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Oryzon announces publication of study on Phelan-McDermid Syndrome (PMS) patients, a form of autism, paving the way for a novel personalized medicine approach with vafidemstat

- **A non-interventional study published in *Frontiers in Psychiatry***
- **Psychometric profile characterization of 30 subjects with Phelan-McDermid Syndrome (PMS), defining three distinct subsets**
- **Study provides clinical scales and thresholds for patient selection in future clinical trials, based on aggressiveness, cognition, and behavioral traits**
- **Conducted in collaboration with the Medical and Molecular Genetics Institute (INGEMM) and the Research Institute La Paz Hospital (IdiPaz) in Madrid**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, March 5th, 2025 - 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, announced today that the final results of an observational clinical study aimed at psychometrically characterizing individuals with Phelan-McDermid syndrome (PMS) carrying deletions or pathogenic variants in SHANK3 have been published online in the journal *Frontiers in Psychiatry*. The purpose of this study was to gather data that could serve as a foundation for a future precision psychiatry clinical trial involving vafidemstat for this patient population.

Agitation and aggression are key components of PMS, and vafidemstat has demonstrated efficacy in reducing agitation and aggression in a basket trial involving patients with Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and Borderline Personality Disorder (BPD). This characterization paves the way for addressing these symptoms in a subset of PMS patients, further expanding the potential application of vafidemstat in reducing aggression in this specific patient population.

Dr. Jordi Xaus, Oryzon's CSO, stated, "The publication of these results in this prestigious clinical psychiatry journal marks a critical first step toward establishing vafidemstat as a novel personalized medicine therapy for relevant psychiatric indications. In recent years, a range of monogenic rare neurodevelopmental disorders linked to alterations in the epigenetic machinery and other key neuronal genes have been identified as potential targets for precision medicine. The use of LSD1 inhibitors has been shown to partially or fully rescue the complex phenotypes caused by these genetic mutations. Vafidemstat is currently the

only LSD1 inhibitor in clinical development in CNS and represents a promising opportunity for these patients."

Dr. Julian Nevado, first author of the study and Head of Structural and Functional Genomics at INGEMM said "There is currently no treatment approved specifically for Phelan-McDermid syndrome. This study is a proof of concept that highlights the importance of patient stratification in PMS. Selecting PMS patients for a clinical trial based on their distinctive clinical and genetic characteristics will be essential in the era of personalized precision medicine."

In this pilot study, we clinically characterized the profile of 30 subjects, all diagnosed of molecularly confirmed PMS, by applying different psychometric scales, including Repetitive Behavior Questionnaire (RBQ), Vineland Adaptive Behavior Scales, ADOS-2, the Battelle developmental inventory screening test and the Behavior Problems Inventory (BPI).

As reported in the publication, unsupervised hierarchical clustering of the collected psychometric data identified three groups of patients, with different cognitive, aggression and behavioral profile scores. Statistically significant differences in deletion sizes were detected comparing the three clusters (corrected by gender), and the size of the deletion appears to be correlated with some of the assayed scores.

A link to access the online publication can be found here.

Oryzon is developing vafidemstat in prevalent multifactorial psychiatric indications like BPD, with a Phase III trial in preparation, or schizophrenia, with the ongoing EVOLUTION Phase IIb trial, but is also committed to exploring the potential of vafidemstat in rare monogenic psychiatric and neurodevelopmental disorders such as PMS or Kabuki Syndrome. In the Phase IIb PORTICO trial in BPD, vafidemstat demonstrated nominal statistical significance in reducing agitation and aggression, also a relevant feature of some PMS patients and a significant caregiver burden that often results in sedation or institutionalization of these PMS patients.

This published study provides relevant data for patient inclusion in a future clinical study exploring vafidemstat actionability for SHANK3-associated psychiatric disorders, including PMS, constituting a good example of how precision medicine may open new avenues to understand and treat Central Nervous System (CNS) disorders, pioneering individual management in PMS.

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. 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 (FDA submission planned in 1H2025). 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 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 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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