Novel Genetic In Vitro Diagnostic Test to Predict Efficacy of BH-200, a V1b Antagonist, in Major Depressive Disorder - A Phase II Randomized Controlled Trial

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Key Insights

The OLIVE trial is, to our knowledge, the first phase 2 randomized clinical trial that integrates a genetic biomarker test to identify patients with stress-axis related major depressive disorder (MDD).

This trial will provide valuable information on the potential of BH-200, a V1b receptor antagonist, as a personalized treatment for MDD patients with a high V1b polygenic score, reflecting central stress axis dysregulation.

The use of pre-specified genetically defined sub-groups for analysis is a viable strategy to assess and further improve the predictive performance of a genetic selection tool.

The use of a genetic *in vitro* diagnostic test as a companion diagnostic to select patients would personalize and enhance effectiveness of treatments for MDD.

Topline results are expected in late 2024.

Background

Dysregulated stress response and major depressive disorder | A substantial subset (~30%) of all patients with MDD appear to have a disturbance in vasopressin and/or CRH signaling, which affects central behavioral & emotional circuits and the peripheral HPA ("stress") axis.[1]

BH-200 (nelivaptan), a vasopressin 1b receptor antagonist, as potential treatment of MDD | BH-200 (nelivaptan) is a V1b receptor antagonist that has shown promise in clinical studies as a potential treatment for major depressive disorder (MDD).[2] We hypothesize that only a subset of patients – those with a dysregulated stress axis – benefit from treatment with BH-200.

Genetic in-vitro diagnostic test to predict treatment outcome | To identify those patients with stress axis deregulation, we developed the V1b polygenic score (V1bPGS), a blood-based, genetic biomarker test that functions as a proxy marker of the clinical dexamethasone/CRH (dex/CRH) test, which predicts patients' predisposition to a dysregulated stress axis.

V1bPGS Biomarker Test

The V1bPGS is based on an interaction analysis with single nucleotide polymorphisms (SNPs) within the V1bR gene. The V1bPGS was developed based on the dex/CRH response in 352 patients with moderate to severe MDD participating in the Munich Antidepressant Signature (MARS) study.[3]

An anchored genome-wide interaction analysis (GWIA) identified 14 SNPs with a significant interaction of the "anchor" SNP rs28373064 (located in *AVPR1B* gene) with the phenotype, represented by the response of ACTH secretion. Probabilistic neural networks are employed to classify a patient into one of three groups (high, medium, low).

The V1bPGS was validated with leave-one-out-cross validation and achieved a predictive performance of the ACTH response in the dex/CRH test of ≥90% sensitivity and specificity (**Table 1**).

The biological plausibility of the 14 SNPs was demonstrated using Bayesian network modeling, which uncovered that the SNPs represented biologically active networks in brain areas including the amygdala, hippocampus, and pituitary.[4]

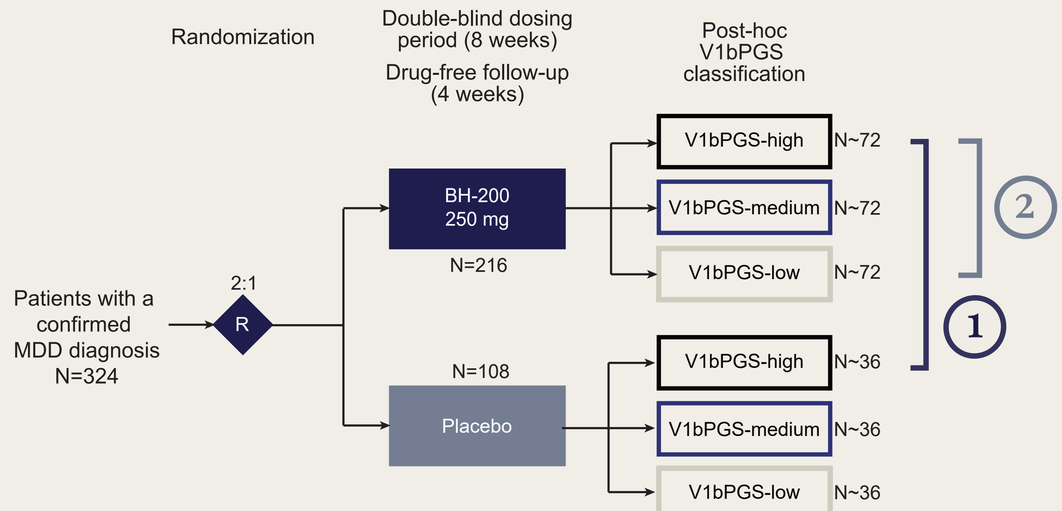
Table 1. Confusion Matrix Of V1bPGS Performance

		Observed clinical phenotype	
		High ACTH Response	**Low or medium ACTH Response**
Predicted by V1BCDx	**High ACTH Response**	105	11
	Low or medium ACTH Response	12	224
		Sensitivity 90%	**Specificity 95%**

Trial Objectives

1. **Primary Objective** | To assess the efficacy of BH-200 (250 mg BID) versus placebo in improving depressive symptoms in V1b-high patients.
2. **Key Secondary Objective** | To compare the improvement of depressive symptoms in V1b-high versus V1b-low patients treated with BH-200 (250 mg BID).

Figure 1. OLIVE Trial Design



Design Features

OLIVE is an ongoing 8-week, randomized, double-blind, multicenter Phase 2, multicentre trial in 8 European countries to assess the efficacy of BH-200 versus placebo in MDD patients (**Figure 1**). Importantly, analyses of objectives and endpoints are prespecified in genetically defined sub-groups, classified by the V1bPGS (high, medium or low).

- Co-development of compound (i.e. BH-200) combined with dedicated genetic biomarker (i.e. V1bPGS).
- Post-hoc testing with the V1bPGS allows flexibility in future development compared to a prospective screening approach. Biological samples of consenting patients will be collected to refine the predictive performance of the V1bPGS by incorporating multi-omic analyses.

Primary Efficacy Endpoint

Change from baseline in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score after 8 weeks of treatment.

Selected Secondary Efficacy Endpoints

- Change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score after 4 weeks and 8 weeks of treatment.
- Response rate (at least 50% reduction in the total score of HAMD-17 compared to baseline).
- Remission rate (total score of HAMD-17 equal to or less than 7)

Key Inclusion Criteria

- Male or female outpatients, 18-75 years of age at the date of informed consent.
- Primary diagnosis of MDD as defined by Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) and confirmed by the Mini International Neuropsychiatric Interview (MINI).
- MADRS score ≥20 at screening and baseline.
- Duration of current episode no longer than 12 months, prior to screening.
- Symptoms of depression present for at least 2 weeks, prior to screening.
- Willingness to stop current antidepressive medication (ongoing psychotherapy and physical activity programs can continue).

Key Exclusion Criteria

Patients with bipolar, schizophrenia spectrum, paranoid, schizoid, schizotypal personality, antisocial, borderline, histrionic and narcissistic personality, and other psychotic disorders; PTSD; a significant risk of suicide; a history of moderate to severe alcohol use and/or substance use disorder will be excluded.

Outlook

It is aimed to enroll 324 patients, with 216 receiving BH-200 and 108 receiving placebo.
The trial started recruiting in Q2 2023.
The trial is expected to read out in Q4 2024.

References

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Disclosures

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