ORYZON GENOMICS

BUY

TARGET PRICE : 8.8€ +132%

COMPANY UPDATE

UPDATES FROM AAIC 19 BODE WELL FOR VAFIDEMSTAT

The company presented a clinical update from its Phase 2a ETHERAL study of vafidemstat, added to standard of care, in Alzheimer's disease. Both platelet count and AST levels were stable during 24 weeks of treatment. ORYZON also presented the blinded data from several efficacy measures that suggested positive clinical trend, albeit it is difficult to draw conclusions due to the presence of placebo arm and a background medication. We currently expect the full results of the study in 2020. Encouraged by presented results, we reiterate our BUY rating and TP of €8.8.

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Confirmed clean safety profile of vafidemstat bodes well for use in AD

The company presented a clinical update from its Phase 2a ETHERAL study at the 2019 Alzheimer's Association International Conference (AAIC 19). Recall, ETHERAL is evaluating one of the company's lead assets, vafidemstat, in combination with standard of care in patients with mild to moderate Alzheimer's disease (AD). Vafidemstat was designed to simultaneously target lysine-specific demethylase 1 (LSD1) and monoamine oxidase B (MAO-B), the enzymes that are involved in the epigenetic mechanisms of gene regulation. Epigenetic modulation allow for the fine tuning of gene expression and were shown to play an important role in the development of AD.

ETHERAL, a 24-week double-blind randomized study, includes three arms: two dosing regimens of vafidemstat and placebo. The study is planned to enroll about 125 AD patients at the European clinical sites, and, according to company, the recruitment in the EU could be completed by the end of July, 2019. ORYZON has also started recruitment at the US sites, where it plans to enroll additional 30 patients. The study includes 24-week placebo-controlled period, which will be followed by 24-week extension period, allowing patients from placebo arm to switch to vafidemstat therapy. The primary endpoint of the study is safety and the tolerability of vafidemstat and the secondary exploratory endpoints include cognitive and functional changes, as well as biomarker analysis. The presentation at AACI 19 mostly covered the safety part and we currently expect the full results from the placebo-controlled part of the trial in 1H20.

The clinical update, presented at AAIC 19, was based on the 104 evaluated patients and showed clean safety profile of the drug (Exhibit 1). Importantly, on the hematologic side, only 2 patients (1.9%) developed neutropenia and 1 patient (0.9%) - thrombocytopenia, as well as 1 case of leukopenia and 1 case of monocytosis were observed. We also note that the platelet count and AST (liver enzymes) were stable during treatment period. Since epigenetic drugs, such as HDAC inhibitors, are known to have dose-limiting hematologic toxicities, their use was restricted predominantly to oncologic conditions. For conditions that are likely to require chronic dosing, such as neurologic disorders, these hematologic toxicities represented a significant safety concern. Thus, we are encouraged by the observed clean safety profile of vafidemstat, which, in our view is suitable for prolonged use in chronic conditions, such as AD.

in € / share	2019e	2020e	2021e
Adjusted EPS	-0.11	-0.26	-0.43
chg.	*n.s.*	*n.s.*	*n.s.*
estimates chg.	*n.s.*	*n.s.*	*n.s.*

au 31/12	2019e	2020e	2021e
PE	n.s.	n.s.	n.s.
EV/Sales	n.s.	n.s.	n.s.
EV/EBITDA	n.s.	n.s.	n.s.
EV/EBITA	n.s.	n.s.	n.s.
FCF yield*	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.

* After tax op. FCF before WCR

key points	
Share price (€)	3.8
Number of Shares (m)	39.1
Market cap. (€m)	149
Free float (€m)	103
ISIN	ES0167733015
Ticker	ORY-ES
DJ Sector	Health Technology

	1m	3m	Ytd
Absolute perf.	+10.8%	+0.5%	+75.5%
Relative perf.	+10.1%	+0.8%	+51.0%

Source : Factset, Invest Securities estimates

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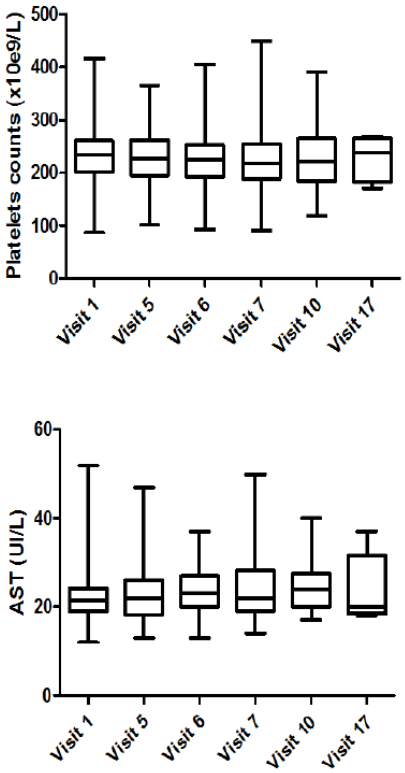
Exhibit 1: Vafidemstat-associated adverse events

Study-drug related TEAEs (ADRs) by SOC and PT (n= 104)	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**4 (3.84 %) 5**
Neutropenia	2 (1.92%) 2
Monocytosis	1 (0.96%) 1
Thrombocytopenia	1 (0.96%) 1
Leukopenia	1 (0.96%) 1
Cardiac Disorder	**6 (5.77 %) 6**
Ear and labyrinth disorders	**1 (0.96%) 1**
Gastrointestinal disorders	**4 (4.80 %) 4**
General disorders and administration site conditions	**2 (1.92%) 2**
Infections and infestations	**1 (0.96%) 1**
Investigations	**11 (13.46 %) 14**
Neutrophil count decreased	2 (1.92%) 2
Monocyte count increased	1 (0.96%) 1
Muscle enzyme increased	1 (0.96%) 1
Electrocardiogram QT prolonged	1 (0.96%) 1
Electrocardiogram PR prolongation	1 (0.96%) 1
Gamma-glutamyltransferase increased	1 (0.96%) 1
Hepatic enzyme abnormal	1 (0.96%) 1
Weight decreased	2 (1.92%) 2
Blood creatine phosphokinase increased	2 (1.92%) 2
Haematology test abnormal	1 (0.96%) 1
Electrocardiogram T wave inversion	1 (0.96%) 1
Metabolism and nutrition disorders	**1 (0.96%) 1**
Musculoskeletal and connective tissue disorders	**1 (0.96%) 1**
Nervous system disorders	**6 (5.77 %) 6**
Psychiatric disorders	**4 (3.84%) 5**
Renal and urinary disorders	**2 (1.92%) 2**
Skin and subcutaneous tissue disorders	**3 (2.88%) 3**
Vascular disorders	**1 (0.96 %) 1**



Source: Company's presentation, AAIC 19

Blinded data provide the first preliminary look into vafidemstat's efficacy in AD

Additionally, the company presented the blinded data from individual patients (n=28) that showed the change in biomarker, S100A8/A9, compared to the level of this protein at the beginning of the treatment period (baseline). S100a8 (calgranulin A) and S100a9 (calgranulin B) proteins have recently emerged as the central inflammatory regulators that drive and reinforce inflammation. The shifts in the abundance of *S100a8* and *S100a9* mRNA were shown to be a robust feature of aging, including the decline in neuronal activity. Moreover, recent studies suggested an important role of *S100a8/a9* specifically in AD, linking the inhibition of *S100a9* expression to the reduction of amyloid plaques in animal models. We note that there was 2 – 13 fold decrease of S100A8/A9 in some patients (Exhibit 2). While the data are blinded and it is difficult to draw any conclusions due to the presence of placebo arm, these results suggest that some patients could benefit from the repression of inflammatory processes in ETHERAL studyF. Interestingly, recently published preclinical study in another neurodegenerative disease, Parkinson's disease (PD), showed that this pathology could also be triggered by inflammation, which can occur long before the onset of neurodegenerative symptoms. Thus, in our view, vafidemstat's therapeutic effects could also take longer time to develop, and the additional 24-weeks extension period could potentially reveal more robust clinical effects.

Furthermore, ORYZON presented several efficacy measures, also in the form of blinded data from individual patients (n=34) (Exhibit 2). Results from the two clinical scales, MMSE and CMAI, suggested no progression of the behavioral symptoms in some of the evaluated patients.

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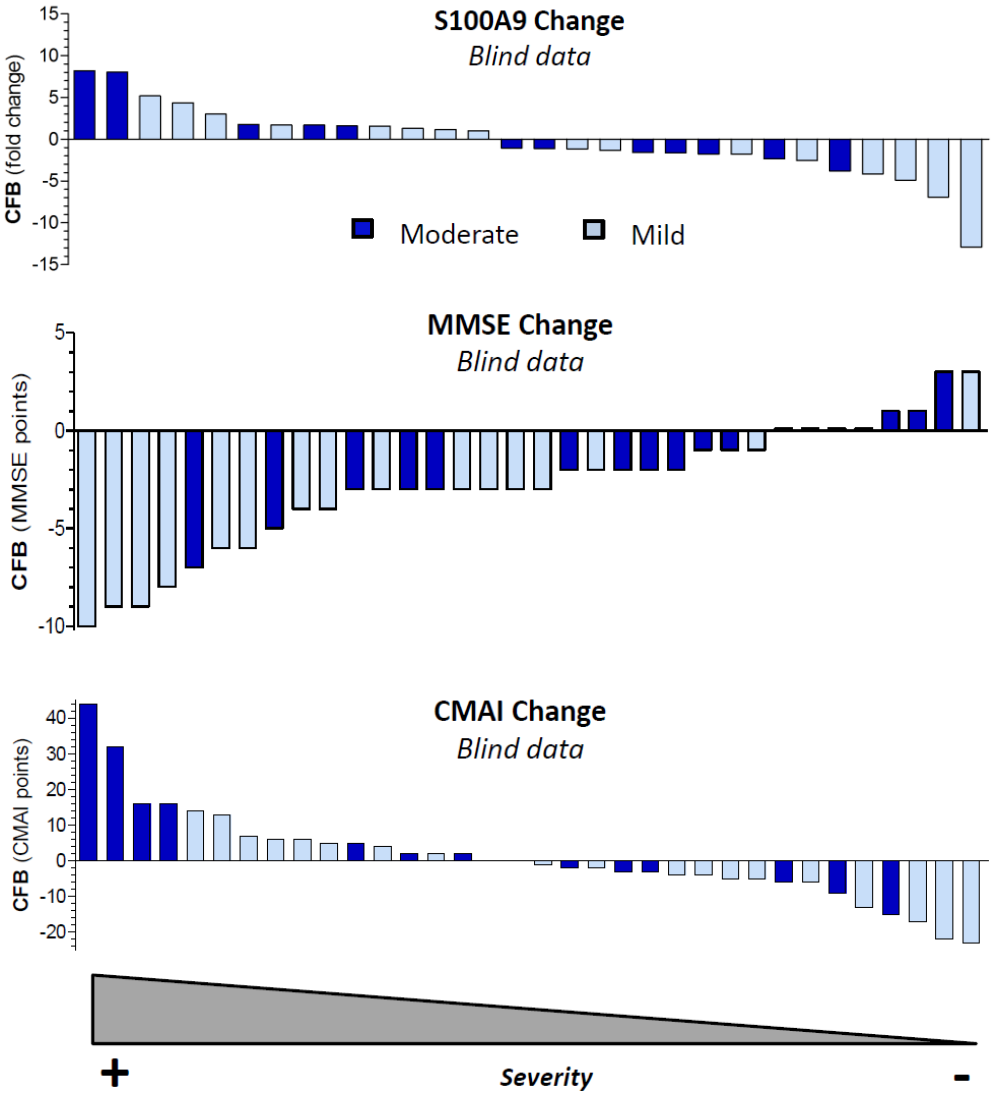
Exhibit 2: Early blinded results on evolution of biomarker and functional scores



Source: Company's presentation, AAIC 19

Mini Mental State Examination (MMSE) is a widely used tool to detect cognitive impairment on the scale from 0 to 30, assessed by a doctor, and Cohen-Mansfield Agitation Inventory (CMAI) evaluates agitation on the scale from 0 to 203, rated by a primary caregiver. Albeit it is difficult to draw any conclusions due to the presence of placebo arm and a background medication (acetylcholine inhibitors), we note that CMAI score was either stable or improved in the majority of presented patients. Considering that vafidemstat is also being evaluated as a therapy to treat aggressive behavior, where it recently showed some promising results (see our note from May 6, 2019), we believe that the presented data bode well for future clinical development of the drug as a behavioral treatment as well. We also note that the secondary endpoints of the study also include Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), a most commonly used endpoint in AD, and we expect the full results of the study (24-weeks placebo-controlled part) in 1H20.

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Overall, considering multiple failures of the amyloid-centered therapies, we believe that the alternative treatments with a broader mechanism of action, such as epigenetic modulators, will play a central role in the future clinical development for AD. One of the most discussed studies that came out of AAIC 19 showed that healthy life style was associated with a lower dementia risk among participants with high genetic risk. In our view, these beneficial effects could be partly explained by epigenetic regulation as well, reinforcing our continued interest in the epigenetic modulators. We note that another asset among this class of drugs, RDN-929 from Rodin Therapeutics, is also under development as a treatment for neurodegenerative diseases. At AAIC 19, Rodin presented clinical data from a Phase 1 study in healthy volunteers, elucidating safety profile of RDN-929, a novel complex-selective HDAC inhibitor. While, in our view, the emerging new drugs is a positive sign for epigenetic therapies, RDN-929 is at the earlier stage of development and has yet to show the signs of clinical activity. We currently project vafidemstat to enter the AD market in 2025 in the US and the EU, generating risk-adjusted revenues of €39M and growing to €495M by 2035.

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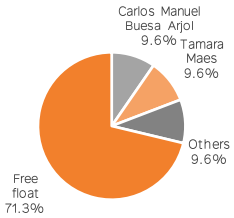
INVESTMENT CASE

ORYZON is a Spanish biotech specializing in the treatment of neurodegenerative diseases and cancer. In all its development programs, the company identifies biomarkers through its genetic and proteomic platforms in order to develop small molecule drugs. The company's Phase 2 assets, iadademstat and vafidemstat, are targeting essential epigenetic mechanisms to treat oncologic and neurodegenerative diseases, respectively.

FINANCIAL DATA

Shareholders



Share information	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
Published EPS (€)	-0.19	-0.15	-0.03	-0.11	-0.26	-0.43	0.53	0.44	0.76
Adjusted EPS (€)	**-0.19**	**-0.15**	**-0.03**	**-0.11**	**-0.26**	**-0.43**	**0.53**	**0.44**	**0.76**
Diff. I.S. vs Consensus	*+12.5%*	*-0.3%*	*-14.1%*	*-27.0%*					
Dividend									

Valuation ratios	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	7.1x	8.7x	5.0x
EV/Sales	111.47x	8265.92x	n.s.	n.s.	n.s.	n.s.	3.17x	5.53x	1.24x
VE/EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	4.7x	6.8x	2.9x
VE/EBITA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	4.7x	6.8x	2.9x
Op. FCF bef. WCR yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	10.3%	8.5%	22.3%
Op. FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	10.3%	8.5%	22.3%
Div. yield (%)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

NB : valuation based on annual average price for past exercise

Entreprise Value (€m)	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
Share price in €	*3.0*	*4.6*	*3.8*	*3.8*	*3.8*	*3.8*	*3.8*	*3.8*	*3.8*
Market cap.	85	156	130	169	169	169	169	169	169
Net Debt	-3	-17	-23	-11	-2	6	-10	-23	-49
Minorities	0	0	0	0	0	0	0	0	0
Provisions/ near-debt	0	0	0	0	0	0	0	0	0
+/- Adjustments	0	0	0	0	0	0	0	0	0
Entreprise Value (EV)	**82**	**139**	**107**	**158**	**167**	**175**	**159**	**146**	**120**

Income statement (€m)	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
Sales	0.7	0.0	0.0	0.0	0.0	0.0	50.0	26.5	96.3
chg.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
EBITDA	-4	-4	-3	-4	-10	-17	34	21	41
EBITA	**-4**	**-4**	**-3**	**-4**	**-10**	**-17**	**34**	**21**	**41**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***-36.9%***	***+89.7%***
EBIT	-4.9	-4.7	-3.3	-5.3	-11.6	-19.0	31.7	18.9	37.8
Financial result	-1	-1	-1	0	0	0	0	0	0
Corp. tax	0	0	3	0	0	0	-9	0	-5
Minorities+affiliates	0	0	0	0	0	0	0	0	0
Net attributable profit	-5.4	-5.2	-1.2	-5.0	-11.3	-18.7	23.3	19.2	33.1
Adjusted net att. profit	**-5.4**	**-5.2**	**-1.2**	**-5.0**	**-11.3**	**-18.7**	**23.3**	**19.2**	**33.1**
chg.		***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***-17.8%***	***+72.5%***

Cash flow statement (€m)	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
EBITDA	-4.1	-3.9	-3.1	-4.0	-10.0	-17.0	34.0	21.5	40.7
Theoretical Tax / EBITA	0.0	0.1	2.5	0.0	0.0	0.0	-8.7	0.0	-5.1
Capex	-7.1	0.6	-7.0	-9.0	-9.0	-9.0	-9.0	-9.0	-9.0
Operating FCF bef. WCR	**-11.2**	**-3.2**	**-7.6**	**-13.0**	**-19.0**	**-26.0**	**16.3**	**12.5**	**26.7**
Change in WCR	-0.1	-0.2	0.3	0.0	0.0	0.0	0.0	0.0	0.0
Operating FCF	**-11.3**	**-3.4**	**-7.3**	**-13.0**	**-19.0**	**-26.0**	**16.3**	**12.5**	**26.7**
Acquisitions/disposals	0.7	5.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Capital increase/decrease	0.3	16.9	11.9	1.3	10.0	18.0	0.0	0.0	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other adjustments	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Published FreeCash Flow	**-10.2**	**18.5**	**4.7**	**-11.7**	**-9.0**	**-8.0**	**16.3**	**12.5**	**26.7**

Balance Sheet (€m)	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
Assets	21	25	32	40	47	55	62	69	75
Intangible assets/GW	19	22	29	37	45	52	59	66	73
WCR	-1	-8	-9	-9	-9	-9	-9	-9	-9
Group equity capital	23	34	45	41	40	40	63	82	115
Minority shareholders	0	0	0	0	0	0	0	0	0
Provisions	0	0	0	0	0	0	0	0	0
Net financial debt	**-2.6**	**-17.2**	**-22.6**	**-11.0**	**-2.0**	**6.0**	**-10.3**	**-22.7**	**-49.4**

Financial ratios	2016	2017	2018	2019e	2020e	2021e	2022e	2023e	2024e
EBITDA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	68.0%	81.1%	42.3%
EBITA margin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	68.0%	81.1%	42.3%
Adjusted Net Profit/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	46.6%	72.5%	34.3%
ROCE	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	64.4%	36.1%	61.8%
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	37.1%	23.4%	28.7%
Gearing	n.s.	n.s.	n.s.	n.s.	n.s.	15.3%	n.s.	n.s.	n.s.
ND/EBITDA (in x)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-0.3x	-1.1x	-1.2x

Source : company, Invest Securities Estimates

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SWOT ANALYSIS

STRENGTHS

- Epigenetic platform
- Numerous clinical development programs
- Solid cash position

WEAKNESS

- No partnership
- Numerous failures in lead indication (AD)
- Tight competition in oncology indications

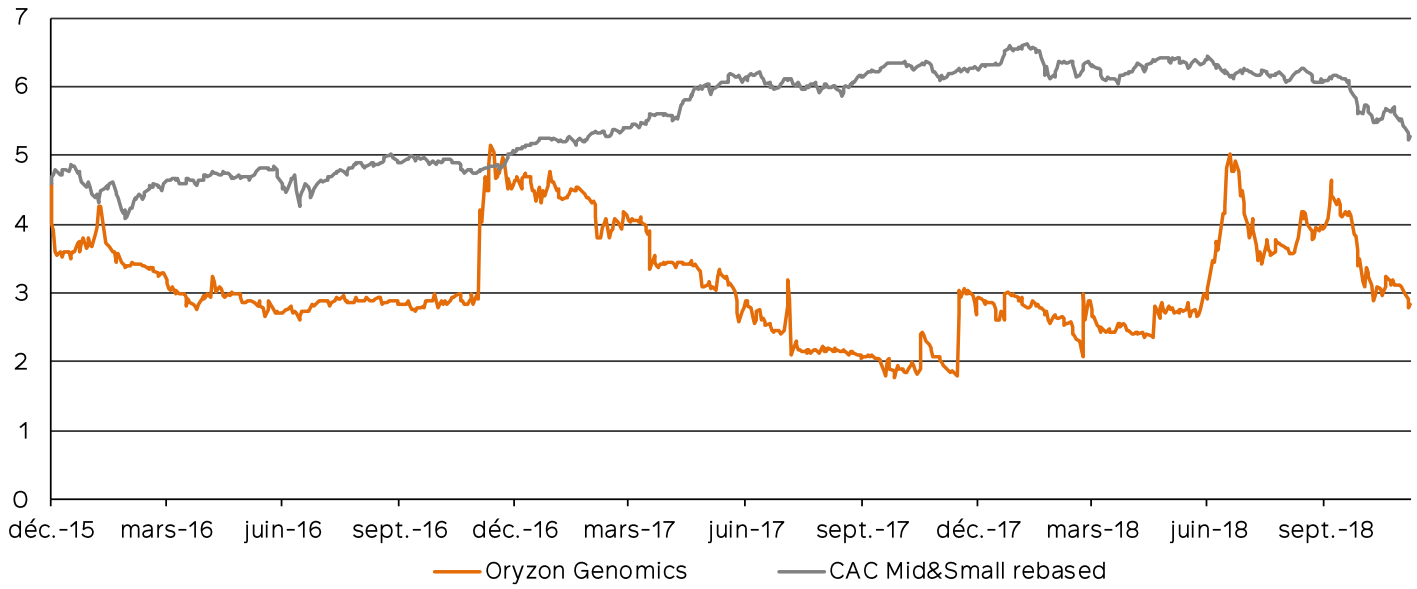
OPPORTUNITIES

- Potential partnership agreement
- Expansion indications for clinical programs
- Preclinical programs to move into clinic

THREATS

- Clinical and regulatory risks
- Commercial risks
- Legal risks

SHARE PRICE CHANGE FOR 5 YEARS



DETECTION OF CONFLICTS OF INTEREST

	Corporate Finance	Détention capitalistique de l'émetteur	Communication préalable à l'émetteur	Intérêt personnel de l'analyste	Contrat de liquidité	Listing Sponsor	Contrat d'analyse
Oryzon Genomi	Non	Non	Oui	Non	Non	Non	Oui

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