EDISON

Oryzon Genomics

Company outlook

Planning iadademstat's path to market

Pharma & biotech

Oryzon is making progress with its two epigenetic drugs, iadademstat for oncology and vafidemstat for CNS indications (both are lysine-specific demethylase 1A, or LSD1, inhibitors). The company's R&D strategy has been to select indications where there is a scientific rationale for intervention with an epigenetic therapy and then conduct quick and relatively small trials, but with patient sample sizes still sufficient to obtain proof-of-concept data. With this strategy, Oryzon has completed multiple trials over the last several years. Importantly, insights from the data have allowed the company to design the next phase of development. At least two new trials with iadademstat could potentially be pivotal. Our valuation is €739m, or €13.9 per share (vs €11.1 per share previously).

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/19	10.3	(4.6)	(0.09)	0.0	N/A	N/A
12/20	9.5	(4.8)	(0.07)	0.0	N/A	N/A
12/21e	9.9	(6.9)	(0.07)	0.0	N/A	N/A
12/22e	9.9	(6.1)	(0.09)	0.0	N/A	N/A

Note: *Normalised, excluding amortisation of acquired intangibles and exceptional items.

Iadademstat: New FRIDA and STELLAR trials

Oryzon plans to submit the Investigational New Drug applications to the FDA and start enrolling patients in its new trials, FRIDA in H122 and STELLAR in H222. The Phase Ib/II FRIDA trial will investigate iadademstat in patients with FLT3-mutated acute myeloid leukaemia (AML) in a second-line setting in combination with the recently approved Xospata (FLT3 inhibitor, Astellas). It is possible that this trial could be used for an accelerated approval. The Phase Ib/II STELLAR trial will investigate iadademstat as a first-line treatment with a checkpoint inhibitor in small cell lung cancer (SCLC). The efficacy will be evaluated using a PFS endpoint, which, if significant, could allow for an application for accelerated approval.

Vafidemstat: Pipeline expansion ongoing

Most of the accumulated data with vafidemstat point to its ability to improve problematic behaviour, namely aggression and agitation or social withdrawal in various CNS disorders. Borderline personality disorder (BPD) remains the lead indication, with overall control of the disease or aggression/agitation management as two possible labels (the Phase IIb PORTICO trial is now enrolling patients). However, Oryzon is expanding the pipeline for vafidemstat with several new indications, namely schizophrenia (negative symptoms), Kabuki syndrome and potentially aggression management in Alzheimer's disease (AD).

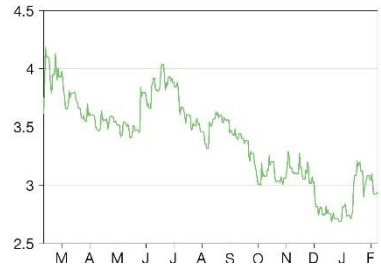
Valuation: €739m, or €13.9 per share

Our valuation is higher at €739m, or €13.9 per share, versus €591m or €11.1/share previously. Oryzon's R&D pipeline has evolved substantially over the last several months. Accordingly, we have extensively revised our rNPV model. In our rNPV model we keep AML (26% of the total rNPV) and SCLC (23%) indications for iadademstat and AD (11%) and BPD (28%) for vafidemstat (albeit our underlying assumptions are updated). We have removed multiple sclerosis, but have added vafidemstat for schizophrenia (10%) as a new opportunity.

9 February 2022

Price	**€2.94**
Market cap	**€156m**
	€:US$1.13
Net cash (€m) at end Q321	16.1
Shares in issue	53.1m
Free float	80%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	7.3	(5.2)	(21.6)
Rel (local)	8.3	(0.8)	(25.7)
52-week high/low		€4.2	€2.7

Business description

Oryzon Genomics is a Spanish biotech focused on epigenetics. Iadademstat is being explored for acute leukaemias and SCLC. Vafidemstat, its 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 Ib/II FRIDA trial first patient in	H122
Phase Ib/II STELLAR trial first patient in	H222
Phase Ib/II HOPE trial first patient in	H122
Final data from Phase IIa ALICE trial	ASH'22

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Edison profile page

Company outlook: On path to market

Oryzon is a pure play in epigenetics and has developed a proprietary platform to create therapeutic inhibitors for a class of enzymes known as histone lysine demethylases (KDMs). Iadademstat, Oryzon's lead oncology asset, is a first-in-class LSD1 inhibitor (also called KDM1A inhibitor). Vafidemstat is a central nervous system (CNS)-optimised LSD1 inhibitor for neurological and neuropsychiatric conditions.

Put simply, epigenetics can be defined as the study of changes in how genes are 'read' (expressed). A number of external factors can switch genes on and off modifying the expression, but without actually making any changes in the sequence of DNA (a more detailed introduction to epigenetics can be found here). Oryzon's technology evolves around histone modifications. Histones are protein complexes, which the DNA is rolled up on. Epigenetic modifications (eg methylation and demethylation) cause changes in this spatial organisation, which lead to different genes becoming accessible for expression or silenced. This process is a part of normal gene expression regulation, but if it falters, it can also be the cause of a variety of diseases.

Epigenetics is relatively young field in terms of drug development. Epigenetic therapies induce profound biological changes, therefore they can have broad action potential, as opposed to targeted therapies, like monoclonal antibodies. This means that Oryzon had no guiding principles when it comes to specific indication selection or treatment setting. For this reason, the strategy of accumulating as much useful clinical data as possible in a variety of settings took some time to deliver, but it has now started paying off.

Exhibit 1: Oryzon's R&D pipeline

Source: Oryzon Genomics; more detailed discussion about our R&D assumptions is in Exhibit 4.

Iadademstat: Designing a path to market

Oryzon is developing iadademstat for patients with AML and SCLC. The two original trials in these indications are the Phase IIa ALICE study in advanced AML (still ongoing, but because it is open label, Oryzon presents regular follow ups) and the Phase IIa CLEPSIDRA study in SCLC (now complete).

The Phase IIa ALICE trial: Final data next year

The ALICE trial, which is investigating iadademstat in combination with azacitidine, is fully enrolled with a total of 36 patients. This is a single-arm, open-label study that enrolled newly diagnosed, elderly AML patients who were administered iadademstat in combination with standard of care chemotherapy drug azacitidine.

Besides **dose-finding** data and **safety/tolerability** evaluation (primary endpoints), the initial efficacy was evaluated using the secondary endpoints **overall response rate** (ORR), **time to response** (TTR) and **duration of response** (DOR).

The latest update was the interim data after 36 months of follow up, which was presented at the ASH 2021 congress in December 2021. Of the 27 evaluable patients, 21 (78%) achieved ORR (62% were complete remission/complete remission with incomplete hematologic recovery). For comparison, ORRs are c 30% in AML patients treated with azacitidine monotherapy. This was the sixth update from the ALICE trial and the maturing data have been very consistent so far (Exhibit 2): the ORR is being reported at c 80%, which is much higher than the historical response rates with classic chemotherapy (c 30%). Moreover, such rates compare well with BCL2 inhibitor venetoclax (AbbVie/Genentech), a novel approved drug for front-line AML treatment. Venetoclax plus azacitidine or decitabine achieved an ORR of 68% in a late-stage trial and the consensus estimate is for sales to reach $1.4bn in AML alone by 2026 (EvaluatePharma).

Patients will be followed for an additional 12 months in the ALICE trial, so the final data from this trial are expected to be released at the ASH conference in **December 2022**.

Exhibit 2: Evolution of Phase IIa ALICE trial efficacy data

	Phase IIa ALICE trial (iadademstat + azacytidine)						Venetoclax + azacitidine or decitabine	Azacitidine
Update/publication	EHA 2019	ASH 2019	EHA 2020	ASH 2020	EHA 2021	ASH 2021	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)	-	-
Evaluable patients	5 patients	8 patients	13 patients	13 patients	18 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)**	68% (99/145)	31% (75/241)

Source: Edison Investment Research, Oryzon Genomics

The Phase Ib/II FRIDA trial: Potential path to market

Rationale

Since the ALICE trial is open label, Oryzon has been able to learn from the data before waiting until the follow-up periods of all the patients have been completed. Encouraged by the observed efficacy signals, Oryzon introduced with its Q321 results report a new Phase Ib/II trial FRIDA, which will investigate iadademstat in patients with FLT3 mutated AML as a second-line treatment (relapsed/refractory AML). Iadademstat will be combined with Xospata (gilteritinib, FLT3 inhibitor, Astellas; 2020 sales of $225m). Xospata is a relatively new drug approved by the FDA in November 2018 as monotherapy for adults with FLT3-positive AML in a relapsed or refractory setting.

In preclinical studies Oryzon saw synergies between iadademstat and Xospata, which is the rationale for this trial. Also, Oryzon has an orphan drug designation granted for AML in the United

States and EU and believes that the FRIDA trial could provide sufficient data to register the drug (presuming a positive outcome). This strategy will also avoid direct competition with venetoclax.

Second-line AML is an underserved population, as 50% of AML patients relapse after first-line treatment. FLT3 is the most common mutation in AML (30%) and patients have an adverse prognosis. Second-line FLT3-mutated patients are now treated with gilteritinib, yet it remains a subpopulation with high medical need.

FRIDA trial design

The FRIDA trial will be an open-label trial with all centres based in the United States and will enrol around 120 patients. It will consist of two parts: Phase Ib will evaluate safety/tolerability and the recommended dose for the Phase II part of the study, which will evaluate the efficacy (the trial protocol is not published yet).

Although there is no direct control arm in the FRIDA study, Oryzon expects that a matched control sample (Xospata monotherapy) will be sufficient as a comparator. Furthermore, the intervention sample is powered enough so that this trial could be used for an accelerated approval (if the data are positive). Oryzon plans to submit the Investigational New Drug application to the FDA and **start enrolling patients in H122**.

The Phase Ib/II STELLAR trial: Using insights from CLEPSIDRA

Like the FRIDA trial, the Phase Ib/II STELLAR trial is a new addition to the R&D pipeline. Oryzon has designed this study using insights gained from the now completed Phase IIa CLEPSIDRA trial. As a reminder, Oryzon presented the final update from the CLEPSIDRA trial at the ESMO conference in September 2020 (our review of the data is here).

Learnings from the CLEPSIDRA trial

CLEPSIDRA was an open-label, single-arm Phase IIa study of iadademstat in combination with platinum and etoposide chemotherapy (triple combination) in relapsed, extensive disease SCLC patients (14 patients enrolled; 10 were evaluable for efficacy), so this was a very advanced setting. The safety profile did not allow for this combination to proceed despite attempts to modify the dosing regimen. The side effects of this specific drug combination were haematological changes, which included decreased platelets, neutrophils and anaemia, in some cases serious. The investigators tried different dosing regimens; however, the conclusion was made that such combination therapy is not suitable in this setting. Notably, iadademstat monotherapy did not show any haematological toxicity, while etoposide and platinum (classical chemotherapy agents) have known haematological side effects.

On the positive side, the data showed efficacy rates that compared well with other therapies in this setting. The ORR of 40% (4/10 partial responses) compared well with the historical averages of SCLC second-line chemotherapy drug topotecan (15–24%) and lurbinectedin (35%). SCLC is generally considered a non-immunogenic cancer, so reported ORRs to immune checkpoint inhibitors are also relatively low: 22% nivolumab plus ipilimumab and 19% pembrolizumab as monotherapy (Saleh, 2019). Furthermore, this efficacy rate was achieved at suboptimal doses of iadademstat (the dose was lowered after the side effects started to appear).

The new Phase Ib/II STELLAR trial design

Oryzon indicated it would explore iadademstat combinations with non-haematotoxic agents in SCLC, which has now materialised in the form of the STELLAR trial. In preclinical studies Oryzon observed synergy between iadademstat and checkpoint inhibitors, which generally have better haematological safety profiles.

The STELLAR trial will investigate iadademstat as a first-line treatment in combination with a checkpoint inhibitor in patients with metastatic SCLC. The study will also be conducted in the United States and will aim to recruit 120 patients. The Phase Ib part will assess the safety/tolerability of the combination and the recommended dose for the Phase II part. The latter will be randomised and controlled with a checkpoint inhibitor (CPI)-only arm. The efficacy will be evaluated using a progression-free survival (PFS) endpoint which, if significant, Oryzon expects will allow for an application for accelerated approval in this setting.

Oryzon plans to submit the Investigational New Drug application to the FDA in H122 and **start enrolling patients in H222**. The study protocol has not been disclosed yet, so further details will be announced in due course.

SCLC is an aggressive form of lung cancer associated with very poor prognosis. It represents around 15% of all lung cancers and 60–70% of patients have extensive-stage disease at diagnosis. Despite intense R&D efforts to improve clinical outcomes, classical platinum/etoposide chemotherapy has remained the most effective regimen for first-line extensive disease SCLC for decades. It is only recently that checkpoint inhibitors have been proven to add clinical benefit.

Vafidemstat: Re-shaping the development pipeline

BPD: The Phase IIb PORTICO trial up and running

The Phase IIb PORTICO trial is now enrolling patients in Europe and the United States. The goal is to enrol 156 subjects (n=78 in each arm) with diagnosed BPD. The patients are randomised to receive vafidemstat or placebo. There will be multiple primary and secondary endpoints, but the trial has two goals: to demonstrate reduction of aggression/agitation and overall BPD improvement. The PORTICO study has an adaptive design with a pre-defined interim analysis to adjust the sample size in case of excessive results variability or an unexpectedly high response in the placebo arm.

As a reminder, BPD as the lead indication for vafidemstat emerged from Oryzon's innovative basket type Phase IIa study REIMAGINE, which investigated vafidemstat in several neuropsychiatric conditions (attention deficit hyperactivity disorder (ADHD), BPD and autism spectrum disorder (ASD)). In those three different indications, vafidemstat not only significantly improved scores across several commonly used subscales that measure agitation and aggression, but also significantly improved the total scores of those same specific psychiatric scales (the results are discussed in detail in our January 2020 report). Although the cohorts were relatively small, the consistent results across several scales and in three different indications were promising. Of the three indications investigated in this trial, Oryzon chose to prioritise BPD, which is relatively prevalent among adults (clinical trials that are easier to run when the population is large), but no specific treatments available.

The PORTICO study treatment period is 14 weeks, so the results should be obtained relatively quickly. Interim data are expected **potentially by the end of 2022**. The development strategy will depend on the data.

Rethinking vafidemstat for AD

Oryzon has been exploring vafidemstat's potential in AD with two clinical studies now completed. The Phase IIa ETHERAL study in mild and moderate AD enrolled 140 patients, who were randomised to received treatment with vafidemstat or placebo for 12 months. In terms of treatment period and sample size, this was a fairly substantial study. Since it was a Phase IIa stage trial, safety and tolerability were the primary endpoints, which were met. The exploratory secondary endpoints included several biomarkers and clinical efficacy. Vafidemstat reduced pro-inflammatory biomarker YKL40 in cerebrospinal fluid (CSF). Other biomarkers in the CSF were unchanged and

there were no significant differences in cognition among the patients receiving vafidemstat or placebo (measured by ADAS-Cog, one of the most commonly used cognition scales in AD).

The scope of the ETHERAL study was broad. It was designed to test even the disease modifying potential of vafidemstat, which is notoriously difficult. Since no effect was observed on cognition, Oryzon is now focusing on a specific setting in AD, which is aggression and agitation in moderately or severely ill patients. The basis for this comes from another trial, Phase IIa REIMAGINE-AD, that Oryzon had completed in parallel to the ETHERAL study. REIMAGINE-AD (like the basket trial REIMAGINE described above) showed that vafidemstat significantly reduced agitation and aggression after 12 months of treatment in these patients with a good safety and tolerability profile (there was even an anecdotal finding that the drug improved cognition in a subset of AD patients).

The idea that vafidemstat could be helpful in controlling aggression and agitation comes from preclinical studies. Vafidemstat demonstrated an ability to reduce aggression, enhance sociability and reverse social withdrawal in animals. Both the REIMAGINE and REIMAGINE-AD studies were initiated while the ETHERAL study was still running. This again demonstrates Oryzon's strategy to explore as many settings as possible given the novel mechanism of action of vafidemstat. The data from the AD trials now point to symptomatic treatment of aggression and agitation in moderately or severely ill patients (although, as mentioned, there were anecdotal improvements in cognition in several patents in the REIMAGINE-AD trial, which presumably will be explored further). Oryzon has not yet communicated any plan for the next study in this setting.

Seismic developments in AD management

The management of AD has seen significant changes in the past year. The FDA approved the first-ever disease-modifying drug, Aduhelm, on 7 June 2021 (anti-Aβ antibody, aducanumab, Biogen). The final data set that supported the approval was rather controversial (one Phase III was considered successful, the second Phase III trial failed). This meant that although much needed, the launch of this drug was troublesome: several of the FDA advisory committee members resigned, Biogen had to voluntarily narrow the label, initial sales did not meet expectations, insurance reimbursement is still not clear and the EMA recommended that the European Commission reject Aduhelm. All this led Biogen to cut the initial price tag of $56k in half. In the latest turn of events the US Centers for Medicare & Medicaid Services offered Aduhelm cover only for patients in clinical trials, implying lack of supportive efficacy data. Although there is no read-across from Aduhelm's story from a technology perspective to Oryzon's vafidemstat and its positioning, we believe the controversial approval from the FDA is a strong indication that regulators are keen to make novel AD treatments (disease modifying, but also symptomatic) available as quickly as possible.

Multiple sclerosis: 'No go' decision after Phase II SATEEN trial

The final data from the Phase II trial SATEEN, which investigated vafidemstat's ability to reduce the inflammation in multiple sclerosis (MS) patients was presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS-2021) on 13–15 October 2021. This randomised, double-blind, placebo-controlled Phase II trial (n=18) aimed to evaluate the safety and tolerability of vafidemstat in relapse-remitting MS (RRMS) or secondary progressive MS (SPMS) patients. The final results showed that:

- Long-term vafidemstat treatment was safe and well tolerated, with drug exposures up to two years; however, there were no statistically significant differences between groups in efficacy endpoints.
- In several patients treated, vafidemstat did show an improvement in one or more clinical endpoints. In addition, some anti-inflammatory activity was observed in most of the vafidemstat-treated patients compared to placebo, which indicates vafidemstat's activity.

Oryzon pointed out that due to its small scale, the SATEEN trial was not powered to get definitive efficacy data. The observed clinical activity in the MS patients supports vafidemstat's potential to reduce the neuroinflammation component in MS. Neuroinflammation is a core feature in MS and also in other CNS conditions. However, when evaluating strategic opportunities, Oryzon has decided not to pursue MS further. Accordingly, we have removed this indication from our valuation model.

Other emerging opportunities for vafidemstat

As mentioned above, Oryzon has been investigating vafidemstat in a variety of neurological and neuropsychiatric conditions. While BPD is now the lead indication, the company is working on several other indications as well. The two newest clinical trials are a **Phase IIb EVOLUTION study** in schizophrenia (recruiting patients) and a **Phase I/II HOPE study** in patients with Kabuki syndrome. The EVOLUTION study is partially funded with public funds and is running in Spain.

Schizophrenia: The Phase IIb EVOLUTION study

The Phase IIb EVOLUTION trial is a double-blind, randomized, placebo-controlled, 24-week trial to evaluate the efficacy and safety of vafidemstat in adult schizophrenia patients, who are receiving antipsychotic therapy. The trial has two primary independent objectives:

- to assess the effect of vafidemstat on negative symptoms of schizophrenia, and
- to assess improvement on cognitive impairment associated with schizophrenia.

The patients (n = 100; 50:50 in both arms) will be treated for six months. The final number of patients needed to assess efficacy will be adjusted during an interim analysis. The scientific rationale for this study is based on vafidemstat's ability via LSD1 inhibition to reduce aggression, enhance sociability and mitigate social withdrawal, as demonstrated in several preclinical models and clinical trials discussed above.

Schizophrenia: Positive vs negative symptoms

Schizophrenia is a chronic and severe mental disorder involving a breakdown in the relation between thought, emotion and behaviour, leading to faulty perception and the inability to function normally. Signs and symptoms can vary. Generally, symptoms are classified into three, sometimes four, categories:

- **Positive symptoms (psychosis)**. Classic examples include visual or auditory hallucinations.
- **Negative symptoms**. This term describes 'a lessening or absence of normal behaviours and functions related to motivation and interest' (Correll and Schooler, 2020). Symptoms include reduced expression of emotion, social withdrawal and lack of interest in everyday activities, accompanied by irrational thoughts.
- **Cognitive symptoms**, such as trouble focusing and problems with working memory.
- A fourth category sometimes is also described as **mood symptoms**.

Antipsychotic medications (also known as neuroleptic medications) diminish the positive symptoms of schizophrenia and prevent relapses. However, there are no approved drugs aimed at negative symptoms. Approximately 80% of patients relapse within one year if antipsychotic medications are stopped, whereas only 20% relapse if treated. So the treatment of positive symptoms is fairly effective. The choice of which drug to use for treatment of a patient depends on many issues, but there is no broad consensus on specific treatment protocols. The current treatment approach is largely trial and error across different medication choices. Negative symptoms generally do not respond well to currently available antipsychotic treatment. For obvious reasons negative

symptoms are generally not the reason that patients seek clinical care, yet they constitute an unmet medical need in schizophrenia, therefore new and effective treatments are urgently needed (Correll and Schooler, 2020). Currently there are no drugs approved by the FDA for the treatment of negative symptoms (Aleman et al, 2017).

The lifetime prevalence of schizophrenia has generally been estimated to be approximately 1% worldwide. Negative symptoms are common with up to 60% of patients having clinically relevant negative symptoms that require treatment (Correll and Schooler, 2020). Negative symptoms can occur at any point in the course of illness, although they are described as the most common first symptom of schizophrenia before the first psychotic episode.

The schizophrenia market: Sidestepping the competition

The current mainstay of the treatment is antipsychotic drugs. So-called typical antipsychotics were developed in the 1950s and examples include haloperidol, chlorpromazine and fluphenazine. Atypical antipsychotics include a newer generation of drugs developed in the 1990s and examples include aripiprazole (Abilify, Bristol Myers Squibb), olanzapine (Zyprexa, Lilly) and quetiapine (Seroquel, AstraZeneca). According to EvaluatePharma, the global antipsychotic drug market was worth $10.2bn in 2020 and is forecast to grow at a 6.2% CAGR over 2020–26. It is a highly fragmented market and most of the drugs used widely to treat the anti-psychotic symptoms of schizophrenia are out of market exclusivity, with generics widely available. From this perspective, Oryzon's focus on negative symptom improvement would entirely sidestep the crowded neuroleptic market.

COVID-19: Phase II ESCAPE study

Like many biotechs that have assets that could prove beneficial in managing the COVID-19 pandemic, Oryzon opportunistically launched a Phase II ESCAPE study that investigated vafidemstat's efficacy in seriously ill patients with COVID-19. Preliminary data were presented at the 31st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID-2021, July 2021). ESCAPE was an open-label, randomized Phase II trial (n=60) aimed to evaluate the efficacy and tolerability of vafidemstat in combination with standard treatment used in hospitals to prevent progression to acute respiratory distress syndrome, a potentially life-threatening complication. Vafidemstat was safe and well tolerated in severe COVID-19 patients. Vafidemstat reduced the exacerbated activation of CD4+ T cells and reduced the release of key inflammatory cytokines. However, there were no significant differences in the number of deaths between the two arms of the study and the patients in both arms of the study recovered quickly.

The lack of clinical effect could be partially explained by the fact that COVID-19 in-hospital management has been rapidly changing with new drugs being approved and quickly becoming standard of care. So, the management of COVID-19 patients significantly has improved since the start of the pandemic, which is a significant confounding factor in all COVID-19 studies.

The rationale for this study is vafidemstat's well documented ability to reduce inflammation. Although the findings from this study support this effect, due to lack of clear clinical benefit we believe that Oryzon is unlikely to pursue this indication alone. Infectious diseases were never the focus for the company. There is a potential for some form of collaboration with other interested players in the area, but so far no news has been released in this regard.

Monogenic neurological diseases

One of the more recent initiatives by Oryzon is to investigate vafidemstat in so-called monogenic diseases. Monogenic diseases result from modifications to a single gene. Many different forms of

brain impairment are associated with monogenic neurological disorders, such as fragile X syndrome, Huntington's disease, monogenic autism or some forms of Parkinson's disease. Up until now, Oryzon investigated vafidemstat in CNS indications that could be described as multifactorial, that is there are no known or clear single cause for BPD, AD or autism. With this new initiative, Oryzon's management has been exploring whether there is potential to use vafidemstat in diseases with a known single gene mutation (a precision medicine approach).

Oryzon identified Kabuki syndrome as the first suitable condition. The rationale comes from preclinical studies and third-party data (Zhang et al, 2021), which show that excessive LSD1 activity may be a key cause. This is a rare form of intellectual disability primarily caused by loss of function mutations in lysine-specific methyltransferase 2D (mutated KMT2D; causes Kabuki syndrome in c 70% of cases). KMT2D normally adds methyl to histones. Since lysine-specific demethylase 1A (LSD1, which is also known as KDM1A) normally removes the methyl groups added by KMT2D, the hypothesis is that inhibition of KDM1A demethylase (or LSD1) activity with vafidemstat (LSD1 inhibitor) may ameliorate the defects stemming from KMT2D mutation. Such effect was proven in animal models (third-party data) and now Oryzon is preparing a clinical trial.

The Phase I/II HOPE study

The Phase I/II HOPE study will be a randomized, double-blind, placebo-controlled trial to investigate vafidemstat's safety and potential to improve the symptoms of Kabuki syndrome. The trial plans to enrol 50–60 patients and will be performed in children older than 12 years and in young adults. Oryzon expects to start enrolling patients in H122 in several hospitals and sites in the United States and eventually in Europe. The trial protocol has not been published yet, but Oryzon indicated that it is designed so that if a clinical benefit is established, the data could serve as the basis for accelerated approval. So although this is the latest initiative in Oryzon's portfolio, the path to market could be quick if the data are positive.

Kabuki syndrome and orphan drug strategy

Kabuki syndrome is a rare disorder that affects multiple systems, including neuro, immune, auditory, and cardiac systems. It is characterised by distinctive facial features, growth retardation and mild to moderate intellectual disability. Life expectancy is not shortened in most cases of Kabuki syndrome. The syndrome was named because of the facial resemblance of affected individuals to stage makeup used in kabuki, a Japanese traditional theatrical form. This condition occurs in approximately one in 32,000 new-borns, so it is a rare disease. There is no specific treatment for Kabuki syndrome; only symptoms are managed.

The HOPE study marks Oryzon's first attempt to develop therapeutics for rare conditions. Orphan drug development strategy is somewhat less standardised than for large indications. The R&D strategy in rare diseases can involve just one trial in less than 200 patients (presuming pharmacokinetic (PK), pharmacodynamic (PD) and safety data are already present), which would be sufficient to register the drug if clinical effect is proven. The commercial strategy differs as well due to the fact that the patient population is small and spread widely. Typically, rare disease patients are connected with their respective patient associations, which tend to be significant advocacy players when it comes to new drug development (in September 2021, Oryzon received a $1m grant from a donor who is on the board of the Kabuki Syndrome Foundation). Another distinctive aspect of orphan drug strategy is pricing. Since the target population is small, the economic incentive to develop drugs has always been dampened. However, in recent years orphan drugs have achieved prices well above $100k per year per patient, which has boosted interest in orphan drug development.

Oryzon is also working with various institutions in order to identify other subsets of patients suitable for its precision medicine approach:

- In autism with researchers at the Seaver Center for Autism Research and Treatment at the Icahn School of Medicine at Mount Sinai Hospital in New York and the Institute of Medical and Molecular Genetics (INGEMM) at Hospital Universitario La Paz of Madrid.
- In schizophrenia with researchers from Columbia University in New York.

The goal of these collaborations is to characterise patients with specific mutations, which could then lead to clinical trials with vafidemstat.

Sensitivities

Oryzon is subject to the usual risks associated with drug development, including establishing a favourable safety/efficacy profile, clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The outcomes from the ALICE and CLEPSIDRA trials are known, so, in our view, the near-term sensitivities are spread across the key new trials (FRIDA, STELLAR, PORTICO, EVOLUTION and HOPE). Our valuation implies the iadademstat trials (FRIDA and STELLAR) carry more value given they have potential to generate data sufficient for registration.

Our risk-adjusted net present valuation (rNPV) is based on a number of assumptions. However, future pricing and market dynamics are hard to predict, especially if competitors are successful. Future financing needs will depend on the scale of operations with preclinical candidates, progress with vafidemstat and iadademstat and any potential revenues from partnerships.

Valuation

Our updated valuation is €739m, or €13.9 per share, vs €591m, or €11.1 per share previously. Given the progress Oryzon has made over the last year, the updated strategy for iadademstat (potentially registrational trials) and the initiation of new trials in new indications, we have extensively revised our rNPV model and R&D assumptions. Exhibit 4 provides a detailed description of the assumptions we have used in our rNPV model. Key changes from our previously published model include:

- **Iadademstat for AML**. This has a new and a smaller target patient population than we previously assumed, but with a higher price tag. We increased the success probability to 30% based on the ALICE trial data and the fact that the new FRIDA trial could allow for an application for approval. The peak sales decreased to $510m from $927m, but the success probability is improved from 15% to 30%. Therefore, the rNPV of this project is higher compared to that previously published.
- **Iadademstat for SCLC**. We have increased the price tag (in line with pricing in the AML project), but decreased the market penetration rate. We also increased the success probability from 8% to 25% based on the CLEPSIDRA trial data and the fact that the new STELLAR trial could allow for an application for approval. The rNPV of this project per share is higher than previously published.
- **Vafidemstat for BPD**. We have kept most of the assumptions for this project unchanged, as Oryzon is making progress in this indication largely in line with our expectations.
- **Vafidemstat in schizophrenia (negative symptoms)**. This is a new project and we have valued it based on assumptions summarised in Exhibit 4.
- **Vafidemstat for aggression management in AD**. We previously modelled vafidemstat's disease-modifying potential in AD. Given the latest clinical data and Oryzon's focus on developing vafidemstat for aggression management, we have revised all assumptions for this

project, as summarised in Exhibit 4. This has led to a smaller target patient population and lower pricing. Therefore, the peak sales are lower. We keep the success probability unchanged at 15% for the time being.

- We have removed **vafidemstat for MS** from our sum-of-the-parts (SOTP) valuation.

Currently we do not include vafidemstat for Kabuki syndrome in our valuation. This project is the most recent initiative and the first attempt to investigate vafidemstat's potential in monogenic diseases. These are rare conditions, so the R&D and commercial strategy is somewhat different from Oryzon's other projects targeting larger indications. We will reassess this opportunity on an ongoing basis.

Exhibit 3: Oryzon NPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
ladademstat	2L AML	2026	510	652.6	30%	190.5	3.6
ladademstat	1L extensive disease SCLC	2026	750	691.7	25%	167.3	3.2
Vafidemstat	BPD	2027	1,660	1,084.4	20%	208.0	3.9
Vafidemstat	Schizophrenia (negative symptoms)	2027	720	544.0	15%	74.3	1.4
Vafidemstat	Aggression in AD	2028	940	581.8	15%	83.1	1.6
Net cash (last reported)				16.1	100%	16.1	0.3
Valuation				**3,570.6**		**739.3**	**13.9**

Source: Edison Investment Research. Note: AML: acute myeloid leukaemia; SCLC: small cell lung cancer; AD: Alzheimer's disease; BPD: borderline personality disorder. €:US$1.13

Exhibit 4: Assumptions for Oryzon's asset valuation

Asset/indication		Comments
ladademstat	2L AML	**Target population**. AML incidence is c 20k in the US and 24k in Europe* (extrapolated), 30% FLT3 mutated, 50% relapse rate. Total calculated addressable population is 6,700. We assume market penetration of 50%. **R&D costs and timelines**. €15m in R&D costs until launch in 2026. Peak sales reached in 6 years. **Pricing**. $150k per patient per year, 50% discount in Europe applied (Xospata list price is up to $214k per patient). **COGS** margin of 1% (small molecule), **S&M** cost margin of 30% (smaller patient population targeted marketing).
	1L extensive disease SCLC	**Target population**. Lung cancer incidence is 236k in the US and 284k in Europe* (extrapolated). SCLC accounts for c 15% of all lung cancer cases. 70% of patients have extensive disease on diagnosis. Total calculated addressable population is 55k. We assume market penetration of 10%. **R&D costs and timelines**. €15m in R&D costs until launch in 2026. Peak sales reached in 6 years. **Pricing**. $150k per patient per year, 50% discount in Europe applied. **COGS** margin of 1% (small molecule), **S&M** cost margin of 50% (larger patient population).
Vafidemstat	BPD	**Target population**. Reported BPD prevalence is 1% in the western markets. Around 50% receive diagnosis and 50% receive treatment. This leads to a total of 1.5 million accessible patients. We assume market penetration of 10%. **R&D costs and timelines**. €20m in total to finish the PORTICO trial and then Phase III trial. Launch in 2027. Peak sales reached in 6 years. **Pricing**. $15k per patient per year (50% discount applied in Europe). A premium to generic antidepressants, which cost from several hundred US dollars to $2,000–3,000, depending on the brand; but at a discount to branded neuroleptics, ie drugs for positive schizophrenia symptoms that achieve prices of $20k+ per patient per year (eg Invega Trinza, Abilify). If vafidemstat shows overall improvement in BPD and not just aggression control, the price tag could be closer to that of neuroleptic drugs, in our view. **COGS** margin of 1% (small molecule), **S&M** cost margin of 50% (larger patient population).
	Schizophrenia negative symptoms	**Target population**. According to the WHO, schizophrenia affects approximately one in 222 adults (0.45%). Negative symptoms are common with up to 60% of patients requiring treatment. We assume 25% will seek or comply with treatment. This leads to a total of 375k accessible patients. We assume market penetration of 10%. **R&D costs and timelines**. €20m in total to finish the EVOLUTION trial and then Phase III trial. Launch in 2028. Peak sales reached in 6 years. **Pricing**. $25k per patient per year (50% discount applied in Europe). In line with branded neuroleptics, ie drugs for positive schizophrenia symptoms that achieve prices of $20k+ per patient per year (eg, Invega Trinza, Abilify). **COGS** margin of 1% (small molecule), **S&M** cost margin of 50% (larger patient population).
	Aggression in AD	**Target population**. Around 6.2m people currently are affected in US. Around 28% of individuals with AD are reported to exhibit aggressive behaviours. We assume around 50% of those will seek specific treatment. This leads to a total calculated addressable population of 1.9m patients. We assume market penetration of 5%. **R&D costs and timelines**. Currently further R&D plans are not announced yet. We assume Phase III trial to start sometime over the next two years. €15m will be spent in R&D costs before launch in 2028. **Pricing**. $10k per patient per year (30% discount applied in Europe). **COGS** margin of 1% (small molecule), **S&M** cost margin of 50% (larger patient population).

Source: Edison Investment Research. Note: *Target countries used in the model are the US, and top 15 European countries (EU4 + the UK, Ireland, Netherlands, Belgium, Luxembourg, Denmark, Finland, Norway, Sweden, Austria and Switzerland).

Financials

Oryzon's total operational spending in the first nine months of 2021 (9M21) was €12.6m ($14.6m), which as expected was somewhat higher than the €10.5m ($12.3m) booked in 9M20 due to a more intensive R&D programme. Oryzon booked €7.7m ($8.9m) as other income, which represents capitalised R&D costs (Oryzon follows local GAAP). After finetuning our estimates, our operating loss forecasts now are €6.9m and €6.1m in 2021 and 2022, respectively. The reported Q321 cash position was €31.0m (cash and short-term investments; net cash €16.1m). Our model suggests the current cash position should be sufficient until 2023 (funding gap is €2.8m in 2023 according to our estimates). Our expected R&D costs until the respective launch dates in each project are in Exhibit 4.

Exhibit 5: Financial summary

€000s	2018	2019	2020	2021e	2022e
Year end 31 December	Spanish GAAP	Spanish GAAP	Spanish GAAP	Spanish GAAP	Spanish GAAP
PROFIT & LOSS					
Revenue	6,781	10,278	9,521	9,857	9,857
Cost of Sales	0	0	0	0	0
Gross Profit	6,781	10,278	9,521	9,857	9,857
Research and development	(7,412)	(11,322)	(11,075)	(12,735)	(11,905)
EBITDA	(2,766)	(3,679)	(4,148)	(6,788)	(5,957)
Operating Profit (before amort. and except.)	(2,905)	(3,820)	(4,293)	(6,936)	(6,106)
Intangible Amortisation	(7)	(9)	0	0	0
Exceptionals	(4)	(11)	0	0	0
Other	0	0	0	0	0
Operating Profit	(2,916)	(3,839)	(4,293)	(6,936)	(6,106)
Exceptionals	0	0	0	0	0
Net Interest	(796)	(737)	(471)	0	0
Profit Before Tax (norm)	(3,701)	(4,557)	(4,765)	(6,936)	(6,106)
Profit Before Tax (reported)	(3,712)	(4,576)	(4,765)	(6,936)	(6,106)
Tax	2,535	892	1,379	3,025	1,508
Profit After Tax (norm)	(1,166)	(3,666)	(3,386)	(3,911)	(4,598)
Profit After Tax (reported)	(1,177)	(3,685)	(3,386)	(3,911)	(4,598)
Average Number of Shares Outstanding (m)	34.6	41.6	49.2	53.1	53.1
EPS - normalised (€)	(0.03)	(0.09)	(0.07)	(0.07)	(0.09)
EPS - reported (€)	(0.03)	(0.09)	(0.07)	(0.07)	(0.09)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	31,786	42,357	51,729	61,592	71,453
Intangible Assets	29,330	39,938	49,216	59,074	68,931
Tangible Assets	665	631	644	649	652
Investments	1,791	1,788	1,869	1,869	1,869
Current Assets	35,664	37,738	42,377	28,501	13,905
Stocks	135	289	317	317	317
Debtors	971	2,071	2,351	2,211	2,281
Cash	34,320	35,111	39,605	25,869	11,203
Other	239	267	105	105	105
Current Liabilities	(10,441)	(10,546)	(7,693)	(7,590)	(7,454)
Creditors	(2,192)	(4,000)	(2,839)	(2,736)	(2,600)
Short term borrowings	(8,249)	(6,547)	(4,854)	(4,854)	(4,854)
Long Term Liabilities	(11,884)	(8,420)	(10,483)	(10,483)	(10,483)
Long term borrowings	(9,977)	(6,699)	(8,680)	(8,680)	(8,680)
Other long term liabilities	(1,907)	(1,721)	(1,803)	(1,803)	(1,803)
Net Assets	45,125	61,129	75,931	72,020	67,422
CASH FLOW					
Operating Cash Flow	(2,799)	(3,610)	(5,432)	(6,751)	(6,164)
Net Interest	2,133	(324)	(247)	0	0
Tax	0	0	862	3,025	1,508
Capex	(170)	(115)	(153)	(153)	(153)
Acquisitions/disposals	0	0	0	0	0
Financing	11,949	18,374	18,181	0	0
Other*	(6,576)	(9,916)	(9,007)	(9,753)	(9,857)
Dividends	0	0	0	0	0
Net Cash Flow	4,538	4,409	4,205	(13,631)	(14,666)
Opening net debt/(cash)	(11,555)	(16,093)	(21,866)	(26,071)	(12,335)
HP finance leases initiated	0	0	0	0	0
Other	0	1,364	0	(105)	0
Closing net debt/(cash)	(16,093)	(21,866)	(26,071)	(12,335)	2,331

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

Contact details	Revenue by geography
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Management team

CEO: Carlos Manuel Buesa Arjol	Chief scientific officer: Jordi Xaus
Dr Buesa co-founded Oryzon Genomics in 2000 and has held the position of chairman of the board of directors since then. He earned his PhD in biochemistry from the University of Barcelona and has completed a senior management programme at IESE in 2005. More recently Mr Buesa has been a member of the boards of various biotechnology companies such as Oncnosi Pharma, Ninfas, Orycamb-Project, Geadig-Pharma, Neurotec Pharma and Palobiofarma.	Dr Xaus holds a degree in biology, a master's degree in immunology and a PhD in biology in the field of immune response control. He was associate professor of immunology at the University of Barcelona until 2001. After that he joined the biotechnology industry, initially at Puleva Biotech as head of the Immunology Department, and later at Palau Pharma as the CSO. During this period, he participated in the licensing and sale of four of the company's compounds. In 2014, he joined Oryzon Genomics where he has held various management positions and currently serves as the CSO.
CFO: Enric Rello Condomines	**Chief business development officer: Saikat Nandi**
Mr Rello joined Oryzon in May 2011. He has a master's degree in administrative management and a degree in business administration and management, in law and in economics from Universidad Abat Oliba – CEU (Barcelona). He began his professional career in advisory services, auditing and consulting, and later specialised in management control and in economic and financial management.	Dr Nandi holds a PhD from Oxford University (UK) in biochemistry. He has over 15 years of professional experience in the healthcare sector and financial services. In his prior asset management roles at AIG and previously at GCF, he has managed public and private healthcare investments totalling more than $1bn. Earlier in his career he served as business development consultant at the New York State Center for Biotechnology, an NIH-designated incubator where he managed strategic partnerships and capital raising activities.
Chief Medical Officer for CNS: Michael Ropacki	**SVP of Clinical Development and Global Medical Affairs: Ana Limón**
Dr Michael Ropacki is the president of a San Francisco-based consultancy firm, Strategic Global Research & Development (SGR&D), which collaborates with sponsors on developing and executing clinical development plans. Prior to his role at SGR&D, Dr Ropacki was most recently senior vice president of clinical development at MedAvante-ProPhase. Before that, he held roles of increasing responsibility at Johnson & Johnson, including director of clinical development, neuroscience, research and development. He completed his internship/residency at University of Oklahoma Health Sciences Center in Psychiatry and holds a PhD from Texas Tech University.	Dr Limón brings more than 15 years' experience in drug development, managing multifunctional teams, conducting research from preclinical to registration-enabling clinical studies in hematologic and solid tumours, as well as medical affairs activities for the launch and support of commercial products. She was 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. Dr Limón holds a PhD in Molecular Biology and Biochemistry from the University of Barcelona.

Principal shareholders	(%)
Carlos Buesa	6.61
Jose Ventura Ferrero	5.48
Tamara Maes	4.70
Josep Maria Echarri	2.33

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