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ORYZON reports financial results and corporate update for quarter ended December 31, 2024

- **Reshaping its Board of Directors at the upcoming Shareholders' meeting with the aim of enhancing U.S. outreach**
- **Preparations for PORTICO-2 Phase III trial with vafidemstat in agitation/aggression in Borderline Personality Disorder ongoing**
- **Final data from REIMAGINE proof-of-concept Phase IIa trial published in Psychiatry and Clinical Neurosciences**
- **Continues to enroll patients in Phase IIb EVOLUTION trial with vafidemstat in schizophrenia**
- **First patients dosed in Investigator-initiated Phase I study of iadademstat with azacitidine in myelodysplastic syndrome, and in NCI-sponsored Phase I study of iadademstat with venetoclax and azacitidine in first-line AML**
- **Continues to recruit patients in FRIDA trial with iadademstat in combination with gilteritinib in relapsed/refractory FLT3-mutant AML patients**
- **Reduction in R&D expenses for the twelve months ended December 31, 2024 as a result of completion of the PORTICO clinical trial; savings of $7.9 M with respect to the twelve months ended December 31, 2023**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, February 27, 2025 - 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 fourth quarter ended December 31, 2024 and provided a corporate update on recent developments.

"The publication of the final dataset from the REIMAGINE study on aggression in autism, ADHD, and borderline personality disorder (BPD) in a prestigious specialized journal has allowed the scientific and investment community to better contextualize and appreciate the relevance of vafidemstat's results in treating aggression in our Phase IIb PORTICO trial," said Dr Carlos Buesa, Oryzon's Chief Executive Officer. "As we mentioned in the previous Note, we 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 also 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 are continuing the preparations to submit the full Phase III protocol to the FDA within the next 1–2 months. We have also continued patient recruitment in our ongoing EVOLUTION trial in schizophrenia in Spain."

Dr Buesa continued, "In oncology, we continue our efforts to further evaluate iadademstat in first line unfit AML patients through two ongoing trials in combination with azacitidine and venetoclax - one under our CRADA agreement with the NCI and another as an investigator-initiated study (IIS) at Oregon Health & Science University (OHSU). The OHSU-led trial has already enrolled the first two cohorts, representing a significant progress in our oncology program and potentially expanding our clinical development options, if results are positive. Additionally, a new IIS sponsored by the Medical College Wisconsin in combination with azacitidine in patients with myelodysplastic syndrome has started to enroll patients. In June, we presented promising initial data from our FRIDA Phase Ib trial at the EHA Conference, showing that iadademstat in combination with gilteritinib in relapsed/refractory FLT3-mutant AML was safe and showed strong antileukemic activity, with encouraging response rates and a faster time to response compared to historical data on gilteritinib alone. With the third cohort enrolled, and as the data matures, we plan to present additional results at ASH in December."

Dr Buesa added, "As the company transitions into a Phase III organization for the first time, we are restructuring our Board of Directors to be more U.S.-centric. The Board will now have three Directors based in the Bay Area, with extensive Nasdaq and industy experience. This will enhance our outreach and strengthen our dialogue with corporate partners and Tier-1 investors. While maintaining strict budgetary discipline and leveraging our Convertible Notes program, we also anticipate additional financial support from the recently approved IPCEI grant from the EU. This funding will be instrumental in advancing our R&D efforts in personalized medicine for CNS and oncology. Meanwhile, the company continues discussions with corporate partners and actively evaluates additional financing opportunities."

Fourth Quarter and Recent Highlights

Vafidemstat in large multifactorial CNS indications:

- Following positive feedback from the end-of-Phase II meeting with the U.S. Food and Drug Administration (FDA), Oryzon is advancing in the 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 to assess agitation/aggression and 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 in 1H2025.

- The final results of the Phase IIa REIMAGINE study, which evaluated the safety and efficacy of vafidemstat on aggression in adult patients with BPD, attention-deficit/hyperactivity disorder (ADHD), and autistic spectrum disorder (ASD), have been published online in the clinical psychiatry

journal Psychiatry and Clinical Neurosciences. As reported in the publication, the study showed that vafidemstat was safe and well-tolerated and elicited significant and consistent reduction in agitation/aggression in patients with BPD, ADHD, and ASD. REIMAGINE was a proof-of-concept trial that laid the foundation for the subsequent PORTICO Phase IIb clinical trial in BPD. A summary of the final data from REIMAGINE had been previously released at the 2020 European Psychiatry Association (EPA) annual meeting.

- Oryzon has continued to strengthen its patent portfolio for vafidemstat during this quarter, with an additional "Decision to grant" communication in its patent family titled "Methods of treating borderline personality disorder", now in Russia. Oryzon has also received "Decision to grant" communications for corresponding patent applications in Europe and Mexico, and a patent has already been granted in Japan, with patent applications pending in other relevant markets. These patents will not expire until at least 2040, excluding potential patent term extensions that may provide additional protection. Additionally, Oryzon recently secured granted patents in Europe, Australia, Korea, Malaysia, Philippines, and Russia under another patent family that covers the use of vafidemstat for the treatment of aggression and social withdrawal, with patent applications pending in additional countries. These patents will not expire until at least 2038, excluding any potential patent term extension that may provide additional years of protection.

- 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. As secondary endpoints the trial will explore 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, while the secondary objectives focus on assessing treatment efficacy. 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 patient has been dosed in the Phase I dose-finding clinical trial of iadademstat in combination with venetoclax and azacitidine in newly diagnosed acute myeloid leukemia (AML),

sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, under the Cooperative Research and Development Agreement (CRADA) signed between Oryzon and the NCI. This Phase I dose-finding study is now actively enrolling patients. Additionally, the Investigator-initiated study (IIS) sponsored by the Oregon Health & Science University (OHSU) Knight Cancer Institute also evaluating the combination of iadademstat with venetoclax and azacitidine in first line AML continues to enroll patients.

- The first patient has been dosed in the IIS Phase I dose-finding trial of iadademstat in combination with azacitidine in myelodysplastic syndrome (MDS), led by the Medical College of Wisconsin (MCW). This Phase I dose-finding study is now actively enrolling patients.

- 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 ready to start enrolling patients. The trial is entitled "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 1Q2025.

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: Fourth quarter 2024 Financial Results

Research and development (R&D) expenses were $2.1 million and $8.7 million for the quarter and twelve months ended December 31, 2024, compared to $3.9 and $16.6 million for the quarter and twelve months ended December 31, 2023. As a result of the completion of the PORTICO clinical trial, the company saves $7.9M with respect to the twelve months ended December 31, 2023.

General and administrative expenses were $0.9 and $3.7 million for the quarter and twelve months ended December 31, 2024, compared to $1.2 and $4.2 million for the quarter and twelve months ended December 31, 2023.

Net losses were $1.0 and $4.6 million for the quarter and twelve months ended December 31, 2024, compared to $1.4 and 5.0 million for the quarter and twelve months ended December 31, 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 $3.8 million (–$0.06 per share) for the twelve months ended December 31, 2024, compared to a negative net result of $3.7 million (–$0.06 per share) for the twelve months ended December 31, 2023.

Cash, cash equivalents, and marketable securities totaled $5.8 million as of December 31, 2024.

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

	December 31th, 2024	December 31th, 2023
Cash and cash equivalents	5,837	13,544
Marketable securities	0	0
Total Assets	112,946	118,125
Deferred revenue	0	0
Total Stockholders' equity	90,428	90,361

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

	Three Months Ended December 31th		Twelve Months Ended December 31th	
	2024	2023	2024	2023
Collaboration Revenue	0	0	0	0
Operating expenses:				
Research and Development	2,116	3,867	8,682	16,631
General and administrative	866	1,187	3,698	4,247
Total operating expenses	2,982	5,054	12,380	20,878
Loss from Operations	-2,982	-5,054	-12,380	-20,878
Other income, net	1,927	3,619	7,785	15,851
Net Loss	-1,055	-1,435	-4,595	-5,027
Net Financial & Tax	-393	-468	787	1,322
Net Result	-1,448	-1,903	-3,808	-3,705
Loss per share allocable to common stockholders:				
Basic	-0.02	-0.03	-0.06	-0.06
Weighted average Shares outstanding				
Basic	64,370,778	58,451,070	62,847,943	57,616,236

[1] Spanish GAAP

*Exchange Euro/Dollar (1.0389 for 2024 and 1.1050 in 2023)

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 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 strong clinical activity 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 and in a trial sponsored by the U.S. National Cancer Institute (NCI) under the Cooperative Research and Development Agreement (CRADA) signed between Oryzon and the NCI to collaborate on further clinical development of iadademstat in different types of hematologic and solid cancers. 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 in a collaborative Phase II trial with the Fox Chase Cancer Center (FCCC) in combination with paclitaxel in R/R neuroendocrine carcinomas, and in a Phase I/II randomized trial in 1L ED-SCLC in combination with ICI sponsored by NCI and led by the Memorial Sloan Kettering Cancer Center (IND approved). 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, 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 (FDA submission planned in 1H2025). 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 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

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Spain

Patricia Cobo/Mario Cordera
Atrevia
+34 91 564 07 25
+34 673 33 97 65
pcobo@atrevia.com
mcordera@atrevia.com

Oryzon

Emili Torrell
Chief BD Officer
+34 93 515 1313

etorrell@oryzon.com

IR & Media, Europe & US

Sandya von der Weid
LifeSci Advisors, LLC
+41 78 680 05 38

svonderweid@lifesciadvisors.com