UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER PURSUANT TO RULE 13a-16 OR 15d-16 UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the month of January 2026.

Commission File Number: 001-40530

GH Research PLC

(Exact name of registrant as specified in its charter)

Joshua Dawson House
Dawson Street
Dublin 2
D02 RY95
Ireland
(Address of principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

Form 20-F ☒ Form 40-F ☐

GH Research PLC (the "Company") announces its participation in a Mini-Panel Session at the 64th American College of Neuropsychopharmacology (ACNP) annual meeting (the "Congress"), where results related to its GH001-TRD-201, GH001-PPD-203 and GH001-BD-202 clinical trials will be discussed. The Congress is scheduled to take place from January 12-15, 2026, in Nassau, Bahamas.

The Mini-Panel Session will be chaired by Prof Michael E. Thase, featuring presentations by Lisa Harding, MD, Kristina M. Deligiannidis, MD, and Roger S. McIntyre, MD. A copy of the presentation for the Mini-Panel session is attached hereto as Exhibit 99.1.

The fact that this presentation is being made available should not be deemed an admission as to the materiality of any information contained in the material. The information contained in the presentation is being provided as of January 15, 2026, and the Company does not undertake any obligation to update the presentation in the future or to update forward-looking statements to reflect subsequent actual results.

EXHIBIT INDEX

99.1	Mini-Panel Session Presentation with Title: Exploring the Therapeutic Potential of Mebufotenin (GH001) Across Depressive Disorders

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: January 15, 2026

GH Research PLC

By: /s/ Julie Ryan
Name: Julie Ryan
Title: Vice President, Finance

Exploring the Therapeutic Potential of Mebufotenin (GH001) Across Depressive Disorders

Chair

Michael E. Thase, MD

Presenters

Lisa Harding, MD
Kristina M. Deligiannidis, MD
Roger S. McIntyre, MD, FRCPC

ACNP 2026 Mini Panel

Chair

Michael E. Thase, MD
Department of Psychiatry,
University of Pennsylvania, and
Corporal Michael J. Crescenz
Veterans Affairs Medical Center
Philadelphia, PA, USA

GH001 Provides Rapid and Significant Antidepressant Effects in Patients with Treatment-Resistant Depression: Efficacy and Safety Results from a Phase 2b, Double-Blind, Randomized Controlled Trial with a 6-Month Open-Label Extension

Lisa Harding, MD
Mood Institute and Yale School of Medicine
Milton, CT, USA

GH001 Is Associated with Improved Self-Reported Maternal Functioning in Patients with Postpartum Depression and Rapid Elimination from Breastmilk

Kristina M. Deligiannidis, MD
Feinstein Institutes for Medical Research
Northwell Health
Manhasset, NY, USA

Rapid Improvement in Anhedonia Following GH001 Treatment in Patients with Treatment-Resistant Depression, Postpartum Depression, and Bipolar II Disorder and a Current Major Depressive Episode

Roger S. McIntyre, MD, FRCPC
Department of Psychiatry, University of Toronto
Toronto, ON, Canada

Disclosures

Author	Disclosures
Michael E. Thase	Consultant – Axsome, Clexio Biosciences, Gerson Lehrman Group, GH Research, Janssen, Johnson & Johnson, Lundbeck, Luye Pharma, Merck, Otsuka, Pfizer, Sage, Seelos Therapeutics, Sunovion, and Takeda. Grant support – Acadia, Alkermes, Axsome, Intra-Cellular Therapies, Janssen, Myriad, National Institute of Mental Health, Otsuka, Patient-Centered Outcomes Research Institute (PCORI), and Takeda. Royalties – American Psychiatric Press, Inc., Guilford Publications, Herald House, Wolters Kluwer, and W. W. Norton & Company. Spouse's employment – Dr. Diane Sloan is a Senior Vice President of OPEN Health, which does business with many companies
Lisa Harding	Advisory board – AbbVie, GH Research, Johnson & Johnson, and Otsuka. Consultant – GH Research and Johnson & Johnson
Kristina M. Deligiannidis	Consultant – Biogen, Brii Biosciences, Gerbera Therapeutics, GH Research, Lipocine, Neurocentria, Reunion Neuroscience, and Sage. Principal investigator for contracted research – DuKang Pharmaceuticals, Sage, and Woebot Health
Roger S. McIntyre	Consultant/speaker – AbbVie, Alkermes, Atai Life Sciences, Axsome, Bausch Health, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eisai, Intra-Cellular Therapies, Janssen, Kris, Lundbeck, Mitsubishi Tanabe, Neumora Therapeutics, NeuraWell, Neurocrine, NewBridge Pharmaceuticals, Novo Nordisk, Otsuka, Pfizer, Purdue, Sage, Sanofi, Sunovion, Takeda, and Viatris. Research grant support – Canadian Institutes of Health Research, Global Alliance for Chronic Diseases, National Natural Science Foundation of China, and the Milken Institute

Psychoactive Molecules as Rapid-Acting Treatment for Depression

- Pharmacotherapy is the first-line treatment recommendation for people with moderate to severe **MDD**[1,2]; however, there is an **unmet need for rapid and effective pharmacological treatments**

- **Less than half** of patients with MDD treated in clinical trials with traditional antidepressant medications (SSRIs, SNRIs, or TCAs) **achieve remission**,[3,4] and the proportion of patients achieving remission in clinical practice may be even smaller[5]

- A growing body of evidence indicates that **psychoactive molecules** may provide rapid reduction in severity of symptoms in patients with psychiatric disorders including **MDD, TRD, BDII depression, and PPD**[6-9]

- Psychoactive molecules including LSD, ayahuasca, psilocybin, MDMA, and mebufotenin have been assessed in **clinical trials** for those indications[6-9]

Abbreviations: BDII = Bipolar II disorder; LSD = Lysergic acid diethylamide; MDD = Major depressive disorder; MDMA = 3,4-methylenedioxymethamphetamine; PPD = Postpartum depression; SNRI = Serotonin-norepinephrine reuptake inhibitor; SSRI = Selective serotonin reuptake inhibitor; TCA = Tricyclic antidepressant; TRD = Treatment-resistant depression.

1. APA Clinical practice guideline for the treatment of depression across three age cohorts. 2019. Available at: https://www.apa.org/depression-guideline. Accessed Oct. 23, 2025. 2. Lam RW, et al. *Can J Psychiatry*. 2024;69(9):641-687. 3. Thase ME, et al. *J Clin Psychiatry*. 2005;66(8):974-981. 4. Machado M, et al. *Curr Med Res Opin*. 2006;22(9):1825-1837. 5. Moller HJ, et al. *World J Biol Psychiatry*. 2008;9(2):102-114. 6. Yao Y, et al. *Psychiatry Res*. 2024;335:115886. 7. Reckweg JT, et al. *Front Psychiatry*. 2023;14:1133414. 8. Aaronson ST, et al. *JAMA Psychiatry*. 2024;81(6):555-562. 9. Jairaj C and Rucker JJ. *J Psychopharmacol*. 2022;36(8):920-931.

GH001 Overview

GH001

Synthetic form of mebufotenin (5-MeO-DMT) for pulmonary inhalation

GH001 has been well tolerated in early-stage trials[1,2] and shows potential to induce a rapid remission of depressive symptoms in patients with TRD[2]

Non-selective 5-HT agonist with high affinity for the 5-HT_{1A} receptor[3-5]

Median duration of psychoactive effects: 11 min

Target indications: TRD, PPD, and BDII + MDE

Phase 2b trial complete in TRD; Phase 2a trials complete in PPD and BDII + MDE

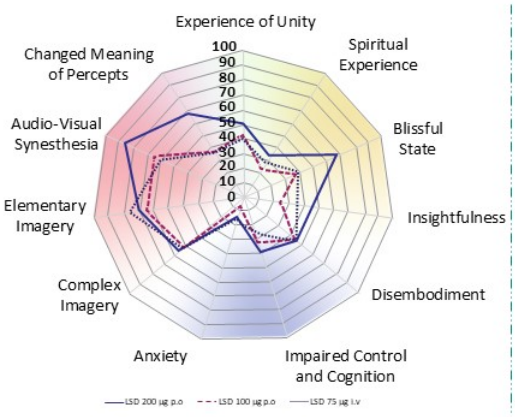
Abbreviations: 5-HT = Serotonin; 5-MeO-DMT = 5-methoxy-N,N-dimethyltryptamine; BDII = Bipolar II disorder; MDE = Major depressive episode; PPD = Postpartum depression; TRD = Treatment-resistant depression.

1. Reckweg J, et al. *Front Pharmacol.* 2021;12:760671. 2. Reckweg JT, et al. *Front Psychiatry.* 2023;14:1133414. 3. Halberstadt AL, et al. *Psychopharmacology (Berl).* 2012;221(4):709-718. 4. Shen HW, et al. *Curr Drug Metab.* 2010;11(8):659-666. 5. Reckweg JT, et al. *J Neurochem.* 2022;162:128-146.

Psychoactive Molecules Are Not Alike: Pharmacology and Phenomenology

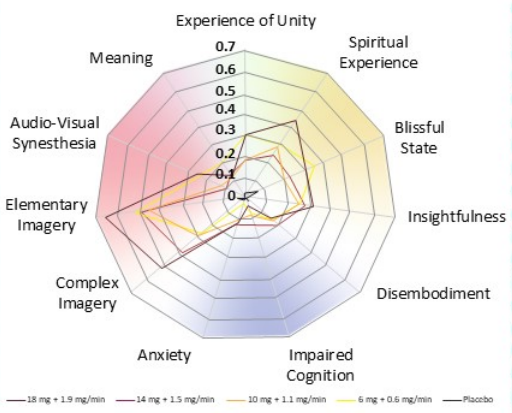
LSD[1,2]

Non-selective serotonin and dopamine agonist



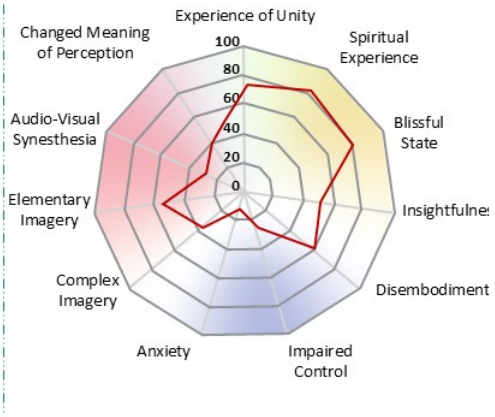
DMT[3,4]

Mixed 5-HT$_{1A}$/5-HT$_{2A}$ agonist



Mebufotenin[5-8]

Non-selective serotonin agonist with high affinity for 5-HT$_{1A}$



Oceanic boundlessness | **Visionary re-structuralization** | **Anxious ego-dissolution**

Abbreviations: 5-HT = 5-Hydroxytryptamine (serotonin); DMT = N,N-Dimethyltryptamine; i.v. = Intravenous; LSD = Lysergic acid diethylamide; p.o. = Oral administration.

1. Liechti ME, et al *Neuropsychopharmacology*. 2017;42:2114–2127 (Figure adapted from source). 2. Holze F, et al. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2024;9(5):472-489. 3. Luan LX, et al. *J Psychopharmacol*. 2024;38(1):56–67 (Figure adapted from source). 4. Nichols DE. *Pharmacol Rev*. 2016;68(2):264-355. 5.Uthaug MV, et al. *Psychopharmacology*. 2019;236:2653-2666 (Figure adapted from source). 6. Shen HW, et al. *Curr Drug Metab*. 2010;11(8):659-66. 7. Halberstadt AL, et al. *Psychopharmacology (Berl)*. 2012;221(4):709-718. 8. Ermakova AO, et al. *Sci Rep*. 2025;15(1):38874.

GH001 Provides Rapid and Significant Antidepressant Effects in Patients with Treatment-Resistant Depression

Efficacy and Safety Results from a Phase 2b, Double-Blind, Randomized Controlled Trial with a 6-Month Open-Label Extension

Lisa Harding, MD
Mood Institute and Yale School of Medicine
Milton, CT, USA

Background

- **TRD** remains one of the most pressing challenges in psychiatry and **affects approximately 30% of patients** treated for MDD[1]

- **Current therapies for TRD are limited**,[2] and there is a large unmet need for treatments that are well tolerated and offer rapid reductions in depressive symptoms and long-term remission

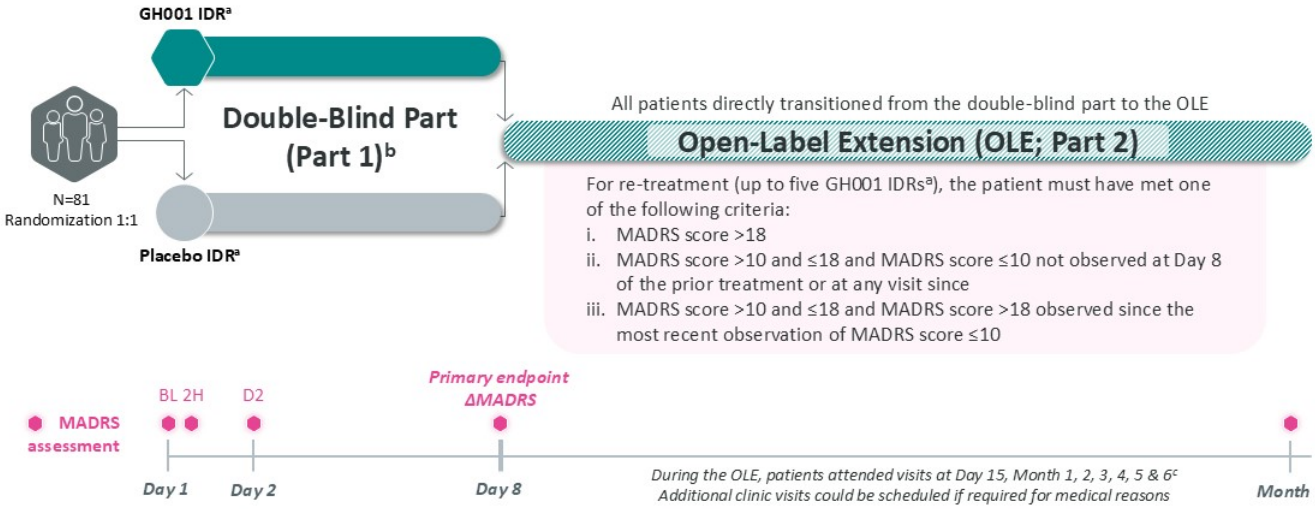
- GH001, a synthetic form of mebufotenin for pulmonary inhalation, has been **well tolerated in early-stage trials**[3,4] and shows potential to **induce rapid remission of depressive symptoms** in patients with TRD[4]

This analysis presents efficacy and safety data for GH001 from a Phase 2b double-blind, placebo-controlled trial, in which patients with TRD received up to five re-treatments of GH001 as an IDR

Abbreviations: IDR = Individualized dosing regimen; MDD = Major depressive disorder; TRD = Treatment-resistant depression.

1. Kubitz N, et al. *PLoS One*. 2013;8(10):e76882. 2. McIntyre RS, et al. *World Psychiatry* 2023;22:394-412. 3. Reckweg J, et al. *Front Pharmacol*. 2021;12:760671. 4. Reckweg JT, et al. *Front Psychiatry*. 2023;14:1133414.

Trial Schematic



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

[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. [b]Efficacy assessments were carried out by independent blinded raters in the double-blind part. [c]Patients also attended assessment visits on Day 2 (telephone call) and Day 8 (in-person) after each re-treatment.
Abbreviations: BL = Baseline; D = Day; H = Hour; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale.
ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05800860, Accessed October 28, 2025.

Eligibility Criteria

Patients were required to meet the trial criteria for TRD as assessed by a trial psychiatrist:

- Single-episode or recurrent MDD (per DSM-5 criteria) without psychotic features, with current episode of ≤2 years[a]
- Current MDE validated per the MGH-SAFER
- HAM-D-17 total score ≥20
- Nonresponse to ≥2 and ≤5 oral antidepressant treatments (assessed using the MGH-ATRQ)

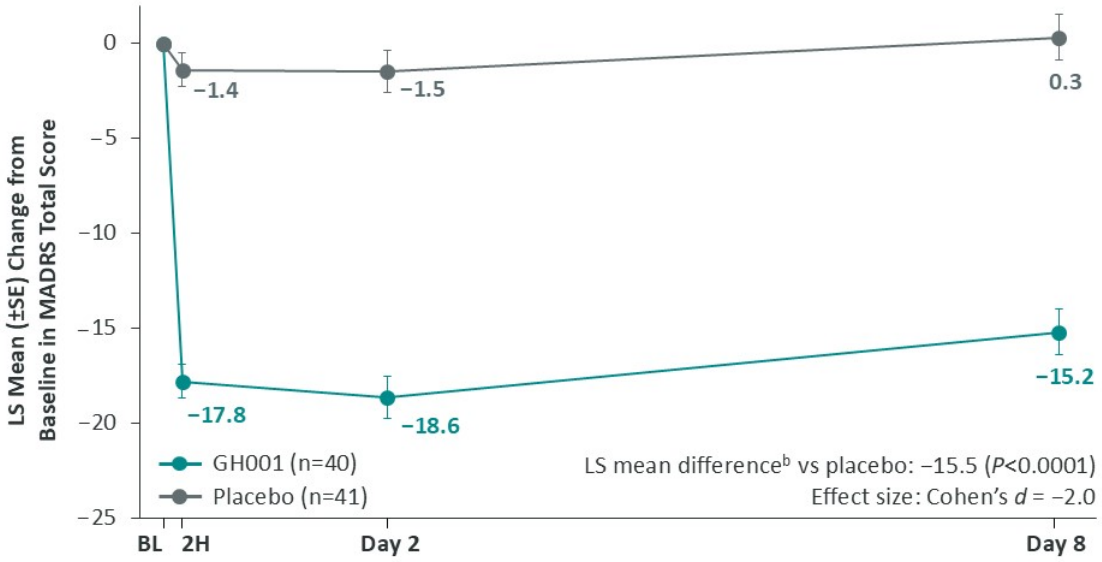
[a]Current MDE confirmed by the Mini-International Neuropsychiatric Interview.
Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HAM-D-17 = 17-Item Hamilton Depression Rating Scale; MDD = Major depressive disorder; MDE = Major depressive episode; MGH-ATRQ = Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; MGH-SAFER = Massachusetts General Hospital – Structured Assessment for Evaluation of Risk; TRD = Treatment-resistant depression.

Baseline Characteristics and Patient Disposition

		N=81
Baseline Demographics		
Age, years, mean (SD)		42.8 (11.2)
Sex, female, n (%)		46 (56.8)
Race, White, n (%)		81 (100)
BMI, kg/m^2, mean (SD)		26.2 (5.5)
Previously used any psychedelic (lifetime), n (%)		9 (11.1)
Baseline Disease Characteristics		
HAM-D-17 total score, mean (SD)		24.8 (2.5)
MADRS total score, mean (SD)		28.6 (5.0)
MDE History at Baseline		
Number of MDEs	Mean (SD)	2.1 (1.3)
	≥3, n (%)	27 (33.3)
Time since first depressive episode, years, mean (SD)		11.7 (9.0)
Duration of current MDE, weeks, mean (SD)		57.1 (78.4)
Patient Disposition, n (%)		
Completed double-blind part		81 (100)
Received GH001 in double-blind part		40 (49.4)
Received placebo in double-blind part		41 (50.6)
Completed OLE		63 (77.8)
Reasons for Discontinuation During the OLE, n (%)		**18 (22.2)**
Withdrawal of consent		7 (38.9)
Started additional antidepressant[a]		6 (33.3)
Protocol deviation		2 (11.1)
Other		2 (11.1)
Adverse event		1 (5.6)

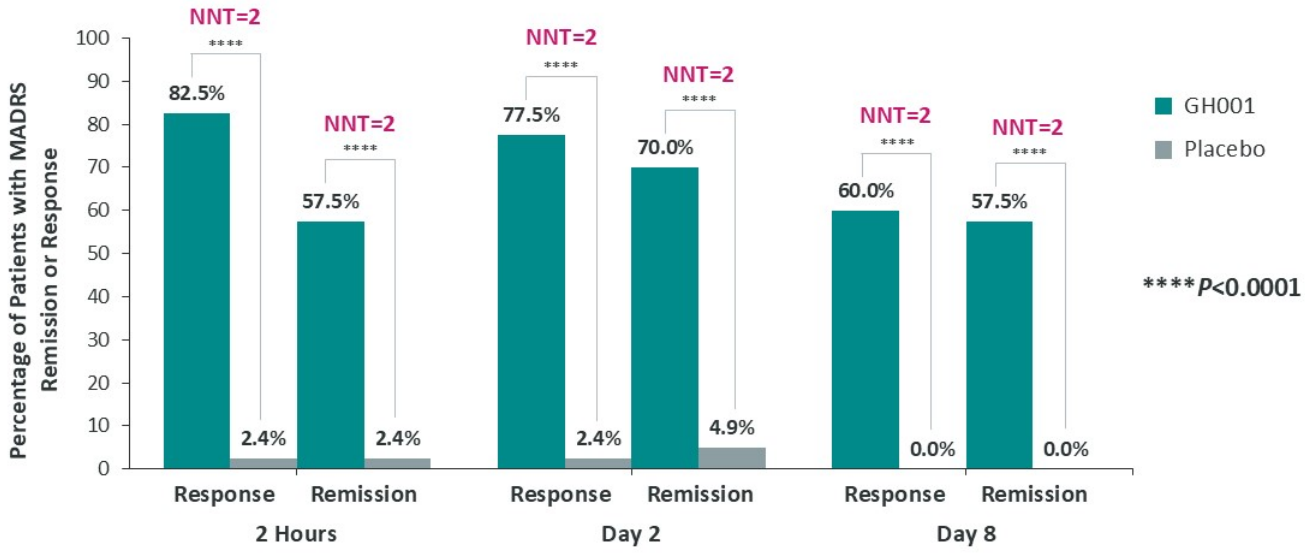
[a]GH001 was administered as a monotherapy and patients who started additional antidepressant treatment were discontinued from the trial.
Abbreviations: BMI = Body mass index; HAM-D-17 = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; OLE = Open-label extension; SD = Standard deviation.

Primary Endpoint: GH001 Led to −15.5 Mean MADRS Reduction from Baseline on Day 8[a] Compared with Placebo in the Double-Blind Period



[a]FDA Guidance notes that efficacy with rapid-acting antidepressants generally should be demonstrated within 1 week, supporting a primary efficacy endpoint within this timeframe.
[b]Adjusted for baseline severity of symptoms (MADRS total score).
Abbreviations: BL = Baseline; FDA = Food and Drug Administration; H = Hour; LS = Least squares; MADRS = Montgomery–Åsberg Depression Rating Scale; SE = Standard error.

GH001 Led to 60.0% Response Rate and 57.5% Remission Rate at Day 8 vs 0% with Placebo in the Double-Blind Period

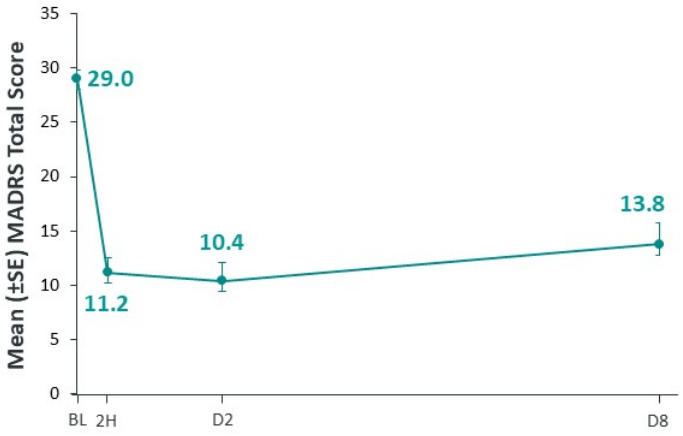


Response: ≥50% reduction from baseline in MADRS total score | **Remission:** MADRS total score ≤10

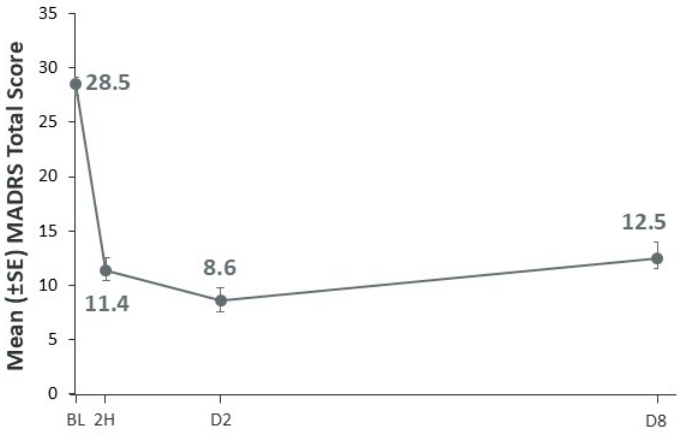
Abbreviations: MADRS = Montgomery–Åsberg Depression Rating Scale; NNT = Number needed to treat.

Reduction in MADRS with GH001 in Double-Blind Part Reproduced in Placebo Group with Their First Active GH001 Treatment in the OLE

Double-Blind
Patients who received GH001 (n=40)

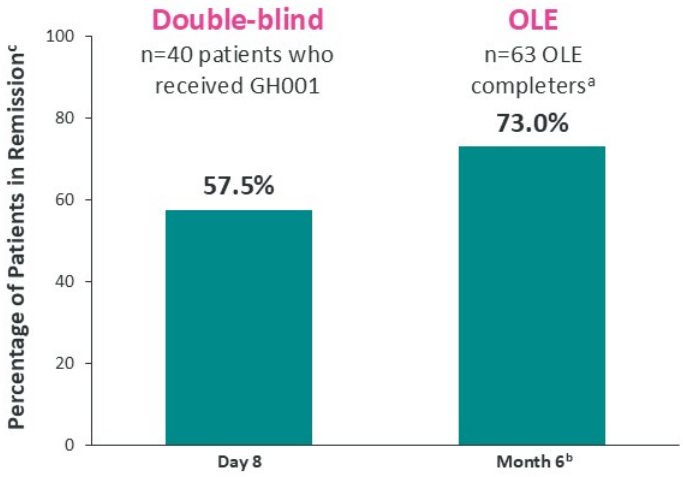


Open-Label Extension
First treatment of placebo group with GH001 (n=41)



Abbreviations: BL = Baseline; D = Day; H = Hour; MADRS = Montgomery–Åsberg Depression Rating Scale; OLE = Open-label extension; SE = Standard error.

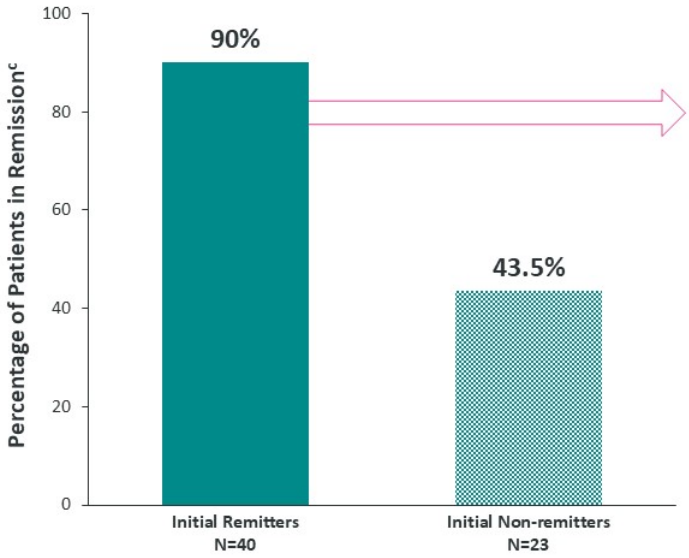
There Was a 73% Remission Rate at 6 Months in OLE Completers



Patients who completed the OLE received a **mean of four treatments** across the 6 months (double-blind part and OLE), with 63.5% (40/63) requiring one to four treatments during the **6 months**

[a]Includes 63 patients who completed the 6-month OLE per protocol (18 patients terminated early are excluded). [b]Approximately 6 months post-study start (median 168 days from Day 1 of double-blind part). [c]Remission defined as MADRS total score ≤10.
Abbreviations: MADRS = Montgomery–Åsberg Depression Rating Scale; OLE = Open-label extension.

Remission Rate at 6 Months[a] in OLE Completers[b]



Of patients who had remission on Day 8 after their first GH001 treatment, 90% were in remission at 6 months

[a]'6 Months' or 'Month 6' (end of trial) was at approximately 6 months post-study start (median 168 days from Day 1 of double-blind part). [b]Includes 63 patients who completed the 6-month OLE per protocol (18 patients terminated early are excluded). [c]Remission defined as a MADRS total score ≤10.
Abbreviations: MADRS = Montgomery–Åsberg Depression Rating Scale; OLE = Open-label extension.

Overview of Adverse Events in the Open-Label Extension

Patients, n (%)	Overall (N=81)	
Overview of Adverse Events		
Any TEAE[a]	72 (88.9)	
Maximum severity of TEAEs		
Mild	28 (34.6)	
Moderate	42 (51.9)	
Severe	2 (2.5)	
Treatment-related TEAEs	65 (80.2)	
Serious TEAEs	1 (1.2)	
Treatment-related serious TEAEs	0	
TEAEs leading to discontinuation	1 (1.2)	
AESIs	30 (37.0)	
Death	0	
TEAEs[a] Occurring in >10% of Patients	**Overall**	**Treatment-related TEAE**
Nausea	37 (45.7)	37 (45.7)
Paresthesia	31 (38.3)	31 (38.3)
Salivary hypersecretion	24 (29.6)	24 (29.6)
Headache	16 (19.8)	11 (13.6)
Muscle tightness	13 (16.0)	13 (16.0)
Feeling cold	12 (14.8)	11 (13.6)
Paresthesia oral	10 (12.3)	10 (12.3)
Upper respiratory tract infection	10 (12.3)	0
Anxiety	9 (11.1)	8 (9.9)

[a]TEAEs were classified according to the Medical Dictionary of Regulatory Activities (MedDRA) Version 26.0.
Abbreviations: AESI = Adverse event of special interest; TEAE = Treatment-emergent adverse event.

GH001 Administration Was Well Tolerated in Patients with TRD up to 6 Months

- During the OLE, TEAEs were observed in 72/81 (88.9%) patients and were **mostly mild or moderate**[a]; one non–treatment-related serious TEAE (migraine) was reported

- **No TEAEs of suicidal intent or suicidal behavior occurred**

- The median **duration of psychoactive effects** after GH001 administration was **11 minutes**

- Patients were deemed **discharge-ready**[b] **by 1 hour** post-dose at **99% of visits**

[a]Two severe treatment-related TEAEs were reported in the OLE; affect lability occurred shortly after administration of GH001 and resolved within 4 minutes and one event of migraine, considered a serious TEAE not related to treatment, started 73 days after the patient's most recent (fourth) administration of GH001. [b]Assessed using the Clinical Assessment of Discharge Readiness.
Abbreviations: ECG = Electrocardiogram; OLE = Open-label extension; PT = Preferred term; SOC = System organ class; TEAE = Treatment-emergent adverse event; TRD = Treatment-resistant depression.

Conclusion

- The primary endpoint was met: GH001 administered as an IDR led to significant MADRS reduction from baseline to Day 8 (−15.5 vs placebo)

- GH001 can maintain long-term remission in TRD, with 73.0% of patients who completed the OLE in remission at 6 months

- GH001 was well tolerated during the 6-month OLE and no treatment-related SAEs or TEAEs of suicidal intent or suicidal behavior occurred

Abbreviations: IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; OLE = Open-label extension; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event; TRD = Treatment-resistant depression.

GH001 Is Associated with Improved Self-Reported Maternal Functioning in Patients with Postpartum Depression and Rapid Elimination from Breastmilk

Kristina M. Deligiannidis, MD
Feinstein Institutes for Medical Research
Northwell Health
Manhasset, NY, USA

Background

- **PPD** is defined as an MDE with onset of mood symptoms during pregnancy or within 4 weeks following delivery[1]

- **PPD** is associated with **adverse effects on maternal well-being and mother-infant relationships** that can negatively impact infant development[2]

- **Breastfeeding** is associated with positive maternal and infant physical and mental health outcomes[3,4]; however, women with depressive disorders may be concerned about initiating pharmacotherapy while breastfeeding[5]

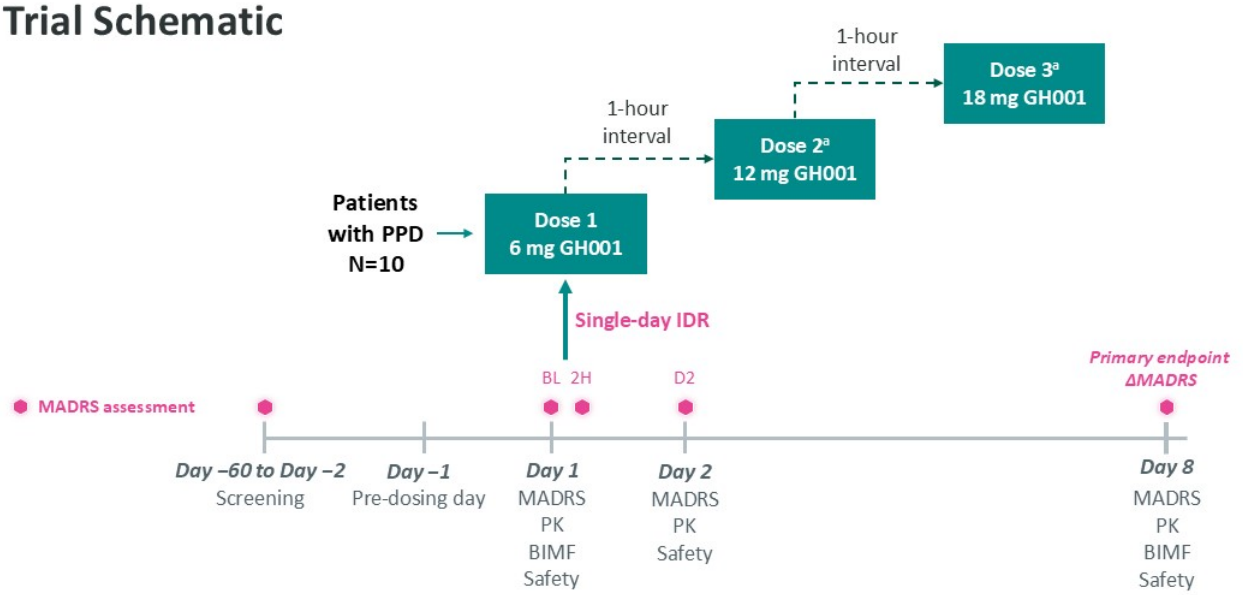
- The potential antidepressant effects and safety of **GH001**, a synthetic form of mebufotenin for pulmonary inhalation, were investigated in a **Phase 2a, single-arm, open-label trial in patients with PPD**

We present data from this Phase 2a trial on antidepressant effects, maternal functioning, and safety in patients with PPD receiving GH001 as well as breastmilk concentrations of mebufotenin in lactating patients

Abbreviations: MDE = Major depressive episode; PPD = Postpartum depression.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013. 2. Field T. *Infant Behav Dev*. 2010;33(1):1-6. 3. Palancı Ay Ö and Aktaş S. *Health Care Women Int*. 2024;45(2):236-250. 4. Modak A, et al. *Cureus*. 2023;15(10):e46730. 5. Fitelson E, et al. *Int J Womens Health*. 2011;3:1-14.

Trial Schematic



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

[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: BIMF = Barkin Index of Maternal Functioning; BL = Baseline; D = Day; H = Hour; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; PK = Pharmacokinetics; PPD = Postpartum depression.

Eligibility Criteria

Women aged 18–45 years were required to meet criteria for PPD as assessed by a trial psychiatrist:

- Diagnosis of MDD[a] (per DSM-5 criteria), without psychotic features, with peripartum onset
- MDD onset no earlier than gestation and no later than the first 4 weeks postpartum
- Was >4 weeks postpartum at dosing and ≤12 months postpartum at screening
- MADRS total score ≥28 at baseline

[a]Confirmed by the MINI.

Abbreviations: DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major depressive disorder; MINI = Mini-International Neuropsychiatric Interview; PPD = Postpartum depression.

Key Assessments

MADRS[1]	• **Primary endpoint:** change from baseline to Day 8 in MADRS total score • Total score range, 0–60 • Higher scores indicate more severe depression
BIMF[2]	• **Patient-centered self-report of maternal functioning** • Total score range, 0–120 • Higher scores indicate better functioning

PK in Breastmilk	• Concentrations were measured using LC-MS/MS in lactating patients:
	  • **Mebufotenin**
	  • **Bufotenin** (psychoactive metabolite)
	  • **5-MIAA** (non-psychoactive terminal metabolite)

Safety	• **Adverse events** were assessed throughout the trial

Abbreviations: 5-MIAA = 5-methoxyindole-3-acetic acid; BIMF = Barkin Index of Maternal Functioning; LC-MS/MS = Liquid chromatography with tandem mass spectrometry; MADRS = Montgomery–Åsberg Depression Rating Scale; PK = Pharmacokinetics.

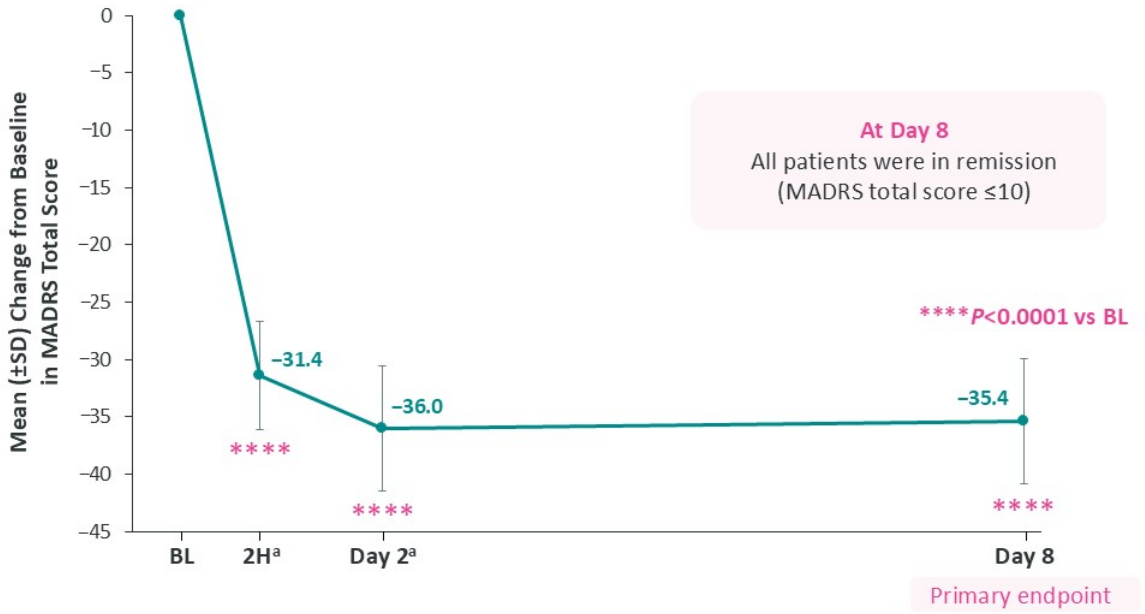
1. Montgomery SA, Asberg M. *Br J Psychiatry*. 1979;134:382-9. 2. Barkin JL, et al. *J Womens Health (Larchmt)*. 2010 Dec;19(12):2239-46.

Demographics and Baseline Clinical Characteristics

	N=10
Demographics	
Sex, female, n (%)	10 (100)
Age, years, mean (SD)	31.6 (5.2)
Ethnicity, n (%)	
Hispanic or Latino	1 (10.0)
Not Hispanic or Latino	9 (90.0)
Race, n (%)	
White	9 (90.0)
Black or African American	1 (10.0)
Parity, mean (SD)	2 (1.0)
Baseline Disease Characteristics	
Duration of current MDE, weeks, mean (SD)	30.9 (12.9)
MADRS total score, mean (SD)	36.7 (4.8)
BIMF total score, mean (SD)[a]	68.8 (15.6)

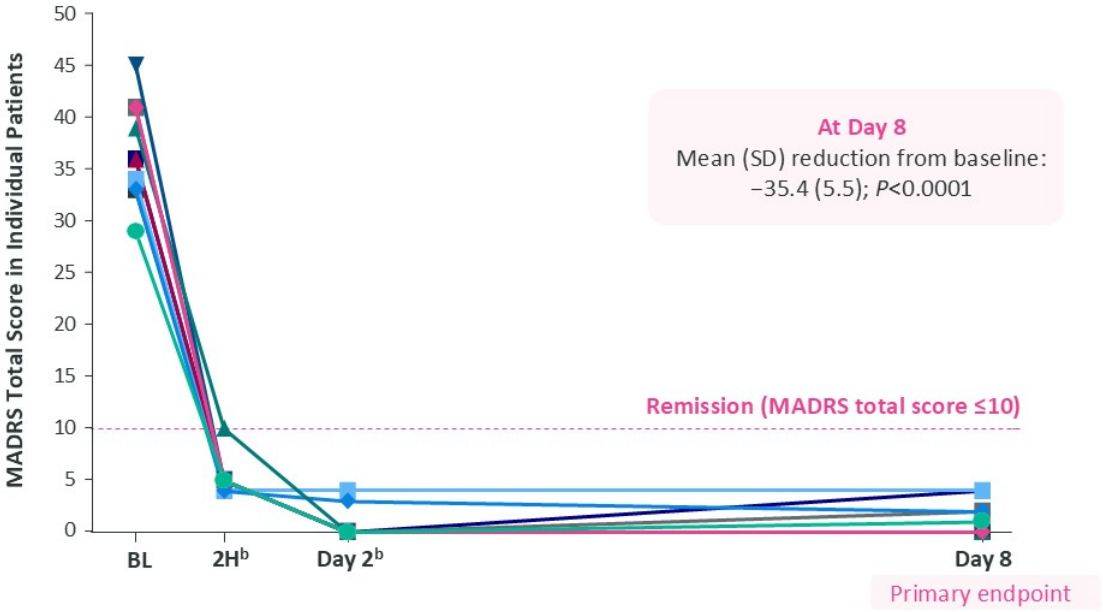
[a]n=8 patients.
Abbreviations: BIMF = Barkin Index of Maternal Functioning; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; SD = Standard deviation.

Primary Endpoint: GH001 Was Associated with Significant Reductions from Baseline on Day 8 in Mean MADRS Total Score in Patients with PPD



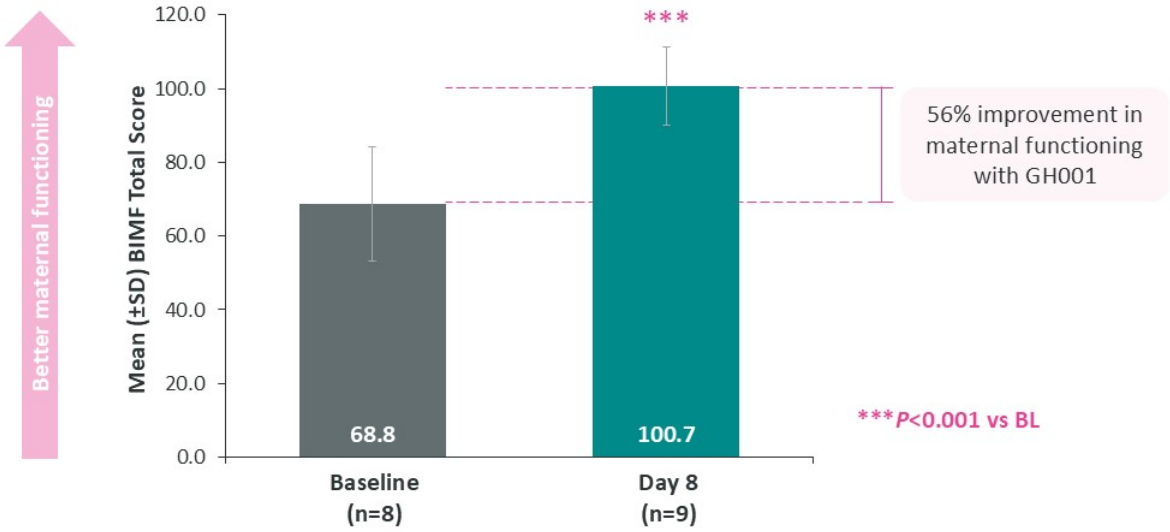
[a]Secondary efficacy endpoint.
Abbreviations: BL = Baseline; H = Hours; MADRS = Montgomery–Åsberg Depression Rating Scale; PPD = Postpartum depression; SD = Standard deviation.

Primary Endpoint: GH001 Led to Substantial Reduction from Baseline on Day 8 in MADRS Total Score in All Patients with PPD



Individual patient data are plotted in the figure, with each color representing 1 patient. [b]Secondary efficacy endpoint.
Abbreviations: BL = Baseline; H = Hours; MADRS = Montgomery–Åsberg Depression Rating Scale; PPD = Postpartum depression; SD = Standard deviation.

BIMF Total Score Improved by a Mean of 34.1 Points from Baseline on Day 8



Improvement from baseline was observed in 6 of 7 BIMF domains on Day 8

Abbreviations: BL = Baseline; BIMF = Barkin Index of Maternal Functioning; SD = Standard deviation.

Mebufotenin and its Metabolites Were Rapidly Eliminated from Breastmilk

Of the four lactating patients, three received GH001 6+12 mg and one received GH001 6+12+18 mg as part of the IDR

	GH001 6+12 mg (n=3)						GH001 6+12+18 mg (n=1)					
	Pre-dose Day 1	1 h post-dose[a]	2.5 h post-dose[a]	~8 h post-dose[a]	Day 2	Day 8	Pre-dose Day 1	1 h post-dose[a]	2.5 h post-dose[a]	~8 h post-dose[a]	Day 2	Day 8
Mebufotenin, ng/mL												
Median (range)	BLQ (BLQ–BLQ)	2.2 (0.2–3.1)	0.3 (BLQ–0.6)	BLQ (BLQ–0.04)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ	1.5	0.3	BLQ	BLQ	BLQ
Bufotenin, ng/mL (psychoactive)												
Median (range)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ (BLQ–BLQ)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
5-MIAA, ng/mL (non-psychoactive)												
Median (range)	BLQ (BLQ–BLQ)	15.4 (13.9–28.5)	12.8 (8.1–13.2)	0.4 (BLQ–0.9)	0.04 (0.03–0.2)	BLQ (BLQ–BLQ)	BLQ	25.1	13.5	0.1	BLQ	BLQ

[a]Time after final dose on Day 1.
Abbreviations: 5-MIAA = 5-methoxyindole-3-acetic acid; BLQ = Below the limit of quantitation; H = Hour; IDR = Individualized dosing regimen.

Safety Summary

Patients, n (%)	Overall (N=10)
Overview of Adverse Events	
Any TEAE	8 (80.0)
Mild	7 (70.0)
Moderate	1 (10.0)
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)

All patients were deemed ready for discharge within the same day of dosing

Abbreviation: TEAE = Treatment-emergent adverse event.

Conclusions

- In adult patients with PPD enrolled in this open-label trial, GH001 as an IDR was associated with significant reduction in MADRS total score from baseline to Day 8
- Improvements were observed across BIMF domains of self-reported maternal functioning
- Mebufotenin and its metabolites (bufotenin and 5-MIAA) were rapidly eliminated from breastmilk
- GH001 was generally well tolerated in patients with PPD

Abbreviations: 5-MIAA = 5-methoxyindole-3-acetic acid; BIMF = Barkin Index of Maternal Functioning; IDR = Individualized dosing regimen; MADRS = Montgomery–Åsberg Depression Rating Scale; PPD = Postpartum depression.

Rapid Improvement in Anhedonia Following GH001 Treatment in Patients with Treatment-Resistant Depression, Postpartum Depression, and Bipolar II Disorder and a Current Major Depressive Episode

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University of Toronto
Toronto, ON, Canada

Background

- **Anhedonia** is a core symptom of MDD, characterized by **a lack of enjoyment** from and engagement in life's experiences, and a **deficit in the ability to feel pleasure**[1]
- In patients with MDD, anhedonia at baseline is often a **predictor of TRD**[2]
- Anhedonia is also associated with **suicidality,**[3,4] **poor quality of life,**[5] **and functional impairment**[5]
- Improvement in anhedonia symptoms in patients with MDD has been correlated with improvements in **physical, psychological, and social functioning and quality of life**[6,7]
- **Safety and efficacy of GH001** were investigated in three patient populations:
  - One Phase 2b trial in patients with **TRD**
  - Two Phase 2a trials: one in patients with **PPD** and one in patients with **BDII and a current MDE** (BDII + MDE)
- In each of the trials, GH001 has demonstrated a **rapid onset of antidepressant effects** and a **favorable safety profile**

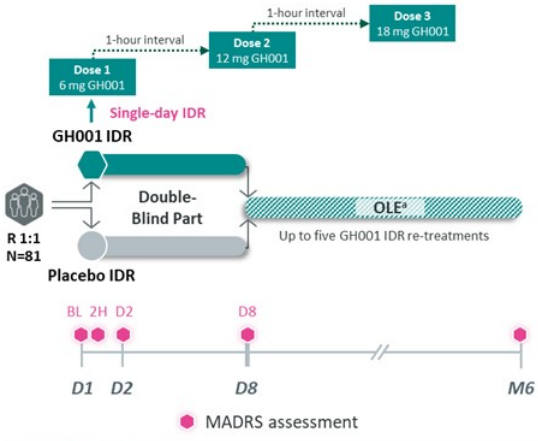
This analysis examined the effect of treatment with GH001 on anhedonia in patients with TRD, PPD, or BDII + MDE in these three trials

Abbreviations: BDII = Bipolar II disorder; MDD = Major depressive disorder; MDE = Major depressive episode; PPD = Postpartum depression; TRD = Treatment-resistant depression.

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013. 2. McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412. 3. Gillies ES, et al. *Psychiatr Res*. 2023;158:209-215. 4. Ballard ED, et al. *J Affect Disord*. 2017;218:195-200. 5. Wong S, et al. *J Affect Disord*. 2024;356:684-698. 6. Cao B, et al. *Front Psychiatry*. 2019;10:17. 7. McIntyre RS, et al. *J Affect Disord*. 2024;363:430-435.

Trial Schematics

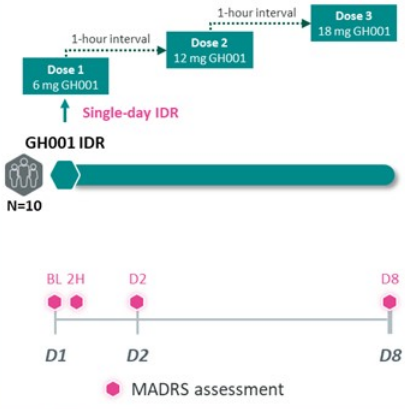
Phase 2b TRD Trial



Key Eligibility Criteria

Adult patients with recurrent or single MDD episode with current episode of ≤2 years, HAM-D-17 total score ≥20, and nonresponse to ≥2 and ≤5 oral antidepressant treatments[b]

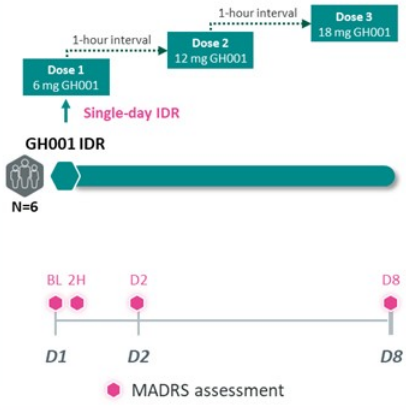
Phase 2a PPD Trial



Key Eligibility Criteria

Women aged 18–45 years with MDD with peri-partum onset[c] and MADRS total score ≥28 at baseline

Phase 2a BDII + MDE Trial



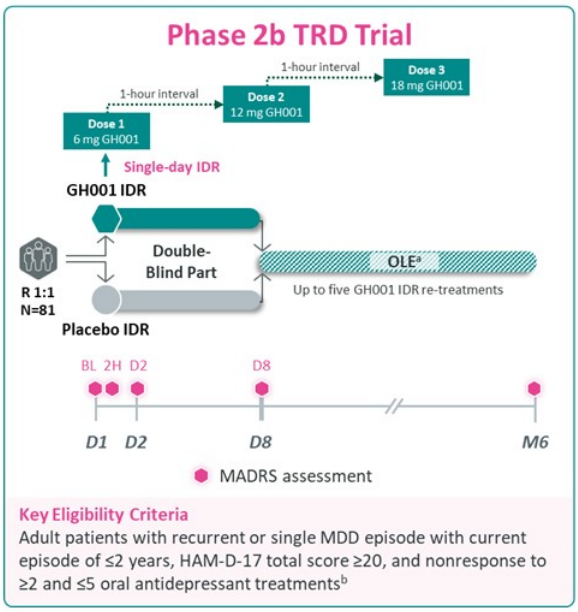
Key Eligibility Criteria

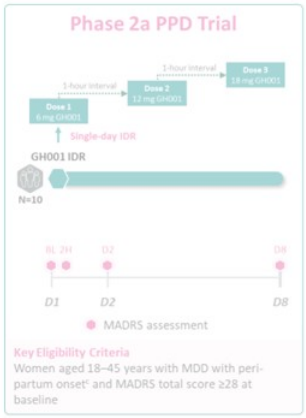
Adult patients with BDII[d] and a current MDE, MADRS total score ≥24, and YMRS total score ≤8 at baseline

[a]In the TRD trial, during the OLE, patients attended visits at Day 15, Month 1, 2, 3, 4, 5 & 6, and also attended assessment visits on Day 2 (telephone call) and Day 8 (in-person) after each re-treatment; MADRS assessment was performed at each visit. [b]MDD episode (per DSM-5 criteria) without psychotic features, current MDE confirmed by the MINI and validated based on the MGH-SAFER criteria interview; nonresponse to antidepressant treatments assessed using the MGH-ATRQ. [c]Per MINI diagnostic criteria. [d]Per DSM-5 diagnostic criteria.

Abbreviations: BDII = Bipolar II disorder; BL = Baseline; D = Day; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; H = Hour; HAM-D-17 = 17-Item Hamilton Depression Rating Scale; IDR = Individualized dosing regimen; M = Month; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major depressive disorder; MDE = Major depressive episode; MGH-ATRQ = Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; MGH-SAFER = Massachusetts General Hospital – Structured Assessment for Evaluation of Risk; MINI = Mini-International Neuropsychiatric Interview; OLE = Open-label extension; PPD = Postpartum depression; R = Randomization; TRD = Treatment-resistant depression; YMRS = Young Mania Rating Scale.

Trial Schematics





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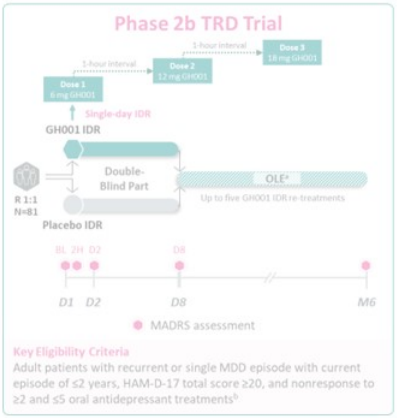
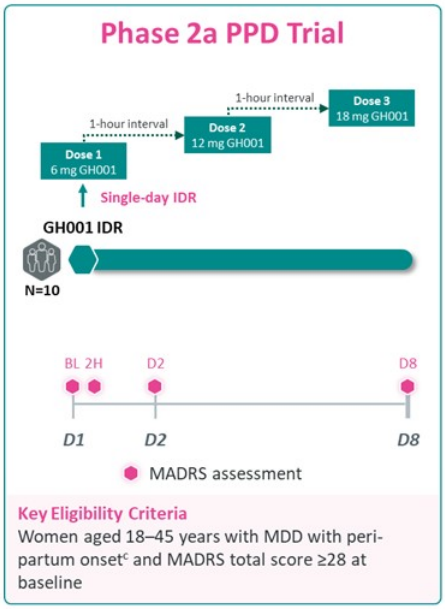
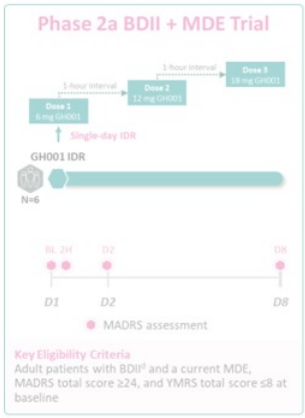
Abbreviations: BDII = Bipolar II disorder; BL = Baseline; D = Day; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; H = Hour; HAM-D-17 = 17-Item Hamilton Depression Rating Scale; IDR = Individualized dosing regimen; M = Month; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major depressive disorder; MDE = Major depressive episode; MGH-ATRQ = Massachusetts General Hospital – Antidepressant Treatment Response Questionnaire; MGH-SAFER = Massachusetts General Hospital – Structured Assessment for Evaluation of Risk; MINI = Mini-International Neuropsychiatric Interview; OLE = Open-label extension; PPD = Postpartum depression; R = Randomization; TRD = Treatment-resistant depression; YMRS = Young Mania Rating Scale.

Trial Schematics







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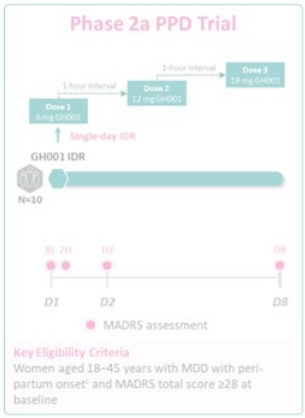
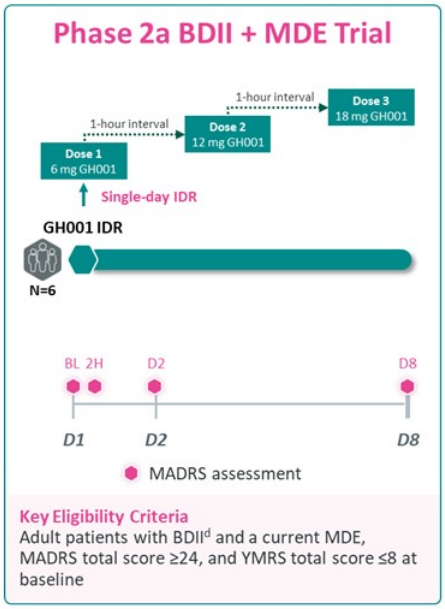
Trial Schematics





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Anhedonia Assessment

MADRS 5-item anhedonia subscale

- The MADRS 5-item anhedonia subscale[1] includes the following MADRS items:

Item 1	Item 2	Item 6	Item 7	Item 8
Apparent sadness	**Reported sadness**	**Concentration difficulties**	**Lassitude**	**Inability to feel**

- Score range, 0–30; lower scores indicate less severe anhedonia

- Clinically meaningful improvement in anhedonia has been reported as an MCIC of –4.6 to –5.5 points based on a published analysis of patients with MDD[2]

Abbreviations: MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder.

1. Cao B, et al. *Front Psychiatry*. 2019;10:17. 2. McIntyre RS. *J Affect Disord*. 2024;363:430-435.

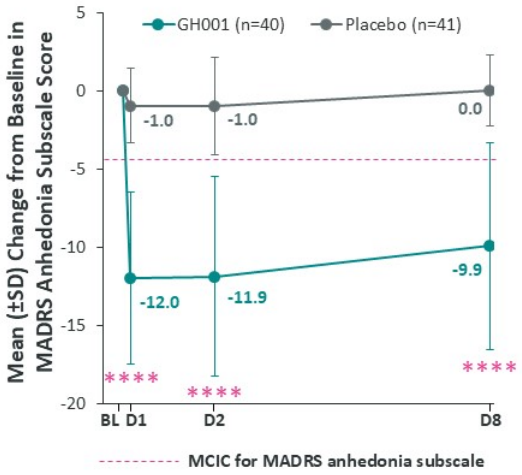
Baseline Characteristics and Disposition

	TRD Trial N=81	PPD Trial N=10	BDII + MDE Trial N=6
Baseline Demographics			
Age, years, mean (SD)	42.8 (11.2)	31.6 (5.2)	44.2 (9.3)
Sex, female, n (%)	46 (56.8)	10 (100)	4 (66.7)
Race, n (%)			
White	81 (100)	9 (90)	6 (100)
Black or African American	0	1 (10)	0
BMI, mean (SD), kg/m^2	26.2 (5.5)	27.6 (6.6)	24.8 (5.0)
Baseline Disease Characteristics			
MADRS total score, mean (SD)	28.6 (5.0)	36.7 (4.8)	32.0 (5.1)
Anhedonia subscale score, mean	17.5	20.8	19.2
CGI-S score, mean (SD)	4.9 (0.7)	4.8 (0.8)	5.0 (0.89)
Number of MDEs, mean (SD)	2.1 (1.3)	1.3 (1.3)	14.0 (12.4)
Duration of current MDE, weeks, mean (SD)	57.1 (78.4)	30.9 (12.9)	20.8 (22.7)
Disposition			
Completed trial, n (%)	–	10 (100)	6 (100)
Double-blind part	81 (100)	–	–
OLE part	63 (77.8)	–	–

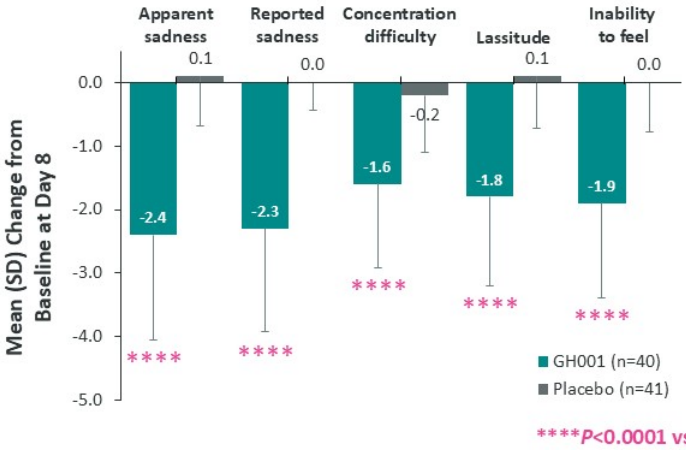
Abbreviations: BDII = Bipolar II disorder; BMI = Body mass index; CGI-S = Clinical Global Impression-Severity; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; OLE = Open-label extension; PPD = Postpartum depression; SD = Standard deviation; TRD = Treatment-resistant depression.

Patients with TRD Who Received Double-Blind Treatment with GH001 Had Rapid and Clinically Meaningful[a] Improvements in MADRS Anhedonia Scores

MADRS Anhedonia Subscale Score



MADRS Anhedonia Subscale Item Scores



****$P<0.0001$ vs placebo

[a]Clinically meaningful improvement in anhedonia has been reported as an MCIC of –4.6 to –5.5 points based on an analysis of patients with MDD.[1]

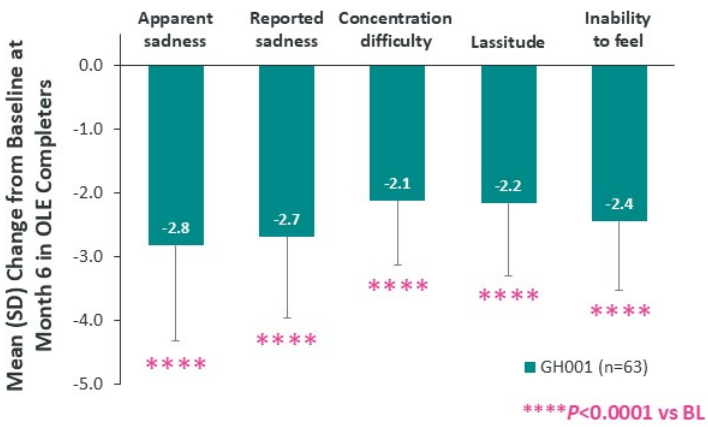
Abbreviations: BL = Baseline; D = Day; MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder; SD = Standard deviation; TRD = Treatment-resistant depression.

1. McIntyre RS. *J Affect Disord*. 2024;363:430-435.

Among Patients Who Completed the TRD Study OLE (n=63), Clinically Meaningful[a] Improvement in MADRS Anhedonia Score Was Maintained at Month 6

In OLE completers (n=63), mean (SD) change from baseline in MADRS anhedonia subscale score was **−12.2 (4.9) at Month 6 (*P*<0.0001)**

MADRS Anhedonia Subscale Item Scores



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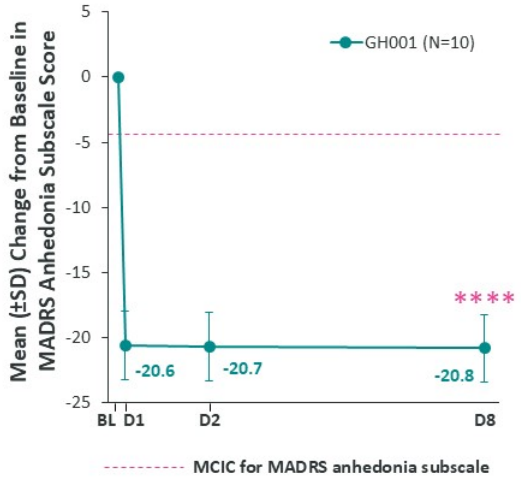
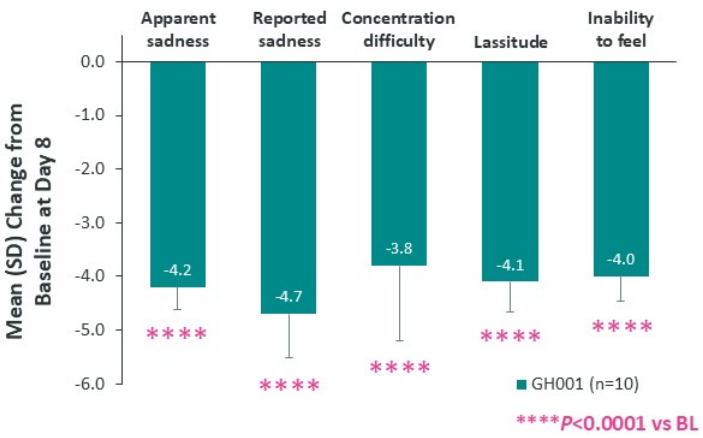
1. McIntyre RS. *J Affect Disord*. 2024;363:430-435.

In Patients with PPD, Clinically Meaningful[a] Improvement in MADRS Anhedonia Score was Observed at Each Assessment

MADRS Anhedonia Subscale Score



MADRS Anhedonia Subscale Item Scores



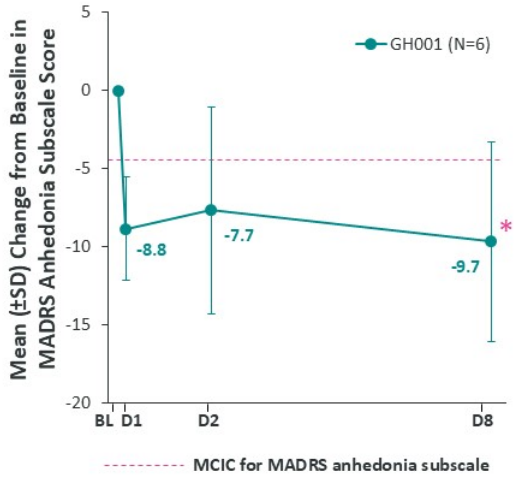
[a]Clinically meaningful improvement in anhedonia has been reported as an MCIC of −4.6 to −5.5 points based on an analysis of patients with MDD.[1]

Abbreviations: BL = Baseline; D = Day; MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder; PPD = Postpartum depression; SD = Standard deviation.

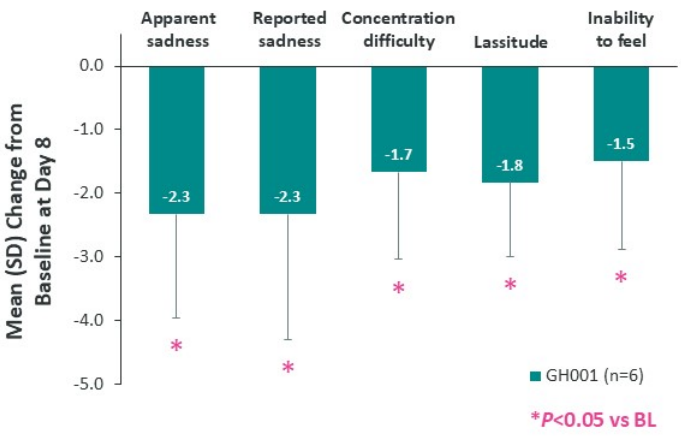
1. McIntyre RS. *J Affect Disord*. 2024;363:430-435.

Patients with BDII + MDE had Clinically Meaningful[a] Improvement in MADRS Anhedonia Score at Day 8 Post-Dose

MADRS Anhedonia Subscale Score



MADRS Anhedonia Subscale Item Scores



[a]Clinically meaningful improvement in anhedonia has been reported as an MCIC of –4.6 to –5.5 points based on an analysis of patients with MDD.[1]

Abbreviations: BDII = Bipolar II disorder; BL = Baseline; D = Day; MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder; MDE = Major depressive episode; SD = Standard deviation.

1. McIntyre RS. *J Affect Disord*. 2024;363:430-435.

GH001 was Well Tolerated in Patients with TRD, PPD, or BDII + MDE

- No treatment-related serious TEAEs were reported across the TRD, PPD and BDII + MDE trials[a]
- In all three trials, TEAEs were mostly mild or moderate in severity
- The most common TEAE in patients treated with GH001 was nausea in the double-blind (17/40 [42.5%]) and OLE (37/81 [45.7%]) parts of the TRD trial; headache was the most common TEAE in the PPD (5/10 [50.0%]) and BDII + MDE (3/6 [50.0%]) trials; no TEAEs of of flashbacks were observed
- No TEAEs of suicidal intent or suicidal behavior occurred in any of the trials
- In the TRD trial, the median duration of psychoactive effects after GH001 administration was 11 minutes and patients were deemed discharge-ready by 1-hour post-dose at 99% of visits

[a]TEAEs were observed in 29/40 (72.5%) patients who received GH001 in the double-blind part of the TRD trial and 72/81 (88.9%) patients in the OLE, 8/10 (80.0%) in the PPD trial, and 5/6 (83.3%) in the BDII + MDE trial.
Abbreviations: BDII = Bipolar II disorder; MDE = Major depressive episode; OLE = Open-label extension; PPD = Postpartum depression; TEAE = Treatment-emergent adverse event; TRD = Treatment-resistant depression.

Conclusion

- The presented trials investigating GH001 for the treatment of TRD, PPD, and BDII + MDE demonstrated rapid reductions in MADRS anhedonia subscale scores
- Improvements in anhedonia subscale scores were clinically meaningful across each of the depressive disorders at Day 8 and were maintained at Month 6 in the OLE of the TRD trial
- Mean reductions were observed in scores for all five items included in the anhedonia subscale
- GH001 was generally well tolerated in patients with TRD, PPD, or BDII + MDE
- These findings suggest that GH001 improves patients' ability to feel pleasure and engage in activities and may improve overall functioning

Abbreviations: BDII = Bipolar II disorder; MADRS = Montgomery–Åsberg Depression Rating Scale; MDE = Major depressive episode; OLE = Open-label extension; PPD = Postpartum depression; TRD = Treatment-resistant depression.

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