EDISON

Oryzon Genomics

Expanding clinical R&D pipeline

Clinical data

Pharma & biotech

Oryzon presented more granular data from Phase I/IIa in acute leukaemia at the American Society of Hematology (ASH) meeting after the positive headline results had been announced earlier. ORY-1001's further development is now in Roche's hands, which also initiated a Phase I trial in a new indication small cell lung cancer (SCLC). Recently Oryzon released preclinical data supporting ORY-2001's potential in multiple sclerosis (MS), which we now include in our valuation. All these developments led to an increase in our Oryzon's valuation to €250m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	15.5	11.3	0.48	0.0	9.4	N/A
12/15	7.2	(0.1)	(0.01)	0.0	N/A	N/A
12/16e	4.8	(4.9)	(0.16)	0.0	N/A	N/A
12/17e	2.8	(6.2)	(0.22)	0.0	N/A	N/A

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

ASH data provide more granularity; SCLC in Phase I

While most of the positive share price-moving ORY-1001 Phase I/IIa data had already been released in the form of an abstract, more details were provided in the poster session at ASH annual meeting on 3 to 6 December 2016. Development of ORY-1001 is now in the hands of Roche, which indicated that a potential path forward in acute leukaemia could be a combination regimen with ORY-1001. Another positive development was the initiation of the Phase I trial in SCLC, which is in line with our expectations.

ORY-2001 for MS is official

Following preclinical data demonstrating proof-of-concept in multiple sclerosis (MS), Oryzon has officially announced that it will pursue this indication alongside Alzheimer's disease (AD) for ORY-2001. Following successful completion of the single ascending dose phase of the Phase I trial with ORY-2001, four ascending doses in the multiple ascending dose phase were already safely tested in healthy volunteers with one more remaining and the trial is on track to deliver safety data in H117. Following this study, Oryzon will be able to run both AD and MS trials in parallel, which will mostly likely depend on prioritization and cash management. A licensing deal is also a possibility, in our view. Huntington's disease (HD) is another target indication, in which Oryzon has expressed interest, but is yet to officially announce this indication as a part of clinical development plan.

Valuation: Increased to €250m or €8.8/share

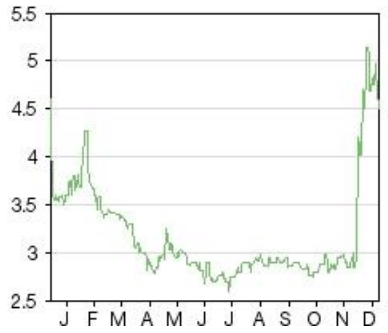
We have increased our Oryzon valuation from €156m or €5.5/share to €250m or €8.8/share following the addition of the MS indication to our valuation, increasing the probability for ORY-1001 in AML to reach the market to 20% and increasing the probability in SCLC to 12%. For the MS indication we project market launch in 2026, with a success probability of 12%, commensurate with an early stage project, and use peak sales of $1.9bn. Roche's evaluation of further ORY-1001 development, ORY-2001's Phase I data and any potential licensing interest from pharma companies are further catalysts for value inflection.

9 December 2016

Price	**€4.51**
Market cap	**€128m**

Net cash (€m) at end of Q316	3.6
Shares in issue	28.5m
Free float	30%
Code	ORY
Primary exchange	Madrid Stock Exchange
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	55.5	56.1	N/A
Rel (local)	52.0	55.4	N/A
52-week high/low		€5.1	€2.6

Business description

Oryzon Genomics is a Spanish biotechnology company focused on developing novel epigenetic compounds. Lead compound ORY-1001 is partnered with Roche, which is responsible for further development in acute leukaemia and SCLC. ORY-2001 has potential for Alzheimer's disease and has entered Phase I. ORY-3001 is a new preclinical asset.

Next events

ORY-2001 Phase I results	H117
News from Roche on ORY-1001 in AML	2017

Analysts

Jonas Peciulis +44 (0)20 3077 5728

Juan Pedro Serrate +44 (0)20 3681 2534

healthcare@edisongroup.com

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ORY-1001 data at ASH

During the poster session at ASH, Oryzon presented more granular data from the positive Phase I/IIa trial. The study included different subsets of relapsed or refractory (RR) acute leukaemia patients treated with ORY-1001, lysine specific demethylase 1 (LSD1) inhibitor. The dose escalation Part 1 (Phase I) included 27 patients treated for 28 days. Part 2 (Phase IIa) was an extension arm with an additional 14 patients with the goal of establishing initial efficacy results and a PK/PD profile.

Interim favourable safety data has already been announced and the final data did not reveal any negative surprises. The most common likely drug-related side effects included low blood platelet count (16.7%), neutropenia (6.7%), fatigue (6.7%), changes in taste (6.7%) and petechiae (6.7%). Our main focus was on initial efficacy signs, which were measured in 14 patients included in the extension arm, of which one dropped out. Since specific subtypes of acute leukaemia are especially susceptible to LSD1 inhibition, the extension arm included patients with mixed lineage leukaemia (MLL; n=6), other MLL gene rearrangement or mutation (n=4) and acute erythroid leukemia (AML M6; n=4). The main findings included:

- Four of six patients with MLL leukaemia showed evidence of blast cell (young, undifferentiated blood cells) differentiation in blood, indicating ORY-1001's ability to induce young rapidly dividing cells (that cause the cancer to spread) to develop into mature cells resembling the normal blood formation process. One MLL patient showed blast clearance from blood.
- There was no significant rise in blast cell count in blood after two cycles of therapy in all four AML M6 patients, indicating the possibility of a stable disease.
- Of the other MLL patients (n = 4), one demonstrated blast differentiation, one progressive disease, one skin disease only (inconclusive) and one patient dropped out.
- In addition to positive findings in blood samples, 23% of patients demonstrated bone marrow responses (3/13 [one MLL patient dropped out]): two M6 patients and one MLL patient.
- Also, a number of pharmacodynamic biomarkers were identified as suitable for monitoring of response to ORY-1001 treatment in certain AML patients.

Although the study was small and the focus was on safety, the efficacy findings can be interpreted as showing potential in acute leukaemia. Notably, impaired differentiation of the leukaemic blasts is at the core of the pathophysiology of the disease. ORY-1001's ability to induce the differentiation of blasts (turn them into normal blood cells) demonstrates it does what it was designed for.

Roche starts SCLC Phase I trial

Roche now has sole responsibility of developing ORY-1001 (Roche's ID RO7051790; also known as RG6016) in preferred indications and recently it initiated the first clinical trial in extensive-stage disease SCLC (ED SCLC). The trial is an open-label, multi-centre study with an estimated 70 ED SCLC patients to be treated with ORY-1001. Safety/toxicity is the primary endpoint, while secondary endpoints will include primary efficacy (overall survival, progression-free survival, objective response) and PK/PD data. The estimated completion date is H219, in line with our original assumption.

When asked about Roche's further steps in leukaemia at the analyst and investor meeting organised by Oryzon on 5 December, Roche's representative explained that it will further analyse the findings in the Phase I/IIa and how these could translate into clinical benefit. Furthermore, current treatments of leukaemia are based on combinations primarily and Roche has already tested ORY-1001 in combination with multiple drugs in preclinical trials. We take this as a confirmation that Roche is interested in progressing ORY-1001's development for leukemia, but likely in an optimal

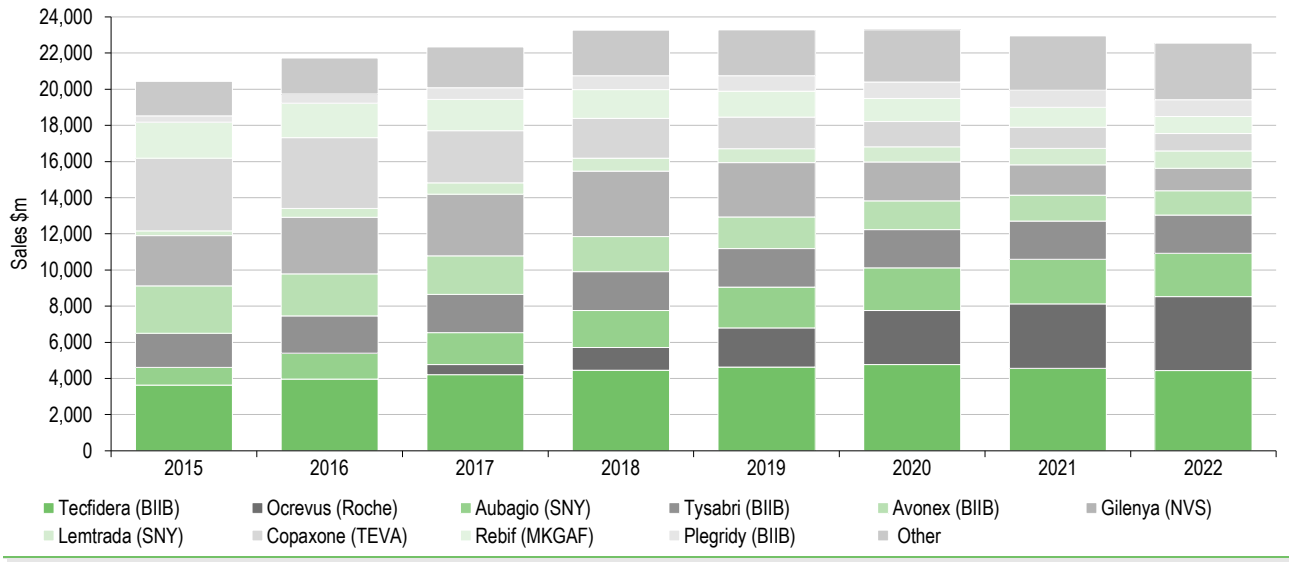
combination to accommodate current clinical practice. The timelines, however, remain unclear at this stage.

MS market potential

Recently Oryzon presented preclinical proof-of-concept of ORY-2001 in MS, which we described in our previous report. MS is an autoimmune disease that attacks and destroys neurons in the central nervous system in variable degrees and causes significant physical disability. The hallmark of MS is episodic relapses that occur months or years apart and affect various anatomic locations. Around 400 thousand people are diagnosed with MS in the US each year and around 85% of those have a relapsing-remitting course of the disease, which is in contrast to the progressive type, when symptoms gradually get worse over time rather than appearing as relapses ('Multiple Sclerosis', Medscape).

Classical management of acute relapses can include systemic corticosteroids, plasma exchange and symptomatic drugs; however, the mainstay of treatment is disease-modifying agents for MS (DMAMS) with the goal of reducing the frequency of relapses and slowing progression. There are a number of DMAMS in the market currently (Exhibit 1) ranging from established to innovative options. The choice of the drug very much depends on circumstances (as opposed to rigorous algorithms) including patient lifestyle, tolerance, adverse effects and the experience of the healthcare provider. Despite the number of available treatment options, MS is still an unmet medical need. If left untreated, more than 30% of patients will develop significant physical disability usually within 20-25 years. Although DMAMS were shown to slow the disability progression within the duration of the trials, long-term effects are still not known. Life expectancy in MS patients is lowered only slightly, but quality of life is heavily affected, with 50-60% patients dying of secondary MS complications such pulmonary or renal causes (Medscape).

Exhibit 1: Top 10+ other multiple sclerosis drug sales worldwide



Source: EvaluatePharma

EvaluatePharma estimates that the MS market will be worth $23bn in 2022, fragmented with no drug significantly outstanding. While ORY-2001 will still need to prove its clinical efficacy, a unique mechanism of action among MS drugs is one differentiating feature. We note that on average an MS drug in the top 10 is expected to generate sales of $1.9bn by 2022.

Valuation

We value Oryzon at €250m or €8.8/share, up from €156m or €5.5/share. The main changes include the addition of the MS indication for ORY-2001, an increase in the success probability from 8% to 12% in SCLC and an increase in the probability in AML to 20%. The latter is slightly more conservative that our standard 30-40% probability for an asset in Phase II, which is justified given that Roche is evaluating the optimal combination for further development. We had already included SCLC in our valuation and make no significant changes to our original R&D assumptions, except for increasing the probability of success from 8% to 12%, which is in line with other Phase I projects in Oryzon's pipeline. The most significant change is the addition of the MS indication using a success probability of 20%. This is higher than other Phase I projects in Oryzon's pipeline and also higher than the industry's average, however, a recent study published by Gasperis-Brigante et al. found that between 1998 and January 2015 cumulative success rates (from Phase I to Phase III) for MS trials are as high as 27% compared to 10% industry's average. We note that according to our calculations a non-risk adjusted NPV for this early stage project is €345m.

MS assumptions

We now include the MS indication in our valuation. Once the currently ongoing Phase I trial with healthy volunteers, ORY-2001 will be ready for Phase II trials with potentially three indications: AD, MS or HD. Oryzon is yet to decide on the latter one, while AD and MS were confirmed to be targeted in Phase II trials. Whether these will run in parallel or sequentially depends on the prioritisation and any partnering interest, in our view. For the time being, we include MS run in parallel with similar R&D assumptions to those we included in our AD model (more details are in our initiation report). Namely, we assume that Oryzon will be able to partner ORY-2001 after Phase II and the partner will cover all development and marketing costs from this point. Before that we include a cost of €20m for the Phase II trial. Our partnering assumptions include a fairly typical deal structure, including an upfront payment, development and sales-related milestones, in addition to royalties on global sales. We assume a total deal value of €426m, which is the average of five licensing deals in MS area over past five years (EvaluatePharma). This includes a €32m upfront payment, while the rest is split for development-related milestones of €131m with the remainder as sales-related and tiered up to 18% royalty rates on global sales. Our revenue model is based on a top-down approach and we use the average sales of top 10 MS drugs of $1.9bn as a benchmark, which is reached seven years after the launch in 2026.

Exhibit 2: Oryzon rNPV valuation

Product	Indication	Launch	Peak sales (US$m)	Value (€m)	Probability (%)	rNPV (€m)	NPV/share (€/share)
ORY-1001	AML	2022	900	246.8	20%	55.9	2.0
ORY-1001	SCLC	2025	635	116.9	12%	20.9	0.7
ORY-2001	AD	2026	4,510	778.1	12%	94.3	3.3
ORY-2001	MS	2026	1,940	344.8	20%	76.8	2.7
Net cash (end-2016)				2.0	100%	2.0	0.1
Valuation				**1,488.6**		**249.9**	**8.8**

Source: Edison Investment Research. Note: *Peak sales are rounded to the nearest US$10m, shown in US$. SCLC = small cell lung cancer; AML = acute myeloid leukaemia; AD = Alzheimer's disease; MS = multiple sclerosis. Net cash includes term deposits.

Financials

We keep our financial forecasts unchanged following our last update after the Q316 results. Although we have included Phase II funding costs in our model starting from 2018, this will depend on Oryzon's strategy and whether it will invest in this stage or will seek to partner. We forecast a

comfortable 2016 year-end cash position of €29.5m (cash and term deposits classed as other current assets) and net cash of €2.0m (including term deposits). In total, during the past 12-18 months Oryzon has managed to attract more than €32m in new funding from various sources including debt at attractive commercial terms. In addition, the company has a history of efficient use of available public grants, which could provide further non-dilutive financing.

Exhibit 3: Financial summary

€000s	2012	2013	2014	2015	2016e	2017e
Year end 31 December	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS						
Revenue	4,353	2,360	15,536	7,185	4,835	2,797
Cost of Sales	0	0	0	0	0	0
Gross Profit	4,353	2,360	15,536	7,185	4,835	2,797
Research and development	(876)	(873)	(1,108)	(3,191)	(4,783)	(3,774)
EBITDA	856	(94)	11,659	688	(3,780)	(5,260)
Operating Profit (before amort. and except.)	559	(370)	11,398	448	(3,898)	(5,378)
Intangible Amortisation	(455)	(657)	(657)	(657)	(817)	(902)
Exceptionals	0	(186)	(4,617)	(24)	0	0
Other	0	0	0	0	0	0
Operating Profit	104	(1,213)	6,124	(233)	(4,715)	(6,281)
Exceptionals	(220)	0	667	(169)	0	0
Net Interest	(582)	(672)	(52)	(553)	(993)	(843)
Profit Before Tax (norm)	(23)	(1,042)	11,346	(105)	(4,891)	(6,221)
Profit Before Tax (reported)	(698)	(1,885)	6,739	(955)	(5,708)	(7,124)
Tax	90	89	(88)	(37)	396	0
Profit After Tax (norm)	67	(953)	11,258	(142)	(4,496)	(6,221)
Profit After Tax (reported)	(608)	(1,796)	6,651	(992)	(5,312)	(7,124)
Average Number of Shares Outstanding (m)	23.0	23.0	23.3	24.5	28.5	28.5
EPS - normalised (€)	0.00	(0.04)	0.48	(0.01)	(0.16)	(0.22)
EPS - (reported) (€)	(0.03)	(0.08)	0.29	(0.04)	(0.19)	(0.25)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	19.7	N/A	75.0	9.6	N/A	N/A
Operating Margin (before GW and except.) (%)	12.8	N/A	73.4	6.2	N/A	N/A
BALANCE SHEET						
Fixed Assets	18,765	20,128	16,059	18,050	21,170	22,946
Intangible Assets	15,062	15,825	12,928	15,188	18,396	20,291
Tangible Assets	1,485	1,159	981	854	736	618
Investments	2,217	3,145	2,150	2,008	2,037	2,037
Current Assets	3,808	2,851	9,999	22,681	30,848	19,810
Stocks	19	2	9	4	11	8
Debtors	977	663	704	940	1,341	1,140
Cash	2,302	2,033	3,633	19,467	23,875	13,040
Other	510	153	5,654	2,270	5,621**	5,621**
Current Liabilities	(2,283)	(2,724)	(3,969)	(5,296)	(4,552)	(4,102)
Creditors	(765)	(1,005)	(1,299)	(2,401)	(1,432)	(1,737)
Short term borrowings	(1,519)	(1,719)	(2,670)	(2,895)	(3,120)	(2,365)
Long Term Liabilities	(9,949)	(11,251)	(8,196)	(7,841)	(26,952)	(25,882)
Long term borrowings	(7,963)	(9,117)	(6,420)	(6,177)	(24,377)	(23,307)
Other long term liabilities	(1,986)	(2,134)	(1,776)	(1,664)	(2,575)	(2,575)
Net Assets	10,341	9,004	13,893	27,594	20,513	12,772
CASH FLOW						
Operating Cash Flow	1,420	(113)	12,178	1,076	(9,275)	(5,595)
Net Interest	(582)	(672)	(52)	(553)	(993)	(843)
Tax	0	0	0	0	396	0
Capex	0	0	0	0	0	0
Acquisitions/disposals	107	(677)	798	0	0	0
Financing	0	0	0	14,725	0	0
Other	(8,125)	(161)	(9,579)	605	(3,920)*	(2,797)*
Dividends	0	0	0	0	0	0
Net Cash Flow	(7,180)	(1,623)	3,345	15,853	(13,792)	(9,234)
Opening net debt/(cash)	0	7,180	8,803	5,458	(10,395)	3,622
HP finance leases initiated	0	0	0	0	0	0
Other	0	0	0	0	(225)	225
Closing net debt/(cash)	7,180	8,803	5,458	(10,395)	3,622	12,632

Source: Edison Investment Research, Oryzon Genomics accounts. Note: Oryzon reports in Spanish GAAP. *Represents cash outflows related to development costs that were capitalised. **Term deposits classed as other current assets.

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 9258 1161
Level 25, Aurora Place
88 Phillip St, Sydney
NSW 2000, Australia

Wellington +64 (0)48 948 555
Level 15, 171 Featherston St
Wellington 6011
New Zealand