EDISON

Oryzon Genomics

Company outlook

More to come after a year of data readouts

Pharma & biotech

As we expected, 2019 was a year of data readouts for epigenetics specialist Oryzon. The company presented new data from the ongoing Phase IIa clinical trials with both assets at eight conferences last year. All readouts were still interim. This and the fact that Phase IIa trials, in general, are relatively small and focus on safety meant that the share price did not reach new highs despite all readouts being positive. Final results from the trials are expected throughout 2020–21 and Oryzon is already initiating a Phase IIb trial with its CNS asset in borderline personality disorder (BPD). This will provide plenty more catalysts in the coming months. Our valuation is slightly higher at €454m or €9.9/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/17	4.3	(4.6)	(0.14)	0.0	N/A	N/A
12/18	6.8	(3.7)	(0.03)	0.0	N/A	N/A
12/19e	9.8	(5.1)	(0.10)	0.0	N/A	N/A
12/20e	9.9	(4.7)	(0.06)	0.0	N/A	N/A

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

Vafidemstat – holistic intervention for CNS disorders

Oryzon has developed a broad R&D programme for vafidemstat, a CNS-optimised inhibitor, and is targeting a range of neurological disorders. The newer Phase IIa REIMAGINE and REIMAGINE-AD projects are exploring vafidemstat's potential in managing aggression in four separate patient cohorts: borderline personality disorder (BPD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and moderate-to-severe Alzheimer's disease (AD). Data from the three REIMAGINE cohorts have been promising and Oryzon seems to have a high level of confidence in BPD, with plans to initiate a Phase IIb trial in the coming months. Data from the REIMAGINE-AD and two earlier Phase IIa trials, ETHERAL (mild-to-moderate AD) and SATEEN (multiple sclerosis) are expected in 2020/21.

Iadademstat – LSD1 inhibitor for cancer

Oryzon is running two Phase IIa trials with iadademstat in acute myeloid leukaemia (AML; ALICE study) and extensive disease small cell lung cancer (SCLC; CLEPSIDRA study). Interim results from both studies were presented in 2019 and both drugs were impressive with initial efficacy signs, while the safety profile seemed to be acceptable (a key consideration for all epigenetic cancer drugs), albeit the patient samples were small. Enrolment in both trials continues and more data are expected in 2020.

Valuation: €454m or €9.9/share

Our valuation of Oryzon is slightly higher at €454m or €9.9 per share, up from €437m or €9.5 per share, mainly due to rolling our model forward. We leave our assumptions unchanged. The main near-term catalysts include vafidemstat Phase IIa REIMAGINE-AD data from AD patients in Q220; vafidemstat Phase IIa ETHERAL EU six-month interim trial results in H120; updated data from iadademstat Phase IIa CLEPSIDRA in SCLC and Phase IIa ALICE in AML some time in 2020.

20 January 2020

Price	**€3.16**
Market cap	**€145m**
Net cash (€m) at end Q319	26.0
Shares in issue	45.8m
Free float	73%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	2.8	14.3	15.1
Rel (local)	2.1	10.3	6.0

52-week high/low €4.40 €2.53

Business description

Oryzon Genomics is a Spanish biotech focused on epigenetics. Iadademstat (Phase IIa) is being explored for acute leukaemias and SCLC; vafidemstat, its CNS product, is in Phase IIa trials in MS, AD and aggression. Newer asset ORY-3001 is being developed for certain orphan indications.

Next events

Vafidemstat Phase IIa REIMAGINE-AD data	H120
Vafidemstat Phase IIa ETHERAL EU six-month interim trial results	H120
Potential start of Phase IIb PORTICO trial with vafidemstat in aggression in BPD	H120
Updated data from iadademstat Phase IIa CLEPSIDRA in SCLC	2020
Updated data from iadademstat Phase IIa ALICE in AML 2020	2020

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Edison profile page

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Investment summary

Moving from Phase IIa to Phase IIb stage

Oryzon was founded in 2000 and currently develops epigenetics-based therapeutics for patients with cancer and CNS disorders. Oryzon has two products in the clinical stage and an active preclinical programme in the LSD1 inhibition field, which is the company's area of expertise. The lead assets are vafidemstat for neurological and neuropsychiatric disorders and iadademstat for haematological and solid tumours. Oryzon is working on seven Phase IIa clinical trials with vafidemstat and iadademstat. In 2019, Oryzon presented multiple datasets from the ongoing trials. So far, all readouts have been promising, albeit the final results are still pending. The first Phase IIb trial that Oryzon seems to be committed to initiate in the coming months is vafidemstat in BPD. Phase IIb proof-of-concept efficacy trials tend to be major catalysts for the share price. Oryzon is headquartered in Barcelona, Spain, with a US office in Cambridge, MA, and employs around 40 people. Oryzon listed its shares on the Madrid Stock Exchange on 14 December 2015.

Financials: Cash reach to 2022

Oryzon's 9M19 total operational spending was €10.5m ($11.5m), as expected somewhat higher than €8.0m ($8.7m) booked in 9M18 due to a more intensive R&D programme. Oryzon booked €7.4m ($8.9m) as other income, which represents capitalised R&D costs (Oryzon follows local GAAP), therefore reported operating income was €3.2m ($3.4m). We have increased our total FY19 operating expenses estimate to €14.2m from €12.4m, but also increased our FY19 income to €9.8m from €6.1m. The net change in our FY19 operating loss estimate was positive at €4.4m vs €6.2m (and €4.3m vs €6.3m in FY20). The reported Q319 cash position was €39.2m (cash and short-term investments; net cash €26.0m) following the private placement in July 2019, which brought in €20m gross; this should be sufficient to reach 2022, in our view.

Valuation: €454m or €9.9/share

As Oryzon is on track to develop its assets in all the indications we include in our valuation, we leave our assumptions unchanged. Our updated valuation is €454m or €9.9/share, slightly up from €322m or €9.4/share mainly due to rolling our model forward. Our valuation includes rNPVs for both assets in the most advanced indications. Oryzon is now running two trials in AD with different goals (aggression management and treatment of the core symptoms). For the time being, we maintain our top-down approach with a single rNPV project as described in our initiation report, where we used sales of existing AD drugs as a benchmark. BPD is the newest addition to our SOTP table following the positive results from the REIMAGINE trial in April 2019. We will consider other indications in the basket trial as well if Oryzon commits to initiate subsequent trials.

Sensitivities: Typical drug developer sensitivities apply

Oryzon is subject to the usual risks associated with drug development, including establishing favourable safety/efficacy profile, clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. Both assets will likely need to be partnered, as later-stage studies in oncology and CNS indications can be costly due to large populations. However, Oryzon has enough cash to progress its assets through mid-stage development to reach meaningful data. We have assumed a deal in our valuation after Phase II for both assets, but we have limited visibility on the timing and terms. 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.

New generation of epigenetic drugs

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 expression, but without actually making any changes in the sequence of DNA. These changes are called epigenetic modifications (a more detailed introduction to epigenetics can be found in our initiation report).

Epigenetics is a relatively young field in terms of drug development and histone deacetylase (HDAC) inhibitors were among the first epigenetic therapeutics brought to market. However, one of the key drawbacks of HDAC inhibitors was low selectivity and the resulting side effects. Oryzon and some third-party researchers[1] have started classifying HDAC inhibitors as the first generation of epigenetic modifying agents and Oryzon's products can be assigned to a second generation of selective inhibitors of histone demethylases (KDMs) alongside other newer compounds in the R&D stage targeting histone methyltransferase (HMTs) and the bromodomain and extraterminal domain (BET) family of epigenetic regulators.

Oryzon has developed a proprietary platform to create therapeutic inhibitors for a class of enzymes known as histone lysine demethylases, also known as KDMs. The two most advanced compounds in Oryzon's pipeline are iadademstat and vafidemstat. Iadademstat is a potent and highly selective LSD1 (lysine specific demethylase 1, also called KDM1A) inhibitor, whereas vafidemstat is a CNS-optimised LSD1 inhibitor. Oryzon's third preclinical candidate, ORY-3001, is also an LSD1 inhibitor. Currently, the company is working on seven Phase II studies and the recent developments include:

Vafidemstat

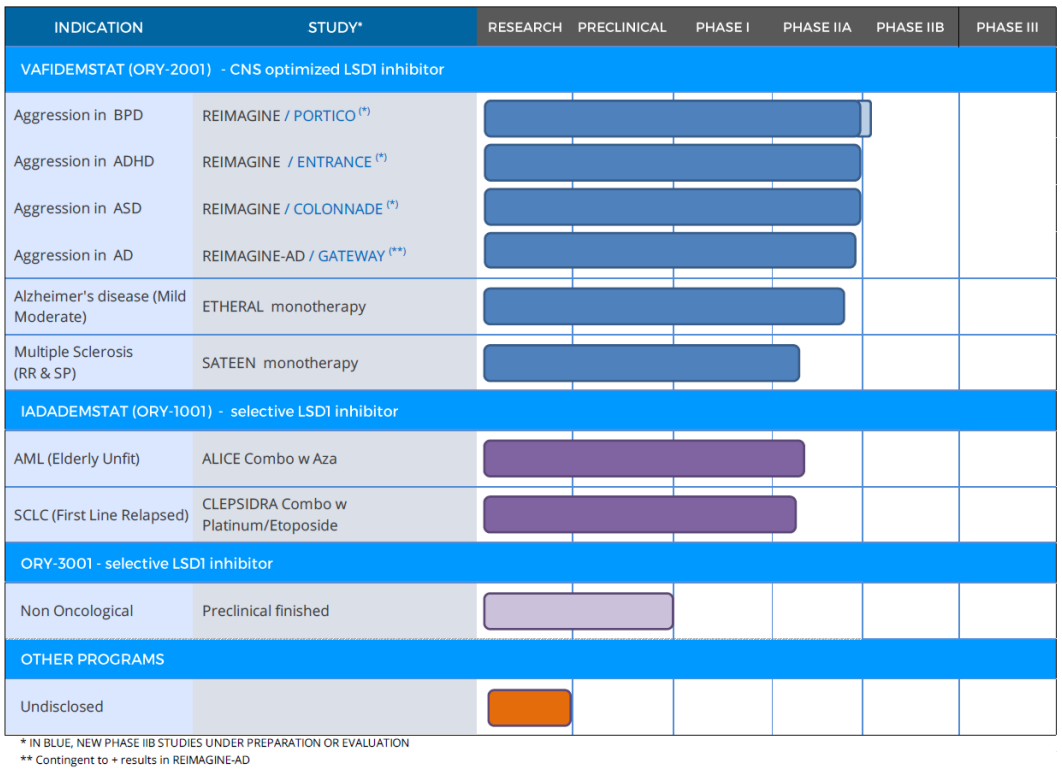
- In October 2019, Oryzon released efficacy results from its Phase IIa REIMAGINE trial with vafidemstat in aggression in psychiatric diseases with improvement seen in all cohorts (BPD, ADHD and ASD).
  - First efficacy data from the Phase IIa trial in aggression in AD (REIMAGINE-AD) are expected in early Q220.
  - Oryzon is now preparing a Phase IIb PORTICO with vafidemstat in BPD.
- In July 2019, the company presented initial safety data from its Phase IIa ETHERAL trial with vafidemstat in mild-to-moderate AD.
- A Phase IIa SATEEN trial with vafidemstat in MS should also report in 2020.

Iadademstat

- On 9 December 2019, Oryzon presented maturing interim data from the Phase IIa ALICE trial (iadademstat plus azacitidine) in AML, which continued to impress.
- In September 2019, Oryzon presented first interim data from its Phase IIa CLEPSIDRA trial with iadademstat in SCLC.

[1] V. Valdespino and P. M. Valdespino. Potential of epigenetic therapies in the management of solid tumors. Cancer Management and Research 2015:7 241–251.

Exhibit 1: Oryzon's R&D pipeline



Source: Oryzon; Note: PORTICO trial is at an advanced stage of preparation; other trials that will follow REIMAGINE study are at the planning stage.

Vafidemstat –LSD1 inhibitor optimised for CNS indications

Vafidemstat as holistic intervention for CNS disorders

Epigenetic therapies induce profound biological changes, therefore they can have broad action potential (as opposed to targeted therapies, like monoclonal antibodies). For this reason, there is a need to identify which disease symptoms are best addressed when using an epigenetic drug. Oryzon's focus on targeting aggression is based on the insights gained from extensive preclinical development of vafidemstat (described in our earlier reports).

In one of the *in vivo* studies, SAMP8 mice (a model used for AD *in vivo* studies) were treated with a range of clinically feasible doses of vafidemstat or a vehicle. SAMR1 mice were treated with a vehicle only and acted as a normal control. Vafidemstat-treated SAMP8 mice showed reduced aggression measured by the number of attacks and clinch attacks compared with SAMP8 control mice, to a similar level to the SAMR1 control mice. Vafidemstat also normalised pathological gene expression changes observed in SAMP8 mice (resembling those in AD) compared with SAMR1 mice.

In another *in vivo* study, Oryzon used a rat isolation model to simulate social avoidance seen in AD patients. Vafidemstat was able to improve social avoidance once the isolated rats were reintroduced into a group of healthy animals (rats are very social rodents and do not tolerate isolation).

Following these data, Oryzon initiated Phase IIa trials REIMAGINE and REIMAGINE-AD focusing on managing aggression in patients with psychiatric (trial in ADHD, BPD and ASD) and neurodegenerative diseases (AD), respectively.

Oryzon's other preclinical data with vafidemstat suggested that it can rescue memory impairment in SAMP8 mice. The Phase IIa ETHERAL trial is now investigating this in mild-to-moderate AD. In an experimental autoimmune encephalomyelitis (EAE) mouse model, a widely used proxy for MS, vafidemstat attenuated CNS inflammation. The Phase IIa SATEEN trial is now investigating this effect in relapsing-remitting MS and secondary-progressive MS patients.

Overall, the preclinical results suggest that vafidemstat could have an effect on cognitive decline, inflammation and behavioural alterations in patients with CNS disorders. This implies a potentially broad, holistic neuropsychiatric intervention. Specific treatments for behavioural alterations such as aggression and social isolation are lacking. A large proportion of AD patients (20–50%) exhibit clinically significant aggression. Currently this is managed by non-pharmacological as well as pharmacological means. There is no FDA-approved specific medication for the treatment of aggression in AD or other neuropsychiatric disorders. Memantine is the only drug approved for AD that has also been shown to reduce agitation and aggression, whereas the other drugs used are more general antipsychotics, antidepressants or anxiolytic drugs and often have unfavourable safety profiles.

Phase I data

The first clinical data with vafidemstat were obtained from a Phase I trial with healthy volunteers and the results were reported in March 2017. The study was double-blind with a single ascending dose (SAD) and multiple ascending dose (MAD) and included more than 100 healthy volunteers. A dose range of 0.2–4.0mg was explored. The main findings were that, overall, vafidemstat was well tolerated. Haematological safety was of special interest to us, as haematopoiesis (blood production) is a known target of LSD1 inhibition. Vafidemstat did not provoke significant clinical or laboratory changes or adverse events in the MAD up to 2.5mg. Originally, the 2.5mg dose was the highest in the MAD range, but Oryzon added a 4mg dose to obtain robust safety data. It therefore appears that the therapeutic window is more than sufficient for further investigation. Sub-1.2mg doses are now used in the neuropsychiatric Phase IIa trials.

Vafidemstat Phase IIa programme

Oryzon has developed a broad R&D programme for this asset and is targeting a range of neurological disorders. Most prominent evolution of the R&D programme in CNS disorders was the decision to conduct a so-called basket trial in several neuropsychiatric disorders and moderate-to-severe AD (the REIMAGINE trial enrols ASD, ADHD and BPD patients; REIMAGINE-AD enrols AD patients). In addition to safety and tolerability, the endpoints in these studies are focused on vafidemstat's potential to control aggression. Oryzon has published interim data in 2019 and the findings were convincing enough for the company to start planning subsequent Phase IIb trials in aggression management in each of these indications (Exhibit 1). According to the latest communication, the Phase IIb PORTICO study in aggression in BPD is at the advanced preparation stage and should start shortly. The other trials are at the planning stage.

In addition to the REIMAGINE and REIMAGINE-AD trials, Oryzon is conducting a Phase IIa ETHERAL study in mild-to-moderate AD, where patients receive vafidemstat as a monotherapy, together with another monotherapy Phase IIa trial, SATEEN, in MS. The endpoints in these studies are focused on safety/tolerability and core disease symptoms.

Basket trial to uncover specific uses of vafidemstat

The basket trials are not uncommon in oncology, where patients with various cancer types are enrolled in early clinical studies to identify the most promising indication, which is then selected for late-stage development. Oryzon believes it can employ a similar strategy to develop vafidemstat for neuropsychiatric disorders due to the observed holistic effects of vafidemstat on aggression and behaviour in the preclinical models. Aggression is one of the more widespread alterations in patients with neurodegenerative and developmental disorders, as a well as social withdrawal and depression.

Phase IIa REIMAGINE trial

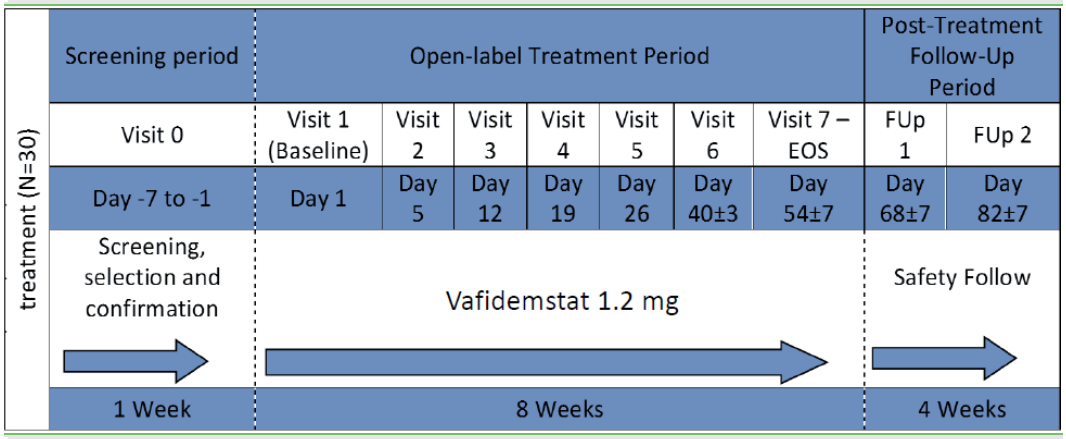
The Phase IIa REIMAGINE trial was a single-arm, open-label study carried out at the Hospital Vall d'Hebrón in Barcelona. While one patient was still in the trial when the data were presented at the CINP conference, the trial has now completed. In total, 30 patients were enrolled: 11 with ADHD, 12 with BPD and 7 with ASD. Patients underwent an open-label treatment with 1.2mg vafidemstat for eight weeks. The study objectives were:

- **Primary objective**: To evaluate the safety and tolerability of vafidemstat.
- **Secondary objectives**: To investigate the efficacy of vafidemstat in aggression in adults with ADHD, BPD or ASD.
- **Exploratory objectives**: To measure plasma levels pre-dose and throughout the study, LSD1 target engagement in peripheral blood mononuclear cells (PBMCs).

The reported outcomes of treatment with vafidemstat were measured using these common neuropsychiatric scales:

- **Aggression was assessed using:**
  - Clinical Global Impression (CGI) Severity (CGI-S) and CGI Improvement (CGI-I) scales.
  - The NPI four-item Agitation/Aggression subscale.
- **Overall patient functioning was assessed using:**
  - Global Improvement on the Neuropsychiatric Inventory (NPI) total score (Total NPI).
  - The BPD checklist (BPDCL).
  - The ADHD Rating Scale (ADHD-RS).

Exhibit 2: Phase IIa REIMAGINE study design



Source: Ramos-Quiroga et al, presentation at CINP, October 2019

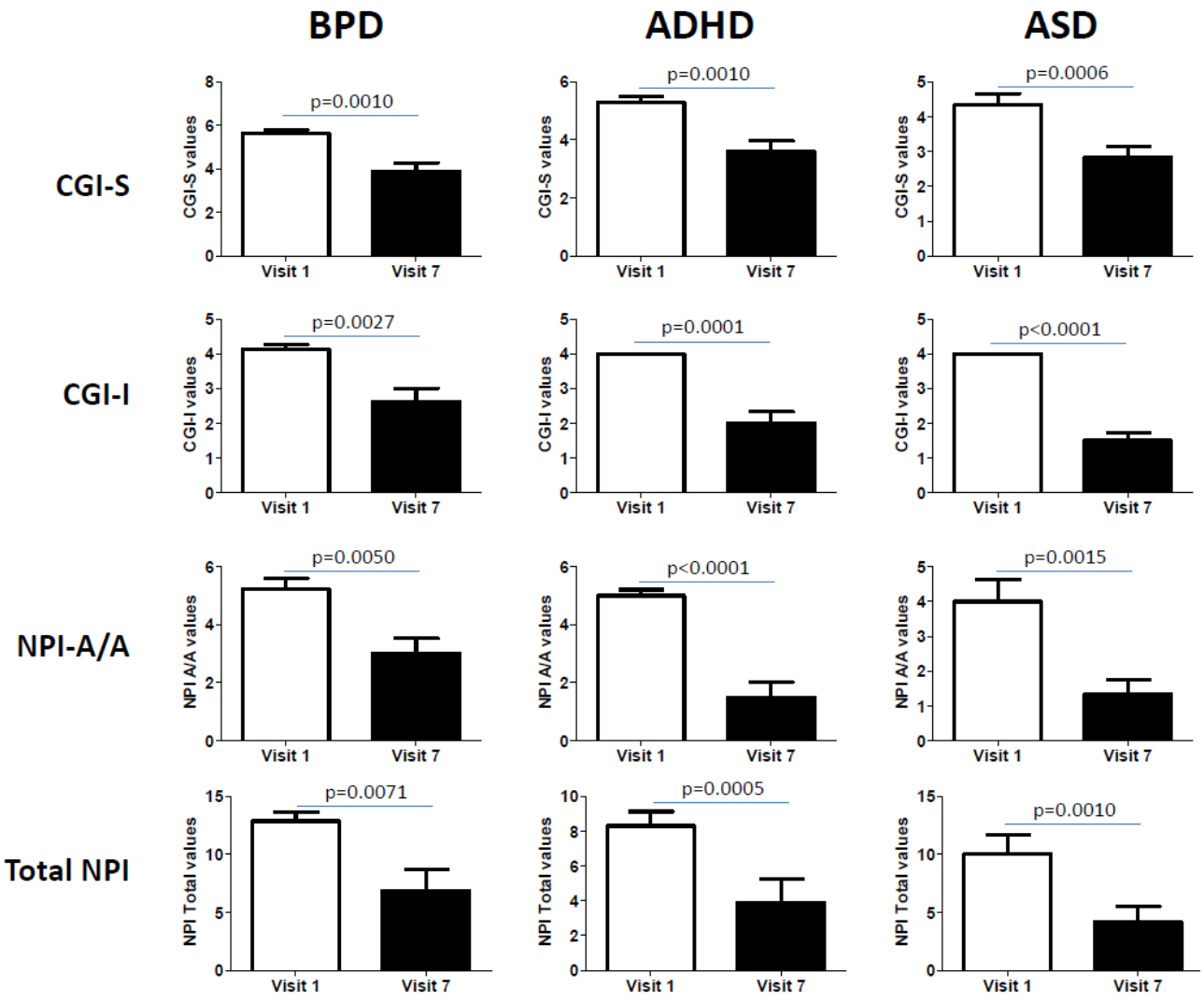
In April 2019, Oryzon released the initial results from the first two cohorts (BPD and ADHD), while the ASD results were released in September 2019. In October 2019, Oryzon presented a poster at the 2019 International College of Neuropsychopharmacology (CINP) meeting in Athens, Greece,

which included expanded datasets from the BPD and ADHD cohorts and aggregated data from all three cohorts.

The latest results showed that, in total, 30 patients were enrolled, 22 of whom finished eight weeks of treatment. One patient was still in the progress and there were 7 dropouts. Two of those 7 patients completed six weeks of treatment, so they were included in the efficacy analysis. The final patient set for efficacy analysis included 10 ADHD, 8 BPD and 6 ASD subjects. The highlights results include:

- The researchers concluded that vafidemstat was safe and well tolerated without clinically relevant adverse events.
- Significant reduction in aggression was measured by the NPI four-item Agitation/Aggression subscale, both in the aggregated data for all subjects ($p<0.0001$) and in each of the three individual cohorts (Exhibit 3).
- Significant reduction in aggression was also measured by the CGI-S and CGI-I scales, both in the aggregated data ($p<0.0001$ for both) and in each of the cohorts.
- Significant global improvement in the NPI total score was demonstrated, both in the aggregated cohorts ($p<0.0001$) and the individual cohorts.
- Disease-specific scales also showed significant improvement. Reduction of BPDCL for BPD reached statistical significance of $p=0.0022$, while reduction of ADHD-RS for ADHD reached $p=0.0496$.
- Statistically significant ($p=0.0033$) reduction in suicidal ideation was obtained in the BPD cohort (using the C-SSRS scale; the ADHD and ASD cohorts were not examined, since suicidal ideation is not a core feature of these disorders).

Exhibit 3: Vafidemstat efficacy per cohort in the Phase IIa REIMAGINE trial



Source: Ramos-Quiroga et al, presentation at CINP, October 2019

Our take

Treatment with vafidemstat in these patients was safe and well tolerated without significant adverse events, including no apparent negative haematological effects, which is a primary consideration of the epigenetic class drugs. This was not surprising, as the dose used in the REIMAGINE trial was substantially below the highest dose reached in Phase I trial (2.5mg). The fact that effectiveness was achieved with relatively low dosing is especially beneficial given that the treatment in these conditions is likely to be chronic.

In 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 psychiatric scales. Although the cohorts were small, the consistency of results across several scales and in three different indications is rather promising, in our view.

In addition, although the primary purpose was to assess the effect on aggression management in these patients, the fact that overall scores also improved suggests that vafidemstat could have a broader psychiatric effect beyond agitation and aggression. This supports the holistic neuropsychiatric intervention idea discussed above.

What's next

In parallel, Oryzon is running a Phase IIa REIMAGINE-AD study to evaluate vafidemstat in aggression in a moderate-to-severe AD population. The trial is now fully recruited with 12 patients, who are receiving the treatment. The duration of the treatment has been expanded to six months from the originally planned two months to evaluate the potential of vafidemstat not only in aggression, but also in other core features of AD. We note that the patients in this trial are more advanced that those in the Phase IIa ETHERAL trial, so once both trials are completed, Oryzon will have comprehensive clinical data covering all clinically relevant stages of the disease. Oryzon guided that the results from the REIMAGINE-AD trial are due in Q220, likely at the Advances in Alzheimer's and Parkinson's Therapies AAT-AD/PD 2020 meeting on 2–5 April 2020 in Vienna, Austria.

All primary and secondary endpoints from the REIMAGINE trial were met with high statistical significance, which immediately prompted Oryzon to announce that it is now planning to expand vafidemstat's R&D beyond the currently ongoing Phase IIa trials in AD and multiple sclerosis. The company mentioned that it is working with specialist KOLs to establish the precise target indication and patient population where vafidemstat would be best positioned. Based on the latest communication (Q319 report and corporate presentation), it seems that all four indications explored in the REIMAGINE programme have the potential to be investigated in dedicated Phase IIb trials (Exhibit 1). The indication given the highest priority seems to be BPD, with plans for the next Phase IIb PORTICO trial at an advanced stage. We believe that BPD is a potentially interesting opportunity characterised by a high unmet need (no specific treatment approved) and a large population of adult patients.

Two Phase IIa trials in AD and MS ongoing

Beyond the REIMAGINE programme, vafidemstat is being tested in two additional Phase IIa trials. A randomised, double-blind, placebo-controlled Phase IIa ETHERAL trial with vafidemstat in mild-to-moderate AD started enrolling patients in June 2018. The patients are treated using placebo control for 24 weeks, which is then followed by a 24-week extension when placebo patients are randomized to vafidemstat treatment. The recruitment has been completed in Europe (n=117), while it is still ongoing in the US (n=30). First safety data from 104 patients were presented in July 2019. Interim results from the European part of the study (24-week treatment period) are expected in H120.

A randomised, double-blind, placebo-controlled, 36-week Phase II SATEEN study (n=24) is evaluating vafidemstat in patients with relapsing-remitting MS and secondary progressive MS. The initial 36-week period is also followed by an extension of 24 weeks when all patients are treated with vafidemstat. In September 2019, Oryzon announced that the extension phase had been prolonged to 18 months in patients with the secondary progressive form of MS, which requires a longer observation period. Oryzon did not provide specific guidance on when the results would be released, but given the extension we would expect some data late in 2020 or early 2021.

Potential biomarker for vafidemstat

Oryzon has identified different biomarkers that could be used to monitor the response to treatment with vafidemstat. The most promising is S100A9, which is a pro-inflammatory protein typically upregulated in the context of inflammation-related neurodegenerative diseases, such as in patients with AD, postoperative cognitive dysfunction and traumatic brain injury. Therefore, the observed downregulation of the S100A9 protein by vafidemstat is particularly interesting. While work is still at an early stage, a progression biomarker may eventually prove invaluable in the context of a late-stage clinical trial designed to prove the potential disease-modifying effect of the drug. This is

because it may be difficult to differentiate clearly between symptomatic and disease-modifying effects just with clinical endpoints (eg cognition, function).

Phase IIa ETHERAL-AD interim data

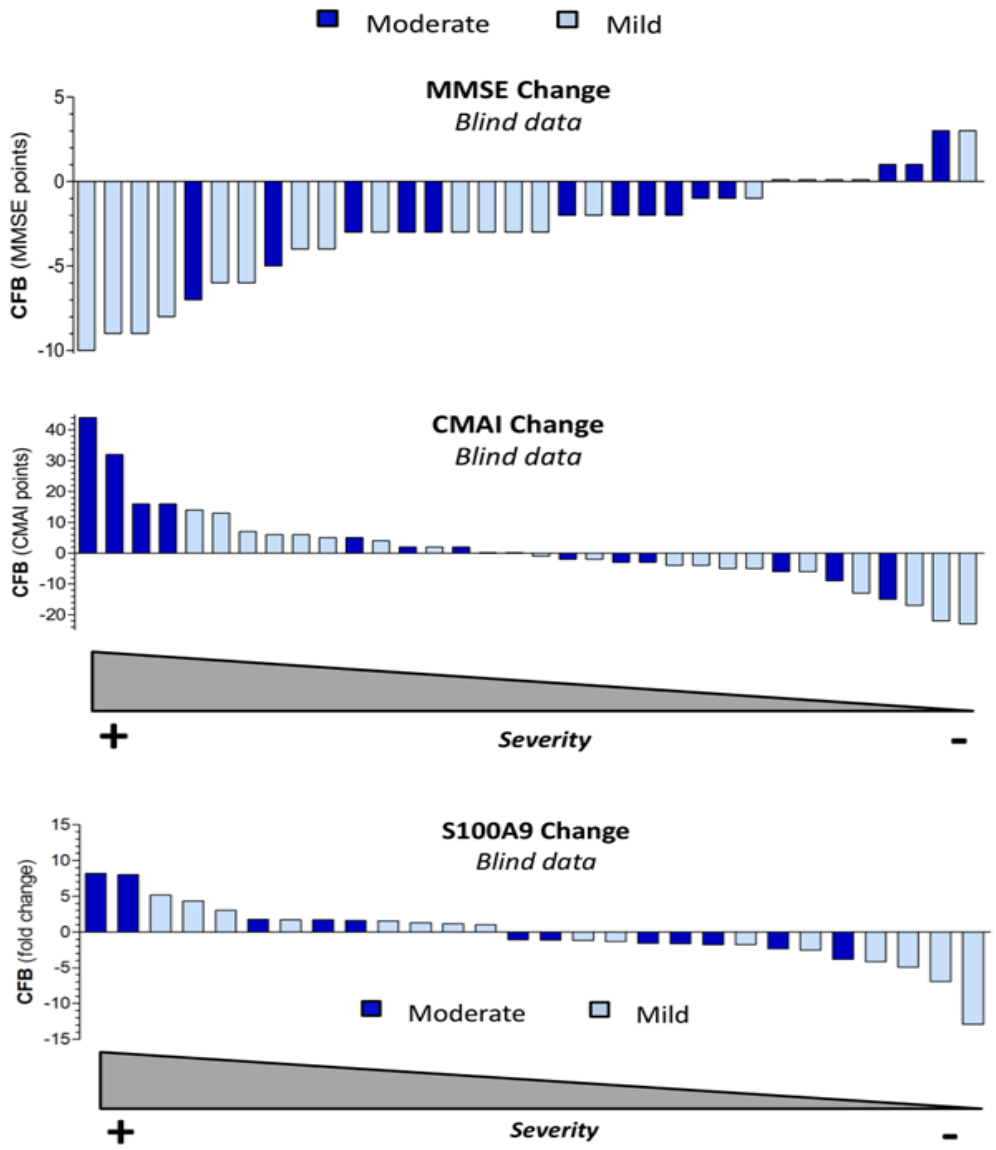
On 15 July 2019, Oryzon presented interim data from the Phase IIa ETHERAL trial at the Alzheimer's Association International Conference (AAIC 2019) in Los Angeles. The interim analysis of the blinded data from the first 104 patients (out of 125 in European centres plus 30 more patients in the US) showed the drug was safe and well tolerated. The trial remains blinded, so no conclusions on efficacy can be made at this point, but Oryzon's presentation included an initial assessment of certain functional parameters and some biomarker data.

Although the primary endpoint of the study is safety and tolerability, secondary endpoints include measures of cognition, function, behaviour and CSF biomarkers, which will provide insights into efficacy. At the time of the interim analysis, 87.5% (91/104) patients had completed at least one month of treatment and no clinically relevant effects on platelets, neutrophils and other haematological parameters were observed. 36 patients completed six months of treatment with no significant safety issues. This confirmed the data from the Phase I trial with healthy volunteers and provides significant reassurance given that any AD treatment would likely be a life-long intervention and that LSD1 is a key regulator of haematopoiesis.

Because the trial remains blinded, no conclusions on efficacy can be made yet, but the poster did describe disease progression in the first 33 patients, who completed 24 weeks of therapy. The researchers said that 'while some patients clearly progress, others maintain baseline values or even improve'. This was shown using selected functional scores (MMSE and CMAI) and the proinflammatory biomarker S100A9 (Exhibit 4).

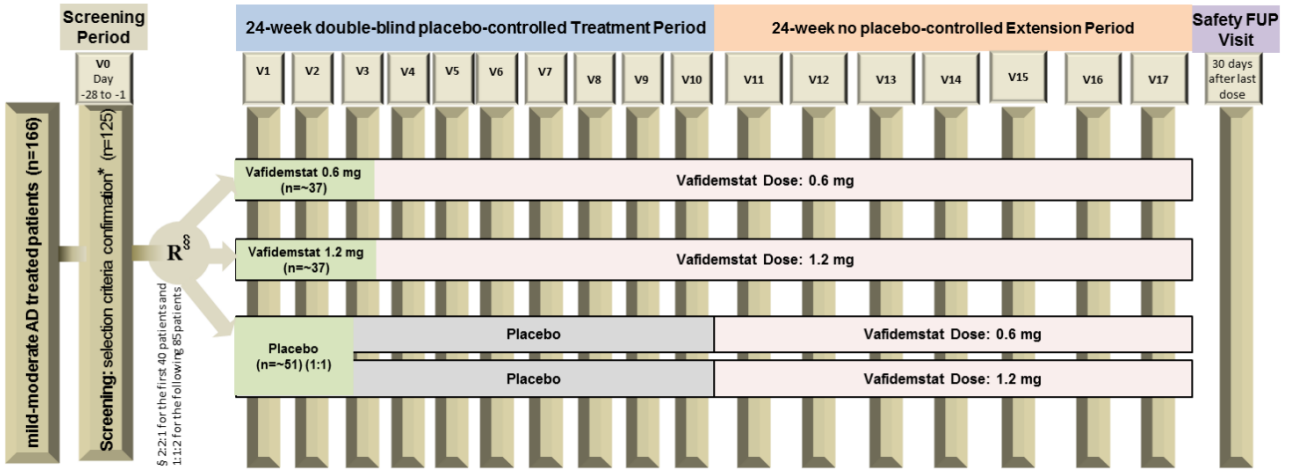
The patients are randomised into three arms (placebo, low dose, high dose) using an adaptive design. The first 24 weeks are placebo-controlled, following which the placebo patients are randomised into vafidemstat therapy for another 24 weeks (low dose or high dose) so that all patients receive treatment (Exhibit 5). Oryzon plans to report the placebo-controlled results (ie from the first 24 weeks) from the European part of the trial in H120. The full results including the extension period and the US data should be reported later in 2020.

Exhibit 4: Functional score and biomarker evolution in blinded data analysis



Source: Bullock et al, AAIC 2019, Oryzon. Note: MMSE = Mini-Mental State Examination; CMAI = Cohen-Mansfield Agitation Inventory; CFB – change from baseline.

Exhibit 5: Phase IIa ETHERAL AD study design



Source: Oryzon. Note: FUP = follow up; V = visit; R = randomisation.

Iadademstat – specific LSD1 inhibitor for cancer

Iadademstat is a highly selective LSD1 inhibitor that can be orally administered. Oryzon's initial focus in developing iadademstat was on acute leukaemias. The drug candidate entered a Phase I/IIa trial in January 2014 and in April 2014 it was licensed to Roche, which has paid $21m in upfront and milestones to Oryzon during the engagement period. Under the terms of the agreement, Oryzon was responsible for finalising the leukaemia Phase I/IIa study (which was already ongoing and sponsored by Oryzon at that time). In December 2016, Oryzon reported supportive preliminary efficacy results from this trial at the ASH conference, which was a major milestone. In parallel, Roche, which was responsible for the global development of iadademstat, initiated a clinical trial in SCLC. In July 2017, Roche decided to discontinue the development of iadademstat and return the rights to Oryzon; according to Oryzon, the decision was due to Roche reprioritising its portfolio and not driven by data.

Oryzon regained the rights from Roche for iadademstat in January 2018 and resumed development in both AML and SCLC. The Phase IIa ALICE study is recruiting elderly AML patients who are treated with iadademstat in combination with azacitidine. Part 1 explored the recommended dose, while Part 2 is evaluating initial clinical activity. The Phase IIa CLEPSIDRA trial is recruiting relapsed, extensive-stage disease SCLC patients who receive iadademstat in combination with platinum-etoposide chemotherapy. Oryzon is also using biomarkers to select a more precise patient population. Similarly, Part 1 established a recommended dose, while Part 2 is evaluating clinical activity. Interim results from both studies were presented in 2019 and more data are expected in 2020.

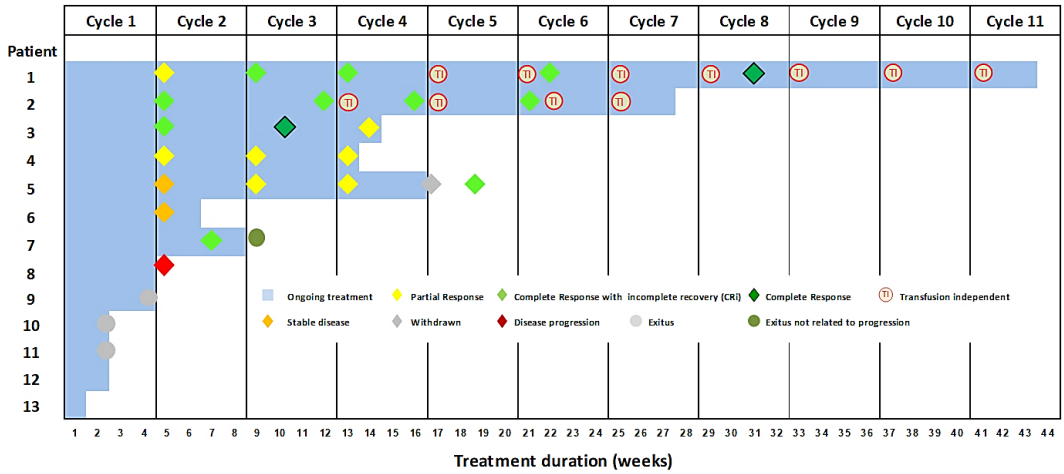
Interim Phase IIa ALICE results

Oryzon presented the most advanced data from the Phase IIa ALICE trial at the 61st ASH annual meeting in Orlando, Florida on 9 December 2019. The single-arm, open-label study is enrolling newly diagnosed, elderly acute myeloid leukaemia (AML) patients and investigates iadademstat in combination with standard-of-care chemotherapy drug azacitidine. Oryzon intends to enrol 18 patients in the ongoing Part 2 of the ALICE trial (expansion cohort; Part 1 dose finding has been completed). At the time of writing the ASH poster, 13 patients have been enrolled in ALICE. Besides dose finding data and PK/PD evaluation (including a set of blood biomarkers), initial efficacy was evaluated as overall response (OR) measured by bone marrow aspirate.

The latest data from the ALICE trial showed that of the 13 enrolled patients, 8 had at least one bone marrow aspirate, and therefore were evaluable (3 patients died before their first BM evaluation and 2 were just starting the treatment). OR results were:

- Six of the 8 evaluable patients (75%) achieved ORs: two complete responses (CRs), three complete responses with incomplete haematologic recovery (CRi) and one partial response (PR).

Exhibit 6: Patients enrolled in the Phase IIa ALICE trial



Source: C Buesa et al. Iadademstat Shows Efficacy in Elderly AML Patients in Combination with Azacitidine. ALICE Trial. Poster presentation at ASH 2019.

Safety/tolerability

Overall, the authors of the ASH poster concluded that the combination of iadademstat and azacitidine shows a good safety profile in elderly AML patients. In Part 1 (dose finding), the recommended dose of 90µg/m^2 was established. Later, the dose was lowered to 60µg/m^2 by the safety monitoring committee (SMC). This decision was made after one patient withdrew consent after experiencing severe fatigue and another patient died due to an intracranial haemorrhage. Oryzon did not see any clinically relevant non-haematological adverse events.

LSD1 inhibitor class drugs are known to have haematological side effects at higher doses. However, these are usually predictable and manageable. We note that proving a clear drug-side effect relationship is not always straightforward. For example, intracranial haemorrhage (haemorrhagic stroke) can have many causes, especially in such elderly, highly ill patients. So, the decision to lower the dose could serve as a precaution. The tolerability of the drug will improve at the lower dose and Oryzon believes this will not come at the expense of efficacy, as existing PK/PD data show that a 60µg/m^2/d level is also able to saturate LSD1 target engagement with a clear biomarker effect.

Putting iadademstat efficacy results in perspective

OR rates in AML patients treated with azacitidine monotherapy are 32% depending on age (Maurillo et al, 2012). A recently published article (DiNardo et al, 2019) described a clinical trial (n=145) where AML patients received venetoclax plus azacitidine or decitabine (both chemical analogs of cytidine) and the OR rate was 67%. Venetoclax (Venclexta, AbbVie/Genentech) is a novel anticancer drug approved (accelerated approval) by the FDA for frontline treatment of AML in combination with azacitidine or decitabine or low-dose cytarabine.

In the first set of data from the ALICE trial published in June 2019, the OR rate was 80% in 5 evaluable patients (3 CRi and 1 PR). The most recent data from 8 evaluable patients (OR rate of 75%) are in line with this result. Given the small sample size, an outcome in just one patient can significantly influence the results. In addition, the trial is not complete yet. However, the OR rates have been consistent so far within the 75–80% range. This is much higher than the historical response rates with classic chemotherapy and compares well with venetoclax's OR of 67%. Consensus expects venetoclax to reach $971m in sales in AML alone by 2024 (EvaluatePharma).

Iadademstat, as a selective LSD1 inhibitor, has been shown to be effective in preclinical AML models, including combinations with azacitidine. In addition, Oryzon has already completed a

Phase I first-in-man trial, where iadademstat was given as a monotherapy, and demonstrated preliminary antileukaemic activity (reviewed in detail in our initiation report).

Next steps

The second part of the ALICE study will enrol a total of 18 patients, so these results will be expanded in the coming months with additional patients and longer follow-up times. Oryzon also indicated that even though the results are not final yet, existing evidence 'may warrant further trials with this combination therapy in a confirmatory study setting'.

Interim Phase IIa CLEPSIDRA results

The most advanced dataset from the ongoing Phase IIa CLEPSIDRA trial with iadademstat in extensive disease SCLC was presented on 28 September 2019 at the ESMO congress in Barcelona. A poster presentation detailed the efficacy results from eight SCLC patients. In CLEPSIDRA patients receive 4–6 cycles of iadademstat plus carboplatin-etoposide chemotherapy (subsequently, the patients may be given iadademstat monotherapy). Patients in the trial are stratified by proprietary biomarkers, which allow identifying SCLC sensitive to LSD1 inhibitors and can position iadademstat as a personalised therapy. The rationale to test iadademstat for SCLC comes from the fact that the inhibition of LSD1 activates the NOTCH pathway, resulting in the suppression of ASCL1 (a known SCLC tumour driver). Complete and durable tumour regression was seen with iadademstat in *in vivo* PDX models (discussed in our previous report).

Results include:

- An OR was seen in 6 out of 8 patients (75%). Of these, 4 patients demonstrated a partial response and 2 had long-term stable disease.

The OR rate of 75% compares well with the historical average of SCLC second-line chemotherapy drug topotecan (15–24%). SCLC is generally considered a non-immunogenic cancer, so OR rates to immune checkpoint inhibitors are also relatively low (22% nivolumab plus ipilimumab; 19% pembrolizumab as monotherapy; Saleh, 2019). The high OR rate in CLEPSIDRA may be due to the use of biomarkers. One of the patients with partial response showed 79% tumour reduction following six cycles of iadademstat plus carboplatin-etoposide and then received iadademstat as monotherapy. This patient is still in remission nine months after the treatment and demonstrated continuous improvement (86% tumour reduction) with iadademstat monotherapy.

Safety/tolerability

The most common side effects were haematological changes seen in patients who received a triple combination and included decreased platelets, neutrophils and anaemia. No other organ-specific side effects, such as neurological, hepatic or renal toxicity, were observed. In addition, iadademstat alone did not cause haematological or other toxicity. Such results are not unexpected as platinum-etoposide chemotherapy is known to have haematological toxicity. The fact that side effects were observed in patients receiving the combination treatment, but not iadademstat alone, would imply better tolerance of the latter. Oryzon will continue to explore different dosing regimens during the reminder of the CLEPSIDRA trial.

Competitive landscape

There is already a handful of first-generation HDAC inhibitors approved by the FDA, with the first being vorinostat (Zolinza) developed by Merck & Co for third-line therapy in cutaneous T-cell lymphoma and marketed in 2006. Because of a lack of specificity, the common feature of these HDACs is a rather unfavourable safety profile. For example, vorinostat received a critical review in 2009 from the European Medicines Agency about the risk/benefit ratio and the trial design, following

which Merck & Co withdrew its marketing application. Despite these hurdles, a number of other HDACs are still being explored in different stages for oncological indications.

We believe that so-called second-generation epigenetic inhibitors are a more relevant peer group for Oryzon's technology since, like the LSD1 inhibitor, they also have greater selectivity for their molecular targets (Exhibit 7). These compounds can be broadly classified into demethylase inhibitors, methyltransferase inhibitors and bromodomain and extra-terminal (BET) inhibitors or acetyl lysine readers. Other targets are also emerging in preclinical research. Second-generation epigenetic inhibitors are still considered in their infancy, with most companies having a lead programme in Phase II or earlier. Oryzon is focused on LSD1 inhibition and is leading in this field in terms of clinical development. It also has programmes in neurodegenerative diseases, while the majority of peers are focused on oncology.

Until recently, GlaxoSmithKline had one of the more advanced LSD1 inhibitors in oncology (GSK2879552), but discontinued its development after a Phase I trial in patients with SCLC, 'as the risk-benefit profile did not favour continuation'. Based on the reported data, GSK's drug candidate caused substantial side effects in most patients and, in stark contrast to Oryzon's iadademstat, GSK2879552 also caused toxicity in other organ systems (predominantly encephalopathy). Oryzon's iadademstat safety profile appears to be significantly better. Only the expected haematological side effects were reported so far and in combination with other chemotherapy agents (not with iadademstat alone). In addition, Oryzon believes that dosing adjustment can increase the tolerability.

Exhibit 7: Selected second-generation, clinical-stage epigenetic inhibitors

Company	Product, type	Phase	Indication	Comment
Histone methyltransferase inhibitors				
Epizyme	Tazemetostat, EHZ2 inhibitor	Multiple trials	Most advanced ongoing Phase III study in epithelioid sarcoma; other Phase I & II studies in non-Hodgkin's lymphoma, synovial sarcoma and solid tumours	Estimated completion of the Phase III study in epithelioid sarcoma in June 2020
Constellation Pharmaceuticals	CPI-1205, EZH2 inhibitor	Phase I/II trials	Metastatic castration-resistant prostate cancer; Solid tumours;	Estimated completion date August 2020 Estimated completion date December 2019
Epizyme	Pinometostat, DOT1L inhibitor	Phase I/II	Acute myeloid leukaemia	Estimated completion date June 2020
GlaxoSmithKline	GSK3326595, PRMT5 inhibitor	Phase I Phase I	Myelodysplastic syndrome, AML Solid tumours, non-Hodgkin's lymphoma	Estimated completion date December 2022 Estimated completion date December 2021
Histone demethylase inhibitors				
Incyte	INCB59872 LSD1 inhibitor	Phase I	Ewing Sarcoma	Estimated completion date December 2020
Imago BioSciences	IMG-7289 LSD1 inhibitor	Phase I/II Phase II	Essential thrombocythemia, Myelofibrosis	Estimated completion date January 2022 Estimated completion date December 2019
Celgene	CC-90011 LSD1 inhibitor	Phase I Phase I/II	Solid tumours and non-Hodgkin's lymphomas Small cell lung carcinoma	Estimated completion date June 2021 Estimated completion date September 2021
BET inhibitors				
GlaxoSmithKline	GSK525762, BET inhibitor	Phase II Phase II	Breast cancer Haematologic malignancies	Estimated completion date January 2021 Estimated completion date January 2023
Constellation Pharmaceuticals	CPI-0610, BET inhibitor	Phase I/II	Myelofibrosis	Estimated completion date August 2021; preliminary positive data released at ASH in December 2019.
Roche	RO6870810, BET inhibitor	Phase I Phase I	Multiple myeloma B-cell lymphomas	Estimated completion date September 2019 Estimated completion date March 2020

Source: Edison Investment Research, EvaluatePharma, clinicaltrials.gov.

Sensitivities

Oryzon is subject to the usual risks associated with drug development, including establishing favourable safety/efficacy profile, clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. We believe a partner will have to come on board before vafidemstat enters large-scale Phase III studies, the timing of which is difficult to forecast. Vafidemstat will also need to be partnered, as later-stage

studies in CNS indications can be very costly due to large populations. However, Oryzon has enough cash to progress vafidemstat through mid-stage development to reach meaningful data. We have assumed a deal in our valuation after Phase II for both assets, but we have limited visibility on the timing and terms. 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.

Financials

Oryzon's 9M19 total operational spending was €10.5m ($11.5m), as expected somewhat higher than the €8.0m ($8.7m) booked in 9M18 due to a more intensive R&D programme. Accordingly, R&D costs increased to €8.2m ($8.9m) from €5.7m ($6.2m), while G&A expenses stayed relatively flat at €2.4m ($2.6m). Oryzon booked €7.4m ($8.9m) as other income, which represents capitalised R&D costs (Oryzon follows local GAAP), therefore reported operating income was €3.2m ($3.4m).

We have increased our total FY19 operating expenses estimate to €14.2m from €12.4m. Income resulting from the capitalised R&D costs (which depends on certain work Oryzon is undertaking) was significantly higher than we expected, and we have therefore increased our FY19 income to €9.8m from €6.1m. The net effect on our FY19 operating loss estimate was positive at €4.4m vs €6.2m (and €4.3m vs €6.3m in FY20).

The reported Q319 cash position was €39.2m (cash and short-term investments; net cash €26.0m) following the private placement in July 2019, which brought in €20m gross. Our model suggests the current cash position should be sufficient until 2022.

Valuation

As Oryzon is on track to develop its assets in all the indications we include in our valuation, we leave our assumptions unchanged. Our new valuation is €454m or €9.9 per share, up from €437m or €9.5 per share mainly due to rolling our model forward. A detailed discussion about our assumptions can be found in our initiation and earlier outlook reports. Our valuation includes rNPVs for both assets in the most advanced indications.

Oryzon is now running two trials in AD with different goals. The first trial, ETHERAL, is focused on vafidemstat's ability to treat the core symptoms of AD, while the newer trial, REIMAGINE-AD, explores vafidemstat in managing aggression in advanced patients. Given the still early stage of development, we do not strictly separate vafidemstat's potential in our model. We maintain the approach described in our initiation report, where we employed a top-down approach and used the sales of existing AD drugs as benchmarks.

BPD is the newest addition to our SOTP table (detailed assumptions discussed in our April 2019 report) following the positive results from the REIMAGINE trial and Oryzon's commitment to start Phase IIb development. We will consider other indications in the basket trial if Oryzon initiates subsequent trials.

Key catalysts in the near to mid-term include:

- Vafidemstat Phase IIa REIMAGINE-AD data from the AD patients in Q220. Likely at the Advances in Alzheimer's and Parkinson's Therapies AAT-AD/PD 2020 meeting on 2–5 April 2020 in Vienna, Austria;
- Vafidemstat Phase IIa ETHERAL EU six-month interim trial results in H120;
- Updated data from iadademstat Phase IIa CLEPSIDRA in SCLC some time in 2020; and

- Updated data from iadademstat Phase IIa ALICE in AML some time in 2020.

Exhibit 8: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability of success (%)	rNPV (€m)	NPV/share (€/share)
Iadademstat (iadademstat)	AML	2023	927	296.7	15%	58.8	1.3
Iadademstat (iadademstat)	SCLC	2026	571	143.7	8%	26.4	0.6
Vafidemstat (vafidemstat)	AD	2026	4,510	1,063.7	15%	167.6	3.7
Vafidemstat (vafidemstat)	MS	2027	1,940	466.4	20%	110.5	2.4
Vafidemstat (vafidemstat)	BPD	2027	1,290	289.3	20%	68.7	1.5
Net cash (est. at end-FY19)				22.1	100%	22.1	0.5
Valuation				**2,281.9**		**454.0**	**9.9**

Source: Edison Investment Research. Note: AML = acute myeloid leukaemia; SCLC = small cell lung cancer; AD = Alzheimer's disease; MS = multiple sclerosis; BPD = borderline personality disorder.

Exhibit 9: Financial summary

€'000s	2017	2018	2019e	2020e
December	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS				
Revenue	4,317	6,781	9,779	9,937
Cost of Sales	0	0	0	0
Gross Profit	4,317	6,781	9,779	9,937
Research and development	(5,306)	(7,412)	(10,954)	(11,060)
EBITDA	(3,498)	(2,766)	(4,234)	(4,108)
Operating Profit (before amort. and except.)	(3,660)	(2,905)	(4,379)	(4,259)
Intangible Amortisation	(664)	(7)	0	0
Exceptionals	0	(4)	0	0
Other	0	0	0	0
Operating Profit	(4,324)	(2,916)	(4,379)	(4,259)
Exceptionals	0	0	0	0
Net Interest	(928)	(796)	(687)	(471)
Profit Before Tax (norm)	(4,588)	(3,701)	(5,066)	(4,730)
Profit Before Tax (reported)	(5,252)	(3,712)	(5,066)	(4,730)
Tax	55	2,535	1,189	1,862
Profit After Tax (norm)	(4,533)	(1,166)	(3,877)	(2,868)
Profit After Tax (reported)	(5,197)	(1,177)	(3,877)	(2,868)
Average Number of Shares Outstanding (m)	31.7	34.6	40.3	45.8
EPS - normalised (€)	(0.14)	(0.03)	(0.10)	(0.06)
EPS - reported (€)	(0.16)	(0.03)	(0.10)	(0.06)
Dividend per share (€)	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	24,914	31,786	41,590	51,546
Intangible Assets	22,458	29,330	39,109	49,046
Tangible Assets	638	665	689	709
Investments	1,818	1,791	1,791	1,791
Current Assets	36,130	35,664	38,023	24,441
Stocks	7	135	310	310
Debtors	857	971	1,700	1,336
Cash	34,950	34,320	35,288	22,070
Other	316	239	725	725
Current Liabilities	(8,696)	(10,441)	(10,469)	(9,711)
Creditors	(1,343)	(2,192)	(3,439)	(2,681)
Short term borrowings	(7,354)	(8,249)	(7,030)	(7,030)
Long Term Liabilities	(17,915)	(11,884)	(7,897)	(7,897)
Long term borrowings	(16,041)	(9,977)	(6,172)	(6,172)
Other long-term liabilities	(1,874)	(1,907)	(1,725)	(1,725)
Net Assets	34,432	45,125	61,247	58,379
CASH FLOW				
Operating Cash Flow	(4,281)	(2,799)	(4,760)	(4,973)
Net Interest	(426)	2,133	0	0
Tax	0	0	1,189	1,862
Capex	(105)	(170)	(170)	(170)
Acquisitions/disposals	0	0	0	0
Financing	16,887	11,949	20,000	0
Other*	653	(6,576)	(15,290)	(9,937)
Dividends	0	0	0	0
Net Cash Flow	12,728	4,538	968	(13,217)
Opening net debt/(cash)	1,172	(11,555)	(16,093)	(22,086)
HP finance leases initiated	0	0	0	0
Other	0	0	(487)	0
Closing net debt/(cash)	(11,555)	(16,093)	(22,086)	(8,868)

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

Contact details	Revenue by geography
Oryzon Genomics Sant Ferran 74 08940 Cornella de Llobregat Barcelona, Spain +34 93 515 1313 https://www.oryzon.com/	N/A

Management team

CEO: Carlos Manuel Buesa Arjol	Chief scientific officer: Tamara Maes
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 board of various biotechnology companies such as Oncnosi Pharma, Ninfas, Orycamb-Project, Geadig-Pharma, Neurotec Pharma and Palobiofarma.	Dr Maes co-founded Oryzon Genomics in 2000 and has served as the chief scientific officer and member of the board of directors since then. She received her PhD in biotechnology from the University of Ghent (Belgium). She is also a director of Mendelion and recently was a member of the Scientific Advisory Board of the Consejo Superior de Investigaciones Científicas. She has been a member of the Scientific Review Board of the Alzheimer's Drug Discovery Foundation since 2016.
CFO: Enric Rello Condomines	**Chief business development officer: Emili Torrell**
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.	Mr Torrell joined Oryzon in February 2007. He holds a degree in veterinary sciences from the Autonomous University of Barcelona, a master's in business administration from ESADE and a master's in documentation from the Centre for Documentation and Patent Studies. He began his career in the development of the pharmaceutical business in 1993 at Almirall Prodesfarma and later specialised in the international arena as international product manager and international marketing manager at Almirall.

Principal shareholders*	(%)
Carlos Buesa	8.21
Tamara Maes	8.17
Jose Ventura Ferrero	5.13
Gescooperativo	2.53
Josep Maria Echarri	2.28

Companies named in this report

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