03 March 2025 • Press Release

Oryzon defines Phase III Trial endpoints for Agitation and Aggression in BPD with input from new Clinical Advisory Board

- **Leading US psychiatric experts join Oryzon's Clinical Advisory Board (CAB) to advance Phase III development of vafidemstat in Borderline Personality Disorder (BPD)**
- **CAB and Oryzon establish primary and key secondary endpoints for Phase III trial, aligned with FDA standards**
- **Oryzon moves forward with plans to submit Phase III protocol to the FDA in 1H 2025**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, March 03, 2025 – Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company and a European leader in epigenetics, today announced that it has established the primary and key secondary endpoints for its planned Phase III clinical trial evaluating vafidemstat in Borderline Personality Disorder (BPD). This milestone was reached in collaboration with Oryzon's newly formed Clinical Advisory Board (CAB), composed of leading experts in psychiatry research and clinical trials for psychiatric disorders.

The CAB's insights have been instrumental in ensuring that the Phase III protocol aligns with FDA expectations and incorporates well-validated, widely recognized assessment scales to measure agitation and aggression in BPD patients. This development follows the successful completion of the Phase IIb PORTICO trial, which received positive feedback from the FDA, and positions Oryzon to submit the Phase III protocol for regulatory review in the first half of 2025.

"We are honored to collaborate with such a distinguished panel of experts as we advance vafidemstat into Phase III development," said Dr. Carlos Buesa, Chief Executive Officer of Oryzon. "Their expertise in psychiatric disorders and clinical trial methodology strengthens our program and ensures that we are well-prepared for the next regulatory interactions. Addressing aggression and agitation in BPD remains an urgent medical need, and we are committed to delivering innovative solutions for these patients."

Oryzon's Clinical Advisory Board Members:

Oryzon's CAB includes internationally recognized leaders in psychiatry and clinical trial research:

- **Dr. Alan F. Schatzberg**, *Kenneth T. Norris, Jr. Professor of Psychiatry and Behavioral Sciences at* ***Stanford University School of Medicine***, former Chair of the Department (1991–2010), and current

Director of the Stanford Mood Disorders Center. A past President of the American Psychiatric Association (2009–2010), he is a leading expert in mood disorders, particularly the neurobiology and treatment of depression.

- **Dr. Eric Hollander**, *Professor of Psychiatry and Director of the Autism and Obsessive Compulsive Spectrum Program at* ***Albert Einstein College of Medicine and Montefiore Medical Center***, is a leading authority on obsessive-compulsive and related disorders. He has received multiple NIMH grants to develop treatments for BPD, with a research focus on the neurobiology of aggression and affective instability in BPD.

- **Dr. Sarah Fineberg**, *Assistant Professor of Psychiatry at* ***Yale University School of Medicine***, specializes in the neurobiology of BPD. Her research explores social cognition and decision-making using computational psychiatry and neuroimaging. She has led clinical trials testing novel interventions for BPD, including sub-anesthetic ketamine for BPD and real-time fMRI neurofeedback.

- **Dr. Emil F. Coccaro**, *George T. Harding III, M.D., Endowed Professor in the Department of Psychiatry and Behavioral Health at* ***The Ohio State University Wexner Medical Center***, is a leading expert in the neurobiology of aggression and impulsivity. His work has significantly advanced the understanding and treatment of impulsive aggression in BPD through pharmacological interventions.

“These are the right experts to help us shape a Phase III program that is both scientifically rigorous and clinically meaningful,” added Dr. Buesa. “It is particularly reassuring that their expert medical opinion and years of practice recognize aggression as one of the most debilitating aspects of many psychiatric disorders, and particularly in borderline personality disorder. Their contributions have been instrumental in defining the primary and secondary endpoints, that will generate robust data for regulatory submissions.”

“Agitation and aggression remain difficult to treat symptoms in neuropsychiatric disorders,” said Dr. Schatzberg. “Pharmacological agents that target epigenetic changes hold great promise for reducing such symptoms and behaviors. LSD1 inhibitors offer a great opportunity for developing compounds that can provide relief for patients who suffer with such symptoms.”

Next Steps in Vafidemstat’s Development

Oryzon remains committed to progressing vafidemstat as a potential first-in-class treatment for agitation and aggression in BPD. Following the FDA’s feedback on the PORTICO trial results, Oryzon plans to submit the Phase III protocol in the first half of 2025, with trial initiation expected soon after, pending regulatory approval and securing the necessary funding.

Beyond BPD, vafidemstat is being evaluated in a Phase IIb trial for the treatment of negative symptoms in schizophrenia (EVOLUTION trial) and is part of Oryzon’s broader CNS precision medicine approach. The company is also exploring additional applications in genetically defined subpopulations and neurodevelopmental disorders.

For more information about the experience of the CAB members, please visit the CAB section in our website, here.

About Oryzon

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company and the European leader in epigenetics, with a strong focus on personalized medicine in CNS disorders and oncology. Oryzon's team is composed of highly qualified professionals from the pharma industry located in Barcelona, Boston, and San Diego. Oryzon has an advanced clinical portfolio with two LSD1 inhibitors, vafidemstat in CNS (Phase III-ready) and iadademstat in oncology (Phase II). The company has other pipeline assets directed against other epigenetic targets like HDAC-6 where a clinical candidate ORY-4001, has been nominated for its possible development in CMT and ALS. In addition, Oryzon has a strong platform for biomarker identification and target validation for a variety of malignant and neurological diseases. For more information, visit www.oryzon.com

About Vafidemstat

Vafidemstat (ORY-2001) is an oral, CNS-optimized LSD1 inhibitor. The molecule acts on several levels: it reduces cognitive impairment, including memory loss and neuroinflammation, and at the same time has neuroprotective effects. In animal studies vafidemstat not only restores memory but reduces the exacerbated aggressiveness of SAMP8 mice, a model for accelerated aging and Alzheimer's disease (AD), to normal levels and also reduces social avoidance and enhances sociability in murine models. In addition, vafidemstat exhibits fast, strong, and durable efficacy in several preclinical models of multiple sclerosis (MS). Oryzon has performed two Phase IIa clinical trials in aggressiveness in patients with different psychiatric disorders (REIMAGINE, see Ferrer et al, Psychiatry & Clin Neurosci, 2025, doi.org/10.1111/pcn.13800) and in aggressive/agitated patients with moderate or severe AD (REIMAGINE-AD), with positive clinical results reported in both. Additional finalized Phase IIa clinical trials with vafidemstat include the ETHERAL trial in patients with Mild to Moderate AD, where a significant reduction of the inflammatory biomarker YKL40 was observed after 6 and 12 months of treatment, and the pilot, small-scale SATEEN trial in Relapse-Remitting and Secondary Progressive MS, where anti-inflammatory activity was also observed. Vafidemstat has also been tested in a Phase II in severe Covid-19 patients (ESCAPE) assessing the capability of the drug to prevent ARDS, one of the most severe complications of the viral infection, where it showed significant anti-inflammatory effects in severe Covid-19 patients. Vafidemstat is currently advancing as a Phase III-ready asset in Borderline Personality disorder (BPD) following completion of the global, randomized, double blind Phase IIb PORTICO trial (final data presented at ECNP-2024). Following receipt of the minutes from the End-of-Phase II meeting with the FDA to discuss PORTICO's results, the company announced plans to move forward with a Phase III PORTICO-2 trial in agitation/aggression in BPD (FDA submission planned in 1H2025). Vafidemstat is also being investigated in a double-blind, randomized, placebo-controlled Phase IIb trial in negative symptoms of schizophrenia (EVOLUTION trial, recruitment ongoing). The company is also deploying a CNS precision medicine approach with vafidemstat in genetically-defined patient subpopulations of certain CNS disorders and is evaluating a clinical trial in Kabuki Syndrome patients. The company is also exploring the clinical development of vafidemstat in other neurodevelopmental syndromes.

FORWARD-LOOKING STATEMENTS

This communication contains, or may contain, forward-looking information and statements about Oryzon, including financial projections and estimates and their underlying assumptions, statements regarding plans, objectives, and expectations with respect to future operations, capital expenditures, synergies, products and services, and statements regarding future performance. Forward-looking statements are statements that are not historical facts and are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates" and similar expressions. Although Oryzon believes that the expectations reflected in such forward-looking statements are reasonable, investors and holders of Oryzon shares are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Oryzon that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the documents sent by Oryzon to the Spanish Comisión Nacional del Mercado de Valores (CNMV), which are accessible to the public. Forward-looking statements are not guarantees of future performance and have not been reviewed by the auditors of Oryzon. You are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date they were made. All subsequent oral or written forward-looking statements attributable to Oryzon or any of its members, directors, officers, employees, or any persons acting on its behalf are expressly qualified in their entirety by the cautionary statement above. All forward-looking statements included herein are based on information available to Oryzon on the date hereof. Except as required by applicable law, Oryzon does not undertake any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise. This document does not constitute an offer or invitation to purchase or subscribe shares in accordance with the provisions of Regulation (EU) 2017/1129 of the European Parliament and of the Council of 14 June 2017, and/or the restated text of the Securities Market Law, approved by Law 6/2023 of 17 March, and its implementing regulations. Nothing in this document constitutes investment advice. In addition, this document does not constitute an offer of purchase, sale or exchange, nor a request for an offer of purchase, sale or exchange of securities, nor a request for any vote or approval in any jurisdiction. The shares of Oryzon Genomics, S.A. may not be offered or sold in the United States of America except pursuant to an effective registration statement under the Securities Act of 1933 or pursuant to a valid exemption from registration..

Spain
Patricia Cobo/Mario Cordera
Atrevia
+34 91 564 07 25
+34 673 33 97 65
pcobo@atrevia.com
mcordera@atrevia.com

Oryzon
Emili Torrell
Chief BD Officer
+34 93 515 1313

etorrell@oryzon.com

IR & Media, Europe & US
Sandya von der Weid
LifeSci Advisors, LLC
+41 78 680 05 38

svonderweid@lifesciadvisors.com