Safety and Tolerability of GH001 in Treatment-Resistant Depression: Results From a Phase 2b, Double-Blind, Randomized, Controlled Trial

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Submitter Wiesław J. Cubała

Affiliation Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

SUBMISSION DETAILS

Abstract Background:
Treatment-resistant depression (TRD) is a chronic condition affecting approximately 30% of patients with major depressive disorder and is associated with a significant human and economic burden to healthcare systems, patients, and their families. At present, only two pharmacotherapies have been approved for the treatment of TRD, highlighting the unmet need for additional safe and effective treatments. Early-phase clinical trials of GH001 suggest it is well tolerated in healthy volunteers and in patients with TRD, postpartum depression, and bipolar II disorder with a current major depressive episode. This trial evaluates the safety and tolerability of GH001 in patients with TRD in a randomized, placebo (PBO)-controlled setting.

Methods:
This was a two-part, Phase 2b trial that assessed the efficacy and safety of GH001 in patients with TRD. Part 1, presented here, was a 7-day, double-blind (DB), randomized, PBO-controlled part where patients were randomized in a 1:1 ratio to receive GH001 or PBO. Part 2 is an ongoing, 6-month, open-label extension (OLE) with up to five GH001 retreatments depending on the patient's clinical status.
In Part 1, patients were randomized to receive an individualized dosing regimen of up to three escalating doses of GH001 (6, 12, and 18 mg) or PBO on a single day with a 1-hour interval between doses. Administration of subsequent doses was based on the patient's subjectively reported psychoactive effects and the safety and tolerability of the previous dose. As in previously conducted GH001 trials, this trial was conducted under the supervision of physicians, nurses, and other qualified healthcare professionals, but without any planned psychotherapeutic intervention before, during, or after dosing. Safety and tolerability of GH001 were assessed up to Day 8 by incidence of treatment-emergent adverse events (TEAEs), vital signs and weight, electrocardiogram (ECG), physical examinations, laboratory assessments, spirometry, and safety assessment tools (Modified Observer's Alertness/Sedation scale, Clinician-Administered Dissociative States Scale [CADSS], Brief Psychiatric Rating Scale positive symptoms subscale [BPRS+], and Columbia-Suicide

Severity Rating Scale [C-SSRS]).

Results:
In the DB part, GH001 was well tolerated in patients with TRD with no serious adverse events reported in either group. TEAEs were observed in 29/40 (72.5%) patients who received GH001 and 3/41 (7.3%) patients who received PBO. All TEAEs in patients who received GH001 were mild (14/29) or moderate (15/29); none were severe. The most commonly reported TEAEs in patients in the GH001 group were nausea (42.5%), salivary hypersecretion (20%), paresthesia (20%), headache (7.5%), and dysgeusia (7.5%). No TEAEs resulted in study drug withdrawal or early withdrawal from the trial in either group. There were no clinically significant changes or adverse events related to vital signs, ECG, or laboratory safety assessments in either group. Similarly, there was no evidence of treatment-emergent effects on suicidal ideation (assessed by the C-SSRS), psychotic symptoms (assessed by the BPRS+), or dissociation at discharge (assessed by the CADSS). By 1 hour postdose, no sedation was observed and 97.4% of patients were discharge-ready.

Conclusion:
The results of the DB part of this trial indicate that GH001 is well tolerated in patients with TRD and has an acceptable safety profile up to 7 days postdose.

Author Listing

* Presenting Author

First Name	Last Name	Affiliation
Wiesław J. *	Cubała *	Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland
Bernhard T.	Baune	Department of Psychiatry, University of Muenster, Muenster, Germany
Narcís	Cardoner	Hospital Santa Creu i Sant Pau, Mental Health Research Group, Institut de Recerca Sant Pau, Universitat Autònoma de Barcelona, CIBERSAM Barcelona, Spain
Rosa Maria	Dueñas Herrero	Parc Sanitari Sant Joan de Deu Hospital de Dia de Numancia, Barcelona, Spain
Luboš	Janů	A-Shine SRO, Pilsen, Czechia

John R.	Kelly	Department of Psychiatry, Tallaght University Hospital, Dublin, Ireland
Shane J.	McInerney	Department of Psychiatry, University of Galway, Galway, Ireland
Alexander	Nawka	Institut Neuropsychiatrické Péče, Praha, Czechia
Tomáš	Páleníček	Psyon s.r.o., Prague, Czechia
Andreas	Reif	Goethe University Frankfurt, University Hospital, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Frankfurt, Germany
Victor	Perez Sola	Centre for Biomedical Research in Mental Health (CIBERSAM ISCIII), Spain; Institute of Mental Heath, Hospital del Mar, Barcelona, Spain; Pompeu Fabra University, Spain
Madhukar H.	Trivedi	Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA
Velichka	Valcheva	GH Research, Dublin, Ireland
Eduard	Vieta	Hospital Clinic de Barcelona, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain
Michael E.	Thase	Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; Corporal Michael J Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA

Signature Wiesław J. Cubała