EDISON

Oryzon Genomics

R&D results

More data support vafidemstat for aggression

Pharma & biotech

On 3 April 2020, Oryzon reported interim data for the first time from its two Phase IIa trials REIMAGINE-AD and ETHERAL. Both explore the company's lead CNS asset vafidemstat (CNS-optimised LSD1 inhibitor) in Alzheimer's disease (AD) patients, but in different disease subgroups and for different purposes. The REIMAGINE-AD study is focused on vafidemstat's potential to control agitation and aggression seen in moderate to severe AD patients. The reported data was positive and echoed the findings from the other patient cohorts in the original REIMAGINE trial reported last year. Data from the ETHERAL trial are preliminary with interesting biomarker findings, but the clinical effect on patient cognition was not seen yet after six months of treatment (12-month treatment data should be available in Q221). Our valuation is marginally higher at €470m or €10.3 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	6.8	(3.7)	(0.03)	0.0	N/A	N/A
12/19	10.3	(4.6)	(0.09)	0.0	N/A	N/A
12/20e	9.9	(4.7)	(0.07)	0.0	N/A	N/A
12/21e	9.9	(4.2)	(0.06)	0.0	N/A	N/A

Note: *Normalised, excluding amortisation of acquired intangibles and exceptional items.

More support for vafidemstat in agitation-aggression

Oryzon has developed a broad R&D programme for vafidemstat and is targeting a range of neurological disorders. Vafidemstat's positive effects on agitation-aggression in REIMAGINE trials seem to be very consistent across different scales and in all patient groups. In our view, the main achievement by Oryzon within its CNS programme to date is the identification that agitation and aggression seems to be the common denominator in all these different conditions, which can be improved with vafidemstat. As opposed to targeted therapies, like monoclonal antibodies for cancer, the effects of an intervention with an epigenetic drug like vafidemstat are not straightforward to predict. The emerging evidence that vafidemstat can help control aggression could turn out to be the key breakthrough in its development.

Phase IIa ETHERAL preliminary data; more to come

Some interesting biomarker data from this trial provided evidence that vafidemstat has an effect on the pathophysiological processes of the Alzheimer's disease. Ultimately Oryzon will have to prove that this translates into clinical effect, ie some lasting symptomatic effect or disease modifying effect in AD patients. The released results did not show that yet, but Oryzon pointed out that this is preliminary data from six months of treatment and more mature data will be reported.

Valuation: €470m or €10.3 per share

Our valuation is marginally higher at €470m or €10.3 per share due to rolling our model forward. We make no changes to our rNPV for the time being, as we have already included borderline personality disorder (BPD) in our model to reflect vafidemstat's potential in aggression and agitation. We may add further indications if Oryzon proceeds with Phase IIb trials. We have also previously included vafidemstat for mild to moderate AD in our valuation and make no changes based on the preliminary findings in the ETHERAL trial, as more mature data are needed.

14 April 2020

Price	**€2.70**
Market cap	**€124m**
Net cash (€m) at end FY19	21.9
Shares in issue	45.8m
Free float	70%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	6.1	(3.4)	(3.3)
Rel (local)	5.0	(8.6)	(23.0)
52-week high/low		€4.4	€1.6

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

Potential start of Phase IIb PORTICO trial with vafidemstat in aggression in BPD. Timeline to be confirmed after the extent of COVID-19 pandemic is known	2020
Updated data from iadademstat Phase IIa CLEPSIDRA in SCLC	2020
Updated data from iadademstat Phase IIa ALICE in AML 2020	2020

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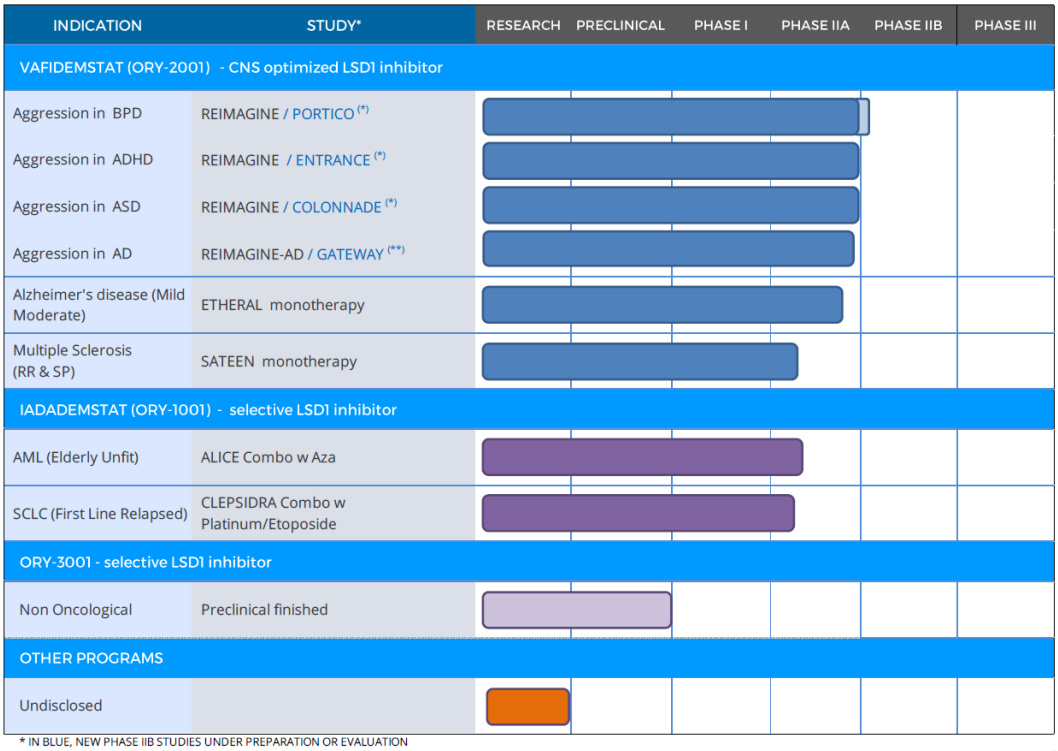
Edison profile page

Vafidemstat R&D update

Oryzon has developed a broad R&D programme for its lead CNS-optimised LSD1 inhibitor vafidemstat and is targeting a range of neurological disorders (Exhibit 1). The newer Phase IIa REIMAGINE and REIMAGINE-AD projects are exploring vafidemstat's potential in managing aggression in four separate patient cohorts: borderline personality disorder (BPD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and moderate-to-severe Alzheimer's disease (AD). Two earlier Phase IIa trials are testing vafidemstat in mild-to-moderate AD (ETHERAL) and multiple sclerosis (SATEEN).

Data from the three REIMAGINE cohorts have been reported throughout 2019 and were promising enough for Oryzon to start planning Phase IIb trials in these indications (Exhibit 1; more details in our recently published outlook report). On 3 April 2020, Oryzon reported interim data for the first time from the REIMAGINE-AD and ETHERAL trials. The Advances in Alzheimer's and Parkinson's Therapies (AAT-AD/PD) 2020 meeting was held in an entirely virtual format due to the COVID-19 pandemic with presentations available online.

Exhibit 1: Oryzon's R&D pipeline



Source: Oryzon. Note: PORTICO trial is at an advanced stage of preparation; other trials that will follow the REIMAGINE study are at the planning stage.

REIMAGINE-AD

As with other patient cohorts in the original REIMAGINE trial (ASD, ADHD and BPD) the key endpoints in the REIMAGINE-AD study are focused on vafidemstat's potential to control agitation and aggression seen in moderate to severe AD patients. This open-label, single-arm trial recruited 12 patients. Initially the study was planned to run for 13 weeks, a similar period to the original REIMAGINE trial, but later it was extended to 24 weeks to better assess the effects on memory (not the primary endpoint, however). One patient withdrew consent during the first two months of treatment. Nine patients completed four months of treatment and seven patients completed six

months. As in the other REIMAGINE cohorts, Oryzon used a variety of different neuropsychiatric scales:

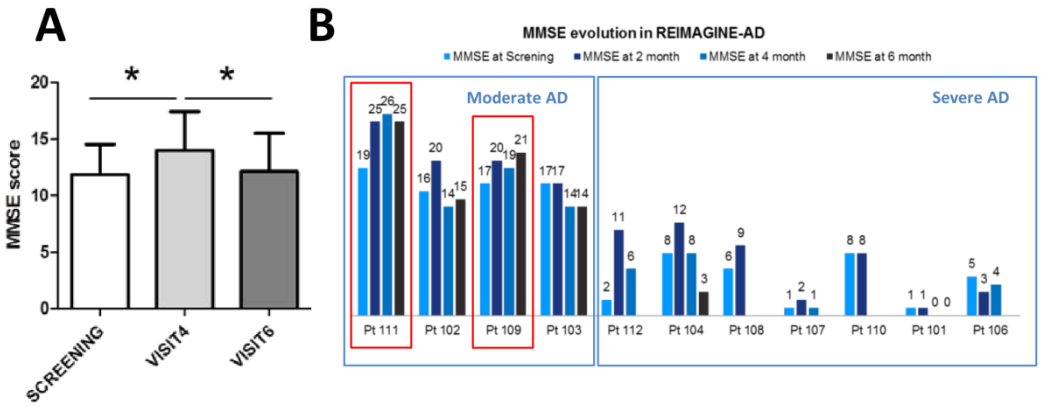
- Agitation and aggression was assessed using:
  - the Clinical Global Impression Improvement (CGI-I) scale,
  - the Cohen-Mansfield Agitation Inventory (CMAI) scale, and
  - the NPI four-item Agitation/Aggression subscale.
- Overall patient functioning was assessed using:
  - global improvement on the Neuropsychiatric Inventory (NPI) total score, and
  - global improvement on the caregiver burden as measured by the Zarit Caregiver Burden Interview (ZBI) scale.

Results showed that after six months of treatment with vafidemstat a statistically significant improvement ($p<0.05$) was seen on all these scales in patients who completed the treatment. In addition, the 1.2mg dose was confirmed to be safe and well tolerated. These results are similar to those seen in other indications from the original REIMAGINE trial.

Memory loss is a key symptom in AD. Although vafidemstat's effect on memory was not the primary goal in the REIMAGINE-AD trial, Oryzon did evaluate 11 patients' MMSE scores (Mini-Mental State Exam, the most common method to evaluate memory). After the completion of two months of treatment, seven patients had improved their MMSE scores, three patients had stable scores and one worsened. The improvement, however, was not maintained after four and six months of treatment (Exhibit 2A). Two of the four moderate AD patients (Exhibit 2B red boxes) demonstrated consistently better scores during the treatment. Oryzon decided to extend the treatment of these two patients to 12 months.

Given the small numbers it is difficult to come to any firm conclusion on vafidemstat's effect on memory, but in AD research the general notion is that once the disease progresses to severe stage, memory impairment is advanced and likely irreversible. Since this trial focused on aggression, the severe AD patients were the appropriate target patient population in this trial. The prevalence of agitated and aggressive behaviour increases as AD severity increases. The MMSE assessment was exploratory and it is interesting to see that two out of four patients in the moderate AD group seemed to benefit in terms of memory improvement. These two patients continue the treatment, so some follow up data could still be reported from this trial.

Exhibit 2: MSSE scores in REIMAGIE-AD study



Source: Oryzon.

Our view

Vafidemstat's effects on agitation and aggression in REIMAGINE-AD were in line with those reported from the other cohorts in the original REIMAGINE trial. The improvement seems to be very

consistent across different scales. We note that by now Oryzon has accumulated data sets from a very diverse group of patients with neuropsychiatric or neurodegenerative diseases. Even within the same indication, for example BPD, the clinical picture of a patient can vary drastically from one subject to another. In our view, the main achievement by Oryzon in its CNS programme is the identification that agitation and aggression seems to be the common denominator in all these different conditions, which can be improved with vafidemstat. Vafidemstat is the most advanced epigenetic drug in development for CNS diseases. As opposed to targeted therapies, like monoclonal antibodies for cancer, an intervention with an epigenetic drug can have profound effects on biology. The emerging evidence that vafidemstat can help control aggression could turn out to be the key breakthrough in its development.

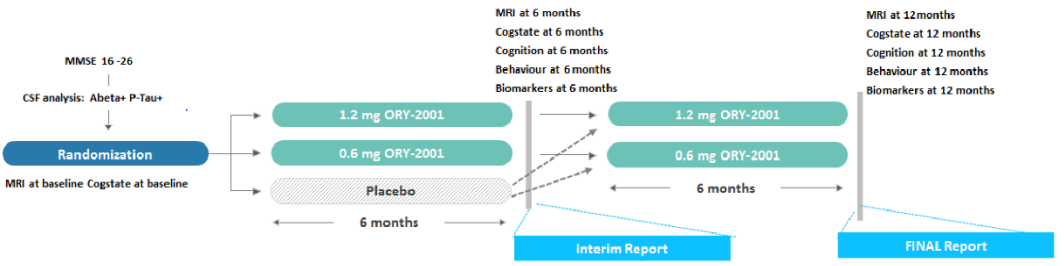
Next steps

As this was a Phase IIa stage study, it recruited a relatively small number of patients, like the other cohorts from the REIMAGINE trial. The next step is to start a larger Phase IIb stage study. Since the results were consistently positive across all indications, Oryzon can prioritise the indications that are most lucrative from a commercial point of view (borderline personality disorder is likely and we include it in our valuation). Oryzon planned to initiate a Phase IIb trial with vafidemstat in aggression in BPD as the first indication, but this will likely be somewhat delayed because of the ongoing COVID-19 pandemic (more details in Financials section below). We expect updates from Oryzon about the next steps in due course.

ETHERAL

The Phase IIa ETHERAL is a randomised, double-blind, three-arm trial (placebo, low dose 0.6mg and high dose 1.2mg) that enrolled mild to moderate AD patients in Europe and the US. After the randomisation the patients are treated for 24 weeks. This is then followed by a 24-week extension when the placebo patients are randomised to receive vafidemstat. The primary goals of the study are safety/tolerability, while secondary endpoints include initial efficacy (cognition, agitation, apathy, depression, quality of life, volumetric MRI) and biomarker results. In total eight biomarkers are assessed including traditional CSF biomarkers, but also novel ones related to inflammation and neuronal damage.

Exhibit 3: Phase IIa ETHERAL study design



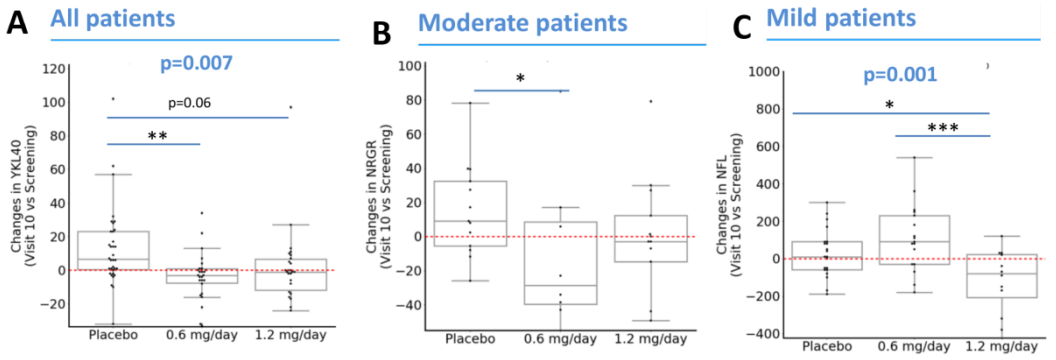
Source: Oryzon.

The recent presentation at the AAT-AD/PD 2020 described the preliminary six-month treatment data from the European part of the trial. In total, 117 patients were enrolled, of which 96 completed the six months of treatment. Drop outs were randomly distributed among the study arms, while seven patients were reported to have severe side effects. Of those seven, four patients, however, were in the placebo group, two in the low-dose vafidemstat group and one in the high-dose vafidemstat group. Such distribution shows that vafidemstat is not causing more side effects than placebo and again demonstrated good safety/tolerability profile. Other key results include:

- ADAS-Cog14 was used to assess the **cognition** (gold standard scale used in many AD trials). No statistically significant differences between the vafidemstat and placebo patients were observed after six months of treatment.

- **Biomarker** analysis delivered some interesting data. There were no differences in traditional CSF biomarker changes, such as Abeta and Tau. However, vafidemstat had an effect on the CSF levels of some of the novel biomarkers, specifically YKL40, neurogranin and plasma neurofilament light chain (NFL).
  - YKL40 is a biomarker of inflammation and was described to be elevated in AD patients. After 6 months of treatment a decrease in the CSF levels was observed (Exhibit 4A).
  - Neurogranin is a protein expressed primarily in the brain and considered a synaptic damage marker in neurodegenerative disorders. The changes between the groups did not reach statistical significance when considering all patients, but a trend to reduced CSF neurogranin levels was observed in vafidemstat treatment arms and statistical significance was achieved in the low dose arm in moderate patients (Exhibit 4B).
  - NFL has been proposed as a blood-based biomarker for neurodegeneration in AD. CSF NFL levels increased throughout the ETHERAL study in all three arms suggesting disease progression. In mild patients the treatment with a vafidemstat 1.2mg dose was able to reduce the increase of NFL (Exhibit 4C).

Exhibit 4: Selected biomarker data from Phase IIa ETHERAL study



Source: Oryzon.

Our view

The primary endpoint of safety and tolerability was achieved. This is important, as epigenetic drugs are known to suppress blood production process, but such an effect is typically seen in cancer treatments where the doses are much higher. Vafidemstat's use in any CNS diseases will likely be chronic, so a good safety profile is crucial.

Some interesting biomarker data provided evidence that vafidemstat has an effect of the pathophysiological processes of the disease. Ultimately, Oryzon will have to prove that this translates into a clinical effect, ie some lasting symptomatic effect or disease modifying effect in AD patients. The released data did not yet prove that, but Oryzon pointed out that this is preliminary data from six months of treatment and more mature data will be reported. The patients are receiving the treatment in the extension phase for another six months. In addition, there is a US study running in parallel. So, Oryzon should obtain much more mature data, which will help to inform how to design the efficacy trials later on. Final 12-month treatment data is expected in Q221.

More on biomarker data: Focus on YKL40

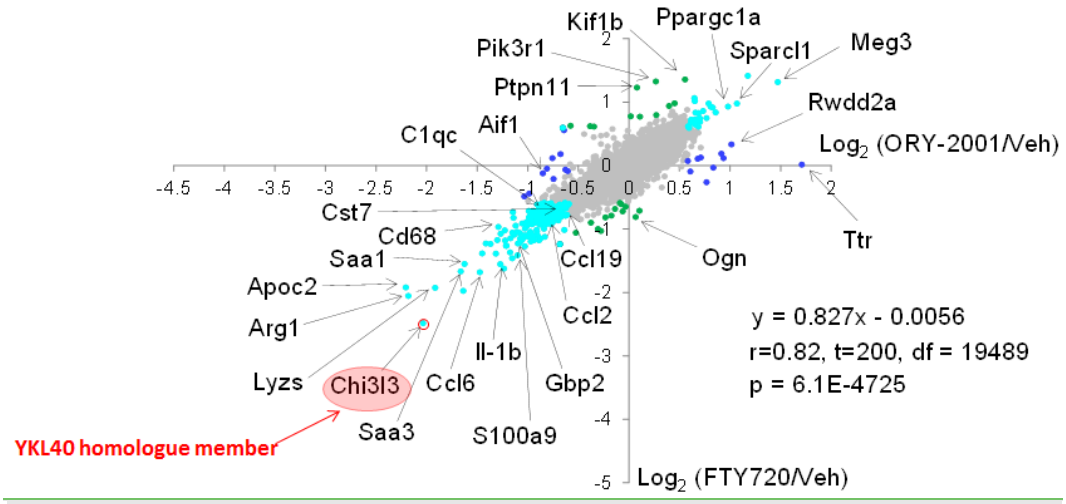
The ETHERAL is a Phase IIa trial, so it is fairly early stage and not designed to provide a definitive answer to whether the drug is clinically effective (this is addressed in Phase IIb/III trials). The ETHERAL trial is meant to explore the effects of vafidemstat in patients and to help inform the design of the subsequent trials. As a result, the biomarker results are the key data to be collected in this trial.

Overall biomarker results suggest that vafidemstat has a pharmacological effect in the brain at both doses in mild to moderate AD patients. YKL40 deserves special attention, as the interest in this biomarker in the AD context has grown significantly over the past several years (Muszyński et al, 2017). In animal studies, an increased expression of the mouse homologue member of the same YKL40 family has been observed in the brains of mice models of AD when compared to aged-matched controls (Colton et al, 2006). Increased expression of YKL40 was also found in brain samples obtained during autopsy of patients who had confirmed AD (Colton et al, 2006). YKL40 levels in CSF were also found to be significantly elevated in AD patients (Rosén et al, 2014 found a 77% increase compared to normal controls).

Oryzon also has its own preclinical data that demonstrates that vafidemstat has a specific effect on YKL40. In 2017 the company presented findings from one of its in vivo studies designed to test vafidemstat in multiple sclerosis (MS), one of the indications of interest for vafidemstat. The accepted animal model for MS is autoimmune encephalomyelitis (EAE). Vafidemstat was compared against fingolimod (Gilenya, Novartis) and the results showed that its anti-inflammatory effects were faster and stronger compared to fingolimod. We described these data in detail in our December 2017 report.

While the aim of that study was to collect more evidence and support the clinical trial in multiple sclerosis (Phase IIa STEEN study is currently ongoing), it also assessed gene expression changes. One of the genes assessed was the mouse homologue member of the YKL40 family. The expression of it was strongly induced in the EAE model when the animals developed the disease. When the animals were treated with vafidemstat, the expression of this biomarker was significantly reduced, especially in the spinal cord (among other improvements in encephalitis symptoms) (Exhibit 5). The new biomarker data from ETHERAL now show that vafidemstat can also lower the human version of YKL40.

Exhibit 5: Gene expression changes in the in vivo EAE model (vafidemstat vs fingolimod)



Source: Oryzon; ORY-2001 is vafidemstat, FTY720 is fingolimod

Financials: COVID-19 impact

Oryzon's total spending in 2019 was €14.1m, up from €9.7m in 2018 as the company has accelerated its clinical R&D. Cash was €35.1m at end-2019 (net cash €21.9m). We expect similar operating spending in 2020 and 2021, so its cash runway is to 2022. This is a relatively comfortable position given the ongoing volatility in the markets due to the COVID-19 pandemic, and will also allow Oryzon to deliver multiple catalysts from the ongoing trials.

With regards to the impact of the ongoing COVID-19 pandemic, Oryzon indicated that some delays with trials may be expected, as patient visits to clinical trial centres are currently restricted. However, to protect Oryzon from data loss, different measures are undertaken, such as remote patient assessment or reduction of site visits. The supply of Oryzon's lead drug candidates, vafidemstat and iadademstat, to patients is uninterrupted. The opening of new sites is restricted at the moment, so we do not expect Oryzon will initiate any studies in the coming weeks or months (the Phase IIb trial in BPD was close to starting). However, given the circumstances, a manageable trial delay is much more preferable to data loss, in our view. If some of the clinical trial work is delayed, Oryzon may be able to save on CRO costs, which will act as a mitigating factor.

Valuation

Our valuation is marginally higher at €470m or €10.3m per share due to rolling our model forward. We make no changes to our rNPV for the time being. To reflect vafidemstat's potential in the treatment of agitation and aggression in CNS patients we have already included BPD, as Oryzon indicated that this could be the first indication from the REIMAGINE cohorts to be included in Phase IIb stage trials. If more indications are confirmed to progress to Phase IIb, we will include them in our model as well. We have also included vafidemstat for mild to moderate AD in our valuation. Based on the preliminary findings in the ETHERAL trial we do not yet make any changes. More mature data is needed to understand vafidemstat's potential in this indication.

A detailed review of all of the company's ongoing programmes including upcoming catalysts can be found in our recent outlook report.

Exhibit 6: 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	307.9	15%	61.0	1.3
Iadademstat (ORY-1001)	SCLC	2026	571	149.1	8%	27.4	0.6
Vafidemstat (ORY-2001)	AD	2026	4,510	1,103.5	15%	173.9	3.8
Vafidemstat (ORY-2001)	MS	2027	1,940	483.9	20%	114.6	2.5
Vafidemstat (ORY-2001)	BPD	2027	1,290	300.2	20%	71.3	1.6
Net cash (end-2019)				21.9	100%	21.9	0.5
Valuation				**2,366.4**		**470.0**	**10.3**

Source: Edison Investment Research. Note: AML = acute myeloid leukaemia; SCLC = small cell lung cancer; AD = Alzheimer's disease; MS = multiple sclerosis; BPD = borderline personality disorder.

Exhibit 7: Financial summary

€000s	2018	2019	2020e	2021e
Year end 31 December	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS				
Revenue	6,781	10,278	9,857	9,857
Cost of Sales	0	0	0	0
Gross Profit	6,781	10,278	9,857	9,857
Research and development	(7,412)	(11,322)	(11,060)	(11,060)
EBITDA	(2,766)	(3,679)	(4,091)	(4,095)
Operating Profit (before amort. and except.)	(3,660)	(2,905)	(2,905)	(3,820)
Intangible Amortisation	(7)	(9)	0	0
Exceptionals	(4)	(11)	0	0
Other	0	0	0	0
Operating Profit	(2,916)	(3,839)	(4,225)	(4,225)
Exceptionals	0	0	0	0
Net Interest	(796)	(737)	(471)	0
Profit Before Tax (norm)	(3,701)	(4,557)	(4,696)	(4,225)
Profit Before Tax (reported)	(3,712)	(4,576)	(4,696)	(4,225)
Tax	2,535	892	1,713	1,302
Profit After Tax (norm)	(1,166)	(3,666)	(2,983)	(2,922)
Profit After Tax (reported)	(1,177)	(3,685)	(2,983)	(2,922)
Average Number of Shares Outstanding (m)	31.7	34.6	41.6	45.8
EPS - normalised (€)	(0.03)	(0.09)	(0.07)	(0.06)
EPS - reported (€)	(0.03)	(0.09)	(0.07)	(0.06)
Dividend per share (€)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	31,786	42,357	52,196	62,039
Intangible Assets	29,330	39,938	49,795	59,653
Tangible Assets	665	631	613	598
Investments	1,791	1,788	1,788	1,788
Current Assets	35,664	37,738	24,012	10,445
Stocks	135	289	289	289
Debtors	971	2,071	1,521	1,796
Cash	34,320	35,111	21,935	8,093
Other	239	267	267	267
Current Liabilities	(10,441)	(10,546)	(9,642)	(8,840)
Creditors	(2,192)	(4,000)	(3,096)	(2,293)
Short term borrowings	(8,249)	(6,547)	(6,547)	(6,547)
Long Term Liabilities	(11,884)	(8,420)	(8,420)	(8,420)
Long term borrowings	(9,977)	(6,699)	(6,699)	(6,699)
Other long term liabilities	(1,907)	(1,721)	(1,721)	(1,721)
Net Assets	45,125	61,129	58,146	55,223
CASH FLOW				
Operating Cash Flow	(2,799)	(3,610)	(4,916)	(5,172)
Net Interest	2,133	(324)	0	0
Tax	0	0	1,713	1,302
Capex	(170)	(115)	(115)	(115)
Acquisitions/disposals	0	0	0	0
Financing	11,949	18,374	0	0
Other*	(6,576)	(9,916)	(9,858)	(9,590)
Dividends	0	0	0	0
Net Cash Flow	4,538	4,409	(13,176)	(13,575)
Opening net debt/(cash)	(11,555)	(16,093)	(21,866)	(8,689)
HP finance leases initiated	0	0	0	0
Other	0	1,364	0	0
Closing net debt/(cash)	(16,093)	(21,866)	(8,689)	4,886

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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