Genetically Defined Subgroup Analysis Reveals Differential response to Vasopressin V1b Antagonism in Patients with MDD Pre-exposed to Antidepressant in the current episode: Post-hoc Analysis of the Phase 2 OLIVE Trial

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MAIN TAKEAWAYS

- BH-200 demonstrated a clinically meaningful signal in pre-exposed MDD participants.
- Use of the polygenic classification tool improves signal detection in the test-positive group, underlining its potential utility for precision psychiatry approaches in future BH-200 studies.
- Consistent findings across HAM-D17 and MADRS strengthen confidence in the clinical relevance of V1b pathway modulation.
- Further trials using biomarker-based enrichment are warranted.

Background

Treatment-resistant depression (TRD), a subtype of Major Depressive Disorder (MDD) defined by suboptimal response to antidepressant treatment, represents a significant unmet medical need. Vasopressin V1b receptor modulation has emerged as a potential mechanism relevant to stress-system dysregulation in MDD. BH-200, a selective V1b receptor antagonist, was evaluated in OLIVE trial (CTIS: 2024-513104-34-00) in adults with MDD. The estimated mean improvement in the 17-item Hamilton Depression Rating Scale (HAM-D17) from baseline to Week 8 in the modified intention-to-treat population (N=331) was larger in the BH-200-treated arm than in the placebo arm (Δ=-2.98, p=0.0003).

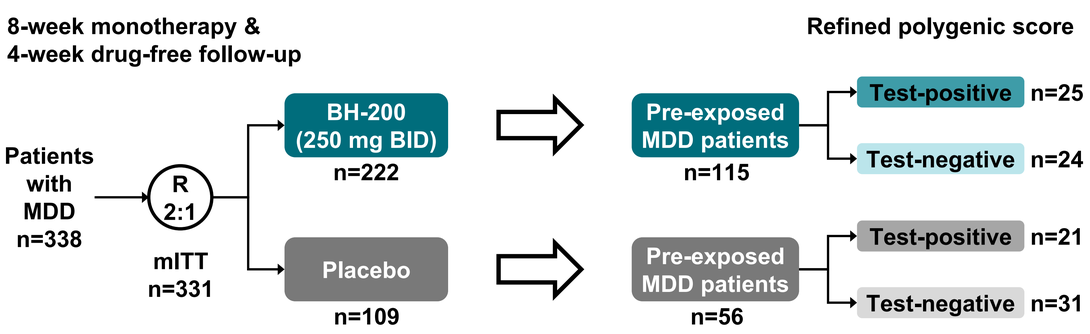
Objectives

1. To determine the antidepressant efficacy of BH-200 compared with placebo in pre-exposed MDD patients for potential use of vasopressin V1b receptor antagonists in TRD,
2. To test whether variation in V1b-related biology, assessed by refined polygenic classification, identifies responders to BH-200 among pre-exposed MDD subjects,
3. To assess the consistency of findings on antidepressant efficacy across HAM-D17 and MADRS outcomes.

Methods

This was a post-hoc analysis of the data from a randomized, placebo-controlled, double-blind, phase 2 OLIVE trial. Analyzed were pre-exposed MDD patients who did not respond to at least one adequate course of antidepressant treatment in their current depressive episode prior to enrolling in the trial. The target endpoint for this analysis was the change in HAM-D17 score from baseline to Week 8. Mixed-model repeated measures (MMRM) analyses were applied. Refined polygenic classification tool, trained post-hoc using repeated cross-validation in the OLIVE dataset with performance measures estimated via repeated nested cross-valiadation to predict BH-200 treatment response (≥50% HAM-D17 total score reduction from baseline), was used to compute test-positive and test-negative strata.

OLIVE trial design

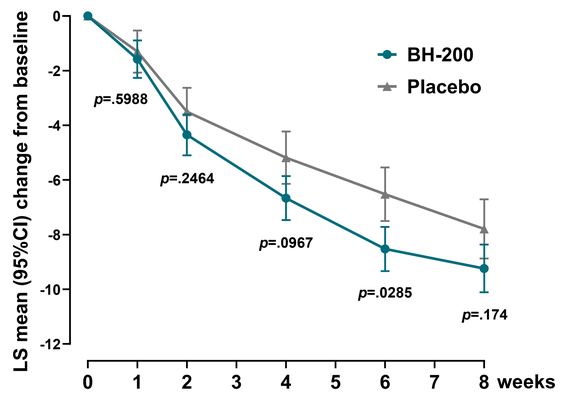


Current analysis

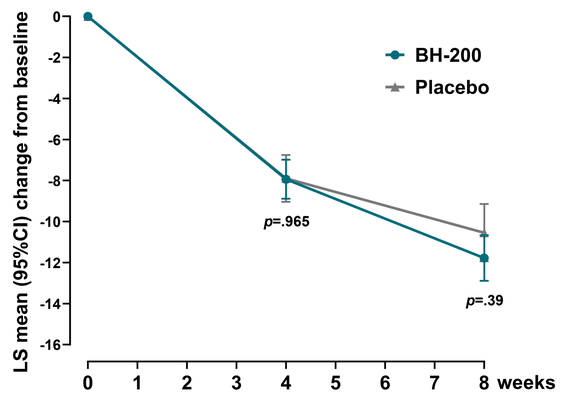
Results

A total of 171 pre-exposed MDD participants were included in the analysis. In the entire pre-exposed population, BH-200 showed greater improvement versus placebo in LS mean change from baseline on HAM-D17, with the difference between treatments amounting to -2.00 (SE=0.91); p=0.0285 at week 6 and -1.45 (SE=1.06); p=0.174 at week 9 for HAM-D17) and -0.05 (SE=1.05); p=.965 at week 6 and -1.23 (SE=1.43); p=.39 at week 8 MADRS.

HAM-D17 total score

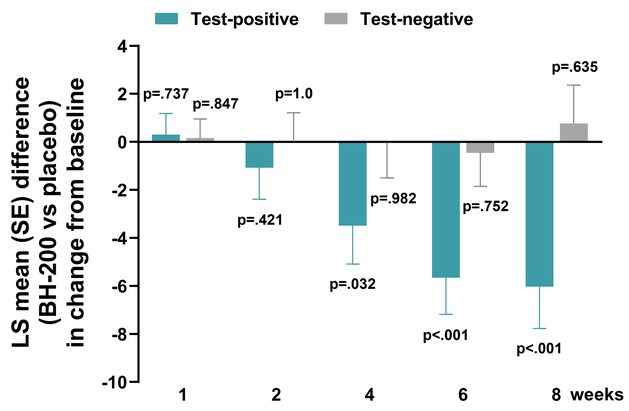


MADRS total score

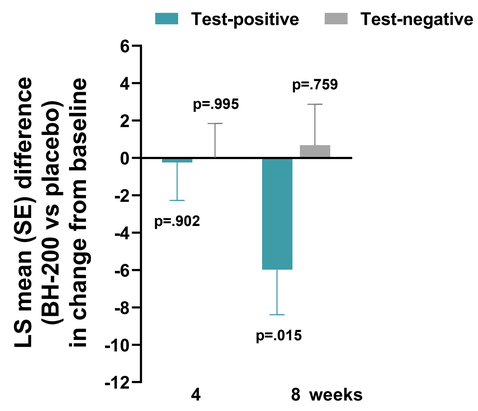


The refined polygenic classification test was positive in 46 of 101 pre-exposed MDD patients; among them, response to trial treatment (≥50% HAM-D17 total score reduction from baseline) was observed in 17 (68%) of 25 patients in the BH-200 arm and 5 (23.8%) of 21 patients in the placebo arm. Note that performance measures were derived in the outer loop using repeated nested cross-validation, hence free of information leakage between training and evaluation. This absence of overfitting was confirmed using a permutation analysis that encapsulated the full model-building process. Among the test-positive patients, the LS mean difference between BH-200 vs placebo in change from baseline for HAM-D17 scores was -5.65 (SE=1.54); p<.001 at week 6 and -6.03 (SE=1.74); p<.001 at week 8, and for MADRS scores it was -5.98 (SE=2.42); p=.015 at week 8.

HAM-D17 total score



MADRS total score



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