Relationship Between Pharmacodynamic Measures and Efficacy in a Clinical Trial of a Novel Serotonergic Agonist for Generalized Anxiety Disorder

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OBJECTIVE

Post hoc analyses from a phase 2a study (NCT06051721) evaluating the predictive utility of acute subjective experience measures in participants with GAD treated with a deuterated form of dimethyltryptamine (HLP004)

CONCLUSIONS

In this post hoc analysis of HLP004 in participants with GAD, the EBI demonstrated high reliability and emerged as the strongest and most consistent predictor of clinical improvement and HAM-A response across multiple analytic approaches

Predictive associations for MEQ-30 and Bowdle subscales were less consistent

These findings suggest that EBI, which measures emotional responses as opposed to more abstract constructs, may represent a useful PD indicator that may be predictive of potential treatment response in patients with GAD to HLP004

References

1. Kishon R, et al. *Npj Ment Health Res.* 2024;3(1):33. **2.** James E, at al. *Hum Psychopharmacol Clin Exp.* 2022;37:e2835. **3.** Weston NM, et al. *Depression Anxiety.* 2020;37:1261-1279. **4.** Brudner RM, et al. *J Psychopharm.* 2025;39(9):950-956. **5.** Roseman L, et al. *Front Pharmacol.* 2018;8:974. **6.** Roseby W, et al. *Front Psychol.* 2025;16:1580663. **7.** Varty GB, et al. Preclinical Characterization of CYB004: a Novel, Deuterated N,N-Dimethyltryptamine (DMT) Analog for the Potential Treatment of Generalized Anxiety Disorder (GAD). Presented at: American College of Neuropsychopharmacology Annual Meeting; December 3–6, 2023; Tampa, FL, USA. **8.** Firth D. *Biometrika.* 1993;80(1):27-38.

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Disclosures

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

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INTRODUCTION

- Psychedelic agents induce an acute alteration of consciousness that is characterized by hallucinatory, emotional, and other behaviors[1]
- Preliminary evidence suggests that psychedelic agents may have potential efficacy for the treatment of a variety of neurological and psychiatric disorders, including generalized anxiety disorder (GAD)[2,3]
- It is hypothesized that the efficacy of these agents is dependent upon eliciting pharmacodynamic (PD) effects of sufficient intensity (either directly or indirectly)[4,5]
  - These include ego dissolution, emotional breakthrough, mystical experiences, and other measures of varying constructs[6]
- While these measures are commonly included in trials of psychedelic agents, the relationships of these measures and correlations with clinical outcomes have not been well characterized
- HLP004 is a deuterated form of the serotonergic agonist dimethyltryptamine being investigated as a potential treatment for GAD[7]

METHODS

Participants and Study Design

- 36 participants were randomized 2:1 to receive HLP004 at 20 mg or 2 mg intramuscularly on Days 1 and 22 (**Figure 1**)
  - Analyses presented are from the 12-week, double-blind period of the study

Analyses

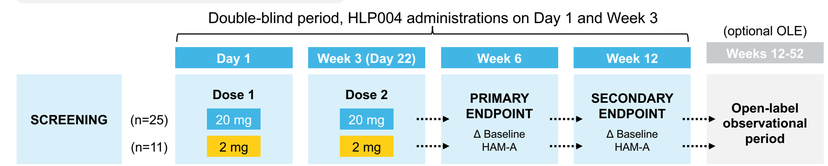
- Psychometric properties of the PD measures were evaluated for internal consistency (Cronbach's α, Day 1) and cross-session reproducibility between the two dosing sessions (two-way random-effects, absolute-agreement, single-measures intraclass correlation coefficient [ICC(2,1)], Day 1 vs Day 22), and inter-scale correlations (Day 1)
- PD measures obtained following the first dosing session (Day 1) were examined in relation to Hamilton Anxiety Rating Scale (HAM-A) outcomes at Weeks 6 and 12
  - HAM-A response (defined as ≥ 50% reduction from baseline) was modeled using penalized logistic regression[8]
  - Continuous HAM-A change from baseline (CfB) was fit using linear regression
  - Mediation of the treatment group effect was further examined by evaluating the causal pathway between dose and HAM-A CfB via the acute psychedelic experience (Emotional Breakthrough Index [EBI]) using bootstrapped causal mediation (2000 resamples)
  - Instrument discrimination was summarized by area under the receiver operating characteristic curve (AUROC), and incremental validity was assessed using the penalized likelihood-ratio test

Methodological Issues Being Addressed

- The PD effects of psychedelic agents are measured using subjective assessments that capture different constructs of the psychedelic experience
- The relationship of these PD measures to clinical outcome measures, especially for GAD, has not been well-characterized

Figure 1. Study Design

Key Inclusion Criteria
- Men and women, 18 to 65 years old
- Moderate to severe GAD (GAD-7 ≥ 10)
- Inadequate response to antidepressant/ anxiolytic medication



Primary Efficacy Endpoint
- Change from baseline HAM-A total score at 6 weeks*

Other Efficacy Endpoints
- HAM-A response†
- GAD-7
- HAM-D
- CGI-I
- CGI-S

PD Endpoints
- MEQ-30
- EBI
- B-VAS

Safety/Tolerability
- TEAEs
- Vital signs

Participants with GAD received HLP004 on Day 1 and Day 22 (Week 3). The study included a 12-week double-blind period, followed by an optional open-label extension through Week 52. Analyses shown are based on data from the double-blind period through Week 12.
B-VAS, Bowdle visual analog scale; CGI-I, Clinical Global Impressions–Improvement; CGI-S, Clinical Global Impressions–Severity; EBI, Emotional Breakthrough Index; GAD, generalized anxiety disorder; GAD-7, GAD 7-item questionnaire; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MEQ-30, Revised Mystical Experience Questionnaire; OLE, open-label extension; PD, pharmacodynamic; TEAE, treatment-emergent adverse event.

RESULTS

EBI and MEQ-30 Show High Internal Consistency and Reproducibility Between Administrations

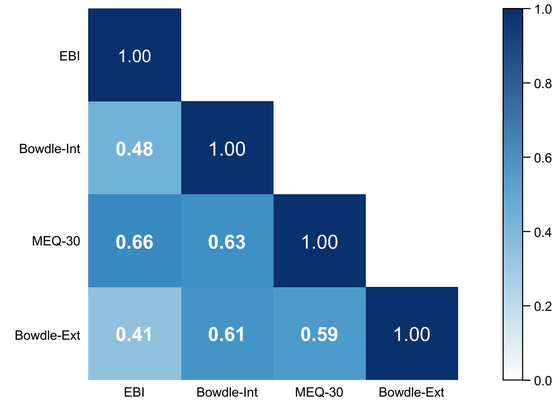
- Exploratory psychometric analyses indicated high internal consistency for EBI (Cronbach's α = 0.94) and the Revised Mystical Experience Questionnaire (MEQ-30; 0.98)
- Cross-session reproducibility of the total scores between the two dosing sessions was good for all four measures (**Table 1**)
- The four PD measures were moderately intercorrelated (**Figure 2**)
- No distinct internal versus external clusters were observed based on pairwise correlations between measures

Table 1. Reproducibility of Subjective PD Scales

Measure	ICC(2,1)	95% CI	N Pairs
EBI	0.78	0.59, 0.89	30
MEQ-30	0.82	0.66, 0.91	30
Bowdle Internal	0.70	0.46, 0.85	30
Bowdle External	0.81	0.63, 0.90	30

CI, confidence interval; EBI, Emotional Breakthrough Index; ICC(2,1), two-way random-effects, absolute-agreement, single-measures intraclass correlation coefficient, Day 1 versus Day 22; MEQ-30, Revised Mystical Experience Questionnaire; PD, pharmacodynamic.

Figure 2. Inter-Scale Correlations (Day 1)



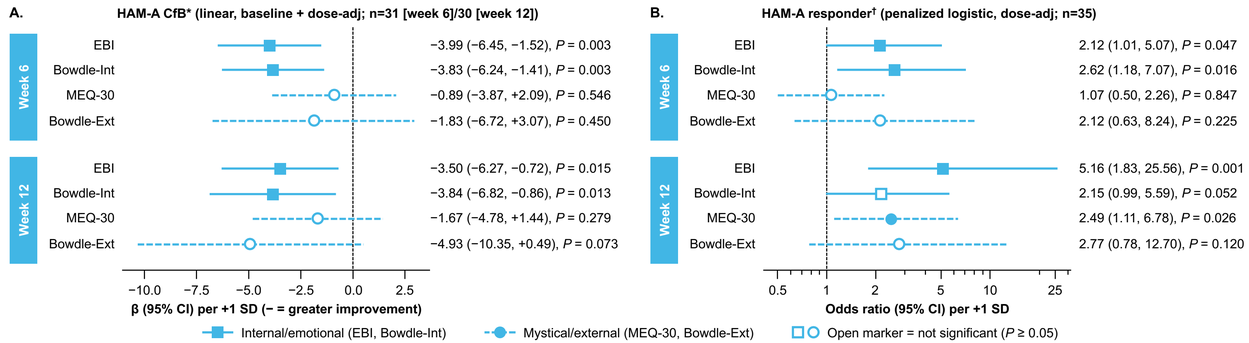
Cells display r among Day 1 PD measures. Darker shading indicates stronger positive correlations.
Bowdle-Ext, Bowdle External score; Bowdle-Int, Bowdle Internal score; EBI, Emotional Breakthrough Index; MEQ-30, Revised Mystical Experience Questionnaire; PD, pharmacodynamic; r, Pearson correlation coefficient.

Logistic and Linear Regression Analysis of PD Measures and HAM-A

- From logistic regression analysis, both EBI score and Bowdle Internal score were associated with greater HAM-A improvement at Weeks 6 and 12 (**Figure 3A**)
- EBI score was the strongest predictor of HAM-A responder, achieving statistical significance at Week 6 (odds ratio [OR] = 2.12, *P* = 0.047) and Week 12 (OR = 5.16, *P* = 0.001; **Figure 3B**)

Figure 3. Predictions of HAM-A (A) CfB and (B) Responder According to Subjective PD Measures

EBI discrimination (AUROC): 0.75 at Week 6 · 0.82 at Week 12

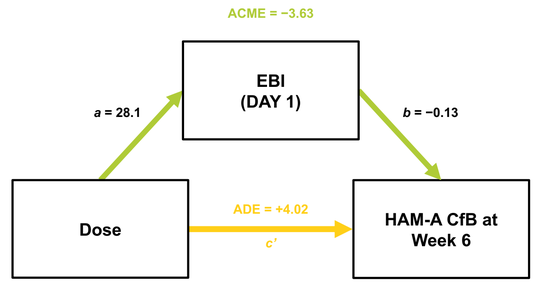


Predictor values were standardized for consistency in both analyses. Lines indicate 95% CI.
*Continuous HAM-A CfB was fit using linear regression, with adjustment for treatment group. Observed CfB values were used in the model. For every 1 SD change in PD measure, HAM-A changes by the β amount holding everything else constant.
†HAM-A responder (defined as ≥ 50% reduction from baseline) was modeled using penalized logistic regression,[8] with adjustment for treatment group and baseline HAM-A score. Missing endpoint values were imputed as non-response.
AUROC, area under the receiver operating characteristic curve; Bowdle-Ext, Bowdle External score; Bowdle-Int, Bowdle Internal score; CfB, change from baseline; CI, confidence interval; EBI, Emotional Breakthrough Index; HAM-A, Hamilton Anxiety Rating Scale, MEQ-30, Revised Mystical Experience Questionnaire; PD, pharmacodynamic; SD, standard deviation.

Mediation Analysis of EBI and HAM-A

- The pathway through EBI was associated with greater HAM-A improvement and was statistically significant at Week 6, Average Causal Mediation Effect (ACME) = -3.63 (95% CI: -9.02, -0.56; *P* = 0.024), but not at Week 12, ACME = -3.32 (95% CI: -9.46, 0.02; *P* = 0.052) (**Figure 4**)
- While the indirect effect was significant at Week 6, the near-zero total effect of dose on HAM-A change indicated an inconsistent mediation pattern
- A beneficial indirect effect through EBI was offset by an opposing direct effect of dose (average direct effect [ADE] = 4.02), yielding a total effect of 0.39

Figure 4. Direct and Indirect Effects of Dose on HAM-A CfB at Week 6

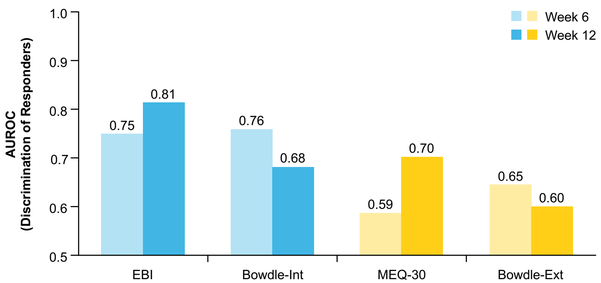


ACME, Average Causal Mediation Effect; ADE, average direct effect; CI, confidence interval; EBI, Emotional Breakthrough Index; HAM-A, Hamilton Anxiety Rating Scale.

Discriminative and Incremental Validity

- A composite internal block (EBI and Bowdle Internal scores) discriminated HAM-A responders from non-responders more accurately than an external block (MEQ-30 and Bowdle External scores) at Week 6 (AUROC = 0.79 vs 0.66) and Week 12 (AUROC = 0.85 vs 0.75)
- At Week 12, EBI added significant predictive value over MEQ-30, $\chi2(1) = 5.69$ (*P* = 0.017), improving discrimination from AUROC = 0.70 to AUROC = 0.82 (ΔAUROC = 0.12), whereas MEQ-30 provided no statistically significant incremental value over the EBI, $\chi2(1) = 0.002$ (*P* = 0.96; ΔAUROC = 0.003)
- Unadjusted discrimination for each individual measure is shown in **Figure 5**

Figure 5. Discrimination of HAM-A Response by Individual PD Experience Measures at Weeks 6 and 12



Measures related to internal subjective experience (EBI and Bowdle-Int) more accurately discriminated responders from non-responders than measures of perceptual or mystical-like experiences (MEQ-30 and Bowdle-Ext).
AUROC, area under the receiver operating characteristic curve; Bowdle-Ext, Bowdle External score; Bowdle-Int, Bowdle Internal score; EBI, Emotional Breakthrough Index; HAM-A, Hamilton Anxiety Rating Scale, MEQ-30, Revised Mystical Experience Questionnaire; PD, pharmacodynamic.