EDISON

Oryzon Genomics

REIMAGINE trial data

First vafidemstat efficacy data

Pharma & biotech

In April 2019, Oryzon released the results from the first two cohorts in the Phase II REIMAGINE trial, namely borderline personality disorder (BPD) and attention deficit hyperactivity disorder (ADHD). The datasets included the first efficacy results, which demonstrated vafidemstat's potential in aggression management in these patients. REIMAGINE is a basket trial, enrolling patients with two neurodegenerative and three psychiatric diseases, hence the cohorts were small (six patients each). All primary and secondary endpoints were met with high statistical significance, which prompted Oryzon to announce that it now plans to expand vafidemstat's R&D beyond the currently ongoing other Phase II trials in Alzheimer's disease (results in H219) and multiple sclerosis. Our valuation is higher at €430m or €11.0/share (€9.3/share previously) with the inclusion of BPD.

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.

Small cohorts, but highly consistent results

In two different indications, BPD and ADHD, vafidemstat not only significantly improved scores across several commonly used subscales that measure agitation and aggression, but also significantly improved the total scores of those psychiatric scales. Albeit the cohorts were small, the consistency of results across several scales and in two different indications is rather promising, in our view. Treatment with vafidemstat in these patients was safe and well tolerated without significant adverse events, including no unexpected adverse haematological effects.

Vafidemstat R&D expansion warranted

The primary purpose of the REIMAGINE trial was to assess the effect on aggression management in these patients (based on insights from the preclinical trials), but the fact that overall scores improved as well suggests that vafidemstat could have a broader psychiatric effect beyond agitation and aggression. Such results prompted Oryzon to indicate that management will likely expand vafidemstat's development beyond Alzheimer's disease and multiple sclerosis. Oryzon now plans to discuss the best path forward with specialist key opinion leaders (KOLs), hence this is still in an early stage.

Valuation: €430m or €11.0/share

Our valuation is increased to €430m or €11.0/share, from €364m or €9.3/share, mainly due to the addition of the BPD indication to our rNPV model. In the "Basket trial" section of our July 2018 outlook report we indicated we would consider expanding vafidemstat's potential if sufficient efficacy signals are established. This is also in line with Oryzon's intention to expand vafidemstat's R&D and discuss the best path forward with specialist KOLs. We chose to add BPD for several reasons as discussed in the valuation section.

29 April 2019

Price	**€3.70**
Market cap	**€145m**

Net cash (€m) at end Q418	16.1
Shares in issue	39.1m
Free float	70
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	7.7	30.7	54.2
Rel (local)	4.1	26.3	60.6
52-week high/low		€5.03	€2.08

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

Autism spectrum disorder results from the Phase II REIMAGINE trial	9 September 2019
First readouts from Phase IIa studies with iadademstat in AML, SCLC	Q219
Preliminary readouts from Phase IIa with vafidemstat in AD and MS	H219

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Edison profile page

First data sets from Phase II REIMAGINE trial

Design

The Phase II REIMAGINE is a single-arm, open-label study being carried out at the Hospital Vall d'Hebrón in Barcelona and enrolling six patients per indication: Alzheimer's disease (AD), Lewy bodies dementia (LBD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and borderline personality disorder (BPD). Patients will undergo an open-label treatment with vafidemstat for eight weeks. The study objectives are:

- **Primary objective**: To evaluate the safety and tolerability of vafidemstat in adults with AD, LBD, ADHD, BPD or ASD.
- **Secondary objectives**: To investigate the efficacy of vafidemstat in aggression in adults with AD, LBD, ADHD, BPD or ASD.
- **Exploratory objectives**: To measure plasma levels pre-dose and throughout the study, LSD1 target engagement in peripheral blood mononuclear cells (PBMCs).

The REIMAGINE trial with vafidemstat is a so-called basket trial, which employs an innovative design borrowed from drug development in oncology, where the drug is initially explored in a variety of indications before selecting the most promising for the late-stage development. Aggression is often seen in a variety of neurodegenerative and neuropsychiatric conditions. Oryzon believes it can employ a similar strategy to develop vafidemstat for neuropsychiatric disorders due to observed holistic effects on aggression and behaviour in preclinical models with vafidemstat.

Oryzon used these common neuropsychiatric scales to assess the patients:

- **General scales used in psychiatry**
  - Clinical Global Impression (CGI) Severity (CGI-S) and CGI Improvement (CGI-I) scales. A psychiatrist asks the patient specific questions.
  - Global Improvement on the Neuropsychiatric Inventory (NPI) total score. A psychiatrist asks the caregiver specific questions.
- **Disease-specific scales**
  - The BPD checklist (BPDCL) scale
  - The ADHD Rating Scale (ADHD-RS) score
- **Aggression specific**
  - The NPI four-item Agitation/Aggression subscale
  - Three aggression-related BPDCL domains combined score

Results

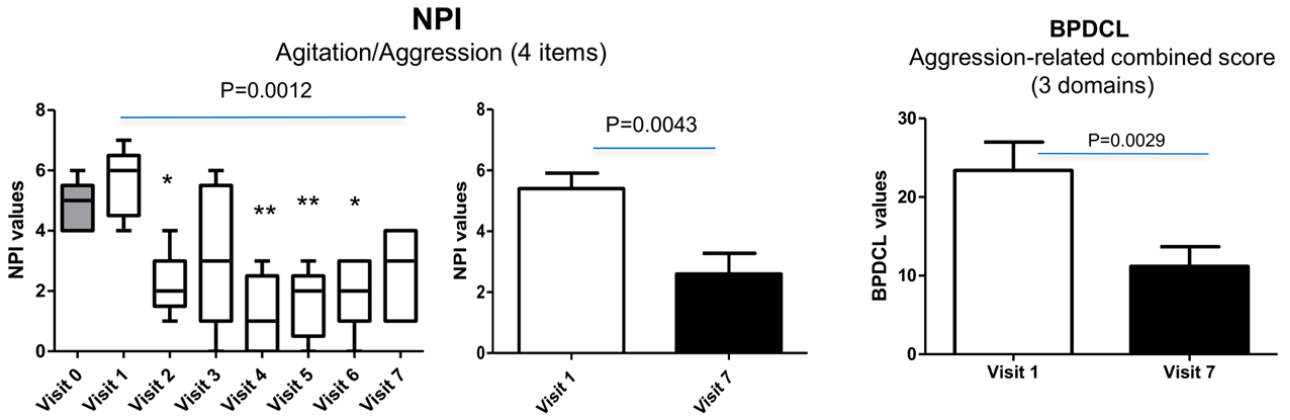
BPD

The first dataset from the REIMAGINE trial was presented from the borderline personality disorder (BPD) cohort at the 27th European Congress of Psychiatry (EPA 2019) in Warsaw, Poland, on 8 April 2019. In this cohort six subjects with diagnosed BPD were treated for two months. Vafidemstat met all the primary and secondary endpoints:

- The treatment was safe and well tolerated without significant adverse events, and pharmacokinetic and target engagement results were in line with previous Phase I data.
- A significant improvement was measured in CGI-S and CGI-I scales (p=0.011 and p=0.017, respectively).

- A significant improvement on the NPI total score (p=0.018):
  - A significant improvement on the NPI 4-item Agitation/Aggression subscale (p=0.004) (Exhibit 1).
- A significant improvement on the total BPD checklist (BPDCL) scale score (p=0.005):
  - Specific improvement on the three aggression-related BPDCL domains combined score (p=0.003).
  - Improvement on the six non-aggression-related BPDCL domains combined score (p=0.023).

Exhibit 1: Vafidemstat's efficacy in BPD as measured by aggression/agitation subscales



Source: Oryzon poster presentation at EPA 2019

ADHD and aggregated data

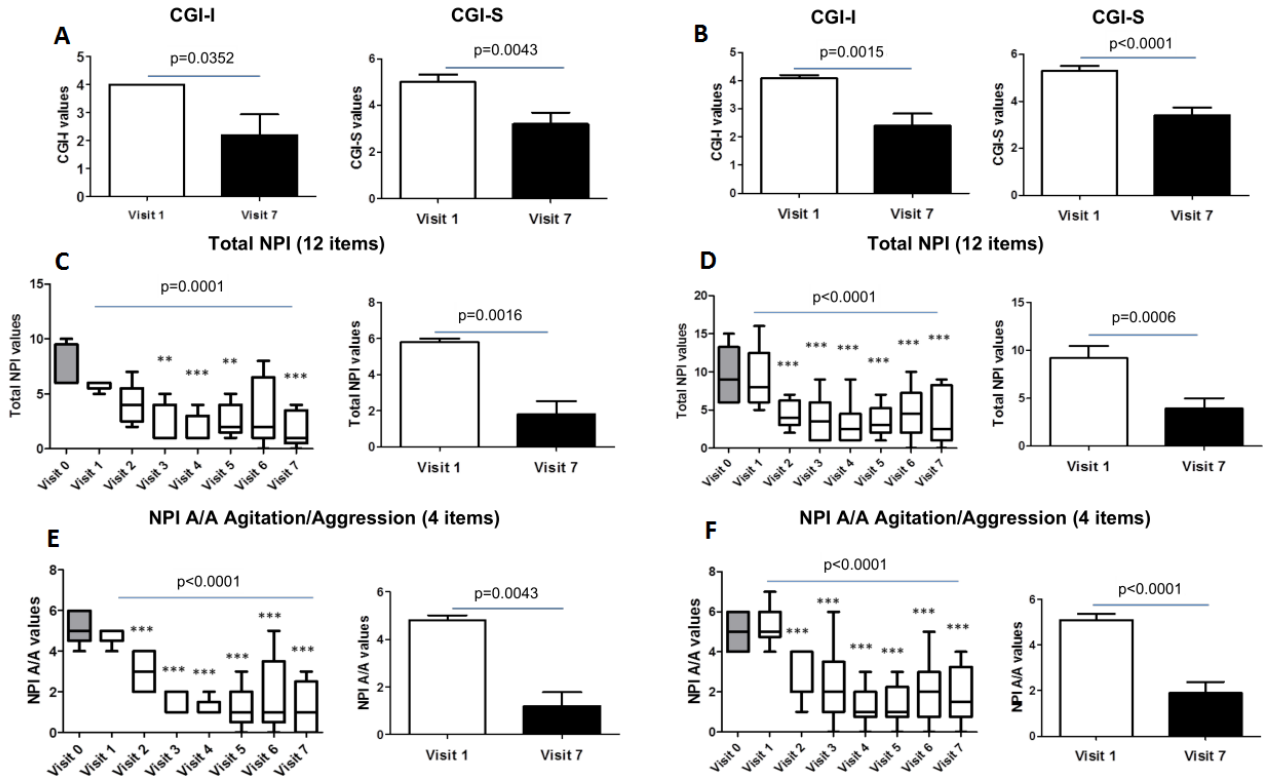
The second dataset from the REIMAGINE trial was presented from the attention deficit hyperactivity disorder (ADHD) cohort at the 7th World Congress on ADHD, 25–28 April in Lisbon, Portugal. Similarly, in this cohort six subjects with diagnosed ADHD were also treated for two months. Vafidemstat again met all the primary and secondary endpoints:

- As in the previous data, no unexpected serious side effects emerged.
- Global improvement on the CGI-S and CGI-I scales was significant (p=0.0043 and p=0.0352, respectively) (Exhibit 2A).
- Global improvement on the NPI total score was significant (p=0.0016) (Exhibit 2C):
  - Specific improvement on the NPI 4-item Agitation/Aggression subscale was also significant (p=0.0043) (Exhibit 2E).
- A significant overall improvement in the ADHD Rating Scale (ADHD-RS) total score was also observed (p=0.0279).

In addition, Oryzon provided some aggregated BPD and ADHD data.

- The aggregated data from ADHD and BPD patients showed that global improvement on the CGI-S and CGI-I scales was statistically even more significant (p<0.0001 and p=0.0015, respectively) than in the ADHD and BPD cohorts alone (Exhibit 2B).
- Similarly, the aggregated data showed that global improvement on the NPI total score and NPI four item Agitation/Aggression subscale exhibited was statistically even more significant (p=0.0006 and p<0.0001, respectively) than the ADHD and BPD cohorts alone (Exhibits 2D and 2F).

Exhibit 2: Vafidemstat's efficacy in ADHD and combined data with BPD



Source: Oryzon poster presentation at the 7th World Congress on ADHD

Our take

Treatment with Vafidemstat in these patients was safe and well tolerated without significant adverse events, including no apparent negative haematological effects, which is a primary consideration of the epigenetic class drugs. This was not surprising, as the dose used in the REIMAGINE trial was substantially below the highest dose reached in Phase I trials (2.5mg). The fact that effectiveness was achieved with relatively low dosing is especially beneficial given that in BPD the treatment most likely would be chronic.

In two different indications vafidemstat not only significantly improved scores across several commonly used subscales that measure agitation and aggression, but also significantly improved the total scores of those psychiatric scales. Albeit the cohorts were small, the consistency of results across several scales and in two different indications is rather promising, in our view. Although the primary purpose was to assess the effect on aggression management in these patients (based on insights from the preclinical trials), the fact that overall scores improved as well suggests that vafidemstat could have a broader psychiatric effect beyond agitation and aggression.

What's next

The next data readout from the autism spectrum disorder is scheduled for the 32nd ECNP Congress, Copenhagen on 9 September 2019. However, in its latest press release about the ADHD data last Thursday, Oryzon clearly indicated that it will explore vafidemstat for psychiatric disorders beyond those currently in clinical trials: AD and MS. The company mentioned that it is now consulting with specialist KOLs to establish a precise target indication and patient population where vafidemstat would be best positioned. We believe that, specifically, BPD appears to be an interesting opportunity characterised by a high unmet need (no specific treatment approved) and a

large population of adult patients. We therefore now include this indication in our valuation (more details follow in the valuation section).

BPD: Indication characteristics and management

Highlights

BPD is characterised by pervasive, marked instability in functioning, mood, interpersonal relationships and, on the severe end of the symptom scale, reality perception distortion. In addition, other conditions are also present, such as major depression, substance abuse or psychotic disorders. Around 70–75% of BPD patients have attempted self-harm at least once, while the estimated rate of completed suicides is 9% (eMedicine/Medscape). Symptoms typically begin in adolescence or young adulthood, but at this early stage typically psychotherapy involving family members is used. Pharmacological intervention tends to be prescribed once a person reaches adulthood. The initial diagnosis is rarely made in patients older than 40 years. The severity of the disease often decreases with age. No laboratory tests are useful and the condition is typically diagnosed by psychiatrists using behavioural diagnostic criteria listed in the guidelines.

Treatment

Management of the disease is difficult and involves a number of psychotherapeutic and pharmacological interventions, which are selected on a case by case basis. The presentation of the disease can vary substantially and pharmacological treatment usually targets symptoms. There are no drugs specifically approved for the condition in the western markets, but pharmacological treatment is being used to treat impulsivity, mood instability and psychosis. So far, mostly selective serotonin reuptake inhibitors (SSRIs) class drugs have been used in BPD patients. SSRIs are mainly indicated to reduce impulsivity and aggression. Neuroleptics (antipsychotics) and opiate receptor antagonists (naltrexone) are also sometimes used, but in smaller number of patients and for a short period of time.

Epidemiology

Given the diversity of the disease, no definitive data exists about the prevalence of BPD, but widely reported estimates suggest that 1–2% of the general population could be affected (eMedicine/Medscape). Percentage of patients that actually receive treatment is also not well understood, but some researchers estimate 50% receive diagnosis and of those 50–80% receive treatment (Gross *et al*, 2002; Lieb *et al*, 2010). Existing epidemiological findings also agree on the fact that BPD is much more prevalent among women, with a female to male ratio of as high as 4:1 (Nasiri *et al*, 2013). No drugs are specifically approved for BPD.

ADHD: Indication characteristics and management

Highlights

ADHD is a developmental condition of inattention and distractibility, with or without accompanying hyperactivity. Therefore, ADHD can be classified into three forms: inattentive, hyperactive-impulsive, and combined (Moffitt *et al*, 2015). Symptoms can range from mild to severe, affecting daily functioning to different extents. Similar to BPD it is diagnosed using behavioural psychiatric tests, as no specific laboratory tests exists. However, MRI, functional MRI and PET scans have been shown in studies to be useful to determine functional and anatomical alteration in certain brain structures of the patients, when compared to healthy persons.

Treatment

In some cases, behavioural therapy involving the person and their family can be effective, but unlike in BPD, psychostimulants are considered the mainstay pharmacological treatment of this disease. Common first-line therapies include:

- methylphenidate (generic, still brought in total $917m in sales in 2018 for different manufacturing companies);
- dextroamphetamine (most forms generic; extended release formulation Adderall XR, which includes four salts of amphetamine, patents about to expire; $383m in sales in 2018, Shire/Takeda); and
- the current market leader is lisdexamfetamine (branded as Vyvanse, Takeda; estimated 2019 sales of $2.3bn, EvaluatePharma).

Epidemiology

Because of relatively well-defined symptoms of ADHD, the epidemiology is understood relatively well. ADHD symptoms start most often in childhood and in 2016 there were 5.4 million children diagnosed with the condition at that time in the US, which corresponds to an 8.4% prevalence rate of all US children. 62% of children with current ADHD were taking medication and 47% had received behavioural treatment for ADHD in the past year; 23.0% had received neither treatment (Danielson *et al*, 2018). As many as 65% of these children will have ADHD or some residual symptoms of ADHD as adults. The prevalence rate of ADHD in the adult general population is 4–5% (Goodman and Thase, 2009). ADHD is three to five times more common in boys than in girls, while in adults, the ratio is closer to even (eMedicine/Medscape).

Valuation

Our valuation is higher at €430m or €11.0 per share, versus €364m or €9.3 per share previously, mainly due to the addition of a new indication in our rNPV. As discussed, the most recent REIMAGINE data and Oryzon's indication that it will pursue more psychiatric indications warrant, in our view, the expansion of the potential of vafidemstat in our model. We chose to include BPD due to several reasons:

- BPD has a high unmet need relative to ADHD, where the pharmacological intervention is fairly structured (frontline and mainstay treatments mostly stimulants);
- BPD usually is fully diagnosed in adulthood, when the pharmacological intervention is considered, as opposed to ADHD, which typically is fully diagnosed in childhood, ie ADHD drug development would require a paediatric R&D strategy from the start; and
- There is a large target population.

Due to the lack of similar drugs that could be used as benchmarks, we have used a bottom-up approach with the following assumptions in our project model:

- **Target population:** 1% prevalence in the western markets (the US and top 14 European countries). 50% receive diagnosis and 50% receive treatment. This leads to a total of 1.5 million accessible adult patients, but we assume only a 10% penetration rate keeping in mind that currently aggression management with vafidemstat is prioritised in these patients. If a broader effect is confirmed, then there is potential for larger penetration, in our view.
- **Pricing:** $10,000 per patient per year (30% discount applied in Europe). A premium to generic antidepressants, which cost from several hundred US dollars to $2,000–3,000, depending on consumer brand or generic. The latest antidepressant (and the only patented currently) esketamine, approved by the FDA, has a price tag of around $7,000 a month alone ($84,000 a

year), however, this drug is indicated for severe depression with a risk of suicide, hence has a more restricted target patient population than we model for vafidemstat in BPD. Another relevant drug is Nuplazid (pimavanserin, atypical antipsychotic) approved by the FDA in 2016. It is indicated for psychosis associated with Parkinson's disease and has a price tag of c $36,000 per patient per year. Parkinson's disease with psychosis is still a substantially smaller target population than we model for BPD, however, such pricing indicates that there is an opportunity for drugs targeted at management of specific symptoms of neurodegenerative/psychiatric diseases. Once Oryzon has developed more detailed plans about vafidemstat's potential positioning in BPD, we will adjust our target patient population and pricing accordingly.

- **Peak sales:** Launch in 2027. Peak sales of $1.3bn seven years after launch.
- **R&D cost:** $14m for Phase IIb and $17m for Phase III.
- **Licensing deal:** Since the antidepressant market is substantially genericised with virtually all drugs off patent, there has been only one relevant licensing deal in recent years. AstraZeneca in-licensed TC-5214 from Targacept for $200m upfront and an additional $1bn in milestone payments. At that time (2009) this drug was perceived as a potential blockbuster. We use 30% of these values in our model, ie $67m upfront and $333m in R&D and commercial milestones (30:70).

We note that these assumptions are subjection to revision as more information is released by Oryzon about a more specific positioning of vafidemstat, eg the design of the next trial.

We maintain our near-term financial and operating forecasts unchanged, but these are subject to revision once more precise plans for additional clinical trials are announced.

Exhibit 3: 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
Vafidemstat (ORY-2001)	BPD	2027	1,290	277.0	20%	65.7	1.7
Net cash (end-2018)				16.1	100%	16.1	0.4
Valuation				**2,179.6**		**429.6**	**11.0**

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 4: Financial summary

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