of participants with ≥1 SAE	0 (0)
Most common TEAEs (no. of events)	
Headache	19
Anxiety	12
Nausea	8
Fatigue	7

Abbreviations: SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

Conclusions

- Efficacy data from an early-stage trial in patients with TRD suggest that intraindividual dose escalation per the IDR within a single day may increase the MADRS remission rate compared to single doses of GH001, whilst avoiding exposing the patient to unnecessarily high doses
- GH001 was well tolerated in healthy volunteers and patients with TRD and has the potential to offer a fast-acting, convenient, effective treatment for TRD and other depressive disorders

References
1. Reckweg J, et al. *Front Pharmacology*. 2021;12:760671. doi:10.3389/fphar.2021.760671.
2. Reckweg JT, et al. *Front Psychiatry*. 2023;14:1133414. doi:10.3389/fpsyt.2023.1133414.
3. Yao Y, et al. *Psychiatry Res*. 2024;335:115886. doi:10.1016/j.psychres.2024.115886.

Disclosures: KD and VV are employees and stock option holders of GH research. POG is an employee and shareholder of GH Research. CBS is a consultant to and shareholder of GH Research. JTR, and JGR are consultants to GH Research. MET is a Professor of Psychiatry at the University of Pennsylvania. MET has received grants from Acadia, Inc; Alkermes; Axsome Therapeutics, Inc; Intracellular, Inc; Janssen Pharmaceuticals, Inc; National Institute of Mental Health; Otsuka Pharmaceuticals Company, Ltd; Patient-Centered Outcomes Research Institute (PCORI); Takeda Pharmaceutical Company, Ltd. MET is on the advisory board for Autobahn Therapeutics; Axsome Therapeutics, Inc; Clexio Biosciences; Gerson Lehrman Group, Inc; GH Research; H Lundbeck, A/S; Janssen Pharmaceuticals, Inc; Johnson & Johnson; Luye Pharma Group, Ltd; Merck & Company, Inc; Object Pharma; Otsuka Pharmaceuticals Company, Ltd; Pfizer, Inc; Sage Pharmaceuticals; Seelos Pharmaceuticals; Sunovion Pharmaceuticals, Inc; Takeda Pharmaceutical Company, Ltd. MET receives royalties from American Psychiatric Association Foundation; Guilford Publications; Herald House; Wolters Kluwer; W Seelows Norton & Company, Inc.

Acknowledgments: The clinical trials discussed in this poster were sponsored by GH Research Ireland Limited (the Sponsor). The Sponsor would like to thank the patients who participated in the clinical trials, as well as their families and caregivers. The Sponsor would like to thank all the investigators who were involved in carrying out these clinical trials. Under the guidance of authors, medical writing and editorial support was provided by Brian Brennan, PhD, and Claire Sweeney, PhD, of GH Research Ireland Limited. Statistical analysis was carried out by Marie Watissee, contracted by GH Research Ireland Limited.

Presented at the American Society of Clinical Psychopharmacology Annual Meeting | Scottsdale, AZ, USA | May 27–30, 2025