ORYZON Launches Pioneering Schizophrenia Precision Medicine Study In Collaboration With Columbia Psychiatry

- **Goal is to characterize the neuropsychiatric symptoms of patients harboring disease-causing *SETD1A* gene mutations**
- **Also includes fundamental research in preclinical *SETD1A* models**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, December 17th, 2020 - Oryzon Genomics, S.A. (ISIN Code: ES0167733015, ORY), a clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with a strong unmet medical need, announced today the start of a precision medicine collaboration in schizophrenia (SCZ) with researchers from Columbia University in New York, Dr. Joseph Gogos, Dr. Sander Markx and Dr. Jeffrey Lieberman.

SETD1A is a histone methyltransferase that is a key SCZ susceptibility gene. This project has two parts: the first is to further characterize the therapeutic actionability of the SETD1A regulator protein encoded by this gene with LSD1 inhibitors at the molecular level in preclinical *Setd1a* models. The second is to perform exhaustive functional psychometric characterization of individuals carrying mutations in the *SETD1A* gene to build a foundation for a subsequent precision psychiatry clinical trial with vafidemstat for *SETD1A*-associated psychiatric disorders.

Recent work published by Dr. Gogos' laboratory at Columbia University has shown that heterozygous loss-of-function (LOF) mutation of the *Setd1a* gene in mice results in alterations in axonal branching and cortical synaptic dynamics, accompanied by specific deficits in working memory that recapitulate human SCZ-related cognitive and behavioral deficits. Critically, administration of an Oryzon's LSD1 inhibitor produced a full rescue of both the behavioral and neuronal disease phenotypes. This work specifically demonstrated that these treatment effects occur in adult animals suggesting that deficiency of Setd1a function during early developmental stages does not irreversibly compromise the function of disease-related neural circuits. This finding opens the door for investigation of intervention with vafidemstat during a therapeutic window in adolescent and adult subjects.

Patients harboring inherited mutations in *SETD1A* have been identified in the Amish founder population in Pennsylvania. Dr. Markx, who is Professor of Psychiatry at Columbia University and the leader of the Columbia Precision Psychiatry group, will conduct a pilot study to characterize clinical profile of these individuals to determine their different degrees of cognitive impairment. This study will inform the potential actionability of the SETD1A regulator protein by inhibition of LSD1 and the best endpoints for a future clinical study with vafidemstat.

Vafidemstat is an LSD1 inhibitor in Phase II clinical development that has shown a very good safety profile and has been shown to be effective in reducing agitation and aggression in clinical studies in patients with Alzheimer's disease, Borderline Personality Disorder (BPD), Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). Vafidemstat is being currently explored in two Phase IIb clinical trials, one in BPD and the other in severe Covid-19 patients. In the field of precision psychiatry, vafidemstat is also being explored in Europe in patients with Phelan-McDermid syndrome – a variety of autism – who harbor a mutation in *SHANK3*.

SETD1A encodes a catalytic subunit of the histone methyltransferase protein complex, named Set/COMPASS. Rare variants in *SETD1A* have been demonstrated in large, unbiased studies to be associated with increased risk for schizophrenia and neurodevelopmental disorders with cognitive impairment. *De novo* mutations in other subunits comprising Set/COMPASS have also been reported in subjects with SCZ and ASD.

Dr. Markx, principal investigator of the study, said: “We are very excited to partner with Oyrzon in carrying out a baseline neuropsychiatric characterization study that will pave the way for one of the first precision psychiatry clinical trials involving vadifemstat for *SETD1A*-associated psychiatric disorders.” Dr. Gogos, Professor at Columbia University, said: “Following the enormous success in human psychiatric genetics, the goal of using knowledge from genetic studies to identify drugs that target specific biological disease mechanisms has begun to be realized. The emergence of this kind of "precise treatments" is an exciting moment in the battle against psychiatric disorders.” Dr. Lieberman, Chair of the Department of Psychiatry with extensive experience in experimental therapeutics, added: “Identifying susceptibility gene products is currently the best approach to identifying novel biologic targets and developing innovative psychopharmacologic treatments”.

Carlos Buesa, Oryzon’s CEO, said: "We are pleased to initiate this ground-breaking collaboration with researchers at the internationally renowned Columbia University. As we have seen in oncology over the last years, precision medicine may open a new way to understand and treat CNS disorders. Epigenetic dysregulation in the histone H3K4 methylation pathway has been proposed to be an important mechanism in the pathogenesis of schizophrenia and autism. Oryzon’s vafidemstat holds exciting therapeutic potential in schizophrenia and we are looking forward to starting this study.”

About Oryzon

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company considered as the European champion in Epigenetics. Oryzon has one of the strongest portfolios in the field. Oryzon’s LSD1 program has rendered two compounds, vafidemstat and iadademstat, in clinical trials. In addition, Oryzon has ongoing programs for developing inhibitors against other epigenetic targets. Oryzon has a strong technological platform for biomarker identification and performs biomarker and target validation for a variety of malignant and neurological diseases. Oryzon has offices in Spain and the United States. 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 a Phase IIa clinical trial in aggressiveness in patients with different psychiatric disorders (REIMAGINE) and in aggressive/agitated patients with moderate or severe AD (REIMAGINE-AD), with positive preliminary clinical results reported. A Phase IIb trial in borderline personality disorder (PORTICO) has been recently authorized. Additional Phase IIa clinical trials with vafidemstat are ongoing in patients with Mild to Moderate AD (ETHERAL), where a significant reduction of the inflammatory biomarker YKL40 has been observed after 6 months of treatment, and in Relapse-Remitting and Secondary Progressive MS (SATEEN). Vafidemstat is also being explored in a Phase II in severe Covid-19 patients assessing the capability of the drug to prevent ARDS, one of the most severe complications of the viral infection.

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 press release is not an offer of securities for sale in the United States or any other jurisdiction. Oryzon's securities may not be offered or sold in the United States absent registration or an exemption from registration. Any public offering of Oryzon's securities to be made in the United States will be made by means of a prospectus that may be obtained from Oryzon or the selling security holder, as applicable, that will contain detailed information about Oryzon and management, as well as financial statements.

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