Efficacy and safety of BH-200, a selective vasopressin V1b receptor antagonist, in the treatment of genetically defined subgroups of patients with major depressive disorder (MDD)

Invited by:
Florian Holsboer,
ACNP Fellow

Hans Eriksson[1], Christine zu Eulenburg[1,2], Daniel Gehrlach[1], Evan Papanastasiou[1], Bertram Müller-Myhsok[1], Ani Damyanova[1], Filip Rybakowski[3], Florian Holsboer[1]

[1]HMNC Holding GmbH, Munich, Germany; [2]University Medical Center Hamburg-Eppendorf, Germany; [3]Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

Contact: hans.eriksson@hmnc-brainhealth.com

MAIN TAKEAWAY

- OLIVE, a large precision psychiatry trial, demonstrated that HPA-axis modulation is a viable approach for the treatment of depression.
- BH-200 induced clinically meaningful antidepressant effects with a HAMD-17 score change of 3 points among all patients treated.
- A novel HPA-axis genetic classifier (V1b polygenic score) identified patients particularly responsive to BH-200, with a change of 4.5 points in the HAMD-17 score.
- Safety profile was consistent with previous trials; liver function test elevations were infrequent, asymptomatic, and reversible.
- OLIVE advances precision psychiatry in MDD and supports further clinical development and refinement of the HPA-axis genetic classifier.

BACKGROUND

HPA-axis dysregulation and depression

Disturbances in hypothalamic–pituitary–adrenal (HPA) axis function have long been implicated in the pathophysiology of major depressive disorder (MDD). Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) drive HPA-axis activity, and CRH and V1b antagonists (e.g., BH-200) have entered clinical development. In a prior phase II trial (DFI5878, NCT00358631), BH-200 demonstrated antidepressant efficacy in the unselected MDD population. Further development of BH-200 was abandoned, likely due to the heterogeneity of depression, with benefits expected primarily in patients with dysregulated HPA axis, as opposed to those with normal HPA-axis function.

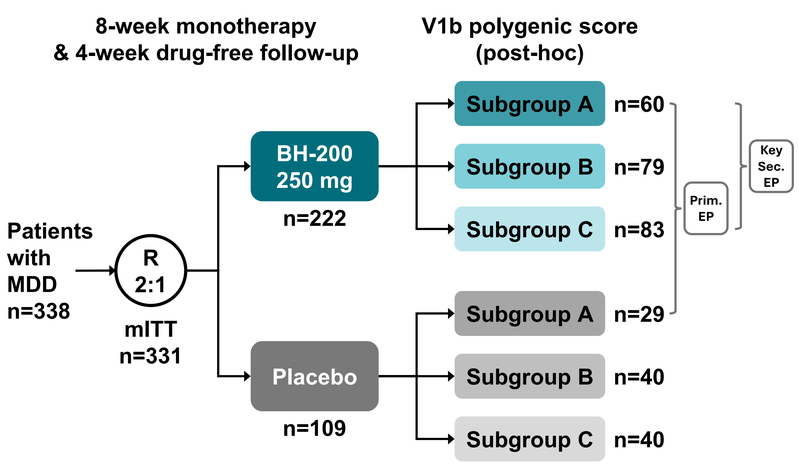
Biomarker-based patient classification

The dexamethasone-CRH (Dex-CRH) test identifies HPA-axis dysregulation; however, it is unsuitable for routine clinical use. Based on translational work at the Max Planck Institute of Psychiatry (Munich, Germany), HMNC Brain Health developed a genetic classifier, the V1b polygenic score (V1bPGS) that emulates the outcome of the Dex-CRH test into three Subgroups: A, B, and C, with a roughly 1:1:1 distribution.

The objectives of the OLIVE trial (EudraCT: 2022-002757-26)

1. Assessment of antidepressant efficacy of BH-200 monotherapy in adults with major depressive disorder.
2. Evaluation of treatment response of the three V1bPGS classes with primary hypothesis based on Subgroup C

PATIENTS AND METHODS



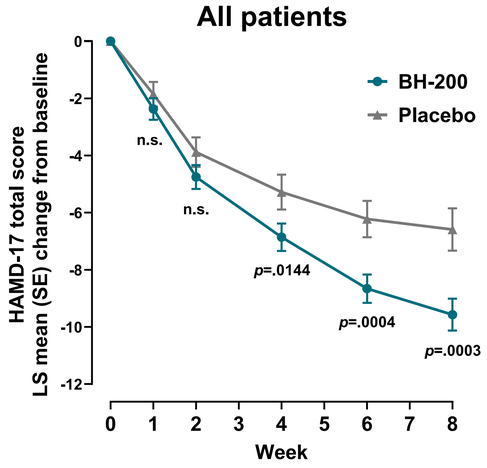
OLIVE was an 8-week, double-blind, randomized, placebo-controlled phase II trial in 338 MDD patients performed across 50 sites in 8 countries. Patients were randomized (2:1) to BH-200 (250 mg BID) or placebo.

The primary endpoint was the change in total score on the 17-item version of the Hamilton Depression Rating Scale (HAMD-17) from baseline to week 8 in a prespecified Subgroup C, defined by HPA-axis genetic classifier V1bPGS. The secondary endpoints included response (HAMD-17 ≥50% reduction), remission (HAMD-17 ≤10), further rating scales, safety, and tolerability.

After the conclusion of trial treatment, patients were classified into three predefined subgroups (A, B, C) using the V1bPGS based on protocol-specified criteria.

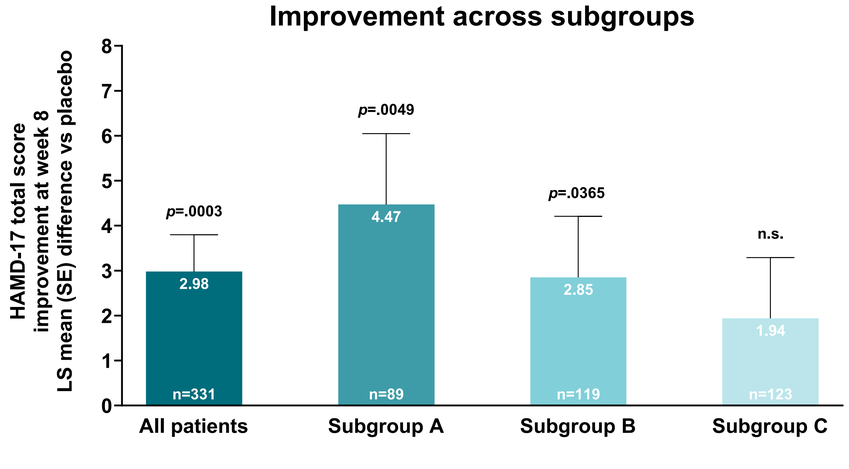
ANTIDEPRESSANT EFFICACY (HAMD-17)

All patients



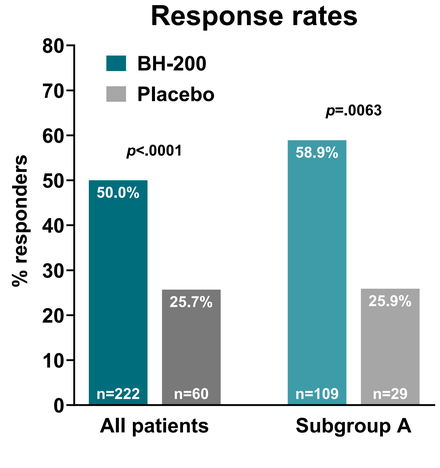
- Clinically meaningful improvement in the full population: 2.98 points HAMD-17 improvement vs placebo at week 8 (p=.0003)
- Effect sizes in line with established antidepressants in similar trials

Improvement across subgroups

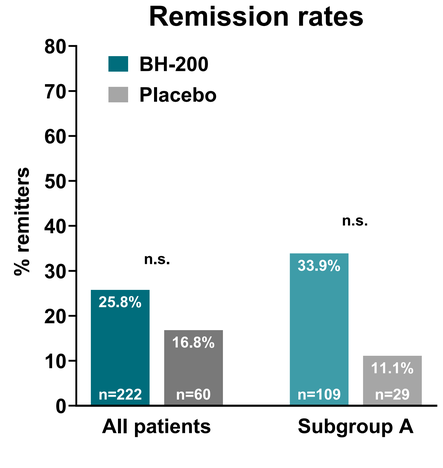


- All three predefined Subgroups showed improvement at week 8.
- The Subgroup C did not separate significantly from placebo (−1.94; p=0.1525). However, the study successfully identified Subgroup A with markedly enhanced benefit (-4.47, p=0.0049)

Response rates



Remission rates



- Response rates at week 8 (at least 50% reduction in HAMD-17 total score from baseline) were higher with BH-200 vs placebo in all patients and in Subgroup A.
- Remission rates at week 8 (HAMD-17 total score equal to or less than 7) tended to be higher in BH-200-treated patients vs placebo, with the most pronounced effect in Subgroup A.

OTHER RATING SCALES

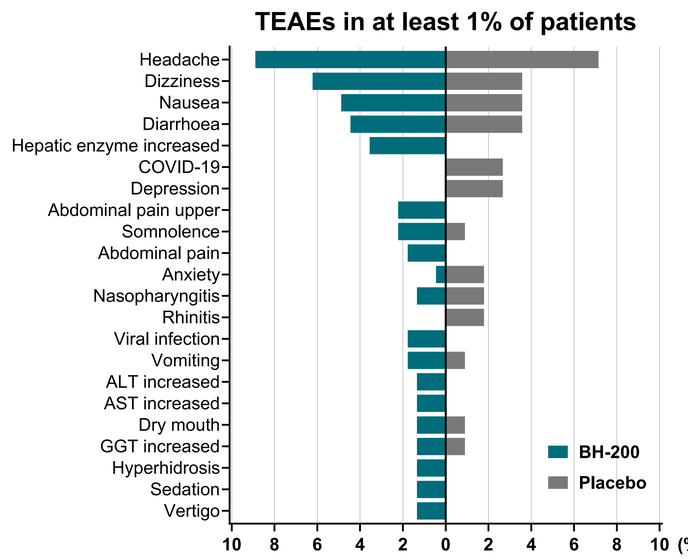
Week 8	MADRS		HADS Total		HADS Depression		HADS Anxiety		CGI-S		SF-36 MCS		SF-36 PCS	
	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value	Δ vs placebo	*p*-value
All patients	-3.3	.0021	-1.79	n.s.	-1.28	.0250	-0.57	n.s.	-0.46	.0006	4.3	.0040	1.1	n.s.
Subgroup A	-5.95	.0011	-3.08	n.s.	-2.13	n.s.	-1.09	n.s.	-0.55	.0038	7.65	.0071	0.49	n.s.
Subgroup B	-1.8	n.s.	-1.58	n.s.	-1.11	n.s.	-0.52	n.s.	-0.45	.0055	1.62	n.s.	2.60	n.s.
Subgroup C	-2.9	n.s.	-1.17	n.s.	-0.89	n.s.	-0.29	n.s.	-0.41	.0114	4.41	n.s.	-0.01	n.s.

Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity (CGI-S), Hospital Anxiety and Depression Scale (HADS), 36-Item Short Form Health Survey (SF-36) mental component scores (MCS) and physical component scores (PCS).

- Consistent improvements in further depression rating scales, with differences (p<.05) in BH-200 vs placebo in MADRS scores (overall and in Subgroup A) and in HADS depressive sub-score (overall) at week 8.
- BH-200 induced improvements vs placebo in patients' functioning as per the CGI-S scale (overall and across Subgroups), and quality of life as per the SF-36 mental component measure (overall and in Subgroup A) at week 8.

SAFETY

- BH-200 was generally well tolerated, with TEAE in 93 patients (41.3%) vs 40 (35.7%) in the placebo arm.
- Most frequent TEAEs in the BH-200 arm included nervous system disorders (17.8% of patients), gastrointestinal disorders (15.1%), investigation abnormalities (6.2%), infections and infestations (4.9%), and psychiatric disorders (2.2%).
- 13 patients (5.8%) in the BH-200 arm had AST/ALT >3× upper limit of normal. All cases resolved during or after treatment.
- Liver function test elevations were mostly asymptomatic and reversible in all cases.
- No serious TEAE occurred in the BH-200 arm.
- 9 patients (4%) discontinued BH-200 due to TEAE related to treatment.



Disclosures: HE, CzE, DG, EP, BMM, and AD are employed by or consultants to HMNC Holding GmbH. FH is a founder and equity owner in HMNC Holding GmbH.

64th American College of Neuropsychopharmacology Annual Meeting | January 12-15, 2026 | Paradise Island, Bahamas