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ORYZON reports financial results and corporate update for quarter ended September 30, 2024

- **Final data from PORTICO, global Phase IIb vafidemstat trial in BPD, presented at the 37th ECNP annual conference in September**
- **Company moving forward with PORTICO-2 Phase III trial preparations following positive feedback from End-of-Phase II meeting with the FDA**
- **Company continues to strengthen IP position for vafidemstat with additional "intention to grant" communications**
- **First cohort dosed in Investigator-initiated Phase Ib study of iadademstat with venetoclax and azacitidine in first-line AML**
- **Reduction in R&D expenses for the nine months ended September 30, 2024 as a result of completion of the PORTICO clinical trial; savings of $5.1M with respect to the nine months ended September 30, 2023**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, October 24, 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, today reported financial results for the nine months ending September 30, 2024 and provided a corporate update on recent developments.

Dr Carlos Buesa, Oryzon's Chief Executive Officer said, "This quarter marked a pivotal moment for our CNS program. At the ECNP 2024 Conference, we presented the full dataset from our Phase IIb PORTICO trial of vafidemstat for Borderline Personality Disorder (BPD), and we observed notable improvements across most study endpoints compared to the topline data released in January. We also received the official minutes from our End-of-Phase II meeting with the FDA, confirming that we can proceed to a Phase III. The FDA indicated that agitation/aggression in BPD may be an acceptable indication, and agreed that we may use the same aggression scale that showed the strongest signal in Phase II. With this positive feedback, we will now begin preparations to submit the full Phase III protocol to the FDA. Careful analysis of the effect sizes in BPD has allowed us to reevaluate and increase the recruitment target for the EVOLUTION trial in schizophrenia, which continues to enroll patients in Spain. Meanwhile, we have strengthened our CNS intellectual property portfolio with additional "intention to grant" communications in two key patent families covering the use of vafidemstat in treating aggression, social withdrawal and BPD. These advancements significantly bolster our IP position for vafidemstat."

Dr Buesa continued, “In oncology, following the very positive results of our ALICE trial with iadademstat in first-line unfit AML patients, we are expanding our efforts to further evaluate therapeutic efficacy in this patient population through two additional trials. One is conducted under our CRADA agreement with the NCI, while the other is in collaboration with Oregon Health & Science University (OHSU) as an investigator-initiated study (IIS). Both trials will assess iadademstat in combination with azacitidine and venetoclax in first-line AML. The OHSU-led IIS trial has already enrolled the first cohort, representing a significant advancement in our oncology program and, if positive, could open additional options for our clinical development strategy. In addition, a new IIS sponsored by the Medical College Wisconsin in combination with azacitidine in patients with myelodysplastic syndrome is being prepared. In June, we presented promising initial data from our ongoing FRIDA Phase Ib trial, evaluating iadademstat in combination with gilteritinib in relapsed/refractory FLT3-mutant AML patients, at the EHA Conference. The data from the first two cohorts demonstrated that the combination was safe and showed strong antileukemic activity, with encouraging response rates and a shorter time to response compared to historical data on gilteritinib alone. We have since completed enrollment of the third cohort, and as the data matures, we plan to present additional results at the EHA Conference next June.”

Dr Buesa added, “The positive outcome of the End-of-Phase II meeting with the FDA has been a turning point for the company, as it transitions into a Phase III company for the first time. While we remain committed to maintaining strict budgetary discipline and leveraging access to our Convertible Notes program, we anticipate receiving further financial support from the recently approved IPCEI grant from the EU, which will provide crucial resources to advance our R&D in personalized medicine for both CNS and oncology. The company is also actively engaged in discussions with corporate partners to explore potential partnerships and will continue evaluating additional financing opportunities.”

Third Quarter and Recent Highlights

Vafidemstat in large multifactorial CNS indications:

- Final data from vafidemstat’s Phase IIb PORTICO trial in BPD were presented 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 held in September in Milan, Italy. A strong improvement in State-Trait Anger Expression Inventory 2 (STAXI-2) Trait Anger, a measure of agitation and aggression, at Weeks 8–12 was observed compared to previous top line data (TLD); nominal statistical significance now of p = 0.0071 (previously 0.0259). An improvement in Borderline Evaluation of Severity (BEST), an overall measure of BPD disease severity, at Weeks 8–12 compared to TLD was also achieved; nominal statistical significance now of p = 0.0260 (previously 0.0423). Vafidemstat showed favorable results over placebo in all primary and secondary efficacy endpoints, as demonstrated by T-Forest plot analysis. 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). Vafidemstat was, as in all previous clinical studies, safe and well-tolerated.

- Oryzon has received the minutes from the end-of-Phase II meeting with the U.S. Food and Drug Administration (FDA). Based on the positive feedback received, ORYZON has started preparations

for Phase III, including the preparation of a full protocol for the PORTICO-2 Phase III trial to submit to the FDA for study approval. The trial will use STAXI-2 Trait anger as a primary efficacy endpoint measure. Secondary endpoints will include both patient-rated and clinician-rated scales, such as CGI-S A/A to assess agitation/aggression, and BEST and CGI-S to assess overall BPD improvement.The estimated total sample size for PORTICO-2 is 350 patients (randomized 1:1 vafidemstat or control), with a trial duration of 18 weeks in total. Subject to FDA's 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. The company expects to obtain FDA's approval for PORTICO-2 by end of 1Q2025.

- Oryzon has continued to strengthen its patent portfolio for vafidemstat during this quarter. The European Patent Office (EPO) recently granted Oryzon's European patent EP3661510B1, titled "Methods of treating behavior alterations"; the granted claims cover the use of vafidemstat for the treatment of aggression and social withdrawal. A corresponding patent has also been granted in South Korea and we have received "intention to grant" communications in Australia and Malaysia. These patents will not expire until at least 2038, excluding any potential patent term extension that may provide additional years of protection. In addition, Oryzon has received "intention to grant" communications in Europe and Mexico for another key patent family related to vafidemstat titled "Methods of treating borderline personality disorder", and a corresponding patent has been granted in Japan. These patents will not expire until at least 2040, excluding potential patent term extensions that may provide additional protection. Another patent, covering the use of vafidemstat to treat ADHD, has also been granted in Japan during this period.

- The EVOLUTION Phase IIb clinical trial evaluating vafidemstat in patients with schizophrenia continues to enroll participants. This study aims to assess the efficacy of vafidemstat, with a primary focus on improving negative symptoms. Following a careful analysis of effect sizes observed in BPD, we have reevaluated and increased the recruitment target for the trial. In addition to negative symptoms, the trial is also exploring as secondary endpoints vafidemstat's efficacy in improving cognitive impairment and positive symptoms in schizophrenia. The project is partially funded by the Spanish Ministry of Science and Innovation and is being conducted at multiple hospitals across Spain.

Vafidemstat in monogenic CNS indications:

- We continue to evaluate the feasibility of a new precision medicine trial in Kabuki Syndrome. The company will decide on a possible submission of an IND for HOPE to the FDA in 2025.

Iadademstat in oncology:

- FRIDA, an open-label, multicenter Phase Ib clinical trial of iadademstat in combination with gilteritinib in patients with relapsed/refractory (R/R) Acute Myeloid Leukemia (AML) harboring a FMS-like tyrosine kinase mutation (FLT3mut+), continues to enroll patients. Following the FDA's new OPTIMUS doctrine, the company continues to explore the minimal dose with clinical activity. The primary objectives of the trial are to evaluate the safety and tolerability of iadademstat in combination with gilteritinib in patients with FLT3mut+ R/R AML and to establish the Recommended Phase 2 Dose (RP2D) for this combination. Secondary objectives include the

evaluation of the treatment efficacy, measured as the rate of complete remission and complete remission with partial hematological recovery (CR/CRh), the Duration of Responses (DoR), and the assessment of Measurable Residual Disease (MRD). The study is being conducted in the U.S. and will accrue up to approximately 45 patients. If successful, Oryzon and the FDA have agreed to hold a meeting to discuss the best plan to further develop this combination in this much-in-need AML population.

- The first patients have been dosed in the Investigator-initiated study (IIS) sponsored by the Oregon Health & Science University (OHSU) Knight Cancer Institute evaluating the combination of iadademstat with venetoclax and azacitidine in first line AML. Dr. Curtis Lachowiez is the Principal Investigator (PI) of the trial. This Phase Ib dose-finding study is now actively enrolling patients.

- Iadademstat will also be evaluated in combination with venetoclax and azacitidine in first-line AML patients in a trial under the Cooperative Research and Development Agreement (CRADA) signed with the National Cancer Institute (NCI) in the United States. The trial will be conducted and sponsored by the NCI, with Dr. Natalie Galanina from the University of Pittsburgh Cancer Institute as the main PI for the trial. The trial plans to enroll 45 patients and, according to NCI, is expected to start enrolling patients in 4Q2024.

- The Company is further expanding the clinical development of iadademstat in hemato-oncology through a new IIS led by the Medical College of Wisconsin, which will evaluate iadademstat in combination with azacitidine in adult subjects with myelodysplastic syndrome.

- The collaborative Phase II basket trial of iadademstat in combination with paclitaxel in platinum R/R small cell lung cancer (SCLC) and extrapulmonary high-grade neuroendocrine tumors (NET trial) continues to enroll patients. This trial is being conducted in the U.S. under a collaborative clinical research agreement with the Fox Chase Cancer Center.

- The Phase I/II trial with iadademstat plus immune checkpoint inhibitors in first line SCLC patients with extensive disease under the CRADA agreement with the NCI, already approved by the FDA, is now ready to start enrolling patients. The trial is titled “A Phase I Dose Finding and Phase II Randomized Trial of Iadademstat Combined With Immune Checkpoint Inhibition Maintenance After Initial Chemoimmunotherapy in Patients With Extensive-Stage Small Cell Lung Cancer” and will be conducted and sponsored by the NCI, with Dr. Charles Rudin from the Memorial Sloan Kettering Cancer Center (MSKCC) as the main PI for the trial, and Dr. Noura Choudhury from University of Chicago as co-PI A number of prestigious cancer centers in the US, including the MSKCC, the JHU Sidney Kimmel Comprehensive Cancer Center and many others will participate. The trial plans to enroll 45-50 patients and is expected to start enrolling patients in 4Q2024.

- The STELLAR trial, a randomized, multicenter Phase II study of iadademstat plus a checkpoint inhibitor in first-line extensive-stage SCLC, will be informed and refined from the findings of the CRADA-MSKCC trial. The company believes that STELLAR could potentially support an application for accelerated approval.

Earlier stage programs:

- ORY-4001, Oryzon’s highly selective histone deacetylase 6 (HDAC6) inhibitor nominated as a clinical

candidate for the treatment of certain neurological diseases such as Charcot-Marie-Tooth disease (CMT), Amyotrophic Lateral Sclerosis (ALS) and others, continues to progress through IND enabling studies to prepare it for clinical studies.

Financial Update: Third quarter 2024 Financial Results

Research and development (R&D) expenses were $1.9 million and $7.1 million for the quarter and nine months ended September 30, 2024, compared to $3.8 and $12.2 million for the quarter and nine months ended September 30, 2023. As a result of the completion of the PORTICO clinical trial, the company saves $5.1M with respect to the third quarter of 2023.

General and administrative expenses were $0.9 and $3.1 million for the quarter and nine months ended September 30, 2024, compared to $0.7 and $2.9 million for the quarter and nine months ended September 30, 2023.

Net losses were $1.1 and $3.8 million for the quarter and nine months ended September 30, 2024, compared to $0.8 and 3.4 million for the quarter and nine months ended September 30, 2023. The result is as expected, given the biotechnology business model where companies in the development phase typically have a long-term maturation period for products and do not have recurrent income.

Negative net result was $2.5 million (–$0.04 per share) for the nine months ended September30, 2024, compared to a negative net result of $1.7 million (–$0.03 per share) for the nine months ended September 30, 2023.

Cash, cash equivalents, and marketable securities totaled $8.4 million as of September 30, 2024.

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ORYZON GENOMICS, S.A.
BALANCE SHEET DATA (UNAUDITED)[1]
(Amounts in thousands US $)

	September 30th, 2024	September 30th, 2023
Cash and cash equivalents	8,442	8,818
Marketable securities	0	0
Total Assets	122,661	108,303
Deferred revenue	0	0
Total Stockholders' equity	96,854	83,920

ORYZON GENOMICS, S.A.
STATEMENTS OF OPERATIONS (UNAUDITED)[1]
(US $, amounts in thousands except per share data)

	Three Months Ended Septembre 30th		Nine Months Ended September 30th	
	2024	2023	2024	2023
Collaboration Revenue	0	0	0	0
Operating expenses:				
Research and Development	1,915	3,821	7,076	12,237
General and administrative	879	674	3,051	2,934
Total operating expenses	2,794	4,495	10,127	15,171
Loss from Operations	-2,794	-4,495	-10,127	-15,171
Other income, net	1,671	3,669	6,312	11,728
Net Loss	-1,123	-826	-3,815	-3,443
Net Financial & Tax	-256	-300	1,272	1,716
Net Result	-1,379	-1,126	-2,543	-1,727
Loss per share allocable to common stockholders:				
Basic	-0.02	-0.02	-0.04	-0.03
Weighted average Shares outstanding				
Basic	63,383,939	58,154,298	62,336,626	57,234,937

[1] Spanish GAAP

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 Iadademstat

Iadademstat (ORY-1001) is a small oral molecule, which acts as a highly selective inhibitor of the epigenetic enzyme LSD1 and has a powerful differentiating effect in hematologic cancers (see Maes et al., Cancer Cell 2018 Mar 12; 33 (3): 495-511.e12.doi: 10.1016 / j.ccell.2018.02.002.). A FiM Phase I/IIa clinical trial with iadademstat in R/R AML patients demonstrated the safety and good tolerability of the drug and preliminary signs of antileukemic activity, including a CRi (see Salamero et al, J Clin Oncol, 2020, 38(36): 4260-4273. doi: 10.1200/JCO.19.03250). Iadademstat has shown encouraging safety and efficacy data in combination with azacitidine in a Phase IIa trial in elder 1L AML patients (ALICE trial) (see Salamero et al., ASH 2022 oral presentation & The Lancet Haematology, 2024, 11(7):e487-e498). Iadademstat is currently being evaluated in combination with gilteritinib in the ongoing Phase Ib FRIDA trial in patients with relapsed/refractory AML with FLT3 mutations, and in combination with azacitidine and venetoclax in 1L AML in an investigator-initiated study led by OHSU. Beyond hematological cancers, the inhibition of LSD1 has been proposed as a valid therapeutic approach in some solid tumors such as small cell lung cancer (SCLC), neuroendocrine tumors (NET), medulloblastoma and others. In a Phase IIa trial in combination with platinum/etoposide in second line ED-SCLC patients (CLEPSIDRA trial), preliminary activity and safety results have been reported (see Navarro et al., ESMO 2018 poster). Iadademstat is being evaluated in a collaborative Phase II basket study with the Fox Chase Cancer Center (FCCC) in combination with paclitaxel in R/R neuroendocrine carcinomas, and the company is preparing a new trial in combination with immune checkpoint inhibitors (ICI) in SCLC. Oryzon has entered into a Cooperative Research and Development Agreement (CRADA) with the U.S. National Cancer Institute (NCI) to collaborate on potential further clinical development of iadademstat in different types of solid and hematological cancers; the first two trials will evaluate iadademstat in combination with ICI in SCLC and in combination with azacitidine and venetoclax in 1L AML. Oryzon is further expanding the clinical development of iadademstat through additional investigator-initiated studies. Iadademstat has orphan drug designation for SCLC in the US and for AML in the US and EU.

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. Following receipt of the minutes from the End-of-Phase II meeting with the FDA to discuss PORTICO's results, the company recently announced plans to move forward with a Phase III PORTICO-2 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 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 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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