Oryzon announces $1 million grant from Kabuki syndrome philanthropists to support a precision medicine Phase I/II trial with vafidemstat

- **HOPE will be the first clinical trial in precision medicine with vafidemstat in neurodevelopmental diseases**
- **Multicentric study to assess the efficacy of vafidemstat in Kabuki syndrome patients**
- **Expected to start in early 2022**
- **In collaboration with the Kennedy-Krieger Institute**

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, September 21st, 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 a one million USD grant to support a new clinical trial with our Phase II LSD1 inhibitor vafidemstat in patients with Kabuki syndrome (KS). The grant was awarded by a patient family whose other philanthropic endeavors include founding the Roya Kabuki clinic at Boston Children's Hospital and sitting on the board of the Kabuki Syndrome Foundation (KSF).

The company expects to start a Phase I/II trial, named HOPE, which will be a multicenter, multi-arm, randomized, double-blind and placebo-controlled trial to explore the safety and efficacy of vafidemstat in improving several impairments described in KS patients. The trial will be performed in children older than 12 years and in young adults.

The company is finalizing the protocol design for this new trial with researchers from the Kennedy Krieger Institute (KKI), key opinion leaders, regulatory experts in rare diseases and other stakeholders. We expect to start this clinical trial in the first half of 2022 in several hospitals and sites in the United States and, possibly, in Europe. Considering the FDA and EMA precedents in rare diseases and CNS disorders, we believe that if the HOPE trial demonstrates relevant clinical improvements, it may potentially serve as the basis for accelerated approval in the EU and the United States.

Janet Lee, Executive Director of the Kabuki Syndrome Foundation, has commented: "This investment is an extraordinary opportunity to support a ground-breaking therapeutic candidate for Kabuki syndrome, to improve the quality of life of children and families around the globe. The Kabuki Syndrome Foundation is proud to partner with Oryzon and key opinion leaders to further our mission of advocating for the advancement of research and therapeutic treatments. We look forward to working with global patient

advocacy groups and the broader Kabuki syndrome community on efforts that support clinical trial readiness and enrollment opportunities to ensure the patient voice is at the center of this clinical study."

Dr. Carlos Buesa, President and CEO of Oryzon, said: "We are enormously grateful to this patient's family for their generous support to this trial and excited to work with the KSF and the scientists from the KKI and the rest of the research community. The scientific literature has shown that LSD1 inhibition may compensate the effects of a number of genetic failures happening in KS and other CNS disorders. HOPE is the first step in a set of innovative personalized medicine trials we are planning with vafidemstat that may bring hope to very much in need patients, in this case KS kids."

There is a strong molecular rationale for LSD1 inhibition as a possible therapy in KS. In type I KS, the loss of one allele of the KMT2D gene produces a hypomethylated status in the chromatin of neuronal cells and an aberrant transcriptional program. LSD1 inhibition can compensate this effect, and apparently many others downstream as a consequence. Researchers at Johns Hopkins University, using a KS mouse model with a mutated KMT2D allele, have shown that the number of histone methyl-marks in the hippocampus is significantly diminished in these KS animals, but when treated with a LSD1 inhibitor, the hippocampus histone methyl-marks recovered to almost normal levels. Remarkably, this normalization of the methyl-marks in the hippocampus also correlated with morphological and functional effects. Neurogenesis deficiency in the hippocampus was rescued and the elongation and branching defects of hippocampal neurons were also restored. Finally, the correlate at morphological level had also a translation in functional readouts like the recovery on the visuospatial learning and memory deficits and the rescue of the immunological impairments in these KMT2D (+/-) KS animals[1].

Vafidemstat is currently in Phase IIb trials in borderline personality disorder and schizophrenia, and has shown a positive safety and tolerability profile in more than 300 subjects dosed up to now, some of them up to 2 years.

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 a first-in-class, 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 also 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 protective anti-autoimmune efficacy in several preclinical models of multiple sclerosis (MS). In 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), vafidemstat has shown positive preliminary clinical results. Additional finalized Phase IIa clinical trials with vafidemstat include the ETHERAL trial in patients with

[1] Li Zhang, et al., Inhibition of KDM1A activity restores adult neurogenesis and improves hippocampal memory in a mouse model of Kabuki syndrome Molecular Therapy - Methods & Clinical Development Volume 20, p779-791, March 12, 2021 doi:10.1016/j.omtm.2021.02.011

Mild to Moderate AD, where a significant reduction of the CSF 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 . 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. Currently, vafidemstat is in two Phase IIb trials in borderline personality disorder (PORTICO) and in schizophrenia patients (EVOLUTION). The company is also deploying a CNS precision medicine approach with vafidemstat in genetically-defined patient subpopulations of certain CNS disorders.

About Kabuki Syndrome

Kabuki Syndrome (KS) is an autosomal monogenic disorder characterized by congenital abnormalities that affect the development and function of multiple bodily systems, often manifesting as impaired mental and physical growth and craniofacial and skeletal abnormalities. Patients may also have cardiac malformations and around 30% of patients develop immunological impairments. KS is caused by heterozygous loss-of-function mutations in either of two genes with complementary functions: KMT2D on human chromosome 12 (for KS type I, representing more than 70% of all KS patients) or lysine-specific demethylase 6A. Both genes facilitate the opening of chromatin and promote gene expression. KS occurs in 1/30,000 births. This represents a prevalence of 3,000 and 3,500 patients in the United States and the EU, respectively, who are younger than 25 and are affected by this syndrome. There is currently no approved treatment for this condition.

About Kabuki Syndrome Foundation

Founded in 2017, the Kabuki Syndrome Foundation (https://www.kabukisyndromefoundation.org/) is a 501(c)(3) non-profit corporation whose mission is to drive research efforts that show promise to treat, prevent or cure Kabuki Syndrome through fundraising, knowledge-sharing and collaborating with researchers around the world.

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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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