EDISON

Oryzon Genomics

Refreshed outlook with near-term catalysts

Company outlook

Healthcare

10 March 2026

We update our investment view on Oryzon Genomics following the company's FY25 results and refreshed profile. This includes an array of near-term milestones for iadademstat, lead asset for oncological- and non-oncological haematological diseases, such as clinical trial readouts for the ALICE-2 and RESTORE trials in 2026, in acute myeloid leukaemia (AML) and sickle cell disease (SCD), respectively. Separately, lead central nervous system (CNS) asset vafidemstat is Phase III-ready, as management is finalising the protocol for a pivotal-stage programme with European and US regulators in borderline personality disorder (BPD). As of end-2025, the company's current gross cash position of €28.4m should provide operational headroom through H127. Reflecting these developments, our valuation for Oryzon stands at €938.2m, or €11.7/share.

Year end	Revenue (€m)	PBT (€m)	EPS (€)	DPS (€)	P/E (x)	Yield (%)
12/24	7.4	(5.6)	(0.06)	0.00	N/A	N/A
12/25	10.9	(5.6)	(0.04)	0.00	N/A	N/A
12/26e	13.2	(6.6)	(0.05)	0.00	N/A	N/A
12/27e	71.5	44.0	0.58	0.00	4.7	N/A

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

Defining iadademstat's route(s) to market

Oryzon is refocusing near-term efforts on its value-generating iadademstat programmes, which offer multiple upcoming catalysts. In frontline AML, the priority is ALICE-2, evaluating iadademstat in combination with venetoclax and azacitidine (Ven-Aza). Interim data from 10 patients showed an overall response rate (ORR) of 100% and a complete response (CR) rate of 90%, indicating potentially competitive efficacy. A final readout is expected in Q426, representing a key inflection point. If successful, Oryzon plans to advance to a registrational Phase II/III trial with potential for accelerated approval. In SCD, the RESTORE study is ongoing, with interim updates expected throughout 2026. Positive results could support progression into a registrational Phase II/III trial targeting an accelerated approval pathway.

Vafidemstat: Gearing up for pivotal-stage execution

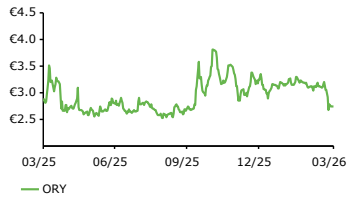
Oryzon's most advanced CNS programme targets BPD, following the Phase IIb PORTICO trial in which vafidemstat outperformed placebo across all efficacy measures. The company submitted its Phase III protocol to the FDA in mid-2025 and remains in discussions with regulators to finalise endpoints and address certain non-clinical considerations. With a newly appointed CMO for CNS and ongoing qualitative work to support the validity of proposed clinical endpoints, Oryzon is progressing towards pivotal development, with BPD representing a longer-term value driver.

Valuation: €938.2m or €11.7 per share

We refresh our valuation for Oryzon to reflect the strategic refocus towards iadademstat alongside vafidemstat. We now include SCD and autism spectrum disorder (ASD) in our valuation, while removing Alzheimer's disease and small-cell lung cancer, which remain longer-term upside opportunities. Reflecting the above and the latest net cash, our valuation adjusts modestly to €11.7/share, from €11.4.

Price	**€2.77**
Market cap	**€221m**
	$1.18/€
Net cash at 31 December 2025	€16.5m
Shares in issue	79.9m
Free float	82.0%
Code	ORY
Primary exchange	MADRID
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(10.4)	(12.5)	(1.8)
52-week high/low		€4.0	€2.4

Business description

Spanish biotech Oryzon Genomics is focused on epigenetics. Iadademstat is being explored for haematological diseases, including acute myeloid leukaemia and sickle cell disease, alongside other indications. Central nervous system asset vafidemstat has completed several Phase IIa trials and a Phase IIb trial in borderline personality disorder (Phase III clinical trial protocol submitted to the FDA). It is also currently involved in a Phase IIb trial for schizophrenia, and management is preparing for an additional Phase II trial in autism spectrum disorder.

Next events

RESTORE (SCD) interim update	Mid-2026
ALICE-2 (AML) final readout	Q426
PORTICO-2 (BPD) preparation	2026

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Investment summary

Company description: Promising offerings in both haematology and CNS

Oryzon Genomics is a clinical-stage biopharmaceutical company developing novel epigenetic therapies targeting lysine specific demethylase 1 (LSD1, or KDM1A) across a broad range of indications. The company is leveraging its LSD1 biology capabilities to advance two differentiated candidates: iadademstat (for oncological and haematological diseases) and vafidemstat (optimised for CNS conditions). While management previously aimed to reposition Oryzon into a CNS-focused company, the current strategic emphasis is on oncology/haematology due to its potential to offer a denser, more sequential set of milestones over the next couple of years, while keeping CNS as a longer-term value pillar. Iadademstat is currently being investigated across multiple Oryzon-sponsored, investigator-sponsored and collaborative studies, including with the National Cancer Institute (NCI). The priority programmes are in first-line AML, based on the treatment landscape evolving to position Ven-Aza as a first-line therapy, alongside SCD. Encouraging early efficacy signals in AML support a clear registrational strategy, with a key trial readout expected in Q426, before plans for a seamless Phase II/III programme and potential accelerated approval. In parallel, the RESTORE study in SCD has defined near-term milestones, expected to inform the next stage of development. Vafidemstat has been tested in several Phase II studies and it is considered Phase III-ready in BPD. Management plans to have the registrational protocol confirmed with regulators within 2026. Additional programmes include schizophrenia and ASD.

Valuation: Adjusts marginally to €938.2m or €11.7 per share

We update our model and valuation for Oryzon following the FY25 strategic update, which highlighted a renewed focus on iadademstat amid increasing clinical momentum. While the drug continues to be explored across several investigator-sponsored and collaborative studies, management's internal development efforts appear increasingly concentrated on first-line AML and SCD. In AML, we model iadademstat as an add-on to the Ven-Aza backbone in chemo-ineligible patients (c 50% of newly diagnosed cases), implying peak sales of c $800m, assuming 20% peak penetration; we assign a 30% probability of success and model a 2030 launch. In SCD, we estimate peak sales potential of c $1.1bn, assuming 20% peak penetration and a 2031 launch; we assign a success probability of 20% to the programme. We remove small-cell lung cancer from our valuation for now, but note the long-term optionality from the programme. For vafidemstat, we retain BPD and schizophrenia as the key CNS indications, while adding ASD and removing Alzheimer's disease from our valuation. BPD remains the largest value contributor (c 33% of our valuation). We assume a licensing deal in 2027 ($1.5bn total value, $150m upfront) for vafidemstat. Overall, our valuation adjusts modestly to €938.2m (€11.7/share) from €909.3m (€11.4/share) previously.

Financials: Cash runway through H127

Oryzon ended FY25 with a net cash position of €16.5m, including €28.4m in gross cash and €11.8m in total debt. Notably, €5.9m of reported short-term financial liabilities relates to advance funding received under the €13.3m Med4Cure Important Project of Common European Interest (IPCEI) grant. FY25 cash burn remained broadly stable, with a free cash outflow of €13.4m despite higher R&D activity linked to ongoing clinical programmes. Based on our updated cash burn projections and the planned clinical studies in AML and SCD, we estimate that Oryzon's current resources provide a funding runway through H127.

Sensitivities: Usual biotech risks somewhat offset by diverse pipelines

Oryzon is subject to the typical risks associated with drug development, including the unpredictable outcome of trials, regulatory discussions, the success of competitors, alongside the usual financing and commercial risks. Our model currently assumes a licensing deal for vafidemstat in 2027, but we acknowledge the challenge in accurately predicting the timing and nature of such transactions. Iadademstat and vafidemstat have both been tested in a relatively large number of participants, meaning that safety is well established. We highlight that Oryzon is unique in that it is focused on both oncology and CNS, including an array of indications, adding some diversity to the company's offering and somewhat de-risking binary event risk. However, key medium-term sensitivities will be in establishing efficacy in the chemo-unfit AML in combination with Ven-Aza for iadademstat and finalising a Phase III protocol for vafidemstat in BPD. These would be key milestones to transition both candidates to the late stages of clinical development.

Iadademstat offers a pipeline within a candidate

Iadademstat (ORY-1001) is an orally administered small molecule inhibitor of LSD1, a histone-modifying enzyme responsible for epigenetic modulation. LSD1 forms parts of complexes implicated in the regulation of genes associated with multiple cancers, as exemplified by the range of active clinical programmes being pursued by Oryzon and in collaboration with external investigators (Exhibit 1). The safety profile of the candidate has been established, having been tested in c 225 participants across various Phase I and Phase II clinical studies.

Exhibit 1: Oryzon's pipeline of programmes for iadademstat

Indication	Sponsor	Preclinical	Phase I	Phase II	Phase III	Status/Upcoming catalysts*
Acute Myeloid Leukemia (AML) 1L unfit patients: combination w/ azacitidine	Oryzon			ALICE		Completed. Published (Lancet Hematol)
1L AML unfit patients: combination w/ azacitidine + venetoclax	OHSU		IIS-ALICE-2			**EHA-2026/ASH-2026**
1L AML unfit patients: combination w/ azacitidine + venetoclax	NCI		CRADA-AML			
Refractory/Relapsed AML FLT3 mutation+ pts, combination w/ gilteritinib	Oryzon			FRIDA		**EHA-2026/ASH-2026**
Myelodysplastic Syndrome (MDS) combination w/ azacitidine	MCW		IIS-X005			**ASH-2026**
MPN: combination w/ ASTX727	NCI			CRADA-MPN		**ASH-2026**
Extensive-Disease Small Cell Lung Cancer (ED-SCLC) 1L patients: combination w/ ICI	NCI			CRADA-SCLC		**ESMO 2026**
Extensive-Disease Small Cell Lung Cancer (ED-SCLC) 1L/2L pts: combination w/ ICI + SBRT	Yale		IIS-TIARA			
Sickle Cell Disease (SCD)	Oryzon		RESTORE			**ASH-2026**
Essential Thrombocythemia (ET)	Oryzon			IDEAL		**Approved by EMA. ASH-2026**

Source: Oryzon Genomics. *Note: tentative meetings listed.

Oryzon's top strategic (fully-owned) priority with iadademstat is in AML and its potential here has been highlighted by publications in *Cancer Cell*, *Journal of Clinical Oncology* and *The Lancet Haematology*. In normal haematopoietic development (blood production), blood cells have a defined lifespan and must be continually replaced. These cells are produced by the proliferation and differentiation of a small population of self-sustaining haematopoietic stem cells. During differentiation, the subsequent generation of haematopoietic stem cells progresses through various intermediate maturational stages, which are partially mediated by epigenetic modifiers, such as LSD1. In leukaemia, this process of cellular maturation is aberrant. The leukaemic stem cells do not differentiate normally, leading to the accumulation of immature blast cells in bone marrow and blood. Specifically with LSD1, the enzyme is required for leukemic stem cell survival and blocking leukemic cell differentiation, and hence, iadademstat's mode of action is to inhibit leukemic stem cell survival and promote the death of leukaemia cells.

Expanded scope for iadademstat in AML

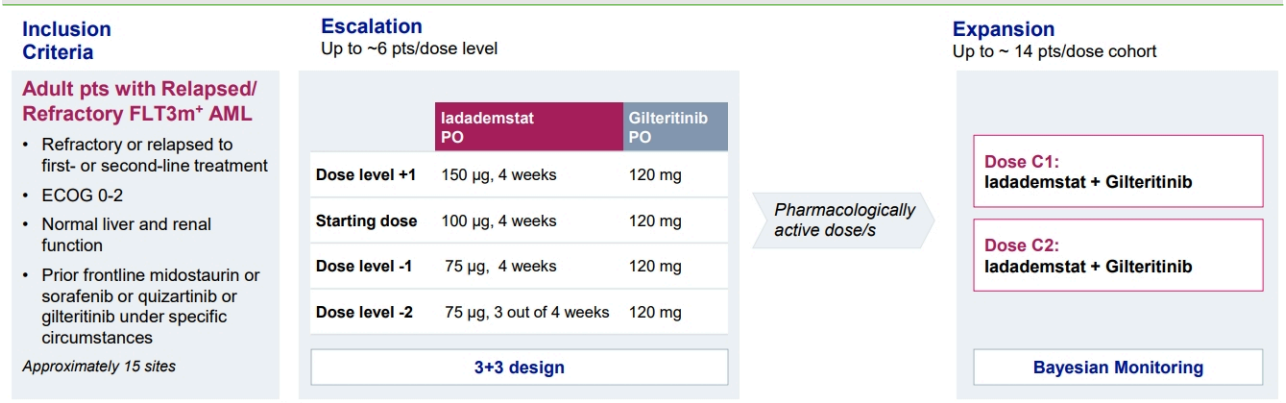
Following an AML diagnosis, patients fit for chemotherapy undergo induction chemotherapy, intended to kill as many leukaemia cells as possible. A 3+7 treatment regimen is employed, involving three days of anthracycline chemotherapy and seven days of cytarabine chemotherapy. While some patients see signs of success following such treatment, relapse rates are high. Should chemo-fit patients relapse, they are then offered oral azacitidine or, if they are eligible, an allogenic haematopoietic stem cell transplantation (allo-HSCT), which is the only potentially curative treatment option for AML patients who have already undergone induction chemotherapy. However, relapse remains a risk even after HSCT. Further, a significant portion of AML patients are ineligible for allo-HSCT and chemotherapy, due to their age or state of health. Chemo-unfit patients are treated with Ven-Aza, a combination found to be particularly effective and growing in promise (fortified by data from the PARADIGM trial, presented at ASH 2025), such that the treatment landscape is potentially evolving to move Ven-Aza as a first-line therapy in both chemo-fit and chemo-unfit AML populations. We note that in recent years, targeted agents such as FLT3 inhibitors have also improved outcomes in defined subgroups, though these relate to specific populations. While these advances are promising, long-term survival remains an ongoing challenge and treatment-related toxicity can be substantial. Further, certain AML subtypes, such as p53 positive patients

(who have a genetic alteration in their TP53 tumour suppressor gene), are often considered higher risk and do not typically benefit as much from Ven-Aza treatment, leading to shorter overall survival (OS) rates. There remains a clear unmet need for more effective and better tolerated therapies that can deliver durable remissions across both broad and genetically diverse AML patient populations, including both the first-line setting and in relapsed or refractory disease. While Oryzon was previously focused on iadademstat in combination with azacitidine within the unfit setting (Phase IIa ALICE trial) and in combination with gilteritinib in the relapsed/refractory setting for patients harbouring the FLT3 mutation (Phase Ib FRIDA trial), Oryzon's new strategy targets the expanded population that may benefit from Ven-Aza in the first-line setting.

ALICE (Oryzon-sponsored) was a single-arm, open-label Phase IIa study (n=36) that enrolled newly diagnosed, elderly AML patients who were administered iadademstat in combination with azacitidine, targeting the first-line setting. Final results were presented in December 2022 after the 48-month follow-up. Besides dose-finding data and safety/tolerability evaluation (primary endpoints), initial efficacy was evaluated using various secondary endpoints, including ORR, comprising CR, incomplete haematologic recovery (CRi) and partial responses (PR). Of the 27 evaluable patients at study completion, 22 (82%) achieved an ORR, comprising 14 CRs (or CRi), and eight PRs. Notably, 10 CR/CRi patients (71%) achieved transfusion independence for red blood cells and platelets (meaning a patient no longer requires regular blood transfusions to maintain adequate blood counts), a result that we believe may elicit a positive impact on overall patient compliance for future studies. 10 out of 11 CR/CRi patients (91%) evaluable for measurable residual disease (MRD) at the end of the study were also shown to be MRD negative, serving as a promising prognostic marker.

FRIDA (Oryzon-sponsored) is an open-label Phase Ib study (expected n=45) evaluating iadademstat in combination with gilteritinib for relapsed/refractory AML patients harbouring the FLT3 mutation in the second-line setting and it is currently ongoing (Exhibit 2). The primary analysis will be focused on safety and a recommended Phase II dose, with secondary endpoint measures of efficacy, including ORR and composite complete remission (CCR), which includes CR, CR with partial haematologic recovery (CRh) and CRi. The most recent update was presented at ASH 2025. As of this presentation, 37 patients were enrolled, with four dose-level cohorts evaluated in the escalation stage. The study is now in the expansion stage at one selected active dose where there are 17 patients enrolled at this level. Preliminary efficacy data show a CCR rate of 67% and a CR+CRh rate of 47% in the 15 evaluable patients at this dose. We believe this compares favourably to the monotherapy data for gilteritinib (CR+CRh rate of 34%). We also note that approximately half of the patients included in FRIDA had previously failed on venetoclax treatment, meaning it includes a population known to exhibit poor responses to gilteritinib monotherapy who are in urgent need of more effective treatment options. Subsequent updates are expected at EHA 2026 and ASH 2026. While encouraging for this defined subgroup, as mentioned above, we highlight that Oryzon's top priority is now to build on the encouraging ALICE results. While ALICE tested iadademstat in combination with azacitidine, the company will now prioritise the exploration of iadademstat in combination with Ven-Aza as with the ongoing ALICE-2 trial, for which an encouraging update was also presented at ASH 2025.

Exhibit 2: Design of the Phase Ib FRIDA trial



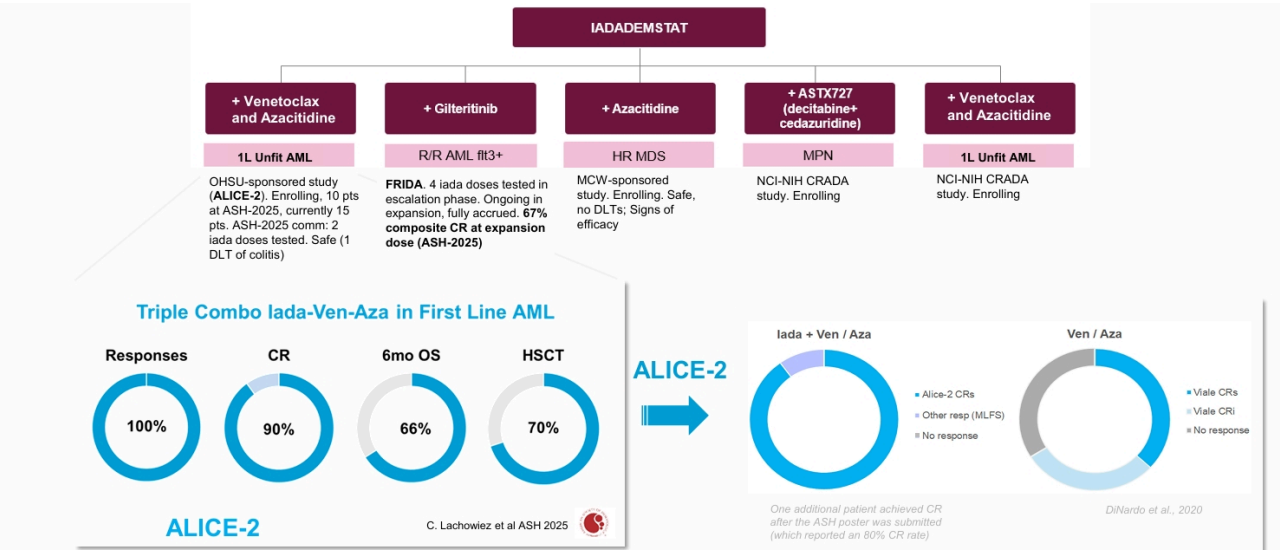
Source: Oryzon Genomics

ALICE-2 (sponsored by Oregon Health & Science University, OHSU) is an open-label Phase Ib study (expected n=24), designed to assess the potential synergy of the triple combination, iadademstat with Ven-Aza, in the broader chemo-unfit AML population targeting the first-line setting. While the primary endpoint measure is dose-limiting toxicities, secondary endpoints focus on efficacy, including ORR and CCR, where CCR includes CR, CRh and CRi. Data from the first 10 patients was reported at ASH 2025, and show an encouraging 100% ORR, with 90% of patients achieving a pure CR (comparing favourably to the Ven-Aza alone pure CR rate of 66%, though we caution against direct read across between clinical trials, Exhibit 3). The ALICE-2 interim update also showed that 70% of patients transitioned to

allo-HSCT. Median OS was not reached and the six-month OS rate was 66%. Dose-finding for maximum tolerated dose (MTD) determination is ongoing and the trial continues to enrol participants, with the goal of reaching 21 MTD-evaluable patients. Importantly, in terms of safety, the triple combination was found to be safe and well tolerated at this stage.

Subsequent readouts are anticipated at EHA 2026 (with data expected from up to 16 patients, c 75% of the planned enrolment) and ASH 2026, with the latter update (expected in Q426) potentially being the final data readout, representing a significant upcoming inflection point for investor attention. With the encouraging initial data to date in this broader AML population, Oryzon is now planning ALICE-3, providing a potential path to market. We note that in addition to the ALICE programmes, the NCI, under a cooperative research and development agreement, is running a Phase I study of iadademstat in combination with Ven-Aza in first-line AML (as with ALICE-2), potentially adding to the data package in this setting.

Exhibit 3: Iadademstat's encouraging ALICE-2 interim data and pipeline in a candidate offering



Source: Oryzon Genomics

ALICE-3 (to be sponsored and conducted by Oryzon) is intended to be a Phase II/III clinical trial, with the potential to become a registrational programme. Oryzon expects this to have the potential for accelerated approval based on CR-based endpoints for adverse-risk populations (explained in further detail below) and full approval based on the OS outcomes. In terms of timelines, management currently guides for regulatory interactions within H127 and an initiation of ALICE-3 within the same year, which would represent a major milestone. Management then expects c 24 months for ALICE-3 to reach full enrolment, which is estimated to be c 300 patients.

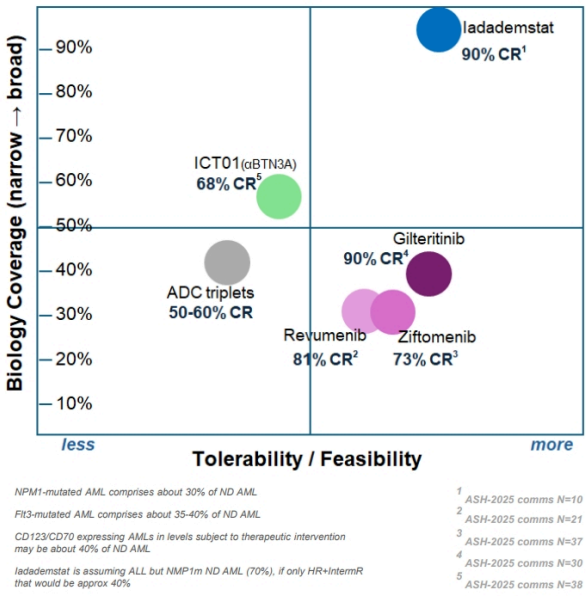
Oryzon's strategy to pursue the development of iadademstat in combination with Ven-Aza stems from its potential to provide a mechanistic advantage over alternative approaches (Exhibit 4), with it being mutation agnostic and, therefore, with applicability to both adverse-risk and intermediate-risk patient groups (Exhibit 5). Exhibit 4 shows a comparison of iadademstat plus Ven-Aza, to other triplet combinations:

- Iadademstat plus Ven-Aza offers broad biological coverage, with iadademstat being mutation agnostic, as exemplified with the ALICE and FRIDA data and, to date, has shown a favourable safety profile.
- Menin inhibitors (such as revumenib and ziftomenib) plus Ven-Aza have more limited biological coverage (specific for NPM1), with some concerns around resistance mechanisms.
- FLT3 inhibitors (gilteritinib) plus Ven-Aza are restricted in terms of the mutation they target (FLT3) and have some resistance concerns.
- Antibody-drug conjugates (such as ICT01) represent a newer technology and, while they show some promise (ICT01 was granted breakthrough therapy designation by the FDA in first-line unfit AML in January 2026), there have been some tolerability concerns. However, both efficacy and tolerability are yet to be determined, as these technologies are in the earlier stages of clinical development.

In Exhibit 5, the Kaplan-Meier curve dissects OS across 279 cases of AML patients treated with Ven-Aza, and identifies three groups based on the mutations, where the brown refers to the p53 positive adverse-risk group, the blue to FLT3 positive and N/KRAS positive intermediate risk group, and the green to the wild-type low-risk group. The adverse-risk and intermediate-risk populations therefore represent the greatest opportunity for incremental benefit to the Ven-Aza

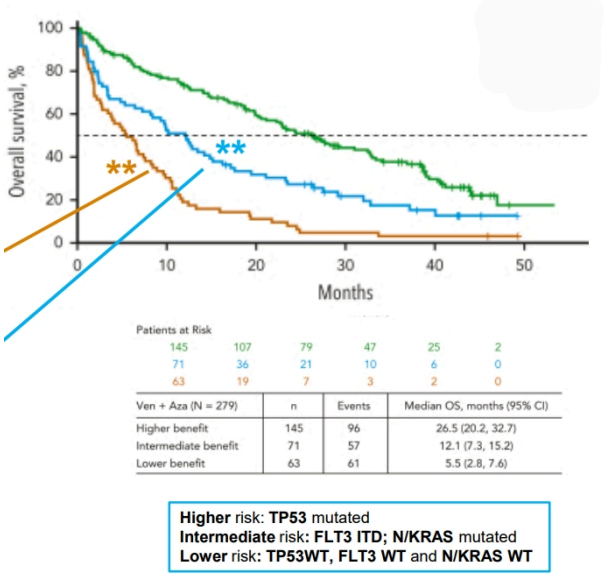
combination and these groups are where iadademstat has shown promise in the ALICE and FRIDA trials to date.

Exhibit 4: Iadademstat positioning versus alternative approaches



Source: Oryzon Genomics

Exhibit 5: Rationale for broad iadademstat positioning in first-line AML



Source: Oryzon Genomics

Oryzon will target both of these groups with ALICE-3, including the adverse-risk group through an accelerated approval pathway based on CR endpoints as part of the same trial, with full approval for both groups based on OS. This approach has been somewhat validated by positive FDA feedback on current ongoing trials for menin inhibitors for AML (Exhibit 6). Management has also noted that, given the adverse-risk of p53 positive patients, it is possible that the FDA may be amenable to comparing this randomised arm against a control arm based on real-world data. Should the FDA be supportive of this approach, it could allow the trial to include c 300 participants (comprising 100 patients in the adverse-risk group, and two arms of 100 patients of intermediate risk).

Exhibit 6: FDA validation of Oryzon's approach through an accelerated approval pathway

Product	Mechanism	Company	Trial	Target enrolment	Target population	Combination	Primary endpoint	Launch date
Revumenib	Menin inhibitor	Syndax	EVOLVE-2	n=415	Chemo-unfit; NMP1m/KMT2Ar	Ven-Aza	CR rate (accelerated approval), OS for full approval, both in NMP1 setting	March 2025
Ziftomenib	Menin inhibitor	Kura	KOMET-017	n=1300	Chemo-unfit; NMP1m	Ven-Aza	CR rate (accelerated approval), OS for full approval, both in NMP1 setting	September 2025
Bleximenib	Menin inhibitor	J&J	CAMELOT-2	n=600	Chemo-unfit; NMP1m/KMT2Ar	Ven-Aza	CR rate (accelerated approval), OS for full approval, both in NMP1 setting	April 2025
Iadademstat	**LSD1 inhibitor**	**Oryzon**	**ALICE-3**	**n=300**	**Chemo-unfit; adverse- and intermediate-risk**	Ven-Aza	**CR rate (accelerated approval), OS for full approval**	**Targeting 2027**

Source: Oryzon Genomics, Edison Investment Research

We note that iadademstat's mechanism of action against leukemic stem cells opens its potential application to additional indications. Potential expansion opportunities include:

- Essential thrombocythemia (ET): in February 2026, Oryzon announced that the European Medicines Agency provided regulatory clearance to launch a Phase II study of iadademstat in patients with ET, a rare form of myeloproliferative neoplasm, a type of chronic blood cancer. Many patients face resistance or intolerance issues with current treatment options, creating a significant unmet medical need. Oryzon's clinical trial, termed IDEAL, will be a multicentre, single-arm study, based in Spain, in adult patients with ET who are resistant or intolerant to hydroxyurea. Primary outcome measures will be safety and tolerability, with secondary outcome measures focused on testing durable clinical haematologic response rates, pharmacokinetic and pharmacodynamics, and evaluating the duration of haematologic remissions. IDEAL (which will be sponsored by Oryzon) is expected to commence within Q126. Interm data will be presented at ASH 2026.
- Myelodysplastic syndrome (MDS): an investigator-initiated Phase I study, led by the Medical College of Wisconsin, is ongoing. The first patient was dosed as part of this programme in January 2025 and it continues to enrol patients.
- Myeloproliferative neoplasm (MPN): a Phase II programme, sponsored and conducted by the NCI, is underway to investigate the potential synergy between iadademstat and ASTX727 (oral decitabine and cedazuridine) in MPNs.

50 patients will be randomised (25 patients in each arm) to receive either ASTX727 alone or in combination with iadademstat. We understand that subsequent updates are expected at ASH 2026.

A potentially differentiated offering in sickle cell disease

SCD is a hereditary blood disorder defined by the production of abnormal haemoglobin, known as haemoglobin S, which alters the shape and function of red blood cells. In SCD patients, red blood cells adopt a rigid, sickle-like shape, rather than the normal flexible, disk-like shape. These distorted cells are prone to obstruction within small blood vessels, leading to recurrent attacks of severe pain (sickle cell crisis or vaso-occlusive crisis, VOC), as well as progressive damage to all major organs. Unlike haematological malignancies, SCD is not driven by uncontrolled cellular proliferation but by a single gene mutation in the beta globin gene.

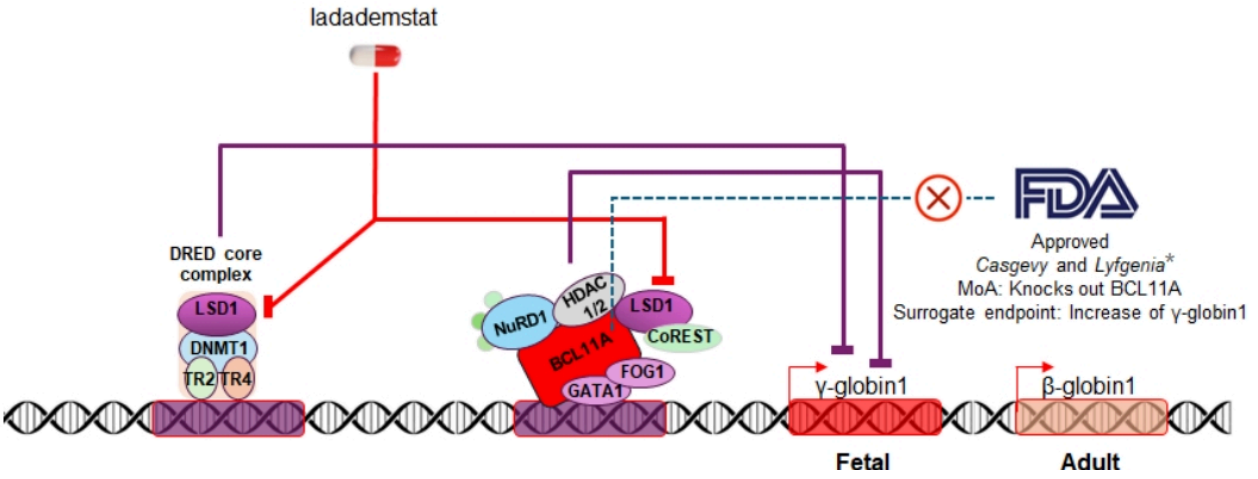
The molecular basis of SCD lies in a point mutation in the haemoglobin subunit beta (HBB) gene, which alters the beta globin chain, leading to profound changes in haemoglobin behaviour, promoting the polymerisation of haemoglobin S and subsequent red blood cell deformation. SCD follows an autosomal recessive inheritance pattern (which refers to a way in which this genetic condition can be passed down from parent to child) and predominantly affects individuals of African descent, though is also prevalent across Europe, the US and Latin America, with over eight million people affected worldwide. Clinically, patients may experience anaemia, fatigue, recurrent infections, stroke and cumulative organ complications involving the kidneys, lungs and heart. Despite improvements in supportive care, median life expectancy remains significantly reduced compared to the general population, particularly in regions with limited access to comprehensive care.

The treatment landscape for SCD has evolved meaningfully in recent years, though substantial unmet need persists. Hydroxyurea (approved in the 1990s) remains a backbone therapy and functions in part by increasing levels of foetal haemoglobin, a form of haemoglobin that does not sickle, and can dilute the effects of haemoglobin S. More recently approved agents include crizanlizumab and L-glutamine, intended to alleviate sickle cell crises. We note that while Pfizer's Oxbryta (generic name: voxelotor) was on the market for SCD, it was withdrawn by Pfizer in September 2024 due to the benefits not outweighing the risks in the approved population, though the strong sales of the drug ($328m in the US alone in 2022) highlight a potentially compelling market opportunity. Allogeneic haematopoietic stem cell transplantation provides a potential cure but is limited by eligibility (health of the patient) and donor availability, among other transplant-related risks. A key milestone in the field was the development of gene therapies, which are designed to induce foetal haemoglobin production or directly correct the HBB mutation. In December 2023, the FDA approved Casgevy (generic name: exagamglogene autotemcel, the first FDA-approved CRISPR-based therapy), which is designed to change a gene already in the body, and Lyfgenia (generic name: lovotibeglogene autotemcel), which is designed to add a modified gene into the body. While they have generated significant interest, their expensive price tags and complex delivery currently constrain broad accessibility. Consequently, there remains a clear demand for disease modifying, orally available agents that can safely and sustainably increase foetal haemoglobin and reduce clinical complications.

Mechanistically, iadademstat inhibits LSD1, a key component of multi-protein complexes that suppress the transcription of the foetal globin genes HBG1 and HBG2. These genes encode gamma globin, a component of foetal haemoglobin, which does not undergo the pathological polymerisation seen with haemoglobin S. By inhibiting LSD1 within such complexes, iadademstat may relieve epigenetic repression at gamma globin, and restore HBG1/2 expression. The resulting increase in foetal haemoglobin has the potential to dilute haemoglobin S within red blood cells, thereby reducing sickling, haemolysis (premature destruction of red blood cells, releasing haemoglobin into surrounding plasma) and downstream VOC (Exhibit 7). This approach aligns with clinically validated strategies that use foetal haemoglobin induction as a surrogate endpoint, but seeks to achieve this through a targeted, orally administered small molecule modulation of epigenetic control. Preclinical research has supported iadademstat's potential application in SCD and the candidate is currently being assessed in the clinic.

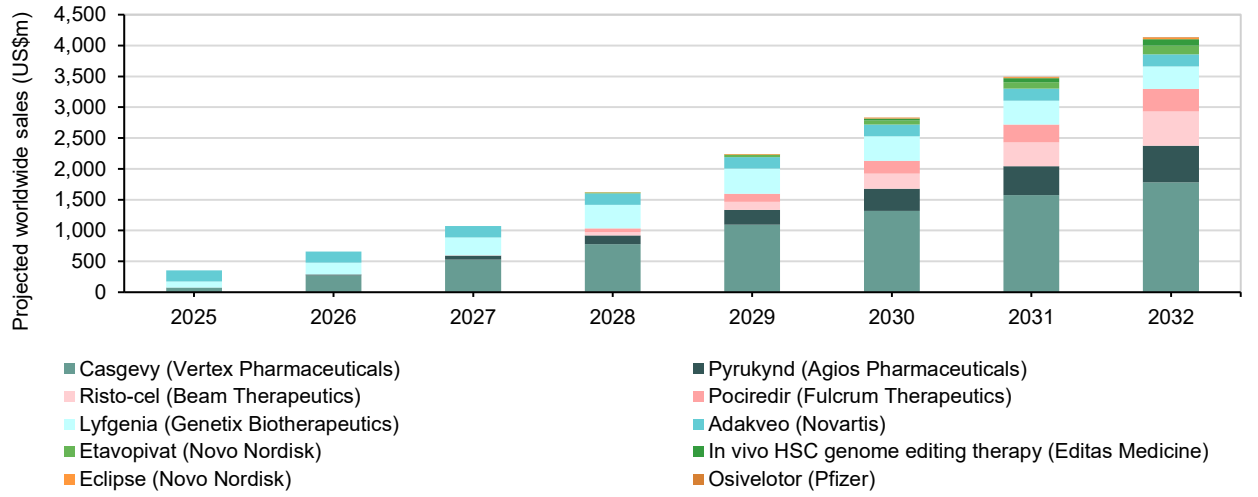
The global SCD treatment market recorded sales of $0.4bn in 2025 and is projected to reach c $4.1bn by 2032, growing at a sizeable compound annual growth rate of 42.2% (according to Evaluate Pharma), supported by improved diagnosis, expanded newborn screening and therapeutic innovation (Exhibit 8). Prevalence is rising in Western markets due to demographic shifts, with c 80k patients estimated in the US and another c 100k across Europe and Japan. Industry activity has intensified, exemplified by continued pipeline investments from both large pharmaceutical and specialist biotech companies, such as Oryzon. Questions around durability, affordability and real-world implementation of existing complex therapies underscore the ongoing opportunity for differentiated approaches aimed at modulating disease biology, with improved convenience and scalability over current treatment options.

Exhibit 7: Iadademstat's mechanism of action to address SCD



Source: Oryzon Genomics

Exhibit 8: Projected sales for the SCD treatment market



Source: Evaluate Pharma, Edison Investment Research

RESTORE (Oryzon-sponsored) is a multi-centre, open-label, 24-week, Phase Ib study (expected n=40) in SCD patients. It has been designed to investigate safety and tolerability as primary outcome measures, but additional objectives include determination of a recommended dose for Phase II and, importantly, assessments of the extent to which iadademstat induces foetal haemoglobin expression (an FDA-recognised outcome measure for SCD treatment). As of Oryzon's FY25 results update, two cohorts had been enrolled and the trial continues to actively enrol patients across several sites in Spain. By approximately mid-2026, management expects to have established the safety of iadademstat in this new patient population and obtain initial biomarker data to indicate the candidate's potential activity. In H226 (likely at ASH 2026), management expects to confirm the initial assessment of efficacy in SCD, potentially representing an important upcoming catalyst. Final data are anticipated in Q227.

Should the results of RESTORE be supportive, Oryzon intends to proceed with a registrational Phase II/III trial (termed RESTORE-2), following a similar plan to the AML programme. This will target an accelerated approval path based on a foetal haemoglobin-based endpoint in up to 90 participants, followed by a potential full approval based on VOC-based measures in a total of up to 135 patients. The trial is expected to launch from H227, and Oryzon expects to require c 18 months to complete enrolment. Subject to delays, this means that by 2030, Oryzon may be ready to present this potentially registrational data package to the FDA. Our projections are slightly more conservative and we model commercial launch in 2031.

Additional iadademstat programmes add incremental shots at goal

Beyond the haematological disease space, iadademstat is also being explored in solid tumours, specifically looking at extensive-stage small cell lung cancer (ES-SCLC). Under a cooperative research and development agreement with

the NCI, iadademstat is being assessed in combination with immune checkpoint inhibitors in a Phase I/II trial, targeting the first-line ES-SCLC setting. Patient recruitment commenced in April 2025, and the study has been designed to enrol a total of 45–50 patients. Primary outcome measures are based on safety, tolerability, dose-finding and efficacy, and multiple leading US-based cancer centres are involved in this trial, including the Memorial Sloan Kettering Cancer Center. As communicated in Oryzon's latest update, this programme continues to actively enrol patients. Separately, Oryzon recently announced a new Phase Ib trial, sponsored and conducted by Yale University, testing iadademstat in combination with immune checkpoint inhibitors and radiotherapy. This has been designed to assess safety, tolerability and efficacy, targeting the first- or second-line setting; enrolment is already underway.

Should the results of these early-stage studies be successful, they may support Oryzon's plans for its STELLAR programme, which will be a randomised, multi-centre Phase II trial of iadademstat in combination with a checkpoint inhibitor for ES-SCLC, targeting the first-line setting. While not the top priority for Oryzon, given the increased focus on oncological and non-haematological diseases, we believe they could provide incremental shots at goal for the candidate.

Vafidemstat represents a sizeable longer-term opportunity in CNS

Vafidemstat (ORY-2001) is also an orally administered LSD1 inhibitor but, in this case, it has been optimised to address conditions of the CNS. To our knowledge, it is the only drug candidate in active clinical development that targets LSD1 for this disease area. It has been designed to induce the expression of genes involved in neuronal plasticity, which refers to the ability of the brain to change its structure, organisation and function in response to external stimuli. In other words, neuronal plasticity is the ability of the nervous system to rewire itself and, in this sense, vafidemstat is intended to restore the brain's response to stress by regulating genes involved in control of stress cues. As such, the candidate has been shown to improve sociability, reduce aggression and improve memory, opening its application to a host of CNS conditions, including (but not limited to) BPD, schizophrenia, ASD and attention deficit hyperactivity disorder (ADHD) (Exhibit 9). Beyond the programmes listed below, Oryzon is also exploring the potential of vafidemstat to address some rare genetically driven neurodevelopmental disorders in earlier-stage programmes, based on its epigenetic mechanism of action. Some of the additional indications being targeted include Phelan-McDermid syndrome (PMS), Fragile X syndrome and Kabuki syndrome.

Oryzon has investigated the potential of vafidemstat across multiple studies involving various CNS conditions and it has been assessed in over 425 participants, including six Phase II studies. Importantly, this has created a robust data package in terms of safety, with vafidemstat showing comparable safety outcomes to placebo, confirming that the candidate is safe and well tolerated with once daily dosing (1.2mg/day). In terms of side effects, it has not shown any evidence of inducing weight gain, sedation, sexual dysfunction or extrapyramidal symptoms (drug-induced movement disorders), offering improvements on the common side effects associated with many current CNS drugs. In terms of efficacy, Oryzon is specifically exploring the potential of vafidemstat to address agitation and aggression, prevalent traits among the aforementioned CNS conditions. The most advanced programme is in BPD, which we discuss in further detail below.

Exhibit 9: Oryzon's pipeline of programmes for vafidemstat

Indication	Sponsor	Preclinical	Phase I	Phase II	Phase III	Status/upcoming catalysts
Borderline Personality Disorder (BPD) Agitation/Aggression	Oryzon			PORTICO-2	Submitted	Phase III in preparation
Schizophrenia Negative Symptoms / Positive Symptoms / CIAS	Oryzon			EVOLUTION		EU expansion in 2026; readout in 2H2027
Autism Spectrum Disorder (ASD) Aggression / Repetitive Behavior	Oryzon			HOPE-2		PhII in preparation; to initiate in 1H2026

Source: Oryzon Genomics

Addressing unmet needs in BPD…

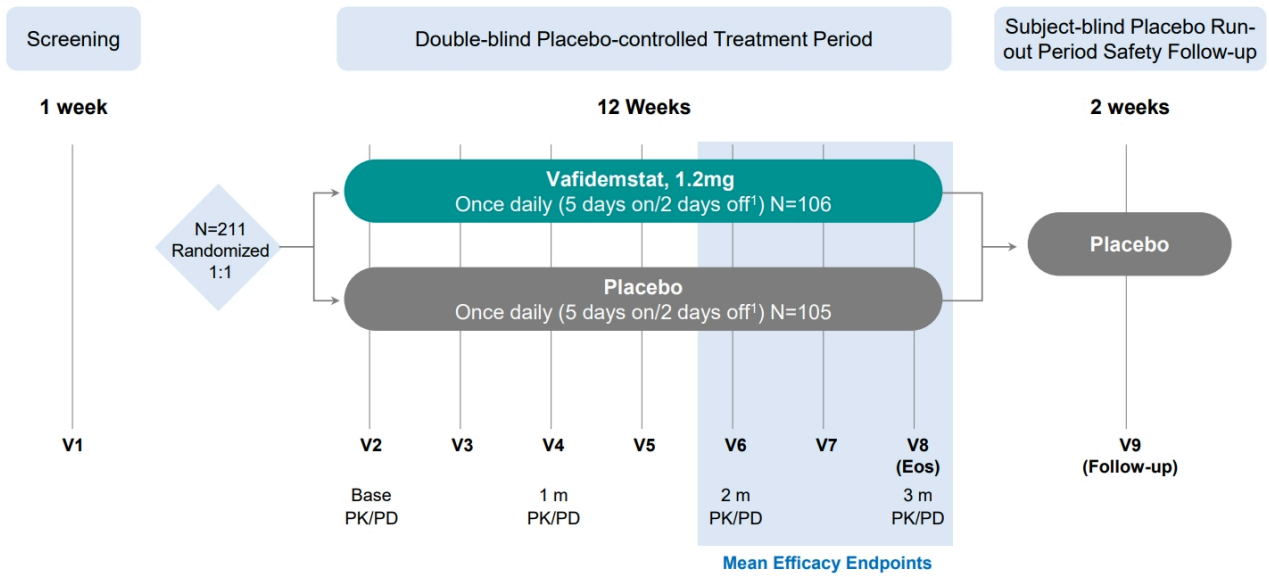
BPD is a severe and chronic neuropsychiatric condition characterised by pervasive instability in mood, self-image and interpersonal relationships. Clinically, this presents with marked emotional dysregulation, impulsivity, fear of abandonment and recurrent episodes of self-harm and/or suicidal behaviours. Agitation and aggression (A/A) is common and can be highly disruptive, leading to strained relationships, occupational impairment and crisis-driven utilisation

of healthcare resources. As a result, quality of life is often profoundly reduced for both patients and their families, with substantial societal and economic burden. Despite it having a global prevalence of 1–2%, there are currently no FDA-approved drugs specifically indicated for BPD. Instead, clinicians are limited to prescribing medications such as antipsychotics and mood stabilisers off label, supported by psychotherapy, often with limited durable effectiveness. A/A in particular represents an area of significant unmet medical need, as these symptoms drive emergency situations, increasing the risk of harm to both the patient and those around them. In our view, the absence of approved, evidence-based medicines tailored to these core symptoms highlights a clear opportunity for Oryzon in a field that has seen limited drug development progress to date.

...Backed by encouraging clinical data

The latest from the clinic for Oryzon in BPD was the Phase IIb PORTICO trial, for which top-line results were announced in January 2024, followed by the presentation of more detailed final data in September 2024. PORTICO was a randomised, placebo-controlled, double-blinded 14-week study. To be included, participants had to have a confirmed BPD diagnosis, reach a defined threshold for A/A based on the Agitation-Aggression Psychiatric Inventory Clinician Report and be on a stable regimen of background pharmacotherapy. Psychotherapy alongside treatment was also permitted, provided this was consistent throughout the trial duration. Patients (n=211) were randomised 1:1 to receive either vafidemstat or placebo (Exhibit 10). The trial involved 27 sites, including 14 in the US and 13 across Europe.

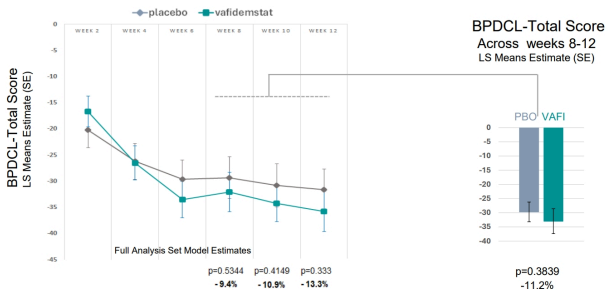
Exhibit 10: Design of the Phase IIb PORTICO trial



Source: Oryzon Genomics

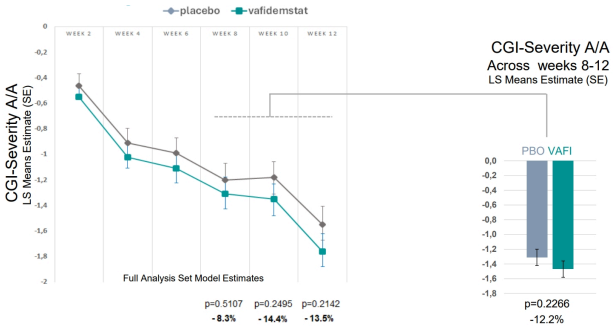
The primary endpoints were improvement in Borderline Personality Disorder Checklist (BPDCL; a patient-completed assessment) and improvement in Clinical Global Impression – Severity Agitation/ Aggression (CGI-S A/A; a clinician-completed assessment on overall patient functioning), both from baseline to weeks 8–12. The results showed that treatment with vafidemstat did not demonstrate a statistically significant improvement over placebo as measured by either of the primary endpoints. The final analysis did reveal an improvement (in terms of p-values) relative to the top-line results, though these primary endpoints still did not achieve statistical significance (Exhibit 11 and Exhibit 12). However, an important trend observed throughout all the trial data was a separation in performance between the vafidemstat and placebo arms from week four through to week 12, albeit without statistical significance in the BPDCL (p=0.3839 in the final analysis, versus initial top-line readout of p=0.412) and CGI-S A/A (p=0.2266 in the final analysis versus initial top-line readout of p=0.25) data. While this was not the preferred outcome, we believe it showed a positive trend favouring vafidemstat based on both patient- and clinician-reported measures.

Exhibit 11: PORTICO BPDCL final analysis data



Source: Oryzon Genomics

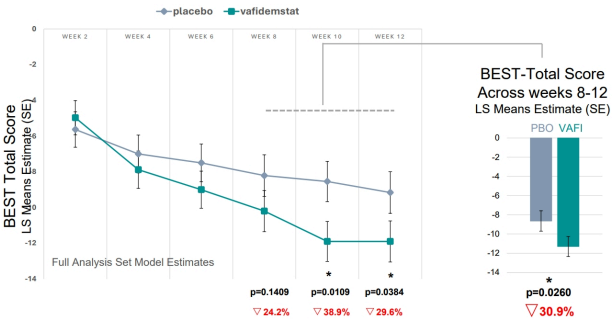
Exhibit 12: PORTICO CGI-S A/A final analysis data



Source: Oryzon Genomics

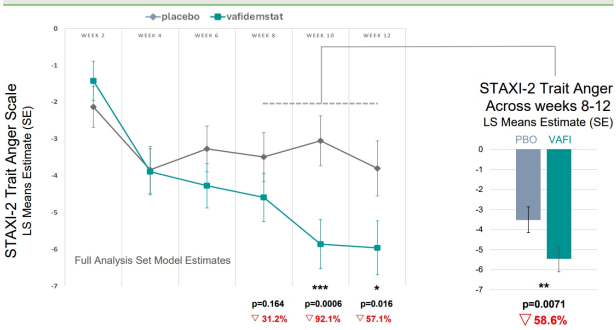
Two of the key secondary endpoints included improvements from baseline to weeks 8–12, as well as change over time, as measured by Borderline Evaluation of Severity (BEST; a patient-completed assessment) and State-Trait Anger Expression Inventory 2 (STAXI-2; a patient-completed assessment) Trait Anger. Encouragingly, the data showed statistically significant improvements across both measures, following the trend of a distinct separation in performance from week four to week 12 for the two arms (Exhibit 13 and Exhibit 14). The BEST data demonstrated a distinct, statistically significant benefit in overall BPD severity (p=0.0260 in the final analysis), with the maximum relative reduction in the vafidemstat group reported as 38.9% at week 10, with an average reduction of 30.9% across weeks 8–12. The STAXI-2 Trait Anger final data revealed a clinically meaningful improvement in agitation and aggression (p=0.0071 in the final analysis). The relative reduction reached a maximum of 92.1% at week 10, with an average reduction of 58.6% across weeks 8–12.

Exhibit 13: PORTICO BEST final analysis data



Source: Oryzon Genomics

Exhibit 14: PORTICO STAXI-2 Trait Anger final analysis data



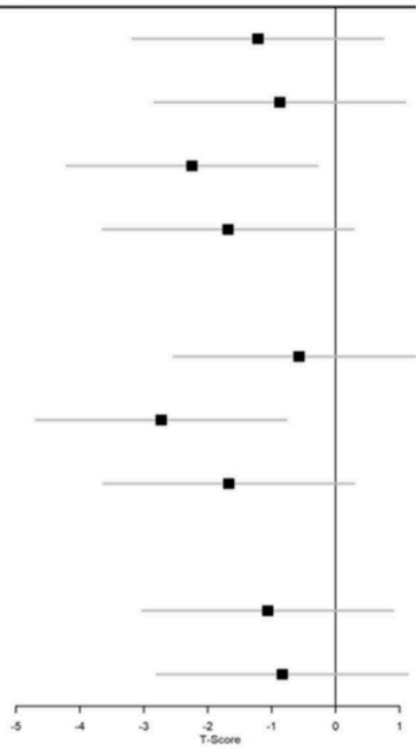
Source: Oryzon Genomics

While it was disappointing that statistical significance was not achieved with the two primary efficacy measures, it is our opinion that the overall results show that vafidemstat has the potential to offer clinically meaningful benefits for BPD patients. This has been corroborated by various key opinion leader (KOL) events hosted by Oryzon, where it has been noted that improvements greater than 25% should be considered highly favourable (across any measure of overall severity and A/A). How regulators view these endpoints will therefore be very important for the future of the programme. We highlight that as there are no gold-standard endpoints in BPD, to our knowledge, the trial investigated a sizeable number of secondary and exploratory endpoints, in addition to the two primary efficacy measures, and all cases favoured vafidemstat over placebo. KOLs have agreed that it is rare to see all data favouring the experimental arm versus placebo to this extent in a psychiatric condition such as BPD, emphasising the opportunity for Oryzon, in our view. This is exemplified with a forest plot to show the Global Statistical Test (GST) data (Exhibit 15). As BPD is a multisymptomatic condition, the GST analysis is intended to assess whether the treatment was efficacious across various aspects of the condition (eg psychiatric, behavioural, functional).

Exhibit 15: PORTICO GST final analysis data

Full Analysis Set

Parameter	Cohen's D	GST P-value	Difference	CI	T-Score	P-value
CGI - Severity	-0.1672		-0.16	(-0.42,0.10)	-1.21	0.2266
BPDCL - Total Score	-0.1202	0.2134	-3.44	(-11.22,4.34)	-0.87	0.3839
BEST - Total Score	-0.3093	0.0811	-2.67	(-5.02,-0.32)	-2.25	0.0260
BDI - Total Score	-0.2316	0.0661	-2.61	(-5.68,0.45)	-1.68	0.0944
STAXI						
State Anger Scale Raw Score	-0.0787	0.0853	-0.57	(-2.53,1.39)	-0.57	0.5684
Trait Anger Scale Raw Score	-0.3755	0.0397	-2.02	(-3.49,-0.56)	-2.73	0.0071
Anger Expression Index Raw Score	-0.2300	0.0362	-2.62	(-5.72,0.48)	-1.67	0.0966
STAI						
State Anxiety Raw Score	-0.1461	0.0403	-1.54	(-4.41,1.33)	-1.06	0.2901
Trait Anxiety Raw Score**	-0.1148	0.0503	-1.05	(-3.54,1.44)	-0.83	0.4057



Source: Oryzon Genomics

Next steps for vafidemstat in BPD

Following the conclusion of PORTICO, Oryzon had a productive end-of-Phase II meeting with the FDA. Importantly, the regulators acknowledged A/A as a therapeutic indication, adding confidence to Oryzon's BPD programme. The company has been conducting additional research and working with the FDA to align on the most suitable endpoints for a subsequent Phase III programme (termed PORTICO-2), though we understand that this is an ongoing process. For now, we understand that PORTICO-2 is likely to be designed as a randomised, double-blinded, placebo-controlled, multi-centre Phase III trial (expected n=350), to evaluate the safety and efficacy of vafidemstat in BPD patients, though confirmation is yet to be received.

As per the Oryzon's FY25 results update, the company had received written feedback on various aspects of the proposed programme, including trial endpoints, alongside some non-clinical considerations. Management has confirmed that its ongoing dialogue with the FDA has been constructive and plans to resubmit a revised protocol based on the feedback. We note that such interactions with regulators are usual in drug development, especially in a case like this, where there is no precedent for BPD. Oryzon is undertaking a range of activities, including a qualitative research programme focused on potential clinical outcome measures, to support the protocol resubmission. We expect the company to keep the market up to date regarding next steps, including when the protocol is resubmitted and when subsequent interactions with the FDA are underway.

Oryzon appointed a new CMO in CNS, Dr Rolando Gutierrez-Esteinou, in February 2026. Dr Gutierrez-Esteinou is a Harvard-trained psychiatrist and experienced clinical development executive with more than 20 years of experience in CNS drug development, including oversight of late-stage clinical trials and global development strategy. This appointment is intended to reinforce Oryzon's medical leadership as it progresses vafidemstat towards Phase III clinical development.

Expandable opportunities for vafidemstat within the CNS space

Beyond BPD, vafidemstat is also being actively investigated in schizophrenia and ASD, representing expandable opportunities for the candidate.

Schizophrenia: The Phase IIb EVOLUTION trial commenced in November 2021 and is currently ongoing, evaluating vafidemstat in schizophrenia, which afflicts c 1% of the global population. EVOLUTION is a double-blinded, randomised, placebo-controlled study, primarily looking to address the negative symptoms of schizophrenia (eg affective flattering; alogia anhedonia; social withdrawal), which current antipsychotics often fail to durably address, with outcomes related to positive symptoms (eg hallucinations; delusions; disorganised speech or behaviour) and cognitive impairment (eg impaired memory and attention, reduced executive function) as secondary focuses. While the programme had previously planned to enrol 220 participants, insights from PORTICO, alongside an adjustment to the endpoints to focus on negative schizophrenia symptoms, led to a revised protocol for EVOLUTION, where it was deemed that only 84 participants would be required to demonstrate a meaningful benefit, as communicated in Oryzon's Q225 results update. While the precise number of participants currently enrolled has not been reported, management has confirmed that recruitment is ongoing as planned. We highlight that EVOLUTION was previously limited to hospital sites across Spain, meaning that the pace of recruitment was relatively slow. However, the trial is being expanded in 2026 to include additional sites across Europe. We view this as a positive update for the programme, including a wider demographic and offering potential to accelerate recruitment. Top-line results are anticipated in H227, representing a notable upcoming potential catalyst. The programme is fully financed with current company resources.

ASD: The newest programme for vafidemstat is HOPE-2, which will include both genetically defined ASD subpopulations as well as sporadic (non-genetic) subpopulations, though the initial focus will be on PMS. The decision to pursue ASD as an additional indication for vafidemstat stems from prior clinical research, notably the Phase IIa REIMAGINE trial. HOPE-2 will be a Phase II trial, financially supported by the IPCEI grant (Med4Cure project). HOPE-2 will be based at sites in Spain and we understand that preparations are still underway. We believe that this could represent an attractive opportunity for Oryzon, with potential to maximise the value proposition for lead CNS asset vafidemstat should the clinical data be supportive. HOPE-2 is expected to launch within H126. The programme is fully financed using a portion of the IPCEI grant.

Management team

CEO: Carlos Buesa. Carlos founded the company in 2000 and has served as chairman of the board of directors and CEO since then. He holds a PhD in biology from the University of Barcelona. He was a postdoctoral researcher with a European Union grant and a senior researcher at the Flemish Institute of Biotechnology. He has completed several advanced programmes in finance, business development, international trade and negotiation. In 2005 he completed senior management studies at the IESE Business School. He has obtained the IC-A Diploma in good corporate governance from the Instituto de Consejeros Administradores de España. In recent years, he has been a director of various biotechnology companies and is a founding partner of Mendelion. He was the first president of the Catalan Association of Biocompanies and has been a member and vice-president representing Oryzon on the board of directors of the Spanish Association of Biocompanies in several mandates, and is currently a member of the board. Finally, he was a member of the board of directors of Inveready Seed Capital and Inveready Biotech from 7 September 2008 and 10 October 2012, respectively, until June 2021.

COO and CFO: Enric Rello. Enric has a doctorate in economics and business administration, a master's in administrative management, business administration and management, a law and economics degree from the Abat Oliba CEU University and a degree in business administration from the University of Barcelona. He holds a postgraduate degree in legal practice from the Ilustre Colegio de la Abogacía de Barcelona and attended a senior management programme and an HBS finance excellence programme at Harvard Business School. Enric began his career in the field of consultancy, audit and consulting, later specialising in management control and economic financial management in the environmental and industrial machinery (2007–11) and pharmaceutical industries (1993–2006). In the latter, he has held the positions of financial controller, controller manager and CFO in Sandoz (Novartis). In May 2011, he joined Oryzon as CFO and later assumed the responsibilities of COO. He is a university professor in the Department of Economics and Business at the Abat Oliba CEU University.

CSO: Dr Jordi Xaus. Jordi holds a degree in biology and a master's in immunology, both from the University of Barcelona. He received his doctorate in biology from the University of Barcelona in the field of immune response control. He completed scientific training with pre and postdoctoral stays at Sanford Burnham Prebys Medical Discovery Institute and at Genentech. He is the author of almost 100 scientific publications and 10 patents, and director of six doctoral theses. He was associate professor of immunology at the University of Barcelona until 2001, before joining the biotech industry. Initially, he worked at Puleva Biotech as head of immunology and later as director of biomedicine and member of the board. In 2007, he joined Palau Pharma and in 2012, he was nominated CSO. In 2014, he joined Oryzon where he held various management positions and contributed to the clinical transition of the epigenetic molecules iadademstat

and vafidemstat. In January 2020, he was appointed as director of the clinical portfolio and innovation. Since July 2021, he has been Oryzon's CSO. His training is complemented by the completion of the postgraduate programme executive master in operations and innovation from ESADE Business School.

CMO for CNS: Dr Rolando Gutierrez-Esteinou. Rolando is a Harvard-trained psychiatrist and global clinical development executive, with more than 20 years of leadership experience in advancing drug development programmes in neuroscience and psychiatry. His experience spans clinical development from Phase I through Phase IV across major neuropsychiatric disorders. He has contributed to multiple late-stage development programs and regulatory submissions, including supplemental new drug applications and label expansions for established CNS therapies. He has led regulatory interactions with major global health authorities, including the US FDA, the EMA and Japan's Pharmaceuticals and Medical Devices Agency. More recently, Rolando served as CMO at Atai Life Sciences, where he oversaw a portfolio of clinical-stage CNS programmes and built a multidisciplinary development organisation supporting multiple trials across psychiatric indications. Throughout his career, he has held senior leadership roles across global pharmaceutical companies (including Johnson & Johnson, Bristol Myers Squibb and Novartis), as well as in biotech and CRO environments. Rolando completed his psychiatry residency at Harvard Medical School and held research fellowships at Harvard/McLean Hospital and the US National Institutes of Health.

Sensitivities

As with all biotechnology companies, Oryzon is subject to the risks associated with drug development. These include the unpredictable nature of clinical trials, regulatory discussions, the success of competitors, alongside the usual financing and commercial risks faced by biotech companies. In our model, we currently assume Oryzon will self-sponsor the registrational trials in AML and SCD and we model a licensing deal for vafidemstat in 2027, meaning that our valuation is sensitive to the exact timing and terms of these potential deals. We note that the forecasting of licensing deals in the healthcare sector is intrinsically challenging.

In our view, iadademstat and vafidemstat both have established safety profiles, having been investigated in at least 200 and 425 participants, respectively. Therefore, medium-term R&D sensitivities are largely associated with clinical execution. For iadademstat, Oryzon is currently aiming to establish efficacy in chemo-unfit AML patients and, while this is an indication that has been previously targeted by the company with promising data, the current target positioning of the broader population in combination with Ven-Aza represents a newer approach in a competitive field. The final data readout for ALICE-2, expected in Q426, will represent a key inflection point for this programme. For vafidemstat, the candidate has shown proof-of-concept in BPD in the Phase IIb PORTICO trial by demonstrating its benefit over placebo across all tested efficacy measures, but it did fail to meet the primary endpoints with statistical significance. Therefore, meaningful value creation rests on the company finalising, and receiving regulatory clearance for, the subsequent Phase III PORTICO-2 programme, where the choice of suitable endpoints will be an important factor. While the current expected timelines represent a slight delay from prior guidance, we highlight that this should not be a significant concern as such iterations with regulators for the design of registrational programmes is usual in drug development, in particular for a case like this where there is no precedent in this indication.

Following Oryzon's FY25 results, the gross cash position stands at €28.4m, providing a cash runway through to H127, past several key upcoming inflection points, providing some flexibility. The requirement for further funding may depend on the company's plans to expand its clinical programmes for its clinical candidates and potential partner interest, which may alleviate the necessity for dilutive financing.

Financials

Operating performance: R&D expenses reflected increased clinical intensity

Oryzon's FY25 results were broadly in line with our expectations. The company recorded an operating loss of €5.7m in FY25, up 29.1% y-o-y (€4.4m in FY24). Operating expenses for the year rose materially by 46% y-o-y to €17.1m (€11.7m in FY24), with the increase driven primarily by a c 70% increase in R&D expenses to €9.1m. The sharp jump in R&D expenses primarily reflected increased allocation towards clinical trials in FY25 (we expect this to relate primarily to the EVOLUTION trial in schizophrenia) as well as the acceleration of activities related to the VANDAM project, under which the company received a €13.3m grant in July 2025. We believe this grant will support the upcoming Phase IIb HOPE-2 trial, testing vafidemstat in aggression related to ASD. R&D expenses accounted for 53.5% of the total

operating expenses for the year, versus 45.9% in FY24. While the company has several ongoing clinical programmes, a number of them are investigator-sponsored or NCI-sponsored, where Oryzon's contribution is restricted to providing the drug candidate to the trial. The company capitalises its R&D, reflected in the cash flow statement as the purchase of intangible assets (€7.7m in FY24 vs €14.5m in the previous year). Personnel expenses/SG&A for the period also rose 31.2% y-o-y to €4.5m and primarily consisted of salaries and wages (€3.0m), provisions (€0.9m) and social security expenses (€0.6m). Free cash outflow during FY24 was €13.4m, in line with the €13.5m recorded in FY24.

Balance sheet: Cash runway through H127

Oryzon ended FY25 with a net cash balance of €16.5m. This includes €28.4m in gross cash and cash equivalents, €6.7m in long-term debt (credit institutions: €3.1m, others: €3.7m) and €5.1m in short-term debt (credit institutions: €4.5m, others: €0.6m). The company has reported €6.5m as other short-term financial liabilities on the balance sheet in FY25, of which €5.9m relates to advance financing received under the €13.26m ($15m) non-dilutive grant as part of the Med4Cure initiative, part of the IPCEI framework. We have excluded this €5.9m payment from our calculation of net debt. Based on our updated cash burn projections for the planned clinical studies in AML and SCD, we estimate the company to be funded through H127.

Estimate revisions

Based on the FY25 results and near-term visibility, we adjust our FY26 R&D forecasts, which we raise to €12m, from €7.5m previously, to reflect the revised pipeline focus and plans recently disclosed by the company. Correspondingly, the other income estimate for FY26 increases to €13.2m (€8.5m previously). We also raise our SG&A expectations to €4.6m (previously €4.2m) to reflect the FY25 run rate. The other major change to our estimates is driven by potential licensing income from a partnering deal for vafidemstat, which we had previously anticipated in FY26 but have now pushed back to FY27 based on the updated trial timelines shared by Oryzon. Overall, we now project an operating loss of €6.3m for FY26, versus a profit of €36.5m previously. With the model roll forward, we also introduce FY27 estimates, projecting an operating profit of €44.4m for the year, supported by upfront inflows from a potential licensing deal for vafidemstat.

Valuation

We update our model and valuation for Oryzon following the company's recent strategic update alongside its FY25 results, which highlighted a renewed emphasis on iadademstat amid growing clinical momentum across both oncology and non-oncology haematological indications. While iadademstat continues to be evaluated across several investigator-initiated and NCI-sponsored studies (including AML, small-cell lung cancer, myelodysplastic syndrome and myeloproliferative neoplasms), management's internal development focus appears increasingly concentrated on first-line AML (supported by encouraging early data from the ALICE-2 trial) and SCD following the initiation of the RESTORE study in late 2025. We understand that development in these two indications will be self-funded through potentially registrational Phase II/III trials. Reflecting this strategic prioritisation, we update our model assumptions and remove small-cell lung cancer as a near-term focus, although we continue to recognise its longer-term optionality.

For vafidemstat, we continue to model BPD and schizophrenia as core indications and include ASD ahead of the planned initiation of the Phase IIb HOPE-2 trial. Conversely, we remove Alzheimer's disease from our valuation, reflecting its diminishing strategic relevance relative to the company's three priority CNS indications.

We outline our key modelling changes and assumptions for the target indications below.

Iadademstat

First-line AML

While Oryzon's pipeline includes programmes in both first-line AML and the relapsed/refractory FLT3-mutated setting, our model currently focuses on iadademstat in the broader first-line AML population, given the larger commercial opportunity. Specifically, we assume targeting chemo-ineligible patients, which represent approximately 50% of newly diagnosed AML cases, where Ven-Aza is the current standard of care. We expect iadademstat to be evaluated as an add-on to this backbone regimen. Based on AML incidence rates, this corresponds to an addressable population of roughly 10,000 patients in the US and 12,000 in Europe. We assume a net realised price of $150,000 per patient in the US and a more conservative $75,000 in Europe, increasing annually by 1.5%. With the ALICE-3 study expected to initiate in Q127 (c 300 patients and estimated trial cost of $45m, assuming c $150,000 per patient), we model a 2030

launch. Assuming 20% peak market penetration, we estimate peak sales potential of approximately $800m and assign the programme a 30% probability of success.

We derive an rNPV of €632.8m or €2.2 per share for Iadademstat in first-line AML (18.3% of our overall valuation for the company).

SCD

Based on management guidance, we model a target population of approximately 100,000 patients in the US and 220,000 across other developed markets. We assume the addressable population comprises patients aged less than or equal to four years old, which we estimate represents around 80% of the total SCD population, translating to roughly 75,000 patients in the US and 180,000 in other target geographies. Given the chronic nature of the disease, we assume a lower annual treatment cost relative to AML, modelling a net realised price of $50,000 per patient in the US and $25,000 in other developed markets. We estimate trial-related costs of c $15m for the RESTORE-2 study, expected to initiate in H227 with approximately 135 patients to be enrolled. We model a 2031 launch, and assuming 20% peak market penetration, estimate peak sales potential of c $1.1bn, achieved by 2037. We assign a 20% probability of success to this programme.

Overall, the SCD programme contributes 16.0% to our total valuation for Oryzon.

Vafidemstat

BPD

Despite the increasing strategic focus on iadademstat, we continue to view vafidemstat as the primary driver of Oryzon's investment case, led by the BPD programme. The company continues to prepare for the Phase III protocol resubmission, which we understand is targeted before year-end 2026. Reflecting this timeline, we adjust our model to assume Phase III initiation in 2027 and a market launch in 2031 (previously 2030), while leaving all other key assumptions unchanged.

Despite the slight delay in launch timing, BPD remains the largest contributor to our valuation, accounting for 32.6% of our implied value for Oryzon.

Schizophrenia

With the Phase IIb EVOLUTION trial expanding to additional sites across Europe, management now expects top-line data in 2027. Accordingly, we push back our estimated launch timeline by one year to 2032, while keeping our other modelling assumptions unchanged.

The schizophrenia programme contributes 14.7% to our overall valuation.

ASD

Ahead of further guidance from management on the target population, we estimate an addressable market of around 300,000 patients in the US and 400,000 in Europe. This assumes that 60% of ASD patients exhibit aggression or repetitive behaviours, with 50% of these patients seeking treatment. We model a conservative 10% peak market penetration for vafidemstat in this population.

We assume annual treatment costs of $10,000 in the US and $5,000 in Europe, with market launch in 2032 and peak sales of c $628m by 2038. We assign a 20% probability of success to the programme. Notably, the HOPE-2 trial is supported by $15m in funding under the Med4Cure IPCEI EU initiative, reducing Oryzon's development burden.

The ASD programme contributes 16.6% to our overall valuation.

Partnership assumption and valuation

Our model assumes a licensing agreement for vafidemstat in 2027, with a total deal value of $1.5bn, including $150m upfront and tiered royalties of 15–18%, with the partner assuming responsibility for subsequent clinical development and commercialisation.

Incorporating the above changes and the latest net cash position, our valuation for Oryzon adjusts modestly to €938.2m (€11.7/share), compared with €909.3m (€11.4/share) previously. Exhibit 16 presents a breakdown of our risk-adjusted

net present value (rNPV) valuation for Oryzon.

Exhibit 16: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability	rNPV (€m)	NPV/share (€/share)
Iadademstat	1L AML	2030	816	632.8	30%	172.1	2.2
	SCD	2031	1,135	778.1	20%	150.4	1.9
Vafidemstat	BPD	2031	1,675	636.5	40%	305.7	3.8
	Schizophrenia, negative symptoms	2032	723	425.0	25%	137.8	1.7
	Aggression related to ASD	2032	628	472.4	20%	155.7	1.9
Net cash at end-December 2025				16.5	100%	16.5	0.2
Valuation				**2,961.4**		**938.2**	**11.7**

Source: Edison Investment Research

Exhibit 17: Financial summary

Accounts: Spanish GAAP. Year end 31 December (€000s)	2023	2024	2025	2026e	2027e
INCOME STATEMENT					
Total revenues	**14,192**	**7,359**	**10,934**	**13,200**	**71,450**
Cost of sales	(244)	(302)	(282)	(297)	(311)
Gross profit	13,948	7,057	10,652	12,903	71,139
Gross margin %	*98%*	*96%*	*97%*	*98%*	*100%*
SG&A (expenses)	(3,390)	(3,447)	(4,524)	(4,569)	(4,615)
R&D costs	(12,177)	(5,369)	(9,139)	(12,000)	(19,500)
Other operating income/(expense)	(2,777)	(2,596)	(2,563)	(2,500)	(2,500)
Exceptionals and adjustments	0	79	(2)	0	0
Reported EBITDA	**(4,396)**	**(4,275)**	**(5,576)**	**(6,166)**	**44,524**
Depreciation and amortisation	(153)	(148)	(134)	(120)	(96)
Reported EBIT	**(4,549)**	**(4,423)**	**(5,710)**	**(6,286)**	**44,428**
Finance income/(expense)	(1,555)	(1,148)	112	(363)	(429)
Other income/(expense)	0	0	0	0	0
Reported PBT	**(6,104)**	**(5,571)**	**(5,598)**	**(6,649)**	**43,999**
Income tax expense (includes exceptionals)	2,751	1,906	2,993	2,449	2,721
Reported net income	**(3,353)**	**(3,665)**	**(2,605)**	**(4,200)**	**46,720**
Basic average number of shares, m	57.6	62.8	74.4	79.9	79.9
Basic EPS (€)	(0.06)	(0.06)	(0.04)	(0.05)	0.58
Adjusted EBITDA	(4,396)	(4,355)	(5,574)	(6,166)	44,524
Adjusted EBIT	(4,549)	(4,502)	(5,708)	(6,286)	44,428
Adjusted PBT	(6,004)	(5,740)	(5,544)	(6,649)	43,999
Adjusted EPS (€)	(0.06)	(0.06)	(0.03)	(0.05)	0.58
BALANCE SHEET					
Property, plant and equipment	481	356	380	279	205
Intangible assets	89,895	97,096	109,218	122,398	143,826
Investments	26	127	126	126	126
Deferred tax assets	2,222	2,390	4,133	4,133	4,133
Total non-current assets	**92,624**	**99,969**	**113,857**	**126,937**	**148,291**
Cash and equivalents	12,257	5,619	28,354	5,724	29,087
Trade and other receivables	1,909	3,019	2,203	2,611	2,407
Inventories	6	3	4	4	4
Other current assets	104	107	92	92	92
Total current assets	**14,276**	**8,748**	**30,652**	**8,431**	**31,590**
Deferred tax liabilities	2,222	2,390	4,133	4,133	4,133
Long term debt	6,335	7,455	6,756	4,353	3,672
Other non-current liabilities	155	91	20	20	20
Total non-current liabilities	**8,711**	**9,935**	**10,909**	**8,506**	**7,825**
Trade and other payables	4,210	2,878	3,661	3,269	3,465
Short term debt	12,194	8,809	11,004	8,856	7,134
Other current liabilities	11	52	2	2	2
Total current liabilities	**16,414**	**11,739**	**14,667**	**12,127**	**10,601**
Equity attributable to company	81,775	87,042	117,849	113,649	160,370
CASH FLOW STATEMENT					
Profit before tax	**(6,104)**	**(5,571)**	**(5,598)**	**(6,649)**	**43,999**
Cash from operations (CFO)	**(575)**	**(5,690)**	**(2,356)**	**(4,879)**	**47,216**
Capex	0	(102)	(58)	0	0
Acquisition of intangible assets	(14,503)	(7,710)	(10,980)	(13,200)	(21,450)
Other investing activities	(1)	0	0	0	0
Cash used in investing activities (CFIA)	**(14,504)**	**(7,811)**	**(11,037)**	**(13,200)**	**(21,450)**
Net proceeds from issue of shares	(1,880)	1,497	28,654	0	0
Movements in debt	7,901	5,374	3,122	(4,551)	(2,403)
Other financing activities	0	0	4,357	0	0
Cash from financing activities (CFF)	**6,021**	**6,871**	**36,133**	**(4,551)**	**(2,403)**
Increase/(decrease) in cash and equivalents	**(9,060)**	**(6,638)**	**22,735**	**(22,630)**	**23,364**
Currency translation differences and other	(3)	(9)	(4)	0	0
Cash and equivalents at start of period	**21,317**	**12,257**	**5,619**	**28,354**	**5,724**
Cash and equivalents at end of period	**12,257**	**5,619**	**28,354**	**5,724**	**29,087**
Net (debt) cash	(6,078)	(10,538)	10,628	(7,475)	18,281
Free cash flow (CFO + Net capex + Intangible assets)	(15,078)	(13,501)	(13,393)	(18,079)	25,766

Source: Oryzon Genomics, Edison Investment Research

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Revenue by geography

N/A

Management team

CEO: Carlos Buesa

Carlos founded the company in 2000 and has served as chairman of the board of directors and CEO since then. He holds a PhD in biology from the University of Barcelona. He was a postdoctoral researcher with a European Union grant and a senior researcher at the Flemish Institute of Biotechnology. He has completed several advanced programmes in finance, business development, international trade and negotiation. In 2005 he completed senior management studies at the IESE Business School. He has obtained the IC-A Diploma in good corporate governance from the Instituto de Consejeros Administradores de España. In recent years, he has been a director of various biotechnology companies and is a founding partner of Mendelion. He was the first president of the Catalan Association of Biocompanies and has been a member and vice-president representing Oryzon on the board of directors of the Spanish Association of Biocompanies in several mandates and is currently a member of the board. Finally, he was a member of the board of directors of Inveready Seed Capital and Inveready Biotech from 7 September 2008 and 10 October 2012, respectively, until June 2021.

CFO and COO: Enric Rello

Enric has a doctorate in economics and business administration, a master's in administrative management, business administration and management, a law and economics degree from the Abat Oliba CEU University and a degree in business administration from the University of Barcelona. He holds a postgraduate degree in legal practice from the Ilustre Colegio de la Abogacía de Barcelona and attended a senior management programme and an HBS finance excellence programme at Harvard Business School. Enric began his career in the field of consultancy, audit and consulting, later specialising in management control and economic financial management in the environmental and industrial machinery (2007–11) and pharmaceutical industries (1993–2006). In the latter, he held the positions of financial controller, controller manager and CFO at Sandoz (Novartis). In May 2011, he joined Oryzon as CFO and later assumed the responsibilities of COO. He is a university professor in the Department of Economics and Business at the Abat Oliba CEU University.

CSO: Jordi Xaus

Jordi holds a degree in biology and a master's in immunology, both from the University of Barcelona. He received his doctorate in biology from the University of Barcelona in the field of immune response control. He completed scientific training with pre and postdoctoral stays at Sanford Burnham Prebys Medical Discovery Institute and at Genentech. He is the author of almost 100 scientific publications and 10 patents and director of six doctoral theses. He was associate professor of immunology at the University of Barcelona until 2001, before joining the biotech industry. Initially, he worked at Puleva Biotech as head of immunology and later as director of biomedicine and member of the board. In 2007, he joined Palau Pharma and in 2012, he was nominated CSO. In 2014, he joined Oryzon where he held various management positions and contributed to the clinical transition of the epigenetic molecules iadademstat and vafidemstat. In January 2020, he was appointed as director of the clinical portfolio and innovation. Since July 2021, he has been Oryzon's CSO. His training is complemented by the completion of the postgraduate programme executive master in operations and innovation from ESADE Business School.

CMO for CNS: Rolando Gutierrez-Esteinou

Rolando is a Harvard-trained psychiatrist and global clinical development executive, with more than 20 years of leadership experience in advancing drug development programmes in neuroscience and psychiatry. His experience spans clinical development from Phase I through Phase IV across major neuropsychiatric disorders. He has contributed to multiple late-stage development programmes and regulatory submissions, including supplemental new drug applications and label expansions for established CNS therapies. He has led regulatory interactions with major global health authorities, including the US FDA, the EMA and Japan's Pharmaceuticals and Medical Devices Agency. More recently, Rolando served as CMO at Atai Life Sciences, where he oversaw a portfolio of clinical-stage CNS programmes and built a multidisciplinary development organisation supporting multiple trials across psychiatric indications. Throughout his career, he has held senior leadership roles across global pharmaceutical companies (including Johnson & Johnson, Bristol Myers Squibb and Novartis), as well as in biotech and CRO environments. Rolando completed his psychiatry residency at Harvard Medical School and held research fellowships at Harvard/McLean Hospital and the US National Institutes of Health.

SVP of clinical development and global medical affairs: Dr Ana Limón

Ana holds a PhD in molecular biology and biochemistry from the University of Barcelona. She was a post-doctoral fellow at The Fels Institute for Cancer Research and Molecular Biology and at Dana Farber Cancer Institute in the fields of cell cycle regulation and cancer immunology and AIDS, respectively. She was a research associate at the Department of Medical Oncology at Dana Farber Cancer Institute working on the characterisation of leukemic stem cells before moving to industry. She was the senior medical scientific liaison for all oncology assets at Amgen before moving to Millennium/Takeda where she held positions of increasing responsibility to become head of oncology pipeline, global medical affairs at Takeda. In 2021, she moved to Deciphera Pharmaceuticals where she was product leader responsible for commercial and pipeline assets. Ana has more than 15 years' experience in drug development, managing multifunctional teams, conducting research from preclinical to registration-enabling clinical studies in haematologic and solid tumours, as well as medical affairs activities for the launch and support of commercial products.

Chief intellectual property officer: Neus Virgili

Neus is a qualified European patent attorney with over 25 years' experience as a corporate patent attorney in the pharmaceutical field. She has a BSc in organic chemistry from the University of Barcelona. She started her career in 1991 in J. Uriach y Compañía (Grupo Uriach), where she set up the patent department and had full responsibility for all patent-related work of the company. In 2006, she joined Palau Pharma as head of the patent department. From 2009 to 2011, Neus was responsible for coordinating all legal matters of the company, being appointed chief patent officer and legal affairs. Neus has been chief intellectual property officer at Oryzon since September 2011.

Principal shareholders

	%
Carlos Buesa	8.82
Tamara Maes	6.24
Jose Ventura	4.27
Josep Echarri	1.56
Gescooperativo	0.27

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