ORYZON Epigenetic drugs for a better world PRESS RELEASE 2017

ORYZON presented new preclinical data of ORY-2001 therapeutic activity in Multiple Sclerosis at ACTRIMS-2017

ORY-2001 Reduces Lymphocyte Egress and Demyelination in Experimental Autoimmune Encephalomyelitis

Data highlights the Epigenetic Axis in Multiple Sclerosis

BARCELONA, SPAIN and CAMBRIDGE, MA, February 27, 2017 – Oryzon Genomics (ISIN Code: ES0167733015, ORY), a public clinical-stage biopharmaceutical company leveraging epigenetics to develop therapies in diseases with strong unmet medical need, presented last Friday new preclinical data of therapeutic activity in Multiple Sclerosis (MS) of ORY-2001, a novel epigenetic drug for the treatment of neurodegenerative diseases at the 2nd Annual Conference of the "*Americas Committee for Treatment and Research in Multiple Sclerosis*" (ACTRIMS) in Orlando, Fl. USA.

Dr. Tamara Maes, Vice President and Chief Scientific Officer of the Company, presented positive preclinical data expanding on those previously presented at the ECTRIMS European Conference last September in London. The poster entitled "*ORY-2001 Reduces Lymphocyte Egress and Demyelination in Experimental Autoimmune Encephalomyelitis and Highlights the Epigenetic Axis in Multiple Sclerosis*" showed results produced in the Experimental Autoimmune Encephalomyelitis model. In that model mice are injected with fragments of a peptide (MOG) that triggers a very specific autoimmune reaction, which in turn produces a violent inflammatory reaction and the production of antibodies against the myelin protecting the motor neurons of the animal. As a consequence, there is a gradual demyelination and a development of different degrees of paralysis that can become extremely severe. The results presented at ACTRIMS demonstrate that ORY-2001, administered in a wide range of doses from the moment the mice begin to show the first symptoms, provides an effective and long lasting protection in terms of survival and mobility of the animals even at the lower doses of ORY-2001 (0.05 mg/kg). We thus anticipate a good therapeutic window. Analysis of spleenocytes from ORY-2001-treated animals showed that MOG-induced but not alpha-CD3-induced T cell proliferation was significantly decreased, pointing at a selective effect on specific MOG-induced immune response but not a general systemic immunosuppressive effect. The histopathological analysis, carried out 2 weeks after the first symptoms, showed a strong reduction of infiltration of inflammatory cells and demyelination plaques in the lumbar region of the spinal cord and its total disappearance in the cervical region in animals treated with 0.5 mg/kg of ORY-2001 compared to vehicle-treated animals. In addition, treatment with ORY-2001 resulted in a significant increase in the number of immune cells retained in the spleen and lymph nodes of treated animals, suggesting a reduced egress of lymphocytes from immune tissues. ORY-2001 also caused a reduction in the levels of various pro-inflammatory cytokines such as IL-6 and IL-1beta and of chemokines such as IP-10 and MCP-1, which are involved in the recruitment of the inflammatory and encephalitogenic cells known as Th1 into the spinal cord leading to the destruction of motor neurons. Whole Genome Microarray and Pathway analysis of the spinal cord shows that 39 out of 48 down-regulated genes are linked to pathways related to the immune system.

Although the main mechanisms of action characterized to explain the therapeutic effect of drugs recently approved for the treatment of MS such as fingolimod and dimethylfumarate are not epigenetic, there is now evidence in the scientific literature demonstrating that these drugs also act on epigenetic modulators known as histone deacetylases (HDACs). Interestingly, certain HDACs and LSD1, the target of ORY-2001, often act together in the same protein complexes that regulate gene expression in brain cells and other organs. The data obtained with ORY-2001, an inhibitor of LSD1 and MAOB, point to a convergence in the

mechanism of action of these drugs and reveal the existence of an epigenetic axis, hitherto unknown, that could control the disease or could be used to manage the disease.

In addition, ORY-2001 produces the observed effects at doses that do not produce haematological or lymphocytic effects and without signs of gastrointestinal toxicity, which are some of the various adverse effects common in these approved drugs, suggesting that drugs acting on LSD1 could be cleaner than current drugs acting on HDACs.

It is worth mentioning that several experimental HDAC inhibitors have been linked to beneficial memory effects in various Alzheimer's (AD) and other dementia models. It has also been recently shown that the aforementioned MS drug, fingolimod, used at high doses improves memory in other mouse models[(1)]. This is consistent with Oryzon's data obtained with ORY-2001 showing that this drug enhances memory in AD and produces a potent and lasting protection in the EAE-MS model, and ratifies the hypothesis that epigenetic mechanisms may underlie different phenomena in the brain including memory function and neuroinflammatory pathways.

ORY-2001 is a highly selective dual LSD1-MAOB inhibitor. The molecule, which focuses on cognitive decline and memory loss, has a good safety profile and therapeutic index in preclinical trials. In nontransgenic AD mouse models, long-term treatments with the drug demonstrated a marked cognitive improvement. The company is also exploring its use in the context of other CNS neuroinflammatory disorders such as Multiple Sclerosis. The ongoing Phase I trial with ORY-2001, initiated in early 2016 to determine its safety, tolerability and kinetics in healthy volunteers, will be completed in a few weeks. Shall the preliminary results be confirmed, Oryzon's clinical development plan contemplates the initiation of several Phase II studies later this year to assess its safety and efficacy in diseases such as Multiple Sclerosis, Alzheimer's and other neurodegenerative or neuroinflammatory diseases.

LSD1 is an epigenetic modulator, which regulates histone methylation. Epigenetic approaches to modify the progression of various neurodegenerative diseases focus on producing changes in patterns of gene expression in neurons and also in glia cells and are of interest for the pharmaceutical industry.

Oryzon has a highly competitive and productive Epigenetic Platform centered in LSD1 with the first forerunner program licensed to Roche (ORY-1001/RG6016), that has recently finished Phase I/IIA in acute leukemia and is currently being explored in an ongoing Phase I clinical trial in small-cell lung cancer, validating scientifically and clinically the platform. This Platform has so far produced two additional drugs: ORY-2001, and ORY-3001, a third epigenetic compound, also against LSD1, in preclinical development for a yet undisclosed non-oncological orphan indication.

(1) Hait, N C et al., Active, phosphorylated fingolimod inhibits histone deacetylases and facilitates fear extinction memory. Nature Neuroscience 17, 971–980 (2014)

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 and a clinical asset already partnered with Roche. Oryzon's LSD1 program is currently covered by + 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 Barcelona and Cambridge, Massachusetts. For more information, visit www.oryzon.com.

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