ROTH Capital Partners

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COMPANY NOTE | EQUITY RESEARCH | April 30, 2018

Healthcare: Biotechnology

Oryzon Genomics SA | ORY.SM - €2.38 - MADRID | *Buy*

Initiation of Coverage

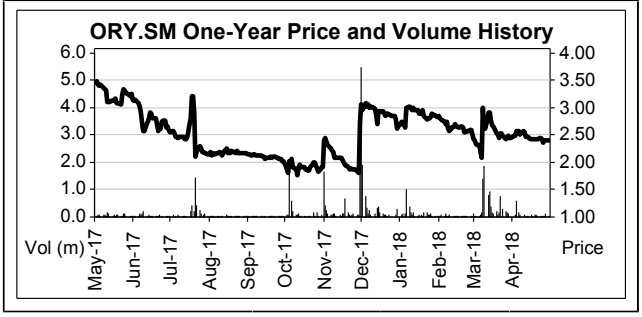
Stock Data	
52-Week Low - High	€1.75 - €3.60
Shares Out. (mil)	34.16
Mkt. Cap.(mil)	€81.3
3-Mo. Avg. Vol.	161,653
12-Mo.Price Target	€15.00
Cash (mil)	€35.1
Tot. Debt (mil)	€0.0

EPS $

Yr Dec	—2017—	—2018E—	—2019E—
		Curr	Curr
1Q	-	(0.05)E	-
2Q	-	(0.05)E	-
3Q	-	(0.06)E	-
4Q	-	(0.06)E	-
YEAR	(0.20)A	(0.22)E	(0.26)E
P/E	NM	NM	NM

Revenue ($ millions)

Yr Dec	—2017—	—2018E—	—2019E—
		Curr	Curr
1Q	-	0.0E	-
2Q	-	0.0E	-
3Q	-	0.0E	-
4Q	-	0.0E	-
YEAR	0.0A	0.0E	0.0E



ORY.SM: New Age Epigenetics; Initiating with Buy and €15 PT

Running with the bulls. In our view, the Spanish biotech Oryzon is the most diversified epigenetics play in the public market. We believe that the key to realizing the therapeutic potential of epigenetics is diversification outside of late-stage oncology and into indications where the disease can be reprogrammed via chronic treatment. We then recommend Oryzon not only as a fundamental play in epigenetics, but also as a near-to-medium term value play when considering its relatively low profile on the Madrid Exchange despite its wide clinical pipeline (AML, SCLC, AD, MS).

Why we like Oryzon's oncology program. Oryzon's therapeutic target, the lysine-specific demethylase 1 (LSD1), has one of the widest publication footprints in epigenetics (second to EZH2 and BRD4). Yet, in our view big pharma is still incapable of appreciating epigenetic agents, and the recent return of the LSD1 inhibitor ORY-1001 from Roche to Oryzon may be the best thing to happen to this agent. We believe that the Phase 1 data generated by former-partner Roche are promising, and we applaud Oryzon's clinical reboot in AML and SCLC. In our view, ORY-1001's journey through pharma and back is similar to that of the EZH2 inhibitor tazemetostat from Epizyme (EPZM-Buy), and Oryzon's speed in repositioning and executing on its re-acquired asset could unlock value similar to what we have seen with tazemetostat.

Why we like Oryzon's neuro program. Regarding past and present efforts around neurotransmitter and amyloid/tau targeting in Alzheimer's disease (AD), we stand by the adage: "the definition of insanity is doing the same thing over and over again, but expecting different results." Instead, we guide investors to review new approaches and new targets. We see good rationale for an epigenetic approach to neurotherapeutics, especially in AD, supported by basic science, clinical findings, and recent investment. Unlike older epigenetic agents, Oryzon's ORY-2001 (LSD1/MAO-B inhibitor) is brain-penetrant and with a clean safety record (106-patient Phase 1 complete). Meanwhile, two exploratory Phase 2 studies are now ongoing: a 26-week 90-patient study in mild/moderate AD, and a 36-week 24-patient study in multiple sclerosis (MS). We believe that any positive preliminary findings from either study in 1Q19 would be transformational to Oryzon's value.

Our thoughts on value: Olé! We base our valuation on ORY-1001 in AML and ORY-2001 in AD, and view other clinical programs (SCLC, MS) and the preclinical pipeline as upside. We project €450M peak WW sales in AML (€4/share via DCF/NPV), and €4.7B peak WW sales in AD (€10/share via DCF/NPV). Importantly, when calculating their value/share we discount both programs heavily using empirical probabilities of success in their respective stages and indications (20% in AML, 5% in AD). Overall, we view Oryzon's current value as attractive when considering the risk/reward of clinical readouts in the next 12 months, or when viewing it fundamentally as a pure and diversified epigenetics play.

Important Disclosures & Regulation AC Certification(s) are located on page 61 to 62 of this report.

Investment summary 1/3: The company in a nutshell

Oryzon is a clinical stage biotech company focused on the development of **epigenetic therapeutics** across multiple indications. Oryzon's clinical portfolio includes:

(a) **ORY-1001**, an LSD1 inhibitor, which has completed a Phase 1 study in acute leukemia, and is currently **advancing into Phase 1/2** studies in **acute myelogenous leukemia** (AML) and **small cell lung cancer** (SCLC).

(b) **ORY-2001**, a dual LSD1 and MAO-B inhibitor, which has completed a large Phase 1 study in healthy volunteers, and is **currently in Phase 2a** studies in **Alzheimer's disease** (AD) and **multiple sclerosis** (MS).

Oryzon's **preclinical** portfolio includes **ORY-3001**, a selective LSD1 inhibitor currently being evaluated in murine and simian models of **sickle cell disease** (SCD)

Program	Target	Indication	Stage
ORY-1001	LSD1	Acute Leukemia (AML)	Phase 2A
ORY-1001	LSD1	Small Cell Lung Cancer (SCLC)	Phase 1
ORY-2001	LSD1, MAO-B	Alzheimer's Disease (AD)	Phase 2A
ORY-2001	LSD1, MAO-B	Multiple Sclerosis (MS)	Phase 2A
ORY-3001	LSD1	Sickle Cell Disease (SCD)	Pre-IND

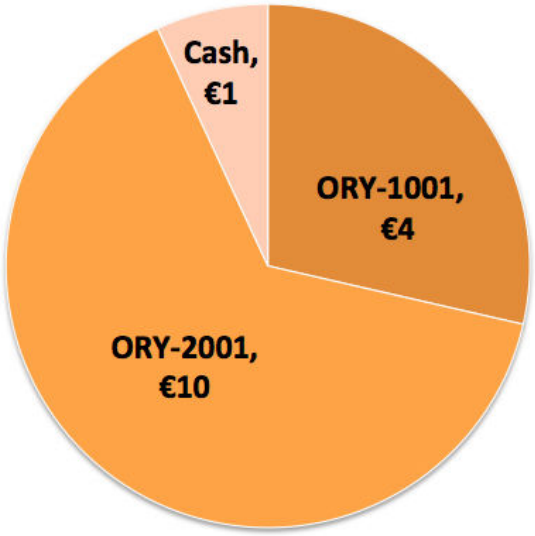
Source: www.oryzon.com and ROTH Capital Partners research.

Investment summary 2/3: Quantifying the upside

We base our valuation of Oryzon on **ORY-1001 in AML** and **ORY-2001 in AD**, and view other clinical programs (SCLC, MS) and the preclinical pipeline as upside.

- We project €450M in peak WW sales from ORY-1001 in AML, translating to **€4/share** via DCF/NPV.
- We project €4.7B in peak WW sales from ORY-2001 in AD, translating to **€10/share** via DCF/NPV.

Our ORY €15/share price target



Source: ROTH Capital Partners research.

When calculating value/share, we **discount both programs heavily** using empirical probabilities of success in their respective stages and indications (20% for a Phase 1/2 asset in AML; 5% for a Phase 1/2 asset in neurodegenerative diseases).

Overall, **we view Oryzon's current value as attractive** when considering:

- the quality of the oncology data in hand;
- the valuation and take-out premium of pure-play epigenetic assets in the past;
- the differentiated approach to neurodegenerative disease;
- the risk/reward spread of multiple clinical readouts in the next 12 months.

Investment summary 3/3: Value drivers during the next 12 months

Updates from Oryzon: With two clinical programs in oncology (AML, SCLC) and two in neurology (AD, MS) under way in 2018, we expect preliminary data from all in early 2019. In addition, we expect the sickle cell program to continue advancing towards the clinic. In our view, any positive incrementals from the neuro programs (positive exploratory findings) are likely to have a disproportional positive effect on value.

Updates from the field: On the oncology front, we advise keeping an eye on LSD1 inhibitors from GSK (GSK-NC), Incyte (INCY-NC), and Imago (private), which are crowded in acute leukemia, leaving SCLC relatively clear for Oryzon. On the neuro front, we believe that Oryzon's epigenetic approach is sufficiently differentiated from other programs in AD, and is unlikely to be impacted by their news flow. We do however advise keeping an eye on any AD data from MAO-B targeting (rasagiline) and HDAC targeting (Rodin Therapeutics), which may indirectly validate functional components of ORY-2001's action in AD.

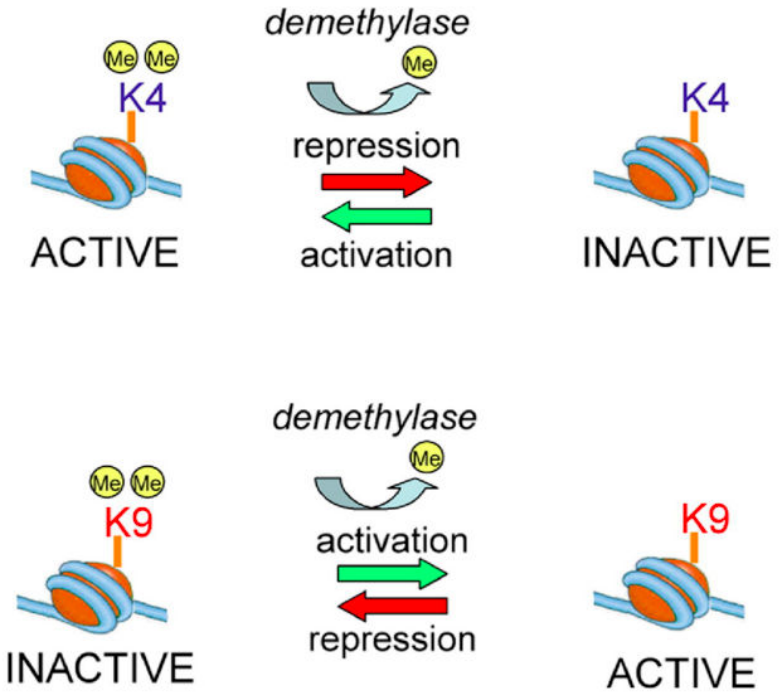
Updates from regulators: Given recent effort to modernize drug approval, we advice keeping an eye on the FDA's next move around its recent draft guidance on AD, which in our view is likely to make the development of biomarker-guided targeted agents faster and easier.

Timing	Program	Event
1H18	ORY-1001	Started Phase 1 in SCLC
1H18	ORY-1001	Started Phase 2 in AML
1H18	ORY-2001	Started Phase 2A in AD
1H18	ORY-2001	Started Phase 2A in MS
1Q19	ORY-1001	Preliminary data in AML, SCLC
1Q19	ORY-2001	Preliminary data in AD, MS

Source: www.oryzon.com and ROTH Capital Partners research.

Chapter 1: ORY-1001 in Oncology

LSD1: What does it do?



- **Chromatin targets:**
  Histone 3 Lysine 4 (H3K4) and Lysine 9 (H3K9)

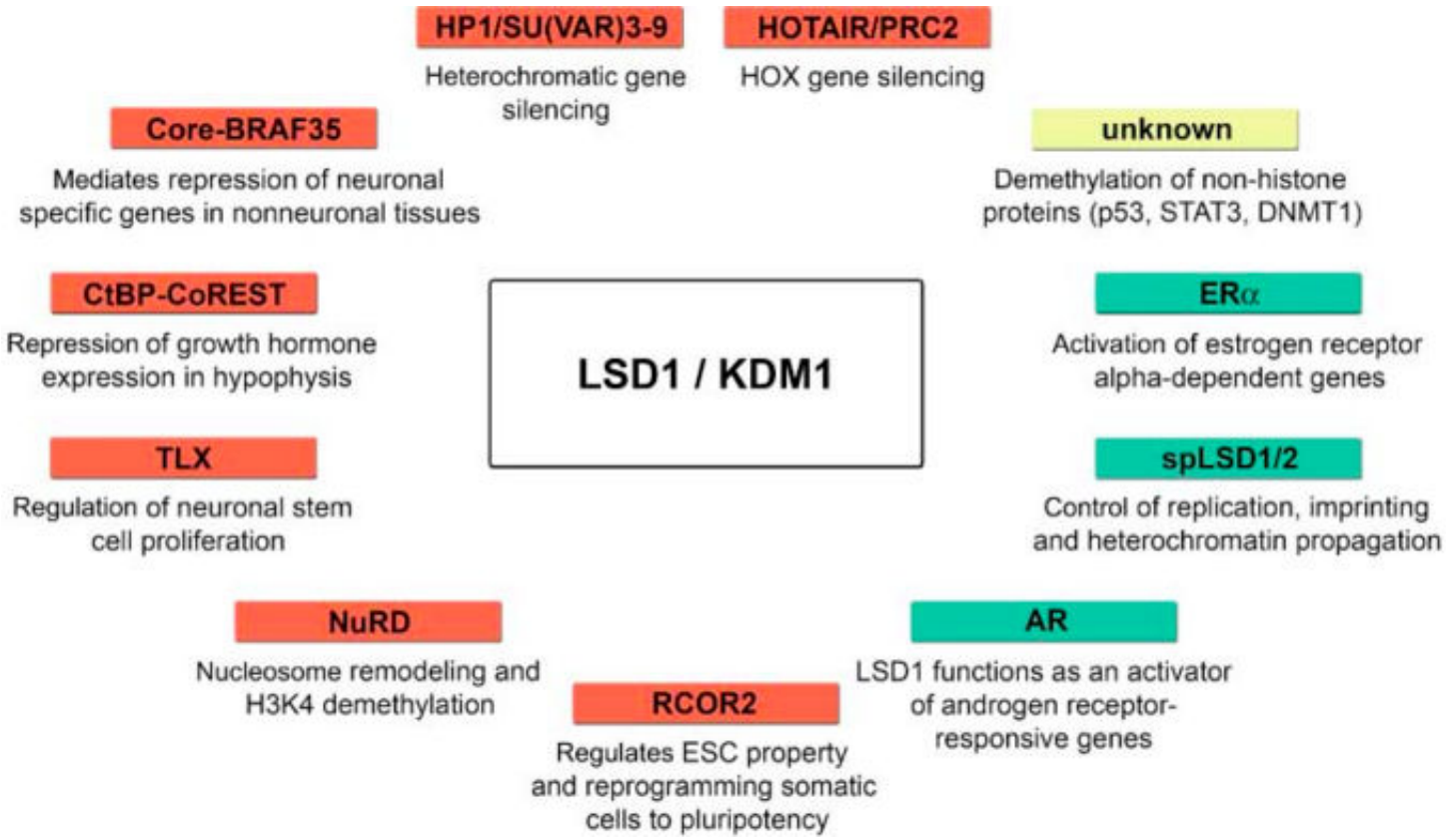
- **Chemical function:**
  Catalyzes the removal of one or two methyl groups from the histone tail lysine residue.

- **Biologic function:**
  Lysine demethylation aids the transition of chromatin from active (transcription on) to inactive (transcription off), or vice versa, depending on which one of two target lysines is demethylated.

Source: Cell. 2005. Volume 122, Issue 5, p654–658.

LSD1: Why does it matter?

Key **physiologic** roles: stem cell maintenance and differentiation.
Key **oncogenic** roles: compromised differentiation, enhanced cell motility, and metabolic reprogramming.



Source: Biol Chem. 2013 Aug;394(8):1019-28.

Targeting LSD1 selectively with ORY-1001: Why AML?

- In AML patients, recurring somatic mutations in genes coding for epigenetic proteins are responsible for pre-leukemic alterations in experimental models.
- Chromosomal translocations, the first oncogenic insult in most AMLs, are directly or indirectly responsible for epigenetic dysfunctions.
- Expression of LSD1 is elevated across multiple cell lines and tumor types and is correlated directly with worse prognosis.
- AML cell lines harboring MLL and AML-ETO translocations have shown high sensitivity to LSD1 inhibitors.
- Knockdown of LSD1 provokes de-repression of TAL1 target genes in T-ALL Jurkat cells and blocks activation of Notch targets in Notch-dependent T-ALL.
- LSD1 disruption in combination with ATRA has been proposed for promyelocytic leukemia (APL).

Source:
Nat Rev Cancer 12, 599–612.
Cancer Res. 76, 1975–1988.
Blood. 2018 Apr 12;131(15):1730-1742
Cancer Cell. 2018. 33, 495–511.

Drugging AML: Our take on development and regulatory trends

Acute myelogenous leukemia (AML) is the most common acute leukemia in adults, with an annual incidence of 20K+ in the U.S. and dismal survival (~25% in 5 years).

We see the following trends taking hold in AML therapeutics:

- Increased sophistication in quantifying **surrogate clinical endpoints** typically used in early trials (e.g. MRD), allowing for better drug candidates now being selected to advance to further trials.
  - ✓ **Promising for an epigenetic agent**
- A shift from clinical or phenotypic definition of disease subsets to genetic or biomarker-related **segmentation**, which may be able to overcome patient heterogeneity in trials.
  - ✓ **Promising for an epigenetic agent**
- A shift from genetically- and cellularly-agnostic therapies (chemo and cytotoxics) to **targeted** agents (FLT3, IDH, RAR, etc.). In other words, a shift from cytoreduction (targets disease burden) to clone elimination and/or blast **differentiation** (targeting or **reprogramming** the disease itself).
  - ✓ **Promising for an epigenetic agent**
- A beginning shift in **regulatory flexibility** toward certain cancers more than others, AML being among them (four approvals in last year, two of them surprisingly not on a survival endpoint).
  - ✓ **Promising for an epigenetic agent**

ORY-1001's affair with Roche: Lost time, but not lost opportunity

- With the exception of GSK (which in our view understands and appreciates epigenetics), we believe that big pharma has empirically not known what to do with epigenetic programs in oncology, whether in internal or competitive context. In the last decade, we have seen several examples of big pharma partnering of epigenetic programs when they are thematically hot, only to later drop them prior to full proof-of-concept or proof-of-value.

Brief chronology of ORY-1001 events:

- **2014**: **Roche** and Oryzon enter demethylase $500M+ collaboration deal; ORY-1001 is the lead program.
- **2016**: Roche presents **Phase 1** data in AML at ASH, and announces the start of a parallel SCLC study.
- **2017**: Collaboration is terminated, **rights revert back** to Oryzon.
- **2018**: **Oryzon ramps up** ORY-1001 program into parallel oncology indications.

- In our view, Roche's licensing of ORY-1001 was a **premature BD move**, in part driven by the urgent innovation mandate of Roche's Translational Clinical Research Center (TCRC), and **not integrated** with the clinical needs and ability of the wider organization. We believe that the asset bounce back to Oryzon may now be viewed as lost time, but not as lost value or opportunity.

Source: www.oryzon.com

ORY-1001: Roche bounce-back reminds us of tazemetostat

- As a reminder, **tazemetostat** is an inhibitor of the histone methyltrasferase **EZH2**, in development by Epizyme (EZPM-Buy). It is the most clinically advanced **epigenetic** agent at this time (in our view, widest clinical footprint, and latest development stage).

Brief chronology of tazemetostat events:

- **2011**: **Eisai** and Epizyme enter EZH2 $200M+ deal; tazemetostat is lead program.
- **2014**: Eisai presents **Phase 1** data in NHL and genetically-defined solid tumors.
- **2015**: Collaboration is terminated, **rights revert back** to Epizyme.
- **2015-2018**: **Epizyme ramps up** tazemetostat program into multiple indications; in our view, tazemetostat is the sole driver of EPZM's present $1.1B valuation, while data generated in NHL (FL) and solid tumors (INI-) may support NDA within next year.

- In our view, **ORY-1001's journey** through pharma and back is **similar to tazemetostat's**. In perspective, we believe that being bounced back from Eisai to Epizyme (EPZM-Buy) was the best thing to happen to tazemetostat, and to Epizyme's valuation.

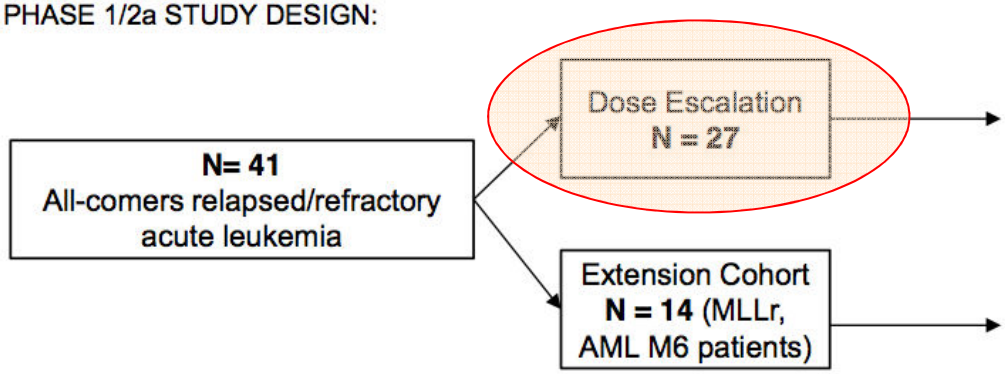
- Based on our view of epigenetics, we believe that both targets (EZH2 and LSD1) and both drugs (tazemetostat and ORY-1001) have **similar potential across oncology**. Oryzon's ability to now execute on its re-acquired ORY-1001 program could unlock value similar to what we have seen with tazemetostat.

Source: Epizyme SEC filings.

ORY-1001 in R/R AML: Our thoughts on Roche's dose escalation cohort

- ORY-1001 PO QD in a 28-day cycle (5d ON / 2d OFF x 4wk).
  - We would have opted for a different dosing layout to avoid 2 days off for an epigenetic therapy.
- 26 R/R AML + 1 R/R ALL, overall mean age 66.5 (range 40-81).
  - Average age for AML, good patient cohort (remember that age is best and strongest prognostic).
- 20 completed cycle 1, 9 started cycle 2, 3 completed cycle 2, 3 started and completed cycle 3.
  - We are not surprised by these ratios in R/R AML, but we would have designed a faster step up / escalation, to maximize exposure and POC data.
- Most frequent AE was thrombocytopenia (7 events, 5 subjects).
  - Standard finding in AML protocols, often secondary to disease itself.
- 22 experienced 32 SAEs of which two (Cohort 8 - 220 µg/m2/d) were possibly related to ORY-1001 and considered DLTs: Gr5 lobar pneumonia and Gr3 febrile neutropenia (in combination with Gr2 fatigue and Gr2 erythema multiforme).
  - Both DTLs sound like standard primary disease exacerbations to us; we are not concerned about the drug's tox, and wonder if 140mg may be too low for RP2D.
- 1 CRi and 5 cases of suggestive clinical response at cohorts 3, 5, 6 and 7.
  - In our view, encouraging for a slow dose escalation with limited cycle exposure.

PHASE 1/2a STUDY DESIGN:



ORY-1001 Dose Escalation Cohorts:

Cohort	Dose
Cohort 1	5 ug/m²/d
Cohort 2	15 ug/m²/d
Cohort 3	30 ug/m²/d
Cohort 4	45 ug/m²/d
Cohort 5	60 ug/m²/d
Cohort 6	80 ug/m²/d
Cohort 7	140 ug/m²/d
Cohort 8	220 ug/m²/d

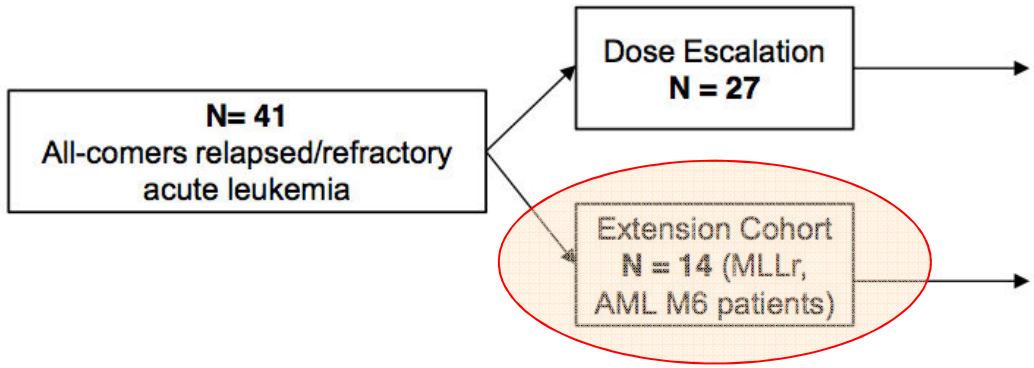
ORY-1001 dose: 140 µg/m²/d

Source: Blood 2016 128:4060.

ORY-1001 in R/R AML: Our thoughts on Roche's expansion cohort

- 14 patients with R/R AML (10 MLL-translocated; 4 acute erythroleukemia/M6) mean age 57 (range 30-78).
  - We would have focused on all-comers, and then tried to identify a genetic or biomarker carve-out retrospectively.
- 8/27 SAEs related to treatment, including differentiation syndrome in two patients.
  - In our view, this is the most important finding of the whole study: differentiation syndrome confirms to us that this is acting epigenetically, and can differentiate leukemic blasts in a clinically meaningful way. After this, in our view, it is only a matter of finding the exact population and background therapy (if any).
- 5/14 (36%) objective responses: 2/14 SDs in with t(9;11) and 3/14 PRs (1 MLL after 3 cycles, and 2 M6).
  - In our view, this is very good for a Phase 1 with a non-debulking agent, especially when considering our criticism of the dosing scheme and homogenous cohort.
- Morphologic blast differentiation in blood and/or BM in 9/14 (5 MLL and 4 M6).
  - In line with the differentiation syndrome, supports basic MoA and rest of the clinical data. In our view, this is very good; this is where the AML story will be built upon.

PHASE 1/2a STUDY DESIGN:



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ORY-1001 dose: 140 µg/m²/d

Source: Blood 2016 128:4060.

ORY-1001: What do we think of the oncology data in hand so far?

- We like the Phase 1 data: based on what we can see, **ORY-1001 looks like an epigenetic agent**.
- In our view, there is enough Phase 1 activity to convince us that the agent **should move forward**. Importantly, we see evidence of all the activity that we would want to see from an epigenetic agent:
  - Blast **differentiation**, both cellular and clinical, peaking with differentiation syndrome from monotherapy.
  - Some **clinical responses** across the spectrum (CRs, PRs, and SDs, reinforcing that responses are not flukes).
  - Only tox paralleling the myelosuppression of the disease itself, which again is mechanistically in line with an epigenetic intervention, and makes us comfortable the agent overall.
- In our view, the **tox profile is good**, especially since we see no major flags from updosing in an AML cohort, which is just about one of the sickest oncology cohorts to take a chance with an epigenetic agent (safety signals would appear first in the marrow, which in an AML patient is suppressed to begin with). This **bodes well for the advance of ORY-1001 in combination and in other oncology indications**, especially in solid tumors, in our opinion.
- Overall, since ORY-1001 looks like a classic epigenetic agent clinically, then we believe that the optimal positioning in oncology should involve **chronic dosing or as long-term as possible** (further up from last line, closer to front line), and/or **in combination with other targeted non-cytotoxic agents**, which Oryzon has already shown synergies with.

ORY-1001: The future in AML is in combos of targeted agents

What does Oryzon's preclinical data suggest about ORY-1001 combo synergies in AML?

Tier 1 synergy:

- **ATRA (retinoid derivative)**
  - Key standard in APL, with high cure rates. In our view, no opportunity for combo.
  - However, a more selective ratinoid, SY-1425 from Syros (SYRS-Neutral) is being tested in AML: monotherapy data was underwhelming, combo being explored (SY-1425 MoA compatible with epigenetic combo, in our view).

- **Ara-C (nucleoside analogue)**
  - Low dose Ara-C (LDAC) is standard of choice for unfit AML patients ex-US (in our view, better than HMAs).
  - Response bar has been set by venetoclax combo, currently in Phase 3.

- **Quizartinib (FLT3 inhibitor)**
  - Currently in Phase 3 in AML (identical design/positioning as the approved midostaurin, but study is not head-to-head with midostaurin); we expect a win and approval.
  - Key goal for FLT3 inhibitors will be option for maintenance therapy (midostaurin did not receive a maintenance claim in label); maintenance therapy is an ideal position for an epigenetic combo.

Source: Cancer Cell 33, 495–511, March 12, 2018

ORY-1001: The future in AML is in combos of targeted agents

What does Oryzon's preclinical data suggest about ORY-1001 combo synergies in AML?

Tier 2 synergy:

- **Azacitidine / Decitabine (DNMT1 inhibitors; HMAs)**
  - Key standard in AML patients unfit for induction therapy.
  - Most experimental agents able to improve on HMA response rate as add-ons.
  - Response bar has been set by venetoclax combo, currently in Phase 3 (response 70-80%).

- **SAHA (HDAC inhibitor, tool compound)**
  - In our view, the most interesting potential combo, mechanistically.
  - Previously, HDACs have not amounted to much in oncology (outside of CTCL/PTCL), due to non-specific activity and narrow therapeutic window. However, combo with another epigenetic agent could tackle prior challenges.

- **ABT 737 (BCL2 inhibitor)**
  - Interestingly, the BCL2 target synergy extended to both myeloid and lymphoid cell lines.
  - Overall, we view this a potential high-value but low probability combo, given how crowded and competitive the arena of venetoclax combos is at the moment. However, we highlight that there may be considerably more opportunity for new BCL2 combos in myeloid rather than lymphoid diseases.

Source: Cancer Cell 33, 495–511, March 12, 2018

LSD1 in SCLS: GSK vs. Roche/Oryzon

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers and is an extremely aggressive tumor with a high rate of recurrence.

Roche initiated a study of ORY-1001 in SCLC prior to termination of the deal with Oryzon in 2017.

GSK had already started a study of its LSD1 inhibitor in SCLC two years prior:
NCT02034123: Investigation of GSK2879552 in Subjects With Relapsed/Refractory SCLC

However, now in 2018, the GSK study appears discontinued, opening space for ORY-1001.

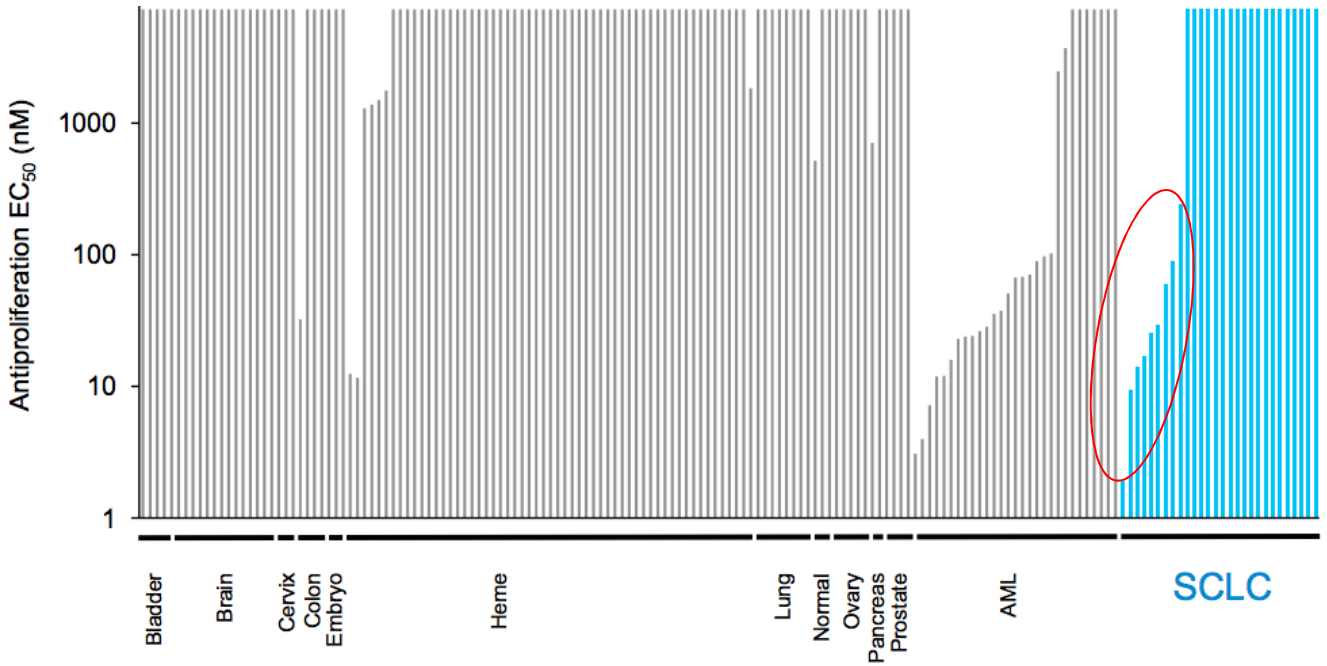
ClinicalTrials.gov Identifier: NCT02034123

Recruitment Status : Terminated (The risk benefit in relapsed refractory SCLC does not favor continuation of the study)
First Posted : January 13, 2014
Last Update Posted : April 5, 2018

Source: clinicaltrials.gov

LSD1 in SCLS: Was GSK flying blind?

While the reason for the discontinuation of GSK's program in SCLC has not been disclosed, we speculated based on preclinical data of that agent: the anti-tumor activity of the agent **was weaker in SCLC than in AML** (see figure), and showed **clustering of effect**. This suggest to us that a predictive biomarker may be necessary for the clinical success of LSD1 targeting in SCLC. GSK's preclinical work had identified DNA hypomethylation as a potential biomarker for sensitivity, but we do not know if this was applied in the study.



Source: Cancer Cell 28, 57–69, July 13, 2015

LSD1 in SCLS: Oryzon to pick up where Roche left off, with lessons from GSK

Preclinical SCLC data from ORY-1001 appears in line with our conclusions from published literature on the GSK agent: there is segregation of response.

- In a xenograft model, combination of ORY-1001 with SOC improves potency and duration of response.
- In a PDX model, 6/10 mice treated with ORY-1001 did not show relapse after 300 days.

Overall, we believe that it should be possible to tackle SCLC with an LSD1 inhibitor, with two caveats:

- In combination therapy (etop/carbo?)
- With an effective patient pre-selection strategy (DNA hypomethylation?)

Oryzon plans to pick up the SCLC program where Roche left off: Phase 1/2 start anticipated in 1H18, using patient stratification via biomarkers.

LSD1 in oncology: Competitor #1 to watch = GSK

GSK may have given up in SCLC, but appears to still be charging ahead in hem/onc: the original Phase 1 monotherapy program in R/R AML, seems to have recently spawned a Phase 1/2 combo study in high-risk MDS.

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	37 participants
Allocation:	Non-Randomized
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of **GSK2879552** Given Orally in Subjects With Relapsed/Refractory Acute Myeloid Leukemia
Actual Study Start Date :	August 27, 2014
Estimated Primary Completion Date :	February 15, 2019
Estimated Study Completion Date :	February 15, 2019

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	74 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase I/II, Open-label, 2 Arm Study to Investigate the Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics of **GSK2879552** Administered Alone or in Combination With Azacitidine, in Adult Subjects With IPSS-R High and Very High Risk Myelodysplastic Syndromes (MDS) Previously Treated With Hypomethylating Agents (HMA)
Actual Study Start Date :	July 31, 2017
Estimated Primary Completion Date :	May 15, 2019
Estimated Study Completion Date :	May 15, 2019

Source: clinicaltrials.gov

LSD1 in oncology: Competitor #2 to watch = Incyte

Incyte's (INCY-NC) LSD1 inhibitor INCB059872 is positioned in an oncology basket study (competitive) and in sickle cell disease (orthogonal).

We believe that Incyte is committed to epigenetic development, and to that extent, its LSD1 program should be watched (also watch its BRD program).

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	180 participants
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies
Study Start Date :	May 2016
Estimated Primary Completion Date :	March 2019
Estimated Study Completion Date :	March 2020

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	30 participants
Allocation:	Non-Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 1 Open-Label, Dose-Escalation Study to Evaluate Safety, Pharmacokinetic, and Biological Activity of INCB059872 in Subjects With Sickle Cell Disease
Actual Study Start Date :	April 27, 2017
Estimated Primary Completion Date :	September 2018
Estimated Study Completion Date :	September 2018

Source: clinicaltrials.gov

LSD1 in oncology: Competitor #3 to watch = Imago

Imago's (private; Clarus- & Frazier-backed) LSD1 inhibitor IMG-7289 has been around for a few years, and has been moving relatively slowly.

However, it appears to still be moving forward in AML/MDS (competitive) and in myelofibrosis (orthogonal).

Note that the AML/MDS study is in combo with ATRA, which has shown preclinical synergy with LSD1 even in the hands of Oryzon.

February 1, 2018

Imago BioSciences Receives FDA Approval of IND Application for the Treatment of Myeloid Malignancies

September 19, 2017

Imago BioSciences Doses First Patients in Phase 1/2 Study of IMG-7289 in Myelofibrosis

July 18, 2017

Imago BioSciences Doses first Patients in the Phase 2a Portion of the Study of IMG-7289 in Acute Myeloid Leukemia and Myelodysplastic Syndrome

November 8, 2016

Imago BioSciences Enrolls First Patients in Phase 1/2 Study of IMG-7289 in Acute Myeloid Leukemia and Myelodysplastic Syndrome

December 7, 2015

Imago BioSciences Announces Preclinical Data on LSD1 Inhibitor at Annual Meeting of the American Society of Hematology (ASH)

Source: imagobio.com

LSD1 in oncology: Competitor #4 to watch = Salarius

Salarius (private) LSD1 inhibitor seclidemstat is further behind all other players, but unlike the others it is a reversible inhibitor (it binds at the active site rather than at FAD).

This suggests lower tox / wider therapeutic window. We look forward to initial PK data, since continuous target coverage is essential in epigenetics (as we learned from GSK's now defunct EZH2 program).

We like Salarius' orthogonal pilot positioning in Ewing's sarcoma (good MoA rationale, and potential clinical & regulatory slack), with further optionality in prostate and breast.

Program	Discovery	Lead Opt	Preclinical	Phase 1
LSD1 Demethylase				
Seclidemstat Ewing				2018
Seclidemstat Prostate				2018
Seclidemstat Breast & Ovarian				2018
Second Generation			2019	
Target #2		2019		

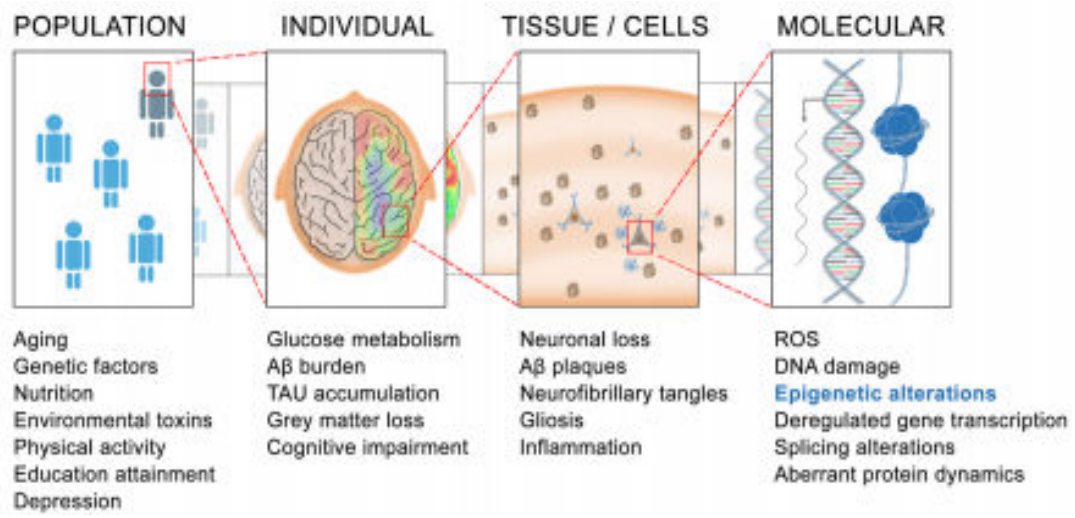
Source: salariuspharma.com

Chapter 2: ORY-2001 in Alzheimer's Disease

Therapeutic targets in Alzheimer's disease, in perspective

According to the 2017 clinical trial report of the Alzheimer Drug Discovery Foundation, AD therapeutics remains disproportionally occupied by approaches which have only been associated with failures previously (200 failures).

- In total, 126 active clinical trials: 33 in Phase 1, 68 in Phase 2, 25 in Phase 3.
- Mechanistic focus: misfolded proteins (32%), neurotransmitters (18%), mitochondrial proteins (11%).

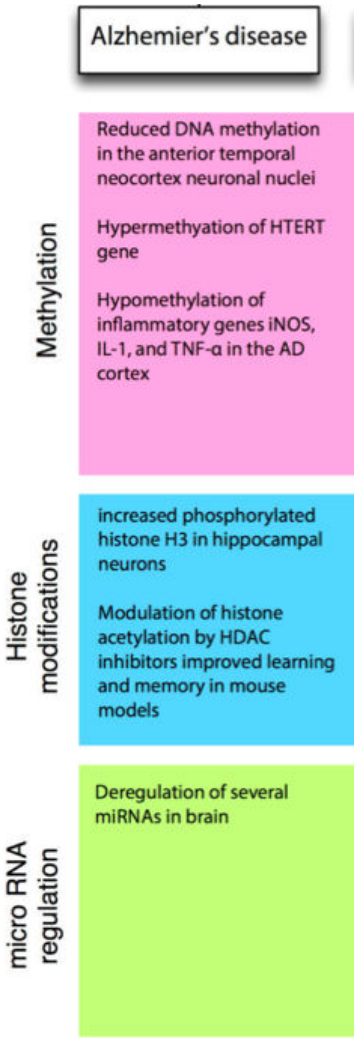


Source: Sanchez-Mutt et al. Frontiers in Behavioral Neuroscience 2015

Only two companies are exploring epigenetics in AD:

- **Oryzon's** LSD1/MAO-B inhibitor ORY-2001 is currently in Phase 2A in mild/moderate AD.
- **Rodin's** complex-selective HDAC inhibitor is currently in pre-IND studies.

Multiple data points in AD tell us that "something is going on" epigenetically



- SORL1 and ABCA7, genes related to Aβ production, were found to be hypermethylated in brains of patients with AD (Yu et al. JAMA Neurol 2015).
- DNA methylation are correlated with the burden of amyloid plaques in brain tissue (De Jager et al. Nat Neurosci 2014).
- Expression of HDAC6, as a tau-interacting protein and a potential modulator of tau phosphorylation and accumulation, is elevated in frozen cerebral cortical and hippocampal tissues of AD patients (*Ding et al. Journal of Neurochemistry, 2008).*
- SIRT1 reduced formation of plaques in preclinical AD models, while SIRT1 is significantly decreased in the parietal cortex of AD patients (*Julien et al. Experimental Neurology, 2009).*
- Trimethylation of H3K9, a marker of gene silencing and condensation of heterochromatin structure, was significantly increased in the temporal cortex and hippocampus of a twin with AD. (*Ryu et al. Alzheimer & Dementia, 2008*).
- Phosphorylation of H3S10, a key regulator in chromatin compaction during cell division, is elevated in the cytoplasm of neurons in the hippocampus of AD patients (*Ogawa et al. Acta Neuropathologica, 2003*).
- Hypermethylation of the promoter of SORBS3 protein involved in synaptic function is seen in the frontal cortex of AD patients (Sanchez-Mut et al. Brain 2013, Siegmund PLoS One 2007).

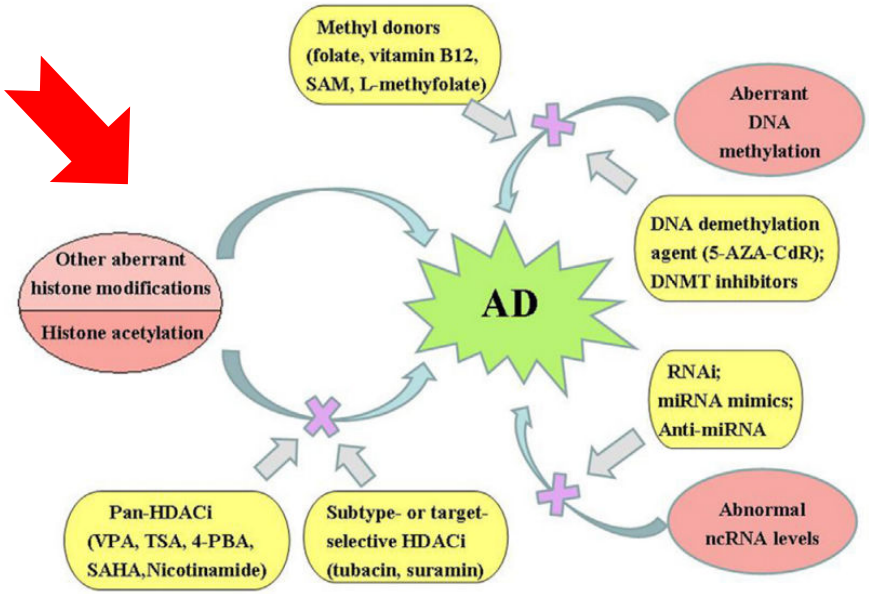
Source: Lovrecic et al. Intech Neurodegenrative Disease 2013.

Molecular observations implicate HDACs and their repressive complexes

A comprehensive recent report compared the genome-wide levels of H4K16ac (acetylated lysine 16 in histone 4; HDAC2 target) in the lateral temporal lobe of AD patients versus young and old cognitively normal controls. (Nativio et al. Epub, 2018 Mar 5).

While normal aging showed H4K16ac enrichment, AD showed dramatic losses of H4K16ac around genes linked to aging. Further, there were associations between genomic locations of significant H4K16ac changes and genomic variants previously identified from AD studies.

Overall, we like the hypothesis that AD is a case of dysregulated aging with specific changes to chromatin structure, view histone modification as a target to modulating that chromatin structure.



Source: Ageing Research Reviews 12 (2013) 1024–1041.

So then, why not target HDACs?

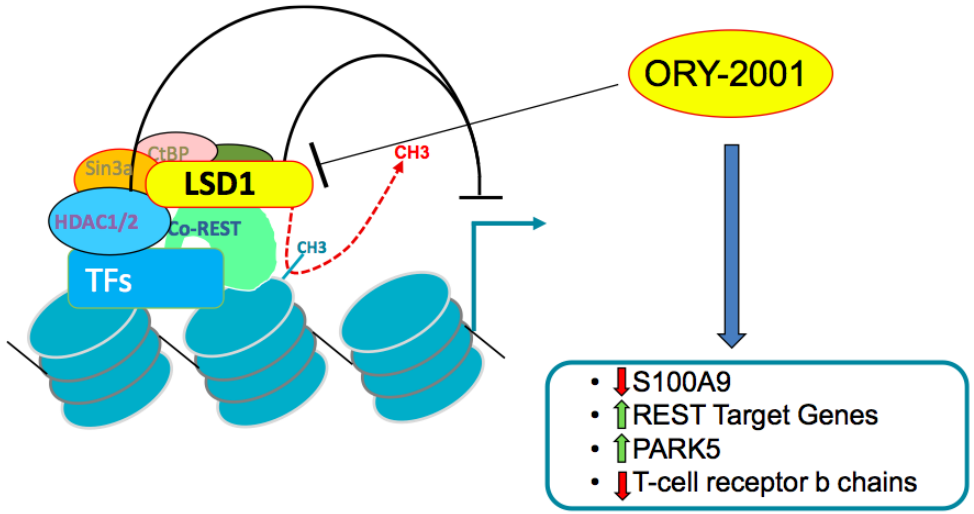
The problem has always been the therapeutic window of HDAC inhibitors.

This is why these compounds have found a small niche in oncology (CTCL, PTCL), but have not amounted to much else primarily due to their effects on hematopoiesis and the bone marrow.

We highlight one ongoing HDAC-I program in neuro from Rodin, which may have cracked the therapeutic window problem (see page 42).

How to tackle HDAC-related repressive complexes? Enter LSD1.

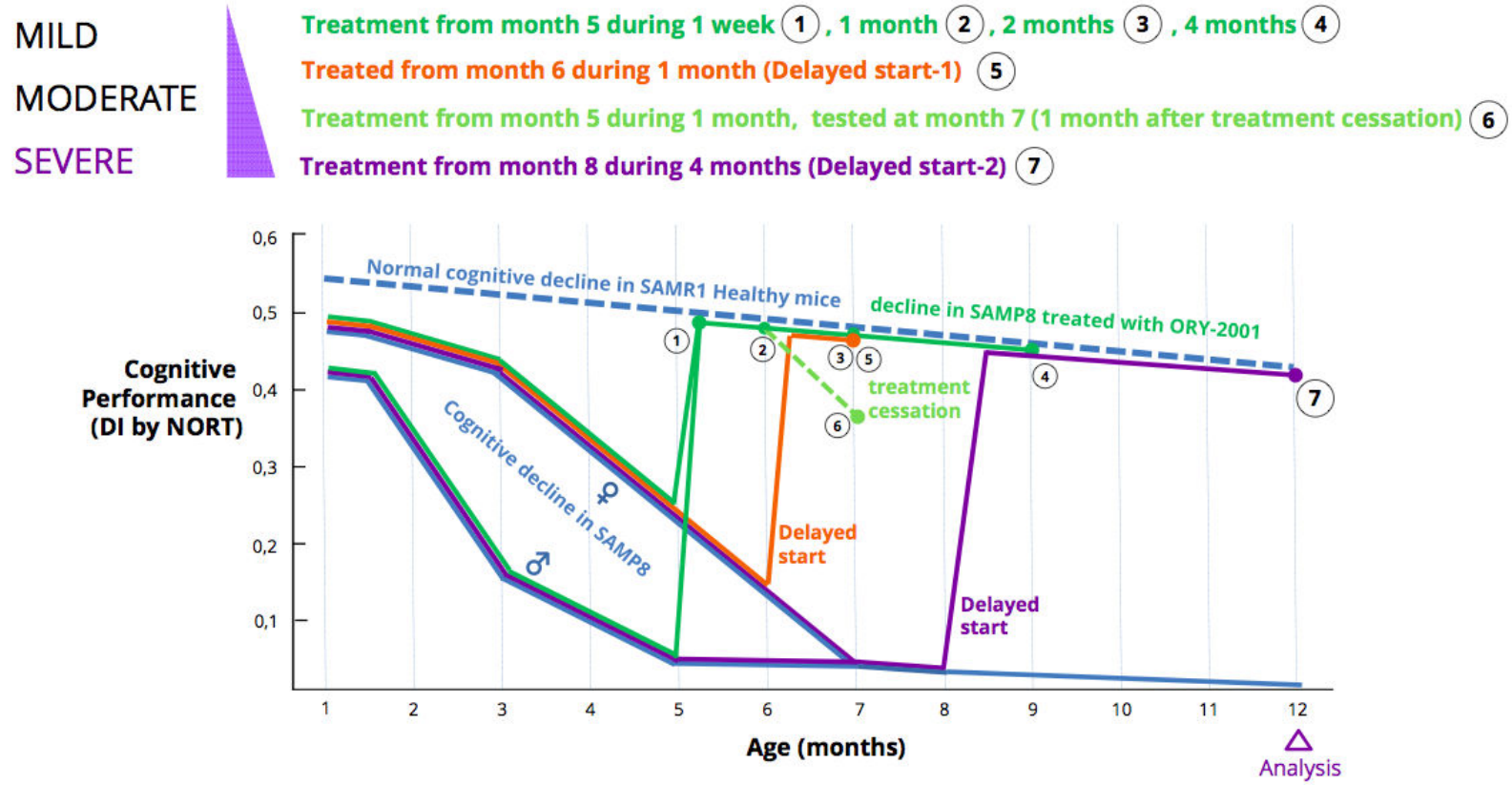
- LSD1 is part of the same repressive complexes as HDAC 1/2.
- Unlike specific HDACs which have been historically difficult to target selectively, it is possible to selectively target LSD1.
- Oryzon's compound ORY-2001 is a dual inhibitor of LSD1 and MAO-B, a related FAD-dependent enzyme also relevant in neuro.



Source: www.oryzon.com

What can ORY-2001 do? **One**: Cognition

Oryzon has treated 200+ SAMP8 mice (naturally occuring mouse line that displays a phenotype of accelerated aging) in 10 different experiments and showed **memory rescue**. Importantly, the mouse results are suggestive of **disease modifying** potential.

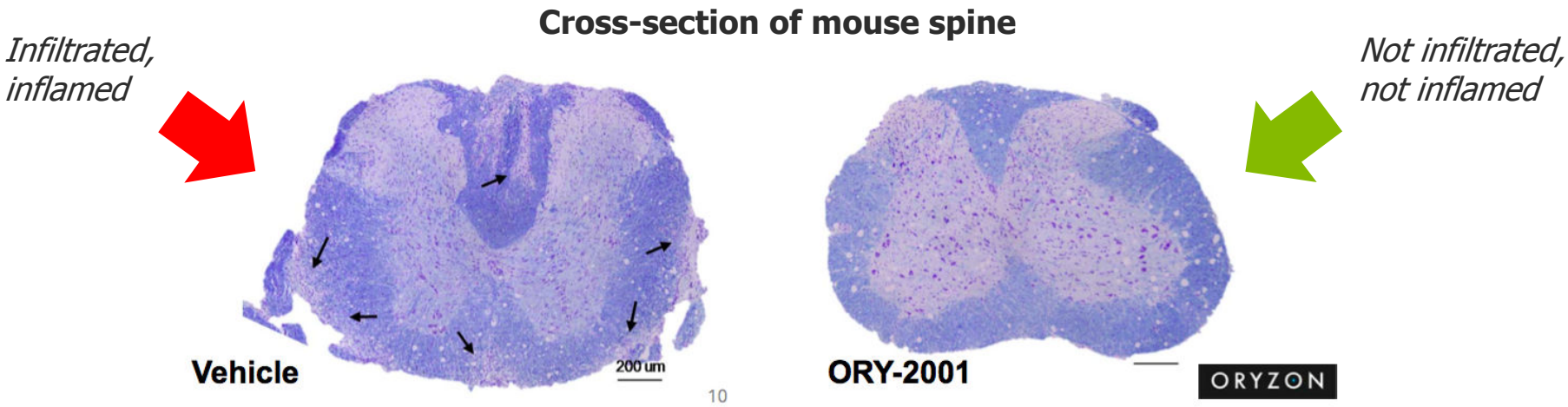


Source: www.oryzon.com

What can ORY-2001 do? **Two**: Inflammation & infiltration

Misfolded and aggregated proteins bind to pattern recognition receptors on microglia and astroglia triggering an innate immune response that is characterized by release of inflammatory mediators. Inflammatory mediators contribute to disease progression and severity.

Preclinical data with ORY-2001 shows reduced immune infiltration in the CNS, sparing demyelination and reducing associated clinical score in models.

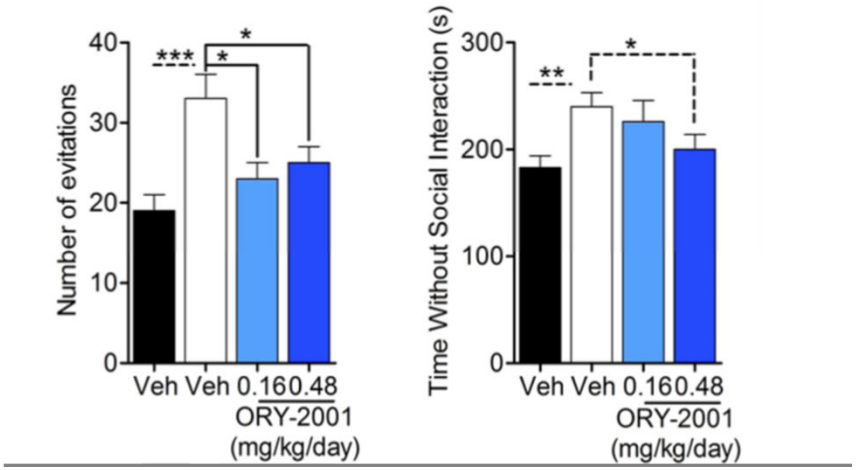


Source: www.oryzon.com, and McManu et al. Alzheimer's Research & Therapy 2017, Whittington et al. Front Immunol. 2017.

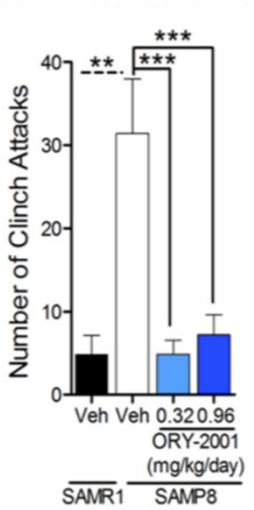
What can ORY-2001 do? **Three**: Aggression & social withdrawal

Patients with AD exhibits neuropsychiatric symptoms including aggression, agitation, depression, and social withdrawal associated with cognitive decline and memory loss.

In mouse work, ORY-2001 normalizes social behavior by reducing aggressiveness quantified by clinch attacks, and reducing social withdrawal.



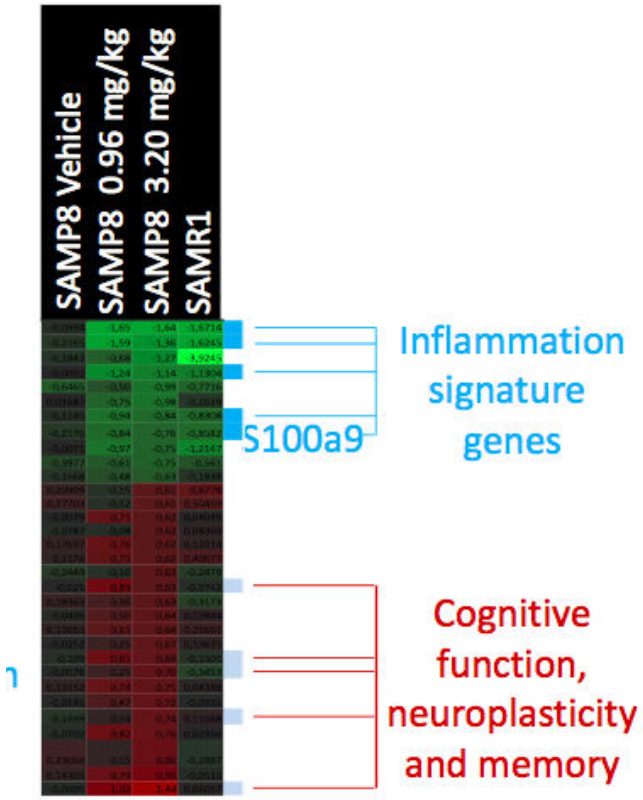
Rats with neurodevelopmental deficits show reduced social avoidance with treatment of ORY-2001.



Mice with accelerated aging show reduction in aggression with ORY-2001 treatment.

Source: Lanchtot et al. Alzheimer's and Dementia 2017, World Alzheimer Report 2015; www.oryzon.com

Important: ORY-2001 action has a genetic fingerprint which may allow clinical evaluation via expression signatures or physiologic biomarkers



- ORY-2001 up-regulates **expression of genes related to improved cognitive function**, neuroplasticity and memory, including: Egr, Fos, Nr4a1, Npas4, Arc.
- ORY-2001 down-regulates **expression of genes related to immune reaction** and inflammation, including S100A9 and T-cell receptor b chains.

Effect on S100A9 important for future clinical studies?

Therapeutically: S100A9 knockdown attenuates memory impairment and reduced amyloid plaque burden (Ha et al. PloS One 2010).

For biomarker tracking: S100A9 may correlate with dementia progression similarly to Aβ and tau-proteins (Horvath et al. ACS Chem. Neurosci., 2016).

Source: www.oryzon.com

Epigenetic targeting in chronic conditions: Early hurdles for development

The few epigenetic therapies available today (HDAC and DNMT inhibitors) have found use in Hem/Onc, in our view for the following reasons:

- In the Hem part of Hem/Onc: because epigenetic interference typically first manifests in the bone marrow, and alters blood counts.
- In the Onc part of Hem/Onc: because the therapeutic window of epigenetic drugs so far has not been good enough to venture into non-terminal diseases.

Then, in our view, it is imperative that new epigenetic agents clear a safety & tolerability hurdle before moving into a chronic disease. It is importable that they are cleared in:

- A larger than normal Phase 1 study.
- A wide population spectrum, inclusive of all ages.

On the efficacy front, and in the interest of target engagement, in our view it is important that new epigenetic agents are oral and able to maintain therapeutic coverage with no interruption (i.e. contiguous half-life and dosing schedule).

Oryzon's drug ORY-2001 meets all of these requirements, as shown by the recent Phase 1 study.

ORY-2001 Phase 1-derisked: Systemically clean, brain penetrant, good PK/PD

			Young			Elderly
			SAD		MAD	
	Dose (mg)	Log_{10}[Dose (mg/m2)]		CSF		
I	0.2	-1.0	6 (2)	-	6 (2)	-
II	0.6	-0.4	6 (2)	-	6 (2)	-
III	1.0	-0.2	-	-	6 (2)	-
IV	1.5	0.0	6 (2)	-	6 (2)	-
	2.0	0.1	-	9*	-	-
V	2.5	0.2	6 (2)	-	6 (2)	3(1)
VI	4.0	0.4	6 (2)	9*	3 (1)	-

ORY-2001 dose levels used in the Phase I trial in healthy volunteers
Number of treated subjects (Number of placebo treated subjects)
* SUB= CSF Sub study n per dose

Source: Poster P4-576, AAIC 2017.

Single center Phase 1 study with ORY-2001 SAD and MAD in 106 subject (young and elderly):

- **No significant clinical or laboratory changes or adverse events in the MAD up to 2.5 mg** (transient platelet impact in the 4 mg cohort in the MAD); no effects on neutrophil compartment.
- Rapid oral absorption; almost lineal behavior with a **half-life of 22 hours**; moderate systemic accumulation after 5 days of administration.
- **Brain penetration** demonstrated by measuring ORY-2001 in CSF and ex-vivo experiments conducted in parallel with the Phase I trial show that drug binds human brain enzyme.

ORY-2001 in AD: Phase 2A study in mild/moderate AD is now rolling

- ETHERAL (Epigenetic THERapy in ALzheimer's Disease) started in 1Q18:
  - 90 patients with **mild/moderate AD** (MMSE 16-26, CDR 1-2)
  - Randomization 2:2:1 (two doses of therapy, 1 placebo)
  - **26-week** treatment (oral daily), plus 6-month open label extension
- Endpoints:
  - Primary: AE frequency/severity
  - Exploratory **cognitive**: MMSE, ADAS-cog 14, Cogstate battery
  - Exploratory **functional**: CDR-SB, Dependence scale
  - Exploratory **biomarkers**: MRI, CSF (AD, Novel e.g. S100A9, YKL40), other TBD.
- Importantly, the company expects to launch a **twin study in the U.S**.
- We expect to see **data in early 2019**. We believe that there is a high probability of observing at least one **positive signal within the exploratory protocol** (given LSD1 rationale and MAO-B prior data), which will then allow Oryzon to **fine-tune a subsequent protocol in line with recent FDA and EMA guidance** on the integration of biomarkers and clinical evaluation.

Source: www.oryzon.com

ORY-2001's MAO-B targeting component: What do other MAO-B agents look like?

- MAO-B is an enzyme that breaks down dopamine in the brain. Two MAO-B inhibitors, selegiline and rasagiline, are used for treatment of Parkinson's disease (PD).
- MAO-B activity was shown to be elevated in AD, painting a target on this enzyme in this indication. However, so far, MAO-B inhibitors have failed to succeed in AD:

- **Lazabemide**: monotherapy in mild-to-moderate AD in one Phase 2 and two Phase 3 studies; pivotal studies showed **cognitive and functional benefit**, but scratched due to **hepatotoxicity**.
- **Selegiline**: combo with alpha-tocopherol in moderate AD in Phase 2; **no clinically meaningful benefit** despite some delay in functional deterioration.
- **Sembragiline**: combo with acetylcholinesterase inhibitors in moderate AD in Phase 2; **no benefit** in cognition or function.
- **Rasagiline**: monotherapy in mild-to-moderate AD in Phase 2; awaiting data in early 2019.

Source: Nave et al J. of Alzheimer Disease r 2017, Sano et al. NEJM 1997

Prior MAO-B failures: Any lessons for ORY-2001?

Lazabemide: **monotherapy** in **mild-to-moderate** AD in one Phase 2 and two Phase 3 studies; pivotal studies showed cognitive and functional benefit, but scratched due to hepatotoxicity.

Selegiline: **combo** with alpha-tocopherol in **moderate** AD in a large Phase 2; no clinically meaningful benefit despite some delay in functional deterioration.

Sembragiline: **combo** with acetylcholinesterase inhibitors in **moderate** AD in Phase 2; no benefit in cognition or function.

Rasagiline: **monotherapy** in **mild-to-moderate** AD in Phase 2; awaiting data in early 2019.

Do we see a pattern?

In our view, history is suggestive of an ideal setting for MAO-B targeting: as monotherapy and early in the disease.

We believe that MAO-B targeting may be active, but not too active in AD (advanced disease and/or other drug may mask weak MAO-B effect). Thus, the only agent to be tested as monotherapy in early disease then hit on efficacy but failed on safety.

Importantly, we believe that the pending rasagiline study is likely to show a positive signal; if so, this will be validating for Oryzon (ORY-2001 should compound any MAO-B effect with some LSD1 effect in mild/moderate AD).

AD & the FDA: New draft guidance may signal change in regulatory standards

- In February, the FDA published guidance integrating lessons-learned from repeated failures of previous trials and redefined regulatory terms for staging and meaningful endpoints of clinical trials.
- Key points of the guidance: strong encouragement for biomarker identification, time/event analysis and signals to a more flexible regulatory path (accelerated approval, surrogate endpoints).

FDA Statement

Statement from FDA Commissioner Scott Gottlieb, M.D. on advancing the development of novel treatments for neurological conditions; part of broader effort on modernizing FDA's new drug review programs

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release February 15, 2018

Early Alzheimer's Disease: Developing Drugs for Treatment
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Source: www.fda.gov

AD & the EMA: Latest guidance not too bold, but may catch up with the FDA in time

In February, the EMA adopted a long-standing draft of its next guidelines for AD.

In our our view, the document is not as revolutionary (reactionary?) as the FDA's (as it pertains to the importance of biomarkers).

However, we believe that what is important here is that Europeans are also actively thinking and moving on this subject, and could evolve quickly in step with the FDA.

Source: www.ema.europa.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 February 2018
CPMP/EWP/553/95 Rev.2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

Draft agreed by CNSWP	December 2015
Adopted by CHMP for release for consultation	28 January 2016
Start of public consultation	01 February 2016
End of consultation (deadline for comments)	31 July 2016
Agreed by CNSWP	December 2017
Adopted by CHMP	22 February 2018
Date of coming into effect	1 September 2018

Digging into the FDA's new draft guidance: Early focus on biomarkers

AD Stage 1

Disease:
- pathophysiological changes, but no functional impairment.

Endpoints:
- Pathophysiologic changes by various **biomarkers** as primary efficacy measure can be used for **accelerated approval**.
- Confirmation of clinical benefit later required for full approval.

AD Stage 2

Disease:
- Pathophysiological changes, detectable abnormalities, but no functional impairment.

Endpoints:
- Effect on sensitive measures of **neuropsych performance across multiple tests/scales**.
- Endpoints from Stage 3 measured at sufficient duration to allow evaluation.

AD Stage 3

Disease:
- Pathophysiological changes, more visible abnormalities, mild functional impairment.

Endpoints:
- Independent assessment of daily function and cognitive effects.
- Functional deficits and impact arising from early cognitive impairment.

What does this mean?

- At this stage, not much practically, in our view. As a reminder, this is still draft guidance.
- However, we believe that having the words "**biomarker**" and "**accelerated approval**" in the same sentence is a major step forward, which should now allow companies such as Oryzon (with targeted therapies with mechanistic connection to biomarkers) to have intelligent conversations with the FDA about **intelligent study design**. In our view, the prospect of accelerated approval in AD is now on the table for everyone.

Source: www.fda.gov

ORY-2001: Preclinical dossier and Phase 1 study highlight potential in AD

Then, overall:

- ORY-2001, a small molecule that selectively inhibits LSD1 and MAO-B, shows preclinical effects in neuroinflammation and neuroprotection, as well as effects on behavioral phenomena such as aggression/agitation and social withdrawal.
- A large safety study in healthy volunteers showed good tolerability and safety unlike more traditional epigenetic agents and MAO-B targeted agents, which in our view bodes well for evaluating chronic dosing in a mild-moderate AD patient population.
- Oryzon could benefit from ongoing changes in regulatory thinking, especially new thinking on the use of biomarkers in early disease, and the use of behavioral and neuropsychiatric symptom improvement.
- Oryzon recently started a Phase 2A randomized, double-blind, placebo-controlled, parallel-group, multicenter study in mild/moderate of AD patients, with multiple exploratory endpoints, and with preliminary data expected in 1Q19.

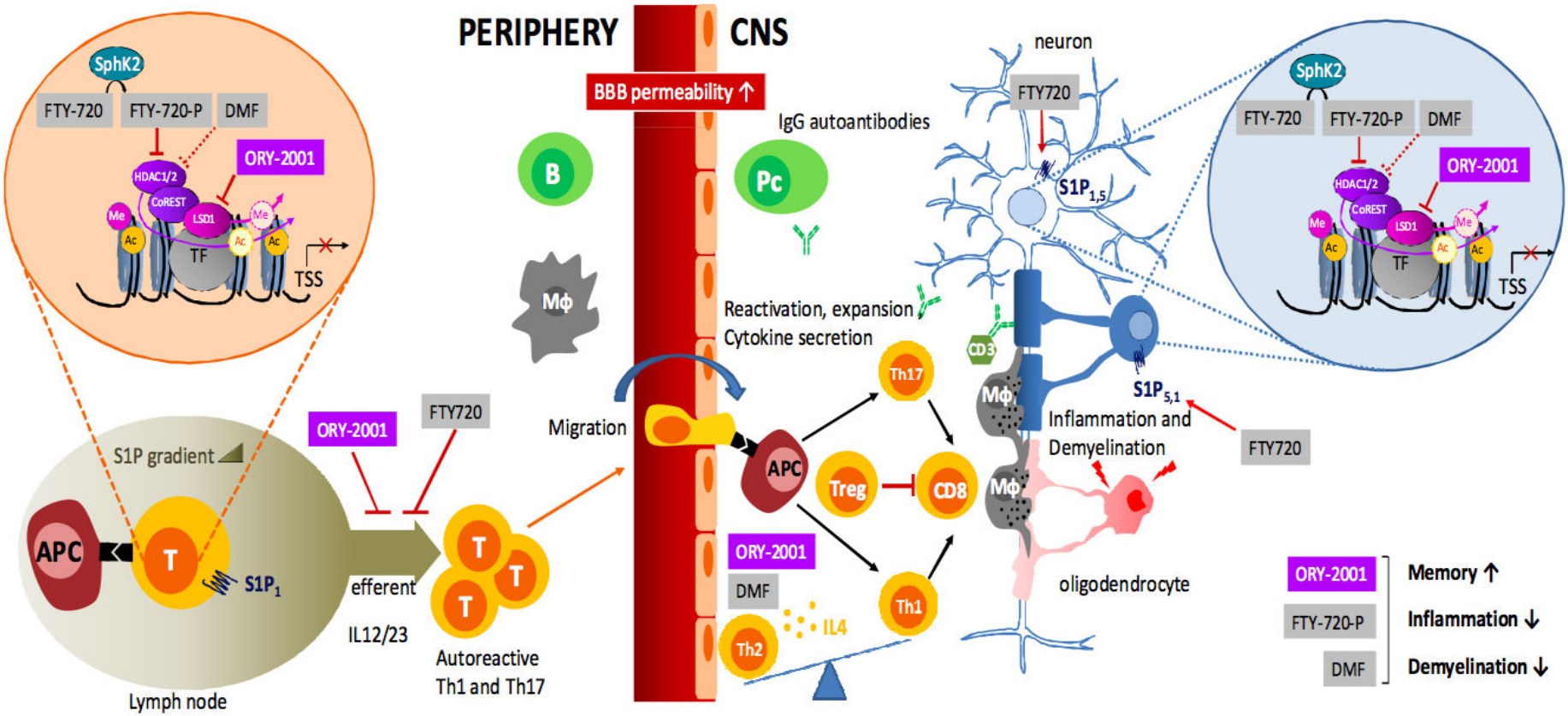
Who else is leveraging epigenetics in AD? Keep an eye on Rodin Therapeutics

- Similarly to Oryzon, **Rodin Therapeutics (private)** is taking an epigenetic approach to tackling neuro and psych disorders, with a lead focus on Alzheimer's.
- Rodin's compounds are able to target defined subsets of HDAC complexes (including HDAC2), leading to upregulation of key pro-synaptic genes and **increased synaptic formation and density**, which in turn is expected to lead to functional improvement.
- Importantly, Rodin's proprietary HDAC inhibitors are expected to have **good brain PK, and low bone marrow toxicity** (which has previously been a challenge even for HDAC inhibitors used in oncology).
- On the clinical front, the translational strategy in Alzheimer's would include **evaluating first synaptic deficits** and **then therapeutic effect** in a **genetically-defined population** via SV2A PET ligand, which can be used for accurate synapse quantification.
- In perspective, HDACs (especially 1 and 2) and LSD1 are functionally related and participate in the same transcriptional complexes in the neuronal epigenome. We believe that any incremental updates, clinical or otherwise, from one of these programs should (to a certain degree) give us hints on what to expect from the other.

Source: rodintherapeutics.com

Chapter 3: Programs in Multiple Sclerosis and Sickle Cell Disease

ORY-2001 in neuroinflammation: LSD1 is an important node in MS pathophysiology



Source: Poster LB192, ACTRIMS 2017.

ORY-2001 in MS: Oryzon's preclinical data supports MS effort

- *In mouse models:*
  - ORY-2001 decreases the TMEV clinical score in dose dependent ways, reduces lymphocyte infiltration of immune cells in the spinal cord and microglial activation, and improves axon integrity preventing demyelination (TMEV is a mouse model of autoimmune encephalomyelitis, via viral infection).
  - The therapeutic effects of ORY-2001 can be achieved at doses that do not significantly affect hematology or lymphocyte counts, a common side effect in MS drugs, and without signs of gastro-intestinal toxicity.
- *In perspective, relative to an MS standard:*
  - The gene expression response to ORY-2001 and fingolimod in spinal cord and brain is highly similar.
  - ORY-2001 is more effective and faster acting than fingolimod in the effector phase.
  - Fingolimod is a sphingosine-1-phosphate (S1p) receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction. However, fingolimod also has direct CNS effects, distinguishing it from immunologically targeted MS therapies.

Source: Poster P656, ECTRIMS/ACTRIMS 2017.

ORY-2001 in MS: Phase 2A Spanish study in MS is already rolling

- Recently, Oryzon started a Phase 2a trial of ORY-2001 in MS (SATEEN: SAfety, Tolerability and Efficacy in an epigenetic approach to treat Multiple Sclerosis):
  - Randomized, double-blind, placebo-controlled study;
  - 36 week treatment of 3 parallel-groups, followed by an open label extension;
  - 4 Spanish hospitals enrolling patients with relapsing-remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS);
  - FPI in 1Q18; LPO expected in December 2018.
- **We expect preliminary SATEEN data in MS in early 2019.**

Source: Poster P040, ACTRIMS 2018.

Preclinical pipeline: ORY-3001 advancing in Sickle Cell Disease (SCD)

- Oryzon presented data from its next-gen LSD1 inhibitor ORY-3001 in SCD at ASH 2017:
  - SCD is a genetic disease caused by mutation in the hemoglobin gene leading to the production of abnormally shaped red blood cells and anemia.
  - LSD1 is a component of co-repressor complexes that repress γ-globin gene expression and a therapeutic target for HbF reactivation.
  - Oral administration of varying doses ORY-3001 to SCD transgenic mice increased γ-globin expression and the percentage of circulating erythrocytes and reticulocytes positive for HbF (F cells and F retics).
  - The same effects of ORY-3001 were reproduced in baboons, which are the best animal model for testing the activity of HbF-inducing drugs due to conservation of structure and developmental regulation of the β-globin locus among simian primates.
  - Overall, across both models, ORY-3001 up-regulated HbF gene expression ~8-10x and F retic levels ~300%.
- We believe that diversification into benign hematology is a smart move for Oryzon. Of note, Oryzon's program in SCD is timely: we have recently seen other epigenetic approaches to this disease from larger players with expertise in epigenetics: (a) Epizyme with a preclinical G9a inhibitor IND-enabling studies in 2018); (b) Incyte with a clinical LSD1 inhibitor (Phase 1 in 2018).

Source: Blood 2017 130:356; and EPZM and INCY SEC filings.

Chapter 3: Our Value Considerations and Projections

What do other epigenetics companies look like?

Public epigenetic companies: we highlight the following three as epigenetic pure plays. Of these, in our view Epizyme (in red) is the most applicable, given the focus on an epigenetic enzyme (yet limited within oncology).

In perspective, Epizyme as the first public pure play in epigenetics was trading at an **EV between ~$600-900M** when it had only two epigenetic programs in Phase 1, limited only to oncology (EZH2 and Dot1L).

Company	Ticker	Key Target	Indication: Stage	Market Cap
Epizyme	EPZM	EZH2	R/R NHL, solid tumors	$914M
Syndax	SNDX	HDAC	IO combo solid tumors: P1	$264M
		HDAC	HT combo breast ca: P3	
Resverlogix	RVX	BRD	CVD risk in diabetes	$182M

Private epigenetic companies: we highlight the following three as epigenetic pure plays. Of these, in our view Rodin (in red) is the most applicable, given the focus on Alzheimer's disease.

Company	Key Backer	Key Target	Indication: Stage	Last Round
Rodin	Atlas	HDAC	AD: pre-IND	3Q17: $27M
Constellation	Third Rock	EZH2	HT combo CRPC: P 1/2	2Q18: $100M
		BRD	R/R MF: P 1/2	
Foghorn	Flagship	TBD	TBD	1Q18: $50M

Source: ROTH Capital Partners research.

Any lessons from past M&A in pure epigenetics?

We know of two cases of **pure** epigenetic acquisitions, both around bromodomain inhibitors with Phase 1 data in leukemia/lymphoma.

In our view: (a) **BRD** inhibitors are **blunt** instruments, despite counting as epigenetic therapeutics (i.e. LSD1 is a superior target), and (b) **preliminary** clinical data from both of these BRD inhibitors was **underwhelming**.

Company	Buyer	Key Target	Indication: Stage	Year: Upfront/Contingency
Tensha	Roche	BRD	Hem/Onc: P1	2016: $115M / $420M
Oncoethix	Merck	BRD	Hem/Onc: P1	2014: $110M / $265M

Source: ROTH Capital Partners research.

Our takeaway: based on limited data from the field, it looks like big pharma has placed a specific value on **early-stage oncology** one-hit wonders in epigenetics (**$100M** extending to $400M).

Then, Oryzon's **current valuation may be fully justified by its hem/onc epigenetic program alone** (ORY-1001), at its current clinical stage (with upside from further development, in our view), with **no value yet factored in** from any other programs (SCLC, AD, MS).

Valuation: We discount program success based on empirical industry statistics

Probability of success. For valuation purposes, typically in our models we assign an overall probability of success to each therapeutic asset. This probability is inclusive of clinical, regulatory and commercial risk, and is based on: (a) empirical industry data related to the stage of clinical development (**see below**); and (b) our perception of the intrinsic risk of the technology in question.

Overall from P1	15 %
Overall from P2	25 %
Overall from P3	60 %
Overall from Approval	90 %

	MBC	DiMasi	CMR Self-originated	CMR In-licensed	Tang	Abrantes-Metz	Keegan
Phase 1		100 %				81 %	
Phase 2	60–82 %	71 %			80 %	58 %	
Phase 3	42–61 %	31 %			30 %	57 %	
Registration	65–88 %				80 %		
Approval	90–92 %						
Overall from P1	15–40 %	22 %	7 %	14 %		26 %	15 %
Overall from P2	25–49 %	22 %	12 %	20 %		33 %	25 %
Overall from P3	59–81 %	31 %	63 %	63 %		57 %	60 %
Overall from Approval	90–92 %		94 %	94 %			90 %

A guide to the empirical probability of success of therapeutic agents depending on their stage of development. Source: massbio.com

Valuation: We discount Oryzon's oncology and neuro programs very differently

Historically, the attrition rate in oncology therapeutics is similar to (and sometimes lower than) that in general therapeutics, with early / Phase 1 clinical assets typically having a 15-20% chance of making it to the market.

See table on previous slide.

Historically, the attrition rate in AD therapeutics is high, with 72% of agents failing in Phase 1, 92% failing in Phase 2, and 98% failing in Phase 3 (vs. compounded success rate of development of oncology compounds at 19%).

Cummings et al. Alzheimer's Research & Therapy. 2014. 6:37.

In line with the above, we then assign the following coefficients of probability of success in our model:

ORY-1001 (P1/2 in AML): 20%

ORY-2001 (P1/2 in AD): 5%

ORY-1001 in AML: We model for €450M in annual WW sales by 2028

We assume Phase 2 data in R/R AML in 2019, a pivotal program in 2019-2022, and a potential commercial launch by 2023.

ORY-1001	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
ORY-1001 WW Sales	€ -	€ -	€ -	€ -	€ -	€ 50	€ 185	€ 333	€ 417	€ 442	€ 450
ORY-1001 WW Revenue to Oryzon	€ -	€ -	€ -	€ -	€ -	€ 50	€ 156	€ 246	€ 284	€ 292	€ 297
ORY-1001 US Revenue											
US new AML cases per year	21,666	21,833	22,001	22,170	22,341	22,513	22,686	22,861	23,037	23,215	23,393
Growth Rate	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*
Percent patients eventually R/R	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*
Patients eligible for ORY-1001	11,916	12,008	12,101	12,194	12,288	12,382	12,478	12,574	12,670	12,768	12,866
Penetration of eligible patients						*4%*	*12%*	*18%*	*20%*	*20%*	*20%*
Number of patients on ORY-1001					-	495	1,497	2,263	2,534	2,554	2,573
Avg Annual Cost (x €1000)						100	101	102	103	104	105
YoY price increase							*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*
ORY-1001 US Revenue	€ -	€ -	€ -	€ -	€ -	€ 50	€ 151	€ 231	€ 261	€ 266	€ 270
ORY-1001 EU Revenue	€ -	€ -	€ -	€ -	€ -	€ -	€ 33	€ 102	€ 156	€ 176	€ 179
EU Royalty	€ -	€ -	€ -	€ -	€ -	€ -	€ 5	€ 15	€ 23	€ 26	€ 27
EU royalty rate	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EU/US adjustment factor	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*
% of US market	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*
% of US penetration	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
% of US treatment cost	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*

Source: ROTH Capital Partners research.

ORY-2001 in AD: We model for €4.7B in annual WW sales by 2028

We assume Phase 2 data in mild/mod AD in 2019, a pivotal program in 2020-2023, and a potential commercial launch by 2024.

ORY-2001	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
ORY-2001 WW Sales	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,308	€ 2,911	€ 4,265	€ 4,727
ORY-2001 WW Revenue to Oryzon	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,107	€ 2,296	€ 3,010	€ 3,127
ORY-2001 US Revenue											
AD prevalence (x 1000)	5,500	5,555	5,611	5,667	5,723	5,781	5,838	5,897	5,956	6,015	6,075
Growth Rate	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*
Percent mild/moderate disease	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*
Patients eligible for ORY-2011 (x 1000)	3,300	3,333	3,366	3,400	3,434	3,468	3,503	3,538	3,573	3,609	3,645
Penetration of eligible patients							*1%*	*3%*	*6%*	*8%*	*8%*
Number of patients on ORY-2001 (x 1000)					-		35	106	214	271	273
Avg Annual Cost (x €1000)							10	10	10	10	10
YoY price increase								*1.0%*	*1.0%*	*1.0%*	*1.0%*
US Revenue	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,072	€ 2,187	€ 2,789	€ 2,845
ORY-2001 EU Revenue	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 236	€ 724	€ 1,476	€ 1,883
EU Royalty	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 35	€ 109	€ 221	€ 282
EU royalty rate	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EU/US adjustment factor	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*
% of US market	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*
% of US penetration	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
% of US treatment cost	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*

Source: ROTH Capital Partners research.

ROTH Capital Partners

Oryzon (ORY)

Jotin Marango, MD, PhD

Valuation: We include only ORY-1001 in onc/AML and ORY-2001 in neuro/AD

Our 12-month price target of **€15/share** (**€4 for ORY-1001 in AML, €10 for ORY-2001 in AD, and €1 in cash**) is based on a DCF-SoP analysis using a 12% discount rate and 1% growth rate. This price target also incorporates our assigned probabilities of success for each program.

ORY-1001 in AML	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Total Revenue	0	0	0	0	0	50	156	246	284	292	297
Net Income	(10)	(15)	(15)	(18)	(20)	15	84	144	170	177	179
Periods	0.00	0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75
Discounted income	(10)	(15)	(15)	(18)	(20)	9	45	69	73	68	62

ORY-2001 in AD	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Total Revenue	0	0	0	0	0	0	350	1,107	2,296	3,010	3,127
Net Income	(10)	(18)	(18)	(28)	(33)	(35)	196	688	1,475	1,969	2,071
Periods	0.00	0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75
Discounted income	(10)	(18)	(18)	(28)	(21)	(20)	100	312	594	705	660

ORY-1001, AML Valuation		
Discount Rate		12%
Growth Rate		1%
CPV		868
CPV/share	€	21.69
Adj CPV/share	€	4.34

ORY-2001, AD Valuation		
Discount Rate		12%
Growth Rate		1%
CPV		7,830
CPV/share	€	195.76
Adj CPV/share	€	9.79

Share Valuation	Probability		Adj Value		Full Value
ORY-1001, AML	20%	€	4	€	22
ORY-2001, AD	5%	€	10	€	196
Cash		€	1	€	1
Price Target		**€**	**15**	€	219

Source: ROTH Capital Partners research.

VALUATION

Our 12-month price target of €15/share (€4/share for ORY-1001 in AML + €10/share for ORY-2001 in AD + €1/share in cash) is based on a DCF-SoP analysis using a 12% discount rate and 1% growth rate. Factors which could impede the achievement of our target price include, but are not limited to: (1) failure and/ or setbacks of the drugs in clinical studies; (2) failure of the drugs to gain regulatory approval; and (3) smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

RISKS

Experimental therapeutic product risk. The company's risk profile is based primarily, in our belief, on the company's thesis being based on the clinical and commercial prospects of pipeline candidates. Current funding at the company is being directed toward these programs and should there be any missteps, negative trial data or delays, this could impact the stock negatively. Adding additional risk to both programs is their early stage nature. Drug development is fraught with failures and this risk is increased significantly during the earlier stages of development.

Development timeline risk. The company's shares could be subject to increased volatility, in our belief, based on the time frame required to get meaningful proof of concept data from the planned clinical program. Positive clinical data could yield a potential accelerated path toward approval, however we currently project that our modeled drug candidates ORY-1001 and ORY-2001 may only reach the market in 2023 and 2024, respectively. Investors may choose to delay investment in the company, despite potential excitement, until meaningful clinical data is generated.

Financing risk. As with a majority of development-stage biotechnology companies, the ability to maintain sufficient funding is critical to the progress of pipeline candidates. Should the company experience problems raising sufficient capital, its development programs' progress could be significantly impeded, leading to both delays in development timelines as well as potential negative effects on investor confidence. Each of these could have a negative impact on share price.

COMPANY DESCRIPTION

Oryzon Genomics S.A., headquartered in Barcelona, Spain, is a clinical stage biotechnology company focused on the discovery and development of epigenetic therapies in oncology and neurodegenerative diseases. Its first clinical asset, ORY-1001, an inhibitor of the histone demethylase LSD1, is currently advancing into a Phase 2 study in acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS), and a Phase 1 study in small cell lung cancer (SCLC). Its second clinical asset, ORY-2001, a dual inhibitor of LSD1 and MAO-B, is currently in proof-of-concept Phase 2 studies in Alzheimer's disease (AD) and multiple sclerosis (MS).

Oryzon Genomics, S.A.
Income Statement
(in $'1000s)

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	2015	2016	2017	Mar Q1:18E	Jun Q2:18E	Sep Q3:18E	Dec Q4:18E	2018E	2019E
Collaborations	4,647	775	20	-	-	-	-	-	-
Total revenues	4,647	775	20	-	-	-	-	-	-
Research and development	4053	5,492	6,363	1,252	1,315	1,380	1,449	5,396	8,094
General and administrative	4624	5,011	4,502	1,287	1,351	1,419	1,490	5,547	6,102
Total operating expenses	8,677	10,503	10,865	2,539	2,666	2,799	2,939	10,943	14,196
Loss from operations	(4,030)	(9,728)	(10,845)	(2,539)	(2,666)	(2,799)	(2,939)	(10,943)	(14,196)
Other income	3774	4,903	5,659	957	967	977	987	3,888	4,567
Tax	-829	(918)	(1,047)	(190)	(190)	(190)	(190)	(760)	(999)
Net loss	(1,085)	(5,743)	(6,233)	(1,772)	(1,889)	(2,012)	(2,142)	(7,815)	(10,628)
Net loss per share	(0.04)	(0.21)	(0.20)	(0.05)	(0.05)	(0.06)	(0.06)	(0.22)	(0.26)
Weighted average shares	24,729	27,569	31,711	34,111	34,793	35,489	36,199	35,148	40,181

Source: www.oryzon.com and ROTH Capital Partners research.

Oryzon Genomics, S.A.
Revenue Model
(in €'MM except patient numbers)

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ORY-1001	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**	**2025E**	**2026E**	**2027E**	**2028E**
ORY-1001 WW Sales	€ -	€ -	€ -	€ -	€ -	€ 50	€ 185	€ 333	€ 417	€ 442	€ 450
ORY-1001 WW Revenue to Oryzon	€ -	€ -	€ -	€ -	€ -	€ 50	€ 156	€ 246	€ 284	€ 292	€ 297
ORY-1001 US Sales											
US new AML cases per year	21,666	21,833	22,001	22,170	22,341	22,513	22,686	22,861	23,037	23,215	23,393
Growth Rate	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*	*0.77%*
Percent patients eventually R/R	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*	*55%*
Patients eligible for ORY-1001	11,916	12,008	12,101	12,194	12,288	12,382	12,478	12,574	12,670	12,768	12,866
Penetration of eligible patients						*4%*	*12%*	*18%*	*20%*	*20%*	*20%*
Number of patients on ORY-1001					-	495	1,497	2,263	2,534	2,554	2,573
Avg Annual Cost (x €1000)						100	101	102	103	104	105
YoY price increase							*1.0%*	*1.0%*	*1.0%*	*1.0%*	*1.0%*
ORY-1001 US Revenue	€ -	€ -	€ -	€ -	€ -	€ 50	€ 151	€ 231	€ 261	€ 266	€ 270
ORY-1001 EU Sales	**€ -**	**€ -**	**€ -**	**€ -**		**€ -**	**€ 33**	**€ 102**	**€ 156**	**€ 176**	**€ 179**
EU Royalty	€ -	€ -	€ -	€ -	€ -	€ -	€ 5	€ 15	€ 23	€ 26	€ 27
EU royalty rate	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EU/US adjustment factor	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*
% of US market	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*
% of US penetration	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
% of US treatment cost	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*

ORY-2001	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**	**2025E**	**2026E**	**2027E**	**2028E**
ORY-2001 WW Sales	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,308	€ 2,911	€ 4,265	€ 4,727
ORY-2001 WW Revenue to Oryzon	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,107	€ 2,296	€ 3,010	€ 3,127
ORY-2001 US Sales											
AD prevalence (x 1000)	5,500	5,555	5,611	5,667	5,723	5,781	5,838	5,897	5,956	6,015	6,075
Growth Rate	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*	*1.00%*
Percent mild/moderate disease	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*	*60%*
Patients eligible for ORY-2011 (x 1000)	3,300	3,333	3,366	3,400	3,434	3,468	3,503	3,538	3,573	3,609	3,645
Penetration of eligible patients							*1%*	*3%*	*6%*	*8%*	*8%*
Number of patients on ORY-2001 (x 1000)					-		35	106	214	271	273
Avg Annual Cost (x €1000)							10	10	10	10	10
YoY price increase								*1.0%*	*1.0%*	*1.0%*	*1.0%*
US Revenue	€ -	€ -	€ -	€ -	€ -	€ -	€ 350	€ 1,072	€ 2,187	€ 2,789	€ 2,845
ORY-2001 EU Sales	**€ -**	**€ -**	**€ -**	**€ -**		**€ -**	**€ -**	**€ 236**	**€ 724**	**€ 1,476**	**€ 1,883**
EU Royalty	€ -	€ -	€ -	€ -	€ -	€ -	€ -	€ 35	€ 109	€ 221	€ 282
EU royalty rate	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
EU/US adjustment factor	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*	*68%*
% of US market	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*	*120%*
% of US penetration	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
% of US treatment cost	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*

Source: ROTH Capital Partners research.

Oryzon Genomics, S.A.
Valuation
(in €'MM, except per share values)

Jotin Marango, M.D., Ph.D.
ROTH Capital Partners, LLC
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ORY-1001 in AML	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Total Revenue	0	0	0	0	0	50	156	246	284	292	297
Net Income	(10)	(15)	(15)	(18)	(20)	15	84	144	170	177	179
Periods	0.00	0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75
Discounted income	(10)	(15)	(15)	(18)	(20)	9	45	69	73	68	62

ORY-2001 in AD	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
Total Revenue	0	0	0	0	0	0	350	1,107	2,296	3,010	3,127
Net Income	(10)	(18)	(18)	(28)	(33)	(35)	196	688	1,475	1,969	2,071
Periods	0.00	0.75	1.75	2.75	3.75	4.75	5.75	6.75	7.75	8.75	9.75
Discounted income	(10)	(18)	(18)	(28)	(21)	(20)	100	312	594	705	660

ORY-1001, AML Valuation		
Discount Rate		12%
Growth Rate		1%
CPV		868
CPV/share	€	21.69
Adj CPV/share	€	4.34

ORY-2001, AD Valuation		
Discount Rate		12%
Growth Rate		1%
CPV		7,830
CPV/share	€	195.76
Adj CPV/share	€	9.79

Share Valuation	Probability		Adj Value		Full Value
ORY-1001, AML	20%	€	4	€	22
ORY-2001, AD	5%	€	10	€	196
Cash		€	1	€	1
Price Target		**€**	**15**	€	219

Source: ROTH Capital Partners research.

Oryzon Genomics, S.A.
Condensed Balance Sheet Data
(in $'1000s)

Jotin Marango, M.D., Ph.D.
ROTH Capital Partners, LLC
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	Dec 2015	Dec 2016	Dec 2017
Cash and cash equivalents	21,270	23,220	41,916
Marketable securities	2,449	5,525	170
Total assets	44,505	52,435	73,210
Deferred revenue	393	0	0
Total stockholder's equity	30,148	23,958	41,294

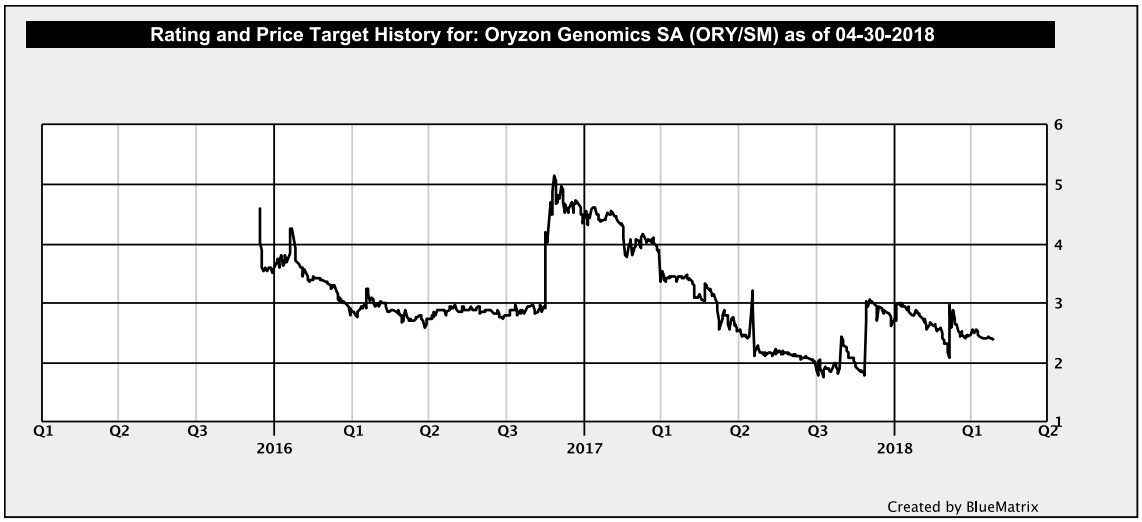
Source: www.oryzon.com

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.

ROTH makes a market in shares of Epizyme, Inc. and Syros Pharmaceuticals, Inc. and as such, buys and sells from customers on a principal basis.



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 04/30/18	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**250**	**71.63**	**136**	**54.40**
Neutral [N]	**47**	**13.47**	**19**	**40.43**
Sell [S]	**4**	**1.15**	**2**	**50.00**
Under Review [UR]	**47**	**13.47**	**26**	**55.32**

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 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 does not publish research or have an opinion about this security.

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