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ORYZON receives European Medicines Agency approval to initiate the HOPE-2 Phase II study of vafidemstat for the treatment of Phelan-McDermid Syndrome (PMS)

- **PMS is a severely disabling genetic disorder related to autism**
- **U.S. prevalence is estimated at approximately 1 in 7,300 people**
- **HOPE-2 is partially funded through Oryzon's VANDAM project under Med4Cure, an Important Project of Common European Interest (IPCEI) on Health**
- **The study is being advanced in collaboration with the Spanish Phelan–McDermid Syndrome Association**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, September 28, 2026 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company and a global leader in epigenetics, today announced that the European Medicines Agency (EMA) has authorized its Clinical Trial Application (CTA) to initiate a Phase II study to evaluate vafidemstat for the treatment of Phelan-McDermid Syndrome (PMS).

The study, named HOPE-2, is a single-center, single-arm, open-label Phase IIa study that will enroll 12 adult patients with Phelan-McDermid Syndrome, a genetic disease associated with autism spectrum disorder (ASD). The primary objective of the study is to evaluate the safety and tolerability of vafidemstat. Secondary objectives include assessing the effect of vafidemstat on anger and aggression, measured by the Aberrant Behavior Checklist (ABC) Irritability Subscale and the Clinical Global Impression of Severity - Anger and Aggression (CGI-S A/A), as well as the efficacy of vafidemstat in the treatment of overall disease in adults with PMS, measured by the Repetitive Behavior Scale-Revised (RBS-R), the Phelan-McDermid Syndrome Assessment of Severity (PMSA-S), and the ABC Subscales: Stereotypic Behaviour, Hyperactivity/Non-compliance, Inappropriate Speech, and Social Withdrawal. Vafidemstat will be administered for 12 weeks. After the first 12 weeks of treatment, the Investigator will assess whether the participant may continue treatment through week 24 based on clinical benefit.

PMS is a highly disabling neurodevelopmental disorder caused by deletions or pathogenic mutations in the SHANK3 gene. It is characterized by varying degrees of developmental delay, intellectual disability, delayed or absent speech, and autism spectrum disorder or symptoms of autism. Despite the high prevalence and substantial burden of aggression in PMS, there are no approved pharmacologic treatments for PMS or

specifically targeting aggression in PMS. As a result, aggression is often managed off-label with medications that have limited efficacy and significant safety concerns.

"The initiation of the HOPE-2 study bolsters our strategy to expand the applicability of vafidemstat in CNS indications," said Rolando Gutierrez-Esteinou, MD, Oryzon's Chief Medical Officer for CNS. "Vafidemstat is the only LSD1 inhibitor in clinical development for Central Nervous System disorders, with a potent and unique mechanism of action that modulates transcriptional programs involved in neural plasticity, neuroinflammation and neuronal excitability. LSD1 inhibition has been shown to trigger a 'reset' of neuronal transcription and reverse social behavior and aggression phenotypes in ASD genetic models, including SHANK3-deficient mice. These preclinical findings and the clinical results observed in the REIMAGINE Phase IIa trial in ASD patients lead us to believe vafidemstat has unique potential to provide a promising treatment option for Phelan-McDermid Syndrome."

Oryzon will collaborate with the Spanish *Phelan-McDermid Syndrome Association* to support the identification of potential participants for the HOPE-2 study.

"The approval of the HOPE-2 study is very important news for our families. Knowing that a potential treatment is being investigated to help manage agitation or aggressive behavior gives us great hope. We would like to thank the Oryzon team for involving us in this process from the outset. For us, it is essential to feel that we are part of these advances and to be able to contribute, drawing on our experience, to help research continue moving forward. We hope this study will bring us closer to new options that can improve the quality of life of our children," said Norma Alhambra, President of the Spanish Phelan-McDermid Syndrome Association.

The HOPE-2 study will be conducted in Spain, as part of Oryzon's VANDAM project. VANDAM, which is part of the Med4Cure Important Project of Common European Interest (IPCEI) on Health, has received funding from the Spanish Ministry of Science, Innovation and Universities and the Centre for the Development of Industrial Technology and Innovation (CDTI), under the Recovery, Transformation and Resilience Plan, funded by the European Union – NextGenerationEU.

About Oryzon

Founded in 2000 and headquartered in Barcelona, Spain, Oryzon (ISIN: ES0167733015) is a clinical-stage biopharmaceutical company and a European leader in epigenetics, with a strong focus on personalized medicine for central nervous system (CNS) disorders and oncology. Oryzon's team comprises highly experienced pharmaceutical professionals based in Barcelona, Boston, and New Jersey. The Company has an advanced clinical portfolio built around two LSD1 inhibitors: iadademstat, its oncology/hematology program, which is being evaluated in several ongoing Phase I and II studies and has demonstrated strong preliminary clinical activity in acute myeloid leukemia, including a 100% overall response rate (ORR) in first-line AML; and vafidemstat, its lead CNS program, which is Phase III–ready in borderline personality disorder (BPD). In addition, Oryzon is advancing a broader epigenetics pipeline targeting other mechanisms, including HDAC6, for which the Company has nominated ORY-4001 as a clinical candidate for potential development in Charcot–Marie–Tooth disease (CMT), amyotrophic lateral sclerosis (ALS), and other neurological disorders. The Company also operates a robust platform for biomarker identification and target validation across malignant and neurological diseases. For more information, visit www.oryzon.com

About Vafidemstat

Vafidemstat (ORY-2001) is an oral, CNS-optimized LSD1 inhibitor with potential to address neuropsychiatric disorders through epigenetic modulation. In preclinical studies, vafidemstat has demonstrated effects on cognition, neuroinflammation, aggression, and social behavior, as well as neuroprotective and anti-inflammatory activity across multiple CNS disease models. Oryzon has completed several Phase II clinical trials with vafidemstat, including the REIMAGINE and REIMAGINE-AD trials in aggression in patients with different psychiatric disorders and in aggressive/agitated patients with moderate or severe AD, respectively, with positive clinical results reported in both trials. Following completion of the global randomized double-blind Phase IIb PORTICO trial in borderline personality disorder (BPD), vafidemstat is advancing as a Phase III-ready asset for aggression in BPD (PhIII in preparation). Vafidemstat is also being evaluated in the ongoing double-blind, randomized, placebo-controlled Phase IIb EVOLUTION trial in negative symptoms of schizophrenia. In addition, Oryzon is deploying a CNS precision medicine approach with vafidemstat in genetically defined patient subpopulations of certain CNS disorders, as well as in neurodevelopmental syndromes, including the HOPE-2 clinical trial in 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 person 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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