Results of a Phase 1 Clinical Trial (GH001-HV-103) to Determine the Safety and Tolerability of Mebufotenin (5-MeO-DMT), Administered via Inhalation (GH001) in Healthy Subjects

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Background

- GH001 is a synthetic form of mebufotenin (5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) developed for pulmonary inhalation
- Mebufotenin acts as a potent agonist on serotonin (5-hydroxytryptamine [5-HT])$_{1A}$ and 5-HT$_{2A}$ receptors, with higher affinity for the 5-HT$_{1A}$ receptor subtype
- A previous Phase 1 open-label trial of GH001, administered as single doses or as an individualized dosing regimen (IDR) demonstrated a favourable safety profile and was well tolerated in healthy volunteers, with an ultra-rapid onset (generally within seconds) and a short duration of psychoactive effects (generally 5–30 minutes)

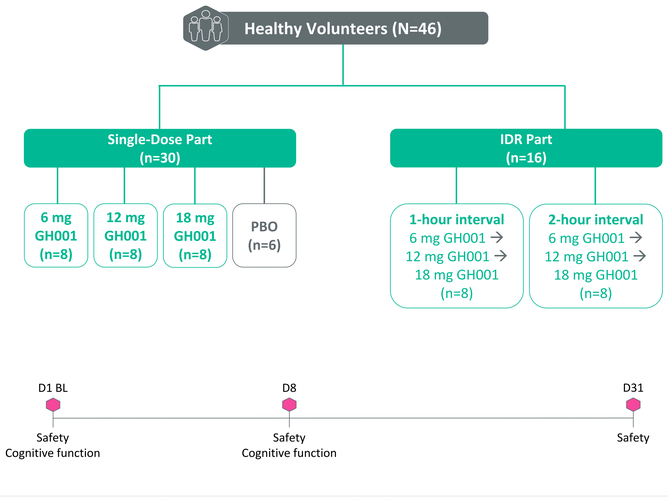
Objective

- To determine the safety and tolerability of a single administration or a single-day IDR of GH001

Methods

- This single-center, Phase 1 trial (NCT05163691) enrolled healthy volunteers aged 18 to <65 years
- The trial consisted of two parts (Figure 1):
  - Part A: single ascending dose, double-blind, placebo-controlled, randomized design in three cohorts (Groups A, B and C)
  - Part B: multiple-dose (IDR), open-label, non-randomized design with scheduled 1-hour (Group D) or two-hour (Group E) intervals between doses
- This trial was conducted under the supervision of qualified healthcare professionals, providing basic psychological support per standard-of-care, but without any planned psychotherapeutic intervention before, during, or after dosing

Figure 1: Trial Schematic (GH001-HV-103)



Abbreviations: BL = Baseline; D = Day; IDR = Individualized dosing regimen; PBO = Placebo.

- Safety and tolerability were assessed up to Day 31 post-dose by incidence of treatment-emergent adverse events (TEAE), electrocardiogram (ECG), vital signs, peak flow respiratory, laboratory assessments, physical examination, and safety assessment tools (Modified Observer's Assessment of Alertness and Sedation [MOAA/S], Columbia-Suicide Severity Rating Scale [C-SSRS], Brief Psychiatric Rating Scale [BPRS], Clinician Administered Dissociative States Scale [CADSS], and Clinical Assessment of Discharge Readiness [CADR])
- Cognitive performance was assessed via verbal memory, psychomotor speed, vigilance and visuospatial working memory

Results

- A total of 46 subjects were enrolled in this trial:
  - Part A: 30 subjects (17 male, 13 female) aged 20–59 were enrolled and completed the trial
  - Part B: A total of 16 subjects (11 male, five female) aged 19–59 were enrolled. All 16 subjects received a 6 mg dose of GH001 as part of the IDR, 15 subjects received a second dose (12 mg), and nine subjects received a third dose (18 mg)
  - One subject discontinued from the study drug after the second dose at their own request

Figure 2: Mean Systolic Blood Pressure (A), Diastolic Blood Pressure (B), and Heart Rate (C) Over Time After Administration Bolus Doses of GH001 or Placebo (Part A)

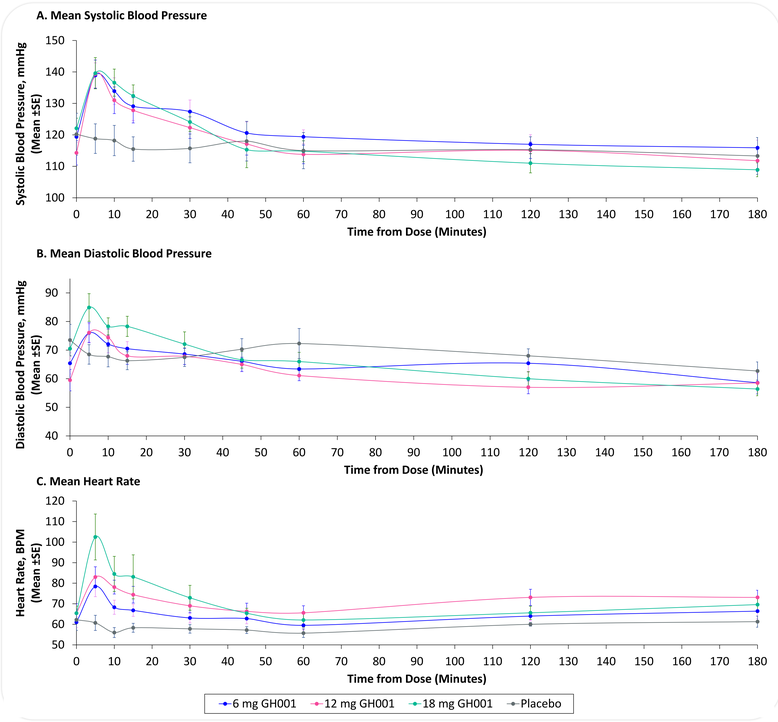


Table 1: Overall Summary of Treatment-Emergent Adverse Events

	Single Dose (Part A)				IDR (Part B)
	6 mg (n=8)	12 mg (n=8)	18 mg (n=8)	Placebo (n=6)	IDR (n=16)
Any TEAE, number of participants (%)					
Headache	3 (37.5)	0	1 (12.5)	0	2 (12.5)
Dizziness	0	0	1 (12.5)	0	0
Dyskinesia	0	0	1 (12.5)	0	0
Somnolence	0	1 (12.5)	0	0	0
Tremor	0	0	1 (12.5)	0	0
Crying	0	0	2 (25.0)	0	2 (12.5)
Catheter site pain	0	1 (12.5)	0	0	0
Chest discomfort	0	1 (12.5)	0	0	0
Fatigue	0	1 (12.5)	0	0	3 (18.8)
Dry mouth	1 (12.5)	0	0	0	0
Hypoesthesia oral	0	1 (12.5)	0	0	0
Retching	0	0	1 (12.5)	0	0
Paraesthesia oral	0	0	0	0	1 (6.3)
Tachycardia	0	0	2 (25.0)	0	0
Tension	0	0	0	0	1 (6.3)
Abnormal dreams	0	0	1 (12.5)	0	1 (6.3)
Irritability	0	1 (12.5)	0	0	0
Oropharyngeal pain	0	0	0	1 (16.7)	0
Nasal congestion	0	0	0	0	2 (12.5)

Abbreviations: IDR = Individualized dosing regimen; TEAE = Treatment-emergent adverse events.

- There were no serious adverse events (SAE) reported in Part A or Part B
- In Part A, there were 20 TEAEs (all mild) reported in 12/24 subjects who received GH001 and one TEAE (mild) in 1/6 subjects who received placebo (Table 1)
  - The most commonly reported TEAEs in the GH001 group (reported by ≥2 subjects) were headache, crying, and tachycardia. The only reported TEAE in the placebo group was oropharyngeal pain.
- In Part B, there were 12 TEAEs (all mild) reported in 9/16 subjects who received GH001 as an IDR (Table 1).
  - The most commonly reported TEAEs (reported by ≥2 subjects) were fatigue, crying, headache, and nasal congestion.
- In Part A and Part B, non-clinically significant, transient increases in blood pressure and heart rate were observed. Results from Part A are shown in Figure 2
- No clinically relevant changes were observed for any cohort in safety laboratory analyses, ECG, alertness and sedation scales, peak flow respiratory or any measures of cognitive function
- All subjects were discharge ready by the end of the dosing day, as assessed by the CADR
- There were no clinically relevant findings related to clinician-rated safety assessments (based on the CADSS, C-SSRS, and BPRS scales)

Conclusions

- Overall, this trial demonstrated that GH001 has an acceptable safety profile and is well tolerated in healthy volunteers at the investigated single-dose levels and with the IDR

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