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Safety and Tolerability Results From a Phase 2b, Double-Blind Trial With an Open-Label Extension of GH001 in Treatment-Resistant Depression

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Background

- Treatment-resistant depression (TRD) is a chronic condition affecting at least 30% of patients with major depressive disorder[1]
- There is an unmet need for additional safe and effective treatments in TRD[2]
- Early-phase clinical trials of GH001, a synthetic, inhaled formulation of mebufotenin (5-methoxy-N,N-dimethyltryptamine), in healthy volunteers and patients with TRD demonstrated it is well tolerated with an acceptable safety profile[3,4]
- This Phase 2b trial evaluated the safety and tolerability of GH001 in patients with TRD and consisted of a double-blind part (Part 1) and a 6-month open-label extension (OLE [Part 2])

Objective

- The objective of this analysis is to present safety and tolerability data for GH001 from the 6-month OLE of a Phase 2b trial in which patients with TRD received up to five re-treatments with GH001 administered as an individualised dosing regimen (IDR)

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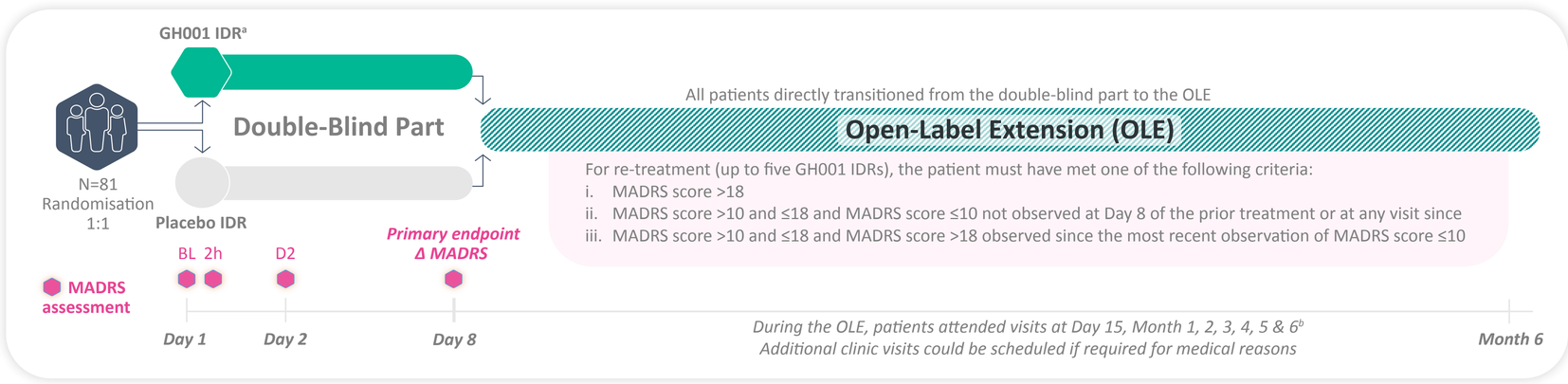
Methods

- 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
  - Part 2 was a 6-month 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)
- This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard of care, and without any planned psychotherapeutic intervention before, during, or after dosing
- OLE safety assessments included treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG), and safety assessment tools (Columbia-Suicide Severity Rating Scale [C-SSRS], Brief Psychiatric Rating Scale positive symptoms subscale [BPRS+], Clinician-Administered Dissociative States Scale [CADSS], Modified Observer's Alertness/Sedation [MOAA/S] scale, and Clinical Assessment of Discharge Readiness [CADR])

Figure 1. Clinical Trial Schematic



[a]The criteria for administration of the second and third doses in the IDR were based on the patient's subjectively reported psychoactive effects and the safety and tolerability at the previous dose level according to the trial physician's judgement.
[b]Patients also attended assessment visits on Day 2 (phone call) and Day 8 after each re-treatment.
Abbreviations: BL = Baseline; D = Day; h = Hour; IDR = Individualised dosing regimen; MADRS = Montgomery-Åsberg Depression Rating Scale.

Results

Double-Blind Part

- A total of 81 patients with TRD were enrolled and randomised in the double-blind part (GH001, n=40; placebo, n=41); all 81 patients completed the double-blind part
  - The mean (SD) age was 42.8 (11.2) years; 56.8% of the patients were female
- TEAEs were observed in 29/40 (72.5%) patients who received GH001 and 3/41 (7.3%) patients who received placebo
- There were no serious or severe TEAEs reported, and no TEAE resulted in study drug withdrawal or early withdrawal from the double-blind part in either treatment group

Open-Label Extension

- All 81 patients transitioned directly to the OLE
- A total of 63 patients completed the OLE
  - Patients who completed the OLE received a mean of four treatments, with 63.5% (40/63) requiring one to four treatments in 6 months
- TEAEs were observed in 72/81 (88.9%) patients who entered the OLE (Table 1)
- Most TEAEs observed in the OLE were mild (72.1%) or moderate (27.5%)
  - Two severe TEAEs were reported:
    - One treatment-related event of affect lability, occurring shortly after administration of GH001 and resolving within 4 minutes
    - One event of migraine, considered a serious TEAE not related to treatment; the event started 73 days after the patient's most recent administration of the GH001 IDR
- One TEAE (a mild TEAE of asthma [exacerbation of pre-existing asthma bronchiale]) resulted in early withdrawal from the OLE

Table 1. Overall Summary of Safety in the OLE

Patients, n (%)	Overall (N=81)	
Any TEAE	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)	
AESIs	30 (37.0)	
Death	0	
TEAEs occurring in ≥5% of patients	**Overall**	**Treatment-related[a]**
Nausea	37 (45.7)	37 (45.7)
Paraesthesia	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)
Paraesthesia oral	10 (12.3)	10 (12.3)
Upper respiratory tract infection	10 (12.3)	0
Anxiety	9 (11.1)	8 (9.9)
Depression	8 (9.9)	0
Abdominal pain	7 (8.6)	4 (4.9)
Affect lability	6 (7.4)	6 (7.4)
Abdominal discomfort	6 (7.4)	4 (4.9)
Abdominal pain upper	5 (6.2)	4 (4.9)
Dysgeusia	5 (6.2)	5 (6.2)
Fatigue	5 (6.2)	5 (6.2)
Hyperhidrosis	5 (6.2)	3 (3.7)
Nasopharyngitis	5 (6.2)	0
Palpitations	5 (6.2)	5 (6.2)

[a]TEAEs that were definitely, probably, or possibly related to study medication according to the study physician. Events with unknown relationship to study drug were counted as drug-related.
Abbreviations: AESIs = Adverse events of special interest; OLE = Open-label extension; TEAE = Treatment-emergent adverse event.

- Adverse events of special interest are listed in Table 2
  - No TEAEs of flashbacks were reported
  - No TEAEs of suicidal intent or suicidal behaviour occurred throughout the 6-month duration of the trial and lower rates of suicidal ideation were observed in comparison to baseline at any timepoint assessed during the trial
  - A TEAE of suicidal ideation occurred in one patient; the event lasted 6 hours before resolving spontaneously

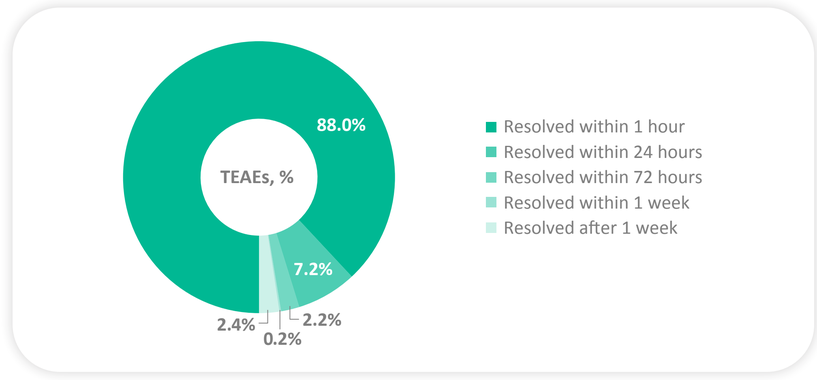
Table 2. Adverse Events of Special Interest Occurring in ≥2 Patients in the OLE

Patients, n (%)	Overall (N=81)
Any treatment-emergent AESI	30 (37.0)
Anxiety	9 (11.1)
Depression	8 (9.9)
Affect lability	6 (7.4)
Abnormal behaviour	2 (2.5)
Amnesia	2 (2.5)
Emotional disorder	2 (2.5)
Feeling abnormal	2 (2.5)
Irritability	2 (2.5)
Psychomotor hyperactivity	2 (2.5)

Abbreviations: AESI = Adverse event of special interest; OLE = Open-label extension.

- Of the treatment-related TEAEs reported at least twice that started within 24 hours of GH001 dosing, most resolved within 1 hour of dosing (Figure 2)

Figure 2. Duration of Treatment-Related TEAEs Reported at Least Twice in the OLE



Abbreviations: OLE = Open-label extension; TEAEs = Treatment-emergent adverse events.

- There were no clinically significant changes in blood pressure or heart rate following administration of GH001 and no treatment-related TEAEs related to vital signs or ECG results
- Of a total of 13 TEAEs (8/81 [9.9%] patients) under the System Organ Class "respiratory, thoracic, and mediastinal disorders," nine (5/81 [6.2%] patients) were considered treatment-related: throat irritation and upper respiratory tract irritation (three events each), cough and dyspnoea (one event each), and the exacerbation of asthma previously described
  - All of these treatment-related TEAEs were mild to moderate in severity and not associated with clinically significant changes in vital signs and, with the exception of the TEAE of asthma previously mentioned, were short-lived, resolved without treatment, and were not associated with any clinically significant changes in spirometry parameters
- There was no evidence of treatment-emergent psychotic symptoms (assessed by the BPRS+)
- No sedation was observed at 1 hour post-dose, with the exception of one treatment visit in one patient where minimal sedation (MOAA/S score 4) was observed, which had resolved by discharge
- There was no evidence of dissociation at discharge (assessed by the CADSS)
- Across 248 treatment visits in the OLE, at 99% of visits, patients were considered to be discharge-ready at 1 hour post-dose on the dosing day (assessed by the CADR)

Conclusions

- The results from the 6-month OLE part of this Phase 2b trial demonstrated that GH001 administered as an IDR in up to five re-treatments was well tolerated in patients with TRD, consistent with findings from early-phase GH001 trials in healthy volunteers and patients with TRD where GH001 was administered as a single dose or as a single IDR[3,4]