Oryzon Genomics S.A. (MADX: ORY) - €3.91 / Share

Oryzon's Pipeline Taking Shape

My last update on Oryzon Genomics (MADX: ORY) was in December 2016 after the company presented encouraging Phase 1/2a data at the American Society of Hematology (ASH) meeting with ORY-1001. ORY-1001 is the company's 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). The Phase 1/2a data presented at ASH demonstrate excellent safety and tolerability, along with initial signs of therapeutic effect in leukemia. The most pronounced effect was observed in patients with a specific FAB subtype of leukemia known as M6/AML. Oryzon's partner, Roche, has taken over the development of ORY-1001 (now called RG6016) for further clinical studies.

Since December, Oryzon has had a number of positive updates for investors, including advancements with its pipeline and the financial position. Below is a look at some of the recent news since ASH and some thoughts on the financial results released last week.

Quick Review of the Financials

On February 24, 2017, Oryzon reported financial results for the fourth quarter and full year ending December 31, 2016. Total collaborative revenue for the quarter was $0.03 million, bringing revenue for the full year to $0.78 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.

Research grants have been a nice source of cash for the company. In December 2016, Oryzon announced a new grant in the form of a loan from the Ministry of Economy and Competitiveness, Government of Spain and FEDER Funds from the European Union and included under the RETOS Collaboration 2016 program. Oryzon will receive approximately $0.8 million through multiyear disbursements for further development of its epigenetic inhibitors against inflammatory indications.

Net loss for the quarter totaled $1.36 million, driven by $1.71 million in R&D and $1.04 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. Net loss for the full year totaled $5.74 million, driven by $5.49 million in R&D and $5.01 million in G&A. The company also recorded $0.92 million in financial and tax expenses during calendar 2016.

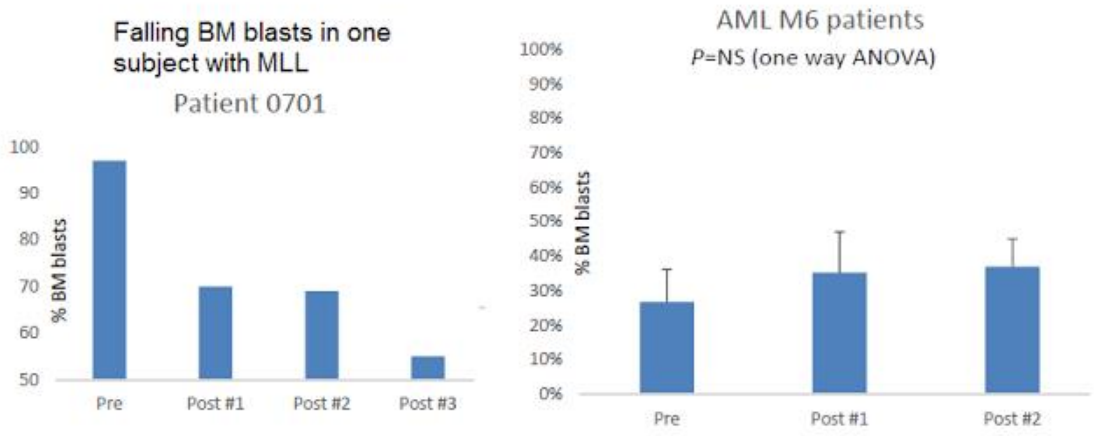
Oryzon exited December 2016 with $28.75 million in cash, equivalents, and short-term investment. Cash increased $5.03 million from December 31, 2015, thanks to the closing of two debt financing transactions in May and September 2016 totaling $16.5 million. I project the operating burn in 2017 will be between approximately $13-15 million; thus, the current balance is sufficient to fund operations well into 2018.

Pipeline Update - RG6016 (formerly ORY-1001)

The fact that ORY-1001 is now being called RG6016 is a clear sign that progress has been made over the past year. Roche is now in charge of future clinical development in both AML and SCLC and Oryzon has the potential to earn in excess of $500 million in development and commercial milestone, along with tiered royalties up to the mid-teens on sales.

Phase 1/2a Data at ASH for RG6016 included a full analysis of the safety, pharmacokinetic, and preliminary therapeutic effect. The data presented at the ASH confirm 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.

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).



- See my full update >> *Phase 1 Data At ASH In AL Looks Good For Oryzon*

Beyond AML, Oryzon and Roche believe that RG6016 has utility in solid tumors. In January 2017, Oryzon announced that Roche commenced patient dosing in a Phase 1 study in patients with small cell lung cancer (SCLC). The Phase 1, open-label, multicenter study is designed to assess the safety and tolerability of RG6016 in participants with relapsed extensive disease SCLC. This dose escalation and expansion study plans to determine the maximum tolerated dose and/or optimal biological dose as a recommended Phase 2 dose for RG6016, based on the safety, tolerability, pharmacokinetic and pharmacodynamic profiles observed after oral administration of the drug. Target enrollment is 70 subjects and will take place in the U.S., Canada, Denmark, France, and Spain. Roche has sole responsibility for this program.

For reference, GlaxoSmithKline progressed a similar LSD1 inhibitor into Phase 1 clinical studies last year. Despite being several months behind in development, RG6016 looks far more potent and offers superior pk to Glaxo's GSK2879552.

The most potent LSD1 inhibitor in cells reported

CODE	LSD1 (IC50 mcM)	K_{inact}/k_i ($sec^{-1} \cdot M^{-1}$)	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

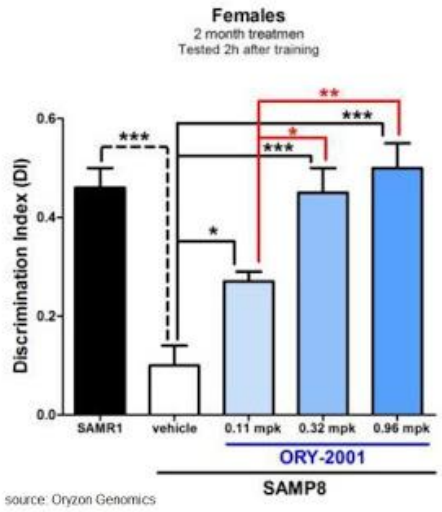
Beyond oncology indications, the potential for LSD1 inhibitors in non-oncology hematological indications is also under investigation. Sickle cell disease (SCD) is a rare genetic disorder affecting an estimated 70,000 to 100,000 individuals in the U.S. Independent data out of the University of Chicago on LSD1 inhibition was 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, RG6016 is targeting potential indications with sales in the billions of dollars. With Roche now in full control of the clinical development program, it will be exciting to see where they take the drug in the coming years.

Pipeline Update - 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). 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. This mechanism is believed to be an important marker of disease status and progression in many neurodegenerative diseases. Preclinical data suggest that ORY-2001 improves cognition, with positive implications for diseases such as Alzheimer's, Parkinson's, and Huntington's disease.

In a non-transgenic mouse model of Alzheimer's disease (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, Oryzon 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 Huntington's 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 an improvement in 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 and pk/pd 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.

Preliminary top-line data are expected at the 13th International Conference on Alzheimer's and Parkinson's Disease in Vienna, Austria on March 31, 2017. I expect that with positive data, Oryzon will move ORY-2001 into a Phase 2 study in patients with Alzheimer's disease during the second half of 2017.

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 2025 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.

ALZHEIMER'S DISEASE

5.4 M people currently affected in US. By 2025 the number of patients will rise to 7.1 million in USA[1]
8.7 million Europeans are also affected [2] and in Asia another potential 10 to 12 million people are diagnosed or suspected to suffer AD.

Drug market projected to reach US $9.5 billion by 2017 [6]

PARKINSON'S DISEASE

Around 6.3 million people have the condition worldwide[3]
It affects over 1 million people in the US, with nearly 60,000 people newly diagnosed every year. [4]

Drug market projected to reach US $2.6 billion in 2020 in the 7MM

HUNTINGTON'S DISEASE

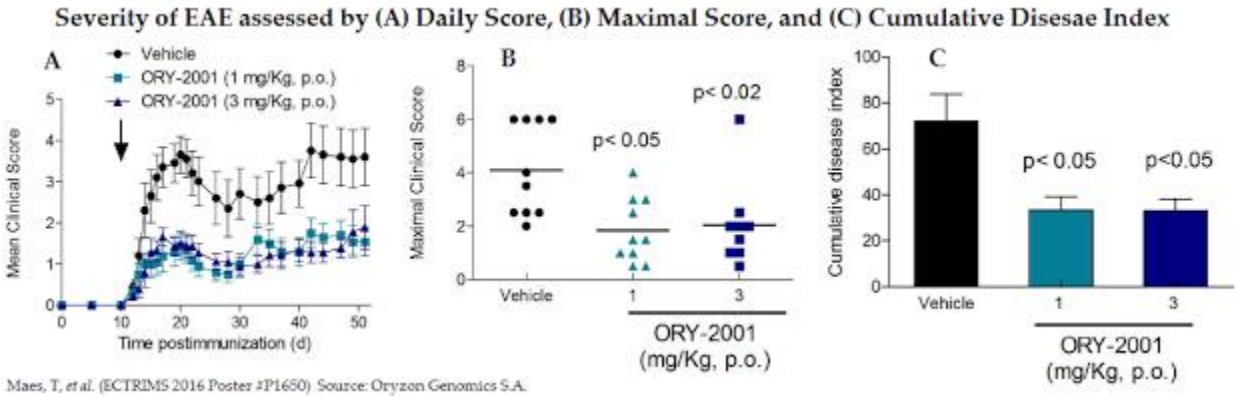
Worldwide prevalence of HD is 5–10 cases per 100,000 persons. There are around 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease [5]
Up to 71,000 patients in Europe.

Drug market projected to reach US$1.3 billion by 2020 [7]

1. Alzheimer'sassociation www.alz.org
2. Alzheimer Europe www.alzheimer-europe.org
3. European Parkinson's Diesease Association http://www.epda.eu.com/
4. American Parkinson Disease Association http://www.apdaparkinson.org/. http://www.ninds.nih.gov/
5. http://www.huntington-assoc.com/
6. http://www.fiercebiotech.com/
7. http://www.strategyr.com

ORYZON

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.



Maes, T, *et al.* (ECTRIMS 2016 Poster #P1650) Source: Oryzon Genomics S.A.

Additional preclinical data on ORY-2001 in MS came at ACTRIMS-2017 in Orlando, Florida in February 2017. The new data build upon what was presented at ECTRIMS last September in London. A poster entitled "*ORY-2001 Reduces Lymphocyte Egress and Demyelination in Experimental Autoimmune Encephalomyelitis and Highlights the Epigenetic Axis in Multiple Sclerosis*" showed that ORY-2001 provides an effective and long lasting protection in terms of survival and mobility in a mouse model of induced autoimmune encephalomyelitis, even at the lowest dose of 0.05 mg/kg tested.

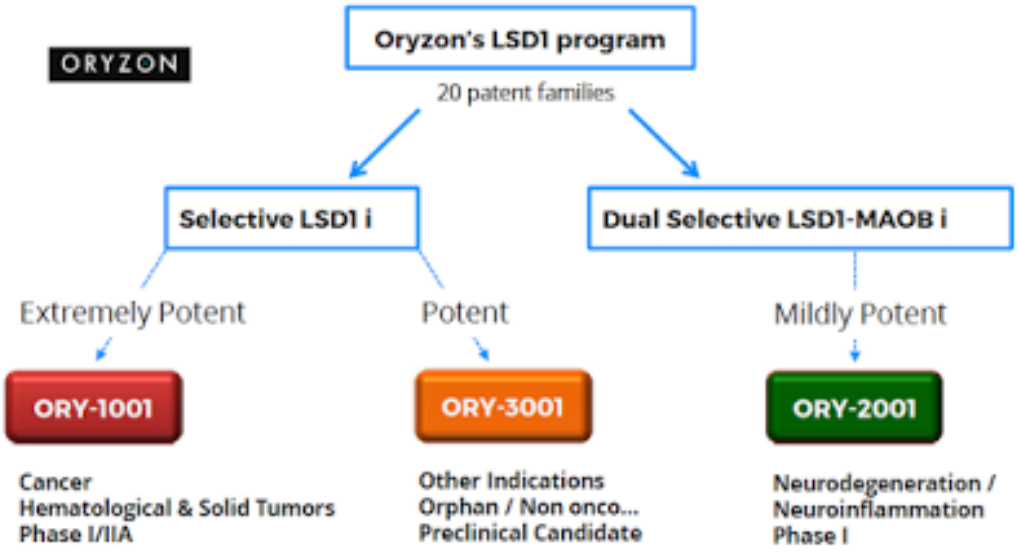
Histopathological analysis showed a strong reduction of infiltration of inflammatory cells and demyelination plaques in the lumbar region of the spinal cord and its total disappearance in the cervical region in animals treated with 0.5 mg/kg of ORY-2001 compared to vehicle-treated animals. In addition, 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. Importantly, the company observed no negative hematological or lymphocytic effects, or gastrointestinal toxicity, which are some of the various adverse effects common in these approved drugs.

Nevertheless, it is worth mentioning that several experimental histone deacetylases inhibitors have been linked to beneficial memory effects in various Alzheimer's and other dementia models. For example, work by Hait NC, *et al.*, 2014 shows that Novartis AG's Gilenya® (fingolimod) used at high doses improves memory in mouse models. This is consistent with Oryzon's data showing that ORY-2001 enhances memory in Alzheimer's and produces a potent and lasting protection in the EAE-MS model and hints at epigenetic mechanisms underlying different phenomena in the brain, including memory function and neuroinflammatory pathways.

Pipeline Update - 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 orphan disease. ORY-3001 is a 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/CTA during the first half of 2017 and move ORY-3001 into clinical Phase 1/2a studies during the second half of 2017.

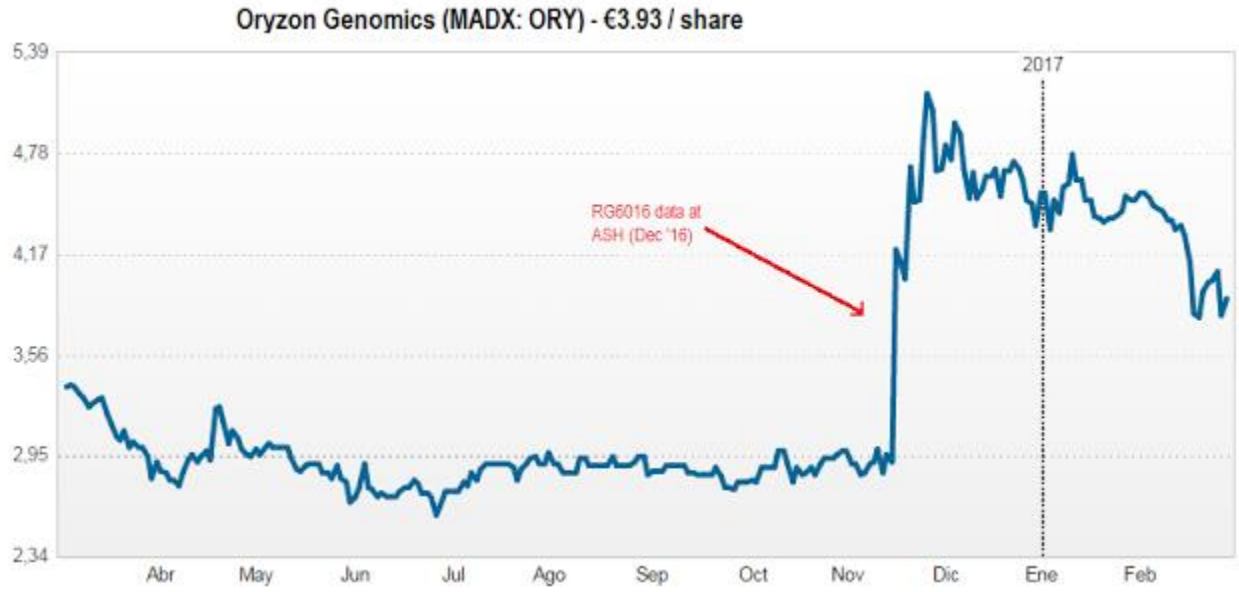


Conclusion

Oryzon is focused on developing epigenetic-based therapies and personalized drugs from its proprietary platform technology. Over the past several months, management has made significant progress moving the pipeline forward. Roche has taken over the development of ORY-1001 - now called RG6016. RG6016 is progressing in two clinical trials for acute leukemia and small cell lung cancer. Oryzon has the potential to earn over $500 million in milestones plus mid-teens royalties on commercial sales of RG6016 at Roche.

The second compound is ORY-2001, under early-stage clinical investigation for the treatment of Alzheimer's disease and other CNS indications. Recent preclinical data show encouraging effect in mouse models of both AD and MS/EAE. I am looking forward to seeing Phase 1 data on ORY-2001 at the end of the month at the 13th International Conference on Alzheimer's and Parkinson's Disease in Vienna, Austria. A third compound, ORY-3001, is nearing clinical studies. Management has stated this candidate will target a non-oncologic orphan indication.

The company currently trades on the Madrid Stock Exchange (MADX: ORY) with a market capitalization of approximately €112 million ($118 million). The shares are up 40% over the past six months, driven by a nice response to the Phase 1/2a clinical data on RG6016 presented at ASH in December 2016. Positive data on ORY-2001 at the end of March 2017 could result in another big move higher for the shares.



Peer-valuation analysis suggests Oryzon should be worth $250 million in value based on a Phase 2 asset in oncology and Phase 1 asset in neurodegenerative diseases. This would essentially be a doubling of the shares. I have yet to factor in any value for ORY-3001, which represents further upside to the story in 2017.

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