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ORYZON to sponsor first Phelan-McDermid syndrome (PMS) burden of illness study

- **Study led by CureShank**
- **Aims to characterize the direct and indirect burden of PMS to patients, caregivers, and US healthcare system**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, September 22, 2025 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company and a European leader in epigenetics, is proud to announce its participation as a sponsor of the first-ever *Phelan-McDermid syndrome (PMS) burden of illness* study. The study is led by CureShank, a research advocacy organization founded by families of individuals affected by PMS, whose mission is to accelerate the development of treatments for the disorder.

This study, recently launched, will collect data from families of individuals living with PMS, health insurance claims and insights from clinical experts, to help quantify the true economic impact of PMS, inform the development of new therapies, and guide future market access strategies.

Jordi Xaus, Oryzon's Chief Scientific Office, said: "Consistent with Oryzon's commitment to rare diseases, we are proud to support CureShank's important initiative. This study not only evaluates the burden of Phelan-McDermid syndrome but also helps identify the key drivers of that burden - critical insights that can guide new interventions and accelerate the development of much-needed treatments to improve the quality-of-life to patients and their families".

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 (ASD) or symptoms of autism. Agitation and aggression are common and distressing behavioral symptoms of PMS, and significantly increase caregiver burden, risk of institutionalization, and make long-term community integration in adulthood problematic. Currently, there are no approved pharmacological treatments for PMS.

LSD1 inhibitors have been shown to "reset" neuronal transcription and reverse social-behavior and aggression phenotypes in several ASD genetic models, including shank3-deficient mice. Building on these findings, and on clinical results obtained with vafidemstat, Oryzon's brain-penetrant, orally active LSD1 inhibitor, in the REIMAGINE Phase IIa proof-of-concept trial in ASD patients, the company is preparing a Phase II trial in individuals with PMS, planned to start in the coming months. This study, named HOPE-2, will evaluate the safety and efficacy of vafidemstat in PMS. HOPE-2 will be conducted in the European Union and will be partially financed by funds received under the EU IPCEI MED4CURE grant in 2025.

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 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. Following completion of the global, randomized, double blind Phase IIb PORTICO trial in Borderline Personality Disorder (BPD), with final data presented at ECNP-2024, vafidemstat is advancing as a Phase III-ready asset for agitation/aggression in BPD (PhIII protocol submitted). 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 preparing a clinical trial in aggression in autistic conditions like Phelan-McDermid syndrome.

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