EDISON

Oryzon Genomics

Corporate outlook

Maturing epigenetics portfolio

Pharma & biotech

Oryzon has been making steady progress with its epigenetics R&D pipeline. Following positive Phase I/IIa trial results in December 2016, ORY-1001, an LSD1 inhibitor, is now in Roche's hands and the company is focusing on its newer programmes: clinical-stage ORY-2001, a dual LSD1/MAOB inhibitor for neurodegenerative diseases and ORY-3001, a selective LSD1 inhibitor, in advanced preclinical studies in non-cancer areas. We have incorporated the recent €18m equity raise into our valuation, which has increased to €308m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	7.2	(0.1)	(0.01)	0.0	N/A	N/A
12/16	5.0	(4.7)	(0.17)	0.0	N/A	N/A
12/17e	4.2	(6.1)	(0.20)	0.0	N/A	N/A
12/18e	4.5	(6.8)	(0.20)	0.0	N/A	N/A

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

New funds secure broad ORY-2001 programme

After Roche took over the development of Oryzon's lead asset, ORY-1001, the company is now focusing on its next-in-line, still wholly owned ORY-2001. The drug candidate delivered its first clinical data in March 2017 and, to ramp up a comprehensive programme in neurodegenerative diseases (initially three indications planned), Oryzon raised €18.2m in a private placement, boosting its end-FY16 cash position to €45.7m (including term deposits; €22.5m net cash). Notably, Oryzon indicated that the majority of the funds were raised from the international, specialised institution investors based in Europe and for the first time in the US. Existing funds should be sufficient to run the operations until H219, which is in line with our model and allows for achieving meaningful data readouts. Oryzon is also keen to explore options for a dual listing in the US.

Accumulating clinical data

Two clinical data readouts in the past few months were major milestones demonstrating Oryzon's maturing R&D pipeline. ORY-1001 entered a Phase I/IIa trial in January 2014 and reported supportive preliminary efficacy results in acute leukaemia in December 2016. Oryzon's partner Roche is now developing ORY-1001 in small cell lung cancer (SCLC) and could expand it into other indications. The first clinical data with ORY-2001 in healthy volunteers were reported at the end of March 2017 and Oryzon now plans to initiate efficacy trials in three neurological disorders – multiple sclerosis (MS), Alzheimer's disease (AD) and Huntington's disease (HD).

Valuation: Risk-adjusted NPV of €308m or €9.0/share

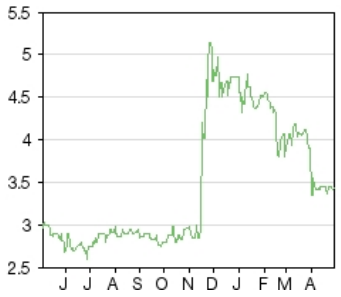
We have increased our valuation of Oryzon from €266m to €308m or €9.0/share (from €9.3/share) on the back of the recent financing round and higher success probability for AD. The main potential catalysts over the next 12-24 months are progress in the SCLC trial run by Roche, initiation of Phase II trials in neurodegenerative disorders with ORY-2001, new preclinical candidates entering the clinic and delivering first human data.

2 May 2017

Price	**€3.42**
Market cap	**€117m**

Net cash (€m) at end Q416 (including term deposits) + fund-raise of €18.2m in March 2017.	22.5
Shares in issue	34.2m
Free float	50%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(3.6)	(24.7)	14.3
Rel (local)	(15.0)	(32.8)	0.0
52-week high/low		€5.1	€2.6

Business description

Oryzon Genomics is a Spanish biotechnology company focused on developing novel epigenetic compounds. Lead compound ORY-1001 is partnered with Roche, which is responsible for further development and is currently conducting a clinical trial in SCLC, but could expand it into other indications. ORY-2001, which has potential for several neurodegenerative diseases, is finishing Phase I. ORY-3001 is a new preclinical asset.

Next events

Initiation of Phase II trials with ORY-2001 in selected indications	H217
News from Roche on ORY-1001 in AML	2017

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Edison profile page

Investment summary

Company description: Expanding the epigenetics pipeline

Oryzon was founded in 2000 by the current CSO Tamara Maes and the CEO Carlos Buesa. It develops epigenetics-based therapeutics for patients with cancer and neurodegenerative disorders. Oryzon currently has two products in the clinical stage and an active preclinical programme in the LSD1 inhibition field, which is the company's area of expertise. The lead asset, ORY-1001, has already been partnered with Roche, which is responsible for further development of the compound after the results from the Phase I/IIa study were reported in December 2016. Data from the Phase I trial with ORY-2001 in healthy volunteers were presented at the end of March 2017 and Oryzon now plans to initiate Phase II trials in several neurological conditions. Oryzon developed all its know-how and IP in epigenetics 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 2015, Oryzon listed its shares on the Madrid Stock Exchange and the company has plans for a dual listing on NASDAQ in the future.

Valuation: rNPV of €308m or €9.0/share

We value Oryzon at €308m or €9.0/share compared to our previous valuation of €266m or €9.3/share. On an absolute basis, our valuation has increased after the recent funding round and higher success probability for AD after the positive Phase I data, but has decreased slightly on a per share basis. We have increased our success probability for the AD indication to 15% (from 12%), which is more conservative compared to MS (20%), reflecting the complexity of this indication and the fact that there are still no disease-modifying drugs for AD. The catalysts over the next 12-24 months include the progress in the SCLC trial run by Roche and potential expansion in other indications; initiation of Phase II trials in neurodegenerative disorders with Oryzon's ORY-2001, which could deliver proof-of-concept in 2019; and new preclinical candidates entering the clinic and delivering first human data (ORY-3001 is the most advanced). Oryzon could also dual-list in the US, which should provide liquidity to shares and improve access to capital.

Financials: Cash runway for at least two to three years

We make no changes to our financial forecasts, besides including the recent fund-raise. In FY16 Oryzon reported revenues of €735k (our estimate was €915k), which consisted of a reimbursement payment from Roche and the recognition of deferred income after a milestone payment of $4m from Roche in July 2015. Oryzon reported FY16 R&D costs of €5.2m, while personnel expenses were €2.5m. Adding other operating costs, Oryzon's FY16 operating loss was €4.6m. The company guided that existing funds should be sufficient to run the operations until H219, which is in line with our model and allows for achieving meaningful data readouts.

Sensitivities: Typical drug developer sensitivities apply

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. ORY-1001 is now fully supported by Roche, which means that the pace of development and indications will solely depend on the large pharma. ORY-2001 will need to be partnered, as later-stage studies can be very costly. We have assumed a deal in our valuation after Phase II, but have limited visibility on the timing and terms. For ORY-1001 we currently include AML and SCLC indications, but it is up to Roche to advance the projects. While the trial in SCLC has already been initiated, Roche is still investigating the data from Phase I/IIa acute leukaemia studies.

Outlook: Maturing epigenetics player

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. Epigenetic modifications cause changes in this spatial organisation, which lead to different genes becoming accessible for expression or silenced. This process is part of normal gene expression regulation, but if it falters can also be the cause of a variety of diseases.

Epigenetics is relatively young field in terms of drug development and histone deacetylases (HDACs) inhibitors were among the first epigenetic therapeutics that were brought to market. However, one of the key drawbacks is low selectivity and resulting side effects. Oryzon and some third-party researchers[1] 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 Competitive landscape, page 10). Oryzon's lead compounds, ORY-1001 and ORY-2001, are among the most advanced second-generation drug candidates in epigenetics. A more detailed introduction to epigenetics can be found in our initiation report.

Exhibit 1: R&D pipeline

Product	Indication and stage	Mechanism of action	Notes
ORY-1001, out-licensed to Roche	Acute leukaemia; reported data from Phase I/IIa; Roche is conducting Phase I in ED SCLC.	Small molecule LSD1 inhibitor - LSD1 is a histone eraser enzyme that removes methyl groups.	Oryzon reported supportive Phase I/IIa data in acute leukaemia at the ASH conference in December 2016. According to the licensing agreement, Roche took over further development and is conducting a Phase I study in SCLC.
ORY-2001	Reported safety and PK/PD data from Phase I with healthy volunteers; Oryzon has published supportive preclinical data for AD and MS and is also considering HD as third indication.	Small molecule LSD1 and MAO B inhibitor	Reported Phase I safety and PK/PD data from healthy volunteers on 31 March 2017 at the ADPD conference. Oryzon plans to initiate clinical trials in MS, AD and HD with MS likely to start first.
ORY-3001	Undisclosed non-oncological diseases	Small molecule LSD1 inhibitor	Oryzon aims to file the investigational new drug (IND) application in H217.
Undisclosed products	Using its proprietary platform, the company has developed other compounds for different epigenetic factors. These projects are in varying preclinical stages and could be progressed to the clinical testing depending on R&D portfolio decisions.		

Source: Edison Investment Research, Oryzon Genomics. Note: ED SCLC = extensive-stage disease small cell lung cancer; ASH = American Society of Hematology; MS = multiple sclerosis; AD = Alzheimer's disease; HD = Huntington's disease; MAOB = monoamine oxidase B; LSD1 = lysine specific demethylase 1; PK/PD = pharmacokinetics/pharmacodynamic.

Oryzon has developed a proprietary platform to create therapeutic inhibitors for a class of enzymes known as histone lysine demethylases, also known as KDMs. The two most advanced compounds in Oryzon's pipeline are ORY-1001 and ORY-2001. ORY-1001 is a potent and highly selective LSD1 (lysine specific demethylase 1, also called KDM1A) inhibitor, while ORY-2001 is bispecific LSD1/MAOB inhibitor. In July 2016, Oryzon revealed its third preclinical candidate, ORY-3001, which is also an LSD1 inhibitor. The company also has a number of additional programmes, mainly other histone demethylases, in various preclinical stages, which if needed could be progressed into the clinical phase. The current status of the projects is summarised in Exhibit 1.

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

ORY-1001: Lead, first-in-class, partnered product

ORY-1001 is a highly selective LSD1 inhibitor that can be orally administered. Oryzon's initial focus in developing ORY-1001 was on acute leukaemias. The drug candidate entered a Phase I/IIa trial in January 2014. The supportive preliminary efficacy results were a major milestone in December 2016, when the company reported the data at the American Society of Hematology (ASH) conference. Acute myeloid leukaemia represents 15-20% of all childhood leukaemias, approximately 33% of adolescent leukaemias and approximately 50% of adult leukaemias.[2] In total there were around 53,900 cases of AML in the US and Europe in 2015.

There are many different types of leukaemia with various genetic and epigenetic origins. The AML subtype, mixed lineage leukaemia (MLL), was an obvious initial target subpopulation of AML backed by encouraging preclinical data. 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.[3] 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 (ie ORY-1001 'unblocks' the development of young, malignant blood cells into mature cells). More detailed analysis of ORY-1001's preclinical data can be found in our initiation report. 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 cases that went into complete remission after treatment.[4]

ORY-1001 data at ASH

In December 2016 at ASH, Oryzon presented data from the positive Phase I/IIa trial. The study included different subsets of relapsed or refractory (RR) acute leukaemia patients treated with ORY-1001. The dose-escalation Part 1 (Phase I) included 27 patients treated for 28 days. Part 2 (Phase IIa) was an extension arm with an additional 14 patients with the goal of establishing initial efficacy results and a PK/PD profile.

The most common, likely drug-related side effects included low blood platelet count (16.7% of total adverse events), neutropenia (6.7%), fatigue (6.7%), changes in taste (6.7%) and petechiae (6.7%). Initial efficacy was explored in 14 patients included in the extension arm, of which one dropped out. Since specific subtypes of acute leukaemia are especially susceptible to LSD1 inhibition, the extension arm included patients with mixed lineage leukaemia (MLL; n=6), other MLL gene rearrangement or mutation (n=4) and acute erythroid leukemia (AML M6; n=4). The main findings included:

- Four of six patients with MLL leukaemia showed evidence of blast cell (young, undifferentiated blood cells) differentiation in blood, indicating ORY-1001's ability to induce young, rapidly dividing cells (that cause the cancer to spread) to develop into mature cells resembling the normal blood formation process. One MLL patient showed blast clearance from blood.
- Taking the four M6 patients together, there was no significant rise in blast cell count after two cycles of therapy, suggesting the possibility of disease stabilisation.

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

[3] 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.

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

- Of the other MLL patients (n=4), one demonstrated blast differentiation, one progressive disease, one skin disease only (inconclusive) and one patient dropped out.
- In addition to positive findings in blood samples, 23% of patients demonstrated bone marrow responses (3/13 [one patient from the other MLL subgroup dropped out]): two M6 patients and one MLL patient.

Although the study was small and the focus was on safety, the efficacy findings can be interpreted as showing potential in acute leukaemia. Notably, impaired differentiation/maturation of the leukaemic blasts is at the core of the disease's pathophysiology. ORY-1001's ability to induce the differentiation of blasts (turn them into normal, mature blood cells) demonstrates that it does what it was designed for.

ORY-1001 out-licensed to Roche

Oryzon signed a partnership agreement with Roche in April 2014. The licensing agreement includes two Oryzon patents that cover ORY-1001 and back-up compounds. 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 could potentially total more than $500m depending on the indications for which Roche decides to develop ORY-1001. Royalties will be tiered up to the mid-teens. Overall, we view the deal terms as attractive for a relatively early-stage asset.

Roche now has sole responsibility for developing ORY-1001 (Roche's ID RO7051790, also known as RG6016) in preferred indications and recently initiated the first clinical trial in extensive-stage disease SCLC (ED SCLC), which we included in our model in the initiation report as a likely indication for Roche to explore. The trial is an open-label, multi-centre study with an estimated 70 ED SCLC patients to be treated with ORY-1001. Safety/toxicity is the primary endpoint, while secondary endpoints will include primary efficacy (overall survival, progression-free survival, objective response) and PK/PD data. The estimated completion date is H219, in line with our original assumption.

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.[4] Stepping further beyond, there is third party evidence that LSD1 is also highly expressed in other solid tumours such as bladder and colorectal cancer, oestrogen-receptor-negative breast cancer and prostate cancer[4]. 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.

When asked about further steps in leukaemia at the analyst and investor meeting organised by Oryzon on 5 December 2016, Roche's representative explained that it will further analyse the findings in the Phase I/IIa and how these could translate into clinical benefit. Furthermore, current treatments of leukaemia are primarily based on combinations and Roche has already tested ORY-1001 in combination with multiple drugs in preclinical trials. We take this as confirmation that Roche is interested in progressing ORY-1001's development for leukemia, but likely in an optimal combination to accommodate current clinical practice. However, the timelines remain unclear at this stage.

ORY-2001 – dual effect for neurodegenerative diseases

ORY-2001 is a first-in-class, selective dual inhibitor of LSD1/MAOB. The first clinical data from Phase I with healthy volunteers were reported in March 2017. Initially, Oryzon is targeting three neurological disorders: AD and MS are the leading indications with supportive, published preclinical

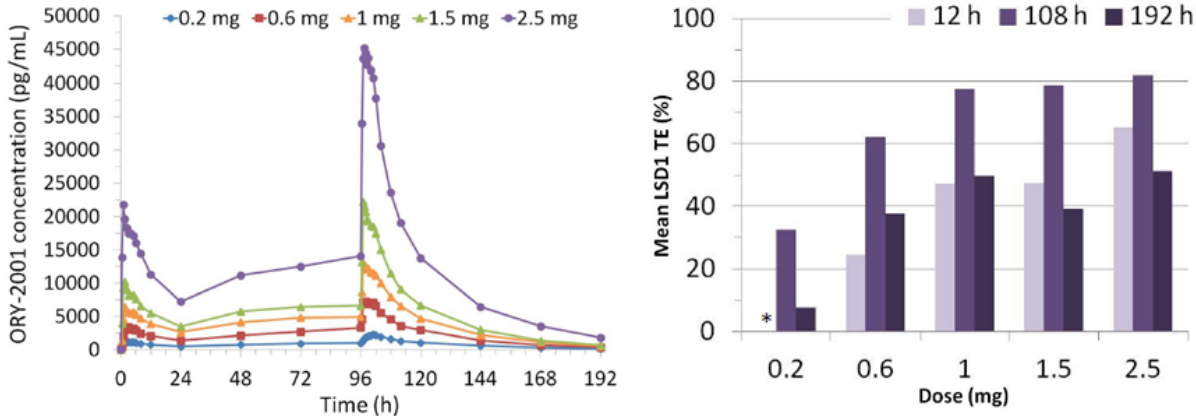
data, while the company's work and third-party data also suggest ORY-2001's potential in HD. Oryzon guided that ORY-2001 should be Phase II ready in H217 and the goal is to initiate in all three indications, with MS likely being the first one.

ORY-2001's first clinical data

The Phase I trial with ORY-2001 was double-blind with a single ascending dose (SAD – subjects receive single doses from the dose range selected for the study) and multiple ascending dose (MAD – subjects receive repeated, increasing doses) and included 80 healthy volunteers. A dose range of 0.2-4.0mg was explored. The main safety and PK/PD findings were:

- Overall, ORY-2001 was well tolerated and did not cause clinically significant changes in both the laboratory test and physical examination up to 4mg in SAD and up to 2.5mg in MAD subgroups.
- Among the complaints, headache episodes were the most common, but moderate in nature.
- Of special interest to us was ORY-2001's haematological safety, as haematopoiesis (blood production) is a known target of LSD1 inhibition. In the SAD subgroup no haematological side effects were observed. In the MAD subgroup platelet reduction was observed at the 2.5mg dose in two out of eight patients, which reversed after the study. Originally, the 2.5mg dose was the highest in the MAD range, but to confirm the trend Oryzon has added a 4mg dose, and it therefore appears that the therapeutic window is more than sufficient for further investigation.
- The PK profile was beneficial with a relatively long half-life after rapid oral absorption and proportional dose-response relationship. In PD tests, dose-dependent target engagement (the percentage of LSD1 bound to ORY-2001) in selected cells (peripheral blood mononuclear cells) was observed (Exhibit 2).

Exhibit 2: Selected PK/PD data from ORY-2001's Phase I trial



Source: Oryzon's data

Rationale for bi-specific effect in neurological disorders

Historically, the recognition of the role of epigenetics and its importance was first described in oncology and then further extended to neurodevelopment and neurodegenerative diseases.[5] 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

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

amount of preclinical work.[6] ORY-2001 is a unique dual inhibitor, which is possible due to the structural similarity of MAOB 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 the inhibition of MAOA, suffered from numerous side effects associated with its more widespread presence. A new generation of selective MAOB inhibitors (eg selegiline) was developed, which cause fewer side effects and are used in early-stage Parkinson's disease. Due to an abundance of data about the effects of MAOB inhibition and its relatively good safety profile, we believe that the downside of potential 'negative' interactions between inhibition of LSD1 and MAOB is significantly reduced, while there is potential upside from synergistic effects. This idea is also supported by Oryzon's preclinical studies.

Preclinical POC of ORY-2001 in multiple sclerosis

MS recently emerged as a second indication after AD for ORY-2001 following publication of preclinical data in this area by Oryzon in September 2016 at the 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and in February 2017 at the second annual conference of the Americas Committee for Treatment & Research in Multiple Sclerosis (ACTRIMS) in Orlando, Florida. ORY-2001 has been tested in preclinical proof-of-concept (POC) trials using the experimental autoimmune encephalomyelitis (EAE) mice model, a widely used proxy for MS. One of the EAE studies included three controlled arms: EAE mice treated with ORY-2001 (dual LSD1/MAOB inhibitor), ORY-LSD1 (proprietary selective LSD1 inhibitor) or rasagiline (a widely used, selective MAOB inhibitor).

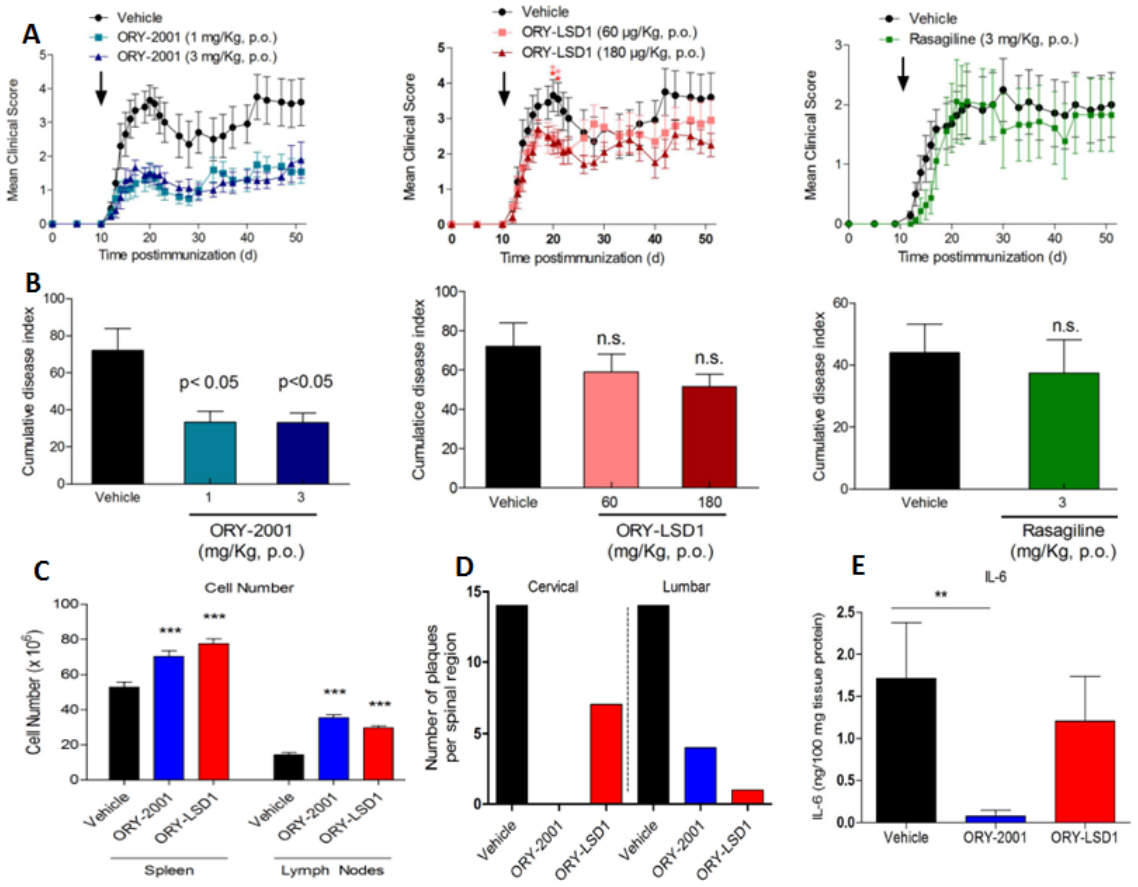
During these studies mice were injected with a specific peptide, which triggered an autoimmune reaction and the production of antibodies against the myelin sheet protecting the motor neurons. A gradual demyelination (destruction of the neurons' protective sheet) leads to the development of different degrees of paralysis, mimicking the natural course of MS. Key findings include:

- Treatment with ORY-2001 effectively reduced the severity of the disease (Exhibit 3A) and cumulative disease index (Exhibit 3B). Dual inhibition of LSD1/MAOB with ORY-2001 was more effective than standalone inhibition of LSD1 with ORY-LSD1 or MAOB with rasagiline. ORY-2001 has also been shown to reduce the EAE clinical score at lower doses (0.5 and 0.05mg/kg).
- The histopathological analysis two weeks after the first symptoms showed absent or substantially lower number of demyelination plaques in the lumbar and cervical regions of ORY-2001-treated animals (Exhibit 3D).
- Treatment with ORY-2001 and ORY-LSD1 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 (egress is usually associated with an inflammatory response) (Exhibit 3C).
- Treatment with ORY-2001 also caused a reduction of various pro-inflammatory cytokines such as IL-6 and IL-1beta and chemokines such as IP-10 and MCP-1, which are involved in inflammation leading to the destruction of motor neurons in MS (Exhibit 3E).

Cumulatively, these findings indicate that ORY-2001 shows an ability to counteract a number of pathophysiological processes associated with MS and that the dual inhibition of LSD1-MAOB (ORY-2001's mechanism of action) appears to be more efficacious in this context than LSD1 inhibition alone. Most recently Oryzon guided that it aims to file the IND application in H217, which would make ORY-2001 a new, first-in-class approach for MS in clinical development.

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

Exhibit 3: Effects of the treatment with ORY-2001, ORY-LSD1 and rasagiline in EAE mice model



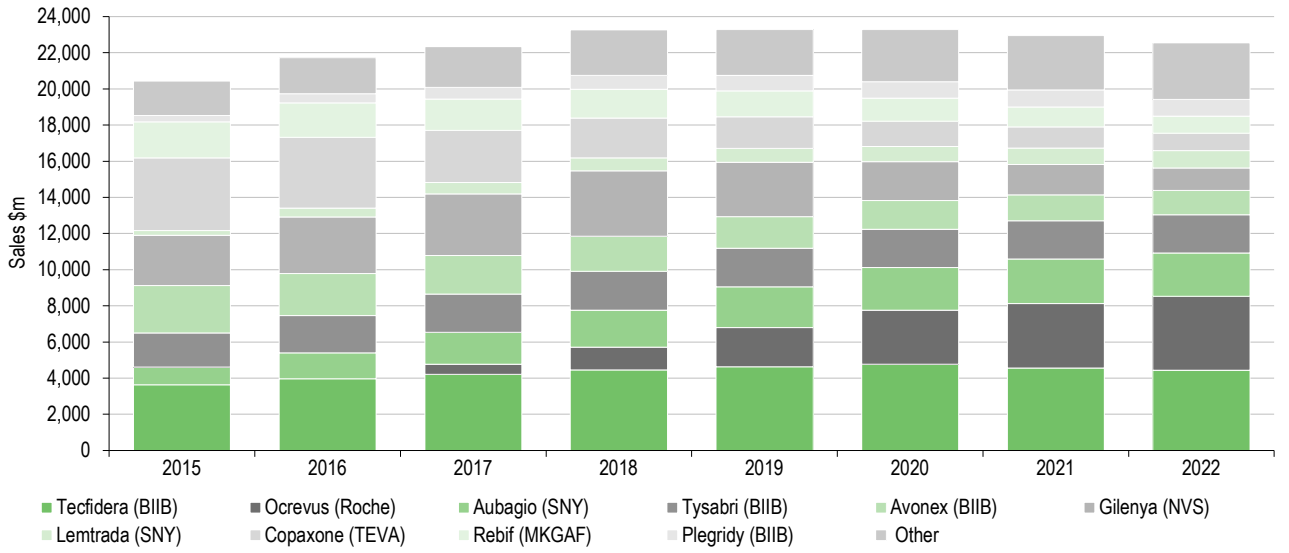
Source: T. Maes et al. Note: Cumulative disease index = the sum of clinical scores reached for each animal every day until day 51 post-immunisation. Clinical score reflects the extent of the paralysis – 0 = no signs; 5.0 = hind and foreleg paralysis.

MS market potential

MS is an autoimmune disease that attacks and destroys neurons in the central nervous system in variable degrees and causes significant physical disability. The hallmark of MS is episodic relapses that occur months or years apart and affect various anatomic locations. Around 400k people are diagnosed with MS in the US each year and around 85% of those have a relapsing-remitting course of the disease, which is in contrast to the progressive type, when symptoms gradually get worse over time rather than appearing as relapses (Multiple Sclerosis, Medscape).

Classic management of acute relapses can include systemic corticosteroids, plasma exchange and symptomatic drugs; however, the mainstay of treatment is disease-modifying agents for MS (DMAMS) with the goal of reducing the frequency of relapses and slowing progression. There are a number of DMAMS in the market currently (Exhibit 4) ranging from established to innovative options. The choice of the drug very much depends on circumstances (as opposed to rigorous algorithms) including patient lifestyle, tolerance, adverse effects and the experience of the healthcare provider.

Exhibit 4: Top 10+ other multiple sclerosis drug sales worldwide



Source: EvaluatePharma

Despite the number of available treatment options, MS is still an unmet medical need. If left untreated, more than 30% of patients will develop significant physical disability usually within 20-25 years. Life expectancy in MS patients is lowered only slightly, but quality of life is heavily affected, with 50-60% patients dying of secondary MS complications such as pulmonary or renal causes (source: Medscape). EvaluatePharma estimates that the MS market will be worth $23bn in 2022, fragmented with no drug significantly outstanding. While ORY-2001 will still need to prove its clinical efficacy, a unique mechanism of action among MS drugs is one differentiating feature. We note that, on average, a branded MS drug in the top 10 is expected to generate sales of $1.9bn by 2022.

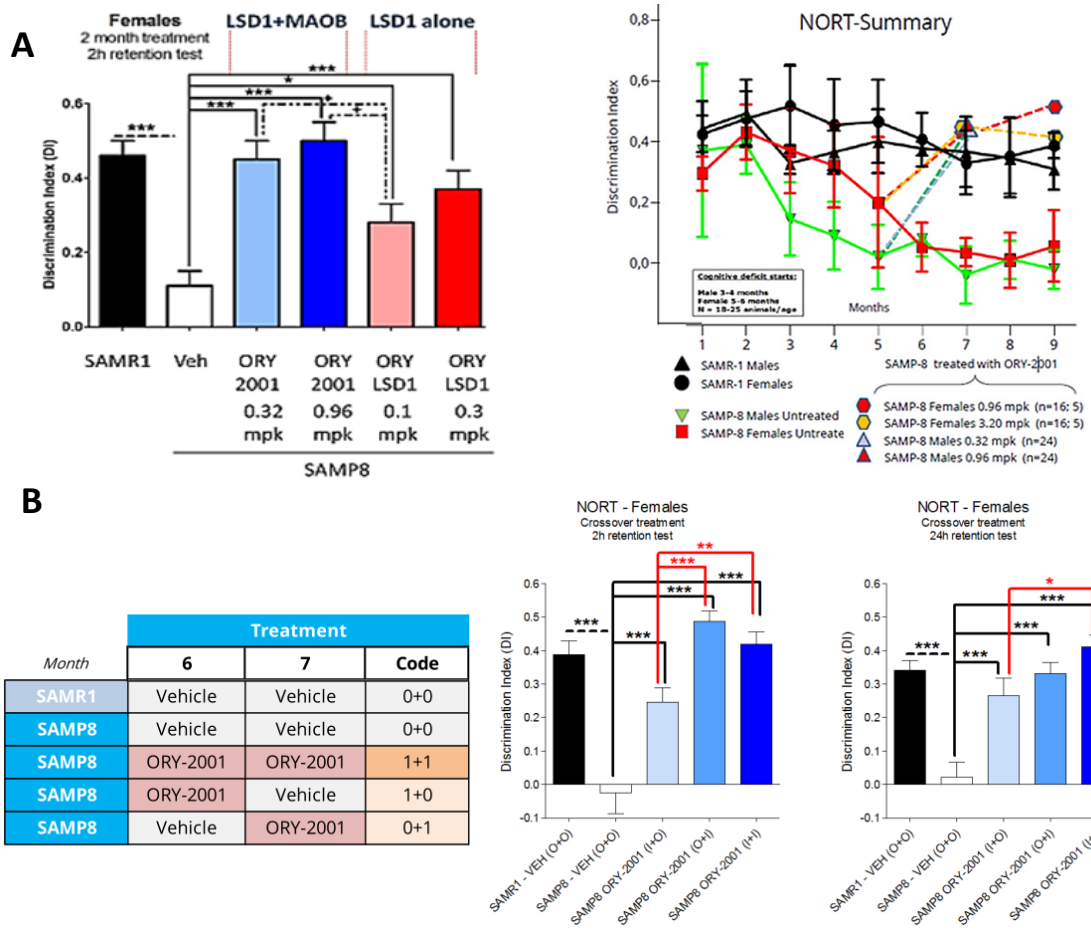
Highlights of preclinical data in AD

AD was the first indication, for which Oryzon published ORY-2001's preclinical data. Oryzon tested the drug in 10 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.
- LSD1 inhibition alone was able to produce a significant effect, but was less pronounced (Exhibit 5A). It appears that memory protection is driven by LSD1 inhibition, but the combination with MAOB inhibition (ie a dual compound, ORY-2001) has a synergistic effect.
- Meta-analysis conducted on this model demonstrates a potentially disease-modifying effect. Using NORT test scores as above, the cognitive decline in 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 to those observed in age-matched SAMR1 mice.
- Oryzon's crossover experiment with SAMP8 mice further supports disease-modifying effects. The mice were treated starting at the sixth or seventh month after the neurological symptoms were already present. The treatment with ORY-2001 or sham was assigned in the pattern showed in Exhibit 5B. ORY-2001 restored memory function after the deficit had developed (1+1 group), the delayed start group (0+1) also experienced the full benefit, while the early start (1+0) group showed significant benefit, which also persisted one month after the treatment.

- treatment interruption

Exhibit 5: Chronic treatment with ORY-2001 protects memory and restores the cognitive function of SAMP8 mice compared to control SAMR1 mice



Month	Treatment		
	6	7	Code
SAMR1	Vehicle	Vehicle	0+0
SAMP8	Vehicle	Vehicle	0+0
SAMP8	ORY-2001	ORY-2001	1+1
SAMP8	ORY-2001	Vehicle	1+0
SAMP8	Vehicle	ORY-2001	0+1

Source: Oryzon. Note: mpk = milligrams/kilo; SAMR1 mice - control

ORY-2001 can be explored in other indications

In addition to AD, Oryzon has preclinical data demonstrating an improvement in 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.

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 and traumatic brain injury. Therefore, the observed downregulation of the 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).[7] The key to convincing regulators of disease-modifying

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

effects (which have never happened in the case of AD) may be the link between the slowdown in the progression of symptoms and a significant effect on validated biomarkers.

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, 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 (Exhibit 6). 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. Oryzon is focused on LSD1 inhibition and is leading in this field in terms of clinical development. Also, Oryzon has unique programmes in neurodegenerative diseases, while the majority of peers are focused on oncology.

Exhibit 6: Selected second-generation, clinical stage epigenetic inhibitors

Company	Product, type	Phase	Indication	Comment
Histone methyltransferase inhibitors				
Epizyme	Tazemetostat, EHZ2 inhibitor	Phase II	Most advanced studies in relapsed/refractory non-Hodgkin lymphoma, solid tumours and mesothelioma	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				
Incyte	INCB59872 LSD1 inhibitor	Phase I/II	Advanced malignancies	Open-label, dose-escalation Phase I/II study in undisclosed advanced malignancies recruiting patients.
Imago BioSciences	IMG-7289 LSD1 inhibitor	Phase I/II	Acute myeloid leukaemia; Myelodysplastic syndromes	Phase I open label, safety and tolerability study recruiting patients. Phase II expansion arm will evaluate longer-term anti-tumour activity.
GlaxoSmithKline	GSK2879552, LSD1 inhibitor	Phase I/II	Small cell lung cancer, AML and Myelodysplastic syndrome	Three separate trials; each constitutes of Part 1 (dose escalation) and 2 (expansion cohort to evaluate clinical activity).
Celgene	CC-90011 LSD1 inhibitor	Phase I	Solid tumours and non-Hodgkin's lymphomas	Phase I open-label, dose-escalation, safety and preliminary efficacy study.
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	Haematological malignancies	Recruiting patients for four separate Phase I trials.
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.
Gilead	GS-5829, BET inhibitor	Phase I	Solid tumours and lymphomas	Recruiting patients for three separate Phase I trials.
Tensha Therapeutics*	TEN-010, BET inhibitor	Phase I	Acute myeloid leukemia and myelodysplastic syndrome	Phase I enrolling patients.

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

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. ORY-1001 is now fully supported by Roche, which means that the pace of the development and the indications will solely depend on the large pharma. ORY-2001 will need to be partnered, as later stage studies can be very costly. However, following recent funding rounds, Oryzon has cash to progress ORY-2001 through mid-stage development to reach meaningful data. We have assumed a deal in our valuation after Phase II, but we have limited visibility on the timing and terms. For ORY-1001 we currently include AML and SCLC indications, but it is up to Roche to advance the projects. While the trial in SCLC has already been initiated, Roche is still investigating the data from Phase I/IIa acute leukaemia studies.

Future pricing and market dynamics are hard to predict, especially if competitors are successful. Oryzon is in a comfortable cash position to finance the operations to H219. Future financing needs will depend on the scale of operations with preclinical candidates, the progress with ORY-2001 and ORY-1001, related milestone payments from Roche and potential revenues from other partnerships, on which there is limited visibility. Any capital raise would likely be a dilutive financing event.

Valuation

We value Oryzon at €308m or €9.0/share compared to our previous valuation of €266m or €9.3/share. On an absolute basis our valuation has increased after the recent financing round and higher success probability for AD after the positive Phase I data. However, it has decreased slightly on a per share basis. We have increased our success probability for the AD indication to 15% (from 12%), but it remains more conservative compared to MS (20%), reflecting the complexity of this indication and the fact that there are still no disease-modifying drugs for AD.

We continue to include the two lead products in our NPV calculations, but are still not including ORY-3001. Oryzon is clearly making progress, with the latest update indicating that this asset may be ready for Phase I in H217. We will revisit ORY-3001 when more details are announced, eg the exact indications that the project will include and potential timelines. As for ORY-1001 and ORY-2001, our assumptions for the indications are unchanged besides the increase in AD success probability. We discussed those in detail in our previous reports: AML, SCLC and AD in our initiation report and MS in our recent update.

Exhibit 7: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales* (US$m)	Value (€m)	Probability (%)	rNPV (€m)	NPV/share (€/share)
ORY-1001	AML	2022	900	259.0	20%	60.0	1.8
ORY-1001	SCLC	2025	635	121.8	12%	21.8	0.6
ORY-2001	AD	2026	4,510	813.0	15%	124.0	3.6
ORY-2001	MS	2026	1,940	359.5	20%	80.1	2.3
Net cash (end-2016 + fund-raise in March 2017)				22.5	100%	22.5	0.7
Valuation				**1,575.8**		**308.4**	**9.0**

Source: Edison Investment Research. Note: *Peak sales are rounded to the nearest US$10m, shown in US$. SCLC = small cell lung cancer; AML = acute myeloid leukaemia; AD = Alzheimer's disease; MS = multiple sclerosis. Net cash includes term deposits.

Financials

We make no changes to our financial forecasts besides including the recent fund-raise. In March 2017, Oryzon raised €18.2m, while the end-FY16 cash position was €27.5m (including term deposits and €22.5m net debt). In total Oryzon issued new shares accounting for 20% of the shares before the issue at a price of €3.20 per share, or 18% discount to the previous day's closing price. The company guided that existing funds should be sufficient to run the operations until H219, which is in line with our model. In FY16 Oryzon reported revenues of €735k (our estimate was €915k), which consisted of a reimbursement payment from Roche according to the R&D collaboration agreement (separate to the ORY-1001 licensing deal) and the recognition of deferred income after a milestone payment of $4m from Roche in July 2015. In addition, the company recorded €4.3m income to account for the capitalisation of the development costs (Oryzon follows Spanish GAAP). Oryzon reported FY16 R&D costs of €5.2m, while personnel expenses were €2.5m. Adding other operating costs, Oryzon's FY16 operating loss was €4.6m.

Exhibit 8: Financial summary

€000s	2013	2014	2015	2016	2017e	2018e
December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS						
Revenue	2,360	15,536	7,185	5,009	4,156	4,515
Cost of Sales	0	0	0	0	0	0
Gross Profit	2,360	15,536	7,185	5,009	4,156	4,515
Research and development	(873)	(1,108)	(3,191)	(5,210)	(5,274)	(6,041)
EBITDA	(94)	11,659	688	(3,721)	(4,749)	(5,537)
Operating Profit (before amort. and except.)	(370)	11,398	448	(3,879)	(4,845)	(5,633)
Intangible Amortisation	(657)	(657)	(657)	(695)	(938)	(1,049)
Exceptionals	(186)	(4,617)	(24)	(4)	0	0
Other	0	0	0	0	0	0
Operating Profit	(1,213)	6,124	(233)	(4,578)	(5,783)	(6,682)
Exceptionals	0	667	(169)	(58)	0	0
Net Interest	(672)	(52)	(553)	(844)	(1,269)	(1,214)
Profit Before Tax (norm)	(1,042)	11,346	(105)	(4,724)	(6,115)	(6,847)
Profit Before Tax (reported)	(1,885)	6,739	(955)	(5,480)	(7,052)	(7,896)
Tax	89	(88)	(37)	32	0	0
Profit After Tax (norm)	(953)	11,258	(142)	(4,692)	(6,115)	(6,847)
Profit After Tax (reported)	(1,796)	6,651	(992)	(5,448)	(7,052)	(7,896)
Average Number of Shares Outstanding (m)	23.0	23.3	24.7	27.6	31.3	34.2
EPS - normalised (€)	(0.04)	0.48	(0.01)	(0.17)	(0.20)	(0.20)
EPS - (reported) (€)	(0.08)	0.29	(0.04)	(0.20)	(0.23)	(0.23)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	75.0	9.6	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	73.4	6.2	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets	20,128	16,059	18,050	21,269	24,390	27,760
Intangible Assets	15,825	12,928	15,188	18,810	22,028	25,494
Tangible Assets	1,159	981	854	696	600	503
Investments	3,145	2,150	2,008	1,763	1,763	1,763
Current Assets	2,851	9,999	22,681	28,475	35,212	22,751
Stocks	2	9	4	8	6	7
Debtors	663	704	940	978	959	969
Cash	2,033	3,633	19,467	22,028	28,786	21,776
Other	153	5,654	2,270	5,461*	5,461*	0
Current Liabilities	(2,724)	(3,969)	(5,296)	(7,597)	(7,557)	(8,277)
Creditors	(1,005)	(1,299)	(2,401)	(2,119)	(2,080)	(2,100)
Short term borrowings	(1,719)	(2,670)	(2,895)	(5,477)	(5,477)	(6,177)
Long Term Liabilities	(11,251)	(8,196)	(7,841)	(19,419)	(19,419)	(18,719)
Long term borrowings	(9,117)	(6,420)	(6,177)	(17,723)	(17,723)	(17,023)
Other long term liabilities	(2,134)	(1,776)	(1,664)	(1,696)	(1,696)	(1,696)
Net Assets	9,004	13,893	27,594	22,729	32,625	23,515
CASH FLOW						
Operating Cash Flow	(113)	12,178	1,076	(4,536)	(6,036)	(6,742)
Net Interest	(672)	(52)	(553)	(471)	(1,269)	(1,214)
Tax	0	0	0	0	0	0
Capex	0	0	0	(28)	0	0
Acquisitions/disposals	(677)	798	0	0	0	0
Financing	0	0	14,725	287	18,219	0
Other	(161)	(9,579)	605	(6,819)**	(4,156)**	946
Dividends	0	0	0	0	0	0
Net Cash Flow	(1,623)	3,345	15,853	(11,567)	6,758	(7,010)
Opening net debt/(cash)	7,180	8,803	5,458	(10,395)	1,172	(5,585)
HP finance leases initiated	0	0	0	0	0	0
Other	0	0	0	0	0	0
Closing net debt/(cash)	8,803	5,458	(10,395)	1,172	(5,585)	1,425

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

Contact details	Revenue by geography
Oryzon Genomics Sant Ferran 74 08940 Cornella de Llobregat Barcelona, Spain +34 93 515 1313 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 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 programme (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 and Palobiofarma.	Ms Maes co-founded Oryzon Genomics in 2000 and has served as the chief scientific officer and member of the board of directors since then. She received her PhD in biotechnology from the University of Ghent (Belgium). She is also a director of Mendelion and recently was a member of the Scientific Advisory Board of the Consejo Superior de Investigaciones Científicas (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 arena as international product manager and international marketing manager at Almirall.

Principal shareholders	(%)
Najeti Ventures	20.54%
Carlos Buesa	10.96%
Tamara Maes	10.96%
Jose Ventura Ferrero	5.43%
Josep Maria Echarri	3.01%
Heights Capital Management	1.29%
Merchbanc	0.86%

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), Incyte Corporation (INCY US), Gilead Silences (GILD US), Constellation Pharmaceuticals, Imago BioSciences.

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