EDISON

Oryzon Genomics

Clinical update

PORTICO update with planned FDA EoP2

Pharma and biotech

Oryzon Genomics has announced top-line results for the Phase IIb trial (PORTICO) assessing vafidemstat in borderline personality disorder (BPD), and while the primary endpoints (Borderline Personality Disorder Checklist (BPDCL) and Clinical Global Impression – Severity Agitation/ Aggression (CGI-S A/A)) did not reach statistical significance, vafidemstat was favoured over placebo in all efficacy measures, with nominal statistical significance in two key secondary endpoints (Borderline Evaluation of Severity (BEST) and State-Trait Anger Expression Inventory 2 (STAXI-2) Trait Anger). Further, the drug was found to be safe and well-tolerated, consistent with prior studies. Management plans to conduct a detailed analysis of the trial data across the coming months and intends to request an end-of-Phase II (EoP2) meeting with the FDA in early Q224 to discuss a potential registrational Phase III programme. There are currently no approved drugs for this indication and hence gold-standard endpoints are yet to be established. We therefore believe that there is still a significant opportunity for Oryzon in this space, however, further clinical progression will be heavily reliant on the EoP2 meeting request and outcome.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/21	10.6	(7.2)	(0.09)	0.0	N/A	N/A
12/22	15.7	(6.4)	(0.07)	0.0	N/A	N/A
12/23e	15.9	(6.6)	(0.07)	0.0	N/A	N/A
12/24e	19.0	(10.0)	(0.13)	0.0	N/A	N/A

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

Progression in BPD rests on EoP2 meeting outcome

The PORTICO top-line results present a setback for the company, but with a chance to salvage the situation, in our view. While it is disappointing that the study did not meet its primary endpoints, encouragement can be taken from the trial achieving statistical significance on key secondary endpoints. Importantly, results across all efficacy measures favoured vafidemstat over placebo, highlighting the potential for the drug in managing a challenging condition that currently has no approved treatment options. It was noted on the corresponding webcast to discuss the results that the PORTICO data allowed informative insights into effect sized for the various efficacy measures, potentially paving the way for a registrational Phase III programme. Management aims to have conducted a detailed analysis of the full data by end-Q124 and to submit an EoP2 request to the FDA in early Q224. Subject to delays, we expect the EoP2 meeting outcome will likely be in Q324, potentially representing a significant inflection point for Oryzon.

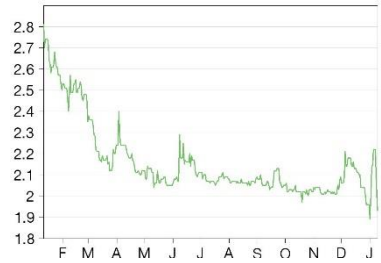
Valuation: Maintained at €900.3m or €15.1 per share

Pending the EoP2 meeting with the FDA and its likely conclusions, we keep our overall valuation for Oryzon unchanged at €900.3m. The per share valuation adjusts slightly to €15.1 (€15.4 previously) due to a higher number of shares outstanding. We plan to revisit our assumptions once there has been an update on the EoP2 meeting.

10 January 2024

Price	**€2.05**
Market cap	**€122m**
Gross cash (€m) at end-September 2023 (excluding drawdowns/conversions from the €45m debt facility announced in Q423)	8.4
Shares in issue	59.7m
Free float	80%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(11.4)	(4.7)	(31.5)
Rel (local)	(10.0)	(13.3)	(40.8)
52-week high/low		€2.88	€1.89

Business description

Oryzon Genomics is a Spanish biotech focused on epigenetics. Iadademstat is being explored for acute leukaemias, small-cell lung cancer and neuroendocrine tumours. Vafidemstat, its central nervous system (CNS) asset, has completed several Phase IIa trials and a Phase IIb trial in borderline personality disorder (now the lead study), and is in a Phase IIb trial in schizophrenia.

Next events

EoP2 meeting request (vafidemstat in BPD)	Q224
FRIDA AML study update	Q224

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Edison profile page

PORTICO results: Improvements in all BPD measures

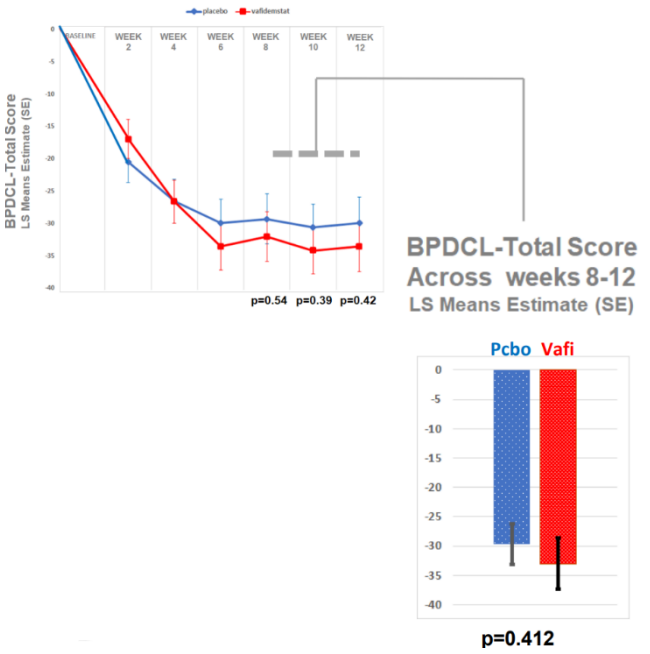
Study design

The PORTICO study was a randomised, placebo-controlled, double-blinded 14-week Phase IIb clinical trial. To be included, participants had to have a confirmed BPD diagnosis, reach a defined threshold for agitation and aggression based on the Agitation-Aggression Psychiatric Inventory Clinician Report, and be on a stable regimen of background pharmacotherapy. Psychotherapy alongside treatment was also permitted, provided this was consistent throughout the trial duration. Patients (n=210) were randomised 1:1 to receive either vafidemstat (1.2mg orally once daily, five days on and two days off, n=106) or placebo (once daily, n=104). The trial involved 27 sites, including 14 in the US and 13 in Europe (Germany, Spain, Bulgaria and Serbia).

Primary efficacy measures

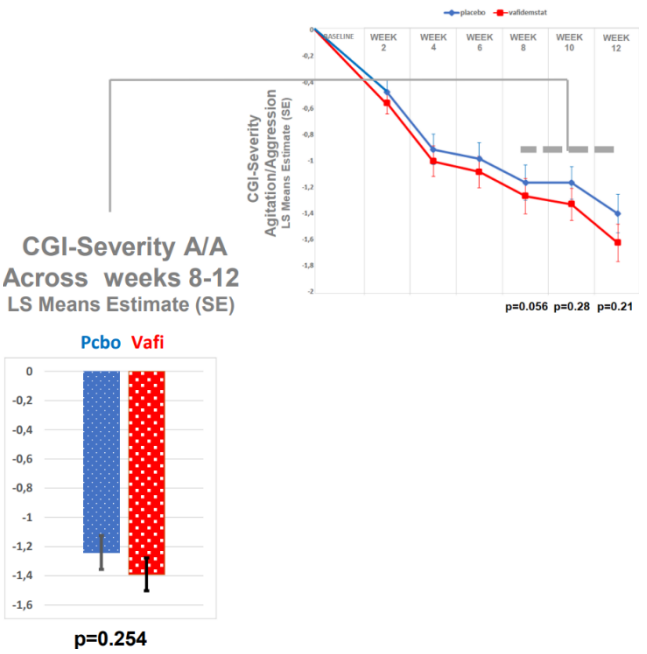
The primary endpoints were improvement in BPDCL (a 47-item patient-completed assessment) and improvement in CGI-S A/A (a clinician-completed assessment on overall patient functioning), both from baseline to weeks 8–12. The results showed that treatment with vafidemstat did not demonstrate a statistically significant improvement over placebo as measured by either of the primary endpoints (Exhibits 1 and 2). However, an important trend, observed throughout all the trial data, was a separation in performance between the vafidemstat and placebo arms from week four through to week 12, and this was true of both the BPDCL and CGI-S A/A data, albeit without statistical significance (p=0.412 for the BPDCL Total Score data; p=0.254 for the CGI-S A/A data). While this is not the preferred outcome, we believe it shows a positive trend favouring vafidemstat based on both clinician- and patient-reported measures. It is our opinion that further clinical development in BPD will be subject to the FDA's interpretation of these results.

Exhibit 1: PORTICO BPDCL Total Score data



Source: Oryzon webcast (7 January 2024)

Exhibit 2: PORTICO CGI-S A/A data

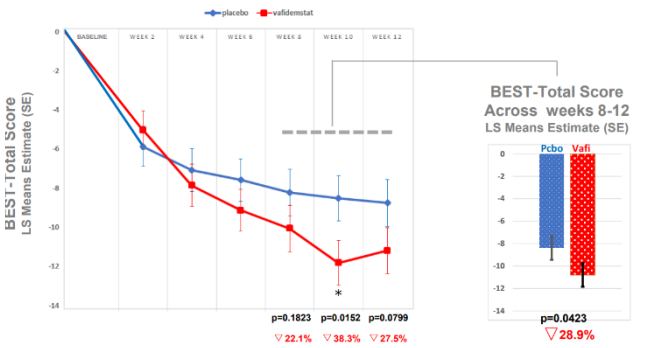


Source: Oryzon webcast (7 January 2024)

Secondary efficacy measures

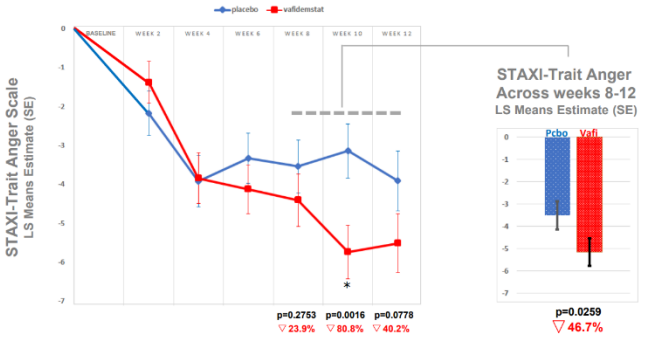
Two of the key secondary endpoints included improvements from baseline to weeks 8–12, as well as change over time, as measured by BEST (a 15-item patient-completed assessment) and STAXI-2 Trait Anger (a 54-item patient-completed assessment). Encouragingly, the data showed statistically significant improvements across both measures, following the trend of a distinct separation in performance from week four to week 12 for the two arms (Exhibits 3 and 4). Notably, the BEST data showed a 38.3% benefit in favour of vafidemstat at week 10 (p=0.0152) and an overall average reduction of 28.9% across weeks 8–12 (p=0.0423). Similarly, the STAXI-2 Trait Anger data showed an improvement from week four to week 12, with an 80.8% benefit at week 10 (p=0.0016) and an overall average reduction of 46.7% across weeks 8–12 (p=0.0259).

Exhibit 3: PORTICO BEST data



Source: Oryzon webcast (7 January 2024)

Exhibit 4: PORTICO STAXI-2 Trait Anger data



Source: Oryzon webcast (7 January 2024)

Safety

On the safety front, vafidemstat was found to be safe and well-tolerated. Treatment emergent adverse events (TEAEs) were comparable across the two arms, slightly lower with vafidemstat versus placebo (54.5% vs 65.4% incidence rates). The majority of TEAEs were recovered or resolved by the end of the study and, importantly, there were no patient deaths/suicides. Suicidal ideation was low; there was once case each in the vafidemstat and placebo arms (overall rate of 0.9%). It was noted that one serious AE, a kidney infection, was recorded in the vafidemstat arm. However, the case was independently determined to be unrelated to treatment. The condition was resolved within seven days and the participant completed the trial without altering their dosing. Overall, the safety profile of vafidemstat was consistent with the favourable profile observed with the drug in prior studies.

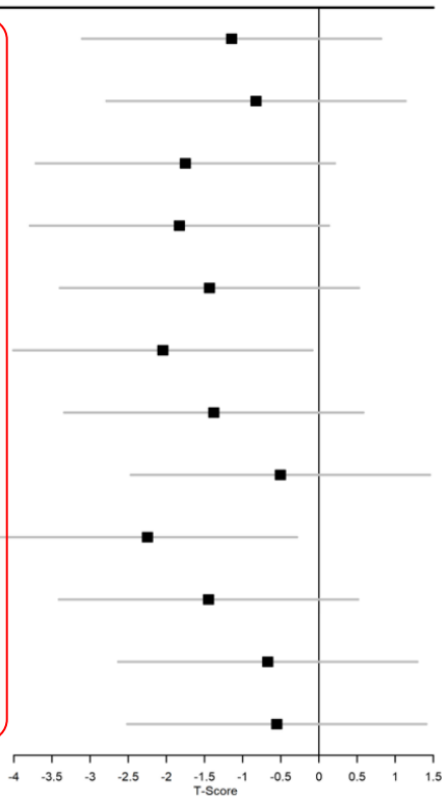
Outlook

While it is disappointing that statistical significance was not achieved with the two primary efficacy measures, we believe the overall results demonstrate that vafidemstat offers a clinically meaningful benefit for BPD patients. This was corroborated in the corresponding webcast, where management noted that a key opinion leader viewed improvements greater than 25% positively (across any measure of overall severity and agitation/aggression), supportive of the most recent clinical data, suggesting that vafidemstat may have the potential to be an effective treatment option for BPD patients. It was also highlighted that as there are no gold-standard endpoints in BPD, the trial investigated a sizeable number of secondary and exploratory endpoints, in addition to the two primary efficacy measures, and all cases favoured vafidemstat over placebo. Management believes it is rare to see all data favouring the experimental arm versus placebo to this extent in a psychiatric indication such as BPD, emphasising the opportunity for Oryzon. This was exemplified with a forest plot to show the Global Statistical Test (GST) data (Exhibit 5). As BPD is a multisymptomatic condition, the GST analysis was intended to assess whether the treatment was efficacious across various aspects of the condition (eg psychiatric, behavioural, functional).

Exhibit 5: PORTICO GST data showing global treatment effect

Full Analysis Set

Parameter	P-value	Difference	CI	T-Score	GST P-value
CGI02-Severity	0.2541	-0.16	(-0.42,0.11)	-1.14	
BPDCL1-Total Score	0.4107	-3.24	(-11.01,4.52)	-0.82	0.2476
BEST01-A_Thoughts and Feelings Score	0.0817	-1.31	(-2.79,0.17)	-1.75	0.1419
BEST01-B_Behaviors Negative Score	0.0692	-0.56	(-1.17,0.04)	-1.83	0.0920
BEST01-C_Behaviors Positive Score*	0.1531	-0.47	(0.17,-1.11)	-1.43	0.0694
BEST01-Total Score	0.0423	-2.43	(-4.77,-0.09)	-2.05	
BD201-Total Score	0.1699	-2.11	(-5.14,0.91)	-1.38	0.0689
STAXI1-State Anger Scale Raw Score	0.6143	-0.49	(-2.38,1.41)	-0.50	0.0845
STAXI1-Trait Anger Scale Raw Score	0.0259	-1.64	(-3.09,-0.20)	-2.25	0.0573
STAXI1-AX Index Raw Score	0.1495	-2.22	(-5.25,0.81)	-1.45	0.0564
STAI01-S-Anxiety Raw Score	0.5035	-0.96	(-3.77,1.86)	-0.67	0.0664
STAI02-T-Anxiety Raw Score	0.5813	-0.67	(-3.05,1.72)	-0.55	0.0819



Source: Oryzon webcast (7 January 2024). Note: Negative T-Score favours vafidemstat over placebo.

Oryzon intends to carry out a detailed analysis of the full data within Q124. This will include an exploration into biomarker correlatives to facilitate future clinical development efforts within this indication. (It was noted that such analyses will also take place for the ongoing EVOLUTION study investigating vafidemstat in schizophrenia). Management then plans to submit a request to the FDA for an EoP2 meeting in early Q224 to discuss a registrational Phase III programme for the treatment of BPD. Subject to delays on these timelines, and in accordance with FDA guidance on EoP2 meetings, we estimate that the EoP2 meeting and outcome will likely be in Q324. We believe that the prospect of continued clinical development in this indication heavily relies on the judgement of the FDA, especially with a lack of regulatory precedent in BPD. Given that BPD is Oryzon's lead central nervous system (CNS) indication, a positive outcome from an EoP2 meeting could represent a significant catalyst for the company, in our view.

Financials and valuation

We evaluated Oryzon's H123 financial performance in our recent update note. Based on the available information, we had estimated the Q323 net debt balance to be €6.6m (including gross cash of €8.4m at end-Q323 and the H123 gross debt balance of €15.0m). The capitalisation situation was bolstered in November 2023, with the company securing funding of up to €45m through a revised convertible bond financing agreement, replacing its previous €20m convertible bond agreement (of which €12m had been drawn down) with Nice & Green, a Switzerland-based institutional investor. As per the new agreement, Oryzon can draw down up to €45m in financing through the initial execution of €8m in two tranches of €4m, and additional tranches of up to €5m

each, at its discretion. However, it is unclear if the company has made any drawdowns from the new facility yet. The new convertible bonds have a maturity of 48 months and can be converted at 94% of the average closing daily volume-weighted price (between conversions). We also note that the conversion price will not exceed a 9.99% discount to the closing price on the date preceding the conversion of the relevant convertible note. Oryzon also holds the right to redeem notes at a premium of 3%. We highlight that this financing agreement will have a share dilution impact – for reference, if conversion happens at the last closing price of €2.05 the company will have to issue c 22m shares (assuming full conversion), diluting current shareholders by c 37% – although we estimate these funds would support operations to end-FY25, based on current cash burn rates (€5.5m in Q323). With these funds at hand, we believe the company is sufficiently capitalised past crucial milestones such as the EoP2 meeting with the FDA and top-line results from ongoing clinical trials, which, if positive, could potentially lead to a partnership agreement(s) and associated cash inflows.

Despite the less than favourable top-line data from the Phase II PORTICO study, we maintain our overall valuation for the indication at €260.1m. We had been conservative with our estimates for vafidemstat in BPD, assuming a probability of success (PoS) of 20% despite it being a late Phase II programme. Based on the recent development, we have decided to keep the PoS and development timelines unchanged until the results from the EoP2 meeting with the FDA are made available. Overall, our valuation remains unchanged at €900.3m. Our per share valuation adjusts to €15.1 (previously €15.4) given a higher number of shares outstanding (59.7m vs 58.6m previously).

Exhibit 6: Valuation of Oryzon

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
Iadademstat	2L AML	2026	510	810.9	30%	239.9	4.0
Iadademstat	1L SCLC	2026	740	858.2	25%	210.9	3.5
Vafidemstat	BPD	2027	1,640	1,340.5	20%	260.1	4.4
Vafidemstat	Schizophrenia, negative symptoms	2027	710	674.5	15%	94.5	1.6
Vafidemstat	Aggression in AD	2028	920	716.7	15%	101.4	1.7
Estimated net debt at end-Q323				(6.6)	100%	(6.6)	(0.1)
Valuation				**4,394.2**		**900.3**	**15.1**

Source: Edison Investment Research

Exhibit 7: Financial summary

Accounts: Year end 31 December (€000s)	2021A	2022A	2023E	2024E
INCOME STATEMENT				
Total revenues	10,615	15,698	15,855	18,995
Cost of sales	(746)	(464)	(487)	(512)
Gross profit	9,869	15,234	15,368	18,483
Gross margin %	93%	97%	97%	97%
SG&A (expenses)	(3,782)	(3,163)	(3,194)	(3,827)
R&D costs	(9,746)	(13,681)	(15,600)	(23,975)
Other income/(expense)	(3,203)	(3,714)	(1,820)	0
Exceptionals and adjustments	(4)	0	0	0
Reported EBITDA	(6,866)	(5,323)	(5,246)	(9,318)
Depreciation and amortisation	144	167	149	131
Reported EBIT	(7,011)	(5,490)	(5,396)	(9,450)
Finance income/(expense)	(169)	(871)	(1,219)	(579)
Other income/(expense)	0	(195)	0	0
Reported PBT	(7,180)	(6,557)	(6,615)	(10,029)
Income tax expense (includes exceptionals)	2,493	2,325	2,409	2,367
Reported net income	(4,687)	(4,231)	(4,206)	(7,662)
Basic average number of shares, m	53.1	55.6	58.8	59.7
Basic EPS (€)	(0.09)	(0.08)	(0.07)	(0.13)
Adjusted EBITDA	(6,862)	(5,323)	(5,246)	(9,318)
Adjusted EBIT	(7,007)	(5,490)	(5,396)	(9,450)
Adjusted PBT	(7,176)	(6,361)	(6,615)	(10,029)
Adjusted EPS (€)	(0.09)	(0.07)	(0.07)	(0.13)
Adjusted diluted EPS (€)	(0.09)	(0.07)	(0.07)	(0.13)
BALANCE SHEET				
Property, plant and equipment	682	611	538	482
Intangible assets	60,254	75,843	89,320	1,01,786
Investments	29	31	31	31
Deferred tax assets	1,812	2,050	2,050	2,050
Total non-current assets	62,778	78,535	91,938	1,04,348
Cash and equivalents	28,725	21,317	925	1,269
Trade and other receivables	3,645	3,709	3,677	3,693
Inventories	104	10	10	10
Other current assets	132	129	129	129
Total current assets	32,606	25,165	4,741	5,102
Deferred tax liabilities	1,812	2,050	2,050	2,050
Long term debt	13,354	10,346	14,486	36,877
Other non-current liabilities	285	0	0	0
Total non-current liabilities	15,451	12,396	16,536	38,927
Trade and other payables	3,518	5,742	4,630	5,186
Short term debt	4,306	12,920	7,077	4,562
Other current liabilities	847	70	70	70
Total current liabilities	8,672	18,732	11,777	9,818
Equity attributable to company	71,262	72,572	68,367	60,705
	0	0	0	0
CASH FLOW STATEMENT				
Profit before tax	(7,180)	(6,557)	(6,615)	(10,029)
Cash from operations (CFO)	(3,626)	(1,848)	(5,136)	(6,991)
Capex	(175)	(76)	(76)	(76)
Acquisitions & disposals net	0	0	0	0
Acquisition of intangible assets	(11,586)	(14,195)	(13,477)	(12,466)
Other investing activities	37	(1)	0	0
Cash used in investing activities (CFIA)	(11,724)	(14,271)	(13,553)	(12,542)
Net proceeds from issue of shares	0	(932)	0	0
Movements in debt	4,123	9,642	(1,703)	19,877
Other financing activities	0	0	0	0
Cash from financing activities (CFF)	4,123	8,710	(1,703)	19,877
Increase/(decrease) in cash and equivalents	(10,880)	(7,408)	(20,392)	344
Currency translation differences and other	348	1	0	0
Cash and equivalents at start of period	39,605	28,725	21,317	925
Cash and equivalents at end of period	28,725	21,317	925	1,269
Net (debt) cash	14,954	3,975	(7,320)	(1,874)
Free cash flow (CFO+ Net capex on tangible assets)	(15,388)	(16,118)	(18,689)	(19,532)

Source: Company reports, Edison Investment Research

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