ORYZON Announces Topline Results from Phase IIb PORTICO study of vafidemstat in Borderline Personality Disorder (BPD)

Company to host Conference Call and live Webcast on
Sunday, January 7, 2024 at 5:30 pm PT.

An executive summary of the data to be presented at the 7th Sachs Annual Neuroscience Innovation Forum, on January 7 at 3:30 pm PT, at the Marine's Memorial Club in San Francisco (USA).

- **Results across all efficacy endpoints consistently favored vafidemstat over placebo. Global Statistical Test (GST p-values) confirms consistent trend across efficacy endpoints**

- **The primary endpoints, improvement in *Borderline Personality Disorder Checklist (BPDCL)* and in agitation/aggression by the *Clinical Global Impression – Severity Agitation/Aggression (CGI-S A/A)*, did not reach statistical significance**

- **Nominal statistical significance was achieved on the secondary endpoint *Borderline Evaluation of Severity (BEST),* an overall measure of BPD disease severity, at weeks 8-12 (p = 0.042)**

- **Nominal statistical significance was also achieved on the secondary endpoint *State-Trait Anger Expression Inventory 2 (STAXI-2) Trait Anger,* a measure of agitation and aggression, at weeks 8-12 (p = 0.026)**

- **Vafidemstat was safe and well tolerated, consistent with the overall safety profile to date**

- **Based on the efficacy and safety results, Oryzon intends to request an FDA end-of-Phase II meeting to discuss a registrational Phase III study for the treatment of BPD**

MADRID, SPAIN and BOSTON, MA, UNITED STATES, January 5th, 2024 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with a strong unmet medical need, today announced topline results from the Phase IIb PORTICO trial, evaluating the efficacy and safety of vafidemstat in Borderline Personality Disorder (BPD).

Webcast/Conference Call Information

ORYZON will host a conference call and webcast on January 7, 2024 at 5:30 pm Pacific Time to discuss PORTICO Phase IIb results. To register for the event please click here. A replay of the webcast will be available on the company's website after the event and will be archived for approximately one month.

Summary of Efficacy Data

A mixed model repeated measures (MMRM) completed on the multiple independent primary endpoints for overall disease as measured by the Borderline Personality Disorder Checklist (BPDCL) and for agitation and aggression by the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) across weeks 8-12 showed for both endpoints a consistent reduction over the values in the placebo group throughout the treatment, which did not reach statistical significance ($p = 0.41$ and $p = 0.25$, respectively).

However, statistically significant overall disease improvement was achieved on the secondary endpoint Borderline Evaluation of Severity (BEST) across weeks 8-12 ($p = 0.042$). The BEST scale was designed to measure BPD symptom severity and adaptive coping responses including negative behaviors and actions such as injuring oneself, thoughts and feelings including mood reactivity, identity disturbance, unstable relationships, paranoia, emptiness, and suicidal thinking, and positive behaviors such as avoidance of self-destructive and/or self-defeating behaviors. The relative reduction observed in the vafidemstat-treated group over the placebo group was consistent throughout the treatment and reached a maximum of 38% at week 10.

Additionally, statistically significant improvement in agitation and aggression as measured by the STAXI-2, Trait Anger ($p = 0.026$) was also demonstrated across weeks 8-12. The Trait Anger scale (10 items) measures the disposition to experience angry feelings as a personality-like trait over time. The relative reduction observed in the vafidemstat-treated group over the placebo group was consistent throughout the treatment and reached a maximum of 80% at week 10.

It was also encouraging to note that all results favored vafidemstat treatment over placebo across the multiple independent primary and secondary efficacy endpoints. Furthermore, the Global Statistical Test (GST p-values) confirms a strong trend effect across all efficacy endpoints. GST is designed to globally address whether a treatment is efficacious across different aspects of a condition. The GST efficiently summarizes a global treatment's effect when the disease is complex and multifactorial.

Summary of Safety and Tolerability Data

Vafidemstat was safe and well-tolerated. Adverse events (AEs) were generally consistent with the safety profile of vafidemstat seen to date, with no new safety findings. The number of subjects with Treatment-Emergent Adverse Events (TEAEs) was slightly lower for those receiving vafidemstat (57.5%) vs placebo

(65.4%). Treatment-Related TEAEs were similar between groups (34.0% of subjects in the vafidemstat arm vs 31.7% in placebo). Those TEAEs leading to Study Discontinuation, Study Drug Withdrawal, or Study Drug Interruption were low overall. Regarding TEAE Severity, the majority were independently assessed by the investigators as Mild (48.1% of subjects in vafidemstat versus 57.7% in placebo) or Moderate (27.4% in vafidemstat versus 33.7% in placebo), with low numbers in both groups experiencing a Severe AE (4.7% in vafidemstat versus 3.8% in placebo). The majority of TEAEs Recovered/Resolved by the end of the trial. There were no deaths in PORTICO, and the only TEAE with sequelae was on placebo.

Dr. Michael Ropacki, Chief Medical Officer, Head of CNS Clinical Development stated, "The results provide support and a path forward for vafidemstat's future clinical development as a potentially promising treatment for overall BPD disease and agitation and aggression. PORTICO's results are highly encouraging given that vafidemstat improved overall BPD severity as reflected by the BEST Total score ($p = 0.042$), all efficacy results favoring vafidemstat over placebo, and the GST analysis. Likewise, the data continue to highlight vafidemstat's promise to reduce agitation and aggression as reflected on the STAXI-2 Trait Anger ($p = 0.026$). To contextualize these findings, the observation that all eleven primary and secondary efficacy endpoints favored vafidemstat over placebo provides consistent support for a positive treatment effect, and indicates that further clinical development of this compound should be pursued. Finally, in a disease with no 'gold standard' measure, PORTICO achieved an important milestone by helping determine what endpoints should be carried forward, as well as establishing the effect size needed to design a well-powered future Phase III BPD clinical trial."

Dr. Douglas V. Faller, Global CMO at Oryzon said "Vafidemstat is the only LSD1 inhibitor in clinical development for CNS indications and induces the expression of genes involved in neuronal plasticity. Vafidemstat also improves sociability, reduces aggression, and improves memory in models of neuropsychiatric diseases. LSD1 inhibition restores NMDR functionality in preclinical models. NMDR dysfunction is one of the proposed causes of BPD. Both our prior pilot study in BPD and now the current PORTICO study results showed consistent signals on reduction in both BPD severity and agitation/aggression (albeit assessed by different scales). Our next steps will be to meet with the FDA to discuss our findings from this study and plan with them a registrational trial. The information we have obtained in this study regarding suitable clinical endpoints in BPD, in which a gold-standard endpoint has not yet been established, will be critical in this planning."

Dr. Carlos Buesa, CEO of Oryzon said "First of all, we would like to thank PORTICO participants, the sites, the investigators, and the teams that helped us achieve this major milestone. Although we have not met the primary endpoints of the study, we still consider the trial results to be very positive and promising. This is the first time, to the best of our knowledge, that a large, randomized Phase II trial in BPD had two secondary endpoints that met statistical significance reflecting clinically meaningful improvements in overall BPD severity and in agitation/aggression. In a disease with currently no approved drugs, and no well-established regulatory endpoints yet, PORTICO's results across these important two endpoints are paving the way to define a registrational Phase III trial, based for the first time on a well-controlled study that has enrolled a truly representative real-world BPD population. We are also excited about our ongoing trial with vafidemstat in schizophrenia, where we are studying improvements in negative and cognitive symptoms."

The company will present the comprehensive and full data package at a psychiatric conference and in a peer-reviewed journal publication.

PORTICO (EudraCT No.: 2020-003469-20, ClinicalTrials.gov Identifier NCT04932291) is 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 210 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. As independent multiple primary endpoints, appropriate adjustments for multiplicity were made to ensure that statistical significance in either one is sufficient to declare success in the trial. In the absence of a well-established regulatory endpoint, the trial investigated several secondary and exploratory endpoints to determine overall improvements in the severity of the disease, as well as reductions in levels of agitation-aggression, anxiety, depression, and cognitive impairment. The trial also investigated the impact on suicidal ideation and explored several correlative biomarkers. An important aim of PORTICO was to learn what potential endpoints would be important to leverage in a future Phase III registrational trial. PORTICO included a total of 27 clinical sites, 14 in the U.S. and 13 in Europe (Germany, Spain, Bulgaria, and Serbia).

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. 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. Currently, vafidemstat is in two Phase IIb trials in borderline personality disorder (PORTICO) and in schizophrenia patients (EVOLUTION). 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 healthcare 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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