

Oryzon Genomics

Q323 update

Q323 recap ahead of key clinical stages

Oryzon's Q323 results recapped the clinical progression across its drug development pipeline. The company continues to develop therapies that address unmet needs related to the central nervous system (CNS) and oncology. As noted previously, an important development was the positive safety data for the PORTICO trial, assessing vafidemstat in patients with borderline personality disorder (BPD). Oryzon continues to enrol patients for its lead oncology trial (FRIDA), investigating iadademstat as a potential treatment for acute myeloid leukaemia (AML) and an update is expected in Q224. Based on current visibility, we have adjusted our FY23 operating loss estimates to €5.4m (vs €3.8m previously). Top-line data from PORTICO and FRIDA are expected to be the next key catalysts. Gross cash at the end of Q323 stood at US\$8.8m (€8.4m), down from US\$14.6m in H123, which we anticipate should fund the company's operations into Q124. We value Oryzon at €900.3m or €15.4/share (up from €874.1m or €15.6/share).

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.

Favourable safety data in PORTICO Phase II

Oryzon continues to progress its Phase IIb PORTICO trial in BPD. Positive aggregated, blinded safety data based on the initial 198 randomised patients (data cut-off of 23 August 2023) were [reported](#) in October 2023, confirming a favourable safety profile for vafidemstat (in a blinded analysis), consistent with seven prior completed clinical trials investigating the drug. In our view, PORTICO represents a potentially significant commercial opportunity for Oryzon as there are currently no FDA-approved treatments for BPD. As the PORTICO trial is now fully recruited (n=210), we await top-line data in Q124, which we consider an important catalyst.

Cash runway into Q124

At end-Q323, Oryzon had a gross cash position of €8.4m. Based on the latest cash burn rate in Q323, we estimate that the company has a cash runway into Q124, excluding upcoming debt obligations. However, we note that the company has an opportunity to raise €8m in convertible bonds, which if executed could extend the runway further to Q224. We estimate the need to raise a total of €50m through FY23–25, shown as illustrative debt in our model.

Valuation: €900.3m or €15.4 per share

We value Oryzon at €900.3m, up from €874.1m previously. The increased valuation comes from the combined effect of rolling our model forward and updating to an estimated net debt balance of €6.6m from a net cash balance of €0.9m previously. However, our per-share valuation declines to €15.4 from €15.6 previously due to the increased number of shares outstanding (58.6m).

Pharma and biotech

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Price €2.00

Market cap €117m

Gross cash balance (€m) at end-September 2023 8.4

Shares in issue 58.6m

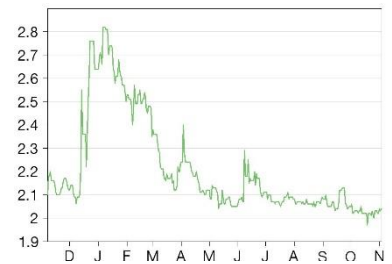
Free float 80%

Code ORY

Primary exchange Madrid Stock Exchange

Secondary exchange N/A

Share price performance



%	1m	3m	12m
Abs	1.0	(1.0)	(1.9)
Rel (local)	(0.4)	(0.8)	(17.0)
52-week high/low	€2.88	€1.97	

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), but Oryzon is rapidly expanding its CNS R&D pipeline.

Next events

PORTICO BPD study top-line results	Q124
FRIDA AML study update	Q224

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Upcoming readouts remain key catalysts

Management recapped on Oryzon's clinical progression across its ongoing activities in the [Q323 release](#). It reaffirmed the company's plans to share important readouts in H124, while it is also preparing for new clinical programmes to supplement its active pipeline focused on lead assets vafidemstat (for CNS) and iadademstat (for oncology), see Exhibit 1. A key highlight remains the recent favourable blinded safety data from the PORTICO Phase IIb trial shared in October 2023 and we await top-line data in early 2024. Oryzon remains on track for its clinical activities in terms of patient recruitment for other ongoing trials (ie EVOLUTION for schizophrenia and FRIDA for AML). Additionally, it is strengthening the pipeline further by advancing its preclinical portfolio, for example ORY-4001 (a selective histone deacetylase 6 inhibitor), which has recently been nominated for clinical development for the treatment of neurological diseases such as Charcot-Marie-Tooth disease and amyotrophic lateral sclerosis.

Vafidemstat in CNS

The company's lead study in the CNS space is [PORTICO](#), a multicentre, double-blind, randomised, placebo-controlled Phase IIb clinical trial evaluating the efficacy and safety of vafidemstat in patients with BPD. The two independent primary objectives for the trial are improvements in agitation and aggression, and overall improvement in BPD severity. Encouraging safety data for this fully enrolled study were reported in October (see our previous [note](#) for details). The last patient is due to be dosed by the end of 2023 and top-line results are expected in Q124, consistent with prior guided timelines.

Oryzon has also made steady progress enrolling patients for the [EVOLUTION](#) trial. This is a Phase IIb study assessing vafidemstat as a potential treatment for negative symptoms (affective flattening, anhedonia and avolition) and cognitive impairment (deficits in memory, attention, learning and executive function) in patients with schizophrenia. We note that there has not been much progress in the field of treatments for schizophrenia since the development of typical antipsychotics (dopamine type 2 receptor antagonists, eg chlorpromazine, haloperidol, pimozide and loxapine) in the 1950s and atypical antipsychotics (which target serotonergic receptors 5-HT_{2A}, eg clozapine, olanzapine, risperidone and quetiapine) in the 1970s. While these drugs have been effective for positive symptoms (hallucinations, delusions) of the condition, they have [limited efficacy](#) against negative and cognitive symptoms. Therefore, we believe there is a significant opportunity for Oryzon to address this unmet need and we anticipate an update on this study in 2024.

Management continues to prepare an investigational new drug (IND) application for the planned Phase I/II HOPE trial in [Kabuki Syndrome](#), a rare congenital disorder. Notably, this will be Oryzon's first clinical effort in developing a precision medicine approach tackling a monogenic CNS indication, meaning a disease known to be caused by a single genetic abnormality. With the clinical successes observed in targeting monogenic diseases in the field of CNS (further information is included in our neuroscience [sector report](#)) and potential upside from pursuing an orphan indication, this represents a significant opportunity for Oryzon, in our view. Management is in the process of finalising the design of this trial with the FDA and is targeting the IND application submission in 2024 with the intention of initiating the trial in the same year.

Iadademstat in oncology

For iadademstat in oncology, Oryzon has continued to enrol patients in the [FRIDA](#) study in Q323, and a new cohort was initiated in the quarter. This is an open-label, multicentre Phase Ib trial assessing iadademstat in combination with gilteritinib as a potential treatment for relapsed/refractory (r/r) AML patients harbouring the FLT3 mutation. The primary objectives include

an assessment of safety and tolerability, and establishing the recommended Phase II dose for this drug combination. Oryzon aims to recruit a total of c 45 patients to the FRIDA trial. We note that the company is targeting the second-line setting in AML, which may expedite the route to market for iadademstat, in our view. We expect updates from this study in Q224.

The Phase II basket trial of iadademstat in combination with paclitaxel in platinum r/r small cell lung cancer (SCLC) and extrapulmonary high-grade neuroendocrine tumours (NET) has also continued to enrol patients across the period. This is being carried out in collaboration with the Fox Chase Cancer Center (FCCC). As part of this collaborative agreement, the FCCC will conduct various combination trials with iadademstat and Oryzon is responsible for the funding, as well as providing technical expertise. Study updates are due to be shared in H224.

Management is also preparing for the Phase Ib/II STELLAR trial. This will be a randomised, multicentre study to investigate iadademstat in combination with an immune checkpoint inhibitor (ICI) for the treatment of extensive-stage SCLC in the first-line setting. In our view, [ICI combination approaches](#) are critical in the development of new oncology treatment regimes, and hence we believe this represents a sensible strategy for Oryzon. Furthermore, management believes that STELLAR could support an accelerated approval application. The IND application is in preparation and due to be submitted in 2024.

Exhibit 1: Oryzon's clinical pipeline

CNS: vafidemstat (ORY-2001) - CNS optimized LSD1 inhibitor				
Indication	Borderline Personality Disorder	Schizophrenia Negative Symptoms & Cognition	Kabuki Syndrome	
Study	PORTICO	EVOLUTION	HOPE	
Phase	Phase IIb	Phase IIb	Phase Ib/II	
Status	Recruitment completed	Recruiting	IND in preparation	
Anticipated Updates/Milestones	Front line data 4Q23-1Q24	Study updates 2024	IND 2024	

Oncology: iadademstat (ORY-1001) - Selective LSD1 inhibitor				
Indication	AML 1L Elderly/Unfit	AML R/R-FI3mut+	NETs R/R	ED-SCLC 1L
Study	ALICE (Combo w azacitidine)	FRIDA (Combo w gilteritinib)	NET Basket (Combo w paclitaxel)	STELLAR (Combo w ICI)
Phase	Phase IIa	Phase Ib	Phase II	Phase Ib/II
Status	Completed	Recruiting	Recruiting (Collaborative Study w FCCC)	IND in preparation
Anticipated Updates/Milestones	Final positive results presented at ASH2022	ASCO-2024, ASH-2024	Study updates 2H24	IND 2024

Source: Oryzon website

Financials

During Q323, R&D expenses (accounting for c 85% of total operating expenses) were down at US\$3.8m from US\$4.3m in Q322. However, year-to-date total R&D expenses for FY23 were higher at US\$12.2m versus US\$11.9m in 9M22. Lower amounts of 'other income' were recorded at US\$3.7m in Q323 (vs US\$4.2m in Q322), which is usually capitalised R&D expense, mirroring the reduced R&D expense during the quarter. Gross cash stood at US\$8.8m at end Q323 compared to US\$14.6m at H123, indicating a total cash burn of US\$5.8m during the quarter.

Based on year-to-date results and visibility of Q423, we have made some adjustments to our FY23 estimates. Overall, we expect Oryzon to continue its R&D activities in Q423 at a similar pace. Hence, based on the Q323 run rate for operating expenses, we have slightly decreased our FY23

R&D and SG&A expense estimates to €15.6m (€17.0m previously) and €3.2m (€3.5m previously), respectively. As Oryzon capitalises its R&D expenses and offsets it as other income, we have also slightly lowered our other income estimate to €15.9m from €17.3m previously. These modifications have translated to an increase in our FY23 free cash outflow estimate to €18.7m compared to €14.5m previously. Our FY24 estimates remain essentially unchanged.

Valuation higher as we approach key milestones

Our valuation for Oryzon increases to €900.3m from €874.1m previously, mainly reflecting rolling forward our model by six months, which more than offsets the impact of the above-mentioned changes in estimates and increased net debt balance. As we move closer to the anticipated product launches (iadademstat in 2026 and vafidemstat in 2027) and expected milestones, our discounted valuation increases, while our long-term term assumptions are unchanged. However, the per-share valuation declines to €15.4 compared to €15.6 previously due to an increased total number of shares outstanding (58.6m in Q323 vs 56.2m in Q123). Based on gross cash of US\$8.8m (€8.4m) in Q323 and the latest cash burn rate of US\$5.8m (€5.5m) in Q323, we estimate that Oryzon has a cash runway to Q124, excluding debt repayment obligations in FY23. We also note that the company has the optionality to raise €8m in convertible bonds in two tranches as part of its [€20m convertible bond programme](#). This could extend the company's cash runway to Q224.

The estimated Q323 net debt balance of €6.6m includes gross cash of €8.4m at end Q323 and the H123 gross debt balance (€15.0m), which is the most recent debt figure the company has reported. Considering the anticipated debt repayments due in H223 (c €2.3m) and debt maturity schedule, we estimate the need to raise a total of €50m through FY23–25, shown as illustrative debt in our model. Alternatively, if the funding is realised through an equity issue instead (assuming at the current trading price of €2.00/share), Oryzon would need to issue 25.0m shares, resulting in our per-share valuation decreasing to €11.4 from €15.4 currently (the number of shares outstanding would increase from 58.6m to 83.6m). A breakdown of our risk-adjusted net present value (NPV) valuation is shown in Exhibit 2.

Exhibit 2: 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	4.1
Iadademstat	1L SCLC	2026	740	858.2	25%	210.9	3.6
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	15.4

Source: Edison Investment Research

Exhibit 3: Financial summary

Accounts: Year end 31 December (€000s)	2021	2022	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	58.2	58.6
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	101,786
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	104,348
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
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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