TH71

Suicidal Ideation and Behavior in Patients with Treatment-Resistant Depression Treated with GH001

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Background

- Treatment-resistant depression (TRD) is a debilitating condition that has been defined as a failure to respond to ≥2 adequate treatments for major depressive disorder (MDD)[1]
- Rates of suicidal ideation in patients with TRD are higher than in patients with treatment-responsive MDD (15% vs 6% of patients, respectively)[2]
  - TRD is also associated with higher rates of attempted suicide, all-cause mortality, and deaths by suicide[3]
- There is a significant unmet need for safe and effective therapies for TRD that do not exacerbate suicidal intent
- In a Phase 2b trial, GH001, a synthetic form of mebufotenin (5-MeO-DMT) for pulmonary inhalation, was well tolerated and resulted in rapid and significant improvements in depressive symptoms in patients with TRD

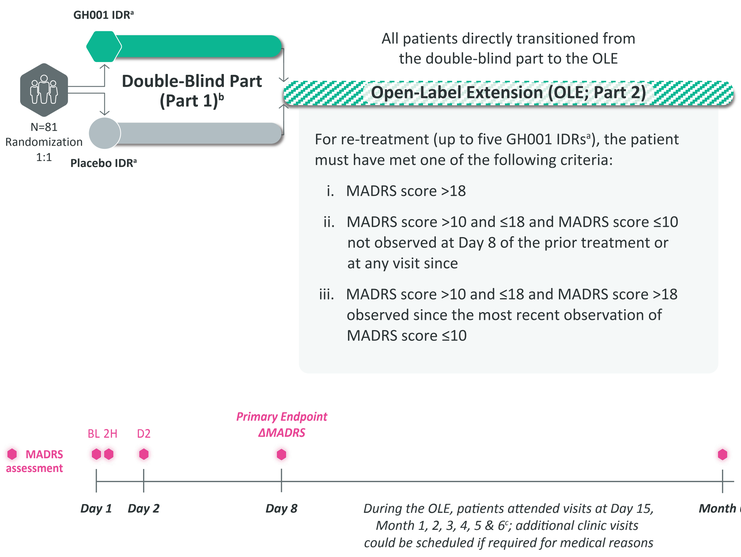
Objective

- We describe the safety effects of GH001 on suicidal ideation and behavior in patients with TRD enrolled in the Phase 2b trial

Methods

- This trial (NCT05800860) included a 7-day, randomized, double-blind part and a 6-month open-label extension (OLE; **Figure 1**)
  - In the double-blind part, patients were randomized 1:1 to receive an individualized dosing regimen (IDR) of up to three escalating doses of GH001 (6, 12, and 18 mg) or placebo IDR on a single day with a 1-hour interval between doses
  - In the OLE, patients received up to five GH001 IDR re-treatments over 6 months as needed, depending on the patient's clinical response and tolerability of previous IDRs
- Trial eligibility criteria excluded patients with suicidal ideation with intent (with items 4 or 5 on the Columbia-Suicide Severity Rating Scale [C-SSRS] endorsed) within the past year, during the screening period, or at baseline; those with suicidal behaviors or non-suicidal self-injury in the past year; and those with a clinical assessment of significant suicide risk
- Suicidal behavior and suicidal ideation were assessed using the C-SSRS at screening; during each treatment period at pre-dose, discharge, Day 2, and Day 8; and at all OLE scheduled visits (Day 15 and monthly up to Month 6/end of treatment)
  - The C-SSRS "baseline/screening" version was used at screening, and the "since last visit" version was used at all subsequent visits
  - Suicidal ideation was defined as "yes" responses to items 1–5 (with items 4 and 5 indicating suicidal ideation with intent), and suicidal behavior was defined as "yes" responses to items 6–10
- Montgomery–Åsberg Depression Rating Scale (MADRS) item 10 (suicidal thoughts) was used to provide further quantification of suicidal ideation, which was indicated by scores ≥2 on a scale from 0–6[4]
- Treatment-emergent adverse events (TEAEs) were assessed at each visit
- Results were analyzed descriptively

Figure 1. Clinical Trial Schematic



[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
- Rates of historic and current suicidal ideation were balanced across treatment groups (**Table 1**)

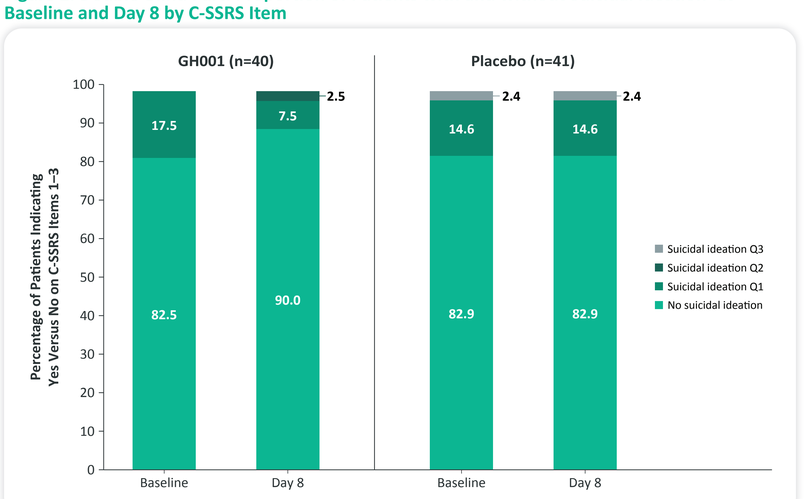
Table 1. Baseline Demographics and Clinical Characteristics

	GH001 (n=40)	Placebo (n=41)
Patient Demographics		
Age, years, mean (SD)	41.6 (11.4)	43.9 (10.9)
Sex, female, n (%)	24 (60.0)	22 (53.7)
Race, White, n (%)	40 (100)	41 (100)
Actively employed, n (%)	33 (82.5)	29 (70.7)
Disease Characteristics		
HAM-D-17 total score, mean (SD)	24.9 (2.6)	24.6 (2.3)
MADRS total score, mean (SD)	29.0 (5.4)	28.2 (4.6)
CGI-S, mean (SD)	4.8 (0.7)	5.0 (0.6)
Suicidality		
Non-suicidal self-injurious behavior		
Lifetime, n (%)	1 (2.5)	0
Past 12 months, n (%)	0	0
Baseline, n (%)	0	0
Suicidal ideation without intent[a]		
Lifetime, n (%)	15 (37.5)	23 (56.1)
Past 12 months, n (%)	10 (25.0)	18 (43.9)
Baseline, n (%)	7 (17.5)	9 (22.0)
Suicidal ideation with intent[a]		
Past 12 months, n (%)	0	0
Baseline, n (%)	0	0
Suicidal behavior[a]		
Past 12 months, n (%)	0	0
Baseline, n (%)	0	0

[a]Suicidal ideation without intent was defined as any "yes" answer to C-SSRS items 1–3; suicidal ideation with intent was defined as any "yes" answer to C-SSRS items 4–5; suicidal behavior was defined as any "yes" answer to C-SSRS items 6–10; patients were counted for each category item to which they answered "yes" and therefore may be counted in more than one item.
Abbreviations: CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; HAM-D-17 = Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; SD = Standard deviation.

- In the GH001 group, suicidal ideation was reported by seven patients at baseline and four at Day 8 (**Figure 2**)
  - No GH001-treated patients developed new-onset suicidal ideation between baseline and Day 8
  - In the placebo group, five patients reported suicidal ideation both at baseline and at Day 8, two reported suicidal ideation at baseline but not Day 8, and two patients without baseline suicidal ideation reported it at Day 8
- No suicidal behaviors were reported in GH001- or placebo-treated patients at baseline or on any scheduled C-SSRS assessments in the double-blind part

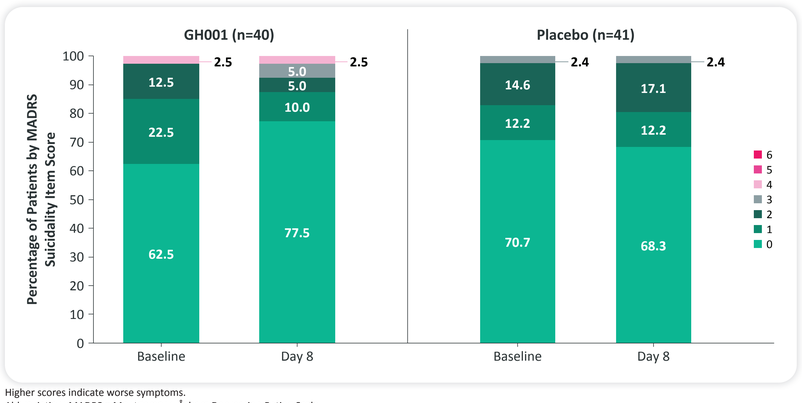
Figure 2. Double-Blind Part: Proportion of Patients with and without Suicidal Ideation[a] at Baseline and Day 8 by C-SSRS Item



[a]Patients responding "yes" to C-SSRS items 1 (wish to be dead), 2 (non-specific active suicidal thoughts), or 3 (active suicidal ideation with any methods); no patients responded "yes" post-dose to items 4 (active suicidal ideation with some intent) or 5 (active suicidal ideation with specific plan).
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; Q = Question.

- Baseline MADRS item 10 (suicidal thoughts) scores were similar between the two treatment groups, and patients who received GH001 did not report worsening of symptoms on Day 8 of the double-blind part as per MADRS item 10 (**Figure 3**)
  - The median (range) change from baseline to Day 8 in MADRS score for item 10 was 0.0 (–2 to 1) for patients who received GH001 and 0.0 (–1 to 2) for patients who received placebo

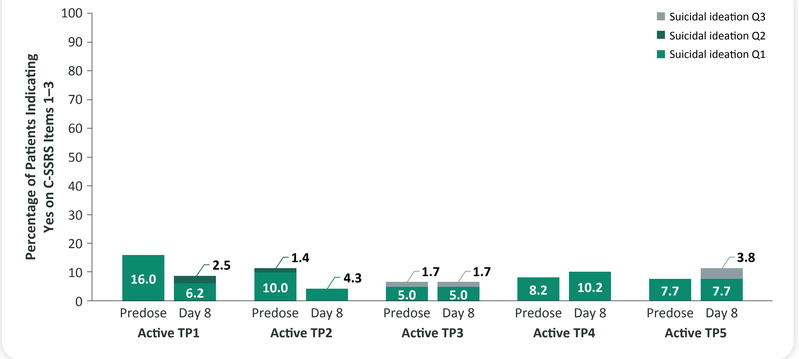
Figure 3. Double-Blind Part: MADRS Suicidality Item 10 Responses at Baseline and Day 8



Higher scores indicate worse symptoms.
Abbreviation: MADRS = Montgomery–Åsberg Depression Rating Scale.

- In the 6-month OLE, the numbers of patients reporting suicidal ideation according to the C-SSRS at all timepoints assessed during the trial were lower than before the first GH001 treatment period; C-SSRS items endorsed during each active treatment period are shown in **Figure 4**

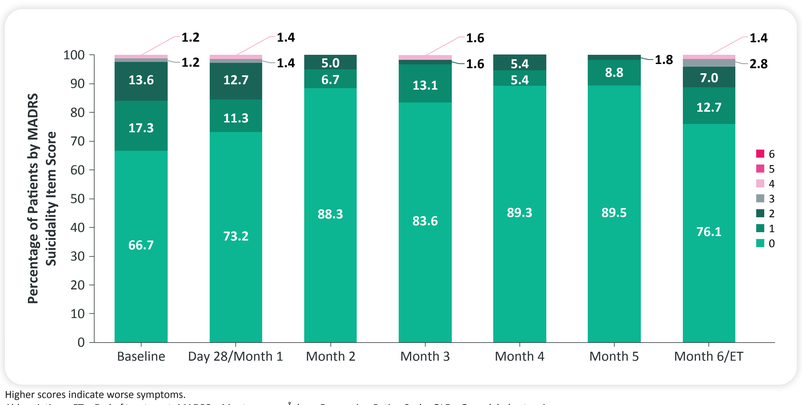
Figure 4. Proportion of Patients Reporting Suicidal Ideation[a] by C-SSRS Item in Each GH001 Treatment Period in the Double-Blind Part and the OLE



[a]Patients responding "yes" to C-SSRS items 1 (wish to be dead), 2 (non-specific active suicidal thoughts), or 3 (active suicidal ideation with any methods); no patients responded "yes" post-dose to items 4 (active suicidal ideation with some intent) or 5 (active suicidal ideation with specific plan).
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; Q = Question; TP = Treatment period.

- During the OLE, the proportions of patients reporting a score of zero on MADRS item 10 at all timepoints during GH001 treatment were greater than that at baseline of the double-blind part (**Figure 5**)
  - The median (range) change from baseline to Month 6 in MADRS score for item 10 was 0.0 (–3 to 2; n=74)

Figure 5. MADRS Suicidality Item 10 Responses at Baseline and by Month in the OLE



Higher scores indicate worse symptoms.
Abbreviations: ET = End of treatment; MADRS = Montgomery–Åsberg Depression Rating Scale; OLE = Open-label extension.

- No TEAEs of suicidal intent or suicidal behavior occurred throughout the 6-month duration of the trial
- A TEAE of suicidal ideation occurred in one patient; the event lasted 6 hours before resolving spontaneously
  - This TEAE was not accompanied by any changes in C-SSRS score beyond the duration for which the thoughts occurred, and the patient did not report any further TEAEs of suicidal ideation during the trial

Conclusions

- In this double-blind, placebo-controlled trial with a 6-month OLE in patients with TRD who were not at acute risk of suicide at baseline, GH001 was not associated with treatment-emergent events of suicidal ideation with intent or suicidal behavior, or with any increased suicidal ideation as measured by the C-SSRS immediately following treatment or over time for up to 6 months
- These results support that GH001 was generally well tolerated and was associated with significant reductions in depressive symptoms without increasing risk of suicide

References

1. McIntyre RS, et al. *World Psychiatry*. 2023;22:394-412.
2. Mrazek DA, et al. *Psychiatr Serv*. 2014;65:977-87.
3. Kern DM, et al. *Brain Behav*. 2023;13:e3171.
4. Montgomery SA, Asberg M. *Br J Psychiatry*. 1979;134:382-9.

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