A phase 2 clinical trial exploring efficacy and safety of the vasopressin V1b antagonist BH-200, a treatment for MDD, evaluating the performance of a genetic classification tool to identify a subset of patients with larger improvement

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MAIN TAKEAWAYS

- Specific inhibition of V1b signaling appears to be associated with a clinically relevant improvement of depressive symptoms.
- The clinical outcome was better in patients characterized genetically by a prespecified tool than in the full MDD population.
- HPA-axis modulators are a viable, novel class of antidepressants that can be combined with a genetic selection tool to enhance the treatment outcome in a subset of MDD patients, showing the promise of precision psychiatry.

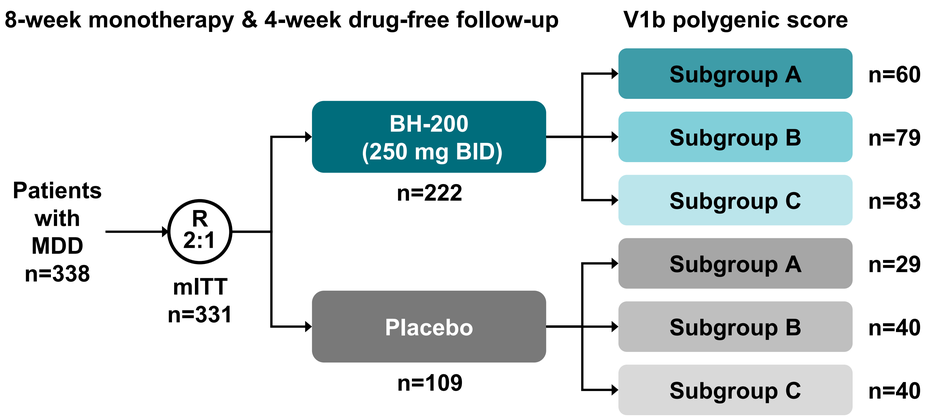
Background

A disturbance in the hypothalamus-pituitary-adrenal axis (HPA-axis) function has been implicated in a subset of depressed individuals. BH-200 is a selective V1b receptor antagonist that has previously shown efficacy in a phase 2 trial (DFI5878, NCT00358631) in major depressive disorder (MDD).

We hypothesized that there is a subset of depressed individuals that shows a more pronounced disturbance in HPA-axis function. In the OLIVE trial, we aimed to identify these patients using a genetic selection tool, the V1b polygenic score (V1bPGS), which classifies patients into three subgroups: A, B, and C. Our initial hypothesis was that Subgroup C benefits most from BH-200.

Methods

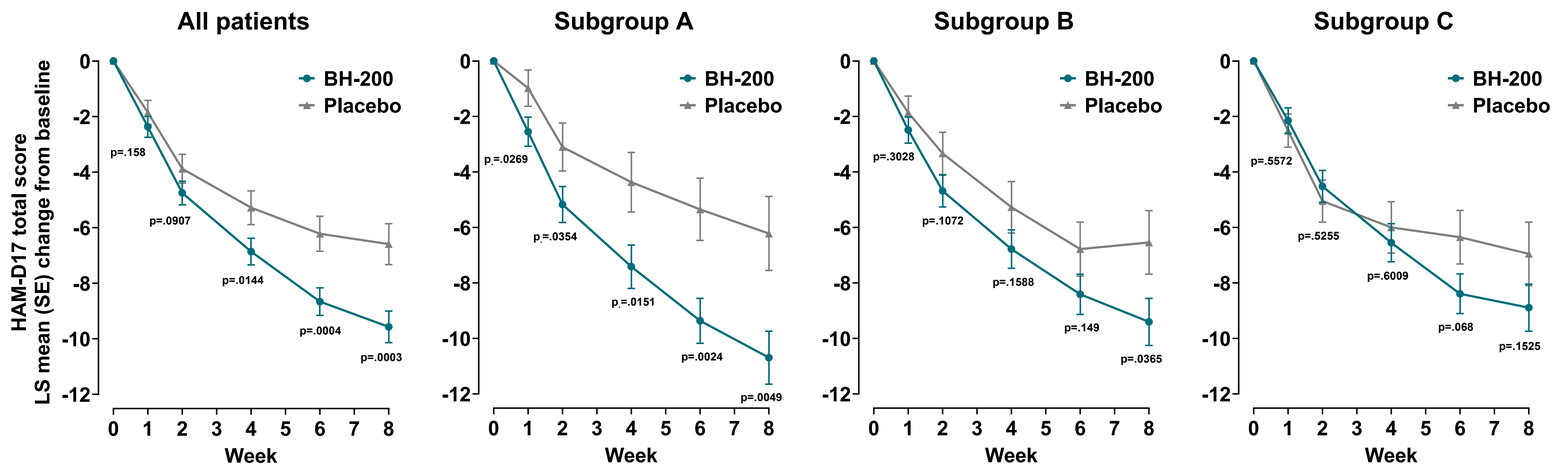
OLIVE (CTIS 2024-513104-34-00) was an 8-week, double-blind, randomized, placebo-controlled phase 2 trial performed across 50 sites in 8 countries. 338 adult MDD patients were included; 331 patients in the modified intention-to-treat population (mITT) were randomized 2:1 to BH-200 (250 mg BID) or placebo.



After the end of trial treatment, patients were classified into three predefined subgroups (A, B, C, prospectively assumed to be distributed 1:1:1) using the genetic classifier V1bPGS based on 14 single-nucleotide polymorphisms, which emulates the outcome of the dexamethasone-CRH test. The primary endpoint was the change in total score on the 17-item Hamilton Depression Rating Scale (HAM-D17) from baseline to week 8 in a prespecified Subgroup C. The key secondary endpoint compared HAM-D17 between BH-200-treated patients in Subgroups C and A. Further secondary endpoints included changes in Montgomery-Åsberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression Scale (HADS), Clinical Global Impression Severity (CGI-S), 36-Item Short Form Survey (SF-36), Sheehan Disability Scale (SDS), safety, and tolerability.

Results

In the mITT set (n=331), the estimated mean improvement from baseline to week 8 was larger in the BH-200 arm than in the placebo arm (Δ=-2.98, p=.0003). Clinically relevant improvements vs placebo at week 8 were observed in each BH-200-treated subgroup, with the highest magnitude of the mean effects observed in Subgroup A (Δ=-4.47, p=.005; Cohen's d: 0.55), followed by Subgroup B (Δ=-2.85, p=.037; Cohen's d: 0.49), and Subgroup C (Δ=-1.94, p=.153; Cohen's d: 0.28). In Group A, all comparisons between BH-200 and placebo from week 1 onward had p<0.05. The improvement from baseline was maintained during the 4-week follow-up.



50.0% of patients in the BH-200 arm and 25.7% in the placebo arm were responders (≥50% decrease in HAM-D17 score from baseline) at week 8; odds ratio (OR) of 3.0. In Subgroup A, 58.9% of patients in the BH-200 arm and 25.9% in the placebo arm were responders by week 8, with an OR=4.2. 25.8% of patients in the BH-200 arm and 16.8% in the placebo arm reached remission (HAM-D17 score ≤7) at week 8; OR=1.6; the corresponding remission rates in Subgroup A were 33.9% and 11.1%; OR=3.8.

The findings from the HAM-D17 scale were supported by consistent improvements on additional depression rating scales, with differences (p<.05) between BH-200 and placebo at week 8 in MADRS scores (in all patients and in Subgroup A), in the HADS depressive subscore (in all patients), and in the CGI-S scale (in all patients and across all Subgroups). BH-200 induced improvements vs placebo at week 8 in the SF-36 mental component measure (MCS) in all patients and in Subgroup A, and in SDS in all patients and in Subgroup B.

	MADRS		HADS Total		HADS Depr.		HADS Anxiety		CGI-S		SF-36 MCS		SF-36 PCS		SDS	
Week 8	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**	**Δ vs placebo**	***p*-value**
Total	**-3.28**	**.0021**	**-1.86**	**.0493**	**-1.32**	**.0209**	-0.60	.1853	**-0.46**	**.0006**	**4.26**	**.004**	1.08	.183	**-2.74**	**.0044**
Subg. A	**-5.95**	**.0011**	-3.08	.0921	-2.13	.0542	-1.09	.2094	**-0.55**	**.0038**	**7.65**	**.0071**	0.49	.752	-3.04	.108
Subg. B	-1.80	.2479	-1.58	.3153	-1.11	.2431	-0.52	.4874	**-0.45**	**.0055**	1.62	.5033	2.60	.0508	**-3.94**	**.013**
Subg. C	-2.94	.0595	-1.17	.4565	-0.89	.35	-0.29	.7004	**-0.41**	**.0114**	4.41	.0706	-0.01	.9937	-1.25	.4289

The most frequent adverse event was headache, in 8.9% of the patients in the BH-200 arm. Three serious adverse events were reported in two patients, all in the placebo arm. In the BH-200 arm, 5.8% of patients had AST or ALT concentrations elevated to >3 times the upper limit of normal. All changes reversed while on treatment or after stopping the treatment.

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