ORYZON receives approval to start EVOLUTION Phase IIb trial with vafidemstat in schizophrenia

- **Clinical Trial Application approved by Spanish Drug Agency**
- **Primary objectives: to assess the effect of vafidemstat to address negative and cognitive symptoms in schizophrenia**
- **Second Phase IIb study of vafidemstat in CNS disorders**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, July 13th, 2021 - 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 it has received approval from the Spanish Drug Agency (AEMPS) for its Clinical Trial Application (CTA) to conduct a Phase IIb clinical trial with vafidemstat in patients with schizophrenia.

EVOLUTION (EudraCT No.: 2021-000350-26) is a multicenter, double-blind, randomized, placebo-controlled, 24-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in adult schizophrenia patients under stable antipsychotic therapy. The trial has two primary independent objectives: to assess the effect of vafidemstat on negative symptoms of schizophrenia, and to assess improvement on cognitive impairment associated with schizophrenia. To accommodate this second ambitious primary objective, patients will be treated for 6 months. The trial includes multiple primary and secondary endpoints focusing on negative and positive symptoms, as well as cognition. The trial will be conducted in 6-10 sites in Spain and aims to include 100 patients in total, with 50 patients in each arm. An interim analysis is foreseen to adjust the final number of patients needed to assess efficacy.

Dr. Carlos Buesa, President and CEO of Oryzon, said: “The initiation of EVOLUTION is another important milestone for our CNS program following the recent start of the PORTICO Phase IIb trial of vafidemstat in borderline personality disorder. We are planning to further expand our clinical development of vafidemstat in personalized medicine trials in genetically defined subpopulations of certain CNS disorders.”

EVOLUTION’s scientific rationale is based on vafidemstat’s ability to inhibit LSD1, reducing aggression, enhancing sociability and mitigating social withdrawal, as demonstrated in several preclinical models (see Maes et al., PLOS ONE 2020 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0233468). Importantly, EVOLUTION builds on clinical data from the Phase IIa REIMAGINE trial, where vafidemstat reduced agitation-aggression in patients with attention deficit hyperactivity disorder, autism spectrum disorder and borderline personality disorder and showed positive global effects across these psychiatric disorders after 2 months of treatment. Vafidemstat has a favorable safety and tolerability profile in multiple Phase I/II clinical trials, with over 300 subjects treated, some for up to 24 months. Vafidemstat has not been

associated with sedation, weight gain or extrapyramidal side effects, which are common in current antipsychotic therapy, nor with any other adverse events.

Oryzon's Chief Medical Officer for CNS, Dr. Michael Ropacki, said: "We believe that modulation of LSD1 has transformative potential in the treatment of various CNS diseases. There is growing evidence suggesting a connection between LSD1 and schizophrenia. We are excited in vafidemstat's potential to treat the negative symptoms of schizophrenia and address cognitive impairment associated with schizophrenia, given there are no approved therapies for these symptoms."

Schizophrenia is a severe mental disorder characterized by positive symptoms such as delusions and hallucinations, negative symptoms including amotivation and social withdrawal, and cognitive symptoms such as deficits in working memory and cognitive flexibility. While new antipsychotics are available to improve the positive symptoms, no approved medications are available yet for the negative symptoms and cognitive impairment that are the most debilitating aspects of this disease. Prevalence of schizophrenia and related psychotic disorders in the US range between 0.25% and 0.64% of the population.

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 Phase II 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. Oryzon is one of the most liquid biotech stocks in Europe with +90 M shares negotiated in 2020 (ORY:SM / ORY.MC / ORYZF US OTC mkt). 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) and in aggressive/agitated patients with moderate or severe AD (REIMAGINE-AD), with positive preliminary 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 months of treatment, and the pilot, small scale SATEEN trial in Relapse-Remitting and Secondary Progressive MS. Two Phase IIb trials in borderline personality disorder (PORTICO) and in schizophrenia patients (EVOLUTION) have been recently authorized. The company is also deploying a CNS precision medicine approach with vafidemstat in genetically-defined patient subpopulations of certain CNS disorders. Vafidemstat is also being explored 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.

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

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