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COMPANY NOTE | EQUITY RESEARCH | May 10, 2023

Healthcare: Biotechnology

Company Update
Estimates Changed

Oryzon Genomics SA | ORY.SM - €2.11 - MADRID | *Buy*

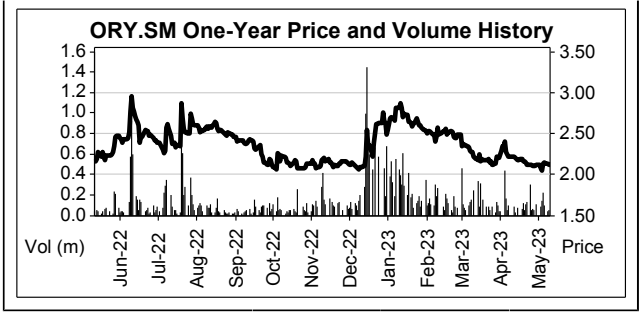
Stock Data	
52-Week Low - High	€1.98 - €3.06
Shares Out. (mil)	55.56
Mkt. Cap.(mil)	€120.47
3-Mo. Avg. Vol.	129,612
12-Mo.Price Target	€15.00
Cash (mil)	$20.0
Tot. Debt (mil)	$21.9

Rev ($M)

Yr Dec	—2022—	—2023E—	—2024E—
		Curr	Curr
1Q	0.0A	0.0A	-
2Q	0.0A	0.0E	-
3Q	0.0A	0.0E	-
4Q	0.0A	0.0E	-
YEAR	0.0A	0.0E	0.0E

EPS $

Yr Dec	—2022—	—2023E—		—2024E—	
		Curr	Prev	Curr	Prev
1Q	(0.03)A	(0.03)A	(0.06)E	-	-
2Q	0.01A	(0.05)E	(0.06)E	-	-
3Q	(0.01)A	(0.07)E	(0.08)E	-	-
4Q	(0.05)A	(0.07)E	(0.09)E	-	-
YEAR	(0.08)A	(0.22)E	(0.29)E	(0.46)E	(0.60)E
P/E	NM	NM	NM	NM	NM



ORY 1Q23: Four Trials Running, Two to Start, Funded Into 1H24 on Current Cash

ORY ended 1Q23 with $20M, enough to fund operations into 1H24, as per our projections, and ORY has access to additional convertible debt financing that it has not yet drawn down. ORY is enrolling patients into four trials, and expects to initiate at least two more. ORY believes that the FRIDA trial, which is its central strategy, is iadademstat's fastest route to market. The FRIDA, SCLC basket, PORTICO, and EVOLUTION trials are enrolling, with enrollment to start by 2024 in the STELLAR and HOPE trials.

Iadademstat

- **FRIDA trial.** ORY has started enrolling patients in its Phase 1b FRIDA trial in rel/ref AML with FLT3 mutations, which will test iadademstat plus gilteritinib in up to 45 patients in the U.S. FRIDA has primary endpoints of safety, tolerability, and determining the RP2D, and secondary endpoints of efficacy (i.e., CR/CRh, DoR, MRD), and ORY will meet with the FDA to best plan development of this combination therapy. ORY believes that the FRIDA trial, which is its central strategy, is iadademstat's fastest route to market.
- **SCLC basket trial.** ORY is also conducting a collaborative Phase 2 basket trial in the U.S. of iadademstat in combination with synergistic agents, such as paclitaxel, in platinum rel/ref SCLC and extrapulmonary high grade neuroendocrine tumors. The first patient was enrolled in January 2023. The trial is being conducted in collaboration with Fox Chase Cancer Center, which will test iadademstat in combination with different therapies.
- **STELLAR trial.** ORY's Phase 1b/2 STELLAR trial in the U.S. in firstline SCLC is being designed, and it is a randomized, multi-center trial of iadademstat plus a checkpoint inhibitor in this setting that could potentially support accelerated approval.

Vafidemstat

- **PORTICO trial.** Active patient recruitment is ongoing in the randomized, 188-patient Phase 2b PORTICO trial in BPD patients at 15-20 centers in the U.S. and Europe. PORTICO's primary endpoints are reduction of aggression/ agitation and overall BPD improvement. ORY presented initial blinded safety data from the first 43 PORTICO patients at the European Conference on Mental Health in September. In short, no serious or severe adverse reactions were reported, with 41 mostly mild adverse reactions reported in 12 patients (blinded, so unknown if vafidemstat or placebo), and with no reactions leading to treatment discontinuation or patient withdrawal. A subsequent pre-defined interim analysis in 1Q23 on the first 90 patients that have completed treatment determined the trial to be non-futile and to therefore continue with enrollment as planned. We anticipate ORY to report topline final results in late 2023 or early 2024, which will hopefully clearly inform the design of a pivotal trial in BPD. In February, ORY sponsored a recent KOL call, during which (*text continued on page 2)*

- *(text continued from page 1)* it discussed its pipeline. The KOLs commenting on PORTICO agreed that antipsychotic use in BPD often leads to polytherapy because the absence of effective BPD drugs leaves physicians just treating a patient's individual symptoms as best they can. Physicians are often simply trying to calm patients down and help with sleep, but there is a substantial side effect price to pay for those benefits, such as weight gain, metabolic syndrome, cholesterol increase, and sexual symptoms. The KOLs are looking for PORTICO to safely demonstrate that vafidemstat can reduce agitation and aggression in these "emotional burn" victims, while enhancing mood and fighting patients' feelings of emptiness, so BPD patients act out less frequently. They claimed that no drug can give even a 10-20% relief from these symptoms.
- **EVOLUTION trial.** The Phase 2b EVOLUTION trial evaluating vafidemstat in schizophrenia continues to enroll patients in Spain and is looking to establish vafidemstat efficacy on negative symptoms and cognitive impairment in patients with schizophrenia. EVOLUTION is partially funded by the Spanish Ministry of Science.
- **HOPE trial.** ORY is working with KOLs to finalize the design of HOPE, a randomized, double-blind, placebo-controlled, 50-60 patient Phase 1/2 personalized medicine trial with vafidemstat in Kabuki Syndrome patients. ORY is talking to regulatory agencies to refine the final design of HOPE, and should be filing an IND in 2023 in the U.S. and possibly filing to start enrolling in Europe as well.
- **Psychiatric pilot trials.** ORY's precision medicine programs in psychiatric disease are progressing, with collaborations in autism at the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai Hospital and the Institute of Medical and Molecular Genetics (INGEMM) at Hospital Universitario La Paz, as well as in schizophrenia with Columbia University. Pilot studies to characterize patients with specific mutations to inform subsequent precision psychiatry trial design with vafidemstat are ongoing with no timing guidance yet for release of results.

HDAC-6 program

- In March, ORY announced that it selected ORY-4001, a selective HDAC-6 inhibitor, as its drug candidate to bring into the clinic for neurological diseases such as Charcot-Marie-Tooth (CMT) and ALS, among others. HDAC-6 inhibitors are believed to be potentially effective treatments for CMT, ALS, and other neurological disorders lacking effective treatments. Last year, ORY and the CMT Research Foundation agreed to explore ORY's HDAC-6 inhibitors, and ORY-4001 was selected due to the positive preclinical results generated under this collaboration. ORY-4001 is highly selective against other HDAC-classes, resulting in a favorable safety profile that avoids hematoxicity, as well as being strongly anti-inflammatory *in vivo*. ORY-4001 has shown multiple positive responses in a validated CMT1A peripheral neuropathy *in vivo* model which reliably recapitulates many of the symptoms of CMT in humans, and it will now enter into IND enabling studies. CMT is a progressive, degenerative peripheral nerve disease affecting 150k U.S. patients and over 3M globally. CMT is caused by a variety of genetic mutations, with CMT1A mutation causing the disease in about half of the patients.

VALUATION

Our 12-month price target of €15, is based on a DCF analysis using a 40% discount rate that is applied to all cash flows and the terminal value, which is based on a 4x multiple of our projected 2030 operating income of $1 billion. We arrive at this valuation by projecting future revenue from vafidemstat in borderline personality disorder and Kabuki syndrome, as well as iadademstat in AML and SCLC.

Factors that could impede shares of ORY.SM from achieving our price target include vafidemstat and iadademstat failing to generate statistically significant clinical results. Also, regulatory agencies could fail to approve these drugs even if pivotal clinical trials are statistical successes, due to the agency viewing the results as not clinically meaningful. Loss of key management personnel could also impede achieving our price target, as could smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

RISKS

- Clinical risk. ORY.SM's clinical staged products could fail to deliver statistically significant results in late-stage clinical trials, substantially reducing the value of ORY.SM's product candidates and therefore our target price.
- Regulatory risk. Even if successful in the clinic, ORY.SM's products could fail to be approved by domestic and/or foreign regulatory bodies, which would reduce ORY.SM’s value and therefore our target price.
- Financing risk. ORY.SM will need additional capital to fund its operations, and such financing may not occur, or it could be substantially dilutive to existing investors.
- Competitive risk. For any future approved ORY.SM products, they may not be well adopted in a competitive marketplace, which would adversely affect ORY.SM's value and therefore our target price.
- High stock price volatility. This issue is common among small-cap biotechnology companies with relatively low trading volumes.

COMPANY DESCRIPTION

Calibri Calibri;;; Adobe Acrobat Reader 23.1.0 cbuesa Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company considere d as the European leader in epigenetics. Oryzon has one of the strongest portfolios in the field, with two LSD1 inhibitors, iadadem stat and vafidemstat, in Phase II clinical trials , and other pipeline assets directed against other epigenetic targets. In addition, Oryzon has a strong platform for biomarker identification and target validation for a variety of malignant and neuro logical diseases. For more information, visit www.oryzon.com

Oryzon Genomics SA
Income Statement
Fiscal Year ends December
(in 000, except per share items)

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	2017A	2018A	2019A	2020A	2021A	1Q22	2Q22	3Q22	4Q22	2022A	1Q23A	2Q23E	3Q23E	4Q23E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Global iadademstat revenue																	25,778	99,451	209,468	313,934	372,470	389,751
Global vafidemstat revenue																	98,463	342,237	520,351	615,106	684,577	721,921
Collaboration revenue	20																					
Total revenue	**20**																**124,241**	**441,689**	**729,819**	**929,040**	**1,057,047**	**1,111,672**
Cost of revenue																-	5,420	17,066	34,941	48,990	59,606	64,604
R&D	6,363	8,489	12,647	13,591	15,118	4,228	4,166	4,274	5,033	17,701	4,372	4,591	4,820	5,061	18,844	22,613	27,135	29,849	31,341	31,655	31,971	32,291
G&A	4,502	2,993	3,176	3,484	5,529	1,343	1,520	659	1,249	4,771	1,223	1,235	1,248	1,260	4,966	7,449	13,408	20,112	22,123	24,335	25,552	26,830
Total operating expenses	**10,865**	**11,482**	**15,823**	**17,075**	**20,647**	**5,571**	**5,686**	**4,933**	**6,282**	**22,472**	**5,595**	**5,826**	**6,068**	**6,321**	**23,810**	**30,061**	**45,963**	**67,027**	**88,405**	**104,980**	**117,129**	**123,724**
Operating income	**(10,845)**	**(11,482)**	**(15,823)**	**(17,075)**	**(20,647)**	**(5,571)**	**(5,686)**	**(4,933)**	**(6,282)**	**(22,472)**	**(5,595)**	**(5,826)**	**(6,068)**	**(6,321)**	**(23,810)**	**(30,061)**	**78,278**	**374,662**	**641,414**	**824,060**	**939,918**	**987,948**
Other income (net)	5,659	8,143	11,522	11,805	12,510	3,826	3,894	4,248	4,693	16,661	4,215	3,000	2,000	2,000	11,215							
Net income (pretax)	**(5,186)**	**(3,339)**	**(4,301)**	**(5,269)**	**(8,137)**	**(1,745)**	**(1,792)**	**(685)**	**(1,589)**	**(5,811)**	**(1,380)**	**(2,826)**	**(4,068)**	**(4,321)**	**(12,595)**	**(30,061)**	**78,278**	**374,662**	**641,414**	**824,060**	**939,918**	**987,948**
Net financial & tax	1,047	(1,991)	(187)	(1,098)	(2,760)	67	(2,139)	(67)	863	(1,276)	392	(250)	(250)	(250)	(358)	(394)	(433)	93,665	160,354	206,015	234,980	246,987
Net income	**(6,233)**	**(1,348)**	**(4,114)**	**(4,171)**	**(5,377)**	**(1,812)**	**347**	**(618)**	**(2,452)**	**(4,535)**	**(1,772)**	**(2,576)**	**(3,818)**	**(4,071)**	**(12,237)**	**(29,668)**	**78,711**	**280,996**	**481,061**	**618,045**	**704,939**	**740,961**
EPS basic	**(0.20)**	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.03)**	**0.01**	**(0.01)**	**(0.05)**	**(0.08)**	**(0.03)**	**(0.05)**	**(0.07)**	**(0.07)**	**(0.22)**	**(0.46)**	**1.16**	**3.94**	**6.42**	**7.86**	**8.53**	**8.54**
EPS diluted	**(0.20)**	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.03)**	**0.01**	**(0.01)**	**(0.05)**	**(0.08)**	**(0.03)**	**(0.05)**	**(0.07)**	**(0.07)**	**(0.22)**	**(0.46)**	**0.96**	**3.29**	**5.41**	**6.67**	**7.30**	**7.35**
Basic shares outstanding	31,711	34,638	41,589	49,235	52,762	52,762	52,762	53,609	54,284	53,354	56,190	56,247	56,303	56,359	56,275	64,716	67,952	71,349	74,917	78,663	82,596	86,725
Diluted shares outstanding	31,711	34,638	41,565	49,235	52,762	52,762	52,762	53,609	54,284	53,354	56,190	56,247	56,303	56,359	56,275	64,716	81,989	85,386	88,954	92,700	96,633	100,763

Source: SEC filings, company press releases, and ROTH MKM

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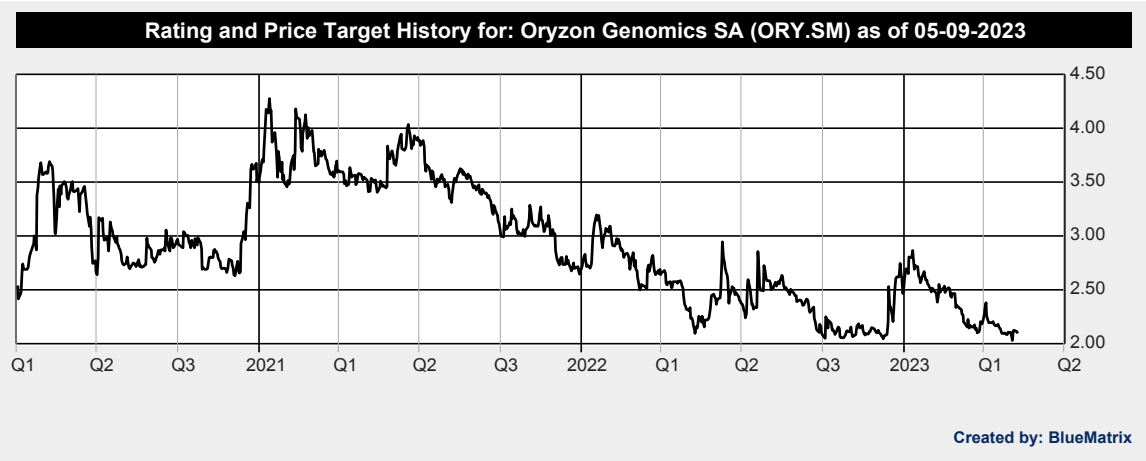
Disclosures:

Shares of Oryzon Genomics SA may be subject to the Securities and Exchange Commission's Penny Stock Rules, which may set forth sales practice requirements for certain low-priced securities.



Each box on the Rating and Price Target History chart above represents a date on which an analyst made a change to a rating or price target, except for the first box, which may only represent the first note written during the past three years. **Distribution Ratings/IB Services** shows the number of companies in each rating category from which Roth or an affiliate received compensation for investment banking services in the past 12 month.

Distribution of IB Services Firmwide

			IB Serv./Past 12 Mos. as of 05/10/23	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**363**	**74.39**	**214**	**58.95**
Neutral [N]	**100**	**20.49**	**31**	**31.00**
Sell [S]	**3**	**0.61**	**0**	**0**
Under Review [UR]	**21**	**4.30**	**6**	**28.57**

Our rating system attempts to incorporate industry, company and/or overall market risk and volatility. Consequently, at any given point in time, our investment rating on a stock and its implied price movement may not correspond to the stated 12-month price target.

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Neutral: A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return between negative 10% and 10% over the next 12 months.

Sell: A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

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