

ORYZON publishes characterization and mechanism of action of vafidemstat, a Phase II clinical stage LSD1 inhibitor, in PLOS ONE

- ❖ Pharmacology and preclinical efficacy reported in rodent models of cognition and behavior
- ❖ Detailed insight into mechanism of action

MADRID, SPAIN and CAMBRIDGE, MA, UNITED STATES, June 1st, 2020 – 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, announces the publication of the pharmacological and preclinical properties of its CNS Phase II clinical stage asset vafidemstat in the peer-reviewed international research journal PLOS ONE. Vafidemstat, a CNS optimized LSD1 inhibitor, is under evaluation in several Phase II studies in different psychiatric and neurodegenerative diseases and, more recently, in a Phase II study in Covid-19.

The manuscript, entitled "*Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations*" and authored by Maes *et al.*, describes the design and characterization of vafidemstat and includes a detailed analysis of its mechanism of action and the evaluation of its pharmacological properties. Vafidemstat efficiently inhibits brain lysine-specific histone demethylase 1 (LSD1, also known as KDM1A) at doses suitable for long-term treatment and corrects memory deficits and behavior alterations such as aggressiveness and lack of sociability in animal models. Inhibition of LSD1 was shown to be key in achieving efficacy.

"Translation of preclinical data from model species to human patients is always a challenge, and this is especially true for CNS diseases," said Dr. Tamara Maes, Oryzon's CSO. "Nevertheless, the way our drug behaves in preclinical species correlates very well with the results obtained so far in human studies. Clinical trials in healthy volunteers and patients have shown vafidemstat's favorable safety profile and pharmacological activity, which underpin its continued development in the CNS space."

Oryzon scientists used proteomics to explain how vafidemstat modulates gene transcription equilibria, frequently found to be disturbed in the brain in psychiatric and neurodegenerative diseases. In particular, how LSD1 is involved in the transcriptional mechanisms governing neuronal plasticity, memory, behavior and response to stress. Vafidemstat also reduces the expression of neuroinflammatory markers. Interestingly, multiple genes modulated by vafidemstat in preclinical models are also differentially expressed in the brains of patients with Alzheimer's disease (AD) and other CNS diseases. These published findings provided preclinical support for the subsequent design of early stage clinical trials and for the evaluation of several therapeutic indications with vafidemstat.

PLOS ONE is a peer-reviewed international journal that publishes multi- and inter-disciplinary research and was founded with the aim of accelerating the pace of scientific advancement. The PLOS ONE article can be found at: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0233468>

Vafidemstat reduced agitation-aggression in Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) and Borderline Personality Disorder (BPD) patients after 2 months of treatment in the Phase IIa basket trial REIMAGINE and in severe and moderate AD patients after 6 months of treatment in the Phase II trial REIMAGINE-AD. In ETHERAL, an ongoing Phase II trial in mild to moderate AD, the primary endpoint was met: the drug was safe and well tolerated after 6 months of treatment. First clear data supporting pharmacological activity in the human brain were also presented: vafidemstat mediated a significant reduction of the CSF levels of the inflammatory biomarker YKL40 in AD patients and a tendency for two other biomarkers. An additional exploratory Phase IIa trial in relapse-remitting and secondary progressive multiple sclerosis, SATEEN, is ongoing.

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 iademstat, 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

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