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# ORYZON announces submission of Phase III protocol to FDA to initiate PORTICO-2 trial of vafidemstat in Borderline Personality Disorder (BPD) patients

- **PORTICO-2 designed to validate vafidemstat's efficacy in reducing aggression in BPD patients**
- **Primary endpoint: STAXI-2 Trait Anger (patient-reported)**
- **Key secondary endpoint: Overt Aggression Scale-Modified (OAS-M) (clinician-rated)**
- **Additional secondary endpoints will assess global clinical improvement**
- **Protocol finalized following FDA guidance and input from leading US psychiatry experts**
- **Upcoming KOL webinar to discuss trial design and the urgent medical need in BPD**

**MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, June 23rd, 2025 -** Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company and a European leader in epigenetics, announced today that it has submitted the clinical trial protocol for its Phase III PORTICO-2 trial to the U.S. Food and Drug Administration (FDA) to initiate a registrational trial to evaluate vafidemstat in patients with Borderline Personality Disorder (BPD). The PORTICO-2 trial builds upon the encouraging results observed in the previous PORTICO Phase IIb study, where vafidemstat demonstrated significant and clinically meaningful reductions in secondary endpoints measuring aggression and overall BPD improvement. Aggression is a key symptom domain in BPD that currently represents a major unmet medical need and will be the primary endpoint in PORTICO-2. Vafidemstat, an orally active LSD1 inhibitor with a novel epigenetic mechanism of action, has shown a favorable safety and tolerability profile across multiple clinical studies.

"The submission of PORTICO-2 to the FDA marks a major step forward for Oryzon and for the field of neuropsychiatry of personality disorders," said Carlos Buesa, Chief Executive Officer of Oryzon. "Borderline Personality Disorder is a highly disabling condition with no approved pharmacological treatments. With its novel epigenetic mechanism, vafidemstat has the potential to become the first targeted therapy specifically

addressing aggression and overall improvement in BPD, offering real hope for patients and clinicians confronting this serious disorder. Vafidemstat has also the potential to manage aggression in other neurodevelopmental and neurodegenerative disorders, and we are planning to explore it in a new trial in aggression in ASD."

The Phase III protocol was developed through multiple interactions and constructive exchanges with the FDA. Its final design was further refined with the scientific contribution of internationally recognized psychiatric experts, including Dr. Alan Schatzberg (Stanford University), Dr. Eric Hollander (Albert Einstein Medical School), Dr. Emil Coccaro (Ohio State University Wexner Medical Center), and Dr. Sarah Fineberg (Yale University).

PORTICO-2 will employ two clinical outcome measures for aggression: the **STAXI-2 Trait Anger scale** (patient-reported) as the primary endpoint, and the **Overt Aggression Scale-Modified (OAS-M)** (clinician-rated) as key secondary endpoint. Additional secondary endpoints will evaluate broader clinical improvements in BPD symptomatology and quality of life.

A dedicated **Key Opinion Leader (KOL) webinar** is planned in the coming weeks to discuss the PORTICO-2 study design, the substantial unmet medical need in BPD, and the role of aggression as a clinical target. Details will be announced in a further communication.

PORTICO-2 will be a randomized, double-blind, placebo-controlled, multi-center study to assess both the efficacy and safety of vafidemstat in BPD patients, and aims to randomize 350 patients.

BPD affects approximately 1-2% of the general population and is characterized by pervasive emotional instability, impulsivity, interpersonal dysfunction, unstable self-image and frequent episodes of aggression and self-harm. More than 75% of BPD patients attempt suicide, and the rate of completed suicide has been estimated to be approximately 10%, 50-times higher than in the general population. Currently, there are no FDA-approved medications specifically indicated for the treatment of BPD, underscoring the urgent need for novel therapeutic approaches.

Additional exploratory data from earlier Phase IIa studies suggest that vafidemstat may also reduce aggression in other patient populations, including Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and Alzheimer's Disease (AD). The company is planning to explore this further in a new trial in aggression in ASD to be conducted within the activities of the Med4Cure IPCEI-EU Grant.

### 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 (PhIII protocol submitted to FDA). 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, as well as in neurodevelopmental syndromes, and is evaluating the feasibility of conducting clinical trials in autistic conditions like Fragile X syndrome and Phelan-McDermid syndrome.

## 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..


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