ORYZON GENOMICS, S.A.

Pursuant to the provisions of article 227 of Law 6/2023, of 17 March, on Securities Markets and Investment Services, ORYZON GENOMICS, S.A. ("ORYZON" or the "Company") hereby gives notice of the following

OTHER RELEVANT INFORMATION

ORYZON announces the receipt of the official meeting minutes from a recent End-of-Phase II meeting for vafidemstat in Borderline Personality Disorder (BPD) with the US Food and Drug Administration (FDA). FDA's feedback supports the initiation of vafidemstat's PORTICO-2 Phase III trial.

The pressrelease that will be distributed today is attached.

Madrid, 1 October 2024

October 1st 2024 • Press Release

ORYZON receives minutes from End-of-Phase II meeting with the FDA on the PORTICO-2 Phase III vafidemstat trial in Borderline Personality Disorder

- **FDA's feedback supports the initiation of the Phase III trial**
- **Agitation-Aggression in Borderline Personality Disorder (BPD) acknowledged as a possible therapeutic indication**
- **Oryzon may use STAXI-2 Trait anger as a primary efficacy endpoint for PORTICO-2**
- **Currently no FDA-approved treatments for BPD**
- **Company to host conference call and live webcast today at 09:00 am EDT (15:00 pm CET)**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, October 1st, 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 today the receipt of the official meeting minutes from a recent End-of-Phase II meeting for vafidemstat in Borderline Personality Disorder (BPD) with the US Food and Drug Administration (FDA). Based on the positive feedback received, ORYZON will now move forward with preparing a full PORTICO-2 Phase III trial protocol to be submitted to the FDA for study approval.

At the End-of-Phase II meeting with the FDA, held in late August, various aspects of vafidemstat's development plan were thoroughly evaluated and discussed. The minutes cover the FDA's opinion on the suitability of the vafidemstat program to date in several critical areas: i) preclinical data, ii) toxicology, iii) clinical pharmacology, and iv) clinical studies. The meeting minutes confirm that both the company and the FDA reached clarity on several key elements of the PORTICO-2 Phase III clinical trial design for vafidemstat. The most significant points are summarized as follows:

- Agitation-aggression in BPD has the potential to be acceptable as a target indication.
- The FDA agrees that Oryzon may pursue a Phase III study using STAXI-2 Trait anger as a primary efficacy endpoint measure, but the company will have to provide additional information to demonstrate that STAXI-2 Trait anger is a clinically meaningful endpoint in this indication (i.e through a Qualitative Research of the scale in BPD patients).
- Secondary endpoints will include both patient-rated and clinician-rated scales, as CGI-S A/A to assess agitation/aggression, and BEST and CGI-S to assess overall BPD improvement.

- A Qualitative Research Study will be conducted with a subset of PORTICO-2 patients to provide further validation of the proposed endpoints. The Qualitative Study protocol will be submitted prior to its initiation for FDA review and feedback.
- Oryzon plans to also provide the psychometric properties and performance for the selected primary and key secondary endpoints for FDA review prior to the initiation of the Phase III study.
- The estimated total sample size for the PORTICO-2 Phase III study is 350 patients (randomized 1:1 vafidemstat or control), with a trial duration of 18 weeks in total.
- Subject to FDA review of the final data, the PORTICO-2 Phase III study has the potential to be one of the two registrational trials required by the FDA.

Using the same scale selected now as primary endpoint for assessing agitation-aggression in BPD in the PORTICO-2 Phase III trial, the STAXI-2 Trait anger scale, the Phase IIb PORTICO study demonstrated a nominally significant and clinically meaningful reduction of agitation and aggression in the vafidemstat group as compared to placebo (FAS analysis, p=0.0071 and 58.6% relative reduction over the placebo group at weeks 8-12, with p values at weeks 10 and 12 of p=0.006 and p=0.016 and relative reductions over placebo group of 92.1% and 57.1% respectively).

“We have gathered a vast amount of data on vafidemstat's neurological effects through foundational research and early-stage clinical trials across various CNS disorders," said Carlos Buesa, CEO of Oryzon. "We are thrilled with the positive outcome of our interactions with the FDA and the prospect of advancing vafidemstat into pivotal Phase III clinical studies for BPD, an area with a significant unmet medical need, as no approved drugs currently exist. Vafidemstat is built on robust science, has consistently demonstrated safety and tolerability, and this Phase III development builds on the promising clinical observations from the PORTICO Phase IIb trial discussed with the FDA. The recent allowances for vafidemstat’s patents in the field of BPD further highlight its commercial potential. This marks a defining moment for Oryzon.”

Michael Ropacki, Oryzon’s CMO for CNS, added, “Following the positive presentation of PORTICO's Final Results at the ECNP New Medication Symposium, where vafidemstat demonstrated nominal statistical significance in reducing agitation and aggression on the STAXI-2 scale across Weeks 8–12, along with improvement in overall disease on the BEST scale and statistical significance on the Global Statistic Test, I am very pleased with the FDA’s End of Phase II feedback. This allows Oryzon to proceed with the planned Phase III pivotal PORTICO-2 trial. We look forward to continued collaboration with the FDA on the trial's protocol and Phase III preparations. These clinically meaningful reductions in agitation/aggression and overall disease improvement seen with vafidemstat strongly support its potential as a pharmacological treatment for BPD, with the promise to significantly improve the lives of BPD patients and their families.”

Based on the positive feedback from the FDA, Oryzon will now start preparations for the Phase III program, including the preparation of a full protocol for PORTICO-2 Phase III trial to submit to the FDA. The company will now also engage with European regulatory agencies following standard practice before initiation of the PORTICO-2 Phase III trial.

Conference Call/Webcast Information

Oryzon invites investors and the general public to join a conference call and webcast with investment analysts today, October 1st, 2024, at 9:00 am EDT (15:00 pm CET) to discuss the outcome of the End-of-

Phase II meeting. To access the live conference call, please register here. Once registered, the conference call will be available via webcast.

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 PORTICO

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). Final data of this trial were presented at the 37th European College of Neuropsychopharmacology (ECNP-2024) congress (see here)

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 negative symptoms of schizophrenia, named EVOLUTION (recruitment ongoing), and another one in Borderline Personality disorder (BPD), named PORTICO, completed and with published final data (see above). Based on PORTICO's results, the company has held 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.

Spain	**Oryzon**	**IR, US**	**IR & Media, Europe**
Patricia Cobo/Mario Cordera	Emili Torrell	Ashley R. Robinson	Sandya von der Weid
Atrevia	Chief Business Officer	LifeSci Advisors, LLC	LifeSci Advisors, LLC
+34 91 564 07 25 +34 673 33 97 65	+34 93 515 1313	+1 617 430 7577	+41 78 680 05 38
pcobo@atrevia.com mcordera@atrevia.com	etorrell@oryzon.com	arr@lifesciadvisors.com	svonderweid@lifesciadvisors.com