July 30th, 2025 • Press Release

ORYZON reports financial results and corporate update for half-year ending June 30, 2025

- **Between December 2024 and July 2025, Oryzon secured financing totaling €52 M, approx. $61 M (€30.0 M from a capital increase, €7.0 M from commercial bank loans, €13.2 M from the EU-IPCEI grant, and €1.8 M from R&D cash-back incentives)**
- **Company has terminated the Convertible Bonds financing facility with Nice&Green**
- **Clinical trial protocol for vafidemstat's Phase III PORTICO-2 trial in BPD submitted to the FDA**
- **Expansion of ongoing Phase IIb EVOLUTION study with vafidemstat in schizophrenia into other EU countries**
- **New Phase II trial in preparation: vafidemstat to target aggression in Autism Spectrum Disorder**
- **Significant clinical progress achieved in ongoing iadademstat's oncology trials in AML (R/R and 1L), MDS and SCLC**
- **Expanding iadademstat into non-malignant hematological indications, with a first clinical trial in sickle cell disease**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, July 30th, 2025 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company and a European leader in epigenetics, today reported financial results for the half-year ended June 30, 2025 and provided a corporate update on recent developments.

Since last December, the company has secured $61 million in funding, including $35.2 million (€30 million) from a successful capital raise completed in April through a straight equity issuance with no warrants attached. Despite challenging market conditions, the offering attracted strong investor demand and was significantly oversubscribed.

"Our successful €30 million capital raise, executed under extraodinarily challenging market conditions, represents a strong vote of confidence in Oryzon's science, clinical pipeline, and long-term value proposition," said Dr Carlos Buesa, Oryzon's Chief Executive Officer. "The proceeds not only reinforce our

financial position but also elevate our visibility in the international biotech arena. This funding enables us to advance our clinical programs with renewed momentum and strategic clarity. We are confident that the clinical progress and data to be presented in the coming quarters will further validate the trust placed in us by the investment community."

Dr. Buesa continued, *"*We are moving closer to becoming a Phase III-stage company, following the submission in June of the Phase III clinical trial protocol for vafidemstat in the treatment of agitation and aggression in Borderline Personality Disorder (BPD) to the FDA. This protocol incorporates all feedback and recommendations received from the agency regarding endpoints. In parallel, additional exploratory data from earlier Phase IIa studies suggest that vafidemstat may also reduce aggression in other patient populations. Building on this, we are now initiating preparations for a new Phase II trial to evaluate vafidemstat in aggression associated with autism spectrum disorder, which will be supported under the recently awarded EU-IPCEI grant. Following the recent financing, we are also expanding the ongoing EVOLUTION trial in schizophrenia, previously conducted exclusively in Spain, into additional European countries. This geographic expansion is designed to accelerate recruitment and further strengthen the robustness of the trial*".*

*"*In oncology, we are pleased with the solid progress being made across all ongoing iadademstat clinical trials," said Dr. Buesa. "This includes the company-sponsored FRIDA trial in relapsed/refractory FLT3-mutated AML, as well as the IIS and CRADA studies in first-line AML, MDS, and small cell lung cancer. We anticipate presenting updates and data from some of these programs at the upcoming ASH-2025 conference this December, marking an important opportunity to share our clinical advances with the broader hematology and oncology community.*"*

Dr. Buesa added, "We are extremely excited to expand iadademstat's clinical evaluation into non-malignant hematological indications, beginning with sickle cell disease (SCD). In SCD, LSD1 inhibition plays a central mechanistic role in re-inducing fetal hemoglobin, needed to rescue the disease phenotype. Our preliminary data in nonhuman primate models have been highly encouraging compared to other agents in development". He added,"The SCD market is substantial, as highlighted by Pfizer's experience with voxelotor (Oxbryta®), which received FDA accelerated approval in 2019. Although the drug was later withdrawn in 2024 due to emerging safety concerns, its initial commercial promise underscored the significant unmet medical need and the market potential in this indication."

First Half and Recent Highlights

Vafidemstat:

- The clinical trial protocol for the PORTICO-2 Phase III trial with vafidemstat in Borderline Personality Disorder (BPD) was submitted to the U.S. Food & Drug Administration (FDA) for approval in June. The primary and key secondary endpoints of the trial have been defined in collaboration with Oryzon's Clinical Advisory Board (CAB), which comprises leading experts in psychiatric research and clinical trials. PORTICO-2 will use two clinical outcome measures to assess aggression: the STAXI-2 Trait anger scale (a patient-reported outcome) as the primary endpoint, and the Overt Aggression Scale-Modified (OAS-M) (a clinician-rated scale) as a key secondary endpoint. Additional secondary endpoints will assess overall BPD improvement and quality of life. The study will enroll

approximately 350 patients, randomized 1:1 to receive vafidemstat or placebo, with a total trial duration of 18 weeks. Subject to FDA's review of the final data, PORTICO-2 has the potential to be one of the two registrational trials required by the FDA for potential approval of vafidemstat in this indication. FDA approval for the study is expected in 2H25.

- A dedicated Key Opinion Leader (KOL) webinar with the participation of Dr. Michael Ropacki, Oryzon's CMO for CNS, and Oryzon's CAB members was held on July 9 to discuss the PORTICO-2 study design, the substantial unmet medical need in BPD, and the role of aggression as a clinical target. A replay of this event is available at the company's website, here.

- Oryzon has announced plans to evaluate vafidemstat for the treatment of aggression in patients with autism spectrum disorder (ASD) in a new Phase II trial. This trial, named HOPE-2, plans to include, *inter alia*, genetically-defined ASD subpopulations, such as individuals with Phelan-McDermid syndrome, and will initially be conducted in Spain as part of the activities supported by the recently granted Med4Cure IPCEI EU initiative.

- 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 evaluate vafidemstat's efficacy in improving cognitive impairment and positive symptoms in schizophrenia. Based on insights gained from the PORTICO trial, a reassessment of the number of patients needed to obtain a clinically meaningful impact has been conducted, and as a result, the trial is being re-sized to a total number of 84 patients. Initially conducted only in Spain, the trial is now being expanded to include additional EU countries.

- Oryzon has continued to strengthen its patent portfolio for vafidemstat during this quarter, with additional "Decision to grant" communications from the Canadian and Israel patent offices for patent applications titled "Methods of treating behavior alterations". The allowed claims cover the use of vafidemstat for the treatment of aggression and social withdrawal. Once issued, these patents will not expire until at least 2038, excluding any potential patent term extension. Corresponding patents have already been granted or allowed in Europe, Australia, Hong Kong, South Korea, Malaysia, the Philippines, and Russia, and additional applications are pending in other countries.

Iadademstat:

- 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 company plans to present the next data update from this trial at ASH-2025.

- The two Phase I dose-finding clinical trials evaluating iadademstat in combination with venetoclax and azacitidine in patients with newly diagnosed AML have continued to actively enroll patients. One trial is sponsored by the National Cancer Institute (NCI) under the Cooperative Research and Development Agreement (CRADA) signed between Oryzon and the NCI, while the other is an Investigator-initiated study (IIS) sponsored by the Oregon Health & Science University (OHSU) Knight Cancer Institute.

- In addition, 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), has also continued to actively enroll patients.

- The Phase I/II trial with iadademstat plus immune checkpoint inhibitors (ICI) in first line small cell lung cancer (SCLC) patients with extensive disease, conducted under the CRADA that Oryzon has in place with the NCI, started to enroll patients in April 2025. The trial will evaluate the safety, tolerability, dose finding and efficacy of iadademstat in combination with an ICI, either atezolizumab or durvalumab, in patients with extensive-stage SCLC who have initially received standard of care chemotherapy and immunotherapy. This study is 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. More than 30 sites accross the U.S. participate in the trial, including renowned institutions such as MSKCC, Johns Hopkins, City of Hope, University of Chicago, and many others. The trial plans to enroll 45-50 patients.

- Beyond oncology, Oryzon has announced plans to evaluate iadademstat in non-malignant hematological disorders, such as sickle cell disease (SCD) and essential thrombocythemia (ET). A clinical trial application (CTA) - the EU equivalent to an IND - for a new Phase Ib trial with iadademstat in SCD has been submitted to the European Medicines Agency (EMA). This trial, named RESTORE (***RE****gulation of* ***S****ickling* ***T****hr****O****ugh* ***R****eprogramming* ***E****pigenetics*), aims to enroll 40 patients. The primary objectives will be to evaluate the safety and tolerability of iadademstat in adult patients with SCD, and to determine its Recommended Phase 2 dose (RP2D). Secondary objectives include assessing iadademstat's activity in inducing fetal hemoglobin, among others. CTA approval is expected in September. A second trial, which will evaluate iadademstat in ET, is currently in preparation, with CTA submission to EMA planned for 2H25.

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: First half 2025 Financial Results

Research and development (R&D) expenses were $3.0 million and $5.8 million for the quarter and six months ended June 30, 2025, compared to $2.3 and $4.9 million for the quarter and six months ended June 30, 2024.

General and administrative expenses were $1.4 and $2.7 million for the quarter and six months ended June 30, 2025, compared to $1.2 and $2.1 million for the quarter and six months ended June 30, 2024.

Net losses were $1.7 and $3.4 million for the quarter and six months ended June 30, 2025, compared to $1.5 and 2.6 million for the quarter and six months ended June 30, 2024. 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 $1.9 million (–$0.03 per share) for the six months ended June 30, 2025, compared to a negative net result of $1.1 million (–$0.02 per share) for the six months ended June 30, 2024.

Cash, cash equivalents, and marketable securities totaled $36.5 million as of June 30, 2025.

In April 2025, the company raised a capital increase of €30 million, as straight equity with no warranties attached, which will be used to fund clinical development and corporate initiatives. Despite the very adverse market conditions, the financing attracted strong demand and was upsized from the original planned €25 million and ended significantly oversubscribed. A US-based institutional investor anchored the round with a €15 million order, with the remaining demand filled by investors across the US, Europe, and Spain. The capital increase was capped at €30 million by the company's Board of Directors.

In July 2025, the company received the full disbursement of the Important Project of Common European Interest (IPCEI) grant, totaling €13.2 million (approximately $15 million USD), for its VANDAM project.

Given the Company's current treasury needs, the financing agreement between Nice & Green and the Company was terminated in July through a payment of €4.7 million. As a result, Oryzon received 1,340,083 of its own shares, increasing its treasury stock to a total of 2,374,666 shares.

ORYZON

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

	June 30th, 2025	June 30th, 2024
Cash and cash equivalents	36,465	10,787
Marketable securities	0	0
Total Assets	162,147	118,474
Deferred revenue	0	0
Total Stockholders' equity	133,869	92,612

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

	Three Months Ended June 30th		Six Months Ended June 30th	
	2025	2024	2025	2024
Collaboration Revenue	0	0	0	0
Operating expenses:				
Research and Development	2,962	2,325	5,760	4,935
General and administrative	1,382	1,222	2,654	2,077
Total operating expenses	4,344	3,547	8,414	7,012
Loss from Operations	-4,344	-3,547	-8,414	-7,012
Other income, net	2,623	2,061	4,976	4,438
Net Loss	-1,721	-1,486	-3,438	-2,574
Net Financial & Tax	1,842	1,599	1,569	1,460
Net Result	121	113	-1,869	-1,114
Loss per share allocable to common stockholders:				
Basic	0.00	0.00	-0.03	-0.02
Weighted average Shares outstanding				
Basic	77,513,039	62,214,547	71,165,325	61,807,215

[1] *Spanish GAAP*

** Exchange Euro/Dollar (1.1720 for 2025 and 1.0705 in 2024)*

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 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. Oryzon is further expanding the clinical development of iadademstat through additional investigator-initiated studies in oncology, and it has announced plans to expand its clinical development in non-oncological hematology indications like sickle cell disease (protocol submitted) and essential thrombocythemia (trial in preparation). 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 (PhIII protocol submitted to FDA). 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, as well as in neurodevelopmental syndromes, and is evaluating the feasibility of conducting clinical trials in autistic conditions like Fragile X syndrome and Phelan-McDermid syndrome.

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 document does not constitute an offer or invitation to purchase or subscribe shares in accordance with the provisions of Regulation (EU) 2017/1129 of the European Parliament and of the Council of 14 June 2017, and/or the restated text of the Securities Market Law, approved by Law 6/2023 of 17 March, and its implementing regulations. Nothing in this document constitutes investment advice. In addition, this document does not constitute an offer of purchase, sale or exchange, nor a request for an offer of purchase, sale or exchange of securities, nor a request for any vote or approval in any jurisdiction. The shares of Oryzon Genomics, S.A. may not be offered or sold in the United States of America except pursuant to an effective registration statement under the Securities Act of 1933 or pursuant to a valid exemption from registration..

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