TH83

Rapid Antidepressant Effects of Inhaled GH001 in Treatment-Resistant Depression: Results from a Phase 2b, Double-Blind, Randomized, Controlled Trial with 6-Month Follow-Up

Lisa Harding[1,2]*, Bernhard T. Baune[3,4,5], Brian Brennan[6], Narcís Cardoner[7], Rosa Maria Dueñas Herrero[8], David Gregory[6], Luboš Janů[9], John R. Kelly[10,11], Shane J. McInerney[12,13], Alexander Nawka[14], Tomáš Páleníček[15], Víctor Pérez Sola[16-19], Andreas Reif[20,21], Fiona Ryan[6], Claire Sweeney[6], Michael E. Thase[22,23], Madhukar H. Trivedi[24], Velichka Valcheva[6], Eduard Vieta[19,25], Wiesław J. Cubała[26]

*Presenting author: Lisa Harding, Mood Institute, Milton, CT, USA, and Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

[1]Mood Institute, Milton, CT, USA; [2]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; [3]Department of Psychiatry, University of Münster, Münster, Germany; [4]Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia; [5]The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia; [6]GH Research, Dublin, Ireland; [7]Hospital Santa Creu i Sant Pau, Mental Health Research Group, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, CIBERSAM, Barcelona, Spain; [8]Parc Sanitari Sant Joan de Deu Hospital de Dia de Numancia, Barcelona, Spain; [9]A-Shine SRO, Pilsen, Czechia; [10]Psychedelic Research Group: Trinity College Dublin and Tallaght University Hospital, Dublin, Ireland; [11]Department of Psychiatry, Tallaght University Hospital, Dublin, Ireland; [12]Department of Psychiatry, University Hospital Galway, Galway, Ireland; [13]Department of Psychiatry, University of Galway, Galway, Ireland; [14]Institut Neuropsychiatrické Péče, Praha, Czechia; [15]Psyon s.r.o., Prague, Czechia; [16]Mental Health Institute, Hospital del Mar, Barcelona, Spain; [17]Neurosciences Research Group, Hospital del Mar Research Institute (IMIM), Barcelona, Spain; [18]Department of Psychiatry and Department of Experimental and Health Sciences, Pompeu Fabra University, Barcelona, Spain; [19]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain; [20]Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt – Goethe University, Frankfurt am Main, Germany; [21]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Theodor-Stern-Kai 7, 60596 Frankfurt am Main, Germany; [22]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [23]Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA; [24]Center for Depression Research and Clinical Care, Peter O'Donnell Jr. Brain Institute and the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA; [25]Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain; [26]Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

Background

- Treatment-resistant depression (TRD) remains one of the most pressing challenges in psychiatry, affecting approximately 30% of patients treated for major depressive disorder (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]

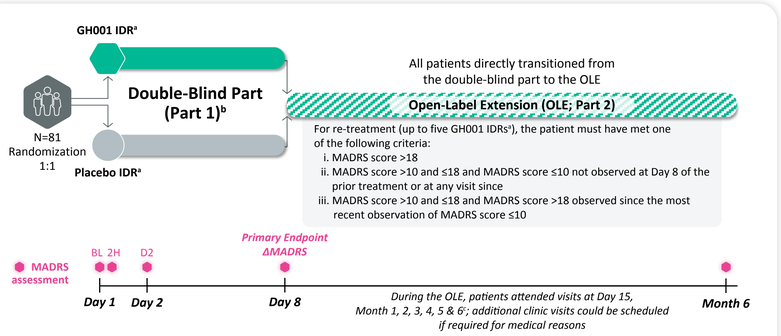
Objective

- This analysis presents the 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 individualized dosing regimen (IDR)

Methods

- This two-part, Phase 2b trial (NCT05800860) enrolled patients with TRD (**Figure 1**):
  - Part 1 was a 7-day, double-blind, placebo-controlled part in which patients were randomised 1:1 to receive an IDR of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo IDR on a single day; there was a 1-hour interval between doses
  - Part 2 was a 6-month open-label extension (OLE) where up to five GH001 IDR re-treatments were administered, depending on the patient's clinical response (re-treatment criteria described in **Figure 1**)
- Patients were required to meet the trial criteria for TRD as assessed by a trial psychiatrist:
  - Recurrent or single major depressive episode without psychotic features, with current episode of ≤2 years and nonresponse to ≥2 and ≤5 oral antidepressant treatments
  - Current major depressive episode based upon the Massachusetts General Hospital – Structured Assessment for Evaluation of Risk (MGH-SAFER) criteria interview
  - 17-Item Hamilton Depression Rating Scale (HAM-D-17) total score ≥20
- The primary endpoint of this trial was mean change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Day 8, as assessed by a blinded rater
- Treatment-emergent adverse events (TEAEs) were assessed throughout the trial

Figure 1. Clinical Trial Design



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 judgment (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.

Results

- Eighty-one patients were randomized (GH001 IDR, 40 and placebo IDR, 41) in the double-blind part, and all transitioned directly into the OLE (**Table 1**)

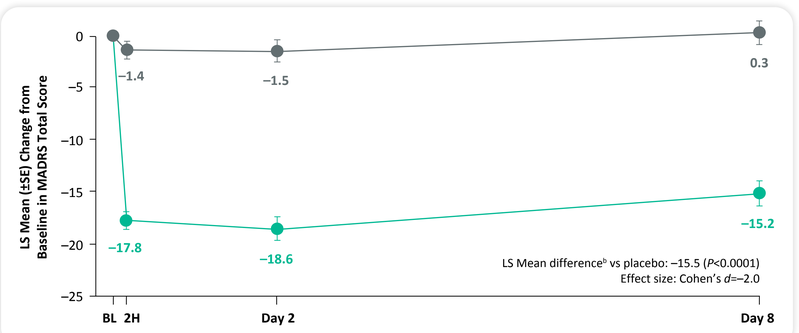
Table 1. Baseline Characteristics and Patient Disposition

	GH001 (N=81)
Patient 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 MDEs, 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 the double-blind part	81 (100)
Received GH001 in the double-blind part	40 (49.4)
Received placebo in the double-blind part	41 (50.6)
Completed the OLE	63 (77.8)
Reasons for Discontinuation During the OLE, n (%)	18 (22.2)
Started additional antidepressant	7 (38.9)
Withdrawal of consent	6 (33.3)
Protocol deviation	2 (11.1)
Other	2 (11.1)
Adverse event	1 (5.6)

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.

- GH001 led to a least squares mean MADRS total score reduction from baseline to Day 8 of −15.5 compared with placebo in the double-blind part (**Figure 2**)

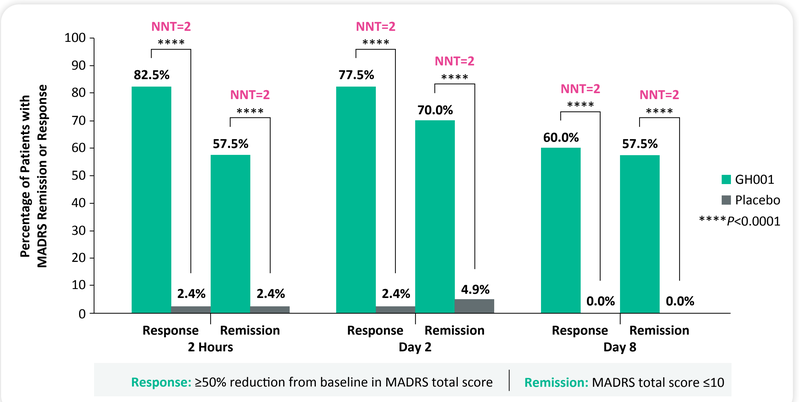
Figure 2. Primary Endpoint: Mean Change in MADRS Total Score from Baseline to Day 8[a] in the Double-Blind Part



[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.[5] [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 treatment was associated with a 60% response rate and a 57.5% remission rate at Day 8 vs 0% with placebo in the double-blind part (**Figure 3**)

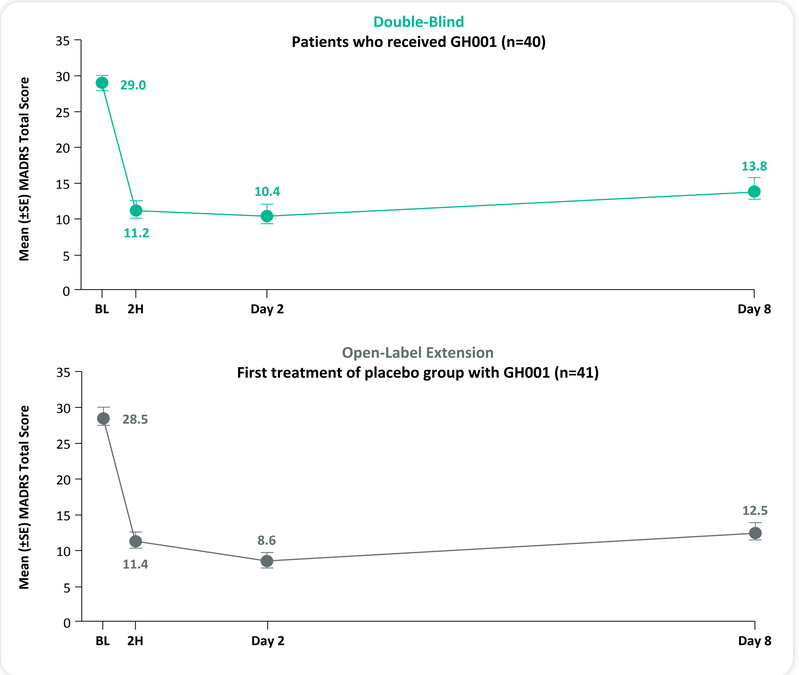
Figure 3. Percentage of Patients with Remission or Response Through Day 8 After Administration of GH001 IDR or Placebo IDR in the Double-Blind Part



Abbreviations: IDR = Individualized dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale; NNT = Number needed to treat.

- The reduction in MADRS total score with GH001 observed in the double-blind part was notably reproduced in the placebo group with their first active GH001 treatment in the OLE (**Figure 4**)

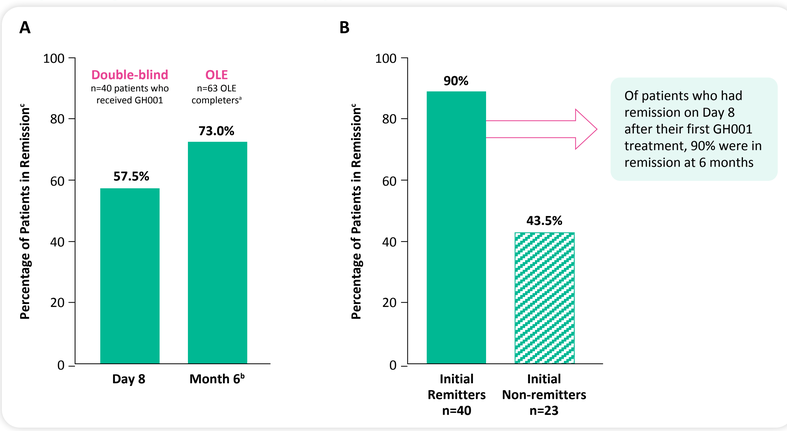
Figure 4. MADRS Total Scores with First GH001 in the Double-Blind Part and the OLE



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

- During the double-blind part, 57.5% of patients who received GH001 were in remission at Day 8; of the 63 patients who completed the OLE, 46 (73.0%) were in remission at 6 months (**Figure 5A**)
  - Patients who completed the OLE received a mean of four treatments across the 6 months (double-blind part and the OLE), with 63.5% (40/63) requiring one to four treatments during the 6 months
  - Among patients who completed the OLE who were in remission on Day 8 after their first active treatment, 90% were in remission at 6 months (**Figure 5B**)

Figure 5. Remission Rate at Day 8 and 6 Months (A) and Remission Rate at 6 Months in OLE Completers by Initial Remission Status (B)



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

- During the OLE, TEAEs were observed in 72/81 patients (88.9%) and were mostly mild or moderate (**Table 2**); 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 by 1 hour post-dose at 99% of visits

Table 2. Overall Summary of Adverse Events in the OLE

	GH001 (N=81)	
Summary 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)	
AESI	30 (37.0)	
Death	0	
TEAEs Occurring in >5% of Patients[a]	Overall	Treatment-related
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)	9 (11.1)
Depression	8 (9.9)	0
Abdominal pain	7 (8.6)	4 (4.9)
Abdominal discomfort	6 (7.4)	4 (4.9)
Affect lability	6 (7.4)	6 (7.4)
Dysgeusia	5 (6.2)	5 (6.2)
Abdominal pain upper	5 (6.2)	4 (4.9)
Fatigue	5 (6.2)	5 (6.2)
Nasopharyngitis	5 (6.2)	0
Palpitations	5 (6.2)	5 (6.2)
Hyperhidrosis	5 (6.2)	3 (3.7)

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

Conclusions

- 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 serious adverse events occurred

References

1. Kubitz N, et al. *PLoS One*. 2013; 8: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. **5.** Food and Drug Administration. Guidance for Industry Major Depressive Disorder: Developing Drugs for Treatment. 2018. Available at: https://www.fda.gov/media/113988/download.

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 guidance of the authors, medical writing and editorial support was provided by Jane A. Phillips, PhD, of OPEN Health, and funded by GH Research.

Disclosures

LH: Advisory Board – AbbVie, GH Research, Johnson & Johnson, and Otsuka. Consultant – GH Research and Johnson & Johnson. **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, and Wyeth. Advisory boards – Biogen, Boehringer Ingelheim, Janssen-Cilag, LivaNova, Lundbeck, Medscape, Novartis, Otsuka, and Teva. Research grants from private industry 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). **BB, DG, FR, CS,** and **VV** are employees and stock option holders of GH Research. **NC:** Grants – Spanish Ministry of Health, Spanish Ministry of Science and Innovation (CIBERSAM), Strategic Plan for Health Research and Innovation (PERIS) 2016–2020, Recercaixa, and La Marató de TV3. Honoraria – Adamed, Elsevier, Exeltis, Janssen, Lundbeck, Pfizer, and Servier. Advisory Boards – Angelini, Esteve, Janssen, Lundbeck, Novartis, Pfizer, and Viatris. Lectures/Meetings – Janssen, Lundbeck, and Pfizer. **RMDH:** Principal investigator – Beckley Psytech and GH Research. Subinvestigator – Compass. LJ: Principal investigator – GH Research. **JRK:** Principal investigator – Compass, GH Research, and Transcend Therapeutics. Consultant – Clerkenwell Health. Grant funding – Health Research Board (ILP-POR-2022-030, DIFA-2023-005, KTA-2024-002. **SJM:** Principal investigator – GH Research and Transcend Therapeutics. Honoraria – Janssen and Lundbeck. **AN:** Principal investigator – GH Research. **TP:** Principal investigator – Compass, GH Research, MAPS, and Ketabon. Shares – Psychedelická klinika s.r.o., Společnost pro podporu neurovědního výzkumu s.r.o., and AVI-X Aviation Experts s.r.o. Founder – PSYRES (Psychedelic Research Foundation). Consultant – CB21 Pharma and GH Research. **VPS:** Consultant, honoraria, or grants – AB-Biotics, AstraZeneca, Bristol Myers Squibb, CIBERSAM, FIS-ISCIII, Janssen Cilag, Lundbeck, Medtronic, Otsuka, and Servier. **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:** 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. **MHT:** Consultant – Acadia, Alkermes, Alto Neuroscience, Axsome, BasePoint Health Management, Biogen, Cerebral, Circular Genomics, Compass, Daiichi Sankyo, GH Research, GreenLight VitalSign6, Heading Health, Janssen, Legion Health, Merck, Mind Medicine, Myriad Neuroscience, Naki Health, Neurocrine Biosciences, Noema Pharma, Orexo, Otsuka America, Otsuka Europe, Otsuka Pharmaceutical Development & Commercialization, Praxis Precision Medicines, PureTech LYT, Relmada Therapeutics, Sage, Seaport Therapeutics, Signant Health, Sparian Biosciences, Titan Pharmaceuticals, Takeda, and WebMD. Grant/research funding – American Foundation for Suicide Prevention, NCATS, NIDA, NIMH, Patient-Centered Outcomes Research Institute (PCORI), Blue Cross Blue Shield of Texas, SAMHSA, and the DoD. Editorial compensation – Elsevier and Oxford University Press. **EV:** Grants – AB-Biotics, AbbVie, Almirall, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celon, Cephalon, Dainippon Sumitomo Pharma, Elan, Ferrer, GH Research, GlaxoSmithKline, Janssen, Lilly, Lundbeck, Orion, Otsuka, Pfizer, Sanofi Aventis, Servier, Sunovion, and Takeda. Honoraria – Abbott, AbbVie, Angelini, AstraZeneca, Bristol Myers Squibb, Cambridge University Press, Elsevier, Farmindustria, Ferrer, Galenica, GlaxoSmithKline, Janssen, Johnson & Johnson, Lilly, Lundbeck, Oxford University Press, Otsuka, Pfizer, Sanofi Aventis, and Viatris. Advisory boards – AbbVie, Angelini, AstraZeneca, Biogen, Biohaven, Bristol Myers Squibb, Celon, Compass, Ferrer, GH Research, Gedeon Richter, HMNC, Idorsia, Janssen, Johnson & Johnson, Jazz, Lilly, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Roche, Sage, Sanofi Aventis, Servier, Shire, Sunovion, Takeda, and Teva. **WJC:** Grants – Acadia, Angelini, Beckley Psytech, GH Research, HMNC Brain Health, Intra-Cellular Therapies, Janssen, MSD, Neumora, Novartis, Otsuka, Recognify Life Sciences. Honoraria – Angelini, GH Research, Janssen, and Novartis. Advisory boards – Douglas Pharmaceuticals, GH Research, Janssen, MSD, and Novartis (relationships reported within the last three years).

Presented at the 64th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) | Paradise Island, Bahamas | January 12–15, 2026