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ORYZON presents the final data from PORTICO, a global Phase IIb vafidemstat trial in Borderline Personality Disorder (BPD), at the European College of Neuropsycopharmacology (ECNP) congress

- **Strong improvement in *State-Trait Anger Expression Inventory 2 (STAXI-2) Trait Anger,* a measure of agitation and aggression, at Weeks 8–12 compared to previous top line data; nominal statistical significance now of p = 0.0071**
- **Improvement in *Borderline Evaluation of Severity (BEST),* an overall measure of BPD disease severity, at Weeks 8–12 compared to previous top line data; nominal statistical significance now of p = 0.0260**
- **Vafidemstat showed favorable results over placebo in all primary and secondary efficacy endpoints, as demonstrated by T-Forest plot analysis**
- **Global Statistical Test (GST p-values) significant and consistent with a global treatment effect favoring vafidemstat**
- **Company presented the data to the FDA and discussed potential registrational Phase III vafidemstat study for the treatment of BPD at a recent End-of-Phase II meeting**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, September 23, 2024 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with strong unmet medical need, announced that it will present today the final data from its Phase IIb PORTICO trial of vafidemstat in patients with Borderline Personality Disorder (BPD) as an oral presentation at the New Medications Symposium, a special symposium focused on clinical trials of new compounds within the 37th European College of Neuropsychopharmacology (ECNP-2024) congress, which is currently being held in Milan (Italy). Oryzon's oral presentation, titled "Final results: Phase 2b PORTICO Study: Efficacy of Vafidemstat in Borderline Personality Disorder", will be delivered by Dr. Michael Ropacki, Oryzon's Chief Medical Officer for CNS. In addition to the oral presentation, the results will also be presented as a poster at ECNP-2024.

PORTICO (EudraCT No.: 2020-003469-20, ClinicalTrials.gov Identifier NCT04932291) was a global double-blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial evaluating the efficacy and safety of vafidemstat at 1.2 mg/day in a BPD population. The study recruited a total of 211 patients, randomized

1:1 in two arms. The trial had two independent primary endpoints: reduction of agitation and aggression and overall disease improvement in BPD severity. In the absence of a well-established regulatory endpoint, the trial also included two secondary endpoints also exploring the reduction of agitation and aggression and overall disease improvement in BPD severity by different scales. PORTICO included a total of 27 clinical sites, 14 in the U.S. and 13 in Europe (Germany, Spain, Bulgaria, and Serbia).

Dr. Michael Ropacki, Oryzon's Chief Medical Officer for CNS stated, "The PORTICO results are exciting and extremely promising in several ways. These full results are improved compared to the topline results shared in January 2024. BPD is a serious mental health disease with great interpersonal, social, and economic burden and vafidemstat potentially proposes a novel treatment option with an epigenetic mechanism-of-action that does not have the side-effect baggage of current off-label treatments. The significant and clinically meaningful reductions in agitation and aggression as well as overall disease improvement produced by vafidemstat offer the first potential pharmacologic treatment to significantly improve the lives of BPD patients and those around them."

Dr. Carlos Buesa, Oryzon's CEO added: "PORTICO marks a significant milestone in BPD research, as this is the first time, to our knowledge, that statistical significance was achieved in a large, randomized Phase IIb trial in BPD. Our study demonstrated meaningful improvements, and vafidemstat seems to produce a holistic effect in the disease. In a recent End-of-Phase II meeting with the FDA we had the opportunity to discuss these results. A positive response from the FDA would trigger immediate preparations of our PORTICO-2 Phase III trial, and would make Oryzon the first, and only, company with a drug in Phase III clinical development in BPD, an indication with a huge unmet medical need and no drugs approved. The recent grants or intention-to-grant notifications for vafidemstat's patents in BPD and aggression received from different Patent Offices highlight the economic potential of this unique program."

Presentation Data Highlights:

The final data show a significant overall improvement compared to the preliminary top-line data (TLD) released in January.

- Notably, the agitation and aggression of patients, as measured by the secondary endpoint STAXI-2 Trait Anger scale, showed a substantial, statistically significant, and clinically meaningful reduction in the vafidemstat arm compared to placebo, with a p-value of 0.0071 across Weeks 8–12 (previously p = 0.0259). The relative reduction in the vafidemstat-treated group over the placebo group reached a maximum of 92.1% at Week 10, with an average reduction of 58.6% across Weeks 8–12 (previously 80.8% and 46.7%, respectively).
- Additionally, the secondary endpoint Borderline Evaluation of Severity (BEST), an overall measure of BPD severity, also showed an improvement compared to TLD, with a p-value of 0.0260 across Weeks 8–12 (previously p = 0.0423). The maximal relative reduction in the vafidemstat-treated group over the placebo group reached 38.9% at Week 10, with an average reduction of 30.9% across Weeks 8–12.
- The p-values for the primary endpoints (CGI-S A/A and BPDCL) also improved compared to the preliminary TLD, but did not reach statistical significance.

- Interestingly, a trend of improvement in depression measured by the BDI-II Total Score by Weeks 8–12 was detected (p= 0.0944), with an average reduction over the placebo group of 42.2% across Weeks 8–12.
- The T-Forest plot analysis showed that all results continued to consistently favor vafidemstat treatment over placebo across all primary and secondary efficacy endpoints.
- Notably, the final analysis confirmed now a global treatment effect favoring vafidemstat by the Global Statistical Test (GST), with the GST p-value showing a statistical significance, particularly when considering global improvement in the severity of the disease and in agitation/aggression (p = 0.0362, previously a strong trend). The GST is designed to assess whether a treatment is effective across different aspects of a condition, efficiently summarizing the overall treatment effect, especially when dealing with complex, multifactorial diseases.
- Vafidemstat was, as in all previous clinical studies, safe and well-tolerated. Adverse events (AEs) were generally consistent with the safety profile of vafidemstat seen to date, with no new safety findings. Treatment-Emergent Adverse Events (TEAEs) were slightly lower in those receiving vafidemstat (57.5% vs 65.4% in the placebo group), though Treatment-Related TEAEs were similar between groups.
- An observation of interest was that vafidemstat-treated patients showed a reduced inclination towards self-harm compared to the ones receiving placebo (1 patient vs 6 patients in the placebo group).

All these data have been presented to the FDA in an end-of-Phase II meeting held recently to discuss a registrational Phase III study for the treatment of BPD.

A copy of the ECNP presentation is available here and the accompanying poster is available 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 and iadademstat in oncology, in several Phase II clinical trials. 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) 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 has been 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 has also been 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 being investigated in neuropsychiatric disorders in two double-blind, randomized, placebo-

controlled Phase IIb trials: one in schizophrenia, named EVOLUTION (recruitment ongoing), and another one in Borderline Personality disorder (BPD), named PORTICO, completed and with published results. Based on PORTICO's results, the company has requested an End-of-Phase II meeting with the FDA to discuss options for a registrational Phase III trial in BPD. The company is also deploying a CNS precision medicine approach with vafidemstat in genetically-defined patient subpopulations of certain CNS disorders and is preparing a clinical trial in Kabuki Syndrome patients. The company is also exploring the clinical development of vafidemstat in other neurodevelopmental syndromes.

About Borderline Personality Disorder

Borderline Personality Disorder (BPD) is one of the most complex, functionally debilitating and costly psychiatric illnesses for health care systems, affecting between 0.5 and 1.6% of the general population. BPD patients often experience emotional instability, impulsivity, irrational beliefs and distorted perception, and intense but unstable relationships with others. Up to 10% of those affected die by suicide. Psychotherapy is the first-line treatment and while medications may be prescribed to treat specific symptoms, there is no FDA-approved treatment for BPD patients. It is estimated that around 1.4 million BPD patients in the U.S. are being treated with off-label drugs, approved for other conditions and which manage symptoms rather than the disease itself.

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 press release is not an offer of securities for sale in the United States or any other jurisdiction. Oryzon's securities may not be offered or sold in the United States absent registration or an exemption from registration. Any public offering of Oryzon's securities to be made in the United States will be made by means of a prospectus that may be obtained from Oryzon or the selling security holder, as applicable, that will contain detailed information about Oryzon and management, as well as financial statements.

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