EDISON

Oryzon Genomics

Initiation of coverage

New frontiers in epigenetics

Pharma & biotech

Oryzon's core expertise lies in developing small molecule inhibitors for epigenetic targets. The company has advanced its lead compound ORY-1001 to a Phase I/IIa trial in acute leukaemia patients, while a second product, ORY-2001, has been recently approved for Phase I and will target Alzheimer's disease (AD). With Roche already on board, Oryzon is a rare pure-play in epigenetics and we value it at €158m or €5.6/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	15.5	11.3	0.48	N/A	N/A	N/A
12/15	7.2	(0.1)	(0.01)	N/A	N/A	N/A
12/16e	2.8	(2.8)	(0.10)	N/A	N/A	N/A
12/17e	2.1	(3.7)	(0.13)	N/A	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of intangibles, exceptional items and share-based payments.

ORY-1001: First LSD1 inhibitor to reach clinical phase

The next major event for Oryzon is the preliminary efficacy data from Part 2 of the ongoing Phase I/IIa study with lead product ORY-1001 in different subsets of acute leukaemia patients. We expect the results around year-end 2016. ORY-1001 is a first-in-class inhibitor of lysine specific demethylase 1 (LSD1), which is best described as a second-generation epigenetic therapeutic agent with increased specificity and novel target compared to a handful of approved first generation HDAC inhibitors. Preclinical models showed that LSD1 is a key effector causing arrest in cell differentiation in subtypes of acute myeloid leukaemia (AML) and that the inhibition of this target could potentially lead to effective treatment of the disease.

Roche already on board

Roche licensed ORY-1001 in April 2014, agreeing to pay >$500m in milestones ($21m paid in upfront and near-term milestones) and tiered royalties (up to 15%), which we view as attractive terms for a relatively early-stage asset. After completion of the ongoing Phase I/IIa, Roche will be solely responsible for further clinical development and commercialisation, which could include expansion into other indications.

ORY-2001: Novel mode of action in AD research

Oryzon's second product, ORY-2001, targets Alzheimer's disease (AD) and has been approved to enter a Phase I trial with healthy volunteers in 2016. ORY-2001 has a dual activity, inhibiting LSD1 and monoamine oxidase B (MAO B), so represents a refreshingly novel mode of action in AD research. Preclinical data indicate that ORY-2001 could potentially have a disease-modifying effect.

Valuation: Risk-adjusted NPV of €158m

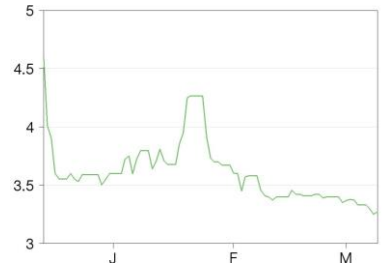
We value Oryzon at €158m or €5.6/share, based on an rNPV using a 12.5% discount rate and year-end 2015 net cash of €12.7m. Gross cash of €19.5m (with another €2.2m in term deposits) at end December should be sufficient to at least 2018. Our model includes only ORY-1001 for subsets of AML and for small-cell lung cancer (SCLC) and ORY-2001 for mild AD patients, but both projects can be expanded into other indications. In the near term, the main value drivers are the preliminary efficacy data from the Phase I/IIa with ORY-1001 and safety data from Phase I with ORY-2001.

10 March 2016

Price	**€3.27**
Market cap	**€93m**

Net cash (€m) at end of December 2015	12.7
Shares in issue	28.47m
Free float	31%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(4.1)	(7.7)	(13.7)
Rel (local)	(12.2)	(0.7)	(5.4)

52-week high/low	105.5p / 87.5p

Business description

Oryzon is a Spanish biotechnology company focused on developing novel epigenetic compounds. Lead compound ORY-1001 is partnered with Roche and is undergoing a Phase I/IIa study for acute leukaemia. ORY-2001 has potential for Alzheimer's disease and has been approved to enter Phase I.

Next events

ORY-1001 Phase I/IIa results	End 2016
ORY-2001 Phase I results	H117

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Edison profile page

Oryzon Genomics is a research client of Edison Investment Research Limited

Investment summary

Company description: Emerging epigenetics player

Oryzon was founded in 2000 by the current CSO Tamara Maes and the CEO Carlos Buesa. It is developing epigenetics-based therapeutics for patients with cancer and neurodegenerative disorders. The two lead products in clinical development target AML and AD patients, but could be expanded into other indications, based on the abundance of preclinical data suggesting efficacy in a broad range of cancers and non-malignant diseases. In addition, the company has a number of other preclinical candidates, which can be progressed depending on R&D priorities and cash management. ORY-1001 has already been partnered with Roche, which is responsible for further development of the compound after the end of the Phase I/IIa study. All Oryzon's know-how and IP in epigenetics has been developed in-house with no royalties to other inventors due. Oryzon is headquartered in Barcelona, Spain, with a US office in Cambridge, MA, and employs around 30 people.

On 14 December, Oryzon listed its shares on the Madrid Stock Exchange. However, this was a technical listing without raising new funds, as the company is already well funded after the €16.5m private financing round in October. The public listing was a strategic step to boost share liquidity in the near term and to provide access to capital markets. Oryzon also has plans for a dual listing on NASDAQ in future.

Valuation: rNPV of €158m or €5.6/share

Our Oryzon valuation is €158m or €5.6/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate and with €12.7m of net cash at end of December 2015. We assume ORY-1001 can achieve peak sales of around $900m in 2028 in subsets of AML patients most susceptible to LSD1 inhibition and $630m in SCLC patients. We use peak sales of $4.5bn for ORY-2001 in 2032 (assumptions detailed in Valuation section), which represents a conservative scenario at this early stage, where the compound will show symptom improvement in AD patients in line with or better than existing non-disease-modifying drugs, such as Aricept or Namenda. But if ORY-2001's disease-modifying effects seen in preclinical studies are found in patients as well, our bottom-up scenario suggests peak sales potential of $9.9bn. The expansion into other indications or progression of the preclinical pipeline is not included at this stage, but represents significant upside. In the near term, the main value drivers are the preliminary efficacy results from the ongoing Phase I/IIa study with ORY-1001 and safety data from Phase I with ORY-2001.

Financials: Cash runway for at least two to three years

At the end of December 2015 Oryzon had an gross cash position of €19.5m with another €2.2m in term deposits classified as other current assets, which we believe should be sufficient to fund operations during the next two to three years. Historically the company has been successful in attracting public grants to fund operations and this should continue. For example, in 2015 Oryzon secured a total of €2.6m in public loans and grants. The company's shares are listed on the Madrid Stock Exchange and management envisions a potential dual listing on NASDAQ in the next two years, depending on market conditions.

Sensitivities: Typical drug developer sensitivities apply

The main sensitivities for Oryzon are the outcomes of the ongoing Phase I/IIa trial with ORY-1001 (preliminary efficacy) and Phase I trial with ORY-2001 (safety and tolerability), with data expected around end of 2016 and in the beginning of 2017 respectively. ORY-1001's future development will solely depend on Roche's decisions, while Oryzon will still have to partner ORY-2001 depending on the clinical proof of concept to be established in Phase II. The company is well funded for the next two to three years; financing needs beyond that will depend on milestone revenues from Roche, potential new partnering activities and the scale of preclinical research.

Company description: Pure-play in epigenetics

Initially Oryzon focused on genomics diagnostics, providing research services to pharmaceutical and agricultural industries. Boosted by fresh capital in 2008, the company has shifted its focus to diagnostic and therapeutic biomarker research within oncology and neurodegeneration using public funding such as government grants or via international programs, when available. With the acquisition of Crystax Pharmaceuticals in 2008, Oryzon has started drug discovery programmes in epigenetics and is now fully focused on this area. The company's business model is to develop drug candidates through Phase II and then to out license. The development pipeline is summarised in Exhibit 1.

Exhibit 1: R&D pipeline

Product	Indication and stage	Mechanism of action	Notes
ORY-1001, partnered with Roche	Acute leukaemia, Phase I/IIa; expansion into other indications will depend on Roche.	Small molecule inhibitor of LSD1, the enzyme responsible for epigenetic modifications.	According to the company, data from Part 1 of Phase I/IIa indicate tolerable safety profile. We expect preliminary efficacy results around year-end of 2016.
ORY-2001	Alzheimer's disease; Phase I; indications in other neurodegenerative diseases such as Parkinson's disease or Huntington's disease are in advanced preclinical stage.	Small molecule dual inhibitor of LSD1 and MAO B with expected synergistic effect in neurodegenerative diseases.	Clinical trial application (CTA) approved for Phase I with healthy volunteers; results expected in the beginning of 2017.
Undisclosed products	Using its proprietary platform, the company has developed other compounds for different epigenetic factors. These projects are in varying preclinical stages and can be progressed to the clinical testing depending on R&D portfolio decisions.		

Source: Edison Investment Research, Oryzon Genomics

Emerging second generation of epigenetic therapeutics

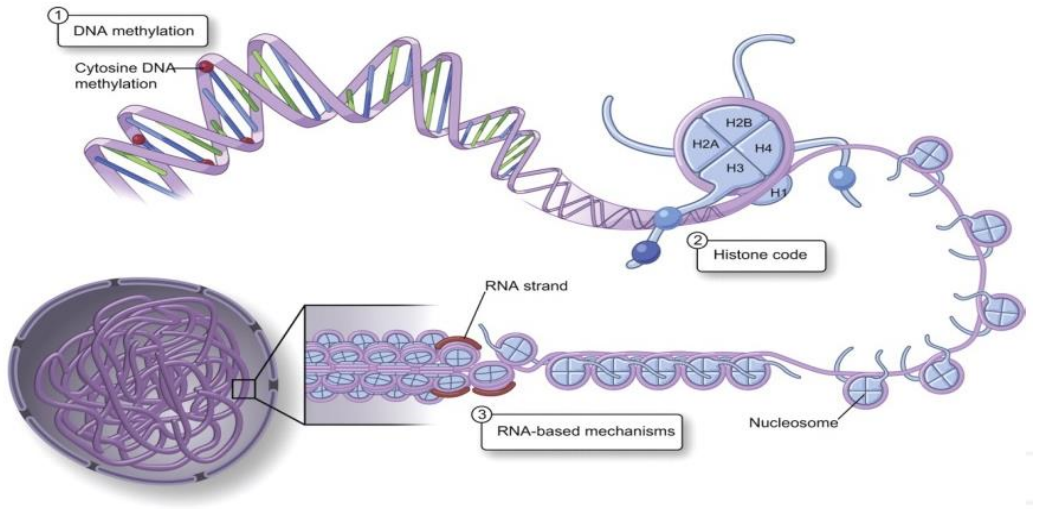
Simplistically, epigenetics can be defined as the study of changes in how genes are 'read' (expressed). A number of external factors can switch genes on and off modifying the expression, but without actually making any changes in the sequence of DNA. These changes are called epigenetic modifications. In cell nuclei the DNA is tightly packed and forms 23 pairs of chromosomes. To achieve that, the DNA is rolled up on protein complexes called histones, which provide compaction and prevent genes being accessible (Exhibit 2). Epigenetic modifications cause changes in this spatial organisation, which lead to different genes becoming accessible for expression or silenced. This process is a part of normal gene expression regulation, but if it falters, can also be the cause of a variety of diseases. There are three main types of epigenetic modifications:

- **DNA methylation** occurs when a methyl group (a chemical tag) is added directly to a specific location on the DNA strand. Such modification most commonly results in gene deactivation.[1]
- **Histone modification** occurs when different chemical tags, such as acetyl or methyl group, are added to a histone tail within the nucleosome complex. This can either increase or decrease gene expression.[1]
- **RNA-based** mechanisms have also been shown to impact the spatial configuration of chromatin[1].

Oryzon's technology evolves around histone modifications; the most common are: acetylation, catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDACs); and methylation, catalysed by histone methyltransferases (HMTs) and histone demethylases (HDMs or KDMs – Oryzon's expertise). Histone modification can occur when enzymes attach (write) or remove (erase) chemical tags from different amino acids like lysine, arginine and serine among others. A third class of enzymes (readers) can bind to specific epigenetic marks and recruit other proteins.

[1] J. de Lartigue. Targeting Epigenetics for Cancer Therapy: Scores of Agents Capture Interest of Researchers. OncLive, accessed at global.onclive.com on Feb 5, 2016.

Exhibit 2: The three fundamental mechanisms of epigenetic gene regulation



Source: Yan et al. J Appl Physiol 2010; 109:916-926

Epigenetics is relatively young field in terms of drug development and HDACs were among the first epigenetic therapeutics that were brought to market. However, one of the key drawbacks of HDACs is low selectivity and resulting side effects. Oryzon and some third-party researchers[2] have started classifying HDACs as the first generation of epigenetic modifying agents and Oryzon's products can be assigned to a second generation of selective inhibitors of histone demethylases (KDMs) alongside other newer compounds in the R&D stages, such as histone methyltransferases (HMTs), BET inhibitors, PRMT5 inhibitors, etc (see our Competitive landscape discussion). Oryzon's lead compounds ORY-1001 and ORY-2001 are among the most advanced second-generation compounds in epigenetics.

Two clinical projects, potential for R&D expansion

Oryzon has developed a proprietary platform to create therapeutic inhibitors for a class of enzymes known as histone lysine demethylases or KDMs. In total, 30 members belong to two 'super families' of iron and flavin adenine dinucleotide (FAD)-dependent amine oxidases (enzymes with broad range of functions). The two most advanced compounds in Oryzon's pipeline are ORY-1001 and ORY-2001. ORY-1001 is a potent and highly selective LSD1 (also called KDM1A) inhibitor, while ORY-2001 is bi-specific LSD1/MAO B inhibitor. ORY-1001 is in Phase I/IIa partnered with Roche and has an orphan drug designation in AML from the European Medicines Agency. ORY-2001 has just entered Phase I for the Alzheimer's disease indication. In addition, Oryzon has a number of additional programmes, mainly other histone demethylases, in various preclinical stages, which if needed can be progressed into the clinical phase.

ORY-1001 – first-in-class LSD1 inhibitor for leukaemia

ORY-1001 is a highly selective LSD1 inhibitor that can be orally administered. LSD1 is a histone eraser enzyme that removes methyl groups. Oryzon is focusing initial development of ORY-1001 on myeloid malignancy. In normal hematopoietic development (blood production process) blood cells have a defined life-span and must be continuously replaced. These cells are produced by the proliferation and differentiation of a small population of self-sustaining hematopoietic stem cells (HSCs). During

[2] V. Valdespino and P. M. Valdespino. Potential of epigenetic therapies in the management of solid tumors. Cancer Management and Research 2015:7 241–251.

differentiation, the progeny of HSCs progresses through various intermediate maturational stages, which are partially mediated by epigenetic modifiers such as LSD1. In leukaemia, this normal process of cellular maturation falters. The leukaemic stem cells (LSCs) do not differentiate appropriately and this results in an accumulation of immature blast cells in bone marrow and blood (therefore sometimes it is called liquid cancer). There are many different types of leukaemia with various genetic and epigenetic origins. Acute myeloid leukaemia represents 15% to 20% of all childhood leukaemias, approximately 33% of adolescent leukaemias and approximately 50% of adult leukaemias[3]. In total there were around 53,900 cases of AML in the US and Europe in 2015.

ORY-1001 highly efficient in MLL models, but needs to reach beyond

So far, preclinical data demonstrated ORY-1001's potential in AML subtype called mixed lineage leukaemia (MLL). It is well known for its chromosomal rearrangement, during which the MLL gene becomes fused with genes present in other chromosomes, leading to either acute myeloid or lymphoid leukaemia. MLL is an aggressive form of AML and current treatments are not very effective with just over a third of patients surviving five years. MLL accounts for about 10% of all AML cases.[3] In the ongoing Phase I/IIa trial Oryzon is exploring initial efficacy on MLL patients, but since the condition is rare, it is also exploring other subtypes, which it believes could be susceptible to LSD1 inhibition. The goal is to capture as many genetic subtypes as possible to be able to treat a wide AML subpopulation.

Highlights of preclinical data in AML/MLL

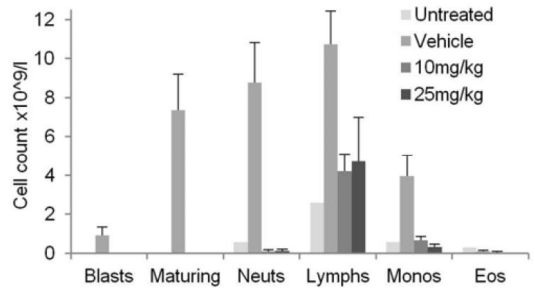
Harris et al's work with ORY-1001's prototype, OG-86, was instrumental in demonstrating preclinical proof-of-concept using a mouse model of human MLL-AF9 leukaemia.[4] Their main conclusion was that LSD1 is a key effector causing an arrest in cell differentiation in MLL and that *in vitro* and *in vivo* inhibition of LSD1 causes changes in gene expression, leading to differentiation of leukaemic immature murine and human cells into normal differentiated blood cells, reducing the viability of leukaemic stem cells. Remarkably LSD1 inhibition leads to a variety of rather different effects on different haematopoietic cells, which can potentially offer a therapeutic window for a successful intervention. Selected key findings include:

- LSD1 inhibition in MLL-AF9 mice prevented progression of AML cells into the circulatory system (Exhibit 3).
- In a bone marrow biopsy, LSD1 inhibition downregulated expression of the leukaemic stem cell marker KIT and reduced the frequency of AML cells with clonogenic potential, but normal haematopoietic stem cells were spared.
- Also in bone marrow biopsy, LSD1 inhibition caused a dose-dependent significant reduction in the frequency of AML colony-forming cells (CFCs), but normal cell colonies were not affected by the treatment (Exhibit 4).
- Inhibition of LSD1 in MLL-AF9 mice led to a reduction in the production of red blood cells and platelets causing anaemia. Notably, according to Oryzon, preliminary data from Part 1 of the ongoing Phase I/IIa indicate a tolerable safety profile in humans. In addition, even if the treatment causes clinically meaningful anaemia, healthy haematopoietic repopulating cells survive, which makes it possible to treat the anaemia with simple blood transfusions, as suggested by Harris et al.

[3] D. Ilencikova and A. Kolenova. MLL Gene Alterations in Acute Myeloid Leukaemia (11q23/MLL+ AML). ISBN 978-953-51-0858-0, January 24, 2013.

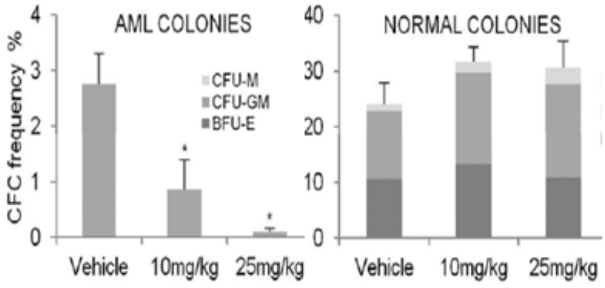
[4] W. J. Harris et al. The Histone Demethylase KDM1A Sustains the Oncogenic Potential of MLL-AF9 Leukemia Stem Cells. Cancer Cell 21, 473–487, April 17, 2012.

Exhibit 3: OG-86 blocked progression of leukaemia cells into the circulatory system



Source: Harris et al. Note: untreated – normal mouse; vehicle – untreated MLL-AF9 mouse. OG-86 is ORY-1001's prototype.

Exhibit 4: OG-86 reduces frequency of AML cell colonies, but does not affect healthy ones



Source: Harris et al. Note: CFU-M, CFU-GM, CFU-E are different subpopulations of white blood cells.

The idea of forced differentiation of immature leukaemic cells into mature myeloid cells is not entirely new. One therapeutic approach that has been successfully used in clinical practice since the 1990s is an induction of the differentiation of leukaemic blasts using all-trans retinoic acid (ATRA), which is a standard therapy in a subtype of AML called acute promyelocytic leukaemia (APML). However, the ability of ATRA to promote leukaemic cell differentiation in APL is specific to this subset of leukaemia. In our view, the fact that such treatment strategy is familiar to oncologists is favourable situation to Oryzon, as this means there is less need for professional education.

Roche to carry on ORY-1001's development after Phase I/IIa

ORY-1001 entered clinical trials in January 2014 and in April that year Oryzon signed a partnership agreement with Roche. The licensing agreement includes two Oryzon's patents that cover ORY-1001 and back-up compounds. Roche will be solely responsible for further development of the compound on successful completion of the ongoing Phase I/IIa study. In addition, Roche can expand into other indications within oncology, as well as non-malignant conditions. Oryzon still has 17 patents in its IP portfolio, which cover other small molecules for different indications, including ORY-2001.

Roche paid an upfront fee of $17m on signing and a milestone payment of $4m was booked in July 2015, triggered by the determination of the recommended dose in Phase I. Development and sales milestones can potentially total more than $500m depending on what indications Roche decides to develop ORY-1001 for. Royalties will be tiered up to the mid-teens. Overall, we view the deal terms as attractive for a relatively early-stage asset. Oryzon also collaborates with the Roche Translation Clinical Research Centre for an initial two-year period, which ends this April. The goal is to share expertise and advance knowledge of LSD1 inhibitors in oncology and haematology. Notably, Roche is reimbursing Oryzon's resources invested in this collaboration.

Phase I/IIa to deliver preliminary efficacy

ORY-1001 was the first specific LSD1 inhibitor to enter a clinical trial in January 2014. Part 1 of the Phase I/IIa study included patients with relapsed or refractory acute leukaemia and demonstrated preliminary safety and tolerability. Part 2 started in November 2015, enrolling genetically selected patients with different subpopulations of AML including MLL. This extension arm will provide preliminary efficacy results and thus represents the next milestone event for the company, which we expect could happen around year-end 2016. Notably, there is limited detail about the trial design, including what endpoints were selected to evaluate preliminary efficacy and what information will be released after the completion of the trial.

MLL is an obvious initial target subpopulation of AML backed by encouraging preclinical data. However, LSD1 is upregulated in other acute leukaemias as well. For example, Lin et al. found LSD1 to be overexpressed in the bone marrow in 90.4% of new AML cases, 77.8% of acute lymphoblastic

leukaemia (ALL) cases; and in all cases of refractory AML or ALL versus only 4.7% of the cases that went into complete remission after treatment.[5] Therefore, in the ongoing Phase I/IIa trial Oryzon is exploring the efficacy in other genetic subtypes of AML. Based on findings in the Phase I/IIa extension arm Roche will decide the way forward to Phase II, which is when there will be more clarity as to exactly what acute leukaemia patient subpopulations will be targeted with ORY-1001.

Potential in other cancers and non-malignant diseases

Oryzon's and third-party preclinical research demonstrated that inhibition of LSD1 might be a valid therapeutic approach in other blood cancers such as acute lymphoblastic leukaemia (ALL). Stepping beyond leukaemias, there is evidence that LSD1 is also highly expressed in different solid tumours such as SCLC, bladder and colorectal cancer, oestrogen-receptor-negative breast cancer and prostate cancer[5]. Roche could potentially expand even further including non-malignant diseases such as sickle cell disease and neurodegeneration, where preclinical data show that LSD1 inhibition may be effective.

Lung cancer next

In our view, SCLC appears to be the most likely indication for Roche to expand. GlaxoSmithKline (GSK) has an LSD1 inhibitor GSK2879552 in Phase I for SCLC. GSK2879552 showed activity in SCLC cell lines and in SCLC xenograft models, providing support for the use of LSD1 inhibitors in non-haematological cancers[5]. As GSK's interest in GSK2879552 validates LSD1 inhibition potential in SCLC and the SCLC market is larger than AML's, Roche may be interested in expanding to this indication. SCLC patients constitute 10-15% of total lung cancer patients, with around 27,650 in the US alone. They respond well to first-line treatment, but almost always relapse. Overall five-year survival is only 5%, reflecting a clear medical need for improved treatment[5].

Competitive landscape

HDACs are regulators of gene expression, which remove the acetyl group from histones. There is already a handful of first-generation HDAC inhibitors approved by the FDA (Exhibit 5) with the first being vorinostat (Zolinza) developed by Merck & Co for third-line therapy of cutaneous T-cell lymphoma and marketed in 2006. Because of a lack of specificity, the common feature of these HDACs is a rather unfavourable safety profile. For example, vorinostat received a critical review in 2009 from the European Medicines Agency (EMA) about the risk/benefit ratio and the trial design, following which Merck & Co withdrew its marketing application.

Despite these hurdles, a number of other HDACs are still being explored in different stages for oncological indications, but we believe that second-generation epigenetic inhibitors are a more relevant peer group for Oryzon's technology since, like the LSD1 inhibitor, they also have greater selectivity for their molecular targets. Second-generation compounds can be broadly classified into demethylase inhibitors, methyltransferase inhibitors and BET (bromodomain and extra-terminal) inhibitors or acetyl lysine readers. Methyl lysine readers (MBTL) are also emerging in preclinical research. Second-generation epigenetic inhibitors are still considered in their infancy with most companies having a lead programme in Phase II or earlier. Epizyme is among the leading peers in this area; it is more advanced than Oryzon but similar in terms of the pipeline breadth and therapeutic areas. It has two lead compounds: tazemetostat, an EHZ2 inhibitor for a range of indications, but primarily focused on non-Hodgkin's lymphoma with an ongoing five-arm phase II study; and pinometostat, a DOT1L inhibitor in Phase I for rearranged mixed lineage leukaemia in children.

[5] T. Maes et al. KDM1 histone lysine demethylases as targets for treatments of oncological and neurodegenerative disease. Epigenomics (2015) 7(4), 609–626.

Exhibit 5: Selected first- and second-generation epigenetic inhibitors

Company	Product, type	Phase	Indication	Comment
First generation				
Celgene Corp.	Romidepsin HDAC I inhibitor	Market	Peripheral and cutaneous T cell lymphoma	Approved by the FDA in 2009. Peak sales of $1m achieved in 2014 in the US.
Merck & Co.	Vorinostat HDAC inhibitor	Market	Cutaneous T cell lymphoma	Approved by the FDA in 2006. Peak sales of $13m achieved in 2016 in the US.
Novartis	Panobinostat HDAC inhibitor	Market	Multiple myeloma	Approved by the FDA in February 2015. Sales of $19m achieved in 2015 in the US.
Onxeo	Belinostat HDAC inhibitor	Market	Peripheral T cell lymphoma	Approved by the FDA in July 2014. Sales of $0.3m achieved in 2015 in the US.
Novartis	Panobinostat HDAC inhibitor	Various	Various	Hodgkin's disease (Phase III), AML (Phase I/II), non-small cell lung cancer (Phase I/II), prostate cancer (Phase I/II), sickle cell disease (Phase I).
Merck & Co.	Vorinostat HDAC inhibitor	Various	Various	Mesothelioma (Phase III), graft-versus-host disease (Phase I/II), brain cancer (Phase I).
Bayer	Entinostat HDAC1/3 inhibitor	Various	Various	Breast cancer (Phase III), AML (Phase II), non-small cell lung cancer (Phase II), melanoma (Phase I/II), renal cancer (Phase I/II).
4SC	Resminostat HDAC inhibitor	Phase II	Various	Hodgkin's disease, liver cancer, non-small cell lung cancer.
Italfarmaco	Givinostat HDAC I/I inhibitor	Phase II	Various	Arthritis, Hodgkin's disease, myeloproliferative disease.
MEI Pharma	Pracinostat HDAC I/II/IV	Phase II	AML and Myelodysplastic syndrome	Start Phase III for AML planned in H216.
Onxeo	Belinostat HDAC inhibitor	Various	Various	Partnered with Spectrum Pharmaceuticals in the US. AML (Phase II), B cell lymphoma (Phase II), non-small cell (Phase I/II) and small cell lung cancer (Phase I), sarcoma (Phase I/II).
Acetylon Pharmaceuticals	Ricolinostat, HDAC6 inhibitor	Phase I/II	Multiple Myeloma	Four ongoing trials with ricolinostat in combination with anticancer drugs. One of the most advanced is a Phase I/II trial with pomalidomide. Interim results from Phase II demonstrated OR rate of > 50% for refractory patients.
Second generation				
Histone methyltransferase inhibitors				
Epizyme	Tazemetostat, EHZ2 inhibitor	Phase II	Five-arm study in relapsed/refractory non-Hodgkin lymphoma ; solid tumours	Initial data from Phase I trials demonstrated tazemetostat led to two complete responses, seven partial responses and one stable disease out of 15 patients.
	Pinometostat, DOT1L inhibitor	Phase I	Mixed lineage leukaemia	Enrolment is expected to be completed in early 2016.
Constellation Pharmaceuticals	CPI-1205, EZH2 inhibitor	Phase I	B-cell Lymphomas	Recruiting patients for Phase I.
GlaxoSmithKline	GSK2816126, EZH2 inhibitor	Phase I	Solid tumours and haematological malignancies	Recruiting for Phase I trial in relapsed/refractory diffuse large B cell lymphoma, transformed follicular lymphoma, other non-Hodgkin's lymphomas, solid tumours and multiple myeloma.
Histone demethylase inhibitors				
GlaxoSmithKline	GSK2879552, LSD1 inhibitor	Phase I	Small cell lung cancer and AML	Two separate trials; each constitutes of Part 1 (dose escalation) and 2 (expansion cohort to evaluate clinical activity).
BET (bromodomain and extra-terminal) inhibitors				
GlaxoSmithKline	GSK525762, BET inhibitor	Phase I	Solid tumours and haematological malignancies	Two separate Phase I trials. One recruiting for patients with r/r hematologic malignancies. Other recruiting for patients with various solid tumours.
Constellation Pharmaceuticals	CPI-0610, BET inhibitor	Phase I	Acute leukaemia, Myelodysplastic syndrome and Myelofibrosis	Recruiting patients for Phase I.
	CPI-0610, BET inhibitor	Phase I	Previously treated multiple myeloma (MM)	Recruiting patients for Phase I. Preclinical results demonstrated sensitivity to CPI-0610, which induced apoptosis and G1 cell cycle arrest.
	CPI-0610, BET inhibitor	Phase I	Relapsed / refractory lymphoma	Preliminary analysis of the ongoing Phase I: reasonably well tolerated; main toxicity was dose-dependent, reversible, non-cumulative thrombocytopenia; a small number of initial patients demonstrated anti-lymphoma activity.
Incyte Corporation	INCB054329, BET inhibitor	Phase I	Advanced malignancies including advanced solid tumour or leukaemia, MM	Phase I study currently recruiting patients. Preclinical data demonstrated inhibition of AML, myeloma and lymphoma cell lines. The drug inhibited tumour growth in animal models of hematologic cancer.
Merck	OTX – 015, BET inhibitor	Phase I	Hematologic malignancies and advanced solid tumours	Results from dose finding part of Phase I study for hematologic malignancies demonstrated that it was well tolerated, thrombocytopenia was reversible and self-limiting.
Gilead	GS-5829, BET inhibitor	Phase I	Solid tumours and lymphomas	Recruiting patients for Phase I.
Tensha Therapeutics*	TEN-010, BET inhibitor	Phase I	NUT midline carcinoma	Phase I enrolling patients. Preclinical studies have demonstrated TEN-010's ability to stop the division of cancer cells.

Source: Edison Investment Research, Oryzon Genomics, BioCentury, clinicaltrials.gov. Note: *Acquired by Roche in January 2016. US sales data only.

ORY-2001 – unique dual synergistic effect

ORY-2001 is a first-in-class, selective dual inhibitor of LSD1/MAO B. ORY-2001's clinical trial application has just been approved for AD and a Phase I trial with 88 healthy volunteers is about to begin to establish the safety profile and pharmacokinetics and the results are expected at the beginning of 2017. While the lead indication is AD, other neurodegenerative diseases can follow.

Rationale for bi-specific effect

Historically, the recognition of epigenetics' role and its importance was first described in oncology and then further extended to neurodevelopment and neurodegenerative diseases.[6] The potential use of LSD1 inhibitors is not limited to oncological diseases and Oryzon's decision to choose oncology and neurodegeneration as primary areas of interest is supported by a significant amount of pre-clinical work.[7] ORY-2001 is a unique dual inhibitor, which is possible due to the structural similarity of MAO B and LSD1.

MAO is a very well-researched target with already marketed drugs, such as the first generation of antidepressants, and has two forms, A and B. Non-specific monoamine oxidase inhibitors were the first type of antidepressants developed, but due to inhibition of MAO A, suffered from numerous side effects associated with its more widespread presence. A new generation of selective MAO B inhibitors (eg selegiline) were developed, which cause fewer side effects and are used in early stage Parkinson's disease, but trials are ongoing to explore the potential of this target for AD as well (Evotec, Avraham Pharmaceuticals). Due to an abundance of data about the effects of MAO B inhibition and its relatively good safety profile, we believe that the downside of potential 'negative' interactions between inhibition of LSD1 and MAO B is significantly reduced, while there is potential upside from synergistic effects. This idea is also supported by Oryzon's preclinical studies.

Highlights of preclinical data in AD

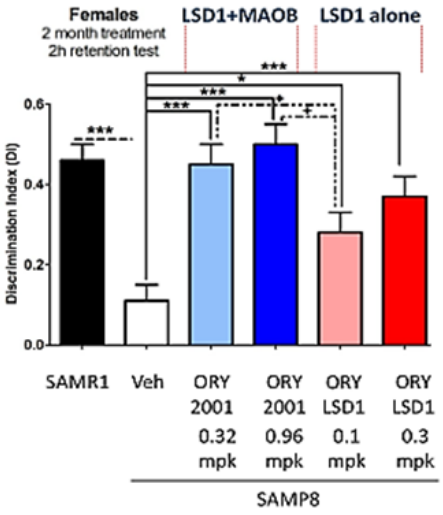
Oryzon tested ORY-2001 in five different oral treatment studies with SAMP8 mice, a non-transgenic model for accelerated ageing and AD. The effect on cognition was examined with an established test, the novel object recognition task (NORT), which uses a calculated discrimination index. Key findings include:

- After two and four months of chronic oral treatment, ORY-2001 provided a dose-dependent and protective effect on the memory of SAMP8 mice compared to age-matched SAMR1 mice.
- This effect could be achieved at low doses that do not affect haematopoiesis, which is crucially important considering chronic nature of the disease.
- MAO B inhibition alone showed a trend of cognitive improvement on the SAMP8 animals, but it was not significant.
- LSD1 inhibition alone was able to produce a significant effect, but was less pronounced (Exhibit 6). It appears that memory protection is driven by the LSD1 inhibition, but the combination with MAO-B inhibition (ie a dual compound, ORY-2001) has a synergistic effect.
- Meta-analysis conducted on this model demonstrates a potentially disease-modifying effect (Exhibit 7). Using NORT test scores as above, the cognitive decline of animals treated with ORY-2001 was compared to untreated SAMP8 mice and control SAMR1 mice. At five months of age, when treatment with ORY-2001 started, the animals already had a cognitive impairment, but ORY-2001 restored the function to similar levels as observed in age-matched SAMR1 mice.

[6] L. Lovrečić et al. The Role of Epigenetics in Neurodegenerative Diseases. Uday Kishore, ISBN 978-953-51-1088-0, May 15, 2013.

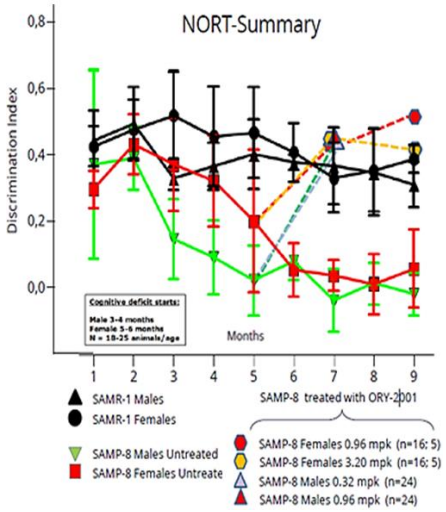
[7] F. Coppede. The potential of epigenetic therapies in neurodegenerative diseases. Front. Genet. 5:220. doi: 10.3389/fgene.2014.00220.

Exhibit 6: Chronic treatment with ORY-2001 protects memory



Source: Oryzon. Note: mpk – milligrams/kilo

Exhibit 7: ORY-2001 restored the cognitive function of SAMP8 mice compared to control SAMR1 mice



Source: Oryzon

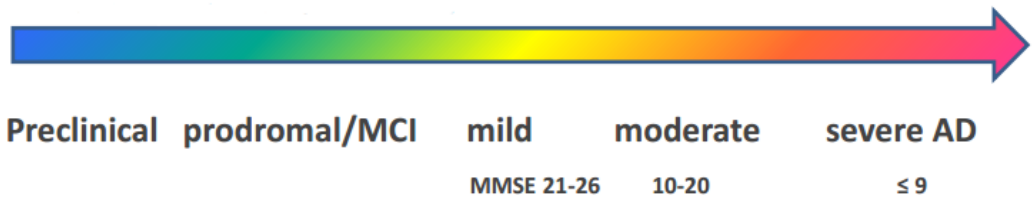
Potential biomarkers

Oryzon has identified different biomarkers that could be used to monitor the response to treatment with ORY-2001. At this stage the most promising is S100A9, which is a pro-inflammatory protein typically upregulated in the context of inflammation-related neurodegenerative diseases, such as in patients with AD, postoperative cognitive dysfunction (POCD) and traumatic brain injury (TBI). Therefore the observed downregulation of S100A9 protein by ORY-2001 is particularly interesting. While the work is still early stage, a progression biomarker may eventually prove invaluable in the context of a late-stage clinical trial designed to prove the disease-modifying effect of a drug. This is because it may be difficult to clearly differentiate between symptomatic and disease-modifying effects just with clinical endpoints (eg cognition, function).[8] The key in convincing regulators of disease-modifying effect (which has never happened in AD's case) may be the link between the slowdown in the progression of clinical signs accompanied with a significant effect on validated biomarkers[8].

Alzheimer's disease and the vast target population

AD is typically recognised as a condition that starts with preclinical stage, when there are no clinical signs of the disease but pathophysiological processes are already noticeable. The next stage is prodromal or minimal cognitive impairment (MCI), which refers to first signs of unspecified dementia. The disease progresses to mild AD and later stages. Accordingly, AD patients' stage should correspond to treatment claims, which can be symptomatic improvement, disease modification or prevention.

Exhibit 8: AD progression



Source: BfArM. Note: MMSE - The Mini Mental State Examination, which is the most commonly used test for complaints of memory problems or in other mental abilities. Max 30 points (healthy individuals).

[8] M. Haberkamp. The changing diagnostic criteria for Alzheimer´s disease – regulatory challenges. BfArM presentation, November 24, 2014.

Following recent high-profile failures of experimental antibody-based treatments mainly targeting amyloid-beta (Abeta) (eg bapineuzumab), there has been a shift of focus to recognising the benefits of treating AD patients in earlier stages of the disease. This, however, poses significant screening challenges, as in the early stages AD can be difficult to distinguish from the decline in cognitive abilities due to normal aging or from the MCI that not always converts to AD. The most recent two major revisions of the AD diagnostic criteria were carried out by the International Working Group for New Research Criteria for the Diagnosis of AD (IWG) and the National Institute on Aging-Alzheimer's Association (NIA-AA) in 2012. As yet, in 2016 the criteria are still not fully validated and undergo constant refinement, including the fact that there are substantial differences between the two versions.[8] For a drug developer this poses challenges in defining the target population using a set of criteria that eventually would also be convincing to the regulatory authorities.

There are 44 million dementia sufferers worldwide, around 60% of whom have AD (World Alzheimer Report 2014) and this figure is expected to more than triple by 2050. The lack of disease-modifying treatments leaves a vast unmet clinical need. Oryzon's primary goal is to evaluate ORY-2001 as a potentially disease-modifying drug; therefore the preliminary target population is defined as early and clinically proven AD patients. For the purpose of our model we will use mild AD prevalence to define the target population, which is around 27% of the total AD population in 2015 (Alzheimer's Association). This translates into 1.4 million AD patients in the US and another 2.4 million in Europe.

Potential in other indications

In addition to AD, Oryzon has in-house preclinical data demonstrating an improvement of survival and recovery in impaired cognition in mouse models of Huntington's disease (HD), as well as further data from experimental studies in other neurodegenerative diseases like Parkinson's disease; this is also supported by third-party studies and could be extended to other dementias. For now, the company focuses on AD, but it may add other indications, which depends mainly on R&D priorities and available resources.

Sensitivities

Oryzon is subject to the usual risks associated with drug development, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The biggest near-term sensitivity for Oryzon is the success or failure of ORY-1001 in Part 2 of the ongoing Phase I/IIa trial. Part 1 focused on the safety profile and established a recommended dose, so the significant side-effect risk is reduced, but still present. Notably, there is limited detail about the trial design, including what endpoints were selected to evaluate preliminary efficacy and what information will be released after the completion of the trial. ORY-2001 is in Phase I with healthy volunteers, so is subject to an unforeseen significant side effect risk, although preclinical models showed efficacy using dose ranges below those causing haematological side effects.

Roche will be solely responsible for further development of ORY-1001 after the end of Phase I/IIa, which means Oryzon will not be able to influence future development decisions, including expansion into other indications. ORY-2001 will need to be partnered, as Phase II and III studies for AD can be very costly. We have assumed a deal in our valuation after Phase II, however, we have limited visibility on the timing and terms. ORY-1001 initially targets AML subtypes and we assume it will be able to capture 25% of the patient population. Any deviations from this represent both upside and downside. AD is a substantial market with a large unmet medical need; hence any disease-modifying therapy is likely to generate significant sales. However, development risk is high, with multiple failures by other companies. We have also included the SCLC indication in our model, but there is no certainty that Roche will progress in this direction.

Future pricing and market dynamics are hard to predict, especially if competitors are successful. We estimate that Oryzon has sufficient cash to fund operations, including the cost of the both ongoing clinical studies, beyond data readout expected around end of 2016 (ORY-1001) and early 2017 (ORY-2001). However, future financing needs will depend on the scale of operations with preclinical candidates, on the progress with ORY-1001, related milestone payments from Roche and potential revenues from other partnerships, for which there is limited visibility. Any capital raise would likely be a dilutive financing event.

Valuation

We value Oryzon at €158m or €5.6/share, based on risk-adjusted NPV analysis, which includes €12.7m net cash at December 2015. As can be seen in Exhibit 9, we only include clinical stage compounds and one preclinical indication, but will revisit this should Oryzon progress with more projects into the clinic. We use a 12.5% discount rate with a 15% and 12% probability for reaching the market for ORY-1001 and ORY-2001 respectively.

Exhibit 9: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability	rNPV (€m)	NPV/Share (€/share)
ORY-1001	AML	2022	900	231.3	15%	41.6	1.5
ORY-1001	SCLC	2025	630*	109.3	8%	15.4	0.5
ORY-2001	AD	2026	4,500*	726.8	12%	88.5	3.1
Net Cash				12.7	100%	12.7	0.4
Valuation				**1,080.1**		**158.2**	**5.6**

Source: Edison Investment Research. Note: *Peak sales are rounded to the nearest US$100m, shown in US$.

Assumptions for ORY-1001

MLL patients are the first AML subpopulation that Oryzon identified in preclinical studies as the most responsive to LSD1 inhibition, but the ongoing Phase I/IIa study explores other genetic subtypes as well. At this stage there is no certainty on what other susceptible subpopulation could be, but we assume that initially ORY-1001 will likely work in around 25% of the total AML population, which translates into c 13,500 patients in the US and Europe per year. Given lack of innovative approved drugs for AML, pricing and market access dynamics still seem attractive at this stage. We assume market penetration of 50% and a price tag of $100,000 per patient. Pfizer's Mylotarg (gemtuzumab ozogamicin) was an antibody-based conjugate with a chemotherapy agent marketed for AML in mid-2000s at a cost of around US$55-60,000, but was withdrawn from the market in 2010 due to efficacy and safety concerns. A premium to this would be justified given ORY-1001's expected efficacy in specific subpopulations such as MLL, which is also an aggressive form of AML with poor prognosis. This translates into peak sales of $900m in 2028, assuming launch in 2022.

The SCLC target population is substantially larger than AML's with a total of c 80,000 cases in the US and Europe in 2015. Unlike non-SCLC, SCLC has not been shown to respond well to targeted therapies.[9] The treatment landscape is still dominated by well-established classic chemotherapeutic agents with no novel drugs in the market as of yet. Given the poor prognosis, any novel effective treatment regime could achieve attractive pricing, which we assume at $30,000 per patient with market penetration of 20% and calculated peak sales of $630m in 2031, assuming launch in 2025.

ORY-1001 is partnered with Roche, which we assume will take over the development after the end of Phase I/IIa. We expect Phase I/IIa results around end of 2016, therefore R&D costs related to ORY-1001 should be limited estimating a total of €1.2m for 2016 and 2017. The announced deal structure includes $21m upfront payment and near-term milestones, $435m development-related milestones, $90m sales-related milestones and a tiered up to 15% royalty rates on global sales. $235m of development-related

[9] Jett JR et al. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians clinical practice guidelines. Chest. 2013 May. 143 (5 Suppl):e400S-19S.

milestones can be triggered by events related to oncology projects; therefore we assume one-third of that can be triggered in the AML project and another third in the SCLC project.

Assumptions for ORY-2001

The key question is whether the disease-modifying effect seen in preclinical studies will be confirmed in AD patients. As there is no approved drug that has done this and the project is still in an early stage, we take a conservative stance and use peak sales of existing symptomatic medicines as a benchmark. Aricept (donepezil) achieved global sales of $3.5bn in 2009 before the patent protection expired in 2010. Including a standard long-term inflation rate of 2.5%, our calculated ORY-2001 peak sales stand at $4.5bn in 2032. Launch is assumed in 2026, which allows enough time for at least a four-year Phase III clinical study.

We also developed a scenario in which ORY-2001 is successfully approved as a disease-modifying AD treatment. As described before, we estimate a total target (mild AD) population of 3.8 million patients in the US and Europe. Pricing dynamics and penetration of ORY-2001 will depend on its efficacy and developments in the AD market and therefore are difficult to predict at this early stage. However, assuming the compound proves to be disease modifying, we estimate a 10% market penetration, which is relatively modest. One study found that persistence rates with oral AD medications (ie how well patients adhered to the therapy) are 40-54%. Assuming a disease modifying effect, the adherence to oral drugs should be even higher. We estimate a reasonable $20,000 per patient per year given the chronic nature of the disease. This translates into ORY-2001's peak sales of $9.9bn in 2032. The combination of a significant unmet need and a large patient population underpins the commercial attractiveness of this market, however, we stick to our scenario with benchmark sales. This will be revisited once ORY-2001's efficacy data starts to accumulate.

We assume that Oryzon will be able to partner ORY-2001 after Phase II and the partner will cover all development and marketing costs from this point. Before that we include a cost of €2m for the ongoing Phase I (safety/tolerability in healthy volunteers) and €20m for the subsequent Phase II. This is at the higher end for a study in this stage, but justified given the chronic nature of the disease with prolonged treatment timelines and the complexities of screening patients. Our partnering assumptions include a fairly typical deal structure, including an upfront payment, development and sales-related milestones, in addition to royalties on global sales. We assume a total deal value of €640m, which is below the $825m deal signed in 2013 between Otsuka and Lundbeck for the Phase III AD asset, a selective serotonin 5-HT6 receptor antagonist. We include a €40m upfront payment, €200m development-related milestones with the remainder as sales-related and tiered up to 18% royalty rates on global sales.

Financials

Oryzon had an estimated gross cash of €19.5m and another €2.2m in term loans at end December 2015, of which €9.1m is in subsidised loans and bank borrowings. This includes the €16.5m gross proceeds of the recent private funding round in October 2015. Our model suggests that existing cash should be sufficient to fund operations at least through to 2018, but the company has a history of efficient use of available public grants, which could add to the runway. After that, financing needs will depend on the scale of operations with preclinical candidates and on the progress with ORY-1001, related milestone payments from Roche and potential revenues from other partnerships. Oryzon had €15.2m booked as intangible assets at end of December 2015, of which the majority is capitalised development costs. Oryzon follows Spanish GAAP and research costs are expensed, while development costs can be capitalised. This is achieved by recognising the costs as revenue in the P&L, cash outflow from investing activities and a subsequent increase in intangible assets.

Oryzon's other revenues in 2014 and 2015 consist of reimbursement payments from Roche according to the R&D collaboration separate to the ORY-1001 deal. Due to uncertainty about the extension of the

R&D collaboration agreement (separate from licencing deal) after it ends in April this year, we include reimbursement payments only until the expiry month. A signing fee of $17m was booked in 2014. R&D spend in 2015 was €4.2m (€2.9m in 2014). We forecast similar R&D expenses in 2016 and 2017, as the costs related to ORY-1001 will wind down, which will be offset by the ramp up of the R&D costs related to ORY-2001.

Exhibit 10: Financial summary

EUR'000s	2012	2013	2014	2015e	2016e	2017e
December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	4,353	2,360	15,536	7,185	2,755	2,077
Cost of Sales	(412)	(183)	(341)	(358)	(294)	(331)
Gross Profit	3,942	2,177	15,195	6,827	2,461	1,746
Research and development	(876)	(873)	(1,108)	(3,453)	(2,874)	(2,949)
EBITDA	856	(94)	11,659	688	(3,010)	(3,768)
Operating Profit (before amort. and except.)	559	(370)	11,398	448	(3,129)	(3,886)
Intangible Amortisation	(455)	(657)	(657)	(657)	(793)	(845)
Exceptionals	(220)	(186)	(3,950)	(193)	0	0
Other	0	0	0	0	0	0
Operating Profit	(116)	(1,213)	6,791	(402)	(3,921)	(4,732)
Net Interest	(582)	(672)	(52)	(553)	281	222
Profit Before Tax (norm)	(23)	(1,042)	11,346	(105)	(2,848)	(3,665)
Profit Before Tax (reported)	(698)	(1,885)	6,739	(955)	(3,641)	(4,510)
Tax	90	89	(88)	(37)	0	0
Profit After Tax (norm)	67	(953)	11,258	(142)	(2,848)	(3,665)
Profit After Tax (reported)	(608)	(1,796)	6,651	(992)	(3,641)	(4,510)
Average Number of Shares Outstanding (m)	23.0	23.0	23.3	24.5	28.5	28.5
EPS - normalised (EUR)	0.00	(0.04)	0.48	(0.01)	(0.10)	(0.13)
EPS - normalised and fully diluted (EUR)	0.00	(0.04)	0.48	(0.01)	(0.10)	(0.13)
EPS - (reported) (EUR)	(0.03)	(0.08)	0.29	(0.04)	(0.13)	(0.16)
Dividend per share (EUR)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	90.5	92.2	97.8	95.0	89.3	84.1
EBITDA Margin (%)	19.7	N/A	75.0	9.6	N/A	N/A
Operating Margin (before GW and except.) (%)	12.8	N/A	73.4	6.2	N/A	N/A
BALANCE SHEET						
Fixed Assets	18,765	20,128	16,059	18,050	19,291	20,405
Intangible Assets	15,062	15,825	12,928	15,188	16,548	17,779
Tangible Assets	1,485	1,159	981	854	736	618
Investments	2,217	3,145	2,150	2,008	2,008	2,008
Current Assets	3,808	2,851	9,999	22,681	15,242	8,955
Stocks	19	2	9	4	10	7
Debtors	977	663	704	940	769	855
Cash	2,302	2,033	3,633	19,467	12,193	8,093
Other	510	153	5,654	2,270	2,270	0
Current Liabilities	(2,283)	(2,724)	(3,969)	(5,296)	(3,567)	(3,752)
Creditors	(765)	(1,005)	(1,299)	(2,401)	(932)	(1,487)
Short term borrowings	(1,519)	(1,719)	(2,670)	(2,895)	(2,635)	(2,265)
Long Term Liabilities	(9,949)	(11,251)	(8,196)	(7,841)	(7,012)	(6,164)
Long term borrowings	(7,963)	(9,117)	(6,420)	(6,177)	(4,737)	(3,667)
Other long term liabilities	(1,986)	(2,134)	(1,776)	(1,664)	(2,275)	(2,497)
Net Assets	10,341	9,004	13,893	27,594	23,953	19,444
CASH FLOW						
Operating Cash Flow	1,420	(113)	12,126	1,076	(3,807)	(804)
Net Interest	(582)	(672)	(52)	(553)	281	222
Tax	0	0	0	0	0	0
Capex	0	0	0	0	0	0
Acquisitions/disposals	107	(677)	798	0	0	0
Financing	0	0	0	14,725	0	0
Other	(8,125)	(161)	(9,579)	605	(2,048)	(2,077)
Dividends	0	0	0	0	0	0
Net Cash Flow	(7,180)	(1,623)	3,293	15,853	(5,574)	(2,659)
Opening net debt/(cash)	0	7,180	8,803	5,458	(10,395)	(4,821)
HP finance leases initiated	0	0	0	0	0	0
Other	0	0	52	0	0	0
Closing net debt/(cash)	7,180	8,803	5,458	(10,395)	(4,821)	(2,161)

Source: Edison Investment Research, Oryzon Genomics. Note: Oryzon reports in Spanish GAAP. *Represents cash outflows related to development costs that were capitalised. **Term deposits classed as other current assets.

Contact details	Revenue by geography
Oryzon Genomics Sant Ferran 74 08940 Cornella de Llobregat Barcelona, Spain Phone (+34) 93 515 1313 Website https://www.oryzon.com/	N/A

Management team

CEO: Carlos Manuel Buesa Arjol	CSO: Tamara Maes
Mr. Buesa co-founded Oryzon Genomics in 2000 and has held the position of the chairman of the board of directors since then. He earned his PhD in biochemistry from the University of Barcelona and has completed a senior management program (PADE) at IESE in 2005. More recently Mr. Buesa has been a member of the board of various biotechnology companies such as Oncnosi Pharma, Ninfas, Orycamb-Project, Geadig-Pharma, Neurotec Pharma, Palobiofarma.	Ms. Maes co-founded Oryzon Genomics in 2000 and has served as the chief scientific officer and a member of the board of directors since then. She received her PhD in biotechnology from the University of Ghent (Belgium). Ms. Maes is also a director of Mendelion and recently was a member of the Scientific Advisory Board of the Consejo Superior de Investigaciones Cientificas (CSIC).
CFO/COO: Enric Rello Condomines	**Chief business development officer: Emili Torrell**
Mr. Rello joined Oryzon in May 2011. He has a master's degree in administrative management and a degree in business administration and management, in law and in economics from Universidad Abat Oliba – CEU (Barcelona). He began his professional career in the area of advisory services, auditing and consulting and later specialised in management control and in economic and financial management.	Mr. Torrell joined Oryzon in February 2007. He holds a degree in veterinary sciences from the Autonomous University of Barcelona, a master's in business administration (MBA) from ESADE, and a master's in documentation from the Centre for documentation and patent studies. He began his career in the development of the pharmaceutical business in 1993 at Almirall Prodesfarma and later specialised in the international area as international product manager and international marketing manager at Almiral.

Principal shareholders	(%)
Najeti Capital Sa	24.65
Buesa Arjol Carlos Manuel	13.15
Maes Tamara	13.15
Ventura Ferrero Jose Maria	6.52
Corp Sant Bernat Sl	3.81
Echarri Torres Jose Maria	3.61
Oryzon Genomics Sa	3.43
Solventis Gestion Sgc Sa	1.83

Companies named in this report

Roche (ROC VX), GlaxoSmithKline (GSK LN), Pfizer (PFE US), Epizyme (EPZM US), Celgene (CELG US), Merck & Co (MRK US), Novartis (NOVN VX), Onxeo (ONXEO FP), Spectrum Pharmaceuticals (SPPI US), Bayer (BAYN GR), 4SC (VSC GR), MEI Pharma (MEIP US), Incyte Corporation (INCY US), Gilead Silences (GILD US).