EDISON

Oryzon Genomics

FY22 results

Catalysts on the horizon in FY23

Pharma and biotech

FY23 is shaping up to be a busy clinical year for Oryzon with readouts and trial initiations expected across its lead assets. The next major clinical milestone for iadademstat in oncology is the initiation of the Phase Ib FRIDA study in second-line FLT3+ relapsed/refractory (r/r) acute myeloid leukaemia (AML) patients with the trial expected to start imminently. Oryzon's lead central nervous system (CNS) clinical asset, vafidemstat, is being assessed for the treatment of borderline personality disorder (BPD) in the Phase IIb PORTICO study. Interim data readouts are expected from the trial in Q123, which we view as the next major upcoming catalyst for investor attention. Our valuation of Oryzon remains largely unchanged at €869.0m or €15.6 per share (previously €846.7m or €15.5/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	(6.6)	(0.07)	0.0	N/A	N/A
12/23e	17.3	(4.2)	(0.03)	0.0	N/A	N/A
12/24e	19.0	(10.0)	(0.14)	0.0	N/A	N/A

Note: *PBT and EPS is normalised, excluding amortisation of acquired intangibles, other income and exceptional items.

FRIDA and PORTICO in focus

While iadademstat is being investigated across multiple indications in oncology, management has stated that the Phase Ib FRIDA study is now central to the company's overall strategy. Second-line AML represents a significantly underserved patient population that management believes could expedite iadademstat's route to market. In CNS, the PORTICO study represents a potentially significant commercial opportunity for Oryzon as there are currently no FDA-approved treatments for BPD. In our view, the 2023 PORTICO interim and top-line readouts may play an important role in shaping management's future development strategy for vafidemstat within its CNS portfolio.

Cash runway into FY24

At end FY22, Oryzon had a gross cash position of €21.3m with total outstanding debt of €17.3m. We estimate that the current annual burn rate of around €16m, excluding debt obligations, will provide a cash runway into H124. We estimate that the company will need to raise an additional c €50m through 2025 (€8m in FY23 considering potential debt repayments) to fund its operations.

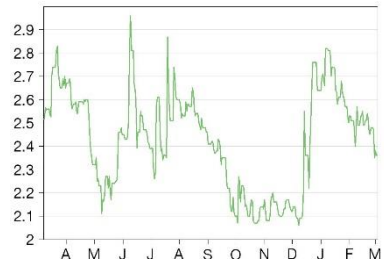
Valuation: €869.0m or €15.6/share

We value Oryzon at €869.0m or €15.6/share (previously €846.7m or €15.5/share). The valuation has been affected slightly by rolling our model forward and updating our exchange rate assumptions to $1.07/€ (from $1.06/€), but our underlying long-term assumptions remain unchanged.

6 March 2023

Price	**€2.11**
Market cap	**€115m**
	US$1.06/€
Net cash (€m) at end-December 2022	4.0
Shares in issue	56.3m
Free float	80%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(6.2)	10.0	(12.8)
Rel (local)	(8.5)	(2.5)	(26.2)
52-week high/low		€2.96	€2.06

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 is now the lead study, but Oryzor is rapidly expanding its CNS R&D pipeline.

Next events

Phase II PORTICO interim data	Q123
Phase Ib FRIDA trial initiation	H123

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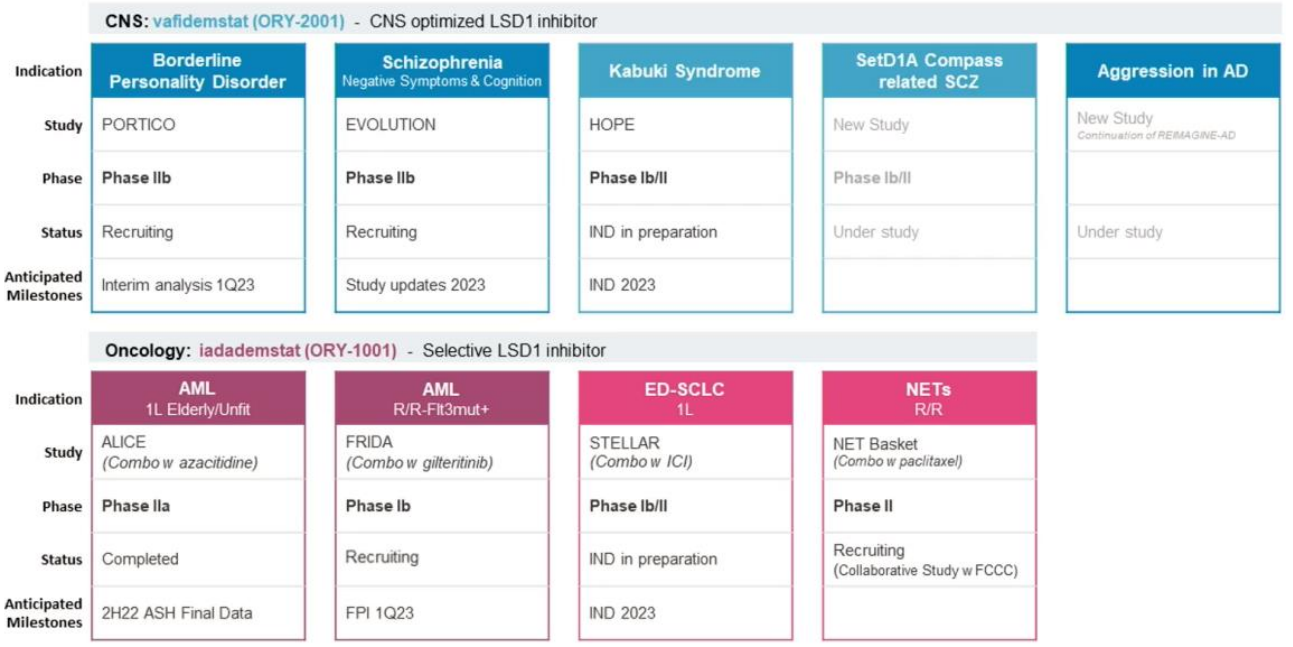
No let up on clinical progression

Following the completion of the ALICE trial, Oryzon's clinical pipeline is continuing momentum with the next anticipated milestone coming in the form of the independent interim and top-line readouts from the PORTICO study. The independent analysis, based on the 90 patients enrolled within the study will provide futility assessment; top-line data are expected in Q423/H124. In oncology, Oryzon is strategically prioritising iadademstat in AML and now expects to initiate the Phase Ib FRIDA in Q123 (previously communicated in H222).

Exhibit 1: Oryzon clinical pipeline



Source: Oryzon KOL event

Positive AML results in ALICE turns attention to FRIDA

Oryzon finished 2022 on a positive note when it presented encouraging data readouts from the Phase IIa ALICE trial investigating its lead oncology asset iadademstat in combination with azacitidine, for the treatment of AML in newly diagnosed elderly/unfit patients. The study met its primary endpoints of safety and tolerability with no major non-haematological or organ-related toxicities. Notably, iadademstat displayed an encouraging efficacy profile, achieving an objective response rate (ORR) of 81% and median overall survival (mOS) of 11.1 months, significantly higher than previously reported values for azacitidine monotherapy (ORR: c 30%; mOS: c 7–8 months), although we note that comparison between trials must be undertaken with caution.

Oryzon intends to keep up the clinical pace of iadademstat in AML with the initiation of the Phase I FRIDA study in a subset of r/r AML patients (FLT3+), an indication that may represent a sizable opportunity in a market segment with less overall competition. The trial will investigate iadademstat in combination with Astella's FDA-approved FLT3 inhibitor gilteritinib (Xospata) for patients with r/r FLT3+ AML in a second-line setting. In our view, a potentially noteworthy result from the ALICE study, and one that may provide insight into the upcoming Phase Ib FRIDA trial, was the observation that those evaluable AML patients (n=3) possessing an FLT3 mutation (FLT3+) all responded to iadademstat treatment. However, we acknowledge that the current data only represent a small number of patients so there may be limitations in extrapolating from this finding.

Additionally, the mOS for gilteritinib monotherapy in FLT3+ r/r AML patients is 9.3 months and, in our view, combinational treatments may provide scope for further improvements. In our recent Oncology ABCs report, we discussed combination therapies being critical for developing new efficacious treatment regimens in oncology and, should similar positive synergistic effects from iadademstat/gilteritinib be observed in patients enrolled in FRIDA, we believe this could represent a significant opportunity for Oryzon. Management had previously communicated that the FRIDA study would be initiated by end 2022, so we expect patient enrolment to start in Q123.

Oncology pipeline momentum continues in solid tumours

In January 2023 Oryzon announced it had enrolled the first patient into its collaborative Phase II trial investigating the use of iadademstat, in combination with paclitaxel for the treatment of r/r small cell lung cancer (SCLC) or high-grade (G3) neuroendocrine carcinomas (NECs). The trial is being conducted in collaboration with the Fox Chase Cancer Center, a leading investigational cancer institute in the US, with Oryzon providing funding, iadademstat and technical advice. In our view, the first patient enrolment marks a significant clinical milestone for the study, opening iadademstat's potential expansion into additional indications.

The company is also looking to file an investigational new drug (IND) application to the FDA in 2023 for the Phase I/II (STELLAR) trial in first line metastatic SCLC (mSCLC), investigating the combination of iadademstat with immune checkpoint inhibitors (ICIs). The ICI atezolizumab (Tecentriq) has been approved as a first line treatment in mSCLC in combination with chemotherapy (carboplatin and etoposide). However, the treatment regime only offers modest improvements in overall survival (OS) compared to chemotherapy alone (median OS 12.3 vs 10.3 months) so an unmet need to achieve sustained disease control continues to exist. Additionally, preclinical studies suggest that LSD1 inhibitors may sensitise SCLC tumours to ICIs, offering potential synergistic benefits for the ICI/iadademstat combination, in our view. While management has communicated that it expects to submit an IND in 2023 for STELLAR, we might expect a slower trial initiation given the company's strategic focus on FRIDA in AML.

Imago deal sets a precedent in LSD1

In Q422 Merck announced it would acquire the LSD1-focused biotech Imago Biosciences for $1.35bn ($36.00 per share in cash), news that saw Imago's stock price jump by c 100% at the time. After completion of the deal in Q123, Oryzon has become one of the most advanced-stage independent LSD1 inhibitor players, as shown in Exhibit 2. Overall, we view the Merck/Imago deal as a highly encouraging precedent transaction in the LSD1 space. Additionally, with the global AML market expected to reach US$9.4bn by 2028 (EvaluatePharma) we see this as a potentially attractive opportunity that may trigger renewed interest from further big pharma players.

Exhibit 2: LSD1 targeting oncology pipeline

Company	Drug	Phase	Indication/s	Notes
Oryzon	Iadademstat	Phase II Phase I Phase II	First line AML r/r FLT3+ AML Neuroendocrine cancers	Phase Ib FRIDA study in r/r FLT3+ AML expected to initiate in Q123 Phase II study in neuroendocrine cancers in combination with paclitaxel initiated in Q123 Preparing new Phase Ib/II trial (STELLAR) in mSCLC
Imago Biosciences (Merck)*	Bomedemstat	Phase II Phase II	Essential thrombocythemia myelofibrosis	Trial readouts expected by end CY22. **Merck announced acquisition of Imago for US$1.35bn**
Jubilant Therapeutics	JB-802	Phase I/II	Advanced solid tumours	Targets both LSD1 and HDAC6
Salarius Pharmaceuticals	Seclidemstat	Phase I	Ewing sarcoma	Study currently on hold due to patient death classified as a suspected unexpected serious adverse reaction
Bristol Myers Squibb / Celgene	Pulrodemstat	Phase I	Solid tumours and non-Hodgkin lymphomas	In combination with either an antibiotic (rifampin) or antifungal (itraconazole)
Otsuka Pharmaceuticals (Astex Pharmaceuticals)	TAS1440	Phase I	r/r AML	In combination with all-trans retinoic acid

Source: EvaluatePharma Note: *Merck acquisition announced on 21 November 2022 and expected to close in Q1 CY23.

Catalyst approach for vafidemstat

Interim readouts in BPD in Q123

The most significant clinical news emerging from Oryzon's ongoing CNS programmes came in the form of interim safety data from its Phase IIb randomised, double-blind PORTICO study, investigating the use of vafidemstat for the treatment of BPD. In September 2022 the company reported no serious adverse events from the first 43 patients enrolled in the trial and that approval for the study to continue had been granted by the PORTICO independent data-monitoring committee. The primary endpoints for the study are overall clinical BPD improvement and improvement in aggression. Interim analysis for 90 patients in PORTICO is anticipated in Q123, the results of which may dictate future patient enrolment (up to 156 are planned to be recruited), and final readouts expected in Q423. The current standard of care in BPD is often off-label prescribed anti-psychotic medications. These therapies act as a sedative; however, they do not treat the symptoms of psychosis observed in BPD patients. Additionally, anti-psychotics are associated with a significant side-effect burden such as weight gain, metabolic syndrome, cholesterol and sexual side effects. With no drugs specifically approved for the treatment of BPD, we see vafidemstat as a potential first to market drug within this indication and, with its observed safety profile to date, offering significant market differentiation against off-label anti-psychotics, provided it can demonstrate efficacy.

Valuation

We value Oryzon at €869m or €15.6/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate and Q422 net cash of €4m. Our underlying long-term assumptions remain unchanged; however, we have rolled our model forward, updated our exchange rate assumption to $1.07/€ (from $1.06/€) and updated net cash. A breakdown of our rNPV valuation is shown in Exhibit 3, which includes five rNPV projects (for more details see our Outlook note). We have not yet included vafidemstat in Kabuki syndrome while we await trial initiation. We have also excluded iadademstat in G3-NECs pending further clinical data from the Phase II basket study to further define the target G3-NEC patient population.

Exhibit 3: Valuation of Oryzon

Product	Indication	Launch	Peak sales ($m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
Iadademstat	2L AML	2026	500	777.8	30%	229.1	4.1
	1L SCLC	2026	730	822.3	25%	201.1	3.6
Vafidemstat	BPD	2027	1,610	1,284.0	20%	247.7	4.5
	Schizophrenia, negative symptoms	2027	700	646.4	15%	89.9	1.6
	Aggression in Alzheimer's disease	2028	910	686.4	15%	97.2	1.7
Net cash end FY22				4.0	100%	4.0	0.1
Valuation				**4,220.9**		**869.0**	**15.6**

Source: Edison Investment Research

Financials

Oryzon's total operational expenses (excluding COGS) stood at €21.0m in FY22, 23.1% (y-o-y) higher than €17.0m in FY21. R&D expenses (€13.7m) constituted c65% of operating expenses in FY22, increasing 40.4% (y-o-y) in FY22 compared to €9.5m in FY21. The higher external R&D expenses were mainly attributed to related CRO service fees for the clinical development of Phase Ib/II clinical trials for iadademstat and vafidemstat molecules, along with preclinical stage projects. Free cash flow (outflow) for the company was 5.0% higher to €16.1m in FY22 from €15.4m in FY21.

Following the FY22 results, we have updated our FY23 estimates and have now introduced FY24 estimates. We forecast FY23 total operating expenses of €20.6m (previously €16.4m), in line with FY22 (€21.0m); however, we expect expenses to grow further in FY24 to €24.0m. We estimate R&D expenses to increase to €17.0m and €24.0m in FY23 and FY24, respectively, as Oryzon continues to progress its assets into later stage clinical studies. We estimate an increase in net cash outflow from operations to €2.8m in FY23 and €7.0m in FY24, respectively, in line with current operational spending and increased R&D activity. In our model, we project that Oryzon will launch its first product into the market in FY26.

In FY22, the company announced that it has entered into a convertible bonds financing agreement with a Swiss institutional investor, Nice & Green, to raise up to €20m over 30 months. The raise is designed to help capitalise the company past key inflection points from ongoing clinical trials in FY22, FY23 and fund clinical development into H124. The financing agreement consists of four tranches, including an initial tranche of €8m, followed by three optional future tranches of €4m each, to be executed at Oryzon's request, subject to customary conditions. By end-FY22, the company subscribed to €8m convertible bonds out of the total €20m plus additional €2m bonds subscription (for €1m arrangement fee and €1m contractual deposit amount) totalling to 100 bonds. Out of the 100 bonds (nominal value of 100k each) subscribed by end FY22, the company had converted 55 bonds into shares with 45 outstanding. We have modelled this as repayment of debt in our model.

Post the reporting period, the company drew a further €4m in a second tranche in January 2023 as part of the financing agreement against 40 convertible bonds. Additionally, we note that in January 2023 the company converted a further 19 bonds into shares. This results in a total of 66 bonds outstanding for conversion as of January 2023.

Based on our forecast cash burn rate and gross cash position (€21.3m) in FY22, we estimate that, excluding debt repayment obligations, Oryzon has a cash runway to H124. We note the company had bank borrowings of €14.0m by end FY22 and €3.3m of convertibles bonds, which are likely to be converted to common shares (similar to previous bonds under the same financing agreement). Considering debt repayments due in FY23, we estimate the need to raise €8m in FY23 and further €20m in FY24 and €22m in FY25. Out of the total €50m cash requirement (shown as illustrative debt), the company may raise €12m through the remaining convertible bond agreement using three optional tranches (€4m already raised through the agreement in January 2023). Alternatively, if the funding is realised through an equity issue instead (assuming at the current trading price of €2.11/share), Oryzon would have to issue 23.7m shares, resulting in our per-share valuation coming down to €11.0/share from $15.6 currently (shares outstanding would increase from 55.6m to 79.3m).

Exhibit 4: Financial summary

Accounts: Year end 31 December (€000s)	2021	2022	2023e	2024e
INCOME STATEMENT				
Total revenues	10,615	15,698	17,268	18,995
Cost of sales	(746)	(464)	(487)	(512)
Gross profit	9,869	15,234	16,781	18,483
Gross margin %	93%	97%	97%	97%
SG&A (expenses)	(3,782)	(3,163)	(3,479)	(3,827)
R&D costs	(9,746)	(13,681)	(16,975)	(23,975)
Other income/(expense)	(3,203)	(3,714)	0	0
Exceptionals and adjustments	(4)	0	0	0
Reported EBITDA	(6,866)	(5,323)	(3,673)	(9,318)
Depreciation and amortisation	144	167	149	131
Reported EBIT	(7,011)	(5,490)	(3,822)	(9,450)
Finance income/(expense)	(169)	(871)	(426)	(579)
Other income/(expense)	0	(195)	0	0
Reported PBT	(7,180)	(6,557)	(4,248)	(10,029)
Income tax expense (includes exceptionals)	2,493	2,325	2,409	2,367
Reported net income	(4,687)	(4,231)	(1,839)	(7,662)
Basic average number of shares, m	53.1	54.3	55.6	55.6
Basic EPS (p)	(0.09)	(0.08)	(0.03)	(0.14)
Adjusted EBITDA	(6,862)	(5,323)	(3,673)	(9,318)
Adjusted EBIT	(7,007)	(5,490)	(3,822)	(9,450)
Adjusted PBT	(7,176)	(6,361)	(4,248)	(10,029)
Adjusted EPS (€)	(0.09)	(0.07)	(0.03)	(0.14)
Adjusted diluted EPS (€)	(0.09)	(0.07)	(0.03)	(0.14)
BALANCE SHEET				
Property, plant and equipment	682	611	538	482
Intangible assets	60,254	75,843	87,460	99,926
Investments	29	31	31	31
Deferred tax assets	1,812	2,050	2,050	2,050
Total non-current assets	62,778	78,535	90,078	102,489
Cash and equivalents	28,725	21,317	5,152	496
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	8,968	4,328
Deferred tax liabilities	1,812	2,050	2,050	2,050
Long term debt*	13,354	10,346	14,486	31,877
Other non-current liabilities	285	0	0	0
Total non-current liabilities	15,451	12,396	16,536	33,927
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	70,733	63,071
	0	0	0	0
CASH FLOW STATEMENT				
Profit before tax	(7,180)	(6,557)	(4,248)	(10,029)
Cash from operations (CFO)	(3,626)	(1,848)	(2,770)	(6,991)
Capex	(175)	(76)	(76)	(76)
Acquisitions & disposals net	0	0	0	0
Acquisition of intangible assets	(11,586)	(14,195)	(11,617)	(12,466)
Other investing activities	37	(1)	0	0
Cash used in investing activities (CFIA)	(11,724)	(14,271)	(11,693)	(12,542)
Net proceeds from issue of shares	0	(932)	0	0
Movements in debt	4,123	9,642	(1,703)	14,877
Other financing activities	0	0	0	0
Cash from financing activities (CFF)	4,123	8,710	(1,703)	14,877
Increase/(decrease) in cash and equivalents	(10,880)	(7,408)	(16,165)	(4,656)
Currency translation differences and other	348	1	0	0
Cash and equivalents at start of period	39,605	28,725	21,317	5,152
Cash and equivalents at end of period	28,725	21,317	5,152	496
Net (debt) cash	14,954	3,975	(3,094)	(2,648)

Source: Oryzon Genomics, Edison Investment Research. Note: Long-term and short debt also include derivatives and other financial liabilities. Oryzon reports in Spanish GAAP. *Includes cash outflows related to development costs that were capitalised.

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