

Safety and Tolerability 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) is a chronic condition affecting approximately 30% of patients with major depressive disorder¹
- There are currently only two pharmacotherapies approved for the treatment of TRD, highlighting the unmet need for additional safe and effective treatments²
- Early-phase clinical trials of GH001, a synthetic form of mebufotenin for pulmonary inhalation, in healthy volunteers and patients with TRD demonstrated it is well tolerated with an acceptable safety profile^{3,4}
- This trial evaluated the safety and tolerability of GH001 in patients with TRD in a randomized, double-blind, placebo-controlled setting

Objective

- The objective of this analysis is to present safety and tolerability data for GH001 from the double-blind part of a Phase 2b trial in which GH001 was administered as an individualized dosing regimen (IDR) to patients with TRD

References

- Kubitz N, et al. *PLoS One*. 2013;8:e76882. **2.** Jha MK, Mathew SJ. *Am J Psychiatry*. 2023;180:190-9.
- Reckweg J, et al. *Front Pharmacol*. 2021;12:760671. **4.** Reckweg JT, et al. *Front Psychiatry*. 2023;14:1133414.

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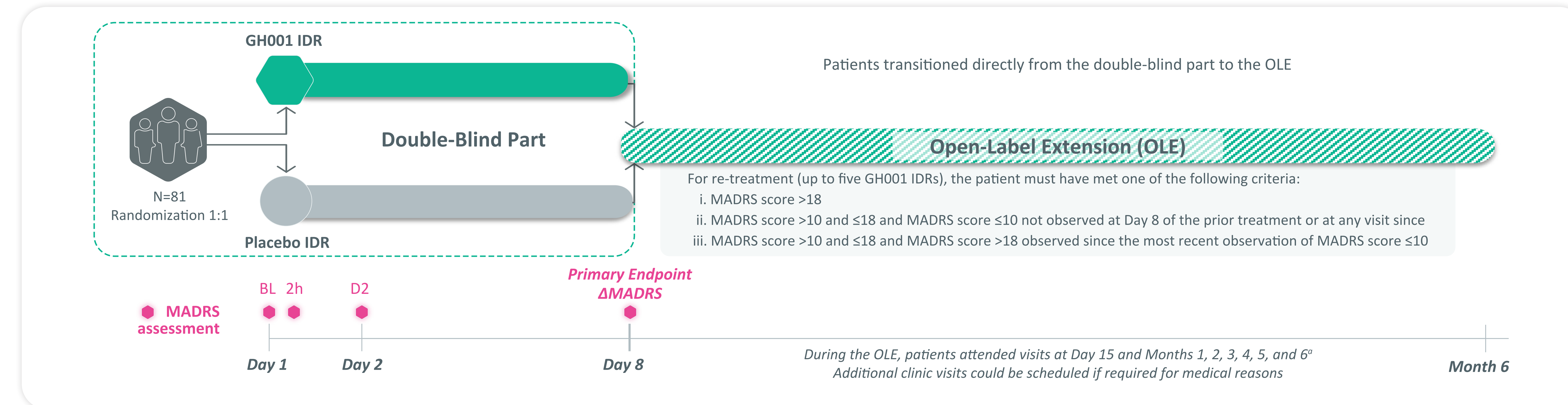
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Methods

- This two-part, Phase 2b trial (NCT05800860) enrolled patients with TRD (Figure 1)
 - The double-blind part (presented here) was a 7-day part in which patients were randomized 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
 - Patients in the 6-month open-label extension received up to five GH001 re-treatments depending on their clinical status (data not presented here)
- This trial was conducted under the supervision of qualified healthcare professionals, providing psychological support per standard of care, but without any planned psychotherapeutic intervention before, during, or after dosing
- Safety assessments (up to Day 8) included treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG), laboratory assessments, 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 Assessment of Alertness and Sedation [MOAA/S] scale, and Clinical Assessment of Discharge Readiness [CADR])

Figure 1. Clinical Trial Schematic



*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 From the Double-Blind Part

- In the double-blind part of this trial, 81 patients with TRD were enrolled; 40 and 41 patients were randomized to receive GH001 or placebo, respectively
 - The mean (SD) age was 42.8 (11.2) years; 56.8% of the patients were female
- There were no serious or severe TEAEs reported (Table 1)
- TEAEs were observed in 29/40 (72.5%) patients who received GH001 and 3/41 (7.3%) patients who received placebo (Table 1)
 - The maximum severity of TEAEs observed in patients who received GH001 was mild in 14/29 patients and moderate in 15/29 patients
 - No TEAE resulted in study drug withdrawal or early withdrawal from the trial in either treatment group in the double-blind part
- No TEAEs of flashbacks were reported

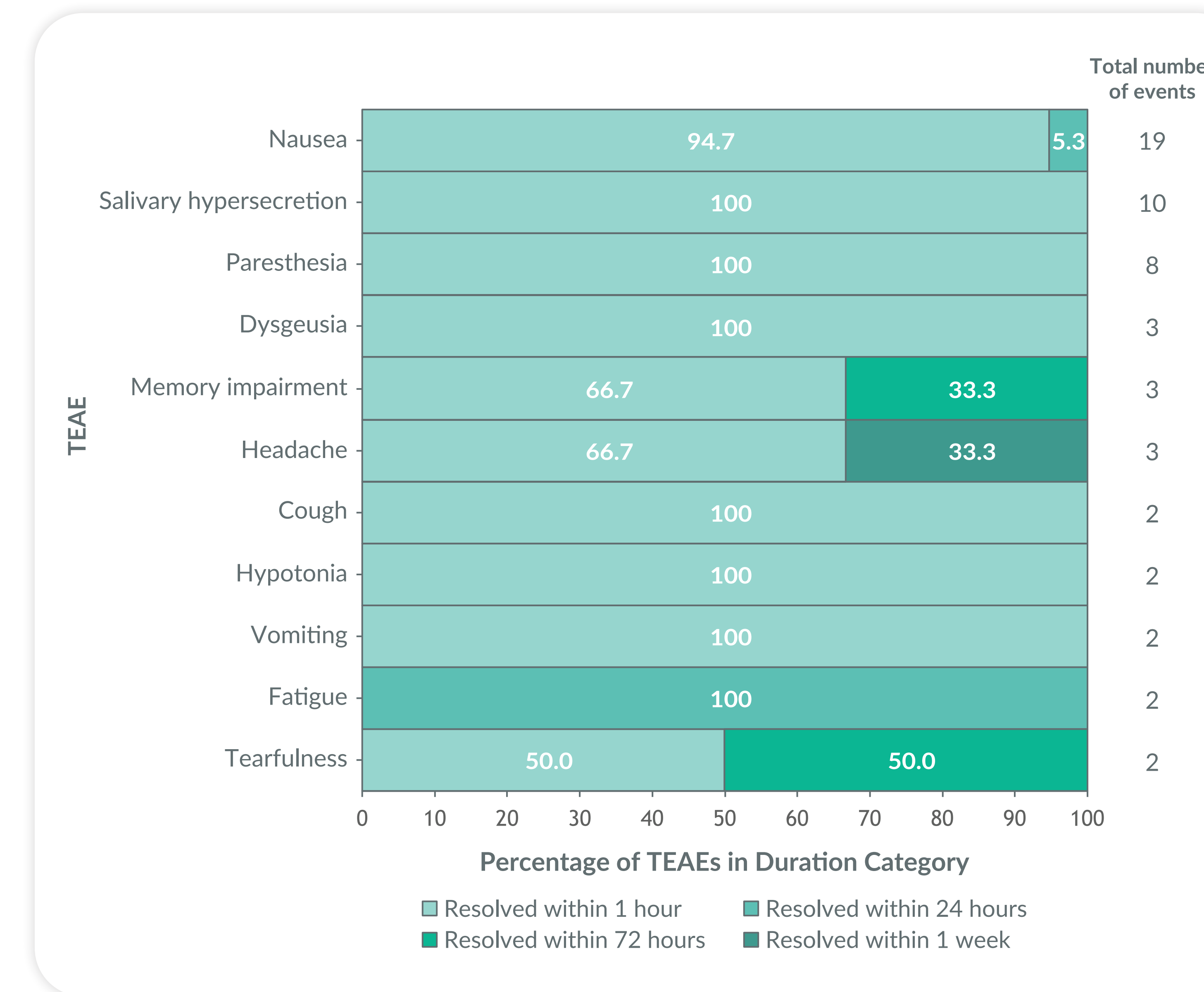
Table 1. Overall Summary of Safety in the Double-Blind Part

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
Treatment-related TEAEs	29 (72.5)	1 (2.4)
Serious TEAE	0	0
AESIs	8 (20.0)	0
Death	0	0
TEAEs occurring in >5% of patients in either group		
Nausea	17 (42.5)	0
Salivary hypersecretion	8 (20.0)	0
Paresthesia	8 (20.0)	0
Headache	3 (7.5)	1 (2.4)
Dysgeusia	3 (7.5)	0

AESI = Adverse event of special interest; TEAE = Treatment-emergent adverse event.

- Of the 81 total TEAEs in the double-blind part, 80.2% of events resolved within 1 hour, 8.6% resolved within 24 hours, 7.4% resolved within 72 hours, and 1.2% resolved within 1 week
 - Of the TEAEs reported at least twice in patients receiving GH001, most resolved within 1 hour of dosing (Figure 2)

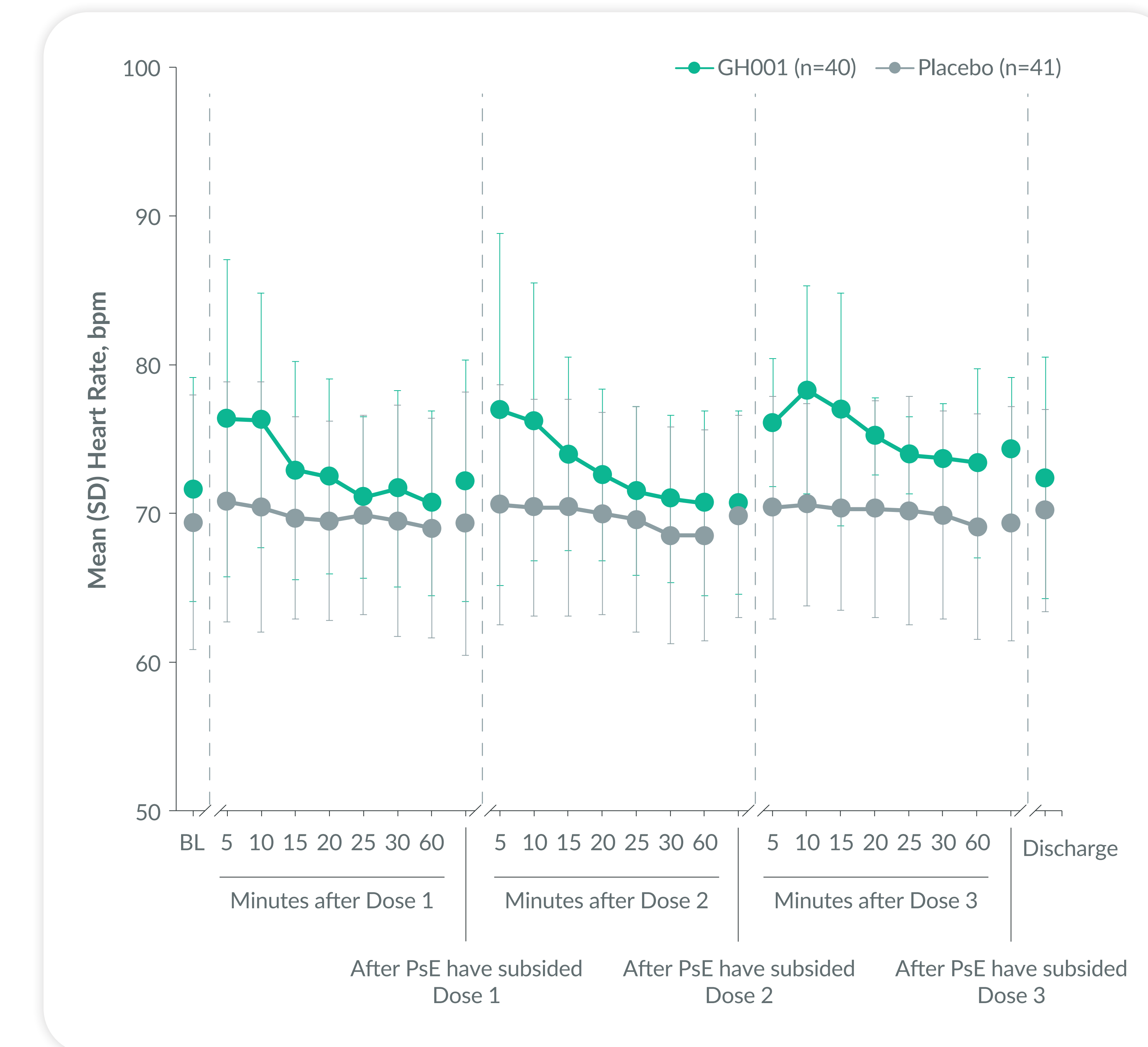
Figure 2. Duration of TEAEs Reported at Least Twice After GH001 Administration in the Double-Blind Part



TEAE = Treatment-emergent adverse event.

- There were no TEAEs related to vital signs or ECG results and no clinically significant changes in blood pressure or heart rate (Figure 3)
- There was no evidence of treatment-emergent worsening of suicidal ideation or behavior (assessed by the C-SSRS), psychotic symptoms (assessed by the BPRS+), or dissociation at discharge (assessed by the CADSS)
- By 1 hour postdose, no sedation was observed (assessed by the MOAA/S scale), and 97.4% of patients were discharge-ready (1 patient was not considered discharge-ready following dosing, but after reassessment later the same day, the patient was determined to be discharge-ready)

Figure 3. Mean Heart Rate After Administration of GH001 or Placebo in the Double-Blind Part



BL = Baseline; bpm = Beats per minute; PsE = Psychoactive effects; SD, standard deviation.

Conclusion

- The results of this analysis of the double-blind part of this Phase 2b trial demonstrated that GH001 administered as an IDR was well tolerated in patients with TRD up to 7 days postdose