Jonathan Aschoff, Ph.D., (646) 616-2795
jaschoff@roth.com

Sales (800) 933-6830, **Trading** (203) 861-9060

COMPANY NOTE | EQUITY RESEARCH | February 29, 2024

Healthcare: Biotechnology

Company Update
Estimates Changed

Oryzon Genomics SA | ORY.SM - €1.87 - MADRID | *Buy*

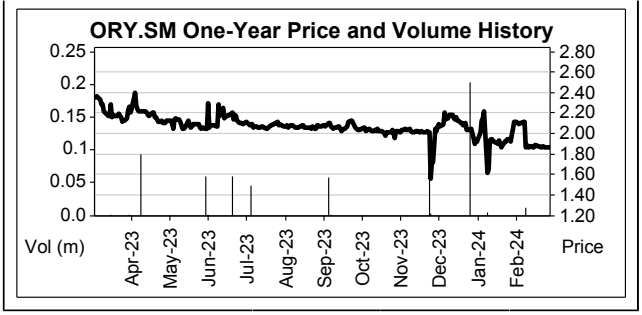
Stock Data	
52-Week Low - High	€1.70 - €2.62
Shares Out. (mil)	61.62
Mkt. Cap.(mil)	€124.56
3-Mo. Avg. Vol.	381
12-Mo.Price Target	€12.00
Cash (mil)	$13.5
Tot. Debt (mil)	€18.5

Rev ($M)

Yr Dec	—2023—	—2024E—	—2025E—
		Curr	Curr
1Q	0.0A	0.0E	-
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	—2023—	—2024E—		—2025E—
		Curr	Prev	Curr
1Q	(0.03)A	(0.03)E	(0.02)E	-
2Q	0.02A	(0.03)E	(0.02)E	-
3Q	(0.02)A	(0.03)E	(0.02)E	-
4Q	(0.03)A	(0.03)E	(0.02)E	-
YEAR	(0.06)A	(0.11)E	(0.09)E	(0.14)E
P/E	NM	NM	NM	NM



ORY 4Q23: PORTICO EOP2 Next, 3 Trials Going, 4 to Start, Funded Through 2024

ORY ended 4Q23 with $13.5M, enough to fund operations through 2024, and ORY has access to additional convertible debt financing. ORY is enrolling three trials, and expects to initiate four more trials. ORY believes that the FRIDA trial, which is its central iadademstat strategy, is iadademstat's fastest route to market. The FRIDA, SCLC basket, and EVOLUTION trials are enrolling, with enrollment still to start for three more iadademstat trials and the HOPE trial. PORTICO's EOP2 meeting for vafidemstat in BPD first requires full PORTICO analysis.

Vafidemstat

- **PORTICO trial.** Earlier in 1Q24, PORTICO showed vafidemstat to be safe, but the trial failed to achieve its primary endpoints, namely the Borderline Personality Disorder Checklist (BPDCL) and the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) across weeks 8-12, both primary endpoints. Although there was a consistent reduction with vafidemstat versus placebo throughout treatment, statistical significance was not achieved (p=0.41 and p=0.25, respectively). As BPD has no well-established trial endpoints, two of PORTICO's secondary endpoints, which were achieved, will help inform the design of a registrational Phase 3 trial. Statistically significant overall disease improvement was achieved on the secondary endpoint of Borderline Evaluation of Severity (BEST) across weeks 8-12 (p=0.042), with a relative reduction for vafidemstat over placebo of 28.9%. BEST measures BPD symptom severity and adaptive coping responses including negative behaviors and actions such as injuring oneself, thoughts and feelings including mood reactivity, identity disturbance, unstable relationships, paranoia, emptiness, and suicidal thinking, and positive behaviors such as avoidance of self-destructive and/or self-defeating behaviors. The relative reduction for vafidemstat versus placebo was maintained throughout treatment and reached a maximum of 38% at week 10. There was also a statistically significant improvement in agitation and aggression as measured by the STAXI-2, Trait Anger (p=0.026), with a relative reduction for vafidemstat over placebo of 46.7%, and which was shown over weeks 8-12. The 10-item Trait Anger scale measures the disposition to experience angry feelings as a personality-like trait over time. The relative reduction for vafidemstat versus placebo was consistent throughout treatment and reached a maximum of 80% at week 10. The Global Statistical Test (GST) confirms a strong trend favoring vafidemstat across all efficacy endpoints. The GST addresses whether a treatment is effective across different aspects of a condition, especially when a disease is as complex and multifactorial as BPD.
- **Next steps in BPD.** Given that all eleven primary and secondary efficacy endpoints favored vafidemstat over placebo indicates that there is a positive treatment effect and that further clinical investigation is warranted, especially in a disease with no approved therapy. PORTICO (n=210; 27 U.S and European sites) is the first large, (*text continues on page 2)*

Important Disclosures & Regulation AC Certification(s) are located on page 6 to 7 of this report.

- *(text continued from page 1)* randomized Phase 2 BPD trial that statistically achieved two secondary endpoints that reflect clinically meaningful improvements in overall BPD severity and in agitation/aggression. Since there are no well-established regulatory endpoints for BPD, PORTICO's secondary endpoint results should help inform the design of a definitive Phase 3 trial. We expect 2 Phase 3 trials of about 400 patients per trial to be conducted and for an EOP2 meeting to be requested as soon as possible once the full PORTICO data analysis has been conducted. We note that 18 BPD trials have failed, and that with no available treatment and no established endpoints, using different primary endpoint(s) is a fair modification.
- **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 2024 in the U.S.

Iadademstat

- **FRIDA trial.** ORY continues to enroll patients in its Phase 1b FRIDA trial in rel/ref AML with FLT3 mutations, which will evaluate iadademstat plus gilteritinib in up to 45 patients in the U.S. at up to 15 centers. 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, if FRIDA is successful. ORY believes that the FRIDA trial, which is its central strategy, is iadademstat's fastest route to market. ORY presented a poster at ASCO 2023 describing FRIDA 's design and reporting that the first dose escalation cohort was completed with no DLTs yet observed. Since ASCO, ORY has started dosing the second FRIDA dose cohort of six patients.
- **First-line AML trial.** Iadademstat in combination with venetoclax and azacitidine will also be evaluated in first-line AML in a Phase 1b dose-finding investigator-initiated trial led by Oregon Health & Science University. The trial has FDA IND approval and should start enrolling patients in 1Q24.
- **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 and enrollment continues. The trial is being conducted in collaboration with Fox Chase Cancer Center, which will test iadademstat in combination with different therapies in trials funded by ORY.
- **STELLAR trial.** ORY's Phase 1b/2 STELLAR trial in the U.S. in first-line 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. We expect STELLAR to start in 1Q24.
- **New SCLC trial.** A new trial to evaluate iadademstat plus a checkpoint inhibitor in first-line metastatic SCLC, will be conducted under ORY's CRADA that was signed with the NCI and is under preparation. MSKCC will lead the trial and we expect its IND to be filed in 1Q24.

Earlier-stage programs

- In 1Q23, 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 is currently progressing through 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. HDAC6 inhibition or depletion has also been previously described as a potentially effective treatment for ALS, protecting against neurodegeneration in various ALS mouse and human iPSC models. Due to the key role altered axonal transport and proteostasis play in both CMT and ALS, ORY will evaluate ORY-4001 in ALS mouse models. To help fund preclinical evaluation of ORY-4001 in ALS, the ALS Association has awarded ORY an almost $500k grant through its Lawrence and Isabel Barnett Drug Development Program.

- ORY received two new grants to further explore the role of epigenetic targets to treat neuronal pathologies, with two collaborative projects with public research centers focused on the discovery and validation of novel biomarkers and epigenetic targets. The projects have a global budget of €2.3M, of which ORY will receive up to €1.4M.

VALUATION

Our 12-month price target of €12, is based on a DCF analysis using a 35% 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 $741 million. 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

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company and the European leader in epigenetics, with a strong focus on personalized medicine in CNS disorders and oncology. Oryzon's team is composed of highly qualified professionals from the pharma industry located in Barcelona, Boston, and San Diego. Oryzon has an advanced clinical portfolio with two LSD1 inhibitors, vafidemstat in CNS and iadademstat in oncology, in several Phase II clinical trials. The company has other pipeline assets directed against other epigenetic targets like HDAC-6, where ORY-4001 has been nominated as clinical candidate for the treatment of certain neurological disorders such as CMT and ALS. In addition, Oryzon has a strong platform for biomarker identification and target validation for a variety of malignant and neurological diseases. For more information, visit www.oryzon.com

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

Jonathan Aschoff, Ph.D. (646) 616-2795
jaschoff@roth.com

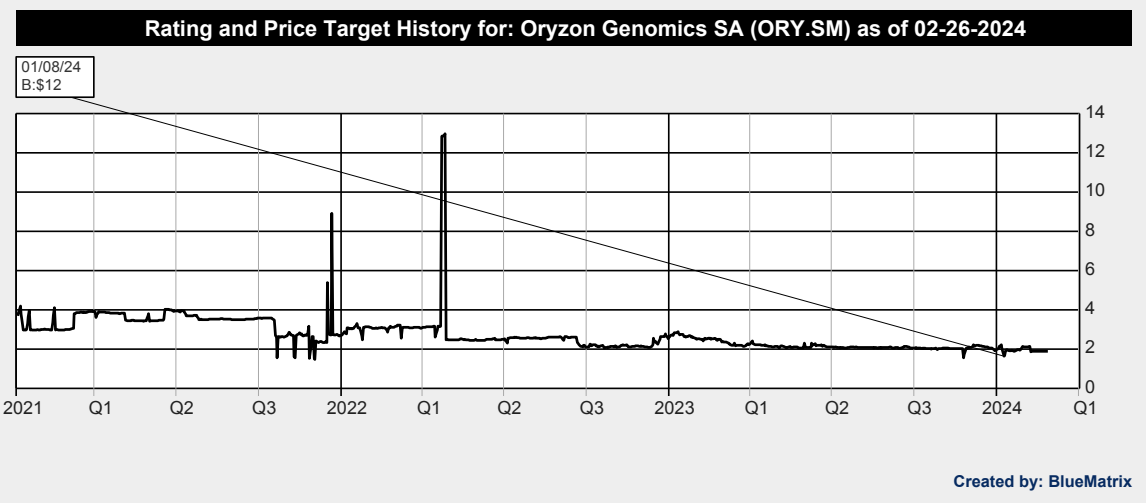
	2018A	2019A	2020A	2021A	2022A	1Q23	2Q23	3Q23	4Q23	2023A	1Q24E	2Q24E	3Q24E	4Q24E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Global iadademstat revenue																-	56,537	114,647	170,103	202,105	212,150
Global vafidemstat revenue																-	-	156,140	331,900	531,986	592,897
Total revenue																-	**56,537**	**270,787**	**502,003**	**734,091**	**805,047**
Cost of revenue																-	7,915	18,588	25,790	31,267	33,779
R&D	8,489	12,647	13,591	15,118	17,701	4,372	4,264	3,821	3,867	16,324	3,906	3,945	3,984	4,024	15,859	16,652	17,484	17,659	17,836	18,014	18,194
G&A	2,993	3,176	3,484	5,529	4,771	1,223	1,096	674	1,187	4,180	1,199	1,211	1,223	1,235	4,868	5,355	9,103	10,013	11,015	11,565	12,144
Total operating expenses	**11,482**	**15,823**	**17,075**	**20,647**	**22,472**	**5,595**	**5,360**	**4,495**	**5,054**	**20,504**	**5,105**	**5,156**	**5,207**	**5,259**	**20,726**	**22,006**	**34,502**	**46,261**	**54,640**	**60,846**	**64,117**
Operating income	**(11,482)**	**(15,823)**	**(17,075)**	**(20,647)**	**(22,472)**	**(5,595)**	**(5,360)**	**(4,495)**	**(5,054)**	**(20,504)**	**(5,105)**	**(5,156)**	**(5,207)**	**(5,259)**	**(20,726)**	**(22,006)**	**22,035**	**224,527**	**447,363**	**673,245**	**740,930**
Other income (net)	8,143	11,522	11,805	12,510	16,661	4,215	4,054	3,669	3,619	15,557	3,000	3,000	3,000	3,000	12,000	12,000	11,000	10,000	8,000	6,000	5,000
Net income (pretax)	**(3,339)**	**(4,301)**	**(5,269)**	**(8,137)**	**(5,811)**	**(1,380)**	**(1,306)**	**(826)**	**(1,435)**	**(4,947)**	**(2,105)**	**(2,156)**	**(2,207)**	**(2,259)**	**(8,726)**	**(10,006)**	**33,035**	**234,527**	**455,363**	**679,245**	**745,930**
Net financial & tax	(1,991)	(187)	(1,098)	(2,760)	(1,276)	392	(2,459)	300	468	(1,299)	(250)	(250)	(250)	(250)	(1,000)	-	8,259	58,632	113,841	169,811	186,483
Net income	**(1,348)**	**(4,114)**	**(4,171)**	**(5,377)**	**(4,535)**	**(1,772)**	**1,153**	**(1,126)**	**(1,903)**	**(3,648)**	**(1,855)**	**(1,906)**	**(1,957)**	**(2,009)**	**(7,726)**	**(10,006)**	**24,776**	**175,895**	**341,522**	**509,434**	**559,448**
EPS basic	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.03)**	**(0.06)**	**(0.03)**	**(0.03)**	**(0.03)**	**(0.03)**	**(0.11)**	**(0.14)**	**0.33**	**2.23**	**4.13**	**5.87**	**6.14**
EPS diluted	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.03)**	**(0.06)**	**(0.03)**	**(0.03)**	**(0.03)**	**(0.03)**	**(0.11)**	**(0.14)**	**0.28**	**1.90**	**3.53**	**5.05**	**5.32**
Basic shares outstanding	34,638	41,589	49,235	52,762	53,354	56,190	57,339	58,154	58,451	57,616	67,219	67,891	67,959	68,027	67,774	71,428	75,000	78,749	82,687	86,821	91,162
Diluted shares outstanding	34,638	41,565	49,235	52,762	53,354	56,190	57,339	58,154	58,451	57,616	67,219	67,891	67,959	68,027	67,774	71,428	89,037	92,787	96,724	100,859	105,200

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

Regulation Analyst Certification ("Reg AC"): The research analyst primarily responsible for the content of this report certifies the following under Reg AC: I hereby certify that all views expressed in this report accurately reflect my personal views about the subject company or companies and its or their securities. I also certify that no part of my compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

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 02/29/24	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**351**	**73.43**	**77**	**21.94**
Neutral [N]	**82**	**17.15**	**5**	**6.10**
Sell [S]	**2**	**0.42**	**0**	**0**
Under Review [UR]	**41**	**8.58**	**3**	**7.32**

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.

Ratings System Definitions - ROTH MKM employs a rating system based on the following:

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

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.

Under Review [UR]: A rating, which at the time it is instituted and or reiterated, indicates the temporary removal of the prior rating, price target and estimates for the security. Prior rating, price target and estimates should no longer be relied upon for UR-rated securities.

Not Covered [NC]: ROTH MKM does not publish research or have an opinion about this security.

ROTH Capital Partners, LLC expects to receive or intends to seek compensation for investment banking or other business relationships with the covered companies mentioned in this report in the next three months. The material, information and facts discussed in this report other than the information regarding ROTH Capital Partners, LLC and its affiliates, are from

sources believed to be reliable, but are in no way guaranteed to be complete or accurate. This report should not be used as a complete analysis of the company, industry or security discussed in the report. Additional information is available upon request. This is not, however, an offer or solicitation of the securities discussed. Any opinions or estimates in this report are subject to change without notice. An investment in the stock may involve risks and uncertainties that could cause actual results to differ materially from the forward-looking statements. Additionally, an investment in the stock may involve a high degree of risk and may not be suitable for all investors. No part of this report may be reproduced in any form without the express written permission of ROTH. Copyright 2024. Member: FINRA/SIPC.