Genetic in-vitro diagnostic test to predict efficacy of BH-200, a V1b antagonist, in major depressive disorder: a phase II randomized controlled trial with post-hoc genetic testing

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Methodological Issue Being Addressed Co-development of a genetic companion diagnostic together with a small molecule drug for major depressive disorder has no precedence and poses several challenges. Here, we would like to present our methodological approach of a pre-planned retrospective analysis of genetically defined sub-populations in the early co-development process of a CDx + Rx (Phase II). We describe the derivation of the v1b polygenic risk score.

Introduction BH-200 (nelivaptan) is a V1b receptor antagonist that has shown potential in clinical studies as treatment for major depressive disorder (MDD). Our hypothesis is that only a subset of patients – those with a dysregulated stress axis – will benefit the most from treatment with a v1b receptor antagonist. We developed a genetic in-vitro diagnostic test – the v1b polygenic score (V1bPGS) - to predict patients' genetic predisposition to a dysregulated stress axis, and consequently a response to a v1b receptor antagonist.

Methods We are conducting an 8-week, randomized, double-blind, multicenter phase II trial in 8 European countries to assess the efficacy of BH-200 versus placebo in MDD patients. Patients are randomized in a 2:1 ratio to receive either 250 mg BH-200 twice daily (BID) or placebo. Importantly, analyses of objectives and endpoints are prespecified in genetically defined sub-groups, classified by the V1bPGS. The V1bPGS is a genetic test predictive of the Dex/CRH challenge test which is regarded as a proxy for a dysregulated stress axis mediated by central vasopressinergic overactivity. Genome-wide interaction analyses (GWIA) identified 14 single-nucleotide polymorphisms associated with the Dex/CRH outcome. Probabilistic Neural Networks are employed to classify a patient into one of three groups (high, medium, low). The primary objective is to assess the efficacy of BH-200 versus Placebo in improving depressive symptoms in V1b-high patients. The key secondary objective is to compare the improvement of depressive symptoms in V1b-high versus V1b-low patients treated with BH-200. Biological samples of consenting patients will be collected to refine the predictive performance of the v1b polygenic score by incorporating multi-omic analyses.

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

Conclusion This trial will provide valuable information on the potential of BH-200 to become a personalized treatment for MDD patients by assessing their V1b polygenic score. The use of pre-specified genetically defined sub-groups for analysis could be the most viable strategy to assess the predictive performance of a selection tool. The resulting data will be used to further

co-develop the V1b polygenic score together with BH-200. The use of a genetic in-vitro diagnostic test as a companion diagnostic to select patients could enchance the effectiveness of treatments for MDD.

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