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Results of a Phase 1 Clinical Trial to Determine the Safety and Tolerability of GH002 (Intravenous Mebufotenin) in Healthy Volunteers

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Background

- Mebufotenin, also known as 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), is a potent psychedelic drug belonging to a group of psychoactive indole-alkylamine drugs
- It acts as a non-selective serotonin (5-hydroxytryptamine [5-HT]) agonist with highest affinity for the 5-HT_{1A} receptor subtype[1]
- Early-phase clinical trials of mebufotenin administered via pulmonary inhalation (GH001) in healthy volunteers demonstrated that GH001 administered as a single dose or as an individualized dosing regimen (IDR) has an acceptable safety profile and is well tolerated, with an ultra-rapid onset (generally within seconds) and a short duration of psychoactive effects[2]
- This trial is the first in which mebufotenin was administered to humans via the intravenous (i.v.) route (GH002), an alternative administration strategy predicted to display the same rapid onset and short duration of psychoactive effects as GH001

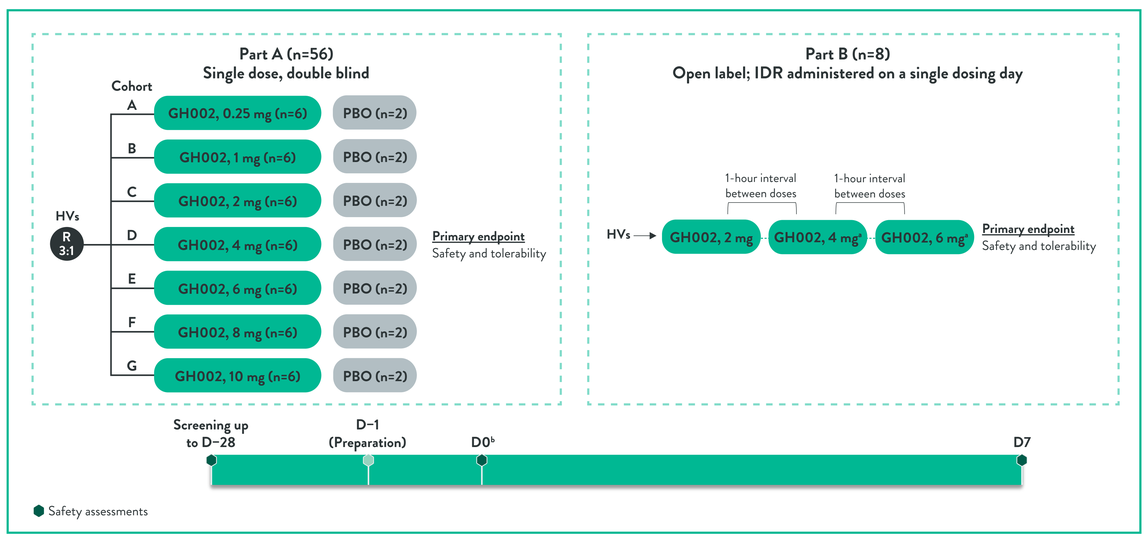
Objective

- To determine the safety and tolerability of a single administration or a single-day IDR of i.v. GH002

Methods

- This single-center, Phase 1 trial (NCT05753956) enrolled healthy volunteers aged 18–45 years who were in good physical and mental health without previously diagnosed psychiatric disorders
- This trial consisted of two parts (Figure 1):
  - Part A: single-dose, double-blind, placebo-controlled, randomized design in which single ascending doses of GH002 in the dose range of 0.25–10 mg or placebo (randomized 3:1) were administered via i.v. bolus injection to seven cohorts (n=8 total per cohort)
  - Part B: multiple-dose, open-label, nonrandomized design in which GH002 was administered via i.v. bolus injection as an IDR consisting of up to three escalating doses (2, 4, and 6 mg) to one cohort of eight healthy volunteers
    - The IDR was administered on a single day with a scheduled 1-hour interval between doses

Figure 1. Clinical Trial Design



[a]In the IDR, criteria for administration of the second and third doses were based on the patient's subjectively reported psychoactive effects, and the safety and tolerability at the previous dose level. [b]Subjects were discharged once all trial assessments were completed and they completed the structured discharge assessment on Day 0.

D = Day; HV = Healthy volunteer; IDR = Individualized dosing regimen; n = Number; PBO = Placebo; R = Randomization.

- Structured psychotherapeutic intervention was not a component of this trial design. Volunteers were under medical supervision from Day −1, until a minimum of 6 hours after (last) dosing on Day 0, with safety follow up to Day 7. Psychological support as per standard of care was available to volunteers for the duration of the trial
- Safety and tolerability were assessed throughout the trial via the following key endpoints: adverse events, electrocardiogram (ECG), vital signs, laboratory assessments, Holter monitoring, sedation as assessed via the Modified Observer's Assessment of Alertness and Sedation (MOAA/S), and symptom scales including the Columbia-Suicide Severity Rating Scale (C-SSRS), Brief Psychiatric Rating Scale (BPRS), and Clinician Administered Dissociative States Scale (CADSS)
- Discharge readiness on the dosing day was assessed by the Clinical Assessment of Discharge Readiness (CADR), and cognition was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB)

Results

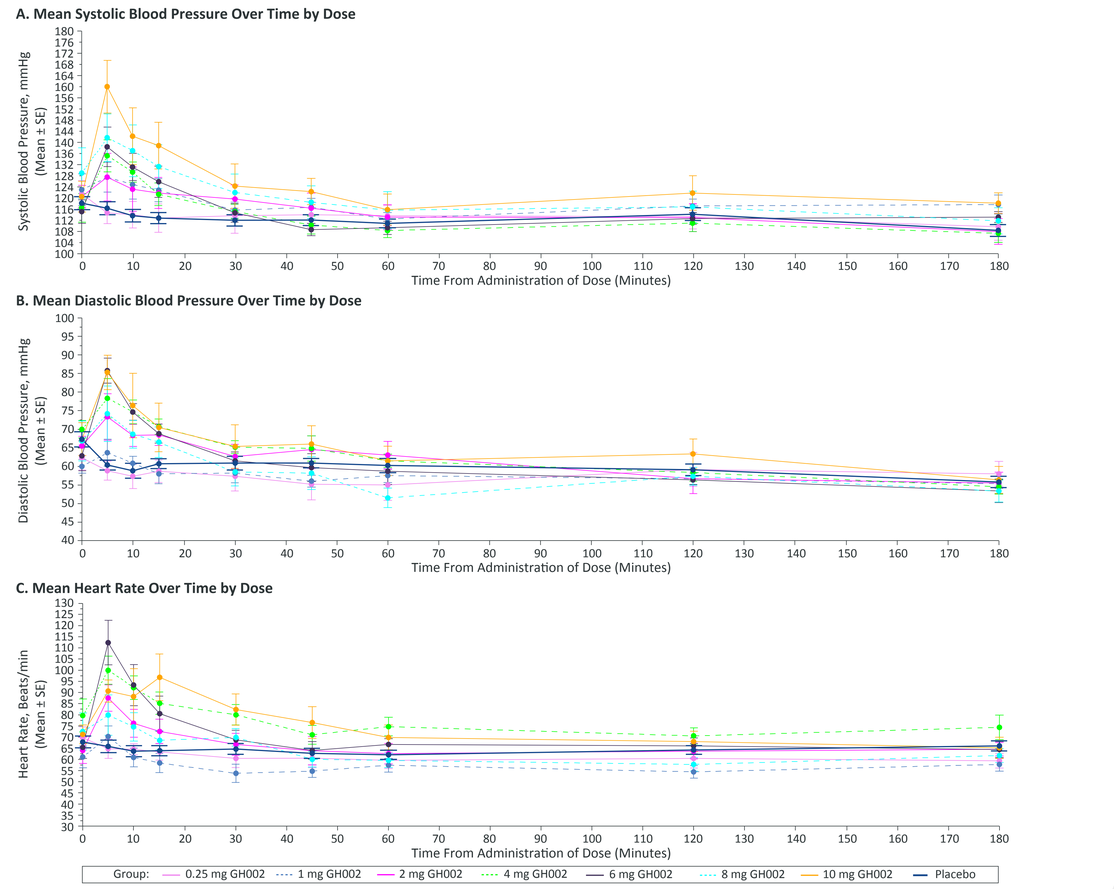
- Overall, 64 healthy volunteers were enrolled, with 56 participants in Part A and eight participants in Part B
  - In Part A, median participant age ranged from 22–28 years across cohorts (range 19–35 years), and about half of participants were male (n=29 [52%])
  - In Part B, median participant age was 27 years (range 22–40 years), and most participants were male (n=7 [88%])
- There were no serious or severe TEAEs reported in either Part A or Part B (Table 1)
- In Part A, TEAEs were observed in 22/42 participants (52%) who received GH002 and in 5/14 participants (36%) who received placebo (Table 1)
  - Most TEAEs observed in participants who received GH002 were mild in severity (98%); only one participant in the 8 mg GH002 cohort reported a TEAE of moderate severity
  - No TEAE led to a change in dose, dose interruption, or study withdrawal
- In Part B, TEAEs were observed in 4/8 participants (50%; Table 1)
  - All TEAEs were mild in severity
  - One participant did not meet dose escalation criteria after the first dose due to a TEAE of dyspnea; the TEAE was mild in severity and considered possibly related to the study drug
- There was no clear relationship between GH002 dose and incidence of TEAEs in either Part A or Part B
- In both trial parts, non-clinically significant increases in blood pressure and heart rate were observed from the first assessed timepoints postdose, with mean values for most parameters returning to baseline by 30 minutes postdose (results from Part A are shown in Figure 2)

Table 1. Overall Summary of Adverse Events (Parts A and B)

Number (%) of Participants	Part A								Part B
	0.25 mg GH002 (n=6)	1 mg GH002 (n=6)	2 mg GH002 (n=6)	4 mg GH002 (n=6)	6 mg GH002 (n=6)	8 mg GH002 (n=6)	10 mg GH002 (n=6)	Placebo (n=14)	GH002 IDR (n=8)
Participants with ≥1 TEAE	2 (33)	2 (33)	4 (67)	5 (83)	3 (50)	3 (50)	3 (50)	5 (36)	4 (50)
Mild	2 (33)	2 (33)	4 (67)	5 (83)	3 (50)	3 (50)	3 (50)	5 (36)	4 (50)
Moderate	0	0	0	0	0	1 (17)	0	0	0
Severe	0	0	0	0	0	0	0	0	0
Participants with ≥1 treatment-related TEAE	1 (17)	1 (17)	4 (67)	4 (67)	2 (33)	3 (50)	3 (50)	1 (7)	4 (50)
Participants with ≥1 TEAE leading to study drug withdrawal	0	0	0	0	0	0	0	0	1 (13)
Most common TEAEs (occurring in ≥2 participants receiving GH002 or placebo in Part A or Part B)									
Fatigue	0	0	2 (33)	1 (17)	1 (17)	1 (17)	1 (17)	0	0
Nausea	1 (17)	1 (17)	0	2 (33)	0	1 (17)	0	0	1 (13)
Dizziness	0	0	2 (33)	1 (17)	0	1 (17)	0	0	0
Abdominal pain	1 (17)	1 (17)	0	1 (17)	0	0	0	0	0
Vomiting	0	1 (17)	0	0	0	1 (17)	1 (17)	0	1 (13)
Emotional distress	0	0	1 (17)	0	0	1 (17)	0	0	0
Head discomfort	0	0	0	1 (17)	0	1 (17)	0	0	1 (13)
Headache	0	0	0	0	2 (33)	0	0	3 (21)	2 (25)
Pain in extremity	0	0	0	0	0	0	2 (33)	0	0
Muscle spasms	0	0	0	0	0	0	2 (33)	0	0
Grunting	0	0	0	0	0	0	2 (33)	0	0
Catheter site-related reaction	0	0	0	0	0	0	0	2 (14)	0

IDR = Individualized dosing regimen; n = Number; TEAE = Treatment-emergent adverse events.

Figure 2. Mean Systolic Blood Pressure (A), Diastolic Blood Pressure (B), and Heart Rate (C) Over Time After Administration of Intravenous Bolus Doses of GH002 or Placebo (Part A)



- No clinically relevant changes were observed for any cohort in safety laboratory analyses, cardiac monitoring (ECG and continuous Holter monitoring), or any measures of cognitive function
- Minimal sedation (as evaluated by the MOAA/S) was observed in one participant just after the psychoactive effects fully subsided; no sedation was observed in any participant by 60 minutes postdose or thereafter
- With the exception of changes associated with TEAEs of emotional distress and poor-quality sleep, there were no clinically relevant findings related to clinician-rated safety assessments (based on the CADSS, CADR, C-SSRS, and BPRS scales)

Conclusions

- Overall, this trial demonstrated that GH002 has an acceptable safety profile and is well tolerated in healthy volunteers at the investigated single-dose levels and with the IDR
- These results warrant further investigation of GH002 in patient populations

References

1. Ermakova AO, et al. *J Psychopharmacol*. 2022;36(3):273-94.
2. Reckweg J, et al. *Front Pharmacol*. 2021;12:760671.

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Statistical analysis was carried out by Marie Watissee, contracted by GH Research.

Author Contributions

All authors provided substantial contributions to study conception and design and/or analysis and interpretation of the data; drafted the poster or revised it critically for important intellectual content; and provided final approval of the version of the poster to be published.

Disclosures

VV, EG-H, and **RK** are employees of GH Research. **THT** is an employee and shareholder of GH Research. **VMcD** is a consultant to GH Research. **PD** is an employee of QPS-Netherlands. **KSA-E** was an employee of QPS-Netherlands during the conduct of this trial and is a current employee of University Medical Center Groningen (UMCG).

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