**ORYZON GENOMICS, S.A.**

Pursuant to the provisions of article 228 of the Restated Text of the Securities Market Act approved by Royal Legislative Decree 4/2015 of 23 October, ORYZON GENOMICS, S.A. ("**ORYZON"** or the "**Company**") hereby gives notice of the following

## SIGNIFICANT FACT

ORYZON announces that it has received approval from the Spanish Medicines Agency (Agencia Española del Medicamento, AEMPS) to conduct a PhIIa clinical trial with ORY-2001 in patients of Alzheimer's Disease (AD).

The pressrelease that will be distributed to the media today is attached.

Madrid, 4 April 2018

# ORYZON receives approval to start ETHERAL: a Phase IIa clinical trial in Alzheimer's Disease with ORY-2001

**This first approval received from the AEMPS in SPAIN**

**The company expects to start enrollment this quarter**

**This is the second Phase II study in CNS with the drug**

**Approvals from other European agencies expected soon**

**MADRID, SPAIN and CAMBRIDGE, MA, April 4, 2018** – Oryzon Genomics (ISIN Code: ES0167733015, ORY), a public clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with strong unmet medical need, has announced today that it has received approval of a Clinical Trial Application (CTA), the European IND equivalent, from the Spanish Drug Agency (AEMPS) to conduct a Phase IIa clinical study with ORY-2001 in patients of Alzheimer's disease (AD). The study will be conducted in different European hospitals in Spain, and also in UK and France once the corresponding approvals from the UK and French regulatory authorities are obtained.

The study, named ETHERAL (**E**pigenetic **THER**apy in **AL**zheimer's Disease), is designed as a randomised, double-blind, placebo-controlled, 3-arm, 26 weeks parallel-group study to evaluate the safety and tolerability of ORY2001 in patients with mild and moderate Alzheimer's disease. The study will involve 90 patients and incorporates measurements in the different domains of the disease as secondary endpoints, including memory and behavior alterations. It will also monitor the variations of diverse, yet significant CSF biomarkers. The company is aiming to launch a twin study in the US soon with a, yet to be determined, number of additional patients.

After the safety Phase I trial carried out in 106 healthy volunteers last year, where the drug proved to be safe and well tolerated under the conditions of the study and where CNS penetrance was established the investigational drug was ready to start trials in the patient population. The company has already started a Phase IIa clinical study with ORY-2001 in patients of Multiple Sclerosis (MS). The study, named SATEEN, is currently being conducted in nine Spanish hospitals, and is designed as a randomised, double-blind, placebo-controlled, 3-arm, 36 weeks parallel-group study to evaluate the safety and tolerability of ORY-2001 in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS). The FPI was enrolled in January and the recruitment is proceeding.

ORY-2001 is an oral and brain penetrant drug that selectively inhibits LSD1 and MAOB. The molecule acts on several levels, reduces cognitive impairment, memory loss and neuroinflammation, and at the same time has neuroprotective effects. The company has recently reported in several scientific conferences that ORY-2001 exerts a holistic action on different types of alterations also seen in patients with AD and other

neurodegenerative disorders. ORY-2001 may act as a disease modifying drug. In AD patients and other neurodegenerative disorders, cognitive deterioration is often accompanied by episodes of agitation, aggression, psychosis, apathy and depression. In preclinical studies, ORY-2001 not only restores memory but reduces the exacerbated aggressiveness of SAMP8 mice, a model for accelerated aging and Alzheimer's disease, to normal levels and also reduces social avoidance in rat models maintained in isolation. In addition, ORY-2001 exhibits fast, strong and durable efficacy in several preclinical models of MS.

Roger Bullock, Oryzon's Chief Medical Officer, commented, "The approval of ETHERAL, the first Phase IIa clinical trial for an epigenetic agent in AD, represents an important milestone for the company and the scientific community. Preclinical studies validate the potential of ORY-2001 to treat cognitive defects and neuroinflammation by increasing the plasticity and functionality of neurons. This is the first step in exploring this novel approach and we have chosen to study this in mild to moderate AD patients where we believe there is still physiological room to make a significant therapeutic intervention, as this is a patient population that is underserved with the conventional approaches".

Carlos Buesa, Oryzon's President and Chief Executive Officer, commented, "ORY-2001 is a molecule with disease modifying potential that acts on different domains that are presented in AD patients. We have identified CSF biomarkers altered in AD that can be modulated by ORY-2001 and whose evolution will be monitored. This opens an important range of possibilities not only for a better understanding of the biology of the disease but also in terms of regulatory development for the drug. We expect to be able soon to start further exploratory studies and we keep committed to explore this epigenetic approach in other neurodegenerative disorders".

**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. The company has one of the strongest portfolios in the field. Oryzon's LSD1 program has resulted in + 20 patent families and has rendered two compounds in clinical trials. In addition, Oryzon has ongoing programs for developing inhibitors against other epigenetic targets. The company has a strong technological platform for biomarker identification and performs biomarker and target validation for a variety of malignant and neurodegenerative diseases. Oryzon's strategy is to develop first in class compounds against novel epigenetic targets through Phase II clinical trials, at which point it is decided on a case by-case basis to either keep the development in-house or to partner or outlicense the compound for late stage development and commercialization. The company has offices in Spain and USA. For more information, visit www.oryzon.com.

**FORWARD-LOOKING STATEMENTS**

This communication contains forward-looking information and statements about Oryzon Genomics, S.A., 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 Genomics, S.A. believes that the expectations reflected in such forward-looking statements are reasonable, investors and holders of Oryzon Genomics, S.A. 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 Genomics, S.A., 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 Genomics, S.A. to the *Comisión Nacional del Mercado de Valores*, which are accessible to the public. Forward-looking statements are not guarantees of future performance. The auditors of Oryzon Genomics, S.A, have not reviewed them. 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 Genomics, S.A. 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 Genomics, S.A. on the date hereof. Except as required by applicable law, Oryzon Genomics, S.A. 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. The Company's securities may not be offered or sold in the United States absent registration or an exemption from registration. Any public offering of the Company's securities to be made in the United States will be made by means of a prospectus that may be obtained from the Company or the selling security holder, as applicable, that will contain detailed information about the Company and management, as well as financial statements.

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