

Understanding and Assessing the Psychedelic Experience From a Phase 1/2a Study of the Deuterated Psilocin Analog HLP003 in Adults With Major Depressive Disorder

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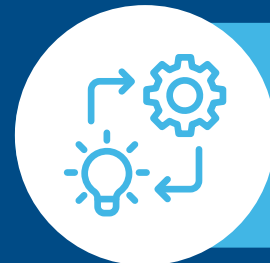
OBJECTIVE

This analysis from a phase 1/2a trial evaluated the pharmacodynamic effects of one or two administrations of 16 mg HLP003 by measuring subjective psychedelic effects using validated ratings scales

CONCLUSIONS



Participants administered 16 mg HLP003 reported subjective psychedelic effects on all scales, while effects with placebo were minimal



The observed effects confirm the pharmacodynamic profile of HLP003, increasing our understanding of the clinical experience



Future studies will evaluate correlations between the subjective psychedelic and antidepressant effects of HLP003

References

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Disclosures

All authors are employees of Helus Pharma and may hold Helus Pharma stock.

INTRODUCTION

- Psychedelics, including psilocybin, induce a transient altered state of consciousness characterized by changes in sensory perception, cognition, emotion, and existential thought^{1,2}

- These subjective perceptual effects, particularly “mystical experiences,” are thought to be contributing factors to the antidepressant effects observed with psilocybin and other psychedelics^{3,4}

- HLP003 is a deuterated psilocin analog that acts as a serotonergic agonist with binding and functional activity on multiple 5-hydroxytryptamine (5-HT)_{2A}^{5,6}

- A phase 1/2a, randomized, double-blind, placebo-controlled trial (NCT05385783) demonstrated that HLP003 was well tolerated and effective in participants with major depressive disorder (MDD) and healthy volunteers⁵

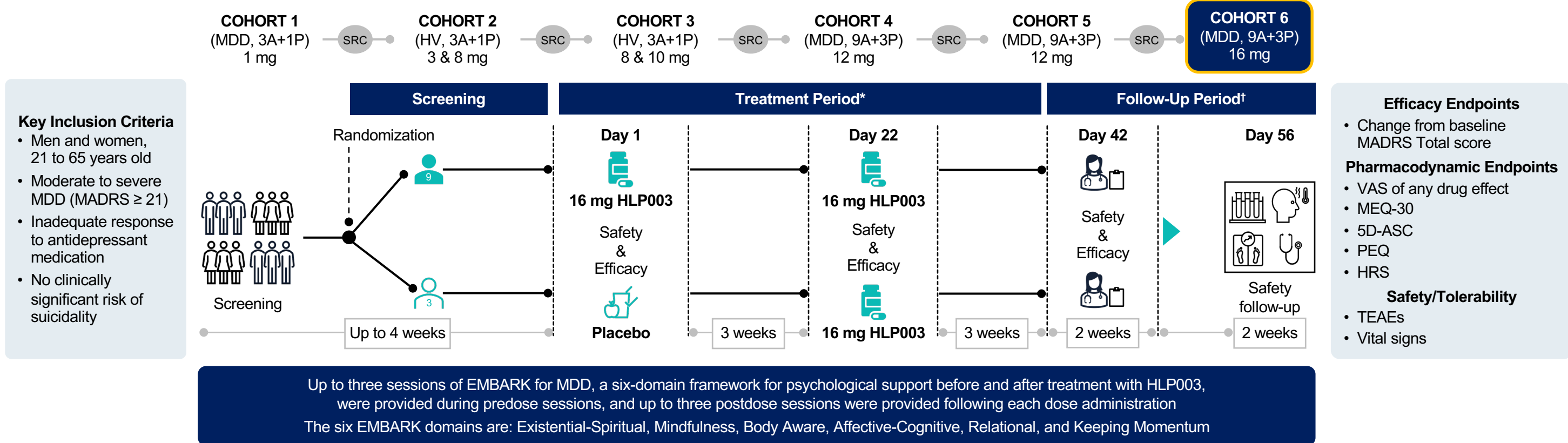
- A single administration of 16 mg HLP003 as an adjunctive treatment produced a –12.99 (95% confidence interval [CI, –22.3, –3.7]; $P < 0.0080$) improvement versus placebo in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Day 21⁶

METHODS

Study Design

- The cohort included in these analyses (Cohort 6) was a subset of participants with MDD enrolled in a phase 1/2a trial randomized to receive 16 mg HLP003 on Days 1 and 22 (n=9) or placebo on Day 1 followed by 16 mg HLP003 on Day 22 (n=3)
 - All participants received psychological support based on the EMBARK framework⁵
 - Efficacy and safety assessments were conducted from Days 1 to 21 (16 mg HLP003 or placebo administration) and Days 22 to 42 (first or second 16 mg HLP003 administration), non-administration Day 56 and during the 12-week follow up period

Figure 1. Phase 1/2a Trial Evaluating Safety, Tolerability, Pharmacokinetics, Psychedelic Effects, and Treatment Efficacy of Ascending Doses of HLP003



*Primary efficacy assessed at Day 21. †Follow-up 12 weeks after Day 42 to assess durability of effects. 5D-ASC, 5-Dimensional Altered States of Consciousness Rating Scale; A, active HLP003; HV, healthy volunteers; HRS, Hallucinogen Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MEQ-30, Revised Mystical Experience Questionnaire; P, placebo; PEQ, Persisting Effects Questionnaire; SRC, Safety Review Committee; TEAE, treatment-emergent adverse event.

RESULTS

Table 1. Demographics and Baseline Clinical Characteristics Were Similar Across Both Treatment Groups

Characteristic	16 mg HLP003/ 16 mg HLP003* (n=9)	Placebo/ 16 mg HLP003† (n=3)
Age, median (range), y	34.0 (25–53)	39.0 (26–49)
Sex, n (%)		
Male	6 (66.7)	1 (33.3)
Female	3 (33.3)	2 (66.7)
Race, n (%)		
White	4 (44.5)	2 (66.7)
Black or African American	5 (55.6)	1 (33.3)
Hispanic/Latino, n (%)	0	1 (33.3)
MADRS total score, mean (SD)	31.4 (4.0)	28.0 (4.6)

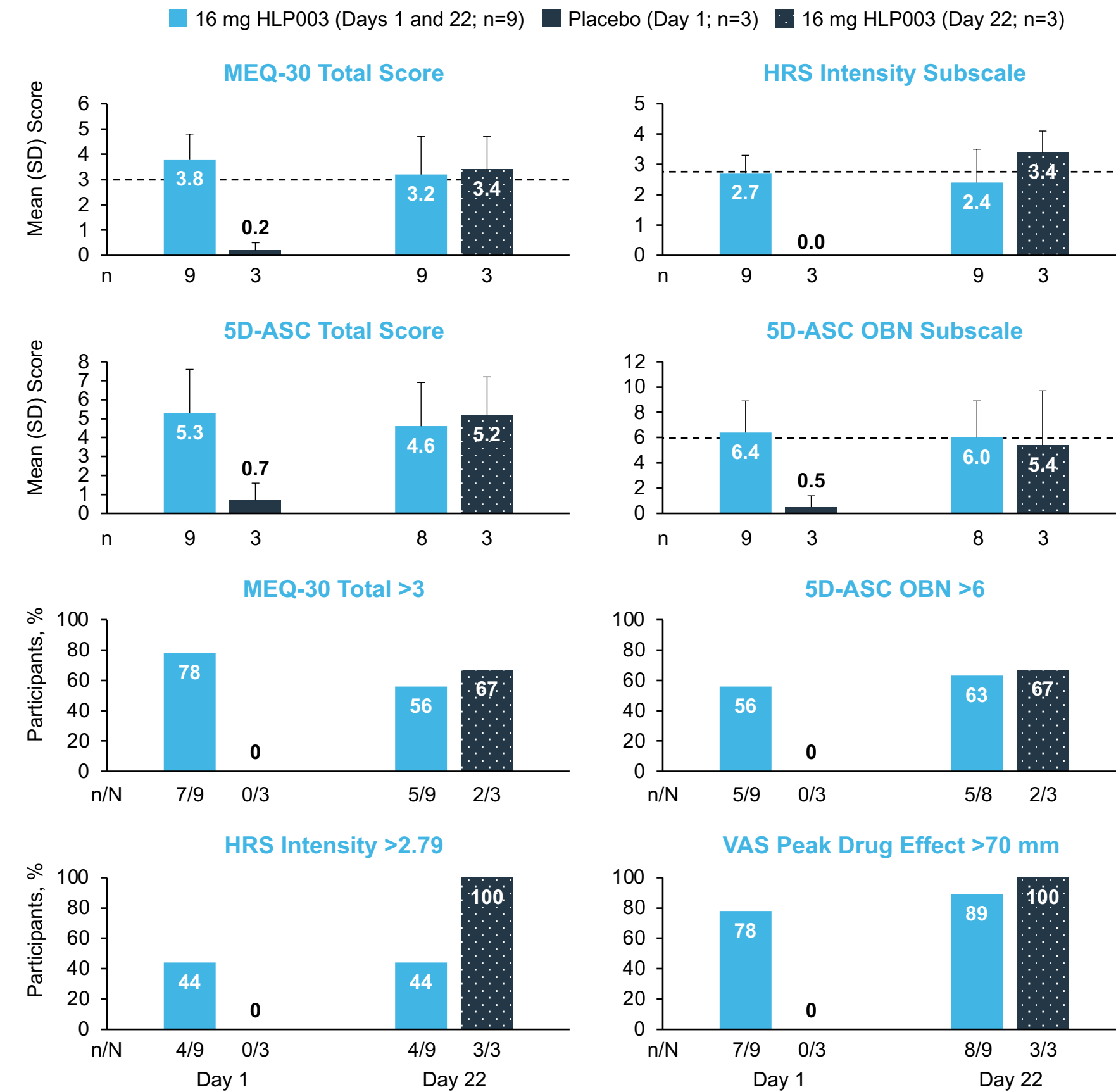
*Administration of 16 mg HLP003 on Days 1 and 22.

†Administration of placebo on Day 1 and 16 mg HLP003 on Day 22. MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation.

Psychedelic Effects

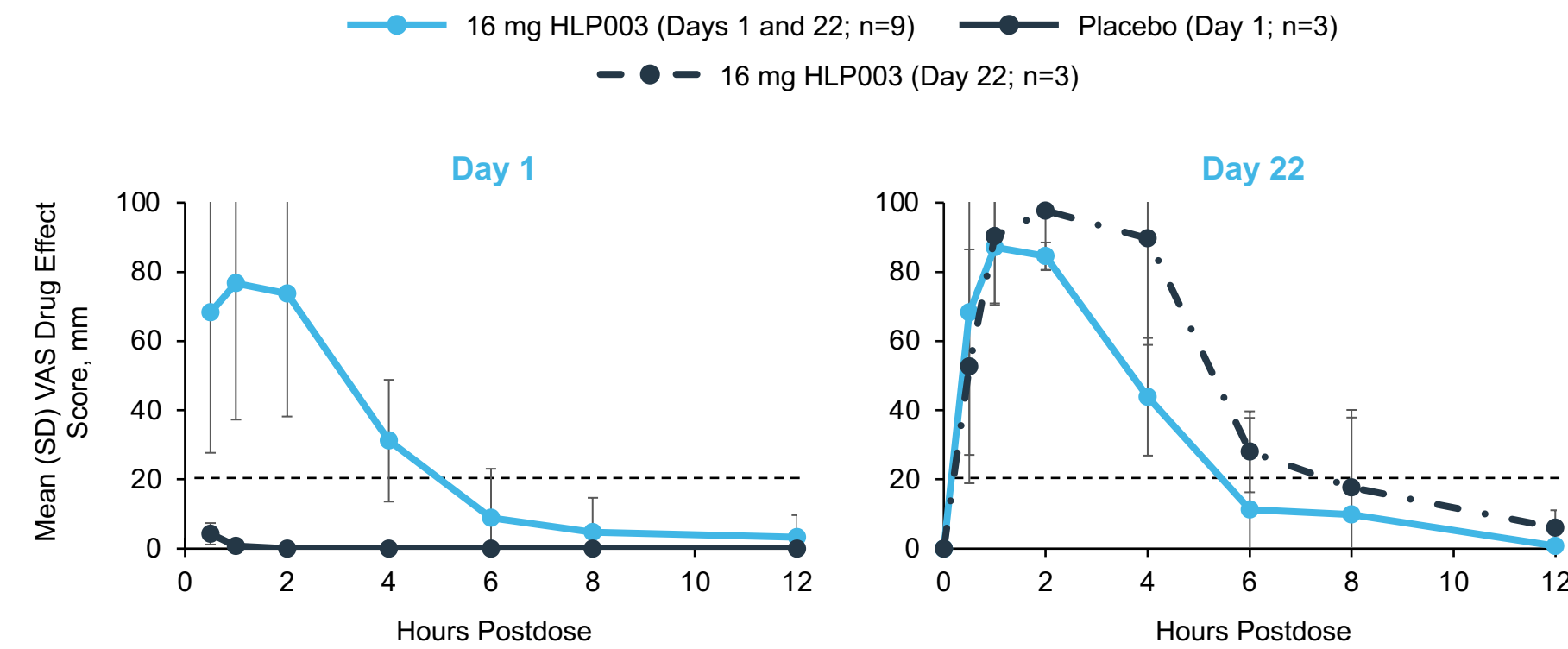
- Mean total and subscale scores for 5D-ASC, HRS, MEQ-30, PEQ, and VAS peak drug effect were higher among participants receiving 16 mg HLP003 versus placebo on Day 1; when all participants were given 16 mg HLP003 on Day 22, mean scores were generally comparable (**Figure 2, Supplementary Table S1**)

Figure 2. Participants Receiving 16 mg HLP003 Reported Subjective Psychedelic Effects on Administration Days 1 and 22



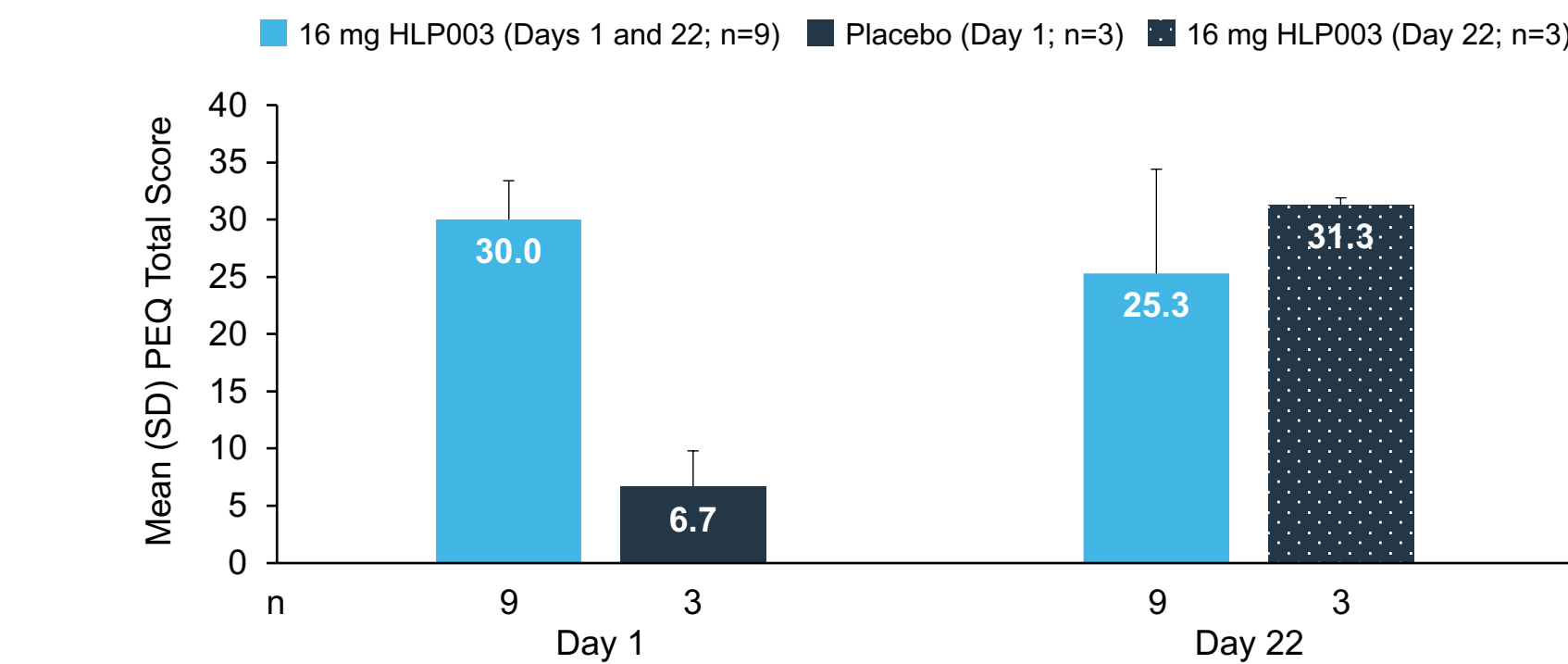
Dotted lines indicate effect thresholds of 3 (MEQ-30), 2.79 (HRS Intensity Subscale), and 6 (5D-ASC OBN Subscale). 5D-ASC, 5-Dimensional Altered States of Consciousness Rating Scale; HRS, Hallucinogen Rating Scale; MEQ-30, Revised Mystical Experience Questionnaire; OBN, oceanic boundlessness subscale; VAS, visual analog scale.

Figure 3. Change From Baseline in Mean (SD) VAS Drug Effect Scores After Administration of 16 mg HLP003



Dotted lines indicates effect threshold of 20 mm. SD, standard deviation; VAS, visual analog scale.

Figure 4. Mean (SD) PEQ Scores After Administration of 16 mg HLP003 on Days 1 and 22



PEQ, Persisting Effects Questionnaire; SD, standard deviation.

Endpoints

- The 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC), Hallucinogen Rating Scale (HRS), Revised Mystical Experience Questionnaire (MEQ-30), and Persisting Effects Questionnaire (PEQ) were assessed 4 to 10 hours postdose on Days 1 and 22 (**Table 1**)
 - All participants received psychological support based on the EMBARK framework⁵
 - The visual analog scale (VAS) rating of “any drug effect” was assessed predose and at regular intervals 0.5 to 12 hours postdose
- Descriptive data are summarized by means, standard deviations, and rate of effect thresholds by visit
- Safety and tolerability were assessed

Table 1. Subjective Psychedelic Effects Were Assessed Using Five Scales After Each Dose

Subjective Effects Scale	Description	Effect Thresholds
5D-ASC ⁷	94-item questionnaire organized into 5 dimensions: oceanic boundlessness, visionary restructuring, vigilance reduction, dread of ego dissolution, auditory alterations	Oceanic boundlessness subscale: >6
HRS ⁸	100-item questionnaire assessing subjective effects of hallucinogenic substances in 6 clinical clusters: somesthesia, affect, perception, cognition, volition, and intensity	Intensity subscale: >2.79
MEQ-30 ⁹	30-item questionnaire divided into domains of mystical, positive mood, transcendence of time and space, and ineffability	Total score: >3
PEQ ¹⁰	5-item questionnaire that assesses the meaningfulness, spiritual significance, psychological insightfulness, and how psychologically challenging was the experience during the study drug administration session	N/A
VAS for any drug effect	A 100-mm line from 0 mm (no drug effect) to 100 mm (extremely felt)	Peak drug effect: >70 mm

5D-ASC, 5-Dimensional Altered States of Consciousness Rating Scale; HRS, Hallucinogen Rating Scale; MEQ-30, Revised Mystical Experience Questionnaire; PEQ, Persisting Effects Questionnaire; VAS, visual analog scale.

Safety

- HLP003 was well tolerated; all adverse events were mild to moderate in severity and generally limited to the day of treatment (**Table 2**)⁶
 - See **Poster #122** for the results of an expanded safety analysis of this cohort

Table 2. Treatment-Related TEAEs Observed With HLP003 or Placebo⁶

TEAE, n (%)	HLP003* (all cohorts; n=35)	Placebo† (all cohorts; n=13)
≥1 TEAE	21 (60.0)	8 (61.5)
Nausea	6 (17.1)	3 (23.1)
Blood pressure increased	5 (14.3)	3 (23.1)
Headache	3 (8.6)	0
Vomiting	2 (5.7)	1 (7.7)
Eructation	1 (2.9)	0
Dizziness	1 (2.9)	0
Affect lability	1 (2.9)	0
Anxiety	2 (5.7)	1 (7.7)
Panic Attack	1 (2.9)	0
Confusional State	1 (2.9)	0
Nasal Congestion	1 (2.9)	0
Tachycardia	1 (2.9)	0

*Administration of HLP003 on Days 1 and 8 for healthy volunteers and Days 1 and 22 for participants with MDD.

†Administration of placebo on Day 1, HLP003 on Day 8 for healthy volunteers, and HLP003 on Day 22 for participants with MDD. MDD, major depressive disorder; TEAE, treatment-emergent adverse event.

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SUPPLEMENTAL RESULTS

Supplementary Table S1. Mean (Range) Psychedelic Scale Scores After Administration of 16 mg HLP003 or Placebo on Days 1 and 22

Psychedelic Scale Scores, Mean (Range)	16 mg HLP003/16 mg HLP003* (n=9)		Placebo/16 mg HLP003† (n=3)	
	Day 1	Day 22	Day 1	Day 22
5D-ASC: Total score	5.3 (1.9–8.3)	4.6 (0.2–6.8)	0.7 (0.0–1.7)	5.2 (3.3–7.3)
5D-ASC: Oceanic boundlessness	6.4 (3.0–10.0)	6.0 (0.0–9.4)	0.5 (0.0–1.6)	5.4 (0.6–8.9)
HRS: Intensity	2.7 (1.8–3.5)	2.4 (1.0–3.8)	0.0 (0.0–0.0)	3.4 (3.0–4.2)
HRS: Somaesthesia	2.2 (0.6–3.1)	2.2 (0.0–3.6)	0.1 (0.0–0.4)	2.4 (2.0–3.0)
HRS: Affect	2.4 (1.2–3.4)	2.2 (0.8–3.2)	0.6 (0.6–0.6)	1.8 (0.8–2.7)
HRS: Perception	2.1 (0.6–3.1)	1.8 (0.4–2.9)	0.4 (0.2–0.5)	2.7 (1.8–3.4)
HRS: Cognition	2.5 (0.7–3.9)	2.3 (0.0–3.6)	0.1 (0.0–0.3)	2.6 (2.2–3.4)
HRS: Volition	1.7 (0.7–3.5)	2.2 (1.0–3.3)	1.8 (1.3–2.0)	1.9 (1.5–2.3)
MEQ-30: Total score	3.8 (2.4–4.9)	3.2 (0.5–5.0)	0.2 (0.0–0.5)	3.4 (2.1–4.7)
MEQ-30: Mystical	3.8 (2.3–4.9)	3.1 (0.0–5.0)	0.1 (0.0–0.3)	3.0 (0.9–4.7)
MEQ-30: Positive mood	3.9 (1.8–5.0)	3.3 (2.0–5.0)	0.5 (0.2–1.0)	3.3 (1.7–4.8)
MEQ-30: Transcendence of time/space	3.7 (0.7–5.0)	3.1 (0.0–5.0)	0.2 (0.0–0.7)	4.3 (3.8–4.7)
MEQ-30: Ineffability	4.4 (3.7–5.0)	3.5 (1.0–5.0)	0.1 (0.0–0.3)	4.2 (3.3–5.0)
PEQ: Total score	30.0 (26–36)	25.3 (6–36)	6.7 (4–10)	31.3 (31–32)
VAS: Peak drug effect (mm)	84.7 (37–100)	93.6 (69–100)	4.3 (1–7)	97.7 (93–100)

*Administration of 16 mg HLP003 on Days 1 and 22.
†Administration of placebo on Day 1 and 16 mg HLP003 on Day 22.
5D-ASC, 5-Dimensional Altered States of Consciousness Rating Scale; HRS, Hallucinogen Rating Scale; MEQ-30, Revised Mystical Experience Questionnaire; PEQ, Persisting Effects Questionnaire; VAS, visual analog scale.