25 August 2025 • Press Release

ORYZON receives European Medicines Agency approval to initiate a Phase Ib study of iadademstat in sickle cell disease

- **First iadademstat clinical trial in non-malignant hematological indications**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, August 25, 2025 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, Ticker: ORY), a clinical-stage biopharmaceutical company and a European leader in epigenetics, today announced that the European Medicines Agency (EMA) has approved its Clinical Trial Application (CTA), the European equivalent to an IND, to initiate a Phase Ib trial of iadademstat in sickle cell disease (SCD). This will be the first clinical trial investigating iadademstat in a non-malignant hematological indication.

The Phase Ib study, named RESTORE (***RE****gulation of* ***S****ickling* ***T****hr****O****ugh* ***R****eprogramming* ***E****pigenetics*), will be conducted at multiple sites in Spain and aims to enroll 40 adult patients with SCD. The trial's primary objectives will be to evaluate the safety and tolerability of iadademstat and to establish its Recommended Phase 2 dose (RP2D). Secondary objectives include assessing iadademstat's activity to induce fetal hemoglobin (HbF), among others.

SCD is a chronic, inherited blood disorder caused by a mutation in the β-globin gene, leading to the production of hemoglobin S (HbS) instead of the normal hemoglobin A. Under low oxygen conditions, HbS tends to polymerize, causing red blood cells to assume a sickle shape, becoming rigid and fragile. This results in microvascular occlusion, hemolysis, and chronic inflammation.

The clinical manifestations of SCD include vaso-occlusion and hemolytic anemia, which lead to vaso-occlusive crises (VOCs), acute and progressive organ damage, reduced quality of life, and premature mortality. SCD is the most common inherited blood disorder in the United States and represents a significant unmet medical need, with limited therapeutic options currently available.

Dr. Ana Limón, Senior Vice-president of Clinical Development and Medical Affairs at Oryzon said, "We are thrilled to be the only LSD1 inhibitor currently into clinical development for SCD. Targeting LSD1 presents a highly promising therapeutic approach for this disease, which affects approximately 7.7 million people worldwide as per 2025 estimates. Iadademstat has produced a significant increase in HbF levels in baboons, the only animal model with strong translational relevance to humans, after just a single dose. Increased HbF levels mitigate — and potentially reverse — the pathological phenotype of the disease, and increases in HbF have already been recognized by the FDA as a clinically meaningful endpoint for the treatment of SCD. The trial has been carefully designed to deliver a rapid and clear signal of biological activity."

According to multiple market research reports, the SCD treatment market is expected to grow substantially — from approximately USD 3 billion in 2025 to around USD 8 billion by 2032. While gene therapies that reinduce HbF have received FDA approval, their widespread use is constrained by technical complexity and very high costs, limiting access for much of the global patient population. Oxbryta, a once-approved oral therapy for SCD, reached annual sales of USD 328 million in a relatively short period of time, before being withdrawn from the market. This underscores both the strong commercial potential and the urgent unmet need for effective, scalable, and accessible treatments for SCD.

Iadademstat is also under active investigation in multiple oncology clinical trials. These include the company-sponsored FRIDA trial in combination with gilteritinib in relapsed/refractory FLT3-mutated acute myeloid leukemia (AML), as well as several trials conducted under a Cooperative Research and Development Agreement (CRADA) in place with the U.S. National Cancer Institute or as investigator-initiated trials conducted by U.S. institutions, including two trials in combination with venetoclax and azacitidine in first-line AML, and a trial in combination with immune checkpoint inhibitors in small cell lung cancer.

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 in oncology through additional CRADA and investigator-initiated studies. In addition, Oryzon is expanding iadademstat's clinical development into non-oncological hematology indications, with trials in sickle cell disease (CTA approved) and essential thrombocythemia (trial in preparation). Iadademstat has orphan drug designation for SCLC in the US and for AML in the US and EU.

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..

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