EDISON

Oryzon Genomics

Clinical trial update

Positive ALICE readouts pave way in AML

Pharma and biotech

Oryzon Genomics has presented the top-line results of its Phase IIa ALICE trial investigating its lead oncology LSD1 inhibitor iadademstat in combination with azacitidine for the treatment of acute myeloid leukaemia (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 reported. Notably, iadademstat also 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). We believe these positive results clearly demonstrate the clinical utility of iadademstat and provide important proof of concept for the drug's use in the AML setting. We value Oryzon at €847m or €15.5 per share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/20	9.5	(4.8)	(0.07)	0.0	N/A	N/A
12/21	10.6	(7.2)	(0.09)	0.0	N/A	N/A
12/22e	14.4	(5.0)	(0.05)	0.0	N/A	N/A
12/23e	15.9	(5.8)	(0.06)	0.0	N/A	N/A

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

FRIDA next on the horizon in second-line AML

With the conclusion of the ALICE study, Oryzon intends to keep up the clinical pace of iadademstat in AML with the initiation of the Phase Ib FRIDA study in relapsed/refractory (r/r) FLT3+ AML patients, which is anticipated in Q422. While the AML market is highly competitive, second-line treatment options in r/r FLT3+ AML remain limited and suboptimal, so we view management's pursuit of this setting as a sensible clinical strategy to maximise the potential opportunity for iadademstat. Additionally, FLT3+ patients in the ALICE study all showed a response to treatment, providing encouraging signs for this AML sub-population in FRIDA.

Recent transactions put LSD1 in the spotlight

The positive readouts from the ALICE trial could not have been more timely, coinciding with some notable deal activity in the LSD1 inhibitor space. In November 2022 Merck announced it would acquire Imago BioSciences for US$1.35bn; Imago BioSciences' lead clinical asset, LSD1 inhibitor bomedemstat, is being investigated in Phase II studies for the treatment of haematological disorders. While Imago and Oryzon's pipelines may not directly correlate, we believe such a transaction is a positive development for LSD1 clinical programmes in general, highlighting big pharma's interest and enhancing their clinical reputation.

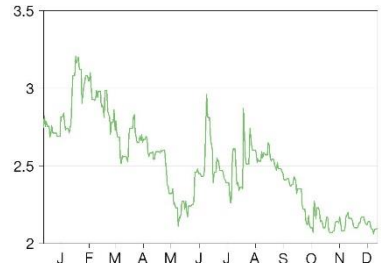
Valuation: €847m or €15.5/share

We value Oryzon at €847m or €15.5/share (previously €861m or €16.2/share). The valuation has been affected by our model rolling forward and the update of our exchange rate assumption to $1.06/€ (from $1.01/€), but our underlying long-term assumptions remain unchanged.

13 December 2022

Price	**€2.11**
Market cap	**€115m**
	US$1.06/€
Net cash (€m) at end-September 2022	9.7
Shares in issue	54.7m
Free float	80%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(2.8)	(13.6)	(23.5)
Rel (local)	(4.7)	(14.3)	(22.6)
52-week high/low		€3.21	€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 Oryzon is rapidly expanding its CNS R&D pipeline.

Next events

Phase II PORTICO interim data	Q123
Phase II ALICE final readout	Q422

Analysts

Soo Romanoff	+44 (0)20 3077 5700
Dr Adam McCarter	+44 (0)20 3077 5700

healthcare@edisongroup.com

Edison profile page

ALICE signs off with positive results

The Phase IIa ALICE study represented one of Oryzon's most advanced clinical oncology programmes. The 48-month open-label study assessed the safety, tolerability, efficacy and optimal dosing of iadademstat in combination with azacitidine as a first-line therapy in adult patients with AML. Being open label, Oryzon was able to provide rolling updates from the trial every six months, consistently displaying impressive response rates in patients, and the latest top-line data did not deviate from this pattern (see Exhibit 1):

Exhibit 1: Evolution of Phase IIa ALICE trial efficacy data

	Phase IIa ALICE trial (iadademstat + azacitidine)								Venetoclax + azacitidine or decitabine	Azacitidine
Update/publication	EHA 2019	ASH 2019	EHA 2020	ASH 2020	EHA 2021	ASH 2021	EHA 2022	ASH 2022	DiNardo et al, 2019	Dombret et al, 2015
Enrolment	17% (6/36)	36% (13/36)	50% (18/36)	50% (18/36)	75% (27/36)	100% (n=36)	100% (n=36)	100% (n=36)	-	-
Evaluable patients	5 patients	8 patients	13 patients	13 patients	18 patients	27 patients	27 patients	27 patients	145 patients	241 patients
ORR (CR, CRi, PR)	**80% (4/5)**	**75% (6/8)**	**77% (10/13)**	**85% (11/13)**	**83% (15/18)**	**78% (21/27)**	**81% (22/27)**	**81% (22/27)**	68% (99/145)	31% (75/241)

Source: Edison Investment Research, Oryzon Genomics

Of the 27 evaluable patients, 22 (81%) achieved an ORR, comprising 14 complete responses (CR) or complete responses with incomplete haematologic recovery (CRi), and eight partial responses (PR). Notably, 10 CR/CRi patients (71%) achieved transfusion independence for red blood cells and platelets, a result that we believe may elicit a positive impact on overall patient compliance for future studies. Nine out of 11 evaluable CR/CRi patients were also shown to be measurable residual disease negative.

The time to response (TTR) was rapid: 19 of 22 ORR patients (86%) responded after two 28-day cycles of treatment; and durable, as 36% of patients responded for more than 12 months and 30% for more than 18 months. Short treatment TTRs are of particular importance for older AML patients and, due to the aggressive nature of chemotherapy treatment, many patients are unable to complete the minimum recommended four cycles of hypomethylating agent (HMA) monotherapy treatment, such as azacitidine, required to achieve a beneficial response. A TTR of 86% achieved by the iadademstat/azacitidine combination after two treatment cycles is therefore clinically significant, in our view.

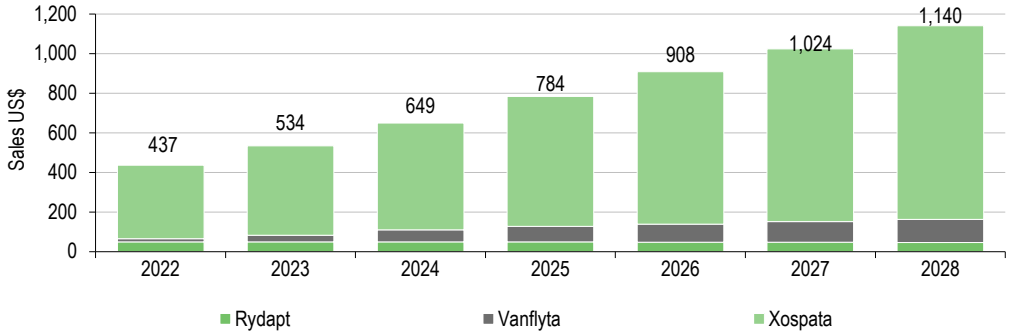
Finally, an mOS of 11.1 months was reported from the ALICE study, a significant improvement over azacytidine monotherapy, which has reported mOS in the range of 7–8 months. The mOS consisted of the combined results from two dosed patient cohorts of 60µg/m^2/day (13 patients) and 90µg/m^2/day (14 patients) with mOS of 8.1 and 12.3 months respectively. While Oryzon is not looking to pursue iadademstat/azacitidine in first-line AML, we believe these results still provide valuable and highly encouraging clinical proof of concept.

Paving the route to market with FRIDA

In our view, a potentially significant 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. FRIDA will investigate iadademstat in combination with Astella's FDA-approved FLT3 inhibitor gilteritinib (Xospata) for patients with relapsed/refractory (r/r) FLT3+ AML in a second-line setting. Approximately 50% of patients relapse after first-line AML treatment and 30% possess an FLT3

mutation. Xospata was approved by the FDA in 2018 as a monotherapy treatment for adults with r/r FLT3+ AML and is anticipated to dominate the FLT3+ AML inhibitor market, with sales of the drug expected to reach US$977m by 2028 (see Exhibit 2):

Exhibit 2: Estimated global sales of FLT3+ inhibitors in AML (US$m)



Source: EvaluatePharma, Edison Investment Research

Additionally, the mOS for Xospata monotherapy treatment 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/Xospata be observed in patients enrolled in FRIDA, we believe this could represent a significant market opportunity for Oryzon.

Having received IND approval, Oryzon has communicated that it expects the first patient to be recruited (FPI) in FRIDA in Q422.

Heightened interest in targeting LSD1

As a reminder, iadademstat is being developed as an inhibitor of the epigenetic target Lysine specific demethylase 1 (LSD1). LSD1 is a gene expression regulator, dysregulation of which has been shown to play a key role in the development of a variety of cancers. With LSD1 contributing to broad, dynamic gene regulation, Oryzon has viewed this as a prime therapeutic target for small molecule inhibition across multiple indications in oncology. Indeed, LSD1 has been identified as a target of interest by both peer biotechs and big pharma. Notably, Merck recently announced that it would acquire the LSD1 focused biotech Imago Biosciences for US$1.35bn ($36.00 per share in cash), news that saw Imago's stock jump by c 100%. Following closure of the deal (expected in Q123), Oryzon will become one of the most advanced independent LSD1 inhibitor players, as shown in Exhibit 3. 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$10.2bn by 2028 (EvaluatePharma) we see this as a potentially attractive opportunity that may trigger renewed interest from further big pharma players.

Exhibit 3: LSD1 targeting oncology pipeline

Company	Drug	Phase	Indication/s	Notes
Oryzon	Iadademstat	Phase II Phase I Phase II	1st line AML r/r FLT3+ AML Neuroendocrine cancers	Phase Ib FRIDA study in r/r FLT3+ AML expected to initiate in Q422 Phase II study in neuroendocrine cancers in combination with paclitaxel expected to initiate in Q422 Preparing new Phase Ib/II trial (STELLAR) in metastatic small cell lung cancer
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 and expected to close in Q1 CY23.

Valuation

We value Oryzon at €847m or €15.5/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate and Q322 net cash of c €9.7m. Our underlying long-term assumptions remain unchanged, and we roll our model forward in time by four months. We have also updated our exchange rate assumption to $1.06/€ (from $1.01/€), which had a c 3% negative impact on our valuation. Our model includes five rNPV projects (Exhibit 4; for more details see our Outlook note).

Exhibit 4: Valuation of Oryzon

Product	Indication	Launch	Peak sales ($m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
Iadademstat	2L AML	2026	500	756.9	30%	221.2	4.0
	1L SCLC	2026	730	800.2	25%	193.8	3.5
Vafidemstat	BPD	2027	1,610	1,251.0	20%	239.7	4.4
	Schizophrenia, negative symptoms	2027	700	629.1	15%	86.3	1.6
	Aggression in Alzheimer's disease	2028	910	671.0	15%	96.0	1.8
Net cash end Q322				9.7	100%	9.7	0.2
Valuation				**4,118.0**		**846.7**	**15.5**

Source: Edison Investment Research. Note: SCLC: small-cell lung cancer.

Exhibit 5: Financial summary

Accounts: Year end 31 December (€000s)	2019	2020	2021	2022e	2023e
INCOME STATEMENT					
Total revenues	10,278	9,521	10,615	14,418	15,860
Cost of sales	(430)	(526)	(746)	(473)	(497)
Gross profit	9,847	8,995	9,869	13,945	15,363
Gross margin %	96%	94%	93%	97%	97%
SG&A (expenses)	(2,983)	(3,541)	(3,782)	(3,513)	(3,864)
R&D costs	(11,322)	(11,075)	(13,023)	(15,403)	(16,975)
Other income/(expense)	779	1,476	73	6	6
Exceptionals and adjustments	(11)	(5)	(4)	0	0
Reported EBITDA	(3,690)	(4,149)	(6,866)	(4,965)	(5,470)
Depreciation and amortisation	150	145	144	180	179
Reported EBIT	(3,839)	(4,294)	(7,011)	(4,784)	(5,291)
Finance income/(expense)	(737)	(485)	(169)	(236)	(511)
Other income/(expense)	0	0	0	0	0
Reported PBT	(4,576)	(4,779)	(7,180)	(5,020)	(5,802)
Income tax expense (includes exceptionals)	892	1,379	2,493	2,138	2,316
Reported net income	(3,685)	(3,400)	(4,687)	(2,882)	(3,486)
Basic average number of shares, m	41.6	49.2	53.1	53.6	54.7
Basic EPS (€)	(0.09)	(0.07)	(0.09)	(0.05)	(0.06)
Adjusted EBITDA	(3,679)	(4,145)	(6,862)	(4,965)	(5,470)
Adjusted EBIT	(3,829)	(4,290)	(7,007)	(4,784)	(5,291)
Adjusted PBT	(4,566)	(4,774)	(7,176)	(5,020)	(5,802)
Adjusted EPS (€)	(0.09)	(0.07)	(0.09)	(0.05)	(0.07)
Adjusted diluted EPS (€)	(0.09)	(0.07)	(0.09)	(0.05)	(0.07)
BALANCE SHEET					
Property, plant and equipment	631	644	682	677	674
Intangible assets	39,938	49,216	60,254	70,811	81,216
Investments	67	66	29	29	29
Deferred tax assets	1,721	1,803	1,812	1,812	1,812
Total non-current assets	42,357	51,729	62,778	73,330	83,731
Cash and equivalents	35,111	39,605	28,725	15,598	9,558
Trade and other receivables	2,071	2,351	3,645	2,998	3,321
Inventories	289	317	104	104	104
Other current assets	267	105	132	132	132
Total current assets	37,738	42,377	32,606	18,833	13,116
Deferred tax liabilities	1,721	1,803	1,812	1,812	1,812
Long term debt	6,699	8,680	13,354	13,354	21,354
Other non-current liabilities	0	0	285	285	285
Total non-current liabilities	8,420	10,483	15,451	15,451	23,451
Trade and other payables	4,000	2,839	3,518	3,179	3,349
Short term debt	6,547	4,854	4,306	4,306	4,306
Other current liabilities	0	0	847	847	847
Total current liabilities	10,546	7,693	8,672	8,332	8,502
Equity attributable to company	61,129	75,931	71,262	68,380	64,894
	0	0	0	0	0
CASH FLOW STATEMENT					
Profit before tax	(4,576)	(4,779)	(7,180)	(5,020)	(5,802)
Cash from operations (CFO)	(3,934)	(4,817)	(3,626)	(2,394)	(3,461)
Capex*	(9,585)	(9,223)	(11,761)	(10,732)	(10,580)
Acquisitions & disposals net	0	0	0	0	0
Acquisition of intangible assets	(9,469)	(9,070)	(11,586)	(10,557)	(10,404)
Other investing activities	8	142	37	0	0
Cash used in investing activities (CFIA)	(19,046)	(18,152)	(23,310)	(21,289)	(20,984)
Net proceeds from issue of shares	18,374	18,181	0	0	0
Movements in debt	(4,112)	200	4,123	0	8,000
Other financing activities	0	0	0	0	0
Cash from financing activities (CFF)	14,262	18,382	4,123	0	8,000
Increase/(decrease) in cash and equivalents	791	4,494	(10,880)	(13,126)	(6,041)
Currency translation differences and other	40	11	348	0	0
Cash and equivalents at start of period	34,320	35,111	39,605	28,725	15,598
Cash and equivalents at end of period	35,111	39,605	28,725	15,598	9,558
Net (debt) cash	21,866	26,071	11,065	(2,061)	(24,102)

Source: Oryzon Genomics, Edison Investment Research. Note: Oryzon reports in Spanish GAAP. *Includes cash outflows related to development costs that were capitalised.

General disclaimer and copyright

This report has been commissioned by Oryzon Genomics and prepared and issued by Edison, in consideration of a fee payable by Oryzon Genomics. Edison Investment Research standard fees are £60,000 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the research department of Edison at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Crown Wealth Group Pty Ltd who holds an Australian Financial Services Licence (Number: 494274). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Edison for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia