BH-200 (nelivaptan), a Vasopressin V1b Receptor Antagonist, in Genetically Defined Subgroups of MDD: Precision Targeting of HPA-Axis Dysregulation in the OLIVE Phase 2 Program

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MAIN TAKEAWAYS

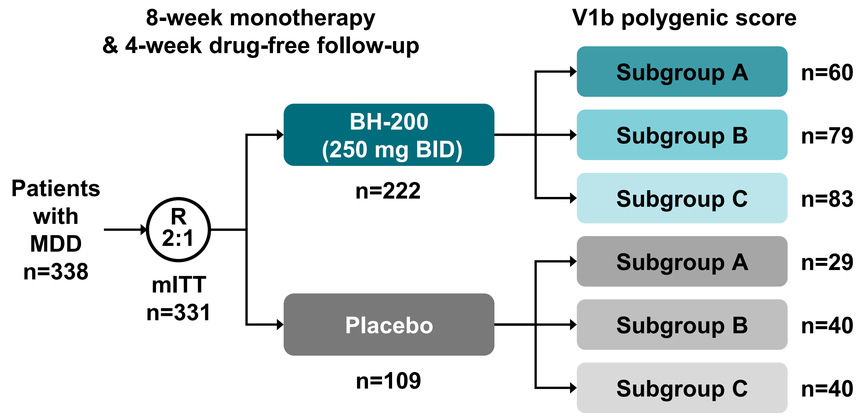
- The OLIVE program demonstrates that vasopressin V1b receptor antagonism is a viable antidepressant mechanism.
- Integration of grounded genetic companion diagnostics can enhance signal detection and enrich for larger clinical benefits.
- This precision psychiatry approach informs the next phase of clinical development for BH-200.

Background

Disturbances of hypothalamic–pituitary–adrenal (HPA) axis function are implicated in a biologically defined subset of patients with major depressive disorder (MDD). Pharmacologic modulation of the stress hormone system, including CRHR1 and vasopressin V1b receptor (V1bR) antagonism, has been explored for decades; however, trials conducted in unselected MDD populations have not led to regulatory approval. We hypothesized that biological heterogeneity dilutes treatment effects and that stress-axis–driven subgroups can be prospectively identified. In a prior positive Phase 2 trial with the selective V1bR antagonist BH-200 (nelivaptan), a bimodal distribution of response suggested distinct responder populations. Because the dexamethasone–CRH (Dex-CRH) test is not practical for routine use, a genetic classifier (V1b polygenic score; V1bPGS) was developed based on vasopressin signaling biology and Dex-CRH–characterized cohorts. The 14-SNP tool assigns patients to three subgroups (A, B, C), reflecting differential ACTH suppression profiles and putative vasopressin pathway activity.

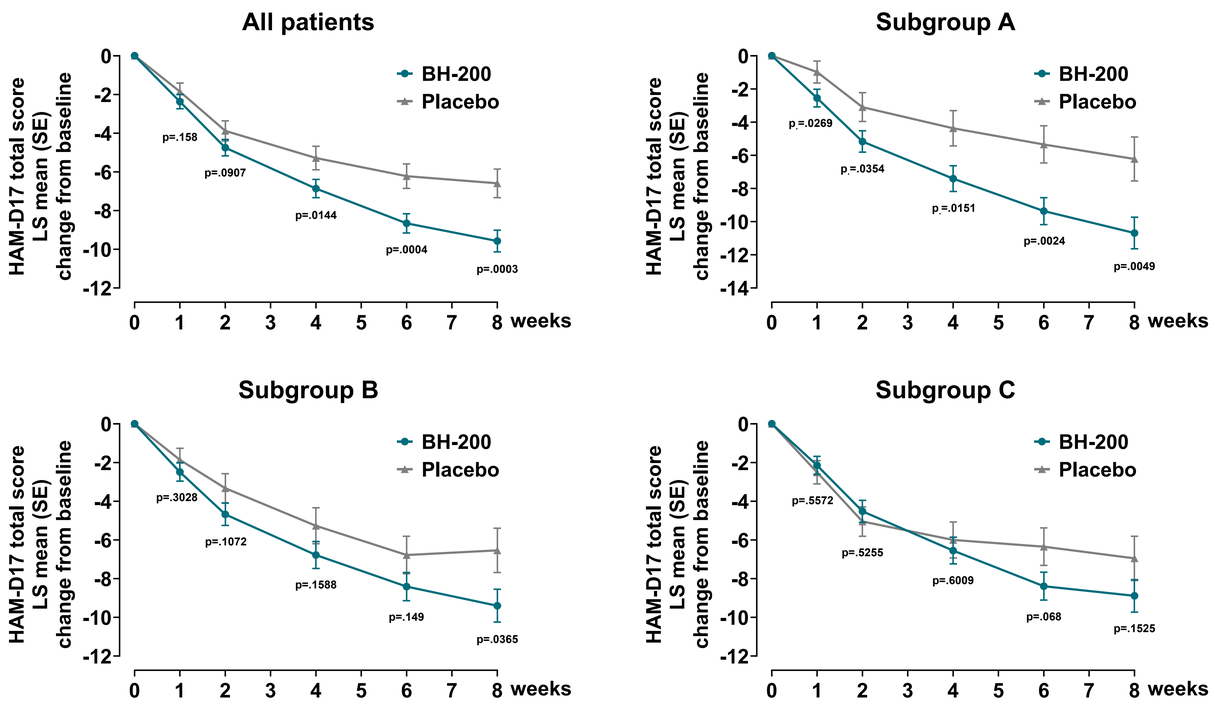
Methods

The OLIVE trial (CTIS 2024-513104-34-00) was a randomized, double-blind, placebo-controlled phase 2 trial conducted in eight European countries. A total of 338 patients with MDD were randomized 2:1 to BH-200 (250 mg BID) or placebo for eight weeks. The prespecified primary endpoint was the change from baseline to Week 8 on the 17-item Hamilton Depression Rating Scale (HAMD-17) in patients classified as Subgroup C. Secondary endpoints included HAMD-17 response and remission, changes in other depression rating scales, quality-of-life and functioning measures, safety, and pharmacokinetics.

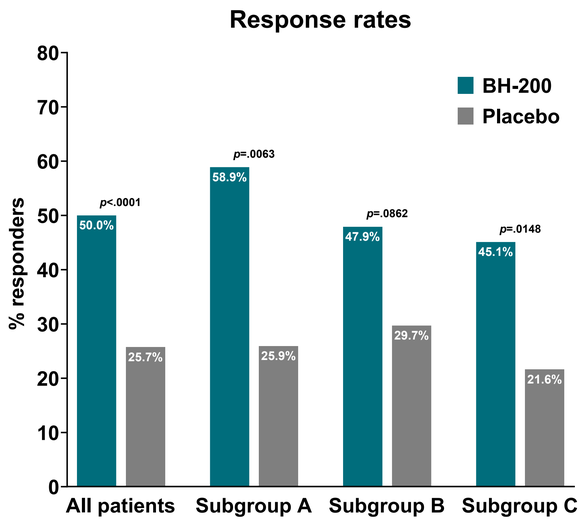


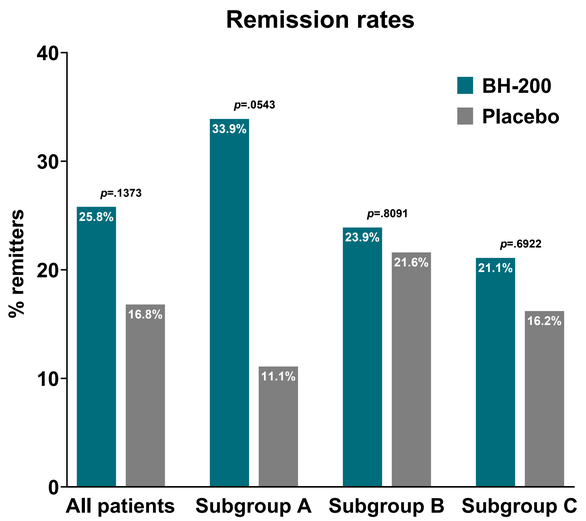
Results

In the modified intention-to-treat population (mITT, N=331), BH-200 demonstrated clinically meaningful improvement versus placebo at week 8 (Δ = −2.98, p = 0.0003; Cohen's d 0.44). Treatment separation emerged early and was sustained over a 4-week follow-up period. In the prespecified primary analysis population (Subgroup C; n=123), the treatment difference at week 8 was statistically non-significant, with Δ = −1.94 (p = 0.1525; Cohen's d 0.28). However, genetic stratification revealed marked heterogeneity of effect. The largest benefit was observed in Subgroup A (n=89), with Δ = −4.47 (p = 0.005; Cohen's d 0.55) at week 8 and separation evident from Week 1 onward.



Response rates (≥50% reduction in HAM-D17) at week 8 in mITT set were 50.0% with BH-200 versus 25.7% with placebo, odds ratio (OR), 2.98 (95% CI, 1.74, 5.10), and remission rates (HAM-D17 ≤7) were 25.8% versus 16.8%, OR 1.62 (95% CI, 0.86, 3.08), respectively. The highest response and remission rates after BH-200 were observed in Subgroup A: response rate of 58.9% versus 25.9% after placebo, OR 4.22 (95% CI, 1.51, 11.83), and remission rate of 33.9% versus 11.1% after placebo, OR 3.82 (95% CI, 0.98, 14.98).





The most frequent adverse event in the BH-200 arm was headache (8.9%). Elevated liver function test values, with AST or ALT concentrations increased to >3 times the upper limit of normal, occurred in 5.8% of BH-200-treated patients. All changes reversed while on treatment or after stopping the treatment. No serious adverse events occurred in the BH-200 arm, and the hepatic enzymes' elevations appear monitorable within standard safety frameworks.

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