EDISON

Oryzon Genomics

Q418 update

A year of data readouts

Pharma & biotech

Oryzon has a total of five Phase II studies ongoing with its two lead assets iadademstat (formerly ORY-1001) and vafidemstat (formerly ORY-2001), which are all expected to have preliminary data readouts in 2019. In November 2018, the company announced the first patients had been recruited in to the iadademstat Phase IIa small cell lung cancer (CLEPSIDRA) and acute myeloid leukaemia (ALICE) studies. A scientific paper was recently published by a third party in Science Signalling, which has revealed a potential mechanism of action of iadademstat (ORY-1001) in pre-clinical SCLC models; this is supportive to Oryzon's ongoing Phase II study in SCLC. Our valuation is slightly higher at €364m or €9.3/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/17	4.3	(4.6)	(0.14)	0.0	N/A	N/A
12/18	6.8	(3.7)	(0.03)	0.0	N/A	N/A
12/19e	6.1	(6.8)	(0.17)	0.0	N/A	N/A
12/20e	6.1	(6.8)	(0.17)	0.0	N/A	N/A

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

All Phase II studies now ongoing, waiting for data

With the first patients now recruited into the new iadademstat Phase IIa SCLC (CLEPSIDRA) and AML (ALICE) studies, all Phase II studies have now commenced and recruitment is progressing. The first preliminary readouts will come in Q219 from the ongoing vafidemstat REIMAGINE study (likely at the European Congress of Psychiatry in early April 2019), iadademstat CLEPSIDRA study (likely at ASCO in June 2019) and iadademstat ALICE study (likely at EHA in June 2019). This will be followed by further multiple readouts from the vafidemstat SATEEN and ETHERAL studies in H219.

Financials: Cash reach to late 2020

Oryzon reported an operating loss of €2.9m in 2018, compared to €4.3m in 2017, which was better than our expected €5.6m. This was mainly due to a combination of slightly lower capitalisation of R&D spend and lower R&D expenses of €7.4m in 2018 vs our expected €8.5m (Oryzon reports using local GAAP and capitalised R&D costs are included as income in EBIT, which was €6.8m in 2018). Oryzon had cash and cash equivalents of €34.5m at the end of Q418 and our fine-tuned total operating loss estimates for 2019 and 2020 are €6.2m and €6.3m, respectively. The y-o-y increase from FY18 is mainly due to more intensive R&D activities expected as the pipeline matures. According to our model, cash reaches in well into H220, in line with management's guideline (Q420).

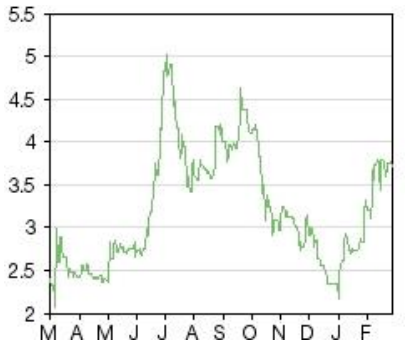
Valuation: €364m or €9.3/share

Our valuation is up slightly at €364m or €9.3/share from €342m or €8.7/share due to rolling our model forward. The reported year-end cash position was €34.5m (cash and short-term investments; net cash €16.2m). Because Oryzon's clinical trials are progressing as planned across all indications, we leave our assumptions unchanged. Data readouts from the ongoing five clinical trials will provide multiple catalysts for the share price this year (detailed below).

27 February 2019

Price	**€3.71**
Market cap	**€145m**
	US$1.14/€
Net cash (€m) at end Q418	16.2
Shares in issue	39.1m
Free float	71%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	30.9	29.3	43.1
Rel (local)	30.3	27.4	53.5
52-week high/low		€5.0	€2.1

Business description

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

Next events

First readouts from Phase IIa study with vafidemstat in aggression	Q219
First readouts from Phase IIa studies with iadademstat in AML, SCLC	Q219
Preliminary readouts from Phase IIa studies with vafidemstat in AD and MS	H219

Analysts

Jonas Peciulis +44 (0)20 3077 5728

Alice Nettleton +44 (0)20 3077 5700

healthcare@edisongroup.com

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Maturing R&D pipeline

Exhibit 1: Oryzon's R&D pipeline

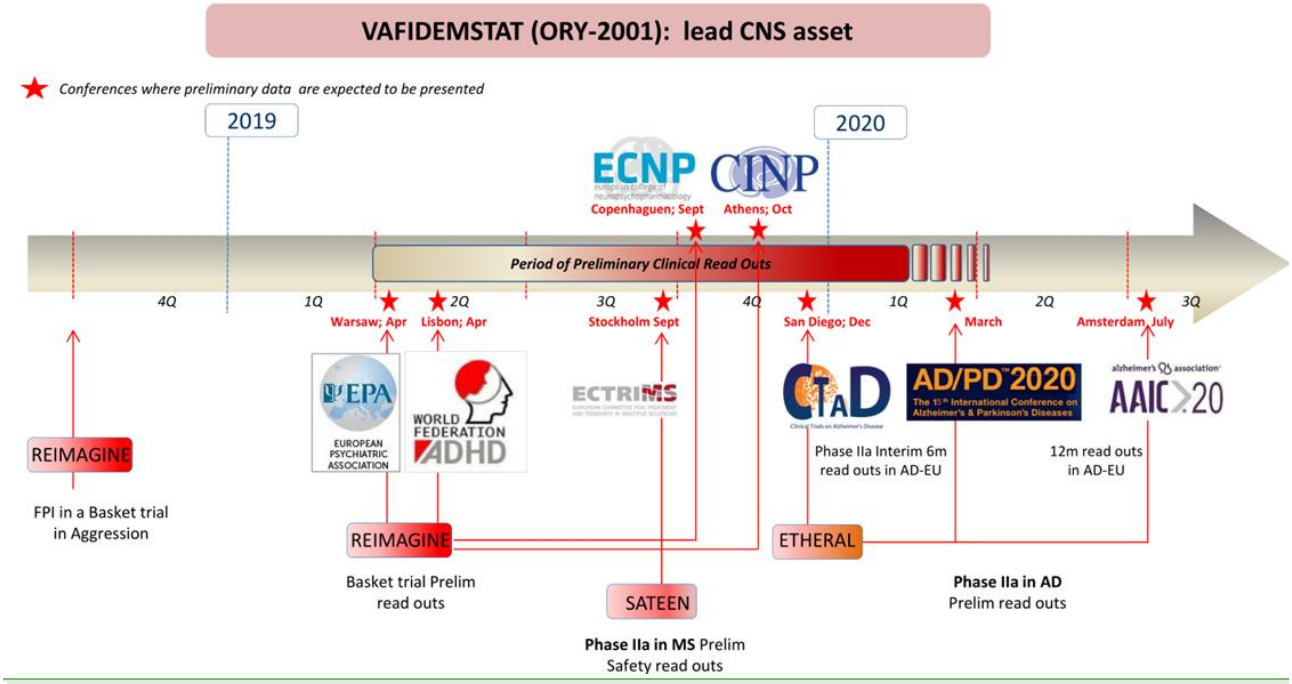
Product	Indication and stage	Mechanism of action	Notes
Iadademstat (ORY-1001)	■ **AML**, Phase IIa ALICE trial in combination with azacitidine ■ **SCLC**, Phase IIa CLEPSIDRA trial in combination with platinum-etoposide	Small molecule LSD1 inhibitor - LSD1 is a histone eraser enzyme that removes methyl groups	■ Oryzon reported supportive Phase I/IIa data in acute leukaemia at the ASH conference in December 2016. ■ Two new Phase IIa trials have been initiated in AML (ALICE) and SCLC (CLEPSIDRA). **First readouts from both trials expected in late Q219.**
Vafidemstat (ORY-2001)	■ **AD**, Phase IIa ETHERAL trial, monotherapy ■ **MS**, Phase II SATEEN trial, monotherapy ■ **Aggression**, Phase IIa REIMAGINE trial, monotherapy	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 (SATEEN) and AD (ETHERAL). **Preliminary readouts expected in H219.** ■ Basket trial REIMAGINE in aggression in several neuropsychiatric disorders initiated. **Preliminary readout expected Q219, followed by more readouts throughout 2019.**
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. Successfully completed regulatory toxicology.

Source: Edison Investment Research, Oryzon Genomics;

Vafidemstat: Preliminary readouts from aggression basket trial start in Q219

The first preliminary data readouts in 2019 will be from the REIMAGINE basket aggression trial with vafidemstat (ORY-2001), the lead CNS asset a dual LSD1/MAOB inhibitor. According to Oryzon's updated R&D newsflow (Exhibit 2), there will be several sequential preliminary readouts from the trial starting in Q219 (potentially at the European Congress of Psychiatry in Warsaw on 6–9 April 2019) and throughout the year. The single-arm, open-label study is being carried out at the Hospital Vall d'Hebrón in Barcelona and is enrolling at least six patients per indication: Alzheimer's disease, 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 Q119. The main goal is the assessment of reduction in aggression.

Exhibit 2: Vafidemstat near-term catalysts



Source: Oryzon

The REIMAGINE trial with vafidemstat is a so-called basket trial (Exhibit 3 details the study design), which employs an innovative design borrowed from drug development in oncology. Aggression is often seen in a variety of neurodegenerative and neuropsychiatric conditions and vafidemstat has demonstrated holistic effects in this regard in preclinical models (for a more detailed overview see our outlook report).

For now precise details about what kind of data will be released have not been disclosed, but the rationale of the trial is to look for signals of efficacy in one or more indication, then decide which setting in psychiatry is best suitable for more advanced trials. Once the data are released and further development is clarified, we will revisit our ORY-2001 valuation model, potentially adding indications beyond current ones Alzheimer's disease and multiple sclerosis.

Exhibit 3: Oryzon's vafidemstat (ORY-2001) REIMAGINE study (Eudra CT number: 2018-002140-88)

Summary design	A single centre, open-label, one-arm, eight-week study to evaluate the efficacy, safety and tolerability of ORY-2001 in aggression in adult population with Alzheimer's disease (AD), Lewy Body Dementia (LBD), Adult attention Deficit Hyperactivity Disorder (ADHD) Borderline Personality Disorder (BPD), Autism Spectrum Disorder (ASD)
Treatment groups	Treatment arm: vafidemstat 1.2mg (Single arm, no placebo control)
Endpoints	Primary endpoints: Safety endpoints including, vital signs, ECG parameters, clinical laboratory parameters Secondary endpoints: Efficacy endpoints including change from baseline/over time in relevant neurological endpoints for each patient group (NPI, MMSE, ADHD-RS, ADOS, BPDCL)
Key inclusion criteria	■ Significant or persistent agitation or aggression that was disruptive to patient's daily living or put the patient at risk of harm for at least three days per week for at least four weeks prior to screening visit. ■ Stable pharmacological treatment as per SmPC of AD, LBD, ADHD, BPD or ASD for at least four months (with the same dose for at least two months) prior to screening – including anti-inflammatories.
Sites	Hospital Vall d'Hebrón, Barcelona
Timelines	Study start: October 2018, last patient out: Q119

Source: EU Clinical Trials Register, Oryzon. Notes: TEAE: Treatment Emergent Adverse Events; NPI: Neuropsychiatric Inventory Questionnaire; MMSE: Mini-Mental State Examination; ADHD-RS: Attention-Deficit/Hyperactivity Disorder Rating Scale; ADOS: Autism Diagnostic Observation Schedule; BPDCL: Borderline Personality Disease Checklist.

Data from vafidemstat in AD and MS also expected this year

Two other Phase IIa trials with ORY-2001 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 preliminary data readouts from both studies are expected in Q319 and Q419 (Exhibit 2).

Iadademstat: First preliminary data readouts from ALICE and CLEPSIDRA trials likely in Q219

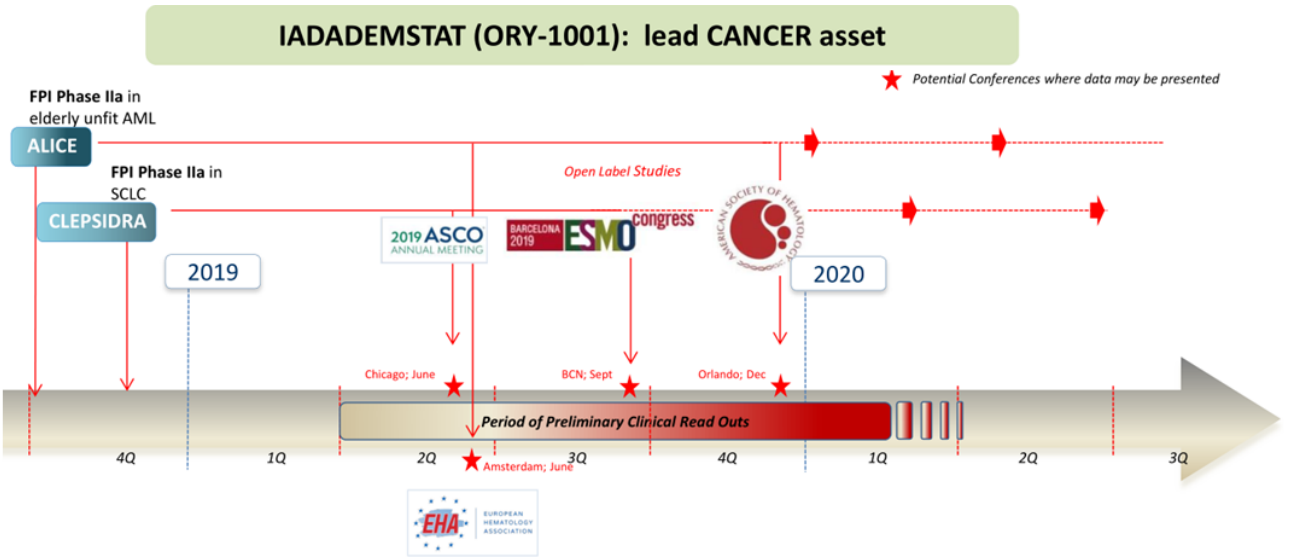
Two Phase IIa studies with iadademstat, a specific LSD1 inhibitor, are ongoing. The Phase IIa ALICE study will recruit elderly AML patients (n=36) who will receive ORY-1001 in combination with standard of care, azacitidine. The other Phase IIa CLEPSIDRA trial will recruit relapsed SCLC patients (n=36) who will receive iadademstat in combination with platinum-etoposide chemotherapy. Interim results from both studies are expected in 2019 with the first significant presentations likely to be first data from the CLESPIDRA study at the ASCO conference (31 May - 4 June 2019 and) the ALICE study at the EHA conference (13 June - 16 June 2019).

One of the main goals of these trials is to understand how iadademstat works in combination with various other drugs. To this end, an article published in Cell by a third-party research team at Harvard Medical School described the findings that inhibiting LSD1 could lead to the activation of immune response and overcome resistance to anti-PD-1 therapy. We reviewed key data on iadademstat and the article in Cell in our last outlook report.

Most recent relevant third party publication (Augert *et al*) provided more insights about the mechanism of action of iadademstat in SCLC. While the drug was shown to be effective in SCLC models before, the details of actual mechanism of action were still missing. The team of researchers from Fred Hutchinson Cancer Research Center and the Department of Genome Sciences, University of Washington (Seattle, WA, US) found that selective inhibition of LSD1 with iadademstat activated the NOTCH pathway, resulting in the suppression of the transcription factor ASCL1. This in turn suppressed SCLC development. *In vivo* patient-derived xenograft (PDX) models showed that there was a correlation between extent of NOTCH pathway activation and suppression of the tumour growth. Furthermore, complete and durable tumor regression occurred using iadademstat in a chemoresistant PDX model.

The NOTCH signalling pathway is a highly conserved cell system present in most multicellular organisms. The transcription factor ASCL1 appears to play an important role in SCLC development, but it is not suitable as a target for classical drug development, ie not “druggable”, while iadademstat appears to achieve that through activation of NOTCH and now has a demonstrated proof-of-concept in *in vivo* models.

Exhibit 4: Iadademstat near-term catalysts



Source: Oryzon

Valuation

Our valuation is slightly higher at €364m or €9.3 per share (from €342m or €8.7/share per share) due to rolling our model forward. As Oryzon is on track to develop its assets in all the indications we include in our valuation, we leave our assumptions unchanged. Since cash reaches well into H220, the existing cash is sufficient to deliver meaningful data from all ongoing trials.

Exhibit 5: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
Iadademstat (ORY-1001)	AML	2023	927	284.1	15%	56.3	1.4
Iadademstat (ORY-1001)	SCLC	2026	571	137.6	8%	25.2	0.6
Vafidemstat (ORY-2001)	AD	2026	4,510	1,018.3	15%	160.5	4.1
Vafidemstat (ORY-2001)	MS	2027	1,940	446.6	20%	105.8	2.7
Net cash (end-2018)				16.2	100%	16.2	0.4
Valuation				**1,902.8**		**364.0**	**9.3**

Source: Edison Investment Research

Exhibit 6: Financial summary

€'000s	2016	2017	2018	2019e	2020e
December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS					
Revenue	5,009	4,317	6,781	6,119	6,137
Cost of Sales	0	0	0	0	0
Gross Profit	5,009	4,317	6,781	6,119	6,137
Research and development	(5,210)	(5,306)	(7,412)	(9,454)	(9,560)
EBITDA	(3,721)	(3,498)	(2,766)	(6,046)	(6,175)
Operating Profit (before amort. and except.)	(3,879)	(3,660)	(2,905)	(6,186)	(6,314)
Intangible Amortisation	(695)	(664)	(7)	(8)	(9)
Exceptionals	(4)	0	(4)	0	0
Other	0	0	0	0	0
Operating Profit	(4,578)	(4,324)	(2,916)	(6,194)	(6,324)
Exceptionals	(58)	0	0	0	0
Net Interest	(844)	(928)	(796)	(586)	(471)
Profit Before Tax (norm)	(4,724)	(4,588)	(3,701)	(6,771)	(6,786)
Profit Before Tax (reported)	(5,480)	(5,252)	(3,712)	(6,780)	(6,795)
Tax	32	55	2,535	0	0
Profit After Tax (norm)	(4,692)	(4,533)	(1,166)	(6,771)	(6,786)
Profit After Tax (reported)	(5,448)	(5,197)	(1,177)	(6,780)	(6,795)
Average Number of Shares Outstanding (m)	27.6	31.7	34.6	39.1	39.1
EPS - normalised (€)	(0.17)	(0.14)	(0.03)	(0.17)	(0.17)
EPS - reported (€)	(0.20)	(0.16)	(0.03)	(0.17)	(0.17)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	21,269	24,914	31,786	37,758	43,807
Intangible Assets	18,810	22,458	29,330	35,441	41,569
Tangible Assets	696	638	665	526	447
Investments	1,763	1,818	1,791	1,791	1,791
Current Assets	28,475	36,130	35,664	16,488	3,856
Stocks	8	7	135	71	103
Debtors	978	857	971	914	943
Cash	22,028	34,950	34,320	15,264	2,572
Other	5,461	316	239	239	239
Current Liabilities	(7,597)	(8,696)	(10,441)	(4,017)	(4,229)
Creditors	(2,119)	(1,343)	(2,192)	(1,767)	(1,979)
Short term borrowings	(5,477)	(7,354)	(8,249)	(2,249)	(2,249)
Long Term Liabilities	(19,419)	(17,915)	(11,884)	(11,884)	(11,884)
Long term borrowings	(17,723)	(16,041)	(9,977)	(9,977)	(9,977)
Other long term liabilities	(1,696)	(1,874)	(1,907)	(1,907)	(1,907)
Net Assets	22,729	34,432	45,125	38,345	31,550
CASH FLOW					
Operating Cash Flow	(4,536)	(4,281)	(2,799)	(6,936)	(6,495)
Net Interest	(471)	(426)	2,133	(586)	(471)
Tax	0	0	0	0	0
Capex	(28)	(105)	(170)	0	0
Acquisitions/disposals	0	0	0	0	0
Financing	287	16,887	11,949	0	0
Other*	(6,819)	653	(6,576)	(5,534)	(5,726)
Dividends	0	0	0	0	0
Net Cash Flow	(11,567)	12,728	4,538	(13,055)	(12,692)
Opening net debt/(cash)	(10,395)	1,172	(11,555)	(16,093)	(3,038)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	1,172	(11,555)	(16,093)	(3,038)	9,655

Source: Edison Investment Research, Oryzon Genomics accounts. Note: Oryzon reports in Spanish GAAP. *Includes cash outflows related to development costs that were capitalised.

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1,185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia