ORYZON reports financial results and corporate update for quarter ended December 31, 2022

Strong clinical progress in both oncology and CNS

Cash, cash equivalents and marketable securities totaled $22.7 million as of December 31, 2022

MADRID, SPAIN and BOSTON, MA, UNITED STATES, February 17th, 2023 – 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, 2022 and provided an update on recent developments.

Dr Carlos Buesa, Oryzon's Chief Executive Officer, said: "We continued to make robust progress on our clinical development this quarter. The final data from iadademstat's Phase II trial in acute myeloid leukemia (AML) reported at ASH confirmed not only a robust percentage of rapid and durable responses alongside good tolerability but, interestingly we also observed clinical responses in myelomonocytic AML patients, and in other patients harboring adverse prognose mutations such as p53+ who usually respond poorly to current therapies. We believe combination approaches with iadademstat will increase therapeutic options for AML patients both in first and second line. Our new FRIDA trial with iadademstat in combination with gilteritinib in relapsed/refractory FLT3-mutant AML patients is now the company's central strategy and, we believe, our fastest route to market. We are also extremely excited with the recent initiation of a collaborative trial with the Fox Chase Cancer Center (FCCC) in the US in neuroendocrine tumors. This collaboration with the Cancer Epigenetics Institute at Fox Chase Cancer Center, a center of excellence for research in both Neuroendocrine Cancers and epigenetics, is part of an ambitious project to explore LSD1 therapeutic potential in neuroendocrine tumors."

Dr Buesa continued, "In CNS, we also made strong progress. We continue to actively recruit patients in the Phase IIb PORTICO trial with vafidemstat in Borderline Personality Disorder in the US and Europe, and expect to conclude the planned interim analysis by end of the first quarter this year. BPD is a highly unmet medical need and an enormous commercial opportunity with limited competition. Enrollment continues to progress in our second Phase IIb EVOLUTION trial in schizophrenia. Furthermore, we continue with our plan to initiate HOPE this year, the first randomized Phase I/II personalized medicine trial with an LSD1 inhibitor, in Kabuki Syndrome patients."

Fourth Quarter and Recent Highlights

Iadademstat in oncology:

- Final data from the recently completed Phase II ALICE trial, which investigated iadademstat in combination with azacitidine in elderly or unfit AML patients, were presented as an oral

communication at the ASH congress in December 2022. The presentation was also shortlisted for inclusion in the final lists of "Highlights of ASH" in the AML Section. Clinical efficacy signals were robust, with ORR of 81%, where 64% of the responders showed a CR/CRi, as well as a good safety profile for the combination of iadademstat and azacitidine. Responses were deep and durable, with 68% of the CR/CRi lasting over 6 months and 71% of CR/CRi achieving transfusion independence, and rapid (by two months). Three patients remained on study for more than 1 year, 2 patients for more than 2 years and 1 patient for more than 3 years. Responses were seen in patients with a diverse array of AML mutations, suggesting a broad applicability for iadademstat in AML. All FLT3+ patients included in ALICE (100%; 3 out of 3) and a high proportion of TP53+ patients (75%; 6 out of 8) responded; patients with monocytic AML subtypes (M4/M5) also showed high response levels (86%; 6 out of 7).

- Oryzon completed the preparations to start FRIDA which is now ready to recruit. FRIDA is a Phase Ib clinical trial in patients with relapsed/refractory (R/R) Acute Myeloid Leukemia (AML) harboring a FMS-like tyrosine kinase mutation (FLT3mut+), which has already received IND approval from the FDA. FRIDA is an open-label, multicenter study of iadademstat plus gilteritinib for the treatment of patients with R/R AML with FLT3 mutations. The primary objectives 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 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. The study will accrue up to approximately 45 patients and 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.

- A 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) has been recently initiated. This trial is conducted in the US under a collaborative clinical research agreement with the Fox Chase Cancer Center (FCCC), under which the FCCC will be conducting different collaborative combination clinical trials with iadademstat, with Oryzon providing funding, the drug and technical expertise. The IND for this trial was approved by the FDA in November 2022 and the first patient was enrolled in January 2023.

- Preparations for new trials in combination in solid tumors are continuing. In SCLC, the STELLAR trial a randomized, multicenter Phase Ib/II study of iadademstat plus a checkpoint inhibitor in first line extensive-stage SCLC is being prepared. The company believes that STELLAR could potentially support an application for accelerated approval.

- The company has been awarded an EU grant under the Eurostars-3 program to further explore the role of iadademstat in oncological immunotherapy approaches. This funding has been awarded to the BRAVE Project (*Breaking immune Resistance of Advanced cancers by HERV-K Vaccination and Epigenetic modulation*), which will be developed in collaboration with the Danish company ImProTher and the University of Copenhagen, which will evaluate the role of iadademstat in several immunotherapy strategies, including checkpoint inhibitors and/or oncological vaccines, in solid

tumors. The project is expected to start on May 1, 2023, with a duration of two years, and has a global budget of 1.4 million euros, with Oryzon contributing approximately 50%.

Vafidemstat in large multifactorial CNS indications:

- The PORTICO Phase IIb clinical trial with vafidemstat in patients with Borderline Personality Disorder (BPD) has continued to actively enroll patients in Europe and the US. PORTICO is a multicenter, double-blind, randomized, placebo-controlled Phase IIb to evaluate the efficacy and safety of vafidemstat in BPD patients. The trial has two independent primary objectives: reduction of aggression/agitation and overall BPD improvement. The study will include 156 patients, with 78 patients in each arm. Preliminary blinded aggregate safety data from the first randomized 43 patients were presented at the 10th European Conference on Mental Health (ECMH) in September. There were no reported serious adverse events. Forty-one adverse reactions, affecting 12 patients treated either with vafidemstat or placebo were reported, most of them mild and none reported as severe, with none leading to treatment discontinuation or patient withdrawal. PORTICO safety data is aligned with aggregated safety data collected from different vafidemstat clinical trials, in which more than 370 subjects have been treated with the drug. Current data of PORTICO continue to support that vafidemstat is safe and well-tolerated. An independent interim analysis to assess the signal size and futility is expected to be done in 1Q23 with the data of the first 90 patients that will have concluded at least 2/3 of the trial.

- The EVOLUTION Phase IIb clinical trial with vafidemstat in patients with schizophrenia has continued to enroll patients. This Phase IIb study aims to evaluate the efficacy of vafidemstat on negative symptoms and cognitive impairment in patients with schizophrenia. This project is partially financed with public funds from the Spanish Ministry of Science and Innovation and is being carried out in various Spanish hospitals.

Vafidemstat in monogenic CNS indications:

- We are finalizing the preparation of a new precision medicine trial in Kabuki Syndrome (KS). This Phase I/II trial, named HOPE, will be a multicenter, multi-arm, randomized, double-blind and placebo-controlled trial to explore the safety and efficacy of vafidemstat in improving several impairments described in KS patients. The trial plans to enroll 50-60 patients and will be carried out in several hospitals and sites in the United States and, possibly, in Europe. The company is in a dialogue with the regulatory agencies to refine the final design of this trial and expects to submit the IND for HOPE to the FDA in 2023.

- Our precision medicine programs in psychiatric disease continue to progress. We have collaborations in autism with researchers at the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai Hospital in New York and the Institute of Medical and Molecular Genetics (INGEMM) at Hospital Universitario La Paz of Madrid and in schizophrenia with researchers from Columbia University in New York. The results of the ongoing pilot studies to

characterize patients with specific mutations to inform subsequent precision psychiatry clinical trials with vafidemstat are ongoing.

Financial Update: Fourth Quarter 2022 Financial Results

Research and development (R&D) expenses were $5.0 and $18.1 million for the quarter and twelve months ended December 31, 2022, compared to $3.9 and $14.8 million for the quarter and twelve months ended December 31, 2021.

General and administrative expenses were $1.2 and $4.8 million for the quarter and twelve months ended December 31, 2022, compared to $2.0 and $5.4 million for the quarter and twelve months ended December 31, 2021.

Net losses were $1.6 and $5.9 million for the quarter and twelve months ended December 31, 2022, compared to $2.4 and $7.9 million for the quarter and twelve months ended December 31, 2021. 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 $4.5 million (-$0.085 per share) for the twelve months ended December 31, 2022, compared to a negative net result of $5.3 million (-$0.101 per share) for the twelve months ended December 31, 2021.

Cash, cash equivalents and marketable securities totaled $22.7 million as of December 31, 2022.

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

	December 31st, 2022	December 31st, 2021
Cash and cash equivalents	22,737	32,534
Marketable securities	0	0
Total Assets	110,606	108,032
Deferred revenue	0	960
Total Stockholders' equity	77,405	80,711

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

	Three Months Ended December 31st		Twelve Months Ended December 31st	
	2022	2021	2022	2021
Collaboration Revenue	0	0	0	0
Operating expenses:				
Research and Development	5,033	3,930	18,050	14,748
General and administrative	1,249	1,957	4,822	5,405
Total operating expenses	6,282	5,887	22,872	20,153
Loss from Operations	-6,282	-5,887	-22,872	-20,153
Other income, net	4,693	3,466	17,016	12,213
Net Loss	-1,589	-2,421	-5,856	-7,940
Net Financial & Tax	-863	62	1,342	2,632
Net Result	-2,452	-2,359	-4,514	-5,308
Loss per share allocable to common stockholders:				
Basic	-0.045	-0.045	-0.085	-0.101
Diluted	-0.043	-0.045	-0.082	-0.101
Weighted average Shares outstanding				
Basic	54,284,176	52,761,554	53,336,257	52,761,554
Diluted	57,503,825	52,761,554	54,856,520	52,761,554

[1] Spanish GAAP

* Exchange Euro/Dollar (1.0666 for 2022 and 1.1326 in 2021)

About Oryzon

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company considered as the European leader in epigenetics. Oryzon has one of the strongest portfolios in the field, with two LSD1 inhibitors, iadademstat and vafidemstat, in Phase II clinical trials, and 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 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). In a recently completed Phase IIa trial in elder 1L-AML patients (ALICE trial), iadademstat has shown encouraging safety and efficacy data in combination with azacitidine (see Salamero et al., ASH 2022 oral presentation). The company has obtained approval from the U.S. FDA for its IND for FRIDA, a Phase Ib trial of iadademstat plus gilteritinib in patients with relapsed/refractory AML with FLT3 mutations. 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 in combination with paclitaxel in R/R neuroendocrine carcinomas, and the company is preparing a new trial in combination 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. In total iadademstat has been dosed so far to more than 100 cancer patients in four clinical trials. 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 antiinflammatory 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.

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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