Oryzon Genomics (MADX: ORY) - €2.90 / share

Oryzon Secures Financing, ORY-1001 Data Expected At ASH

On October 24, 2016, Oryzon Genomics (MADX: ORY) reported financial results for the third quarter ending September 30, 2016. Total collaborative revenue in the third quarter was $0.252 million, bringing revenue for the first nine months of 2016 to $0.785 million. Revenue is derived from collaborative research work with Roche on ORY-1001, deferred recognition of a previous upfront payment from Roche for ORY-1001 in 2014, and non-dilutive research grants that support work on ORY-2001.

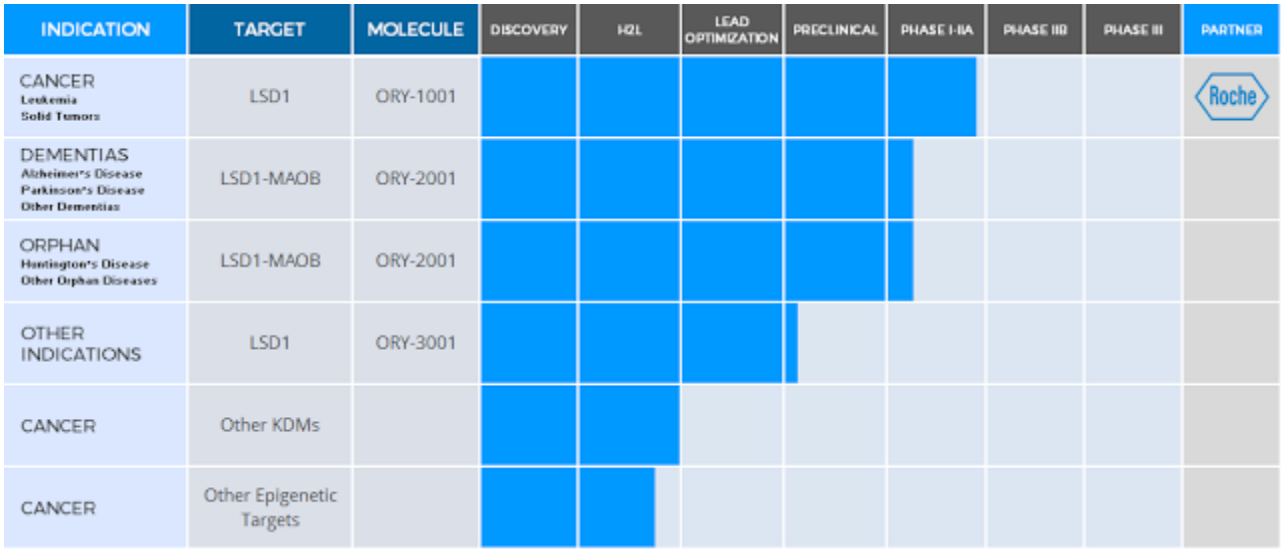
The loss for the quarter totaled $1.5 million, driven by $1.5 million in R&D and $1.4 million in general and administrative costs. Oryzon continues to invest in its therapeutic pipeline, having recently advanced ORY-2001 into a multiple ascending dose study and nominated ORY-3001 for IND-enabling studies in non-oncological conditions.

Oryzon exited September 2016 with $32.1 million in cash, equivalents, and short-term investment. Cash increased $7.8 million from December 31, 2015, thanks to the closing of the second tranche of debt financing of $5.9 million USD. These proceeds come on top of the $11.6 million USD first tranche of debt financing raised in May 2016. In total, Oryzon has raised more than $35.5 million USD since July 2015. I project operating burn over the next year will be between approximately $13-15 million. Thus the current balance is sufficient to fund operations for the next 18 months. There are approximately 28.5 million shares outstanding.

Oryzon Genomics - A Global Leader In Epigenomics

Oryzon is a clinical stage biopharmaceutical company headquartered in Barcelona, Spain. The company is a leader in the development of epigenetics-based therapeutics. Epi is Greek for above, and genetics is the study of genes, heredity, and genetic variation in living organisms. As such, epigenetics is the study of "above the genes", or more specifically, modifications that occur to the genes that result in activation or deactivation of gene expression without alteration in DNA sequence. These modifications are known as epigenetic modifications. The company is applying epigenetics to drug discovery and development in the area of cancer and neuroinflammatory / neurodegenerative diseases.

Oryzon has made significant progress with its development programs over the past year. The company's lead candidate, ORY-1001, has progressed into the second part of a Phase 1/2a clinical study. ORY-1001 is being developed in collaboration with Roche for hematological and solid tumors. Management expects to report preliminary data from this program at the American Society of Hematology (ASH) meeting in December 2016. A second candidate, ORY-2001, has entered the clinical for the treatment of Alzheimer's disease. Oryzon is currently conducting a Phase 1 multiple ascending dose study with ORY-2001 in healthy volunteers. A Phase 2 study is expected to start during the first half of 2017. Recently, a third candidate, ORY-3001, has been nominated for advanced preclinical testing; an IND is expected during the first half of 2017, followed by a Phase 1/2a study in the second half of 2017.



Update On ORY-1001

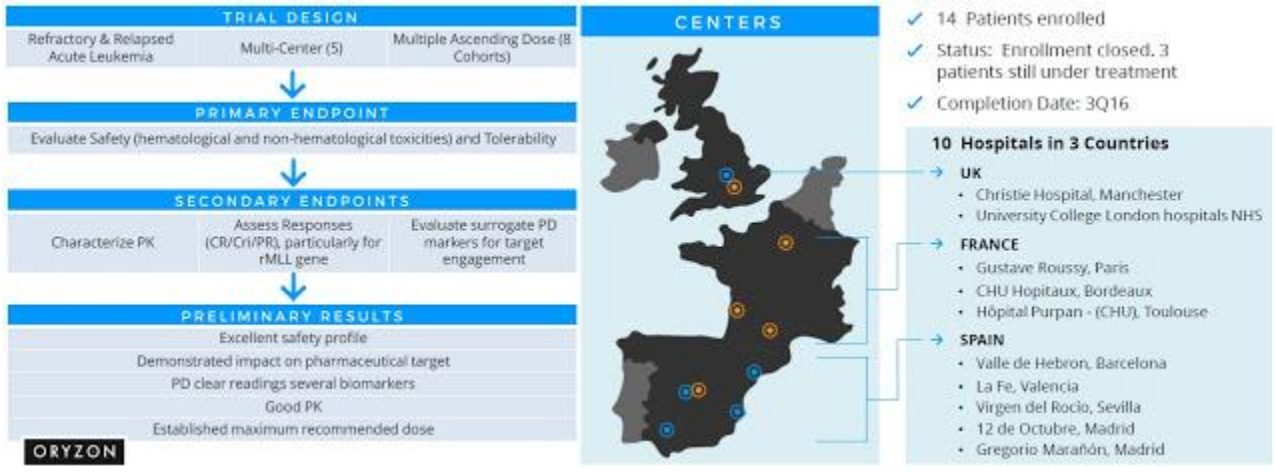
Oryzon Genomics lead clinical-stage candidate is ORY-1001, a potent and highly selective LSD1 inhibitor. LSD1 (also known as KDM1A) plays a key role in the regulation of gene expression and regulation of several proliferation-associated genes implicated in aggressive cancer biology. Preclinical work 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. Proof-of-concept for this approach has been demonstrated in a mouse model of human MLL-AF9 leukemia. ORY-1001 was granted Orphan Drug designation by the European Medicines Agency for Acute Myeloid Leukemia (AML) in July 2013.

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 following completion of the ongoing Phase 1/2a clinical trial. 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. In May 2016, the R&D collaboration with Roche to explore oncology and hematology indications for ORY-1001 was extended by Roche 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.

Oryzon is currently conducting a Phase 1/2a clinical study with ORY-1001 in patients with refractory or relapsed Acute Leukemia. 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 of ORY-1001 in patients with refractory and relapsed acute leukemia. This was successfully completed in late 2015. Preliminary results obtained from the trial demonstrate excellent safety, pharmacokinetics, and pharmacodynamic measures, as well as target biology. No serious drug-related adverse events have been reported, and the company believes they have established the maximum recommended dose for future clinical studies. This work was done at five clinical sites, four in Spain and one in the UK.

Oryzon has since expanded this study into five additional centers in France, Spain, and the UK for the Phase 2a portion of the trial. The enrollment criteria target patients with target mutations such as mixed-lineage leukemia (MLL) and M6. This is a rare subset of disease in which leukemia stem cells are especially sensitive to LSD1 inhibition. The data will allow the company to obtain preliminary signs of efficacy for ORY-1001, setting the stage for future development work to be conducted by Roche. The first patient in the Phase 2 portion of the trial was enrolled in November 2015. Preliminary data are expected to be reported at the American Society of Hematology (ASH) meeting in early December 2016.



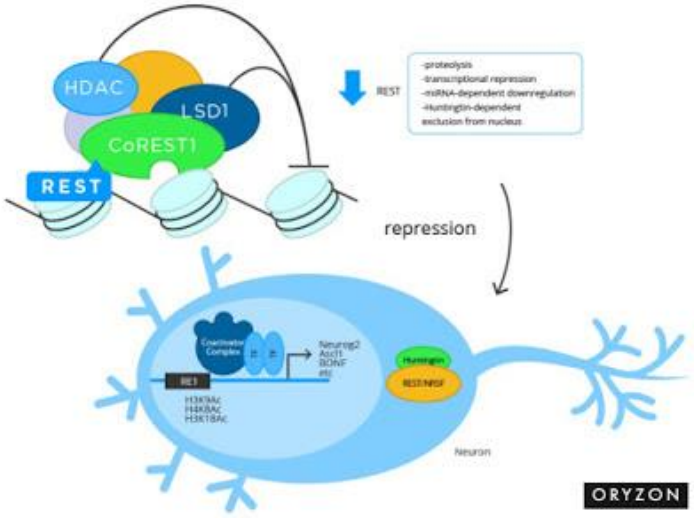
Beyond AML, Oryzon believes that ORY-1001 has utility in solid tumors. For example, LSD1 is overexpressed in multiple tumor types and the ORY-1001 mechanism of action suggests anti-tumor beyond leukemia. GlaxoSmithKline has progressed into Phase 1 clinical development with a similar LSD1 inhibitor, GSK2879552, for small cell lung cancer (SCLC), and based on published data; ORY-1001 looks several times more potent. As such, Roche is expected to follow Oryzon's initial work in AML with a clinical program in SCLC in 2017.

Beyond oncology indications, the potential for LSD1 inhibitors in non-oncology hematological indications is being explored, for example in sickle cell disease (SCD), a rare genetic disorder affecting an estimated 70,000 to 100,000 individuals in the U.S. Independent data out of the University of Chicago on LSD1 inhibition was recently disclosed at the 56th American Society of Hematology (ASH) annual meeting in December 2014 using an Oryzon tool compound. The data highlight the potential for LSD1 inhibitors as treatment options for SCD.

In total, ORY-1001 is targeting potential indications with sales in the billions of dollars. With Roche taking over development responsibilities for the clinical development of ORY-1001 following the completion of the current Phase 2a trial, it will be exciting to see where they take the drug in 2017.

Update On ORY-2001

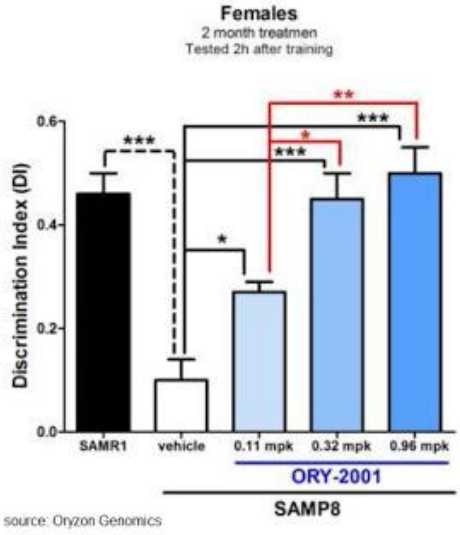
Oryzon's second drug candidate is ORY-2001, a potent and selective, orally available, small molecule inhibitor of LSD1-monoamine oxidase-B (MAO-B). Epigenetic inhibition of LSD1-MAO-B has been shown to have a downstream effect on numerous genes and different biological pathways resulting in consequent transcriptional dysregulation. LSD1 is a key component of the LSD1-REST- CoREST-HDAC1/2 repressor complex involved mainly in controlling developmental programs and modulating neuronal morphology in the CNS. LSD1 is also known to be an important regulator in the maintenance of pluripotency and in specification of neuronal commitment of pluri- or multipotent cells. This mechanism is believed to be an important marker of disease status and its progression in many neurodegenerative diseases, such as Alzheimer's disease.



Initial pharmacology data with ORY-2001 suggests the drug has an excellent pharmacokinetic profile, with a wide therapeutic window and convenient once-daily dosing. Data shows the drug crosses the blood-brain barrier with highly selective anti-LSD1 and MAO-B activity, with no off-target binding.

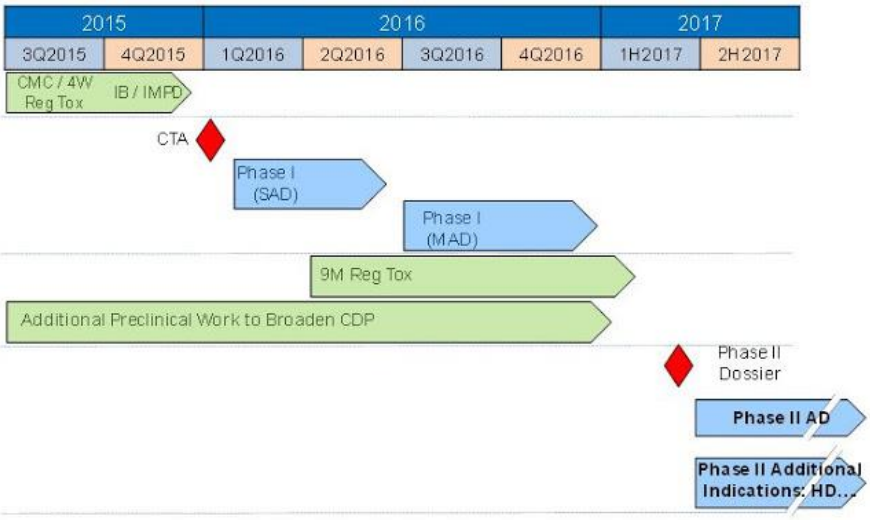
The company will participate at the 2016 Neuroscience Meeting in San Diego held in November. Oryzon will be part of a session titled, "Therapeutics and Protective Strategies for Alzheimer's Disease" on November 16, 2016, at which time the company will present a preclinical update that will provide interesting insights on ORY-2001's mode of action and functional readouts in different models relevant to human disease. There are some very interesting findings with ORY-2001 to discuss.

For example, preclinical data suggest that ORY-2001 improves cognition, with positive implications for diseases such as Alzheimer's and Huntington's disease. In a non-transgenic mouse model of AD, company scientists saw a marked cognitive improvement correlating with changes in the expression of key genes in the hippocampus. In studies partially supported by the Alzheimer's Drug Discovery Foundation, company scientists showed that ORY-2001 provided a dose-responsive protective effect in medium and long-term memory of mice, compared to age-matched SAMP8 mice (see below). Additional preclinical studies with ORY-2001 show improvement of survival and recovery of phenotypic characteristics in mouse models of HD and other neurodegenerative disorders.



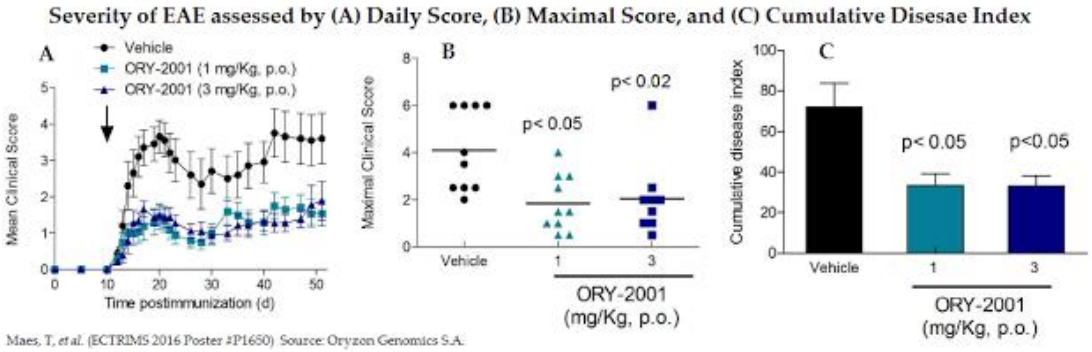
Oryzon has identified different hippocampal biomarkers relative to ORY-2001 treatment. ORY-2001 potently down-regulates the expression of a subset of genes related to immune reactions and inflammation, including S100A9 and T-cell receptor b chains in SAMP-8 mice. Down-regulation of the pro-inflammatory S100A9 protein by ORY-2001 is particularly interesting since S100A9 is emerging as an important contributor to inflammation-related neurodegeneration. For example, S100A9 was found to be increased in patients with Alzheimer's disease, post-operative cognitive dysfunction, and traumatic brain injury (see work by Wang C. *et al.*, 2014). Knockout or knockdown of S100A9 has been shown to be beneficial to memory in APP/PS1 and Tg2576 models of Alzheimer's disease. Additionally, preclinical data shows that ORY-2001 up-regulates genes associated with improved cognitive function, neuroplasticity, and memory.

Oryzon received approval in Spain to initiate a Phase 1 study for ORY-2001 in January 2016. The randomized, double-blind, placebo-controlled single and multiple ascending dose program is designed to investigate the safety, pharmacokinetics, and pharmacodynamics of oral ORY-2001 in healthy subjects as well as an elderly population. The trial is being conducted at a university hospital in Barcelona, Spain. The first patient was dosed in April 2016. The multiple ascending dose cohort began enrolling patients in July 2016. Target enrollment is 48 subjects. 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. A timeline for future development or ORY-2001 pulled from the company's most recent investor presentation can be seen below.



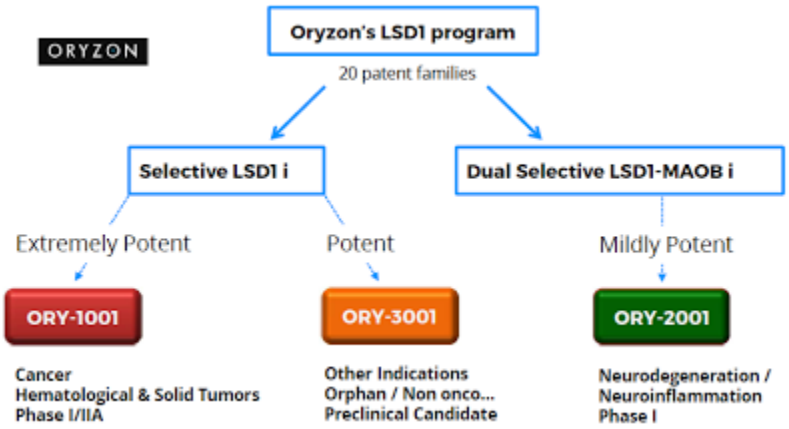
Oryzon owns full rights to the drug; thus, the Phase 2 study could represent a significant valuation inflection for the company if successful. Alzheimer's disease is obviously an enormous market, with approximately 5.4 million Americans affected today. The number is expected to rise to 7.1 million in the U.S. by 2015 according to Alz.org. Alzheimer Europe estimates 8.7 million Europeans are affected by Alzheimer's disease. Another 10 to 12 million people in Asia are also suspected to suffer from Alzheimer's. Little success has been accomplished with respect to new Alzheimer's treatments over the past decade. An epigenomic approach to Alzheimer's, as well as Huntington's disease and Parkinson's disease, represents a novel and exciting new approach to these difficult to treat diseases.

The potential for ORY-2001 even extends to other diseases such as Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE). In September, Oryzon presented preclinical mouse data at ECTRIMS in London that showed treatment with ORY-2001 inhibited the development of EAE and reduced disease incidence and severity measure by daily clinical scores compared to control mice. In fact, 30% of ORY-2001 treated mice almost completely recovered after 40 days; and, the protective effect of ORY-2001 was maintained for a long period of time after cessation of treatment. The company has not made a public statement yet if a clinical development in MS is going to be considered on top of the announced plans in AD.



Update On ORY-3001

In July 2016, Oryzon announced that it had designated its next drug, ORY-3001, for preclinical development. ORY-3001 is a first-in-class specific Lysine Specific Demethylase 1 (LSD1) inhibitor for the treatment of, yet undisclosed, non-oncological conditions. ORY-3001 is an enantiomerically pure, potent and selective compound with good pharmacological properties, orally bioavailable, with optimal PK, safety and selectivity profile. After successful completion of regulatory toxicology studies, the company expects to file the IND during the first half of 2017 and move ORY-3001 into clinical Phase 1/2a studies during the second half of 2017.



Conclusion

Oryzon is focused on developing epigenetic-based therapies and personalized drugs from its proprietary platform technology. The pipeline includes one compound in Phase 1/2a 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. 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.

The company currently trades on the Madrid Stock Exchange (MADX: ORY) with a market capitalization of approximately €83 million ($92 million). Throughout 2016, Oryzon has made significant progress with the advancement of its pipeline. ORY-1001 is progressing in a Phase 2 clinical study, and preliminary results are expected at the ASH conference in December 2016. Peer-valuation analysis suggests a Phase 2 asset in oncology is worth approximately $150 million.

However, positive data at ASH and the fact that the company has partnered with Roche and could receive up to $500 million in milestones on ORY-1001 has the potential to create dramatic upside to this estimate. The ORY-1001 presentation at ASH should act as a major catalyst for the shares heading into 2017.

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. Peer-valuation analysis suggests a Phase 2 Alzheimer's / dementia asset is worth approximately $100 million in value.

Commensurate with the company advancing ORY-2001 into Phase 1 trials and Roche extending the R&D collaboration to explore additional oncology and hematology indications for ORY-1001, I believe $250 million in value. I have yet to factor in any value for ORY-3001.

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