EDISON

Oryzon Genomics

Awaiting for eventful 2019

Corporate outlook

Pharma & biotech

The next year is shaping up to be transformative for Oryzon with two data readouts from Phase IIa trials with ORY-2001 in Alzheimer's disease (AD) and multiple sclerosis (MS). In addition, an innovative design basket trial with ORY-2001 in several neuropsychiatric disorders may also deliver first results next year. Oryzon is resuming the development of ORY-1001 in acute myeloid leukaemia (AML) and small-cell lung cancer (SCLC). While Roche's departure was a setback in 2017, the stars started to align again after the Biogen Abeta antibody data provided a much-needed boost for AD research industry and indirectly for Oryzon's ORY-2001. Furthermore, a fundamental study published in Cell described the potential of LSD1 inhibition in immunooncology setting adding a new dimension to ORY-1001's potential. We value Oryzon at €328m or €9.6/share (vs €9.4/share).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	5.0	(4.7)	(0.17)	0.0	N/A	N/A
12/17	4.3	(4.6)	(0.14)	0.0	N/A	N/A
12/18e	7.0	(5.6)	(0.16)	0.0	N/A	N/A
12/19e	6.3	(7.3)	(0.21)	0.0	N/A	N/A

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

Broadening ORY-2001 programme; catalysts in 2019

Two Phase IIa trials with ORY-2001, a dual LSD1/MAOB inhibitor for CNS indications, are underway. A randomised, double-blind, placebo-controlled, 36-week Phase IIa SATEEN study (n=24) will evaluate ORY-2001 in patients with relapsing-remitting MS and secondary progressive MS. A second randomised, double-blind, placebo-controlled, 24-week Phase IIa ETHERAL trial (n=90) with ORY-2001 in mild-to-moderate AD started enrolling patients in May 2018. The data readouts from both studies are planned around mid-2019. Most recent R&D update from Oryzon now includes a planned (CTA filed) so-called basket trial that will use a novel strategy employed in oncology trials to simultaneously test ORY-2001 in several neuropsychiatric disorders for reduction in aggression. While still an exploratory trial with limited patient numbers, if positive signals are obtained it would mark a significant step beyond neurodegenerative disorders like MS and AD.

Steady course for ORY-1001 maintained

Roche's decision to discontinue the development of ORY-1001 and return the rights to Oryzon was major news last year. Roche cited portfolio reprioritisation as the reason and that the decision was not driven by data. While this was a setback in business development for Oryzon, in our view, ORY-1001's potential has not been compromised. In line with this, Oryzon is now resuming the development of ORY-1001 in AML and SCLC (CTAs filed) with trials planned to start enrolling patients in H218 and interim data potentially coming in 2019.

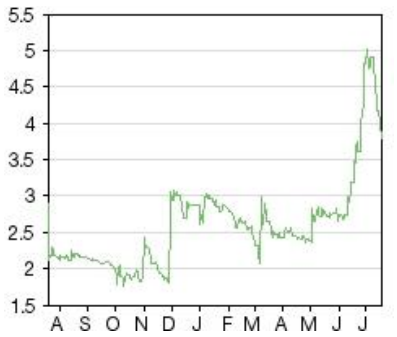
Valuation: Risk-adjusted NPV of €328m or €9.6/share

We have marginally increased our valuation of Oryzon to €328m or €9.6/share from €322m or €9.4/share due to rolling our model forward. Our estimates and valuation assumptions remain unchanged. The key catalysts in the near term are the results from the Phase IIa trials in AD and MS and the basket trial with ORY-2001.

18 July 2018

Price	**€3.80**
Market cap	**€127m**
Net cash (€m) at end Q118 (including term deposits)	9.2
Shares in issue	33.5m
Free float	50%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	19.3	57.7	35.5
Rel (local)	20.9	59.0	48.5
52-week high/low		€5.0	€1.8

Business description

Oryzon Genomics is a Spanish biotech focused on epigenetics. ORY-1001 (Phase I/IIa) is being explored for acute leukaemias and SCLC; ORY-2001, its CNS product, is in Phase IIa trials in MS and AD. Newer asset ORY-3001 is being developed for certain orphan indications.

Next events

Initiation of POC trials with ORY-1001 in selected indications	H218
Results of Phase IIa with ORY-2001 in MS	H119
Results of Phase IIa with ORY-2001 in AD	H119

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Edison profile page

Investment summary

Advancing towards mid-stage trial readouts

Oryzon was founded in 2000 by the CSO Tamara Maes and the CEO Carlos Buesa. It develops epigenetics-based therapeutics for patients with cancer and neurodegenerative disorders. Oryzon 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 assets are ORY-2001 for neurological and neuropsychiatric disorders and ORY-1001 for haematological and solid tumours. Oryzon is running two Phase IIa clinical trials with ORY-2001 in AD and MS and plans to initiate a basket trial in several neuropsychiatric conditions. The results from the Phase I/IIa study with ORY-1001 in acute leukaemias were reported in December 2016 and the company has recently presented further development programme in blood and solid cancers after it had regained global rights to ORY-1001 following Roche's decision to reshape its R&D portfolio and discontinuation of the licensing deal signed in 2014. Oryzon is headquartered in Barcelona, Spain, with a US office in Cambridge, MA, and employs around 40 people. Oryzon listed its shares on the Madrid Stock Exchange on 14 December 2015.

Financials: Cash reach to 2020

We maintain our financial estimates following our last revision after the Q118 results, which were largely in line with expectations. Our R&D cost estimates stand at €8.5m for FY18 and €9.5m for FY19, which are the main cost drivers. The reported Q118 cash position was €30.9m (cash and short-term investments; net cash €9.2m). Our model suggests this should be sufficient to reach 2020.

Valuation: rNPV of €328m or €9.6/share

As Oryzon is on track to develop its assets in all the indications we include in our valuation, we leave our assumptions unchanged. Our updated valuation is €328m or €9.6/share, marginally up from €322m or €9.4/share due to rolling our model forward. Key catalysts within cash reach include readouts from two Phase IIa trials with ORY-2001 in AD and MS and results from the basket trial in neuropsychiatric disorders in 2019. Interim data readouts next year from both planned trials with ORY-1001 in AML and SCLC are also possible.

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. Following the discontinuation of the partnership deal with Roche, Oryzon is now developing ORY-1001 on its own. We believe the asset has not been compromised and the Roche's decision was based on the perspective of portfolio management. Oryzon is continuing the development on its own. We have assumed a licensing deal in our valuation after Phase II for both assets, but we have limited visibility on the timing and terms. Oryzon is in a comfortable cash position to finance the operations to early 2020.

Outlook: Two mid-stage data readouts in 2019

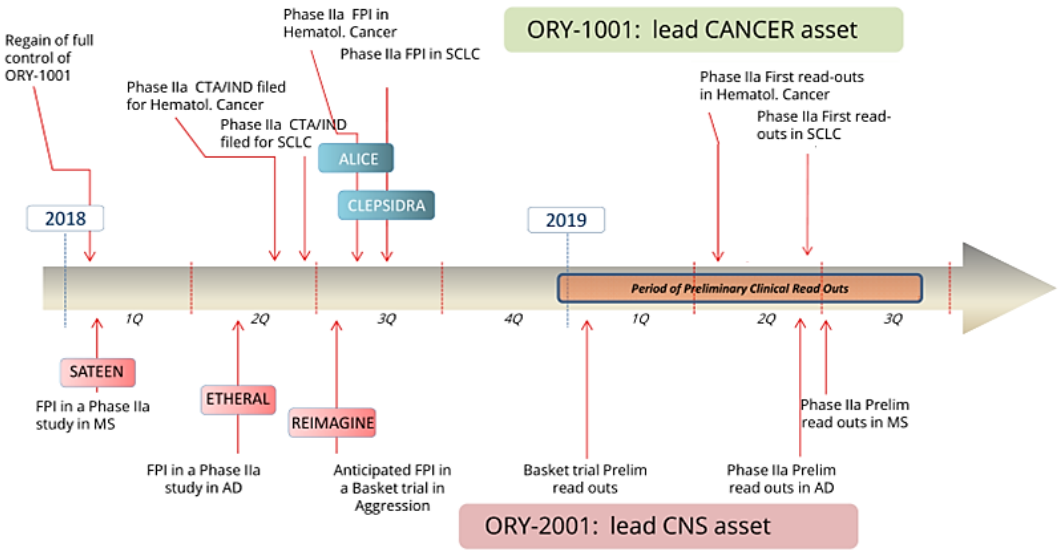
Simplistically, epigenetics can be defined as the study of changes in how genes are 'read' (expressed). A number of external factors can switch genes on and off, modifying expression, but without actually making any changes in the sequence of DNA. These changes are called epigenetic modifications. Epigenetics is relatively young field in terms of drug development and histone deacetylase (HDAC) inhibitors were among the first epigenetic therapeutics 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 HDAC inhibitors 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 stage, such as histone methyltransferases (HMTs), BET inhibitors, PRMT5 inhibitors, etc (see Competitive landscape, page 10; a more detailed introduction to epigenetics can be found in our initiation report). 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, whereas ORY-2001 is a bispecific LSD1/MAOB inhibitor. Oryzon's third preclinical candidate, ORY-3001, is also an LSD1 inhibitor. The current status of the projects is summarised in Exhibit 1.

Exhibit 1: R&D pipeline

Product	Indication and stage	Mechanism of action	Notes
ORY-1001	Acute leukaemia Reported data from Phase I/IIa Two new Phase IIa trials to start in H21	Small moleculeLSD1 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. Two new Phase IIa trials are about to start in AML and SCLC (CTA filed).
ORY-2001	Reported safety and PK/PD data from Phase I with healthy volunteers Two Phase IIa trials in AD and MS ongoing	Small molecule LSD1 and MAOB inhibitor	Reported Phase I safety and PK/PD data from healthy volunteers on 31 March 2017 at the ADPD conference. Oryzon initiated clinical trials in MS and AD. Basket trial in neuropsychiatric disorders planned (CTA filed).
ORY-3001	Undisclosed non-oncological diseases	Small molecule LSD1 inhibitor	Initial positive preclinical data published in sickle cell disease, but further development not disclosed yet.
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: ASH, American Society of Hematology.

Exhibit 2: Expected 2018-2019 newsflow



Source: Oryzon

[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.

Tailwind from recent industry newsflow

LSD1 inhibition stimulates anti-tumour immune response and enable checkpoint blockade

A team of researchers (unrelated to Oryzon) at the Harvard Medical School has found that inhibiting LSD1 could lead to the activation of immune response and increased response to checkpoint inhibition. This detailed fundamental study used in vitro and in vivo with results published in Cell in June 2018. Key findings include:

- Ablation of the LSD1 in cancer cells stimulates anti-tumour T cell immunity and restrains tumour growth. This effect was achieved via an increase of endogenous retroviral elements and decreases of the expression of the RNA-induced silencing complex in the absence of LSD1. This change caused double-stranded RNA stress and activation of type 1 interferon, which stimulated anti-tumour T cells.
- LSD1 depletion enhanced tumour immunogenicity and T cell infiltration in less immunogenic tumours.
- In a melanoma mouse model not responding to checkpoint inhibition, LSD1 depletion elicited significant responses to anti-PD-1 therapy.
- An inverse correlation between LSD1 expression and CD8+ T cell infiltration in various human cancers has been shown.

This study identified LSD1 as a potent inhibitor of anti-tumour immunity and suggested that LSD1 inhibition combined with checkpoint inhibition (PD-(L)1 blockade in this case) is a viable cancer treatment strategy. Once a cancer develops, it often also has mechanisms that suppress the immune response enabling the tumour to 'hide' from the immune cells. The goal of cancer immunotherapies is to change this tumour microenvironment so the patient's own immune system can fight the disease. Checkpoint inhibitors are very effective in certain indications with sales of this new class of drugs growing rapidly. However, a very significant part of the patient population is non-responsive to the treatment (from 40% of melanoma patients to >80% non-small cell lung cancer). The demonstrated ability of LSD1 inhibition to convert a tumor resistant to PD-1 blockade to a tumour responsive to PD-1 blockade may turn 'cold' tumours 'hot' and provide a solution for patients not responding to checkpoint inhibitors.

This study, to our knowledge, for the first time linked the benefit of LSD1 inhibition in the immunooncology setting, adding a new dimension to ORY-1001's potential in terms of what indications it could target and increasing the scope in terms of partnering discussions. In our view, the new findings form strong basis for Oryzon to actively start exploring the potential of its technology in combination with checkpoint inhibitors in a form of internal preclinical programme or by collaborating with external partners interested in such combinations. The combinations of checkpoint inhibitors and epigenetic drugs are already being explored in the industry. For example:

- Incyte is running a Phase I/II trial with three arms testing various combinations of pembrolizumab with its epacadostat (IDO-1 inhibitor), INCB057643 (BET inhibitor) and INCB059872 (LSD1 inhibitor) in solid tumours;
- Constellation Pharma is running a Phase Ib/II study with its CPI-1205 (EZH2 inhibitor) with ipilimumab or pembrolizumab in solid tumours;
- Epizyme is running a safety and PK/PD trial, one arm of which will test its tazemetostat (EZH2 inhibitor) in combination with atezolizumab in relapsed/refractory diffuse large B-cell lymphoma and
- there are also several companies with clinical trial programmes testing HDAC inhibitors with a variety of checkpoint inhibitors.

What sets Oryzon's technology apart, in our view, is that this new study shines light on the very detailed fundamental mechanisms involved in LSD1 inhibition from an immunooncology perspective.

Biogen antibody brought attention back to AD; questions remain

After years of high profile failures in AD research targeting Abeta plaques, the biotech industry received a much-needed positive message in July 2018. Biogen announced that its anti-amyloid beta protofibril antibody BAN2401, partnered with Eisai and originally developed by BioArctic (a Swedish biotech, met its primary endpoint in the Phase II study with mild cognitive impairment or mild AD patients (collectively early AD; n=856). Biogen's and Eisai's share prices increased by 20% and 39% respectively on the news (both large caps), whereas BioArctic's share price jumped 334%. The trial was previously analysed at 12 months using Bayesian analysis with the aim of creating a faster path to market, but an independent data monitoring committee determined that BAN2401 did not meet the criteria for success. However, Biogen and Eisai decided to continue the trial to 18 months. At this point a traditional statistical analysis was performed on the data, which "demonstrated a statistically significant slowing in cognitive decline and reduction of amyloid beta accumulated in the brain". No other data were provided, which will presented at a relevant scientific conference in due course. Even though this announcement is encouraging, it is premature for Abeta targeting antibodies to claim victory, because:

- very little information has been provided so far;
- statistically significant effects were seen in the highest dose arm (10 mg/kg every two weeks);
- the important endpoint used in this second data set was ADCOMS, which is a relatively new cognition score designed to work for MCI AD trials and has not been used in other AD trials; and
- the Bayesian analysis at 12 months was not successful, although the conventional analysis at 18 months showed statistically significant changes appearing as early as six months into treatment with the highest dose.

Given the many failed late-stage attempts in targeting the Abeta plaque theory over the last several years, the investor appetite for AD assets has been reduced. Although questions for Biogen and Eisai remain, the announcement was still sufficient to revive hopes. Just this year three BACE inhibitors that were being explored in late-stage AD trials by large pharma companies failed. Axovant's intepirdine (5-HT_6 antagonist), vTv Therapeutics' azeliragon (RAGE receptor antagonist) also failed over the last few months, while Alzheon's IPO was not successful.

If the excitement around Abeta MAbs continues, it could be a positive driving force for the development of other drug candidates within AD, in our view, even beyond therapies targeting various forms of Abeta, such as Oryzon's epigenetic approach. When it comes to any potential direct read-through for Oryzon's ORY-2001, there is no known connection with Abeta theory besides that ORY-2001 reduces S100A9, a pro-inflammatory protein that has been linked to the physical accretion of Abeta protofibrils. Instead of specific targeting, Oryzon's epigenetic technology induces changes in gene expression with profound biological effects, therefore it is differentiated from Abeta theory products. Oryzon believes this could allow developing drugs not only for AD, but for various other neurological and psychiatric conditions (as discussed below).

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. Oryzon has developed a broad R&D programme for this asset and is targeting a range of neurological disorders. AD and MS are the leading indications with two Phase IIa trials underway, while a new basket trial is planned to

commence in H218, which will explore ORY-2001 use in a variety of neurological indications where aggression is a hallmark.

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 extended to neurodevelopment and neurodegenerative diseases.[2] 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 preclinical work.[3] ORY-2001 is a unique dual inhibitor and its mode of action is possible due to the structural similarity of MAOB and LSD1.

Monoamine oxidases (MAO) are a very well-researched family of enzymes that are targets for already marketed drugs, such as first-generation 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 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.

Two Phase IIa trials in AD and MS ongoing

Two Phase IIa trials with ORY-2001, a dual LSD1/MAOB inhibitor for CNS indications, are underway. A randomised, double-blind, placebo-controlled, 36-week Phase II SATEEN study (n=24) will evaluate ORY-2001 in patients with relapsing-remitting MS and secondary progressive MS. A second randomised, double-blind, placebo-controlled, 24-week Phase IIa ETHERAL trial (n=90) with ORY-2001 in mild-to-moderate AD started enrolling patients in June 2018. The data readouts from both studies are planned around mid-2019 and represent the main catalysts in the near term.

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).[4] The key to convincing regulators of disease-modifying 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.

Basket trial – novel concept in psychotherapeutics R&D

Most recent update from Oryzon on its R&D plans includes a newly designed concept to conduct a so-called basket trial with ORY-2001 in a variety of neuropsychiatric conditions. This concept is similar to drug development strategy in oncology. For example, vemurafenib is an inhibitor of

[2] L. Lovrečić et al. The Role of Epigenetics in Neurodegenerative Diseases. Uday Kishore, 15 May 2013.

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

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

mutated $BRAF^{V600E}$ kinase. Vemurafenib received FDA approval for the treatment of late-stage melanoma with $BRAF^{V600E}$ in August 2011. During the development, vemurafenib was explored in a variety of tumours with $BRAF^{V600E}$ before the specific melanoma indication was determined for late-stage trials. Trials in subsequent indications followed and clinicaltrials.gov lists around 70 active trials with this drug in a variety of combinations.

Oryzon believes it can employ a similar strategy to develop ORY-2001 for neuropsychiatric disorders due to observed holistic effects on aggression and behaviour in preclinical models with LSD1/MAOB inhibition (described below). Aggression is one of the more widespread alterations in patients with neurodegenerative and developmental disorders, as a well as social withdrawal and depression. To establish a more specific psychiatric setting where ORY-2001 could be used, Oryzon plans to initiate a Phase IIa trial (CTA filed with a Spanish agency) and enrol at least six patients per each indication: Alzheimer's dementia, dementia with Lewy bodies, attention deficit hyperactivity disorder, autism spectrum disorder and borderline personality disorder. The open-label treatment with ORY-2001 will last for eight weeks with the last patient out expected in Q418/Q119. The main goal is the assessment of reduction in aggression.

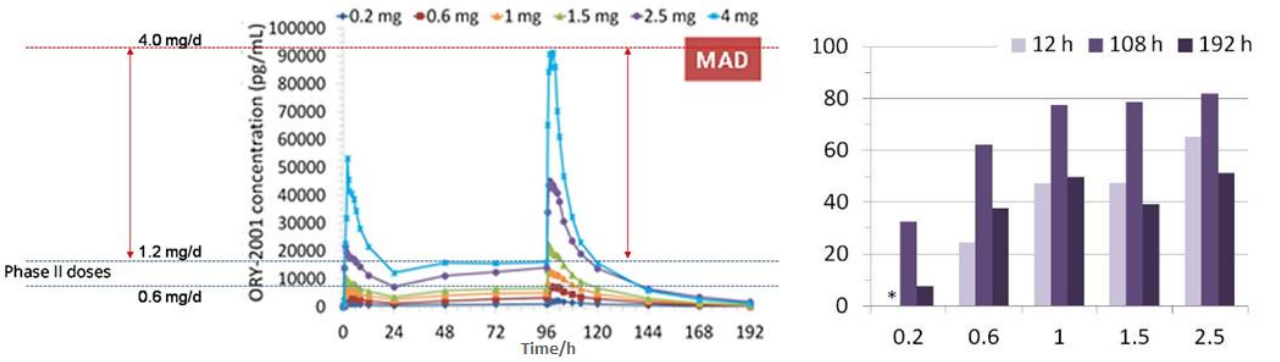
Aggression is a widespread issue in various psychiatric conditions especially where dementia is involved or neurodevelopment is impaired. Therefore, we find such basket trial strategy is the fastest route to establish more precise indications or settings. Given the novelty of the trial design, the small sample sizes and lack of visibility of a more concrete regulatory pathway that could lead to the market, we do not make any change to our OUR-2001 valuation approach. But if this study delivers efficacy signals sufficient to progress to more advanced trials, we will revisit this direction, which would be clearly a step beyond currently targeted AD and MS.

ORY-2001's first clinical data

The results of the Phase I trial with ORY-2001 in healthy volunteers were the first in-human data. The study 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 more than 100 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; 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. Orally administered ORY-2001 was well tolerated and did not provoke significant clinical or laboratory changes or adverse events in the MAD up to 2.5mg. Single and multiple ascending doses were haematologically safe. Originally the 2.5mg dose was the highest in the MAD range, but Oryzon added a 4mg dose to obtain robust safety data. It therefore appears the therapeutic window is more than sufficient for further investigation. Sub-1.2mg doses are used in the Phase IIa trials now.
- The PK profile was beneficial with a relatively long half-life after rapid oral absorption and proportional dose-response relationship. ORY-2001 efficiently crossed the blood-brain barrier and the half-life of 22 hours could allow a once-daily dosing regimen, which is especially useful for patients with neurodegenerative conditions. 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 3).

Exhibit 3: Selected PK/PD data from ORY-2001's Phase I trial



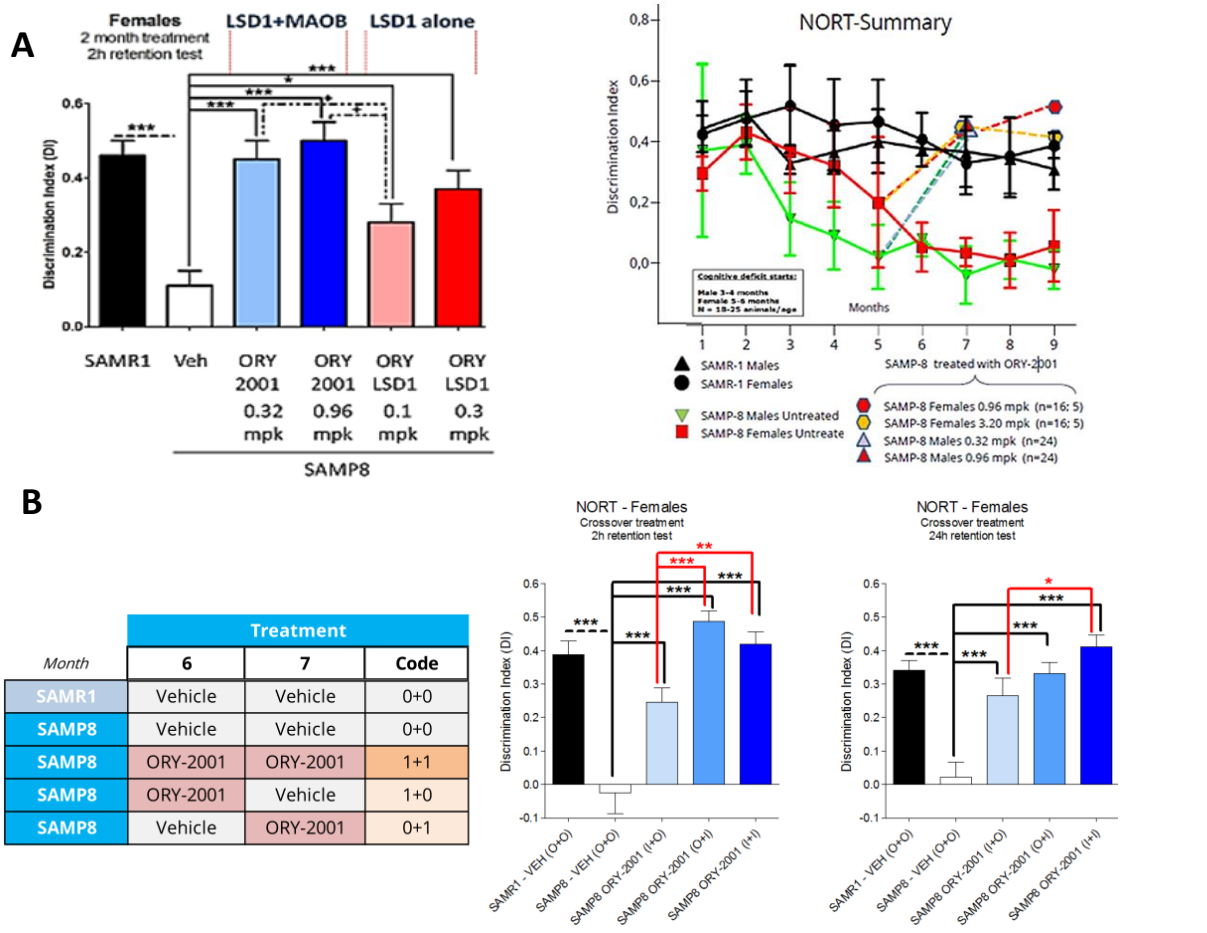
Source: Oryzon

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 more than 340 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 4A). 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 after the neurological symptoms started to show. The treatment with ORY-2001 or sham was assigned in the pattern showed in Exhibit 4B. ORY-2001 restored memory function after the deficit had developed (1+1 group), the delayed start group (0+1) also experienced the full benefit, whereas the early start (1+0) group showed significant benefit, which also persisted one month after the treatment interruption.

Exhibit 4: Chronic treatment with ORY-2001 protects memory and restores the cognitive function of SAMP8 mice compared to control SAMR1 mice



	Treatment		
Month	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.

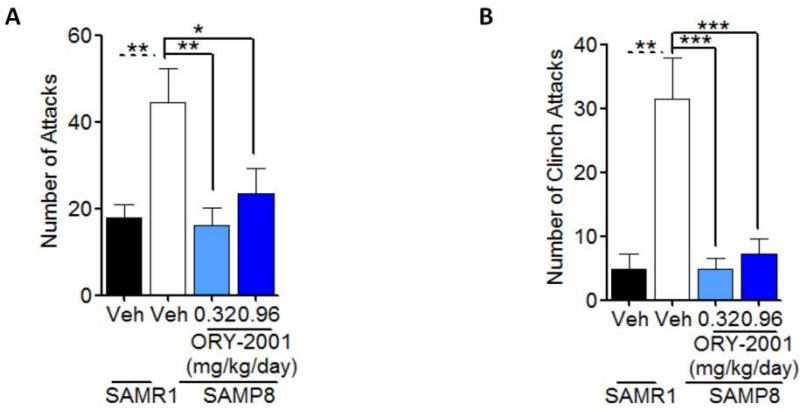
ORY-2001's holistic effects may improve behavioural alterations

Oryzon's more recent preclinical data with ORY-2001 suggested that in addition to rescuing memory impairment, the drug could help to treat the behavioural alterations seen in patients with neurodegenerative diseases. The new data were first presented at the Society for Neuroscience 47th annual meeting, Washington DC, on 11-15 November 2017.

The SAMP8 mice were treated with a range of clinically feasible doses of ORY-2001 or a vehicle. SAMR1 mice were treated with a vehicle only and acted as a normal control. The new data demonstrate ORY-2001's effects on behavioural alterations after six weeks of treatment using a so-called resident intruder (RI) test, which is an established test for aggression and evaluates the response of the test mouse to a new animal introduced to its environment. Gene expression analysis was then carried out on the mice's prefrontal cortices. The main findings were:

- ORY-2001-treated SAMP8 mice showed reduced aggression in the RI test measured by number of attacks and number of clinch attacks compared with SAMP8 control mice, to a similar level to the SAMR1 control mice (Exhibit 5).
- ORY-2001 normalised pathological gene expression changes observed in SAMP8 mice (resembling those in AD) compared with SAMR1 mice, measured by a genome-wide microarray-based survey.

Exhibit 5: RI test showing reduced attacks and clinch attacks by ORY-2001-treated mice

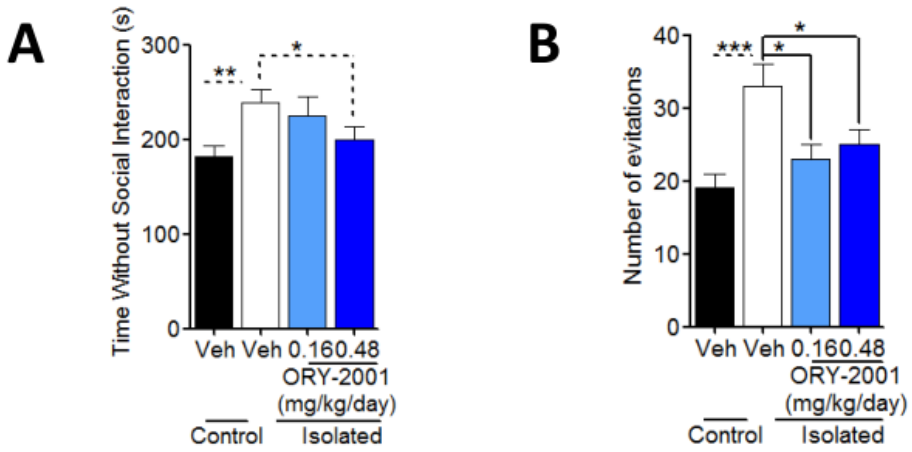


Source: Oryzon Genomics poster presentation

The RI test was also conducted in the rat isolation model with ORY-2001. Rats are very social rodents and do not tolerate isolation. Rat isolation therefore was used as a model for social avoidance seen in AD patients. Rats were divided into control arm (three to four animals per cage) or isolated (one animal per cage). Isolated animals were treated with vehicle or ORY-2001 for five weeks; control animals were given vehicle. After that all animals were tested in the RI test. The findings were:

- No aggressive behaviour was observed in the rats in either group, confirming the social nature of the animals.
- Social avoidance measured by time without social interaction and number of evitations was significantly increased in isolated rats treated with vehicle, indicating the socially detrimental effect of the isolation. However, the treatment with ORY-2001 significantly improved both parameters.

Exhibit 6: RI test demonstrates ORY-2001's efficacy in rat isolation model



Source: Oryzon Genomics poster presentation

These results suggest that ORY-2001 could have an effect on both cognitive decline and behavioural alterations in AD patients. Specific treatments for behavioural alterations such as aggression and social isolation are lacking and so tackling these could help to make ORY-2001 more competitive in the market. A large proportion of AD patients (20-50%) exhibit clinically significant aggression. Currently this is managed by non-pharmacological as well as pharmacological means. There is no FDA approved specific medication for the treatment of aggression in AD or other neuropsychiatric disorders. Memantine is the only drug approved for AD that has also been shown to reduce agitation and aggression, whereas other drugs used are more

general antipsychotics, antidepressants or anxiolytic drugs and often have unfavourable safety profiles.

Preclinical proof-of-concept of ORY-2001 in multiple sclerosis

MS emerged as a second potential indication after AD for ORY-2001 following publication of preclinical data from specific inflammation models by Oryzon at multiple conferences over the last two years. ORY-2001 has been tested in preclinical proof-of-concept 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).

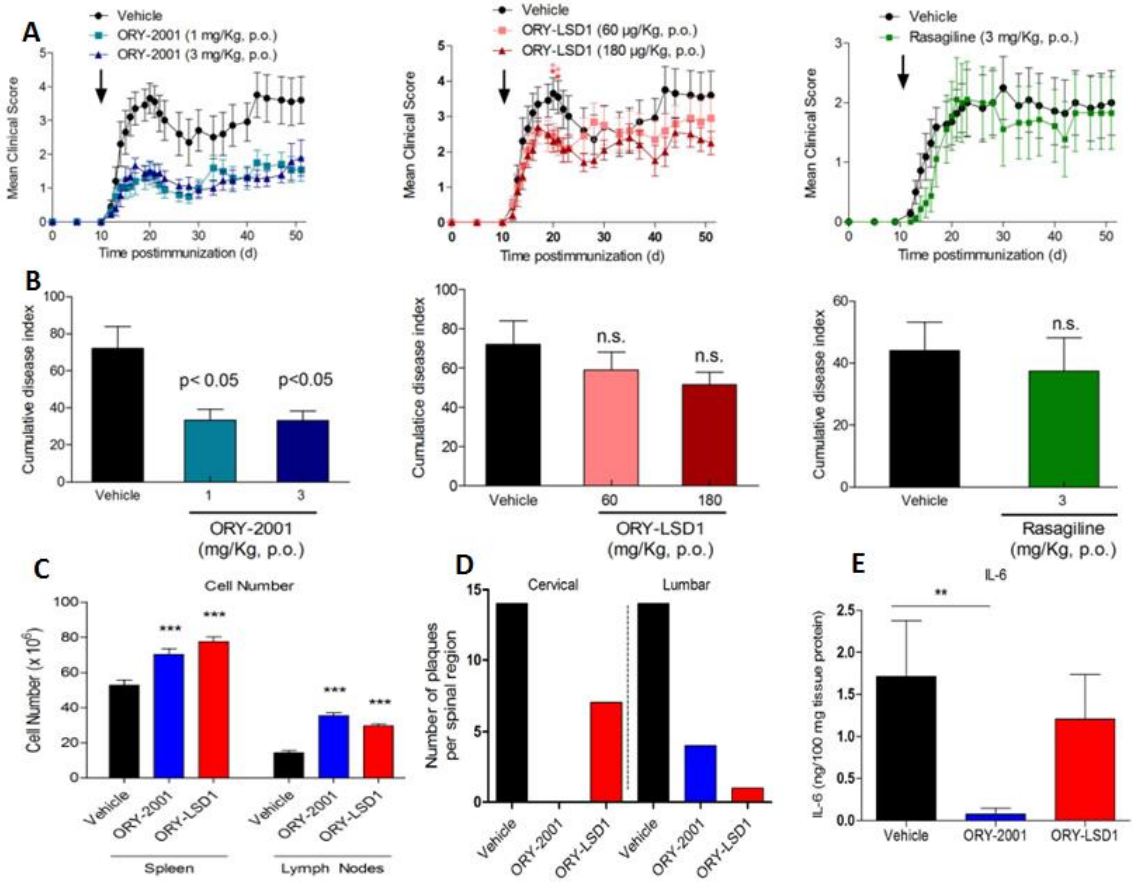
During these studies mice were injected with a specific peptide, which triggered an autoimmune reaction and the production of antibodies against the myelin sheet protecting the motor neurons. A gradual demyelination (destruction of the neurons' protective sheet) leads to the development of different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

- Treatment with ORY-2001 effectively reduced the severity of the disease (Exhibit 7A) and cumulative disease index (Exhibit 7B). 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 7D).
- 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 7C).
- 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 7E).

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.

Oryzon has also presented a head-to-head comparison of ORY-2001 in MS against fingolimod (Gilenya, Novartis; $3.2bn in 2017) in the EAE mouse model. The data showed that ORY-2001 performed as well as or better than fingolimod in reducing immune cell infiltration of CNS tissues, providing neuroprotection and thereby reducing demyelination (detailed analysis in our 14 December 2017 report).

Exhibit 7: 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.

ORY-1001: First-in-class, lead oncology 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 and in April 2014 it was licensed to Roche, which has paid $21m in upfront and milestones to Oryzon during the engagement period. Under the terms of the agreement, Oryzon was responsible for finalising the leukaemia Phase I/IIa study (that was already ongoing and sponsored by Oryzon at that time). In December 2016, Oryzon reported supportive preliminary efficacy results from this trial at the ASH conference, which was a major milestone. In parallel, Roche, which was responsible for the global development of ORY-1001, initiated a clinical trial in SCLC.

In July 2017, Roche decided to discontinue the development of ORY-1001 and return the rights to Oryzon; according to Oryzon the decision was due to Roche reprioritising its portfolio and not driven by data. Oryzon regained the rights from Roche for ORY-1001 in January 2018 and reiterated its plans to continue the development of ORY-1001 in both clinical-stage indications. Oryzon also mentioned that around the time when ORY-1001 was out-licensed to Roche in April 2014, it was contacted by several other companies interested in epigenetic programmes in oncology. In our view, this suggests the company could potentially replace Roche with another partner interested in epigenetics and LSD1 inhibition.

Oryzon has now resumed the development in both AML and SCLC (requests for clinical trial authorisation submitted). Oryzon initially expects to start a Phase IIa study in SCLC and a follow-on Phase IIa in AML in H218. The Phase IIa ALICE study will recruit elderly AML patients who will receive ORY-1001 in combination with azacitidine. Part 1 will explore the recommended dose, while Part 2 will evaluate initial clinical activity. The Phase IIa CLEPSIDRA trial will recruit relapsed, extensive-stage disease SCLC patients who will receive ORY-1001 in combination with platinum-etoposide chemotherapy. Oryzon will use biomarkers to select more precise patient population. Similarly, Part 1 will establish recommended dose, while Part 2 will evaluate clinical activity. Interim results from both studies are expected in 2019.

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 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.
- 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.

Following ASH and once the final results were available, the company has reported that from all patients in the study, anti-leukaemic activity was observed in 29% of patients (12/41), including one CRi (complete remission with incomplete blood count recovery) in the dose finding part of the study. 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. More detailed analysis of ORY-1001's preclinical data can be found in our initiation report.

ORY-3001's first preclinical data in SCD

The precise indication for ORY-3001, a specific LSD1 inhibitor Oryzon's third asset, has not been disclosed yet, only that it will be a non-oncological disease. However, in December 2017, the first published preclinical in vivo data on ORY-3001 revealed it could be effective in sickle cell disease

(SCD), which currently has no cure and has an adverse prognosis. SCD is a genetic disease where an adult gene for haemoglobin (a protein responsible for oxygen transport in red blood cells) is mutated, resulting in abnormal shaped red blood cells that resemble a sickle. This leads to anaemia as red blood cells are not able to pass through the smallest blood vessels, the capillaries. This results in vaso-occlusive crisis, acute or chronic pain, and decreased supply of oxygen to organs, which causes damage and many other symptoms. Currently there is no cure and only symptomatic treatment is used.

There two types of haemoglobin: foetal (HbF) and adult. While HbF represents most of haemoglobin in foetal life, it drops to <1% in normal adults and is found in a few F-cells. The purpose of this study was to investigate whether ORY-3001 has the potential to increase HbF, which could replace the function of the mutated adult Hb. The results showed that oral administration of ORY-3001 increased HbF 10-fold in SCD transgenic mice. So called F reticulocytes (young red blood cells containing HbF) increased 300%. In baboons, F-reticulocytes increased 8-fold. As a next step Oryzon indicated it might continue the development of ORY-3001 for SCD, although no specific details were announced.

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 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 8). Second-generation compounds can be broadly classified into demethylase inhibitors, methyltransferase inhibitors and bromodomain and extra-terminal (BET) inhibitors or acetyl lysine readers. Methyl lysine readers 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. It also has programmes in neurodegenerative diseases, while the majority of peers are focused on oncology.

It is worth noting that epigenetics company Constellation Pharmaceuticals is undergoing an IPO process. The company aims to raise $80m by offering 5.3m shares at a price range of $14-16. At the midpoint, Constellation's market capitalisation would be $430m on a fully diluted basis. The company's main asset is CPI-1205, an EZH2 inhibitor, being explored in two Phase Ib/II trials in metastatic castration resistant prostate cancer and solid tumours in combination with ipilimumab or pembrolizumab. Another asset CPI-0610, BET inhibitor is being tested in Phase II trial in myelofibrosis.

Exhibit 8: 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	Interim data from mesothelioma trial and relapsed/refractory follicular lymphoma reported at ASCO 2018.
Constellation Pharmaceuticals	CPI-1205, EZH2 inhibitor	Phase Ib/II trials	Metastatic castration resistant prostate cancer; Solid tumours;	Recruiting patients. Solid tumour trial explores CPI-1205 in combination with ipilimumab or pembrolizumab.
Histone demethylase inhibitors				
Incyte	INCB59872 LSD1 inhibitor	Phase I/II trials	r/r Ewing sarcoma Sickle cell disease Advanced malignancies	Recruiting patients
Imago BioSciences	IMG-7289 LSD1 inhibitor	Phase I/II trials	Advanced myeloid malignancies Myelofibrosis	Recruiting patients
GlaxoSmithKline	GSK2879552, LSD1 inhibitor	Phase I/II trials	Acute myeloid leukaemia Myelodysplastic syndrome	Recruiting patients
Celgene	CC-90011 LSD1 inhibitor	Phase I trials	Solid tumours and non-Hodgkin's lymphomas	Recruiting patients
BET inhibitors				
GlaxoSmithKline	GSK525762, BET inhibitor	Phase I/I trials	Solid tumours and haematological malignancies	Several Phase I/II trials in different stages in solid tumours and haematological malignancies
Constellation Pharmaceuticals	CPI-0610, BET inhibitor	Phase II	Myelofibrosis	Recruiting patients
Incyte Corporation	INCB054329, BET inhibitor	Phase I trials	Advanced malignancies including advanced solid tumours or leukaemia, MM	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 trials	Solid tumours and lymphomas	Three separate Phase I trials
Roche	RO6870810, BET inhibitor	Phase I trials	Solid tumours and haematological malignancies	Several Phase I trials at different stages

Source: Edison Investment Research, Oryzon Genomics, BioCentury, EvaluatePharma, clinicaltrials.gov.

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. We believe ORY-1001 has not been compromised and Roche's decision was based on the perspective of portfolio management. Oryzon is continuing the development on its own and we believe a new partner will have to come on board before ORY-2001 enters large-scale Phase III studies, the timing of which is difficult to forecast. ORY-2001 will also need to be partnered, as later-stage studies in CNS indications can be very costly due to large populations. However, Oryzon has enough cash to progress ORY-2001 through mid-stage development to reach meaningful data. We have assumed a deal in our valuation after Phase II for both assets, but we have limited visibility on the timing and terms. Future pricing and market dynamics are hard to predict, especially if competitors are successful. Oryzon is in a comfortable cash position to finance operations to early 2020. Future financing needs will depend on the scale of operations with preclinical candidates, the progress with ORY-2001 and ORY-1001 and any potential revenues from partnerships.

Financials and valuation

We maintain our financial estimates following our last revision after the Q118 results, which were largely in line with expectations. Our R&D cost estimates stand at €8.5m for FY18 and €9.5m for FY19, which are the main cost drivers. The reported Q118 cash position was €30.9m (cash and

short-term investments; net cash €9.2m). Our model suggests this should be sufficient to reach 2020.

As Oryzon is on track to develop its assets in all the indications we include in our valuation, we leave our assumptions unchanged. As discussed above, we will revisit ORY-2001 for neuropsychiatric disorders once more detail about the development pathway emerges after the basket trial data are announced. Our new valuation is €328m or €9.6 per share, marginally up from €322m or €9.4 per share due to rolling our model forward. Detailed discussion about assumptions is in our initiation and earlier outlook reports. The changes to ORY-1001's valuation after Roche's departure are described in our August 2017 report.

Exhibit 9: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
ORY-1001	AML	2023	927	262.4	15	48.0	1.4
ORY-1001	SCLC	2026	571	128.4	8	22.2	0.7
ORY-2001	AD	2026	4,510	957.6	15	148.3	4.3
ORY-2001	MS	2027	1,940	423.7	20	100.5	2.9
Net cash (last reported + term loans)				9.2	100	9.2	0.3
Valuation				**1,781.4**		**328.2**	**9.6**

Source: Edison Investment Research

Exhibit 10: Financial summary

€000s	2014	2015	2016	2017	2018e	2019e
December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS						
Revenue	15,536	7,185	5,009	4,317	7,034	6,301
Cost of Sales	0	0	0	0	0	0
Gross Profit	15,536	7,185	5,009	4,317	7,034	6,301
Research and development	(1,108)	(3,191)	(5,210)	(5,306)	(8,502)	(9,454)
EBITDA	11,659	688	(3,721)	(3,498)	(4,678)	(6,350)
Operating Profit (before amort. and except.)	(370)	11,398	11,398	448	(3,879)	(3,660)
Intangible Amortisation	(657)	(657)	(695)	(664)	(767)	(887)
Exceptionals	(4,617)	(24)	(4)	0	0	0
Other	0	0	0	0	0	0
Operating Profit	6,124	(233)	(4,578)	(4,324)	(5,556)	(7,348)
Exceptionals	667	(169)	(58)	0	0	0
Net Interest	(52)	(553)	(844)	(928)	(793)	(802)
Profit Before Tax (norm)	11,346	(105)	(4,724)	(4,588)	(5,582)	(7,263)
Profit Before Tax (reported)	6,739	(955)	(5,480)	(5,252)	(6,349)	(8,150)
Tax	(88)	(37)	32	55	0	0
Profit After Tax (norm)	11,258	(142)	(4,692)	(4,533)	(5,582)	(7,263)
Profit After Tax (reported)	6,651	(992)	(5,448)	(5,197)	(6,349)	(8,150)
Average Number of Shares Outstanding (m)	23.0	23.3	24.7	27.6	31.7	34.2
EPS - normalised (€)	0.48	(0.01)	(0.17)	(0.14)	(0.16)	(0.21)
EPS - (reported) (€)	0.29	(0.04)	(0.20)	(0.16)	(0.19)	(0.24)
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 (%)	75.0	9.6	N/A	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	16,059	18,050	21,269	24,914	31,070	36,373
Intangible Assets	12,928	15,188	18,810	22,458	28,725	34,139
Tangible Assets	981	854	696	638	527	417
Investments	2,150	2,008	1,763	1,818	1,818	1,818
Current Assets	9,999	22,681	28,475	36,130	24,013	10,366
Stocks	9	4	8	7	8	8
Debtors	704	940	978	857	517	687
Cash	3,633	19,467	22,028	34,950	23,488	9,671
Other	5,654	2,270	5,461	316	0	0
Current Liabilities	(3,969)	(5,296)	(7,597)	(8,696)	(9,084)	(8,890)
Creditors	(1,299)	(2,401)	(2,119)	(1,343)	(1,731)	(1,537)
Short term borrowings	(2,670)	(2,895)	(5,477)	(7,354)	(7,354)	(7,354)
Long Term Liabilities	(8,196)	(7,841)	(19,419)	(17,915)	(17,915)	(17,915)
Long term borrowings	(6,420)	(6,177)	(17,723)	(16,041)	(16,041)	(16,041)
Other long term liabilities	(1,776)	(1,664)	(1,696)	(1,874)	(1,874)	(1,874)
Net Assets	13,893	27,594	22,729	34,432	28,083	19,933
CASH FLOW						
Operating Cash Flow	12,178	1,076	(4,536)	(4,281)	(4,621)	(7,393)
Net Interest	(52)	(553)	(471)	(426)	(793)	(802)
Tax	0	0	0	0	0	0
Capex	0	0	(28)	(105)	0	0
Acquisitions/disposals	798	0	0	0	0	0
Financing	0	14,725	287	16,887	0	0
Other*	(9,579)	605	(6,819)	653	(6,048)	(5,622)
Dividends	0	0	0	0	0	0
Net Cash Flow	3,345	15,853	(11,567)	12,728	(11,462)	(13,817)
Opening net debt/(cash)	8,803	5,458	(10,395)	1,172	(11,555)	(93)
HP finance leases initiated	0	0	0	0	0	0
Other	0	0	0	0	0	0
Closing net debt/(cash)	5,458	(10,395)	1,172	(11,555)	(93)	13,724

Source: Edison Investment Research, Oryzon Genomics accounts. Note: Oryzon reports in Spanish GAAP. *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	Chief scientific officer: 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 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.
CFO: 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 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 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.
Chief medical officer: Roger Bullock	**Chief intellectual property officer: Neus Virgili**
Dr. Bullock completed his medical training at Keble College, Oxford University, gaining a BA (Hons) in Physiological Sciences. This was followed by clinical medical training at St Bartholomew's Hospital in London where he gained the MB.BS. Later on he specialized in psychiatry, gained membership of The Royal College of Psychiatry and undertook postgraduate psychiatric training including higher specialist training in geriatric psychiatry which concluded in 1993. Dr. Bullock is considered a world KOL in the space of neurodegenerative diseases. He has extensive experience as clinical researcher, having participated in more than 70 clinical trials in Alzheimer's disease and other CNS conditions.	Ms Virgili is a qualified European patent attorney with 20 years of experience as in the pharmaceutical sector. She also holds B.Sc. in organic chemistry from the University of Barcelona, Spain. She started her career in 1991 in J. Uriach y Compañía (Grupo Uriach), where she set up the Patent Department. In 2006 she joined Palau Pharma, as Head of the patent department. In September 2011, she joined Oryzon as Chief intellectual property officer.

Principal shareholders	(%)
Carlos Buesa	10.96
Tamara Maes	10.96
Jose Ventura Ferrero	5.87
Josep Maria Echarri	3.01
Solventis Gestion	2.84

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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