

Effects of HLP003 on MADRS Individual Items and Anhedonia Subscale in Adults With Major Depressive Disorder: Post Hoc Analysis of a Phase 1/2a Study

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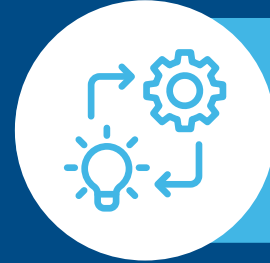
OBJECTIVE

A post hoc analysis of individual MADRS items and the anhedonia subscale score on Days 1, 21, 22, and 42 and during the 12-week follow-up period from this phase 1/2a trial was conducted to further characterize the antidepressant effects of one or two administrations of 16 mg HLP003 in participants with MDD

CONCLUSIONS



In participants with MDD, one administration of 16 mg HLP003 on Day 1 produced rapid, sustained improvements in individual MADRS item and anhedonia subscale scores through Day 21



Following a second administration of 16 mg HLP003, further improvements were observed that lasted through 12 weeks in the follow-up period



These findings support the dosing strategy in the ongoing HLP003 phase 3 studies

References

1. Serretti A. *Clin Psychopharmacol Neurosci*. 2023;21(3):401-409. 2. Cao B, et al. *Front Psychiatry*. 2019;10:17. 3. Varty G, et al. CYB003: A Novel, Orally Active Analog of Psilocybin for the Potential Treatment of Major Depressive Disorder. Presented at: Society for Neuroscience 2022; November 11–14, 2022; San Diego, CA, USA. 4. Krempien S, et al. Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of CYB003, a Deuterated Psilocybin Analog in Patients With Major Depressive Disorder. Presented at: American College of Neuropsychopharmacology Annual Meeting; December 3–6, 2023; Tampa, FL, USA. 5. Brennan W, et al. *Front Psychol*. 2025;16:1637887.

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Disclosures

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

INTRODUCTION

- Anhedonia, an inability to experience pleasure, is a core depressive symptom associated with greater disease severity¹
 - Components of anhedonia, as measured by a subscale score of the Montgomery-Åsberg Depression Rating Scale (MADRS), include apparent and reported sadness, concentration difficulties, lassitude, and inability to feel²
- HLP003 is a deuterated psilocin analog that acts as a serotonergic agonist with binding and functional activity on multiple 5-hydroxytryptamine (5-HT) receptors, including 5-HT_{2A}³
 - 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 volunteers⁴
 - A single dose 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 MADRS total score at Day 21⁴

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 on administration), on non-administration Day 56, and during the 12-week follow up period

Endpoints

- MADRS individual items were assessed at baseline (Day –1), after dose 1 (Days 1, 10, 17, and 21), and after dose 2 (Days 22, 31, 38, and 42)
 - Primary assessment points are Days 21 and 42
 - Durability of effects was assessed at 4, 8, and 12 weeks following the second administration of 16 mg HLP003
- The MADRS anhedonia subscale score consists of items 1, 2, 6, 7, and 8 and were assessed at the same points as the individual items
- Descriptive data are summarized as means, standard deviations (SDs), and mean changes from baseline by visit
- Safety and tolerability were assessed at all visits

RESULTS

Table 1. Demographics and Baseline Clinical Characteristics Were Similar for Participants in 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)
1. Reported sadness	4.0 (0.7)	3.3 (0.6)
2. Apparent sadness	3.7 (1.0)	3.0 (0.0)
3. Inner tension	2.9 (0.9)	2.7 (0.6)
4. Reduced sleep	3.4 (1.3)	3.7 (1.5)
5. Reduced appetite	2.9 (1.4)	2.3 (1.5)
6. Concentration difficulties	3.8 (0.7)	4.0 (0.0)
7. Lassitude	4.3 (0.7)	3.7 (0.6)
8. Inability to feel	3.4 (1.1)	3.3 (1.2)
9. Pessimistic thoughts	2.8 (1.3)	2.0 (1.0)
10. Suicidal thoughts	0.2 (0.7)	0.0 (0.0)
Anhedonia subscale score, mean (SD)	19.2 (2.8)	17.3 (2.1)

*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.

Double-Blind Treatment Period

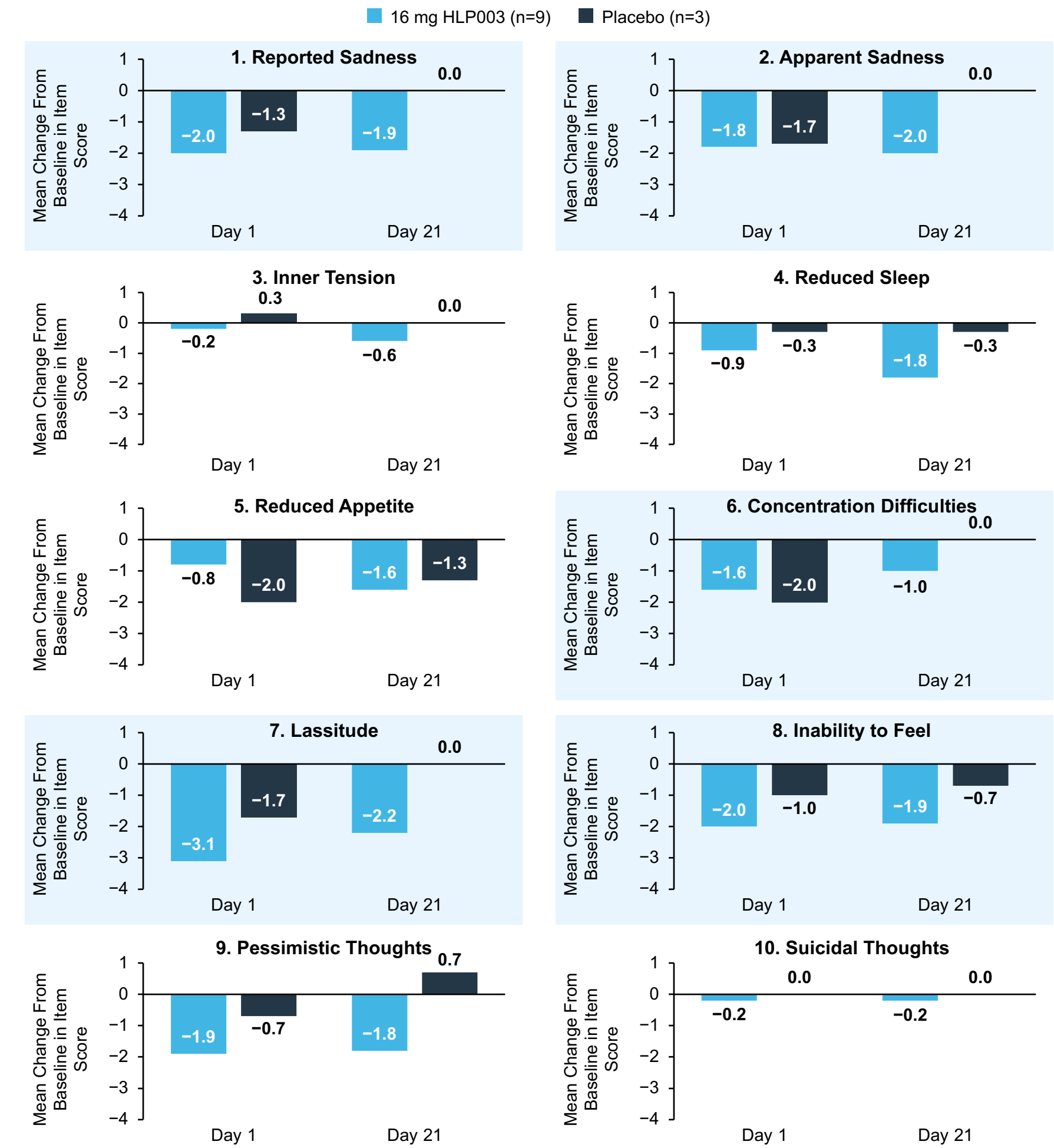
Individual MADRS Items

- Administration of a single dose of 16 mg HLP003 resulted in rapid improvement from baseline in individual MADRS items at Day 1 with reductions across all items lasting to Day 21 (**Figure 2; Supplementary Figure S1**)

Anhedonia Subscale

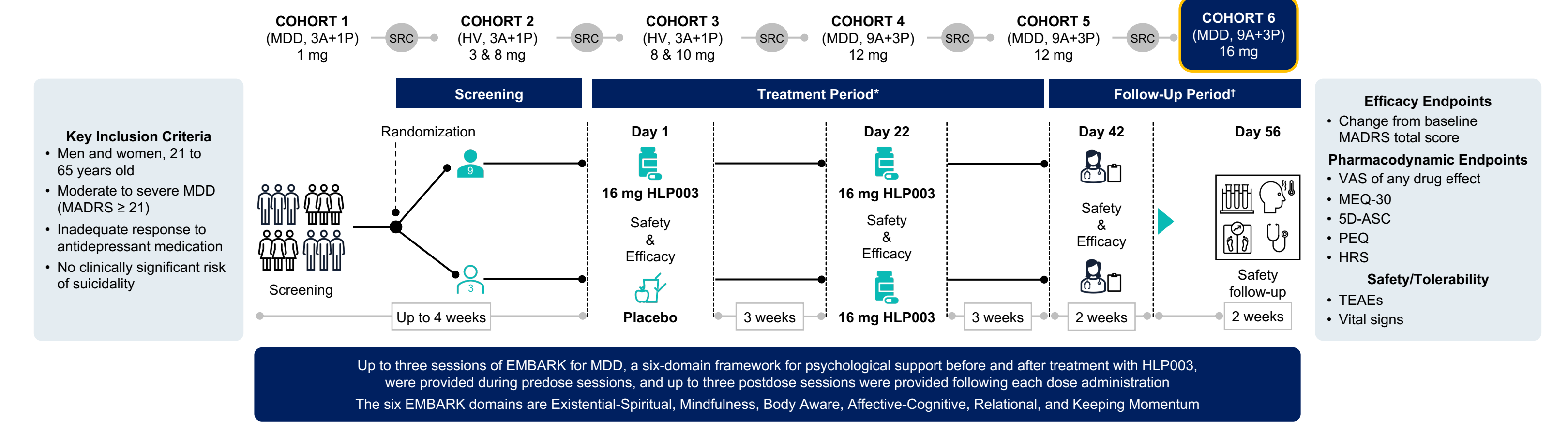
- Anhedonia subscale score decreased beginning on Day 1 following administration of HLP003 16 mg and continued to Day 21 (**Figure 3**)

Figure 2. A Single Administration of 16 mg HLP003 on Day 1 Improved MADRS Individual Item Scores With Sustained Improvement on Day 21



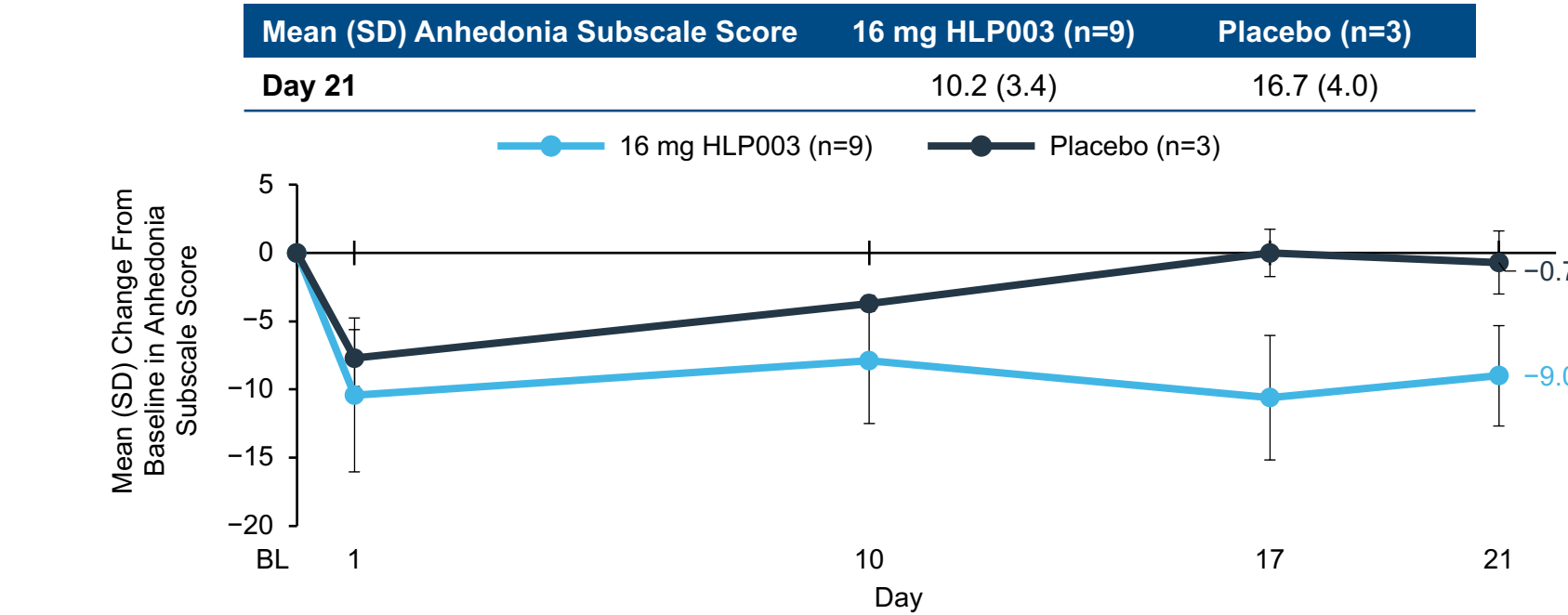
Panels with a blue background comprise the anhedonia subscale score.
MADRS, Montgomery-Åsberg Depression Rating Scale.

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; VAS, visual analog scale.

Figure 3. Improvements in Anhedonia Subscale Score Were Rapid and Sustained Through Day 21 With a Single Administration of 16 mg HLP003

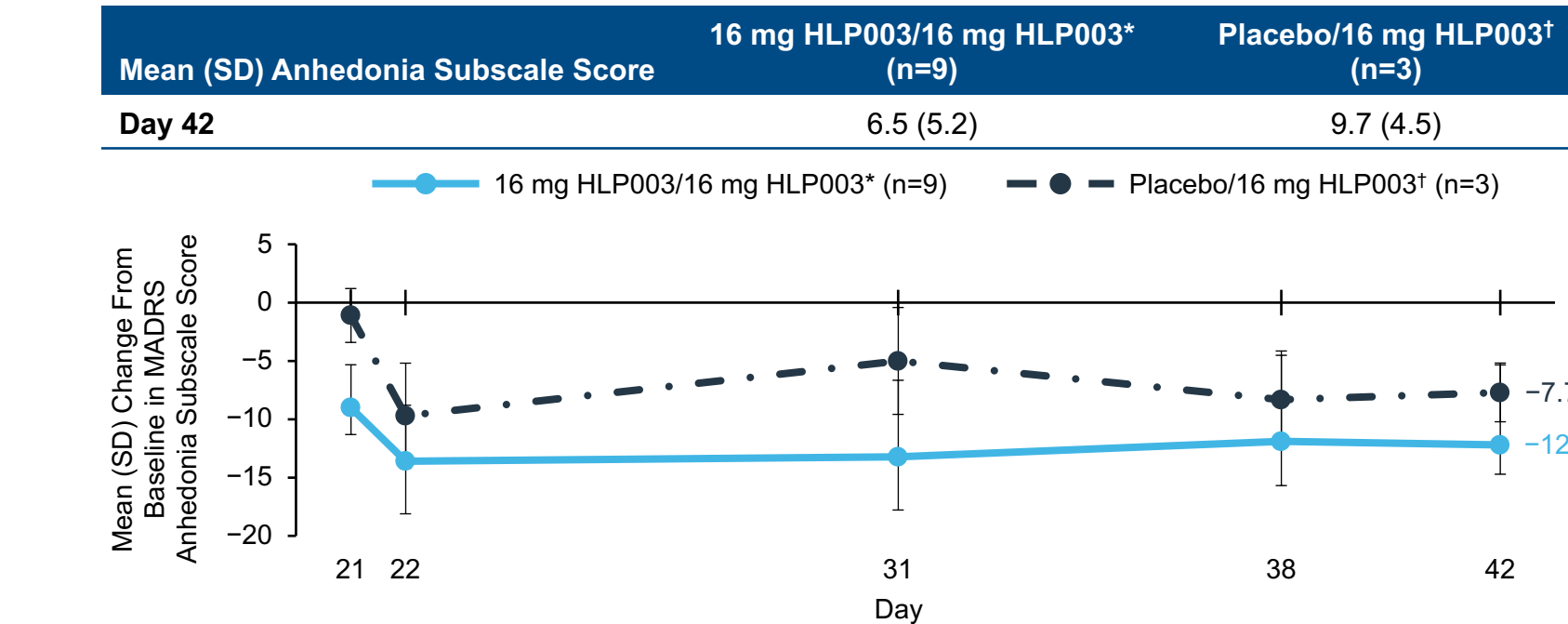


BL, baseline; SD, standard deviation.

Open-Label and Follow-Up Periods

- A second administration of 16 mg HLP003 at Day 22 led to further reductions in MADRS total score, MADRS individual scores for items 1, 2, 6, and 7, and anhedonia subscale score at Day 42; participants receiving a first dose at Day 22 also experienced improvements (**Figure 4; Supplementary Figures S2–S3**)
- Improvements were sustained through follow-up Week 12 in participants who received two administrations of 16 mg HLP003, while improvements for participants who received only one administration were less pronounced (**Supplementary Table S1**)

Figure 4. Improvements in Mean (SD) Anhedonia Subscale Score Were Rapid and Sustained Through Day 42 With the First or Second Administration of 16 mg HLP003 on Day 22



*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.

Safety

- HLP003 was well tolerated; all adverse events were mild to moderate in severity and generally limited to the day of treatment (**Table 2**)⁴
 - See **Poster #122** for the results of an expanded safety analysis of this cohort

Table 2. Treatment-Related TEAEs Observed With HLP003 or Placebo⁴

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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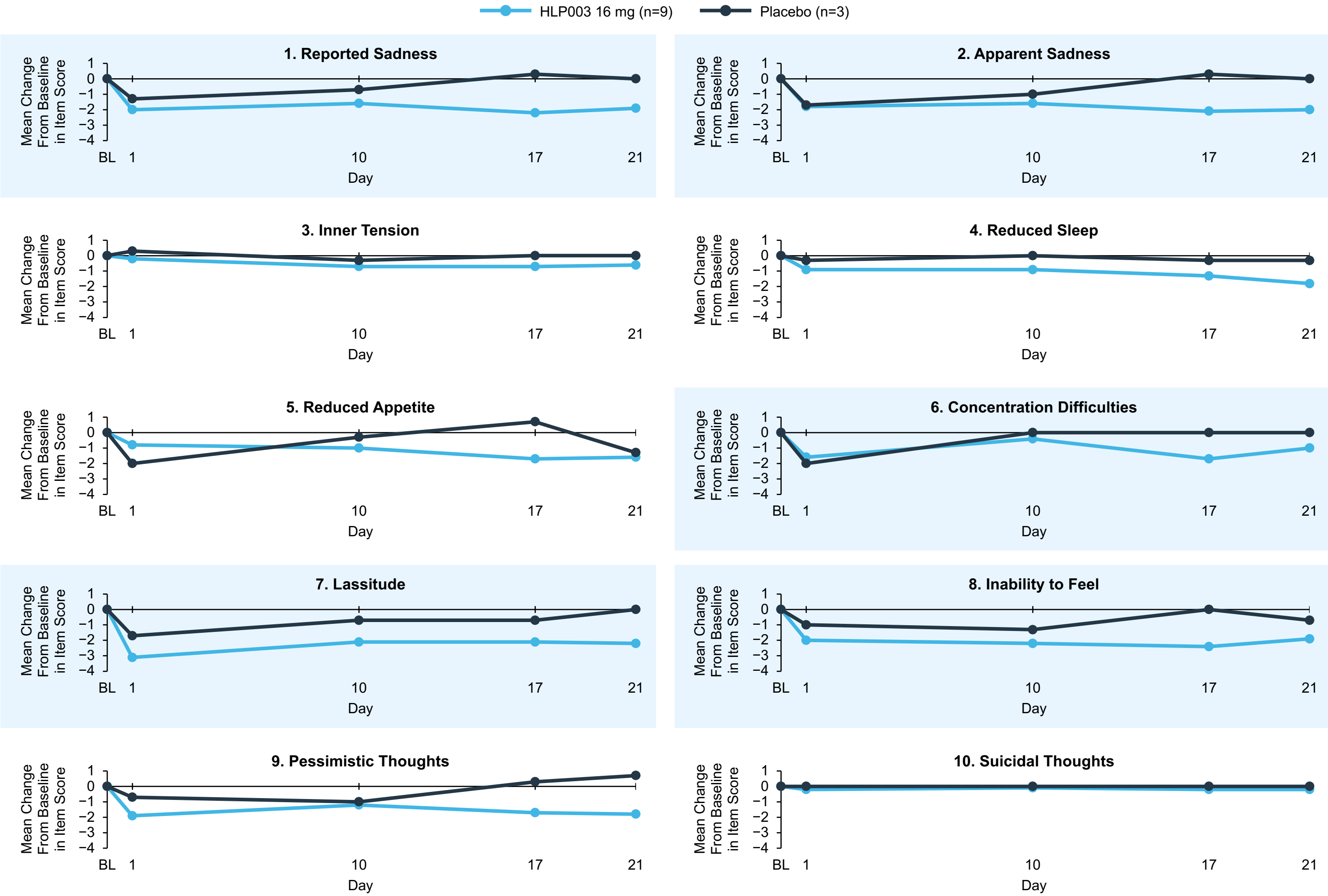
SUPPLEMENTAL RESULTS

Supplementary Table S1. Mean (SD) Change From Baseline in MADRS Total, Individual Item, and Anhedonia Subscale Scores Were Sustained at Follow-Up Week 12 After Two Administrations of HLP003 16 mg

Mean (SD) Change From Baseline in MADRS Score at Follow-Up Week 12	16 mg HLP003/16 mg HLP003* (n=9)	Placebo/16 mg HLP003† (n=3)
MADRS total score	-22.5 (6.3)	-4.0 (14.5)
1. Reported sadness	-2.4 (1.5)	-0.3 (1.5)
2. Apparent sadness	-3.2 (1.3)	-1.0 (2.0)
3. Inner tension	-1.5 (1.5)	0.3 (2.3)
4. Reduced sleep	-3.2 (1.5)	-1.0 (2.7)
5. Reduced appetite	-2.4 (1.3)	0.0 (1.0)
6. Concentration difficulties	-2.6 (0.7)	-1.3 (2.3)
7. Lassitude	-3.1 (1.6)	-0.7 (1.5)
8. Inability to feel	-2.8 (1.2)	-1.0 (1.0)
9. Pessimistic thoughts	-1.6 (1.4)	0.7 (1.2)
10. Suicidal thoughts	0.4 (0.7)	0.3 (0.6)
Anhedonia subscale score	-14.1 (2.9)	-4.3 (7.5)

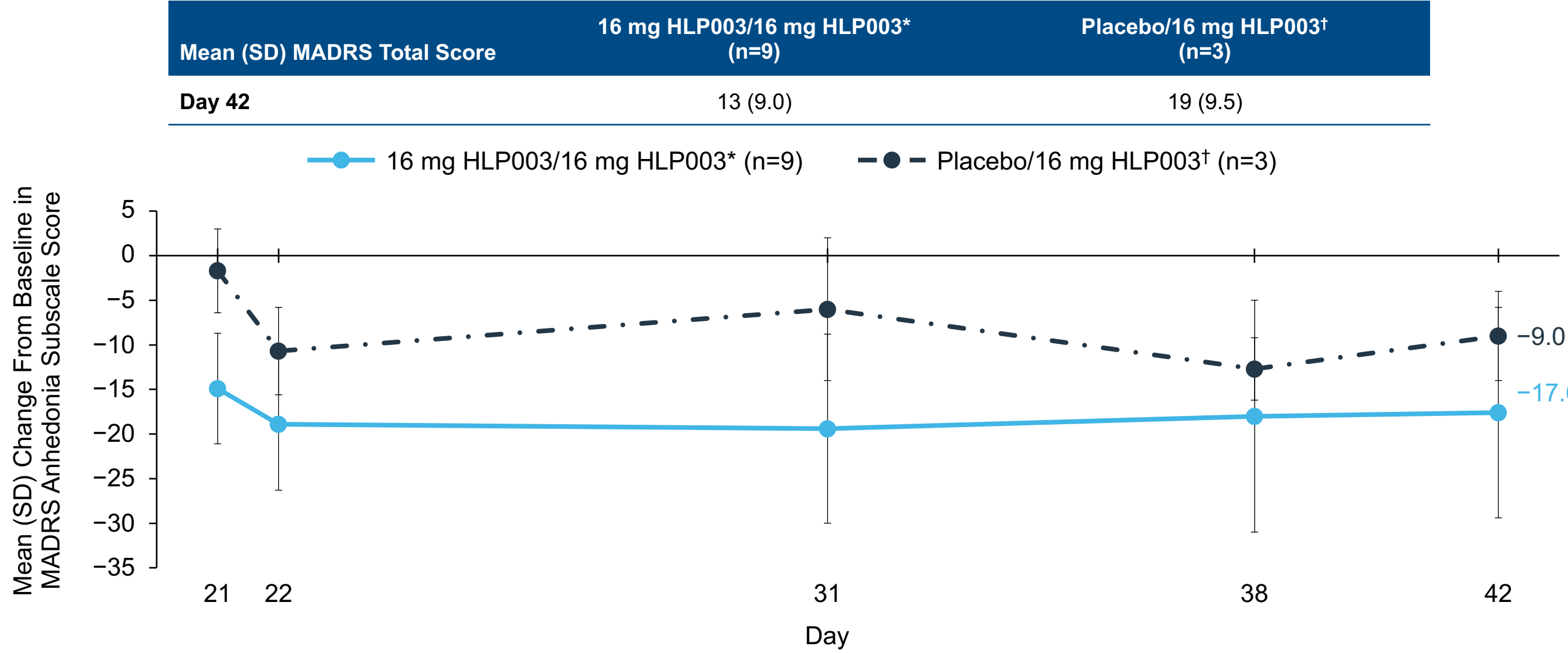
*Administration of 16 mg HLP003 on Days 1 and 22.
†Administration of placebo on Day 1 and 16 mg HLP003 on Day 22.
MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation.

Supplementary Figure S1. 16 mg HLP003 Administration on Day 1 Improved MADRS Individual Item Scores Through Day 21



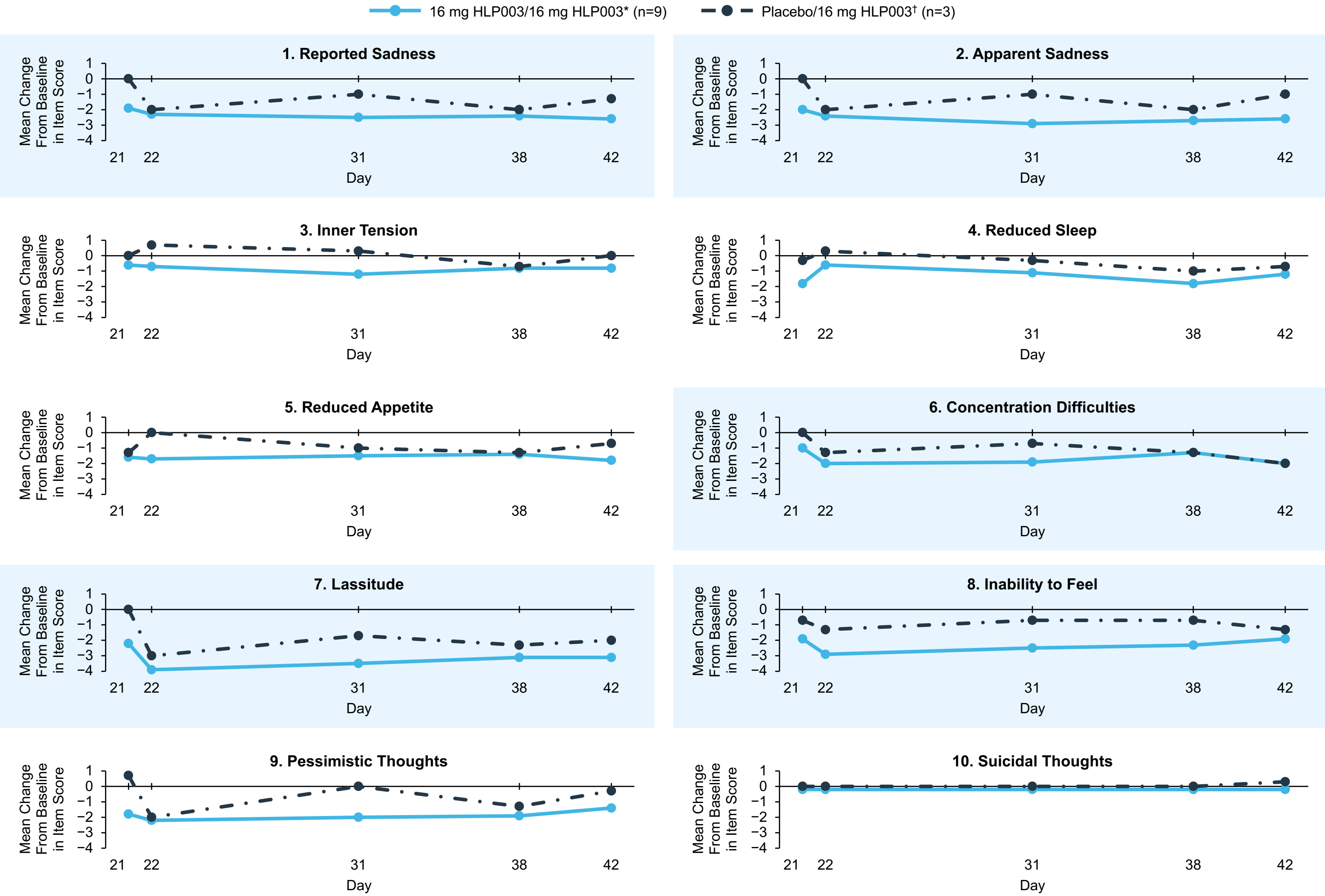
Panels with a blue background comprise the anhedonia subscale score.
BL, baseline; MADRS, Montgomery-Asberg Depression Rating Scale.

Supplementary Figure S2. Mean (SD) Change From Baseline in MADRS Total Score Improved to a Similar Degree Through Day 42 After a First or Second Administration of 16 mg HLP003 on Day 22



*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-Asberg Depression Rating Scale; SD, standard deviation.

Supplementary Figure S3. Mean Change From Baseline in MADRS Individual Item Scores Improved to a Similar Degree Through Day 42 After a First or Second Administration of 16 mg HLP003 on Day 22



Panels with a blue background comprise the anhedonia subscale score.
*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-Asberg Depression Rating Scale.

