

A Phase 3 Clinical Program Evaluating the Efficacy and Safety of the Deuterated Psilocin Analog HLP003 as an Adjunctive Treatment for Major Depressive Disorder (PARADIGM)

Amir Inamdar, MBBS, DNB (Psych), MFPM*; Alexandra Kulikova, PhD; Annette Massa, PharmD; Ken Kramer, PhD; Heather Prichard, PhD; Sunita Shinde, MD; Atul R. Mahableshwarkar, MD

Helus Pharma, Toronto, ON, Canada

* Presenting Author

OBJECTIVE

The phase 3 PARADIGM clinical program (APPROACH/EMBRACE/EXTEND) is evaluating 8 and 16 mg HLP003 as an adjunctive treatment to antidepressant monotherapy and will characterize longitudinal effects, including outcomes associated with re-treatment

CONCLUSIONS

The PARADIGM program will evaluate two different doses of HLP003 compared with placebo to evaluate the efficacy, safety, and long-term durability of this novel serotonergic agonist as an adjunctive treatment for MDD

Results from these studies may inform strategies to treat patients with MDD who inadequately respond to their antidepressant treatment and are seeking an alternative to atypical antipsychotics

References

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Disclosures

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

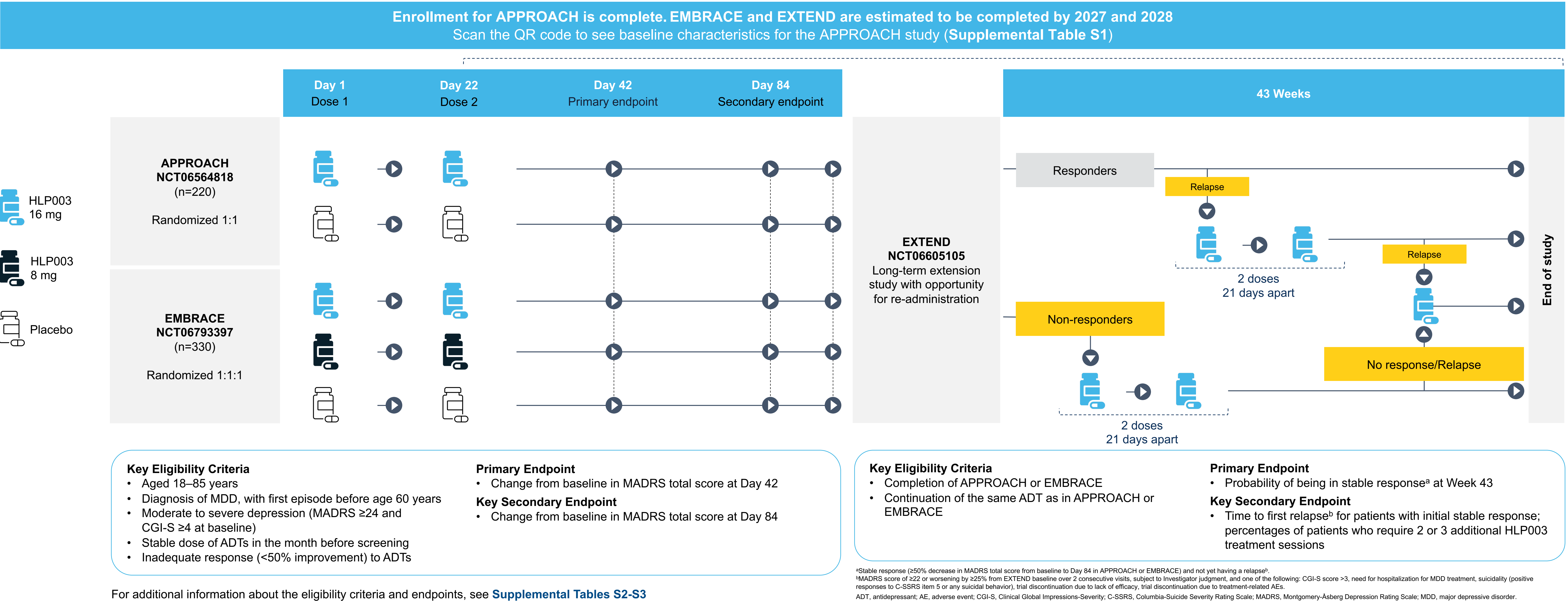
INTRODUCTION

- Approximately 50% of patients with major depressive disorder (MDD) do not adequately respond to first-line treatment; adjunctive treatments may be added to an antidepressant to achieve remission^{1,2}
- HLP003 is a deuterated psilocin analog that acts as a serotonergic agonist with binding and functional activity at multiple 5-hydroxytryptamine (5-HT) receptors, including 5-HT_{2A}, and is in development as an adjunctive treatment for MDD³
- A phase 1/2a, randomized, double-blind, placebo-controlled trial (NCT05385783) provided preliminary evidence that HLP003 was well tolerated and effective in participants with MDD and healthy volunteers⁴
- A single administration of 16 mg HLP003 produced a −12.99 (95% CI [−22.3, −3.7]; *P* < 0.0080)-point improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score versus placebo at Day 21 (**Figure 1**)⁴
 - A second dose at Day 22 sustained improvements through 12 months, with nearly all participants remaining in remission (**Figure 2**)⁵
 - See **Poster #124** and **Poster #122** for an analysis of individual MADRS items and an expanded safety analysis of 16 mg HLP003

METHODS

- The positive findings from the phase 1/2a trial supported initiation of a phase 3 clinical program (PARADIGM) to further investigate HLP003 as a potential adjunctive treatment to antidepressant monotherapy

Figure 3. The PARADIGM Program Consists of Two Phase 3, Multicenter, Randomized, 12-Week, Double-Blind, Placebo-Controlled Studies With a Long-Term Extension



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SUPPLEMENTAL METHODS

Supplemental Table S1. Baseline Demographics for Participants Enrolled in the Phase 3 APPROACH Trial

Characteristic	16 mg HLP003 (n=101)	Placebo (n=101)
Age, median (range), y	44.0 (19–73)	50.0 (18–75)
Sex, n (%)		
Female	65 (64.4)	65 (64.4)
Race, n (%)		
White	79 (78.2)	72 (71.3)
Black or African American	9 (8.9)	18 (17.8)
Asian	6 (5.9)	6 (5.9)
Hispanic/Latino, n (%)	19 (18.8)	17 (16.8)
BMI, mean (SD), kg/m ²	28.9 (5.7)	28.0 (5.7)
MADRS total score, mean (SD)	33.1 (5.3)	33.3 (5.5)

BMI, body mass index; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation.

Supplemental Table S2. Eligibility Criteria for the PARADIGM Program

Trial	Eligibility Criteria
APPROACH (NCT06564818) and EMBRACE (NCT06793397)	Exclusions - Current or previous diagnosis of treatment-resistant MDD (failure of ≥2 ADT treatments), psychotic disorders, bipolar disorder, or borderline personality disorder - First-degree relatives with history of schizophrenia, schizoaffective disorder, or bipolar disorder I - Significant risk of suicide (score of ≥4 on the C-SSRS [lifetime] suicidal ideation subscale or any suicidal behavior [lifetime]) - Exposure to psychedelics ≥10 times lifetime or at any time within 12 months before screening - Ketamine/esketamine use within 6 months of screening
EXTEND (NCT06605105)	Exclusions - New diagnosis of psychiatric disorders excluded from APPROACH and EMBRACE - New awareness of first-degree relatives being diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder type 1 since screening

ADT, antidepressant; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder.

Supplemental Table S3. Primary and Secondary Endpoints in the Trials Assess Acute and Sustained Treatment Effects of HLP003

Trial	Endpoints
APPROACH and EMBRACE	Other secondary endpoints: response ^a and remission ^b at Day 84; sustained ^c response ^a and remission ^b through Day 84; change from baseline in BDI-II, CGI-S, CGI-I, GAD-7, and Q-LES-Q-SF Safety: incidence, severity, and seriousness of TEAEs; laboratory safety assessments; vital signs; ECG; incidence of positive responses to items 4 or 5 on the C-SSRS or any suicidal behavior; incidence of potential abuse-related AEs; MOAA/S scale
EXTEND	Other secondary endpoints: sustained ^c response ^a and remission ^b through week 43; percentage of responders and remitters to 2 doses of HLP003 in EXTEND who later relapse; change from baseline to last visit in total MADRS score among participants who did not respond in APPROACH or EMBRACE; PK parameters Safety: incidence, severity, and seriousness of TEAEs; laboratory safety assessments; vital signs; ECG; incidence of positive responses to items 4 or 5 on the C-SSRS or any suicidal behavior; incidence of potential abuse-related AEs; MOAA/S scale

^a≥50% decrease in MADRS total score from baseline.

^bMADRS total score ≤10.

^cMeeting response or remission criteria on or before Day 42 and sustained with one score greater than that for the response or remission criterion permitted.

AE, adverse event; BDI-II, Beck Depression Inventory-Second Edition; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; GAD-7, Generalized Anxiety Disorder 7-item scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MOAA/S, Modified Observer's Assessment of Alertness and Sedation; PK, pharmacokinetic; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; TEAE, treatment-emergent AE.