ORYZON Initiates Clinical Development of ORY-1001, a Novel LSD1 Inhibitor, in Patients with Acute Myeloid Leukemia

The First Specific LSD1 Inhibitor to Enter the Clinic.

Barcelona, Spain. January 7nd, 2014. ORYZON, a biopharmaceutical company with a strong focus on epigenetics, has announced that has received the approval from the AEMPS on December 26th , 2013 to initiate a Phase I/IIA clinical trial of ORY-1001, a novel and highly selective LSD1 inhibitor, in patients with relapsed or refractory acute leukemia. This first-in-human trial is currently open at the Hospital Vall d'Hebron in Barcelona, Spain and additional study sites in Spain and in the United Kingdom will be incorporated shortly.

The Lysine Specific Demethylase-1 (LSD1; KDM1A) is an epigenetic modulator that regulates gene expression by demethylating lysine K4 and K9 in histone H3. LSD1 is recruited to specific target sites by protein complexes involved in transcriptional regulation of key cellular processes including proliferation and differentiation. Aberrant activity of these transcriptional complexes may result in disease, and may involve LSD1 as a necessary partner. The pivotal role of LSD1 in acute myeloid leukemia (AML) was reported in two key manuscripts published in Cancer CELL and in Nature Medicine. Small molecule inhibitors of LSD1 produce changes in gene expression that lead to differentiation of leukemic blasts into differentiated cells, to reduced proliferation and to a strikingly reduced colony formation capacity of specific subtypes of leukemic stem cells (LSCs).

Dr. Tamara Maes, Chief Scientific Officer of the company said: "Oryzon started a first in class program targeting the epigenetic modulator LSD1 several years ago, and we have developed a broad patent portfolio in the field. We are pleased to announce that our commitment to develop disruptive strategies to combat disease is starting to shed its fruits. We have received regulatory approval and ORY-1001 is the first specific LSD1 inhibitor to enter the clinic. We are hopeful that ORY-1001 will contribute to treatment of leukemia patients and will continue to explore its potential for other oncological diseases."

ORY-1001 is a highly selective LSD1 inhibitor which can be orally administered to patients. ORY-1001 potently affects AML stem cells, a sub-population of cancer cells that has been proposed to be responsible for frequent relapses of the disease. ORY-1001 overcomes the differentiation block and reduces proliferation at sub-nanomolar concentrations in selected AML cell lines. Cells bearing MLL translocations, a common event in AML and ALL, are exquisitely sensitive to ORY-1001 but responsiveness is not limited to MLLtr cells. ORY-1001 also significantly reduces tumor cell load and increases survival time in a mouse model of Acute Lymphoblastic Leukemia.

In August 2013, Oryzon received orphan designation for ORY-1001 for the treatment of Acute Myeloid Leukemia from the EMA. Orphan designation is granted for medicines to be developed for the treatment of rare diseases that are life-threatening or very serious and for which no satisfactory method of treatment of the condition concerned is authorised. The company plans to apply for the same status to the FDA.

Acute Myeloid Leukaemia (AML) is a blood cancer arising from the myeloid lineage of haematopoietic stem cells. Most patients with acute myeloid leukaemia (AML) die from progressive disease after relapse, which is associated with a small sub-fraction of leukemic cells termed leukemic stem cells (LSC). Current therapeutics target only the rapidly proliferating leukemic progenitors, and not the more chemoresistant LSC. The pharmaceutical industry is making a serious effort to develop drugs which selectively target the LSC compartment with minimum toxicity to the normal HSC compartment. LSD1 has been proven to sustain the oncogenic potential of MLL-AF9 leukemia stem cells and it is therefore a good target to test this therapeutic approach.

Epigenetics represents a promising field to the pharmaceutical industry and has shown an intense deal making activity. LSD1 has been proposed as a target for oncology, viral diseases and neurodegeneration. Oryzon Genomics is the global leader in the development of inhibitors of the Lysine Specific Demethylase 1 (LSD1). Oryzon has a wide drug-discovery program on LSD1 with around 900 compounds and two preclinical candidates. According to Carlos Buesa, C.E.O. of the company. "*The initiation the clinical development of our compound represents a milestone for the company that places us as one of the very few clinical companies in the epigenetic field. We are really excited to test clinically the potential of LSD1 as a therapeutic target in hematological cancers with a molecule as refined as ORY-1001. Oryzon's programs are going to play an important role in the demethylases field and we will try to maximize this potential by attracting the right partners to the different programs*"

The company has a second program in neurodegeneration that has been partially funded by the *Alzheimer's Drug Discovery Foundation.* Under this program the clinical candidate ORY-2001 has shown ability to stop progressive cognitive impairment in non transgenic animal models upon long term oral administration. These results will be presented in the *Biotech Showcase 2014* on Jan 15th 2014 at 9:45 at the Parc55 Wyndham-Union Square Hotel, in a talk entitled "**LSD1 Inhibition stops cognitive impairment in Neurodegenerative Diseases".** The company will also attend the 32nd ANNUAL J.P. MORGAN Healthcare Conference on JANUARY 13–16, 2014 at the Westin St. Francis to discuss with the leaders of the industry the potential of epigenetics in devastating diseases.

About Oryzon

Founded in 2000 in Barcelona SPAIN, Oryzon (www.oryzon.com) is currently the European champion in Epìgenetics. The company has one of the most complete technological platforms for biomarker identification in Europe. With a core in genomics, the company has a powerful platform for biomarker and target validation which includes technologies such as RNAi, and a structural genomic platform with a fragment screening approach (NMR and X ray crystallography). The company identifies biomarkers for a variety of malignant and neurodegenerative diseases and develops new drugs against these targets till Phase II.

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