Oryzon Genomics (MADX:ORY) - €4.75 / share

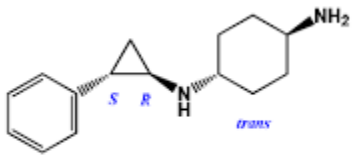
ORY-1001 Phase 1 Data At ASH In AL Looks Good For Oryzon, Roche

Oryzon Genomics (MADX: ORY) is a clinical stage biopharmaceutical company headquartered in Barcelona, Spain. The company is a leader in the development of epigenetics-based therapeutics. Epigenetics is the study of modifications that occur in DNA that results in activation or deactivation of gene expression without alteration in DNA sequence. The company is applying epigenetics to drug discovery and development in the area of cancer and neuroinflammatory / neurodegenerative diseases.

One of Oryzon's lead drug candidates is ORY-1001, a potent and highly selective Lysine Specific Demethylase 1 (LSD1) inhibitor under development for the treatment of acute myeloid leukemia (AML) and small cell lung cancer (SCLC). Oryzon has made significant progress with ORY-1001 over the past year and just recently presented Phase 1 data at the American Society of Hematology (ASH) meeting earlier in the week. Roche, the company's development and commercialization partner, will take over further clinical studies. In fact, Roche noted during Oryzon's analyst / investor presentation at ASH that they have initiated a trial in SCLC with ORY-1001 (to be called RG-6016). Below is a quick review of ORY-1001 and the Phase 1 data.

Quick Background On ORY-1001

ORY-1001 is a potent and highly selective LSD1 inhibitor. LSD1 (also known as KDM1A) is a histone eraser enzyme that removes methyl groups, specifically mono and demethylated H3K4 and H3K9, and by doing so regulates the expression of many genes important in the onset and progression of diseases such as cancer and neurodegenerative disorders. LSD1 belongs to the family of flavin adenine dinucleotide (FAD) dependent amine oxidases, which include known drug targets, such as MAO-A and MAO-B.



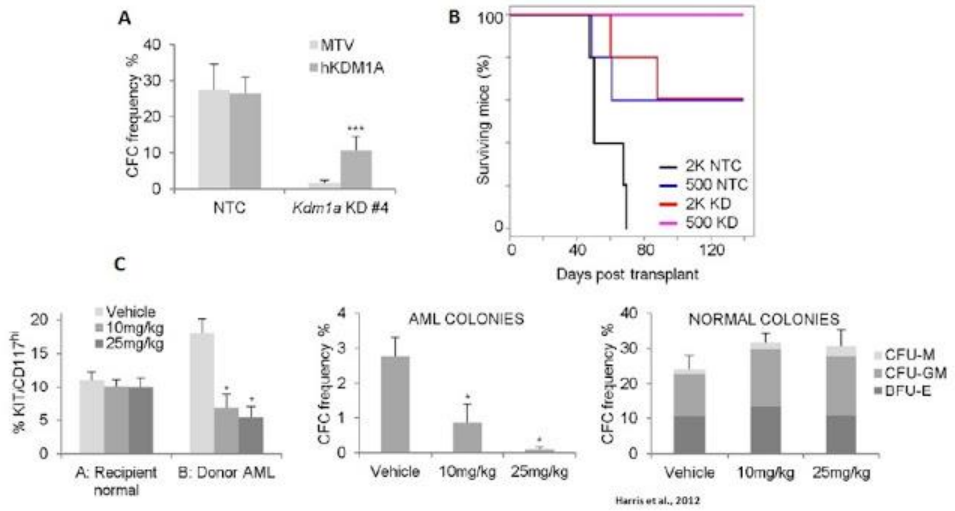
ORY-1001

Many cancers are associated with aberrant gene expression, and the methylation status of histone lysines was recently shown to be important in the dynamic regulation of gene expression. For example, LSD1 expression is upregulated in bladder cancer, small cell lung cancer, and colorectal cancer tumors when compared with the corresponding non-neoplastic tissues (1). LSD1 has also been shown to be overexpressed in some breast cancers and may function as a biomarker of the aggressiveness of the disease (2). Independent analysis also shows expression of LSD1 is upregulated in prostate and brain cancers with aggressive biology (3, 4).

- Proof of Concept For LSD1 in Leukemia -

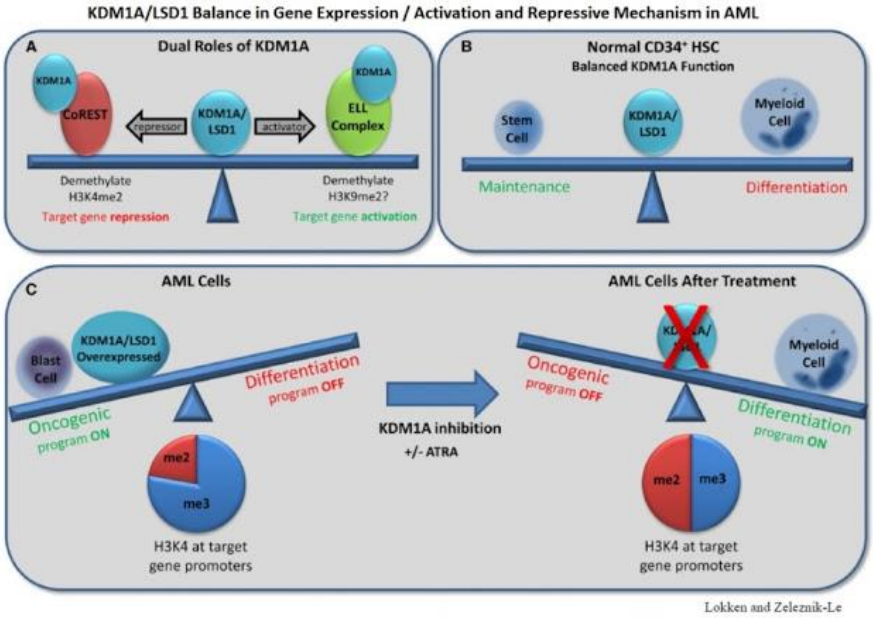
Proof-of-concept for Oryzon's approach has been demonstrated in a mouse model of human AF9 mixed lineage leukemia (MLL). Research published in *Cancer Cell* in 2012 shows that LSD1 (KDM1A) is an essential regulator of leukemia stem cell potential and that the enzyme acts at genomic level to sustain expression of the associated oncogenic program (5). This sustained expression prevents blast cell differentiation and apoptosis. *In vitro* and *in vivo* pharmacologic targeting of KDM1A using OG86, a tranylcypromine analog tool compound designed by Oryzon, active in the nanomolar range, phenocopied KDM1A knockdown in both murine and primary human AML cells exhibiting MLL translocations. By contrast, the clonogenic and repopulating potential of normal hematopoietic stem and progenitor cells was spared. The data establish KDM1A as a key effector of the differentiation block in MLL leukemia, which may be selectively targeted to therapeutic effect.

The figures below show: (A) Mean ± SEM AML-CFC frequencies of control and KDM1A KD murine MLL-AF9 AML cells in the presence of forced expression of human KDMIA, (B) Survival curves of sublethally irradiated syngeneic mice transplanted with 500 (n=5) or 2,000 (n=5) control or KDM1A KD MML-AF9 AML cells, and (C) LSD1 inhibitor targets leukemia blast cells but spares normal healthy hematopoietic progenitor cells.



Preclinical work with ORY-1001 has demonstrated highly (subnanomolar) specific and potent activity against LSD1. Pharmacokinetic data suggests good oral bioavailability with druggable ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. The company is focusing initial development of ORY-1001 on myeloid malignancy, a pathology in which epigenetic dysfunction plays a central role. For example, subtypes of AML exhibit distinct and abnormal patterns of DNA methylation (6). Chromosomal translocations can also induce epigenetic dysfunction leading to the formation of novel oncoproteins in myeloid leukemia (7). Structural lesions involving chromosome 11, band q23, are among the most common cytogenetic abnormalities associated with hematopoietic malignancies such as ALL and AML and are strongly predictive of a poor clinical outcome (8).

Myeloid/lymphoid or mixed-lineage leukemia (MLL) is a histone methyltransferase involved in the epigenetic maintenance of transcriptional memory. Specifically, KDM1A activates or represses genes through its histone demethylase activity, maintaining the balance between hematopoietic stem cells and differentiation to mature myeloid cells. In AML, increased KDM1A expression promotes an oncogenic gene expression program, causing a block in differentiation associated with increased H3K4me3 to H3K4me2 ratio at the promoter of target genes (9). By targeting MLL-associated oncogenic programming through inhibition of KDM1A histone demethylase, differentiation of blast cells can be induced in primary MLL leukemia cells (see figure below).



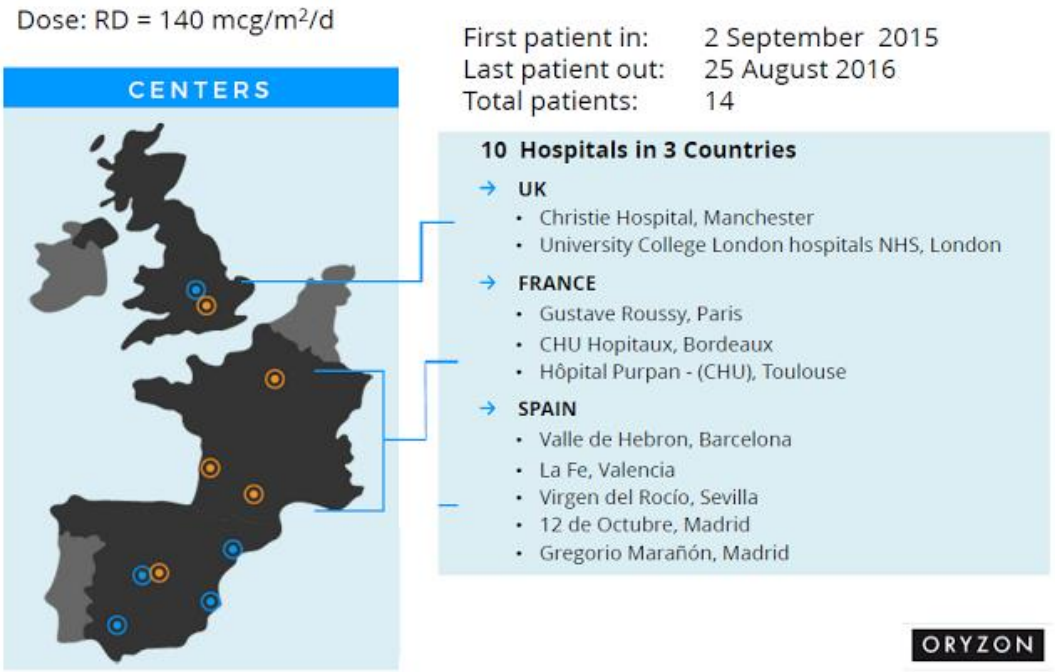
Phase 1/2a PK / Safety, Initial Efficacy Study

Oryzon conducted a Phase 1/2a clinical study with ORY-1001 in patients with refractory or relapsed Acute Leukemia (AL). The Phase 1 portion of the trial was a multicenter, multiple ascending dose escalation study designed to ensure the safety (hematological and non-hematological toxicities), tolerability, and pharmacokinetics (PK) of ORY-1001 in 27 patients with refractory and relapsed unselected AL. Eight ascending doses were examined (5, 15, 30, 45, 60, 80, 140, and 220 μg/m^2/d). This was successfully completed in late 2015 at five clinical sites, four in Spain and one in the UK.

Preliminary results obtained from the trial demonstrate ORY-1001 was well tolerated, with predicted toxicities including thrombocytopenia and anemia, which as invariable and evidence of *in vivo* activity. Investigators concluded that the great majority of adverse events (AEs) and serious adverse events (SAEs) were likely related to the underlying disease and not to the drug. Pharmacokinetics and pharmacodynamic measures were consistent with druggable characteristics. The figure below shows the dose escalation and SAE profile observed during the ascending dose (AD) portion of the trial.

SAE Ascending Dose	
Pneumonia / lung infection	9
Febrile neutropenia	7
Sepsis	5
Intracranial haemorrhage	3
Respiratory failure	2
Line infection	2
Fever	2
Depressed level of consciousness	1
Hepatobiliary disorders	1
Stroke	1
Heart failure	1
Sinusitis	1
Acute myeloid leukemia progression	1
TOTAL	36

Following the successful dose escalation portion, Oryzon expanded this study into five additional centers in France, Spain, and the UK for the Phase 2a extension study (EC). The enrollment criteria target patients with target mutations such as MLL and M6/AML. This is a rare subset of disease in which leukemia stem cells are especially sensitive to LSD1 inhibition.



A full analysis of the safety, pharmacokinetic, and preliminary therapeutic effect of ORY-1001 was presented at the ASH meeting on December 5, 2016. The safety and adverse event profile were within expectations and consistent with previous findings. Investigators concluded that the drug was well tolerated with excellent oral bioavailability and pharmacokinetic parameters. Below is a snapshot of the safety and SAE profile of ORY-1001 in the extension cohort (EC).

SAE Extension Cohort	
Febrile neutropenia	9
Progressive disease	5
Leukocytosis	3
Pulmonary infection	3
Supraventricular tachycardia	2
Rising white cell count/ differentiation syndrome	2
Soft tissue infection (Cellulitis)	1
Acute kidney injury grade III	1
Diarrhoea	1
Bone pain	1
Fever	1
Leukemia cutis	1
Hypotension	1
Thrombocytopenia	1
Sepsis during transfusion	1
Pericarditis	1
Abscess of the anal margin	1
TOTAL	35

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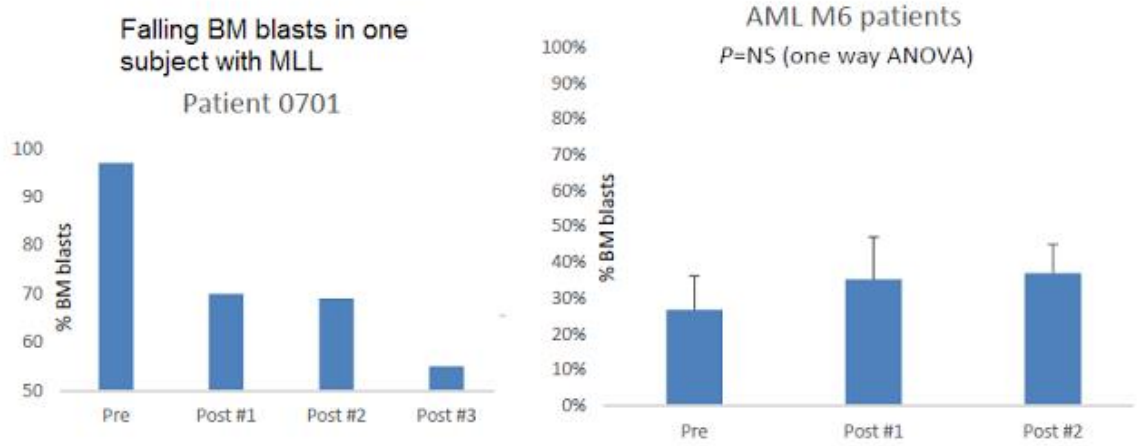
Preliminary Expected ADR Reported

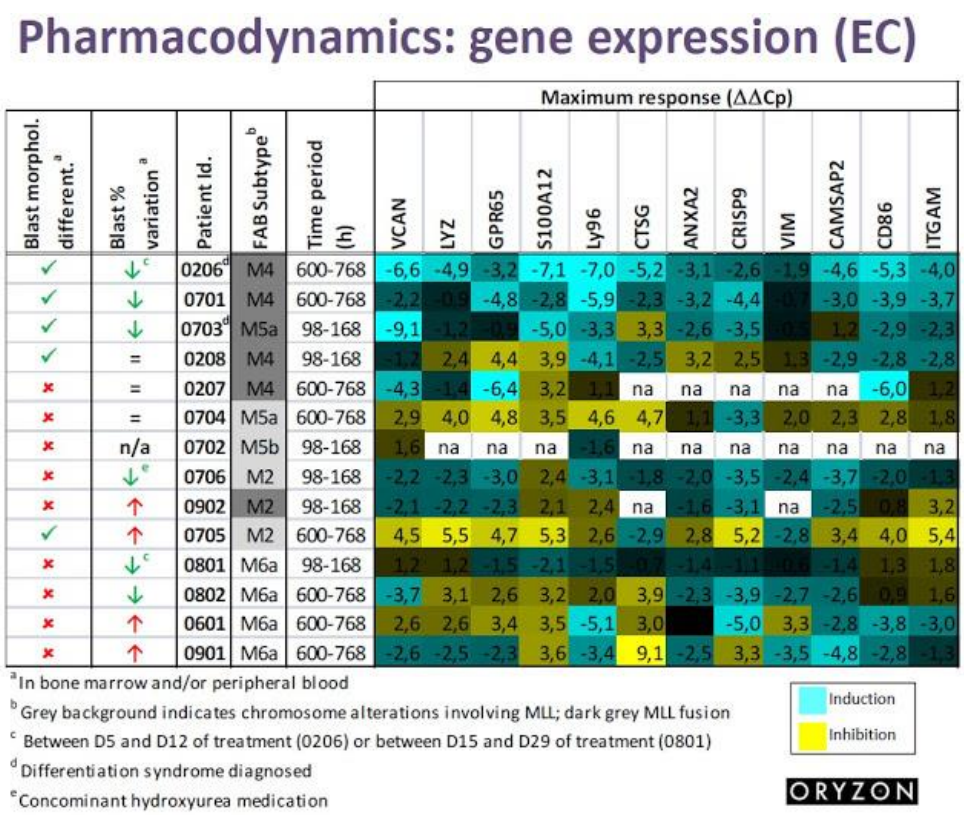
Frequency	Preferred Term	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
System / Organ Class	Blood and lymphatic system disorders				
Very common	Thrombocytopenia	5 (16.7)	0 (0.0)	5 (16.7)	0 (0.0)
Common	Febrile neutropenia	2 (6.7)	1 (3.3)	0 (0.0)	1 (3.3)
	Neutropenia	2 (6.7)	0 (0.0)	2 (6.7)	0 (0.0)
System / Organ Class	Nervous system disorders				
Common	Dysgeusia	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Lethargy	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)
System / Organ Class	Skin and subcutaneous tissue disorders				
Common	Petechiae	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)

Initial signs of therapeutic effect were evident in a number of patients. For example, *in vivo* blast differentiation (including differentiation syndrome) occurred in four of six (67%) subjects with MLL fusion gene. Falling bone marrow blasts was observed in one subject (#0701) following subsequent cycles. Blast cells cleared from blood in another subject (#0207) that achieved stable disease. In subjects with M6/AML, all achieved stable disease (n=4). Results in other subjects (n=4) with MLL were mixed, with one achieving differentiation and another having only residual skin disease, whereas one saw progressive disease and another was unevaluable (withdrew).



To further enhance the understanding the pharmacodynamics of the drug, 12 genes associated with monocyte / macrophage differentiation were monitored by qRT-PCR in the peripheral blood cells of treated patients. As expected from preclinical data, variability in the biomarker induction profile was seen, including differences in time to induction and durability of effect. Investigators believe that the variability in response is due to differences in disease etiology.

For example, analysis of S100A12, VCAN, ITGAM, LY96, CD86, GPR65, CRISP9, ANXA2 and LYZ gene expression allowed for monitoring of response to ORY-1001 treatment in M4/M5 AML patients. Blast count decreased with each cycle in one of six MLL patient and one of six MLL patient presented blast clearance from blood on treatment. Bone marrow response was observed in 23% of all patients in the EC and 100% (4/4) M6 patients presented stable disease. Four of six (67%) MLL fusion gene and one (25%) other MLL rearranged cases presented differentiation by blast morphology. All MLL gene fusion subjects with evaluable PD samples (5/5) showed evidence of blast differentiation by qRT-PCR analysis (see ASH poster of PD data below).



A Unique Asset

Beyond AML, Oryzon and Roche believe that ORY-1001 has utility in solid tumors. For reference, GlaxoSmithKline has progressed into Phase 1 clinical development with a similar LSD1 inhibitor, GSK2879552, for small cell lung cancer (SCLC). Based on published data, ORY-1001 looks several times more potent, with efficacy at low nanomolar concentrations and minimal off-target binding.

The most potent LSD1 inhibitor in cells reported

CODE	LSD1 (IC50 mcM)	K_{inact}/k_i ($sec^{-1}M^{-1}$)	Fold selectivity LSD1 vs MAO-A	Fold selectivity LSD1 vs MAO-B	THP-1 cells differentiation assay (EC50 nM)
ORY-1001	0.018	226315	>5550	>5550	0.8
GSK-2879552	1.183	1076	>80	>80	≈ 100

Roche Takes Over Clinical Development

In April 2014, Oryzon announced they have entered into a worldwide collaboration to research, develop and commercialize inhibitors of LSD1 (KDM1A), including lead molecule ORY-1001, with Roche. Under terms of the agreement, Roche will have sole responsibility for developing and commercializing ORY-1001 and/or its backup compounds beyond the ongoing Phase 1/2a clinical trial in AL. The agreement includes the licensing of two patent families that Oryzon has created around LSD1, and includes options for other Oryzon programs to be incorporated in future.

In return for licensing these rights to Roche, Oryzon received an upfront payment and milestones totaling $23 million to date, plus potential development, commercial and sales milestone payments across hematology, cancer, and non-malignant indications that could exceed $500 million, together with tiered royalties on sales which range up to mid-double digits. The license agreement also included an R&D collaboration with Roche to explore oncology and hematology indications for ORY-1001, which was extended by Roche in April 2016 until March 2017. The extension allows for Oryzon to gain additional insight into the drug's mechanism of action, provided support for its use in indications beyond acute leukemia, and expand the toolbox for future and current clinical trials. The main goal over the next several months is to finalize the transfer of the newly generated technology and knowledge over to Roche.

During Oryzon's ancillary investor meeting at ASH 2016, Gwen Nichols, Oncology Site Head, Roche Translational Clinical Research Center, announced that Roche has initiated a Phase 1 dose finding and expansion study with ORY-1001 (RG-6016) in SCLC. Target enrollment is 70 subjects with relapsed SCLC. Enrollment is expected imminently and will take place in Canada, Denmark, France, and Spain. Roche has sole responsibility for this program. In total, ORY-1001 is targeting potential indications with sales in the billions of dollars.

Conclusion

Oryzon is focused on developing epigenetic-based therapies and personalized drugs from its proprietary platform technology. The pipeline includes one Phase 2 ready compound in oncology, ORY-1001, a highly potent LSD1 inhibitor with exquisite selectivity that has been granted orphan-drug status by the EMA for acute myeloid leukemia, a second compound in Phase 1 clinical trials, ORY-2001, for the treatment of Alzheimer's Disease and other CNS indications that the company may choose to add to its Phase 2 plans, a compound in regulatory preclinical development for non-oncology indications, ORY-3001, and additional programs in other cancer indications in various stages of preclinical development.

Results with ORY-1001 are highly encouraging and point to the potential use of the drug in the treatment of acute leukemia with a novel, best-in-class mechanism of action. AML is notoriously difficult to treat, so a novel mechanism targeting MLL or M6/AML represents an attractive market opportunity. Based on a review of available literature and analysis of peers, the company's strategy seems sounds and likely to create significant shareholder value if successful.

Oryzon currently trades on the Madrid Stock Exchange (MADX: ORY) with a market capitalization of approximately €145 million ($155 million). Throughout 2016, Oryzon has made significant progress with the advancement of its pipeline. Investors have paid attention, and the shares are up nearly 100% in the past few months. That said, peer-valuation analysis suggests a Phase 2 asset in oncology is worth approximately $150-200 million alone, and positive data with ORY-1001 just reported at ASH validates this opportunity. Keep in mind, Oryzon is partnered with Roche and could receive up to $500 million in milestones on ORY-1001 if successfully commercialized.

Beyond ORY-1001, Oryzon has advanced ORY-2001 into a Phase 1 multiple ascending dose study. I expect that with positive data, Oryzon will move ORY-2001 into a Phase 2 study in patients with Alzheimer's disease during the first half of 2017. Recently positive preclinical data with ORY-2001 sets the stage for a potential expansion into other types of dementia, as well as multiple sclerosis and Huntington's disease. Peer-valuation analysis suggests a Phase 2 CNS asset with potential in AD, MS, or HD is worth approximately $100-150 million in value.

Commensurate with the company advancing ORY-2001 into Phase 1 trials and the positive data with ORY-1001 at ASH this week, I believe Oryzon is worth $300 million in value; which, despite the shares being up nearly 100% over the past few months, calls for another doubling in 2017 to €10 per share. I have yet to factor in any value for ORY-3001, which looks easily like another multi-hundred million dollar opportunity. European investors and U.S. investors that seek to buy stocks listed on the Madrid exchange should absolutely put Oryzon Genomics on their radar. The company has plans to list on the Nasdaq exchange probably in 2017, which should further strengthen the company's position in the coming year.

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