EDISON

Oryzon Genomics

FY23 results

Approaching a period of inflection

Pharma and biotech

Oryzon's FY23 results announcement covered an eventful period for the company's pipeline, capped by the release of top-line data from the Phase IIb PORTICO trial for lead CNS asset vafidemstat. With the focus squarely on the planned end of Phase II (EoP2) meeting with the FDA and anticipated clinical updates on the remaining programmes, we see FY24 as a crucial period for the company, with multiple inflection points. Other key upcoming milestones include results from the FRIDA trial (iadademstat in FLT3+ r/r acute myeloid leukaemia; expected in Q224) and a clinical timeline update from the EVOLUTION trial (vafidemstat in schizophrenia; expected in 2024). Based on the current status of the company's programmes and improved visibility, we have adjusted our market strategy, launch timelines and valuation across the company's pipeline, leading to a valuation reset to €11.8/share (€15.1/share previously).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/22	15.7	(6.3)	(0.07)	0.0	N/A	N/A
12/23	14.2	(6.0)	(0.06)	0.0	N/A	N/A
12/24e	12.9	(4.2)	(0.03)	0.0	N/A	N/A
12/25e	33.7	15.5	0.29	0.0	N/A	N/A

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

A catalyst-rich period ahead

We anticipate results from the FDA EoP2 meeting in Q324, marking a major inflection point. Several other updates are expected to be potential catalysts: results from the Phase Ib FRIDA and timeline update from the Phase IIb EVOLUTION trials are expected in 2024 (the former in Q224) and will be keenly watched. The submission of the IND application for the Phase I/II vafidemstat HOPE trial in Kabuki Syndrome is also expected. Further, Oryzon plans to assess iadademstat plus venetoclax and azacitidine in the IIS trial for AML, due to start recruiting in Q124. Additionally, Oryzon is preparing for the CRADA-MSKCC and STELLAR iadademstat trials in SCLC, for which updates are expected throughout 2024.

Cash runway into FY25 with current funds

Oryzon ended FY23 with a gross cash balance of €12.3m, supported by an €8m drawdown from the €45m convertible debt facility. This, along with another €2m in February 2024, should support runway extension into FY25 (excluding upcoming debt repayments). We estimate the company will draw down a further €10m in FY24, and remaining €25m in FY25. We have updated our model to incorporate a potential licensing deal for BPD in FY25 (including a risk-adjusted upfront payment of €20m), with extension to schizophrenia and aggression in Alzheimer's disease (AD) in FY26, inflows from which should provide further non-dilutive funding.

Valuation: Resets to €732.6m or €11.8 per share

Based on the progress of current programmes and improved visibility of pipeline plans, we have made broad adjustments to our go-to-market strategy and launch timelines across all programmes (detailed later). Our valuation for Oryzon resets to €732.6m or €11.8 per share (from €900.3m or €15.1 per share previously).

5 March 2024

Price	**€1.63**
Market cap	**€101m**
Net debt* (€m) at end-December 2023 *Excluding post-period debt-to-equity conversion	6.3
Shares in issue	62.0m
Free float	82%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(13.2)	(21.9)	(30.9)
Rel (local)	(13.3)	(21.1)	(35.0)
52-week high/low		€2.40	€1.63

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 (BPD)	Q224
FRIDA update (AML)	Q224
EVOLUTION trial timeline update	2024

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Edison profile page

Sustained focus on both CNS and oncology

As part of Oryzon's FY23 results, management reaffirmed its commitment to progress its clinical programmes focused on diseases of the central nervous system (CNS) with vafidemstat, and in oncology with iadademstat (Exhibit 1). In addition to the ongoing studies for its clinical-stage assets (discussed in further detail below), Oryzon is also focused on strengthening its preclinical portfolio. ORY-4001 (an inhibitor of histone deacetylase 6, HDAC6) is being developed for the treatment of neurological conditions such as Charcot-Marie-Tooth disease and amyotrophic later sclerosis; it is currently progressing through investigational new drug (IND)-enabling studies. The company announced the receipt of a $0.5m grant in December 2023 from the ALS Association to support this programme. In addition, ORY-3001 (an inhibitor of lysine specific demethylase 1, LSD1) is being developed for sickle cell disease following encouraging preclinical research in this indication.

Exhibit 1: Oryzon's clinical pipeline, focused on CNS and oncology

Program	Study	Preclinical Phase	Phase I		Phase II		Status	Expected Milestone(s)
			Phase Ia	Phase Ib	Phase IIa	Phase IIb		
CNS: Vafidemstat (ORY-2001) - CNS optimized LSD1 inhibitor								
Borderline personality disorder Agitation/Aggression & Overall Improvement	PORTICO						Completed. Study has results	Top line data in January 2024 BioMks & Final Data 2Q2024 EoP2 FDA meeting in 2024
Schizophrenia Negative Symptoms & Cognition	EVOLUTION						Recruiting	Timeline updates 2024
Kabuki Syndrome	HOPE			Phase Ib / II			IND in preparation	IND 2024
Oncology: Iadademstat (ORY-1001) - Selective LSD1 inhibitor								
AML 1L Unfit Patients Combination with azactidine	ALICE						Completed. Study has results	Final positive results presented at ASH2022
AML 1L Unfit Patients Combination with azactidine and venetoclax	IIS-X002			Phase Ib			IND Approved Led by OSHU	FPI 1Q2024
AML R/R-Flt3mut+ Combination with gilteritinib	FRIDA			Phase Ib			Recruiting	EHA-2024, ASH-2024
Neuroendocrine High Grade R/R Combination with paclitaxel	C-X001 NET Basket						Recruiting Collab. Study with FCCC	Study updates 2H24
ED-SCLC 1L Combination with ICI	CRADA-IIS						IND in preparation Led by MSKCC	IND 1Q2024
ED-SCLC 1L Combination with ICI	STELLAR						IND in preparation Company sponsored	IND 2024
Other Programs								
ORY-3001 (LSD1i) Sickle Cell Disease	--						IND enabling tox completed	
ORY-4001(HDAC6i) CMT, ALS	--						IND enabling tox ongoing	2023 PNS Annual Meeting June 2023

ALS: amyotrophic lateral sclerosis; AML: acute myeloid leukemia; CMT: Charcot-Marie-Tooth disease; NET: neuroendocrine tumors; SCLC: small cell lung cancer; ICI: immune checkpoint inhibitor
FCCC: Fox Chase Cancer Center; MSKCC Memorial Sloan Kettering Cancer Center; OSHU Oregon Health & Science University; IIS: investigator-initiated study

Source: Oryzon company website. Note: Red boxes indicate the company's strategic priorities.

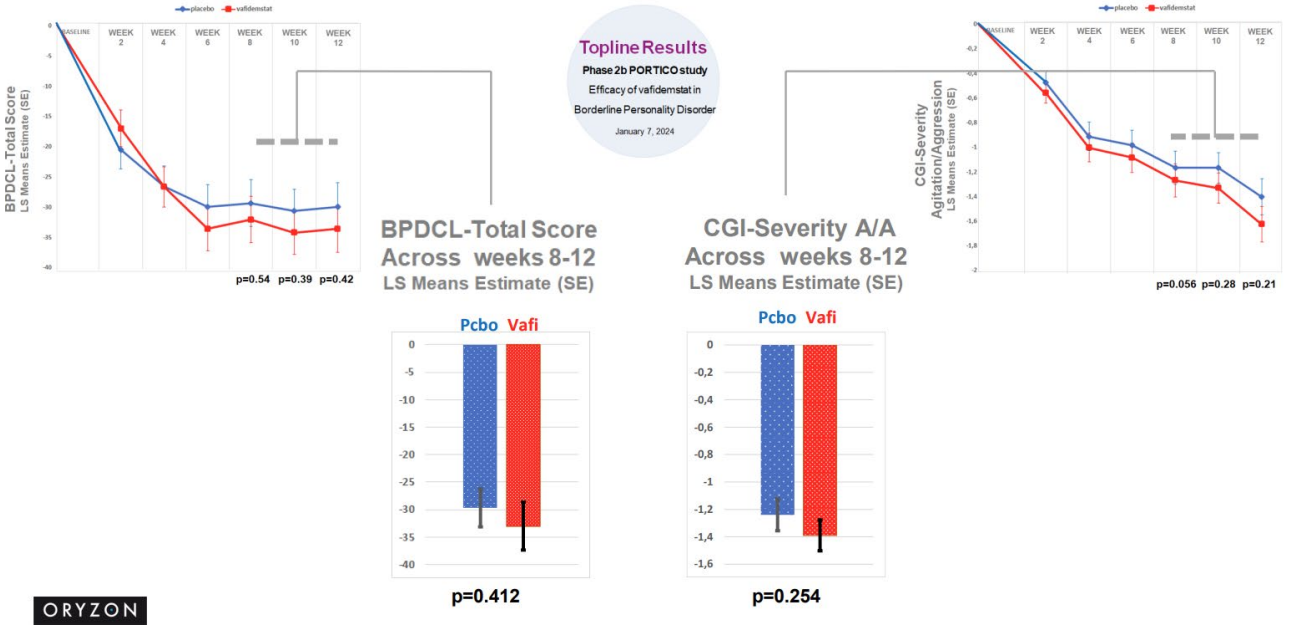
Vafidemstat: Progress in BPD; schizophrenia up next

The latest from the clinic: PORTICO

The most recent clinical results for vafidemstat were from the randomised, placebo-controlled, double-blinded 14-week Phase IIb PORTICO trial. Participants (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). Primary endpoints included improvements in the Borderline Personality Disorder Checklist (BPDCL, a 47-item patient-completed assessment) and Clinical Global Impression – Severity Agitation/Aggression (CGI-S A/A, a clinician-completed assessment on impression of agitation and aggression), both from baseline to weeks 8–12. The results showed that vafidemstat did not demonstrate a statistically significant improvement versus placebo by these

measures (Exhibit 2). However, the data showed a separation in performance between the vafidemstat and placebo arms from week four through to week 12, demonstrating an encouraging trend in favour of vafidemstat based on both clinician- and patient-reported measures.

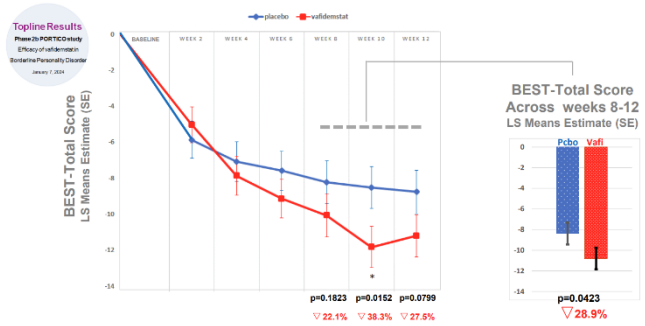
Exhibit 2: PORTICO – primary endpoint data (BPDCL and CGI-S A/A)



Source: Oryzon corporate presentation (January 2024)

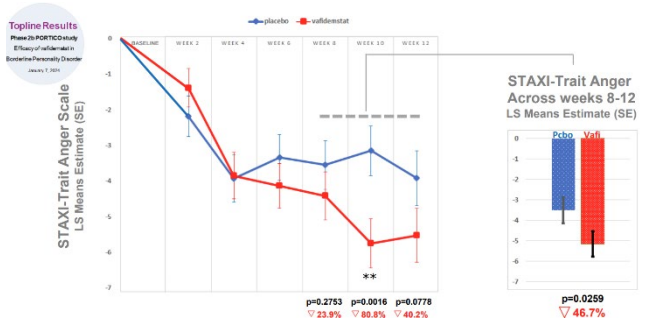
Two of the key PORTICO secondary efficacy endpoints were improvements from baseline to weeks 8–12, as well as change over time in overall BPD severity, measured by Borderline Evaluation of Severity (BEST, a 15-item patient-completed assessment), and in agitation/aggression, measured by State-Trait Anger Expression Inventory 2 (STAXI-2) Trait Anger (a 54-item patient-completed assessment). Encouragingly, the results per these parameters demonstrated statistically significant improvements, also showing a trend of separation from week four to week 12 (Exhibits 3 and 4). The BEST data showed a 38.3% benefit in favour of vafidemstat treatment at week 10, associated with an overall average reduction of 28.9% across weeks 8–12. The STAXI-2 Trait Anger data showed an 80.8% benefit at week 10, with an overall average reduction of 46.7% across weeks 8–12.

Exhibit 3: PORTICO – BEST data



Source: Oryzon corporate presentation (January 2024)

Exhibit 4: PORTICO – STAXI-2 Trait Anger data



Source: Oryzon corporate presentation (January 2024)

In addition to the positive efficacy results, whereby vafidemstat was favoured over placebo for all measures, the drug was also found to be safe and well-tolerated. There was a similar rate of treatment-emergent adverse events across both arms, all of which were resolved by the end of the study. Importantly, there were no patient deaths or suicides, and suicidal ideation was low, a highly

encouraging result, in our view, given the nature of the patient population. For a more detailed discussion of the PORTICO results, we direct readers to our prior update note.

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 borderline personality disorder (BPD) patients. Oryzon hosted a key opinion leader (KOL) event to discuss the PORTICO results and the current treatment landscape in BPD. During the event, the KOLs highlighted that improvements of 25% or more, across any measure of overall severity and agitation/aggression, as demonstrated in PORTICO, mark a clinically meaningful outcome. This was emphasised with a reminder that there are currently no approved drugs specifically for BPD, and the current prescribed therapies are often ineffective. We therefore believe that there is a significant opportunity for Oryzon to deliver an effective treatment option for this underserved patient population.

It is our opinion that further clinical development in BPD will be subject to the FDA's interpretation of the clinical data. Oryzon plans to request an EoP2 meeting with the FDA in Q224, once the full analysis has been complete (including biomarker data), and we expect updates to be shared after this as the information becomes available. If positive, we expect the company to be able to sign a partnership/licensing deal for the asset in FY25.

Updates in schizophrenia looming

As part of the company's year-end update, management has communicated that the EVOLUTION trial continues to enrol patients. This is a double-blind, placebo-controlled, randomised, 24-week Phase IIb study to evaluate the efficacy of vafidemstat for the treatment of negative symptoms (affective flattening; anhedonia; avolition) and cognitive impairment (deficits in memory; attention; learning; executive function) in schizophrenia patients (expected n=100). This clinical programme is being partially financed with public funds from the Spanish Ministry of Science and Innovation; it is being conducted in various Spanish hospitals.

The field of schizophrenia treatment has not seen significant progression since the 1950s, which saw the approval of typical antipsychotics (dopamine type 2 receptor agonists, such as chlorpromazine, haloperidol, pimozide and loxapine). The 1970s saw the development of atypical antipsychotics (target serotoninergic receptors 5-HT2A, such as clozapine, olanzapine, risperidone and quetiapine). While typical and atypical antipsychotics have been effective for positive symptoms (hallucinations, delusions), they have limited efficacy against negative and cognitive symptoms. As the healthcare community's understanding of schizophrenia pathophysiology has evolved in recent years, we expect new treatment approaches to emerge, and believe there is a significant opportunity for Oryzon to address the unmet need in this space. We note that this field has been picking up the pace recently, with two notable transactions in December 2023:

- AbbVie announced the acquisition of Cerevel in a deal worth $8.7bn. Importantly, this gives AbbVie access to Cerevel's promising Phase II asset, emraclidine, which is being developed for the treatment of schizophrenia.
- Bristol Myers Squibb announced the acquisition of Karuna Therapeutics for $330/share in cash (total equity value of $14bn or $12.7bn net of estimated cash acquired). At the centre of this deal was Karuna's KarXT, which is the same class of therapeutic as emraclidine for the treatment of schizophrenia, albeit at a later stage. The FDA has set a PDUFA goal date of 26 September 2024.

In the pipeline: Vafidemstat for Kabuki syndrome

Management has reaffirmed its plans to finalise the design of the Phase I/II HOPE trial in Kabuki syndrome (a rare congenital disorder), and submit an IND application in 2024, with the trial potentially launching by end-2024. We highlight that this would mark Oryzon's first clinical

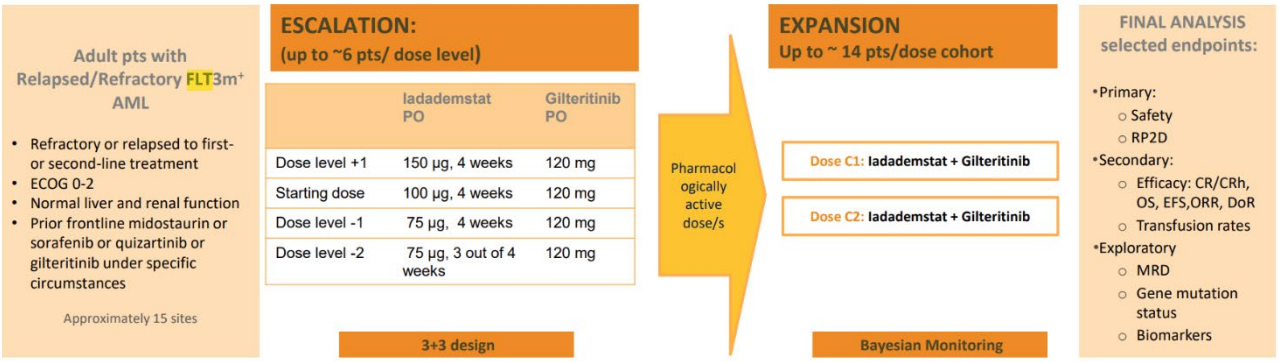
programme with a precision medicine approach for a monogenic CNS indication (a condition known to be caused by a single genetic abnormality), as it will target a genetically-defined patient sub-population. In the case of Kabuki syndrome, 55–80% of cases are caused by variants in the KMT2D gene, and Oryzon believes it can provide an effective treatment option for this orphan indication through inhibition of LSD1, an epigenetic modulator involved in controlling gene expression through histone demethylation. (Additional details on epigenetics and LSD1 can be found below.)

Iadademstat: FRIDA remains the prime focus

A promising opportunity in AML

Aiming to maintain the momentum from the positive results reported in Q422 of the Phase IIa ALICE trial, Oryzon continues to enrol patients for the Phase Ib FRIDA trial (Exhibit 5). This is an open-label, single-arm, multicentre Phase Ib study to investigate iadademstat in combination with gilteritinib in patients with relapsed/refractory (r/r) acute myeloid leukaemia (AML) harbouring the FMS-like tyrosine kinase 3 (FLT3) mutation (expected n=45). Primary objectives include safety, tolerability and determining the recommended Phase II dose for the drug combination. Secondary objectives include evaluation of efficacy, measured as the rate of complete remission and complete remission with partial haematological recovery (CR/CRh), duration of responses (DoR) and the assessment of measurable residual disease (MRD). The first cohort (six patients) has completed treatment, and the combination was found to be safe with early indications of efficacy. The second cohort (six patients) is now fully enrolled and undergoing treatment, while expansion and/or starting of a third cohort is currently under consideration. According to management, initial preliminary data looks promising when compared to gilteritinib alone in historical data, and we expect a more detailed update for FRIDA at the European Hematology Association 2024 conference (13–16 June 2024). We highlight that Oryzon is targeting the second-line (2L) AML treatment setting, which, in our view, could expedite the route to market for iadademstat compared to other drugs in development targeting the first-line (1L) AML setting. Management has communicated that if the trial results are positive, a meeting will be held with the FDA to discuss a potential route to market.

Exhibit 5: FRIDA trial design and selected endpoints



Source: Oryzon corporate presentation (January 2024)

In a new development, the company has announced plans to expand the clinical development of iadademstat in AML with a new investigator-initiated study (IIS). This programme, led by Oregon Health & Science University, will commence with a Phase Ib dose-finding study to evaluate iadademstat in combination with venetoclax and azacitidine as a potential 1L treatment option for AML patients. The FDA green-lighted the IND application for this trial in Q423, and patient enrolment is expected to commence from Q124.

Next up: NETs and SCLC

Beyond AML, iadademstat is also being assessed in combination with paclitaxel in platinum r/r small cell lung cancer (SCLC) and extrapulmonary high-grade neuroendocrine tumours (NETs) in a Phase II basket trial; patient enrolment is ongoing. This programme is being conducted in collaboration with the Fox Chase Cancer Center (FCCC). As part of this collaborative agreement, the FCCC is conducting a basket NET trial with iadademstat, with Oryzon providing the drug, funding and technical expertise. Study updates are expected throughout H224.

In a further development, Oryzon has announced plans to expand the clinical development of iadademstat with a programme conducted under the cooperative research and development agreement (CRADA) signed with the National Cancer Institute (NCI) in the US; this is currently under preparation. The trial (led by the Memorial Sloan Kettering Cancer Center, MSKCC), will explore iadademstat in combination with an immune checkpoint inhibitor (ICI) for the treatment of extensive-stage SCLC (1L setting); the IND application is expected to be submitted to the FDA in Q124.

Accordingly, interim findings from the CRADA-MSKCC trial will be used to refine plans for the Phase Ib/II STELLAR trial (sponsored by Oryzon), as it is in the same space and will have the same design. STELLAR is intended to be a randomised, multicentre study to evaluate iadademstat in combination with an ICI in extensive-stage SCLC (first-line). As we continue to believe that ICI combination approaches will be critical in defining new oncology treatment regimes, it is our opinion that this represents a sensible strategy for Oryzon. Furthermore, Oryzon management believes that STELLAR could support an accelerated approval application; the IND application for STELLAR is expected to be submitted by end-2024. However, we note that the progress of STELLAR could be subject to delays related to the timing of interim readouts from the CRADA-MSKCC trial.

Epigenetics and LSD1

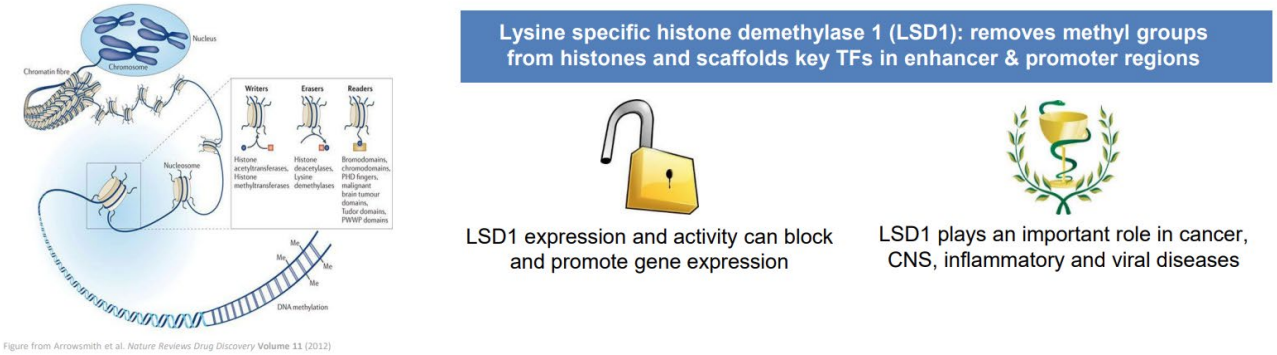
Epigenetics refers to the study of changes in the way genes are expressed ('read'), without alteration of the underlying DNA sequence. Epigenetic modifications can influence how certain genes (sequences of DNA corresponding to units of heredity) are turned on or off, and can be caused by various external stimuli, such as behaviour and environment.

In cell nuclei, DNA is tightly packed and organised into 23 pairs of chromosomes. These structures are comprised of DNA wrapped around protein complexes called histones, which make the genes compact. The resultant structures are called nucleosomes (DNA-wrapped histones), building blocks that make up chromatin, which in turn make up chromosomes. Epigenetic modifications can disrupt the spatial organisation within these structures, changing which genes are accessible for transcription (expression) or inaccessible (silenced). Epigenetic regulation is a natural biological process, but can also be aberrant, contributing to the pathogenesis of various diseases. The term epigenetics encompasses three main types of modification:

- DNA methylation – the addition of a methyl group to DNA, which typically leads to gene silencing by preventing transcriptional machinery from binding. (It is worth noting that epigenetic modifications are often reversible, and hence, demethylation can lead to promoted gene expression.)
- Histone modification – chemical modifications at the histone tail within nucleosome complexes, including (but not limited to) acetylation, methylation and phosphorylation, which alter the chromatin structure to influence gene expression, turning genes on or off.
- Non-coding RNA – DNA is used as instructions for making coding and non-coding RNA. While coding RNA (messenger RNA, or mRNA) is used to make proteins, non-coding RNA regulates gene expression by either promoting or degrading mRNA, turning genes on or off.

Lysine specific demethylase 1 (LSD1, also known as KDM1A) is a histone-modifying enzyme that forms part of complexes responsible for the regulation of genes implicated in both cancer and CNS disorders (Exhibit 6). As LSD1 removes methyl groups from histone tails, Oryzon's lead assets have been designed to inhibit this process, with iadademstat designed specifically for cancer indications (such as AML, SCLC and NETs, where LSD1 expression has been found to be upregulated), while vafidemstat has been optimised for CNS indications (as LSD1 expression also plays an important role in the brain, supported by various preclinical models).

Exhibit 6: Epigenetics and LSD1



Source: Oryzon corporate presentation (January 2024)

Valuation

Following the release of the FY23 results, we have taken stock of the company's pipeline priorities and progression, and revisited our estimates related to expected launch timelines and indications. While Oryzon has continued to make advancements across all its clinical programmes, we now have more clarity on the pace of clinical progression and have therefore adjusted our estimated timelines for commercial launch across the board. We have also updated the commercialisation strategy across various programmes. While we were previously assuming self-commercialisation for all indications, based on its current status, we have now updated our model to reflect potential licensing deals for vafidemstat across all three target indications – BPD, negative symptoms in schizophrenia and aggression in AD. For iadademstat, given the orphan indications targeted and the opportunity of accelerated approval, we currently assume that the company will self-commercialise.

We maintain that Oryzon's most clinically advanced programme is vafidemstat in BPD. The company recently presented data from the Phase IIb PORTICO trial, which, although unsuccessful in meeting its primarily endpoint, did show clinically meaningful and statistically significant benefits on two important secondary endpoints. We continue to see potential in the asset and have therefore kept its probability of success (PoS) unchanged at 20%. However, we now extend the launch timeline by a year to 2028, given the subsequent preparatory work we expect for the Phase III trial following the EoP2 meeting (which we believe will occur in Q224). We also update our model to reflect a potential partnership/licensing deal, contingent on a positive outcome from the EoP2 meeting. We assume that this will happen in FY25, and based on historical deals within schizophrenia (as there is insufficient precedent in BPD) we ascribe a total deal value of €500m, including €100m in upfront payment, along with tiered double-digit royalties (Exhibit 7). We have risk-adjusted the potential upfront payment in the income statement, reflecting a €20m inflow as licensing revenues for FY25. We estimate peak sales to be achieved in 2034, with peak penetration remaining stable to 2037, at which time vafidemstat's composition-of-matter patent (including patent term extension/supplementary protection certificates) is expected to expire in the US (2036 in EU).

For vafidemstat targeting negative symptoms in schizophrenia, the Phase IIb trial continues to enrol patients in Spain, and we expect to receive more clarity on the timelines for readout and clinical plans through 2024. If the Phase IIb data is encouraging, we expect the company to sign a licensing deal in 2026 with the partner subsequently filing for an IND with the US FDA, followed by Phase III trials. We therefore now estimate market launch in 2029 (vs 2027 previously), with the PoS being kept unchanged at 15%. Similarly to BPD, we estimate a deal value of €500m for this indication, albeit with an upfront payment of €50m to account for the risk associated with the slightly earlier stage of this programme compared to BPD. We also assume tiered double-digit royalties and peak sales in 2035, with sales erosion post-2037. Note that a licensing deal for vafidemstat will likely encompass all pursued and future indications, but for ease of modelling, we reflect the consideration separately for each indication.

For aggression in AD, while we await clarity on clinical progression and plans, we believe that the company will pursue the indication as a label extension, with the partner taking on responsibility of further clinical development. We use the same timeline assumptions as the schizophrenia programme, expecting a partnering deal worth €500m, with €50m in upfront receipts. We now expect a launch in 2029 (vs 2028 previously). Note that the company has filed for additional patents for vafidemstat, including methods of treating BPD (patent term to at least 2040 excluding patent term extension) and methods of treating aggression (patent term to at least 2038 excluding patent term extension), which if approved should extend the patent life of the drug across these indications and lead to value uplift for Oryzon.

Exhibit 7: Historical licensing deals in schizophrenia (Phase II)

Deal date	Company	Product	Deal partner	Status on deal date	Upfront payment ($m)	Deal value ($m)
12/10/2022	Royalty Pharma	MK-8189	Merck & Co	Phase II	50	425
16/06/2020	Neurocrine Biosciences	TAK-831	Takeda	Phase II	120	2,015
20/06/2010	Royalty Pharma	BL-1020	BioLineRx	Phase II	60	395
20/11/1997	Novartis	Fanapt	Titan Pharmaceuticals	Phase II	218	503
Average (median)					**90**	**464**

Source: EvaluatePharma

For iadademstat in 2L AML, following the recent update on patient recruitment for the Phase Ib safety tolerability and dose finding FRIDA trial (total 45 patients expected to be recruited on the programme; first cohort of six patients has completed the study; second cohort of six is fully enrolled), we now anticipate this to conclude by mid-2025. We expect this study to inform the recommended dose for subsequent efficacy trials. Management has indicated that the next steps in clinical progression will be discussed with the FDA, provided that the Phase Ib data is encouraging. We expect the next trial (either a Phase II or Phase III registrational trial) to include a larger patient cohort, and will take up to three years to complete, assuming conservative patient recruitment rates. We therefore have adjusted our launch estimate in 2L AML to 2029 (vs 2026 previously). We note that the company has alluded to the possibility of accelerated approval, but we choose to remain more conservative in our estimates for now. We keep the PoS in 2L AML unchanged at 30%. We estimate peak sales across the US and EU in 2035, with sales stable to 2037 in the US and 2038 in the EU. We note that iadademstat's composition-of-matter patent is expected to expire in 2037 in the US and EU and the ODD designation should provide it with 10 years of market exclusivity in the EU, post approval.

For iadademstat in 1L SCLC, we had modelled for the Phase Ib/II STELLAR trial (in combination with ICIs) to commence in 2024, which we have now adjusted given the update from management that it will first undertake the collaborative CRADA-MSKCC trial, based on which the design of the STELLAR trial will be informed and refined. Management expects to file the IND for the STELLAR trial in 2024, and accordingly, we now estimate the trial to commence in 2025. We expect this to be followed by a Phase III trial starting in 2027, and have therefore adjusted our 1L SCLC launch timeline to 2030 (vs 2026 previously). To factor in the increased risk associated with this extended

timeline, we have reduced our PoS slightly to 20% (vs 25% previously). We estimate peak sales in SCLC to come in 2036, with sales erosion following US patent expiry in 2037. Similar to vafidemstat, the company has filed for additional patents for the drug, including combinations with agents like azacitidine, decitabine, venetoclax and others (patent term to at least 2037 excluding patent term extension), combinations with immune checkpoint inhibitors (patent term to at least 2040 excluding patent term extension) and combination with gilteritinib (patent term to at least 2040 excluding patent term extension), which we currently do not factor into our model. If granted, these should extend the patent life for the drug and add to further upside potential.

The aforementioned changes have resulted in our overall risk-adjusted valuation of the company shifting materially to €732.6m, from €900.3m previously. The revised valuation also accounts for adjustments from rolling forward our model, and the latest available pro-forma net debt figure of €4.5m at end-FY23 (€6.3m net debt at end-FY23 adjusted for the debt-to-equity conversion of 178 bonds on 23 January 2024, worth €1.78m). The per share value resets to €11.8/share (from €15.1/share previously), which also reflects the impact from a higher share count (62.0m vs 59.7m previously). Exhibit 8 presents a breakdown of our updated valuation for Oryzon.

Exhibit 8: Valuation of Oryzon

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
Iadademstat	2L AML	2029	555	516.9	30%	147.7	2.4
Iadademstat	1L SCLC	2030	720	605.3	20%	114.3	1.8
Vafidemstat	BPD	2028	1,625	787.3	20%	229.8	3.7
Vafidemstat	Schizophrenia, negative symptoms	2029	702	554.7	15%	115.1	1.9
Vafidemstat	Aggression related to AD	2029	911	652.9	15%	130.2	2.1
Pro-forma net debt at end-Q423*				(4.5)	100%	(4.5)	(0.1)
Valuation				**3,112.6**		**732.6**	**11.8**

Source: Edison Investment Research. Note: *Adjusted for the debt-to-equity conversion of 178 bonds in January 2024, under the €45m financing agreement.

Financials

Oryzon reported an operating loss of €4.5m in FY23, an improvement over the €5.5m loss reported in the previous year. Operating expenses for the year were €18.6m, c 11% lower than the previous period and were supported by lower R&D expenses (€12.2m vs €13.7m in FY22), which accounted for c 65% of the opex. The lower R&D expenses were mainly attributed to lower activity and investments in pre-clinical projects as well period-on-period variation in patient recruitment and clinical trial expense. Personnel expenses/SG&A were broadly stable at €3.4m, versus €3.2m in FY22, and primarily constituted of salaries and wages (€2.9m in FY23). We highlight that the company capitalises its R&D, reflected in the cash flow statement as the purchase of intangible assets (€14.5m in FY23 vs €14.2m in the previous year). Free cash outflow during FY23 was €15.1m, versus €16.1m in FY22.

Following the FY23 results, we have updated our FY24 figures and have introduced FY25 estimates. Based on the FY23 run-rate and visibility on the company's upcoming development plans for its clinical and pre-clinical assets, we have made certain adjustments to our estimates for operating expenses and profitability. Following recent readouts from the Phase IIb PORTICO trial and the subsequent plan to initiate a request for a EoP2 meeting with the FDA in the coming months, we have reduced our estimates for R&D expenses based on the understanding that Phase III trials in BPD are now likely be initiated in 2025, and will be funded by a partner. Our estimates are also affected by the company's recent announcement that it will postpone the initiation of the Phase Ib/II STELLAR study (to evaluate iadademstat in combination with an ICI in first-line extensive-stage SCLC) pending findings from the recently announced CRADA-MSKCC trial, for

which the IND is expected to be filed in Q124. Our revised R&D expense estimate for FY24 is €12.3m (vs €24m previously). We expect this figure to rise only slightly in FY25 and project R&D expenses of €13m. For FY24, our estimated adjusted EBITDA loss improves to €3.1m from €9.3m previously. For FY25, we include risk-adjusted revenue flows from the partnership (€100m upfront payment adjusted for a 20% PoS), which result in an adjusted EBITDA of €16.9m for the year. We expect the free cash outflow for FY24 to be €14.6m, with the figure improving to €4.6m in FY25, benefiting from the assumed upfront payment.

In November 2023, Oryzon entered into a convertible bonds financing agreement with a Swiss institutional investor, Nice & Green, to raise up to €45m in financing. These bonds contain no interest or associated warrants and will have a maturity of 48 months. The notes can subsequently be converted into new shares at a conversion price of 94% of the average closing daily volume-weighted price (between conversions) and 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%. Note that the company had a previous €20m convertible debt agreement with the same investor (signed in July 2022), as part of which the company had drawn down and converted €12m of debt across two tranches. This new agreement supersedes the previous one. As part of this current deal, Oryzon can drawdown an initial €8m across two tranches, to be followed by seven tranches of €1m each and six tranches of up to €5m each. As per the latest available information, the company has utilised €10m from the facility (two €4m tranches disbursed in November and December 2023 and an additional €2m tranche in February 2024). Of the 800 bonds (€10,000 each) issued against the first two €8m tranches, 736 have been converted to equity as of 23 January 2024, against an issue of 3.05m shares of common stock. While it is clear that this financing agreement will have a material share dilution impact if fully utilised (assuming the full €45m facility is disbursed, 3,764 of the 4,500 bonds remain unconverted as of now, requiring the company to issue an additional 23.12m shares, assuming conversion at the current trading price of €1.63/share), we acknowledge that it meets the larger priority of running the company's business operations, a key consideration given the capital market tightness.

Based on our projected cash burn rates (free cash outflow of €13.7m in FY24), we estimate the FY22-end gross cash balance of €12.3m plus the €2m funds drawn down to be sufficient to support operations into FY25. However, we note the upcoming maturities of bank debt in FY24 (€5.6m) and estimate that the company will draw down a further €10m from the financing facility during 2024. We also expected the remaining €25m of the facility to be utilised in FY25. We currently reflect these capital infusions as illustrative debt in our model.

As previously highlighted, we now assume licensing deals in FY25 and FY26 with associated cash inflows that should support breakeven in FY26. Assuming the company is not able to sign a partnership deal and decides to self-commercialise all programmes, we estimate the need to raise a further €45m in funds across FY26 and FY27 (we model for €20m in FY26 and €25m in FY27 as illustrative debt) before it becomes self-sustainable in FY28. Assuming all funding requirements across FY24–27 are realised through equity raises, the company would have to issue 49.1m shares (assuming at the current trading price of €1.63/share), resulting in our per share valuation diluting to €7.3/share, from €11.5/share currently (the number of shares outstanding would increase from 62m to 111.2m).

Exhibit 9: Financial summary

Accounts: Spanish GAAP; year-end 31 December (€000s)	2021	2022	2023	2024e	2025e
INCOME STATEMENT					
Total revenues	10,615	15,698	14,192	12,933	33,650
Cost of sales	(746)	(464)	(244)	(256)	(269)
Gross profit	9,869	15,234	13,948	12,678	33,381
Gross margin %	93%	97%	98%	98%	99%
SG&A (expenses)	(3,782)	(3,163)	(3,390)	(3,424)	(3,458)
R&D costs	(9,746)	(13,681)	(12,177)	(12,318)	(13,000)
Other income/(expense)	(3,203)	(3,714)	(2,777)	0	0
Exceptionals and adjustments	(4)	0	0	0	0
Reported EBITDA	(6,866)	(5,323)	(4,396)	(3,064)	16,923
Depreciation and amortisation	(144)	(167)	(153)	(129)	(111)
Reported EBIT	(7,011)	(5,490)	(4,549)	(3,193)	16,812
Finance income/(expense)	(169)	(1,067)	(1,555)	(1,016)	(1,352)
Other income/(expense)	0	0	0	0	0
Reported PBT	(7,180)	(6,557)	(6,104)	(4,209)	15,459
Income tax expense (includes exceptionals)	2,493	2,325	2,751	2,538	2,645
Reported net income	(4,687)	(4,231)	(3,353)	(1,671)	18,104
Basic average number of shares, m	53.1	53.3	57.6	61.6	62.0
Basic EPS (€)	(0.09)	(0.08)	(0.06)	(0.03)	0.29
Adjusted EBITDA	(6,862)	(5,323)	(4,396)	(3,064)	16,923
Adjusted EBIT	(7,007)	(5,490)	(4,549)	(3,193)	16,812
Adjusted PBT	(6,896)	(6,320)	(6,004)	(4,209)	15,459
Adjusted EPS (€)	(0.08)	(0.07)	(0.06)	(0.03)	0.29
Adjusted diluted EPS (€)	(0.08)	(0.07)	(0.06)	(0.03)	0.29
BALANCE SHEET					
Property, plant and equipment	682	611	481	379	298
Intangible assets	60,254	75,843	89,895	102,802	116,421
Investments	29	31	26	26	26
Deferred tax assets	1,812	2,050	2,222	2,222	2,222
Total non-current assets	62,778	78,535	92,624	105,428	118,967
Cash and equivalents	28,725	21,317	12,257	3,986	30,455
Trade and other receivables	3,645	3,709	1,909	2,809	2,359
Inventories	104	10	6	6	6
Other current assets	132	129	104	104	104
Total current assets	32,606	25,165	14,276	6,905	32,925
Deferred tax liabilities	1,812	2,050	2,222	2,222	2,222
Long term debt	13,354	10,346	6,335	3,172	3,148
Other non-current liabilities	285	0	155	155	155
Total non-current liabilities	15,451	12,396	8,711	5,549	5,525
Trade and other payables	3,518	5,742	4,210	4,976	4,593
Short term debt	4,306	12,920	12,194	19,914	41,776
Other current liabilities	847	70	11	11	11
Total current liabilities	8,672	18,732	16,414	24,901	46,379
Equity attributable to company	71,262	72,572	81,775	81,883	99,987
CASH FLOW STATEMENT					
Profit before tax	(7,180)	(6,557)	(6,104)	(4,209)	15,459
Cash from operations (CFO)	(3,626)	(1,848)	(575)	(1,675)	18,282
Capex	(175)	(76)	0	0	0
Acquisition of intangible assets	(11,586)	(14,195)	(14,503)	(12,933)	(13,650)
Other investing activities	37	(1)	(1)	0	0
Cash used in investing activities (CFIA)	(11,724)	(14,271)	(14,504)	(12,933)	(13,650)
Net proceeds from issue of shares	0	(932)	(1,880)	0	0
Movements in debt	4,123	9,642	7,901	6,338	21,838
Other financing activities	0	0	0	0	0
Cash from financing activities (CFF)	4,123	8,710	6,021	6,338	21,838
Increase/(decrease) in cash and equivalents	(10,880)	(7,408)	(9,060)	(8,271)	26,470
Currency translation differences and other	348	1	(3)	0	0
Cash and equivalents at start of period	39,605	28,725	21,317	12,257	3,986
Cash and equivalents at end of period	28,725	21,317	12,257	3,986	30,455
Net (debt)/cash	11,065	(1,948)	(6,272)	(19,101)	(14,468)
Free cash flow (CFO + net capex + Intangible assets)	(15,388)	(16,118)	(15,078)	(14,609)	4,632

Source: company reports, Edison Investment Research

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