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

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Background

- Treatment-resistant depression (TRD) affects approximately 30% of patients treated for major depressive disorder (MDD)[1]
- Current therapies for TRD are limited and there is a large unmet need for treatments that offer rapid and sustained effects
- Mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) is a non-selective serotonin (5-HT) agonist with high affinity for several receptor subtypes, including the 5-HT_{1A} receptor[2]
- GH001 is a synthetic form of mebufotenin for pulmonary inhalation[3,4]
- Early-stage trials in healthy volunteers and patients with TRD suggest that GH001 is well tolerated and may have the potential to induce an ultra-rapid remission in depressive symptoms[3,4]

Objective

- The aim of this double-blind, placebo-controlled trial was to investigate the safety and efficacy of GH001 in patients with TRD

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Methods

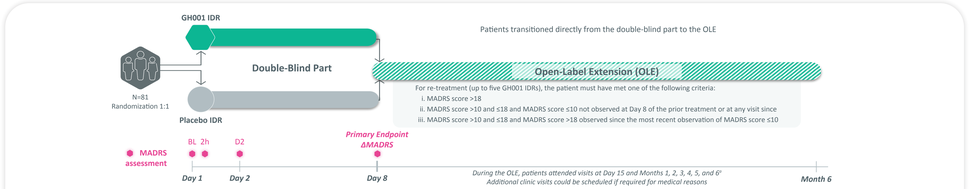
Trial Design

- This Phase 2b multicenter trial consisted of two parts (Figure 1):
  - Double-blind part (described here): a randomized, double-blind, placebo-controlled trial with follow-up to 7 days postdose. Patients were randomized in a 1:1 ratio to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo on a single day; there was a 1-hour interval between doses
  - Open-label extension (OLE): a 6-month trial with up to five GH001 re-treatments administered depending on the patient's clinical status
- Patients were required to meet the trial criteria for TRD as assessed by a trial psychiatrist:
  - Recurrent or single MDD episode without psychotic features, with current episode of ≤2 years
  - 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
  - Nonresponse to ≥2 and ≤5 oral antidepressant treatments

Assessments

- The primary endpoint of the double-blind part of this trial was mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to Day 8, as assessed by a blinded rater
- Secondary endpoints included change in global disease severity as assessed by the Clinical Global Impression – Severity (CGI-S) Scale, anxiety as assessed by the Hamilton Anxiety Rating Scale (HAM-A), and quality of life as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
- Treatment-emergent adverse events (TEAEs) were assessed throughout the trial

Figure 1. Clinical Trial Schematic



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

Results

Double-Blind Part

- A total of 81 patients with TRD were enrolled in the double-blind part (GH001 IDR, n=40; placebo IDR, n=41; Table 1)

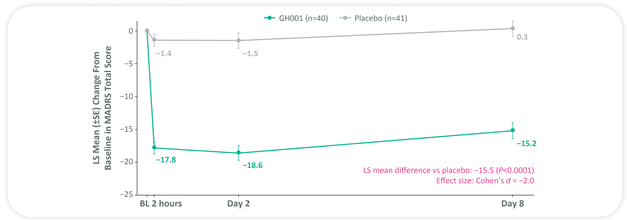
Table 1. Patient Disposition and Characteristics in the Double-Blind Part

		GH001 (n=40)	Placebo (n=41)
Patient Disposition			
Completed double-blind part, n (%)		40 (100)	41 (100)
Patient 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, 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			
HAM-D-17 total score, mean (SD)		24.9 (2.7)	24.6 (2.3)
MADRS total score, mean (SD)		29 (5.4)	28.2 (4.6)
MDE History at Baseline			
Number of MDEs	Mean (SD)	2.1 (1.4)	2.0 (1.1)
	≥3, n (%)	14 (35.0)	13 (31.7)
Time since first depressive episode, years, mean (SD)		11.3 (9.7)	12.2 (8.4)
Duration of current MDE, weeks, mean (SD)		50.8 (28.3)	63.3 (106.9)
Patients Receiving IDR Doses[a]			
First dose (6 mg GH001 or one placebo dose), n (%)		9 (22.5)	0 (0)
Second dose (6+12 mg GH001 or two placebo doses), n (%)		21 (52.5)	0 (0)
Third dose (6+12+18 mg GH001 or three placebo doses), n (%)		10 (25.0)	41 (100)
Duration of PsE[b]			
6 mg (or placebo first dose), minutes, median (range)		9.0 (2–35)	0 (0–15)
12 mg (or placebo second dose), minutes, median (range)		14.0 (4–50)	0 (0–5)
18 mg (or placebo third dose), minutes, median (range)		11.5 (8–50)	0 (0–7)

[a]Up to three doses of GH001 or placebo were administered to each patient. [b]Includes all patients who received respective dose of GH001 or placebo, irrespective of total dose.
BMI = Body mass index; HAM-D-17 = 17-Item Hamilton Depression Rating Scale; IDR = Individualized dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = Major depressive episode; PsE = Psychoactive effects; SD = Standard deviation.

- Change in MADRS total score from baseline to Day 8 was significantly greater with GH001 than with placebo (Figure 2)
  - Statistically significant reductions were also observed in the GH001 group at 2 hours postdose and on Day 2

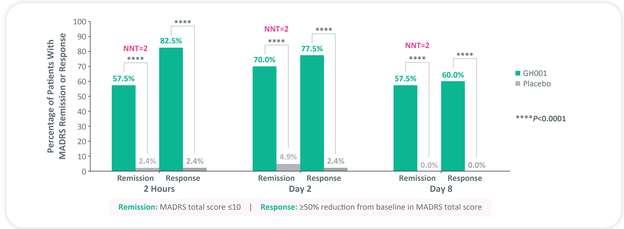
Figure 2. Primary Endpoint[a]: Change in MADRS Total Score From Baseline to Day 8



[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.
BL = Baseline; FDA = Food and Drug Administration; LS = Least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; SE = Standard error.

- On Day 8, remission (MADRS total score ≤10) and response (MADRS total score ≥50% reduction) were achieved in 57.5% and 60.0% of patients treated with GH001, respectively, compared with 0% in the placebo groups (Figure 3)

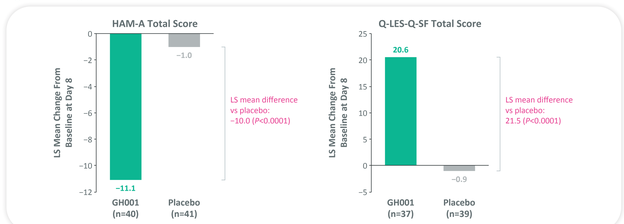
Figure 3. Percentage of Patients With Remission or Response Through Day 8 After Administration of GH001 IDR or Placebo IDR



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

- GH001 led to improvements in anxiety and quality of life vs placebo (Figure 4)

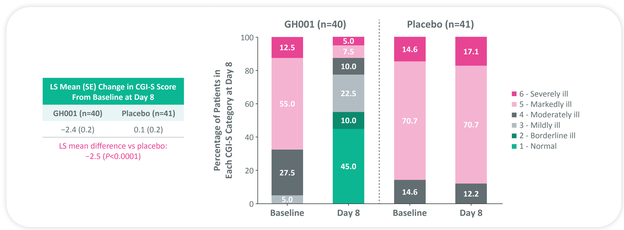
Figure 4. Change From Baseline in HAM-A Total Score and Q-LES-Q-SF Total Score at Day 8



HAM-A = Hamilton Anxiety Rating Scale; LS = Least squares; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form.

- Greater improvements from baseline in global illness severity were also observed with GH001 vs placebo (Figure 5)

Figure 5. CGI-S Scores at Baseline and Day 8



Percentages are for each baseline category within treatment.
CGI-S = Clinical Global Impression – Severity; LS = Least squares; SE = Standard error.

- Inhalation of GH001 was well tolerated; no serious TEAEs were reported, no TEAEs of flashbacks were reported, and all TEAEs were mild or moderate in severity (Table 2)

Table 2. Overall Summary of Adverse Events

Patients, n (%)	GH001 (n=40)	Placebo (n=41)
Any TEAE	29 (72.5)	3 (7.3)
Maximum severity of TEAEs		
Mild	14 (35.0)	2 (4.9)
Moderate	15 (37.5)	1 (2.4)
Severe	0 (0)	0 (0)
Treatment-related TEAEs	29 (72.5)	1 (2.4)
Device-related TEAEs	1 (2.5)	0 (0)
Serious TEAEs	0 (0)	0 (0)
Treatment-related serious TEAEs	0 (0)	0 (0)
TEAEs leading to study drug withdrawal	0 (0)	0 (0)
TEAEs leading to early withdrawal from trial	0 (0)	0 (0)
AESIs	8 (20.0)	0 (0)
Death	0 (0)	0 (0)
Most common TEAEs (occurring in >5% of patients in either group) by Preferred Term		
Nausea	17 (42.5)	0 (0)
Salivary hypersecretion	8 (20.0)	0 (0)
Paresthesia	8 (20.0)	0 (0)
Headache	3 (7.5)	1 (2.4)
Dysgeusia	3 (7.5)	0 (0)

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

Open-Label Extension

- Preliminary results from the 63 patients who completed the OLE indicate that GH001 can maintain long-term remission from TRD, with 73.0% of patients (n=46) who completed the OLE in remission (MADRS total score ≤10) at 6 months
  - Completers (n=63) had a mean MADRS total score of 9.4 at 6 months
  - 63.5% of completers (n=40) received 1–4 treatments with GH001
  - No drug-related serious TEAEs were reported in the OLE; one non-drug-related serious TEAE of Preferred Term status migrainosus was reported 73 days after the patient's most recent administration of the GH001 IDR

Conclusions

Double-Blind Part

- The primary endpoint was met: GH001 administered as an IDR led to significant MADRS reductions from baseline to Day 8 (−15.5 vs placebo)
- Secondary endpoints: Remission rate of 57.5% at Day 8 (placebo, 0%) and improvements in anxiety, global disease severity, and quality of life were observed
- Safety: GH001 was well tolerated

Open-Label Extension

- GH001 can maintain long-term remission in TRD, with 73.0% of patients who completed the OLE in remission at 6 months
- Durable effects with relatively infrequent treatment visits and ultra-rapid MADRS reduction
- No drug-related serious TEAEs were reported in the OLE