

Psychoactive Effects of GH001 in Patients With Treatment-Resistant Depression: Results From a Phase 2b, Double-Blind, Randomised Controlled Trial

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Background

- GH001 is a synthetic form of mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) developed for pulmonary inhalation which has shown potential to treat treatment-resistant depression (TRD)¹
- Previous trials suggest that administration of GH001 elicits strong psychoactive effects (PsE) in healthy volunteers and in patients with TRD^{1,2}
- Recent evidence suggests that the intensity of the acute psychoactive experience may be a predictor of clinical response for psychedelic agents in the treatment of psychiatric disorders³⁻⁵
- Numerous questionnaires including the Mystical Experiences Questionnaire (30 Questions [MEQ30]) and the Challenging Experience Questionnaire (CEQ) exist for quantifying the PsE²; however, these questionnaires are time-consuming to administer and not specific to the PsE of mebufotenin
- The proprietary Peak Experience Scale (PES) was developed to rapidly assess PsE after GH001 administration

Objective

- To describe the PsE of GH001 in the double-blind part of a Phase 2b trial in patients with TRD, as evaluated by the PES, MEQ30, and CEQ

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Methods

Trial Design

- In the double-blind part of this Phase 2b multicentre trial (NCT05800860), patients with TRD were randomised 1:1 to receive an individualised dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo IDR on a single day (1-hour interval between doses) (Figure 1)
- The 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

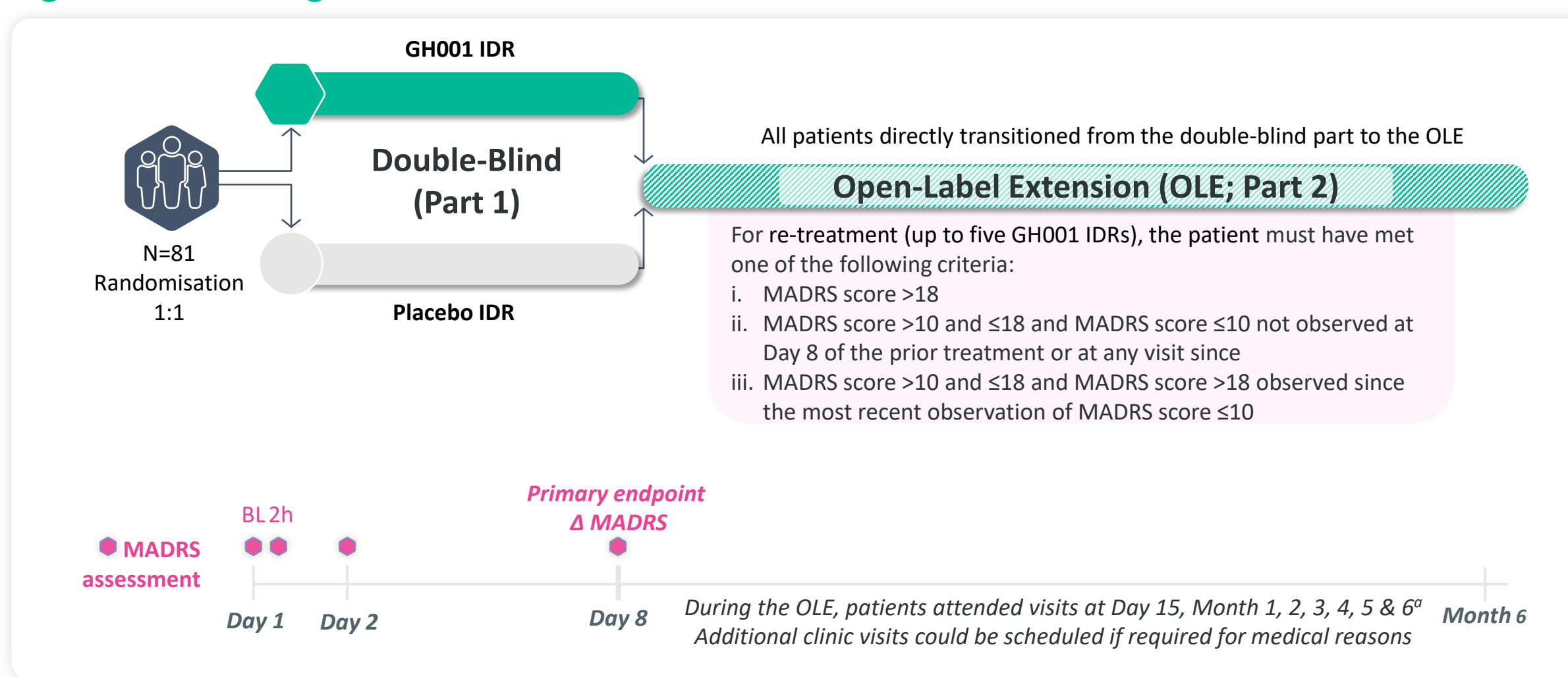
Assessments

- PsE were assessed via the PES, which measures three core features of the PsE (intensity, profoundness, and perceived loss of control), each on a visual analogue scale ranging from 0 to 100, with higher scores indicating stronger PsE (Figure 2)
- A peak experience (PE) was defined as an average

total score of ≥ 75 across the three subscores

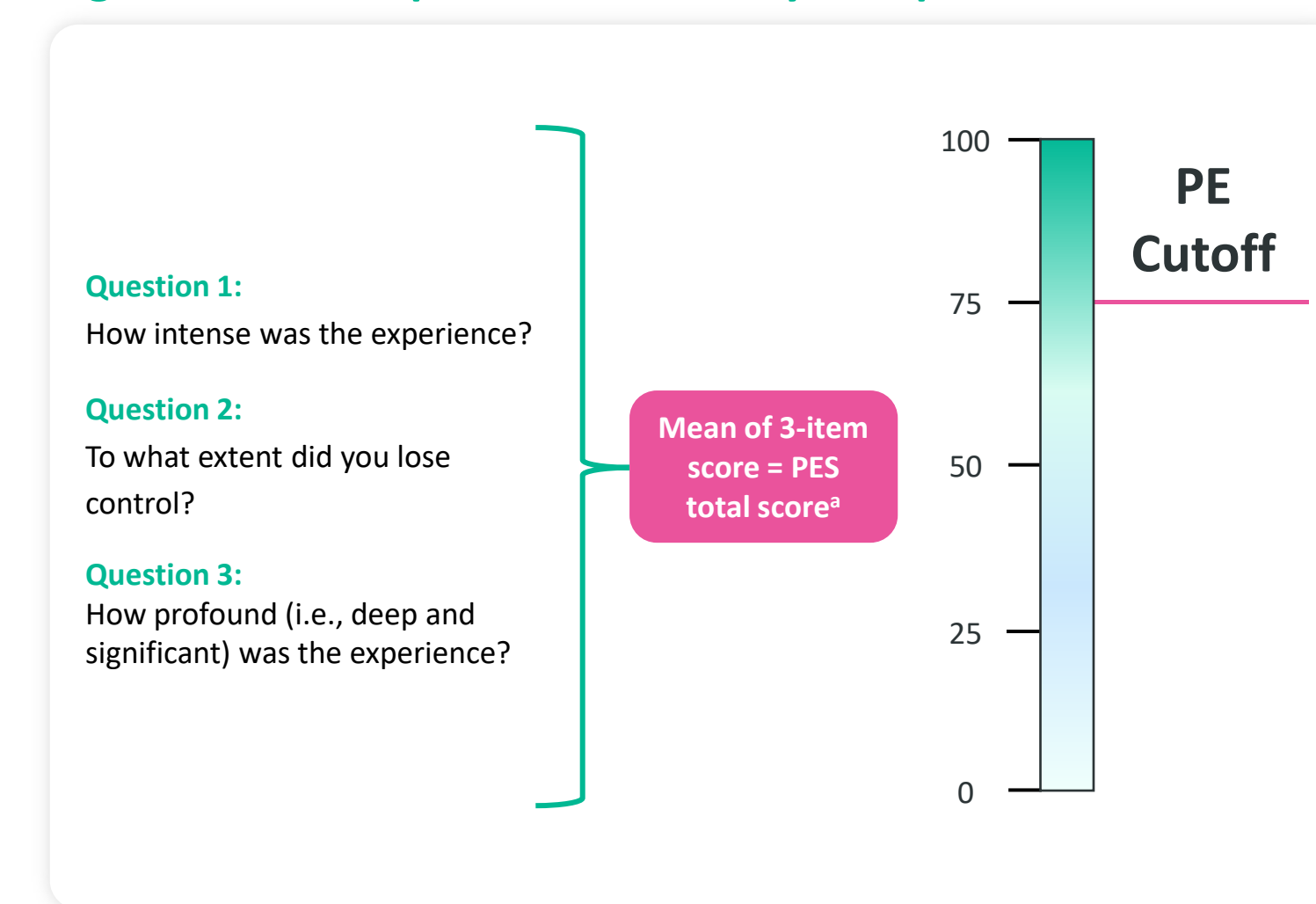
- The MEQ30 was administered to assess mystical-type experiences, and the CEQ was administered to characterise and quantify any potentially challenging experiences
- The three PsE assessments were assessed once the PsE had subsided
- Duration of the PsE, defined as the time from study drug administration to the time when the PsE had subsided, was reported by the investigator

Figure 1. Trial Design



a. Patients also attended assessment visits on Day 2 (phone call) and Day 8 after each re-treatment. Abbreviations: BL = Baseline; h = Hour; IDR = Individualised dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale.

Figure 2. Peak Experience Scale Key Components



a. Patients with a PES total score of ≥ 75 were deemed to have achieved a peak experience. Abbreviations: PE = Peak experience; PES = Peak experience scale.

Results

- In the double-blind part of this trial, 81 patients were randomised to receive a GH001 IDR (n=40) or placebo IDR (n=41)
 - The mean (SD) age was similar in both groups (41.6 [11.4] and 43.9 [10.9] in the GH001 and placebo group, respectively), and most patients were female and had not previously used any psychedelic

Table 1. Baseline Demographics and Clinical Characteristics

	GH001 (N=40)	Placebo (N=41)
Patient Disposition		
Completed double-blind part, n (%)	40 (100)	41 (100)
Demographics		
Age (years), mean (SD)	41.6 (11.4)	43.9 (10.9)
Female, n (%)	24 (60.0)	22 (53.7)
Race, White, n (%)	40 (100)	41 (100)
BMI (kg/m ²) at screening, mean (SD)	24.8 (4.3)	27.5 (6.3)
Previously used any psychedelic (lifetime), n (%)	4 (10.0)	5 (12.2)
Baseline Disease Characteristics		
MADRS Total Score, mean (SD)	29.0 (5.4)	28.2 (4.6)
HAM-D-17 Total Score, mean (SD)	24.9 (2.7)	24.6 (2.3)
Maximum Dose in IDR^a		
6 mg GH001 or one placebo dose, n (%)	9 (22.5)	0 (0)
6+12 mg GH001 or two placebo doses, n (%)	21 (52.5)	0 (0)
6+12+18 mg GH001 or three placebo doses, n (%)	10 (25.0)	41 (100)

^aUp to three doses of GH001 or placebo were administered to each patient. Abbreviations: BMI = Body mass index; HAM-D-17 = Hamilton Depression Rating Scale; IDR = Individualised dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale; SD = Standard deviation.

- Overall, marked PsE were observed in patients receiving GH001 while minimal effects were observed in those receiving placebo
- Investigator-reported durations of PsE in patients who received GH001 were 9, 14 and 11.5 minutes for the 6, 12 and 18 mg doses respectively, and the median duration did not appear to be dose dependent
- In the placebo group, the median PsE duration was 0 for the first, second and third doses and ranged between 0 and 15 minutes
- Total PES scores increased after each subsequent GH001 dose, with median scores per individual dose of 46.7, 85.0, and 95.7 for the 6, 12, and 18 mg doses, respectively (Table 2); PES scores were markedly lower in patients who received placebo (range, 0–20.7)
- Overall, 35 of 40 patients (87.5%) in the GH001 group and no patients in the placebo group achieved a PE at their maximum individual dose level, with 20.0, 61.3, and 80.0% achieving a PE at the 6, 12, and 18 mg GH001 doses, respectively
- In patients who received GH001 and complied with dose escalation per the IDR, 94.6% (35/37) achieved a PE at their maximum individual dose level

- There was no clear dose-related increase in MEQ30 total scores by individual dose with median scores of 1.0, 1.4, and 1.4 after the 6, 12, and 18 mg doses, respectively. In the placebo group, the median MEQ30 total score was zero and ranged from 0 to 1.10
- In the GH001 group, CEQ scores were low, suggesting that the acute PsE were well tolerated in the majority of patients. In the placebo group, the median CEQ total score was zero, ranging between 0 and 0.6

Table 2. Psychoactive Effect Assessment (by Individual Dose)

Assessment	GH001 6 mg	GH001 12 mg	GH001 18 mg	PBO Dose 1	PBO Dose 2	PBO Dose 3
N	40	31	10	41	41	41
Peak Experience Scale^a						
Total score, median (range)	46.7 (1.7, 100)	85.0 (35.3, 100)	95.7 (1, 100)	0.7 (0, 5)	0.7 (0, 11)	0.7 (0, 20.7)
PE achieved, n (%)	8 (20.0)	19 (61.3)	8 (80.0)	0	0	0
Mystical Experience Questionnaire-30^b						
Total score, median (range)	1.0 (0, 4.2)	1.4 (0.4, 4.4)	1.4 (0, 4.1)	0 (0, 0.1)	0 (0, 1.1)	0 (0, 1.1)
Challenging Experience Questionnaire^c						
Total score, median (range)	0.10 (0, 0.6)	0.15 (0, 0.6)	0.24 (0, 0.6)	0 (0, 0.5)	0 (0, 0.6)	0 (0, 0.6)

^aThe PES score comprised of a visual analogue scale (scored 0-100), with a total score ≥ 75 qualifying as a peak experience. ^bThe MEQ total score is the mean weighted average score across the four factor scores and reported as a percentage of the maximum possible score. ^cThe CEQ total score consists of the average of all transformed questionnaire item scores computed to obtain the total CEQ score (range 0-1). Abbreviations: PBO = Placebo; PE = Peak experience.

Conclusions

- Administration of GH001 elicited pronounced PsE, as assessed by the PES
- CEQ scores were low suggesting that the acute PsE were well tolerated in the majority of patients
- The brevity and tolerability of the PsE with GH001, coupled with rapid symptom improvement and a favourable safety profile¹, could enhance treatment tolerability and align more closely with patient and provider preferences for scalable clinical use
- The PsE of GH001 will be further evaluated in the open-label extension, which allows for up to five re-treatments with GH001 over a 6-month period



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