

31st October 2024 • Press Release

ORYZON receives Notice of allowance for patent on novel technology for measuring LSD1 target engagement

- **From the United States Patent and Trademark Office**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, October 31, 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 announced that it has received the Notice of allowance from the United States Patent and Trademark Office (USPTO) for its patent application US2022-0389478, titled “Methods to determine KDM1A target engagement and chemoprobes useful therefor”. This patent protects a novel technology developed by Oryzon to measure the binding of LSD1 inhibitors such as iadademstat or vafidemstat to their therapeutic target, the epigenetic enzyme LSD1 (also known as KDM1A). The Notice of allowance is a formal communication from the USPTO in which it indicates that the patent application has reached the status where it is allowed for issuance as a patent.

Having a method to assess the binding of an inhibitor to its target (“target engagement”), i.e. the interaction of a drug with the protein for which it was designed, is essential for the correct interpretation of the observed biological activity of any compound, whether in preclinical assays or in clinical studies. Contrary to other methods commonly used in the field of epigenetics, based on the analysis of changes in histone methylation levels or gene expression changes, which are indirect and non-specific ways of assessing the activity of the LSD1 protein on epigenetic marks where different epigenetic targets may act, Oryzon's technology allows the direct measurement of the effect of an LSD1 inhibitor on LSD1 activity, making it possible to quantify the fraction of free/active LSD1 in a given sample. This technology is particularly useful in the context of the FDA's Optimus program, which requires the identification of the minimum safe and biologically active dose, as it allows the pharmacodynamics of a given drug dose to be assessed at any time in relation to the observed safety and efficacy effects, allowing to adjust the dose of a drug to be tested in dose-finding studies, and avoiding treating patients with ineffective or, on the contrary, excessive doses.

Neus Virgili, Oryzon's Chief IP Officer, stated, “We are very pleased to have received this notice of allowance from the USPTO for this methodology developed by Oryzon. The allowed claims broadly cover the use of our technology to measure LSD1 target engagement of any LSD1 inhibitor.”

This technology was the subject of a publication by Oryzon scientists in the prestigious Journal of Biological Chemistry. You can access this publication through this [link](#)

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



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