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Antidepressant Efficacy of BH-200 in Patients Classified by a Genetic Selection Tool: Secondary Endpoint Results from the OLIVE Trial

Christine zu Eulenburg[1,2], Evangelos Papanastasiou[1], Ani Damyanova[1], Daniel Gehrlach[1], Hans Eriksson[1]

[1]HMNC Holding GmbH, Wilhelm-Wagenfeld-Straße 20, 80807 Munich, Germany, [2]University Medical Center Hamburg-Eppendorf, Martini-Straße 52, 21049 Hamburg, Germany ✉ Christine.Eulenburg@HMNC-BrainHealth.com

MAIN TAKEAWAYS

- BH-200 showed improvement of depressive symptoms in comparison to placebo in MDD patients across several rating scales.
- These findings were consistently more pronounced in Subgroup A.
- The reported ability to use a genetic tool to identify a subgroup of patients with MDD who respond favorably marks an important milestone in precision psychiatry.

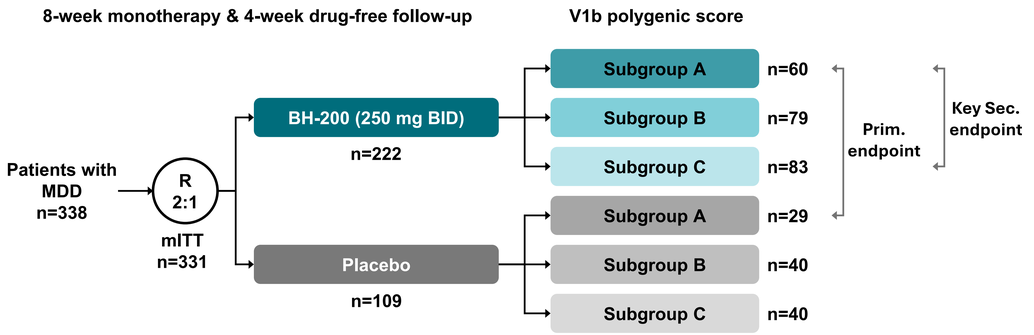
Background

Increasing evidence suggests that depression is a biologically and genetically heterogeneous disorder. A disturbance in the hypothalamus-pituitary-adrenal axis (HPA-axis) function is suggested to be present in a substantial subset of depressed individuals, including those with major depressive disorder (MDD). Several modulators of HPA-axis function, acting on corticotropin-releasing hormone receptor 1 (CRHR1) or vasopressin V1b receptor (V1bR), have been investigated, but none has so far demonstrated the efficacy needed for regulatory approval [1].

BH-200, a selective V1bR antagonist, demonstrated antidepressant efficacy in a previous phase 2 trial (DFI5878, NCT00358631) in 319 unselected patients with 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 [2, 3]. Our initial hypothesis was that Subgroup C benefits most from BH-200.

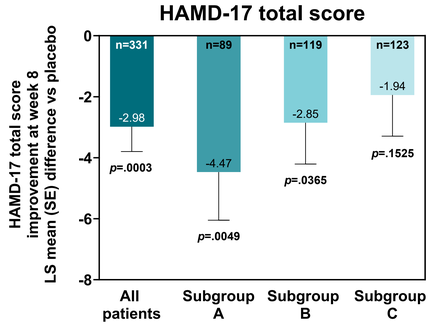
Patients and methods

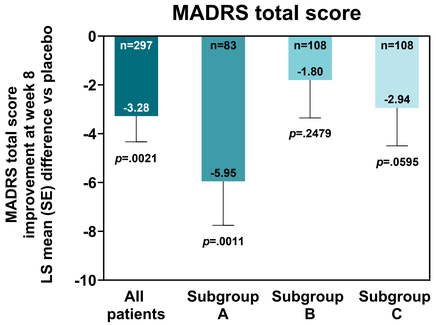
OLIVE (EudraCT: 2022-002757-26) was an 8-week, double-blind, randomized, placebo-controlled phase 2 trial in 338 adult MDD patients (331 in the modified intention-to-treat population, mITT), randomized 2:1 to BH-200 (250 mg BID) or placebo, performed across 50 sites in 8 countries.

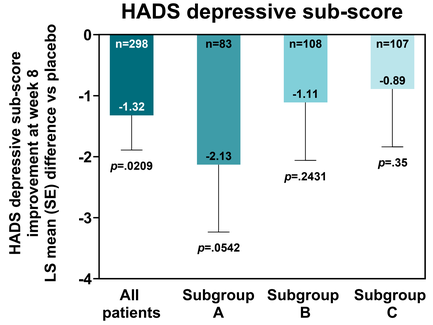


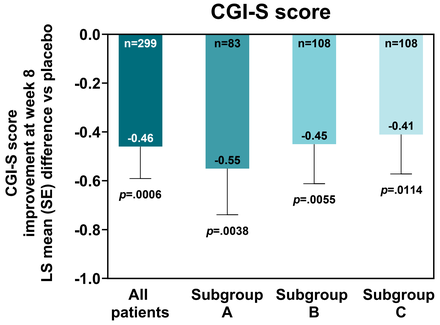
The primary endpoint was the change in total score on the 17-item version of the Hamilton Depression Rating Scale (HAMD-17) from baseline to week 8 in a prespecified Subgroup C, defined by HPA-axis genetic classifier V1bPGS. The key secondary endpoint compared HAMD-17 between BH-200-treated patients 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. After the conclusion of trial treatment, patients were classified into three predefined subgroups (A, B, C, with a roughly 1:1:1 distribution) using the V1bPGS, which emulates the outcome of the dexamethasone-CRH test.

Results: antidepressant efficacy



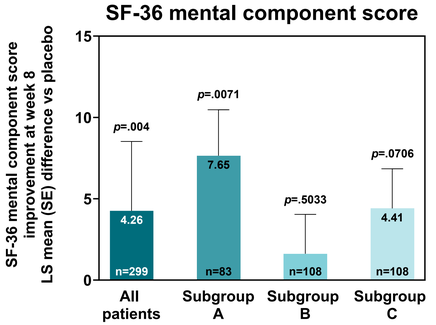


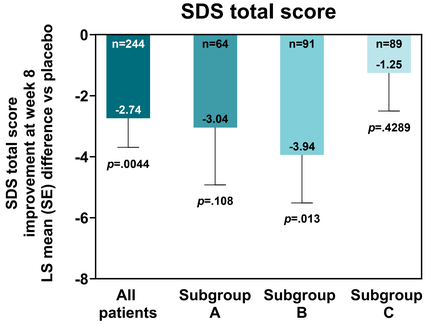




Among 331 patients in the mITT, 8-week BH-200 treatment induced clinically relevant improvements vs placebo with p<0.05 in HAMD-17 total score, MADRS total score, HADS depressive sub-score, and CGI-S score. Analysis by genetic Subgroups using V1bPGS showed a consistent pattern, with the greatest changes relative to placebo observed in Subgroup A for HAMD-17 total score, MADRS total score, and CGI-S score, contrary to our hypothesis that expected the largest benefit in Subgroup C.

QoL and functioning





BH-200 treatment demonstrated, at week 8, a greater improvement than placebo in the SF-36 Mental Component score (in all patients and in Subgroup A) and in the SDS total score (in all patients).

References:

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