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COMPANY NOTE | EQUITY RESEARCH | January 08, 2024

Healthcare: Biotechnology

Company Update
Target Price Changed

Oryzon Genomics SA | ORY.SM - €1.89 - MADRID | *Buy*

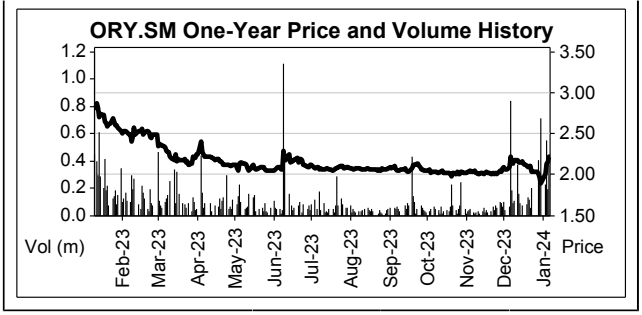
Stock Data	
52-Week Low - High	€1.86 - €2.93
Shares Out. (mil)	59.72
Mkt. Cap.(mil)	€132.27
3-Mo. Avg. Vol.	113,472
12-Mo.Price Target	€12.00
Cash (mil)	$8.8
Tot. Debt (mil)	€20.1

Rev ($M)

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

EPS $

Yr Dec	—2022—	—2023E—	—2024E—
		Curr	Curr
1Q	(0.03)A	(0.03)A	(0.02)E
2Q	0.01A	0.02A	(0.02)E
3Q	(0.01)A	(0.02)A	(0.02)E
4Q	(0.05)A	(0.04)E	(0.02)E
YEAR	(0.08)A	(0.07)E	(0.09)E
P/E	NM	NM	NM



ORY: PORTICO Misses Primary Endpoints, Will Seek FDA Guidance on Phase 3 Design

Late on Friday, ORY reported that its Phase 2b PORTICO trial evaluating vafidemstat versus placebo in BPD missed its two primary endpoints (BPDCL and CGI-S A/A). PORTICO did statistically achieve two secondary endpoints, and every efficacy endpoint measured at least favored vafidemstat over placebo, with vafidemstat being safe and well tolerated. Nominal statistical significance was achieved on the BEST (p=0.042) and STAXI-2 (p=0.026) secondary endpoints. ORY will request an EOP2 meeting with FDA in 2Q24 to discuss Phase 3 trial design in BPD.

- **PORTICO primary endpoints.** ORY reported topline results from its 14-week Phase 2b PORTICO trial evaluating 1.2mg/day vafidemstat in borderline personality disorder (BPD). In short, PORTICO 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.
- **PORTICO secondary endpoints.** However, statistically significant overall disease improvement was achieved on the secondary endpoint of Borderline Evaluation of Severity (BEST) across weeks 8-12 (p=0.042), which 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) 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.
- **PORTICO safety.** Vafidemstat was generally safe and well-tolerated, with the drug's safety profile replicating what has been observed thus far in other trials. Placebo patients with TEAEs somewhat outnumbered vafidemstat patients (65.4% versus 57.5%), and *(continued on page 2)*

- *(continued from page 1)* treatment-related TEAEs were similar between groups (34.0% for vafidemstat versus 31.7% for placebo). TEAEs leading to discontinuation, withdrawal, or interruption were low overall, with most TEAEs being mild (48.1% for vafidemstat versus 57.7% for placebo), or moderate (27.4% for vafidemstat versus 33.7% for placebo), and with low numbers in both groups experiencing a severe AE (4.7% for vafidemstat versus 3.8% for placebo). Most TEAEs recovered/resolved by the end of the trial, and there were no deaths. Although there were eight platelet count reductions for vafidemstat versus 1 for placebo, only 1 of them came anywhere close to mild thrombocytopenia.
- **Next steps.** 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 is the first large (n=210; 27 U.S and European sites), 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 in early 2Q24. 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. PORTICO results will be presented at a psychiatric conference (likely at ASCP) and published in a peer-reviewed journal.
- **Price target revision.** We have moved projected initial revenue for vafidemstat out one year given our expectation that Phase 3 requires some deep analysis prior to planning and that about 800 patients will need to be enrolled across two trials, and as a result, our price target is now €12 from our prior €15.

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 $747 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. 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)

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	2017A	2018A	2019A	2020A	2021A	2022A	1Q23A	2Q23A	3Q23A	4Q23E	2023E	1Q24E	2Q24E	3Q24E	4Q24E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Global iadademstat revenue																	7,653	60,455	121,870	179,719	212,445	222,845
Global vafidemstat revenue																	-	10,395	156,451	332,377	532,622	593,677
Collaboration revenue	20																					
Total revenue	**20**																**7,653**	**70,850**	**278,321**	**512,096**	**745,067**	**816,523**
Cost of revenue																	1,148	9,919	19,643	27,102	32,694	35,271
R&D	6,363	8,489	12,647	13,591	15,118	17,701	4,372	4,264	3,821	3,859	16,316	3,898	3,937	3,976	4,016	15,827	18,992	20,891	21,936	22,155	22,377	22,600
G&A	4,502	2,993	3,176	3,484	5,529	4,771	1,223	1,096	674	809	3,802	817	825	833	842	3,317	5,970	8,956	9,851	10,836	11,378	11,947
Total operating expenses	**10,865**	**11,482**	**15,823**	**17,075**	**20,647**	**22,472**	**5,595**	**5,360**	**4,495**	**4,668**	**20,118**	**4,715**	**4,762**	**4,809**	**4,858**	**19,144**	**26,110**	**39,766**	**51,430**	**60,093**	**66,448**	**69,819**
Operating income	**(10,845)**	**(11,482)**	**(15,823)**	**(17,075)**	**(20,647)**	**(22,472)**	**(5,595)**	**(5,360)**	**(4,495)**	**(4,668)**	**(20,118)**	**(4,715)**	**(4,762)**	**(4,809)**	**(4,858)**	**(19,144)**	**(18,458)**	**31,085**	**226,891**	**452,003**	**678,618**	**746,704**
Other income (net)	5,659	8,143	11,522	11,805	12,510	16,661	4,215	4,054	3,669	2,000	13,938	3,000	3,000	3,000	3,000	12,000						
Net income (pretax)	**(5,186)**	**(3,339)**	**(4,301)**	**(5,269)**	**(8,137)**	**(5,811)**	**(1,380)**	**(1,306)**	**(826)**	**(2,668)**	**(6,180)**	**(1,715)**	**(1,762)**	**(1,809)**	**(1,858)**	**(7,144)**	**(18,458)**	**31,085**	**226,891**	**452,003**	**678,618**	**746,704**
Net financial & tax	1,047	(1,991)	(187)	(1,098)	(2,760)	(1,276)	392	(2,459)	300	(250)	(2,017)	(250)	(250)	(250)	(250)	(1,000)	-	7,771	56,723	113,001	169,655	186,676
Net income	**(6,233)**	**(1,348)**	**(4,114)**	**(4,171)**	**(5,377)**	**(4,535)**	**(1,772)**	**1,153**	**(1,126)**	**(2,418)**	**(4,163)**	**(1,465)**	**(1,512)**	**(1,559)**	**(1,608)**	**(6,144)**	**(18,458)**	**23,313**	**170,168**	**339,002**	**508,964**	**560,028**
EPS basic	**(0.20)**	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.04)**	**(0.07)**	**(0.02)**	**(0.02)**	**(0.02)**	**(0.02)**	**(0.09)**	**(0.26)**	**0.31**	**2.17**	**4.12**	**5.89**	**6.17**
EPS diluted	**(0.20)**	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.04)**	**(0.07)**	**(0.02)**	**(0.02)**	**(0.02)**	**(0.02)**	**(0.09)**	**(0.22)**	**0.26**	**1.84**	**3.52**	**5.06**	**5.34**
Basic shares outstanding	31,711	34,638	41,589	49,235	52,762	53,354	56,190	57,339	58,154	58,212	57,474	66,944	67,614	67,681	67,749	67,497	71,137	74,693	78,428	82,349	86,467	90,790
Diluted shares outstanding	31,711	34,638	41,565	49,235	52,762	53,354	56,190	57,339	58,154	58,212	57,474	66,944	67,614	67,681	67,749	67,497	85,174	88,731	92,465	96,387	100,504	104,827

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 01/08/24	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**346**	**73.15**	**202**	**58.38**
Neutral [N]	**82**	**17.34**	**28**	**34.15**
Sell [S]	**3**	**0.63**	**2**	**66.67**
Under Review [UR]	**40**	**8.46**	**12**	**30.00**

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

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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.

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.

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