A breakthrough epigenetic approach in Alzheimer's disease and other neurodegenerative disorders

Barcelona, 20 de octubre de 2015

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Business Summary

EPIGENETICS

- One of the world leading companies in epigenetics, as a novel way to approach oncology and CNS diseases and personalized medicine

PIPELINE

- 2 programs in clinic by year's end
- Clinic Programs can expand in multiple indications
- Other Programs in Discovery that are progressing fast

PROVEN TRACK

- Cutting edge science endorsed by a world class deal in 2014 with ROCHE
- Management team with demonstrated track record on creating innovative molecules and developing clinical assets in a cost-efficient manner

SOLID IP

- Excellent IP protection with a broad patent portfolio and FTO
- 19 patent families, 8 granted in US + 2 with notice of allowance in US
- All patented technology developed in-house, no owed royalties

WELL FUNDED

- Recently completed mezzanine financing in Europe raising above €15M
- A plan to transition to a public company

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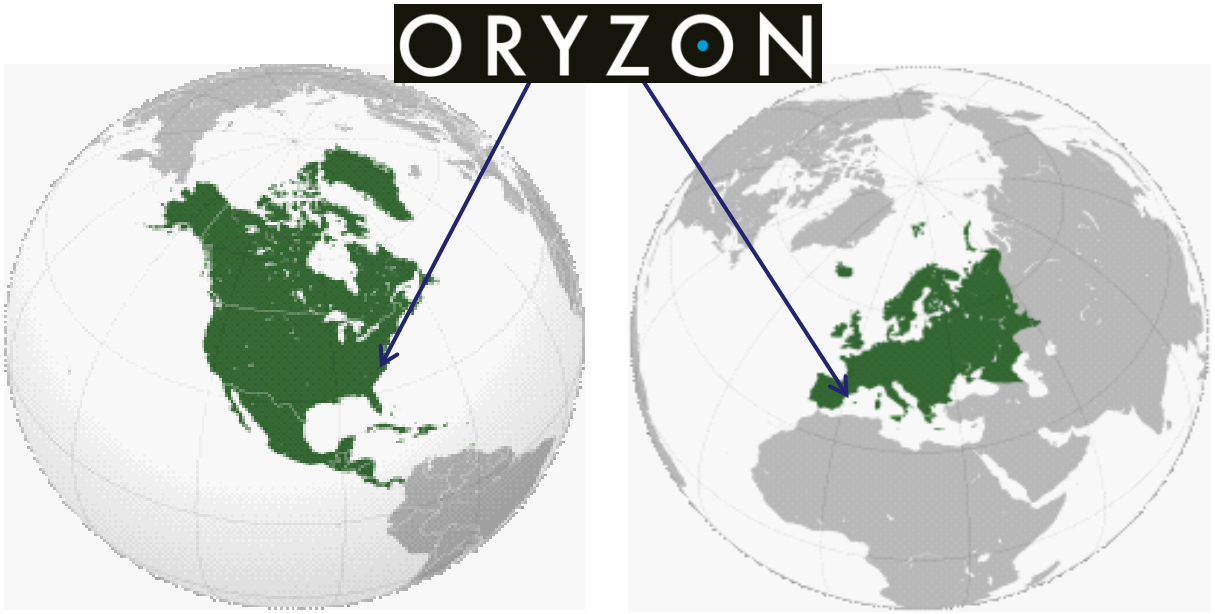
Headquartered in Spain and the US

30 experienced and committed people



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- Clinical Operations
- Investor Relations
- IP/BD/Finance

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International Research Network

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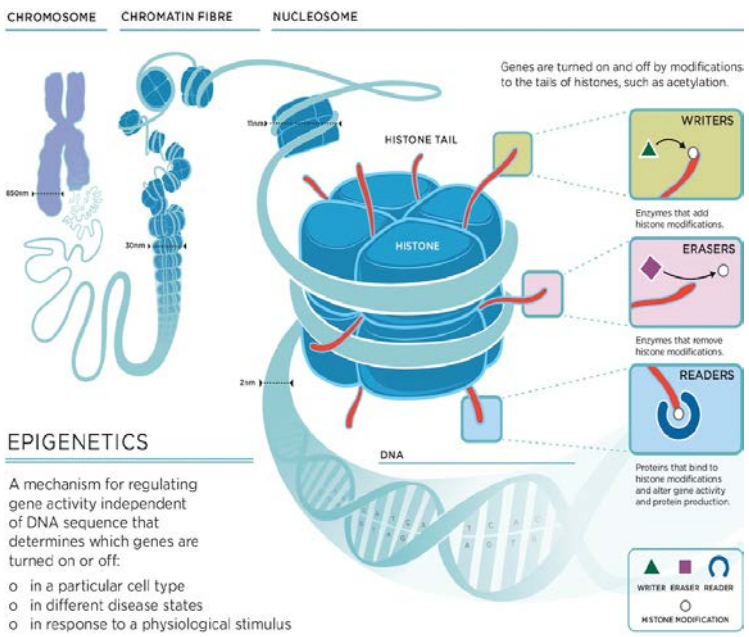
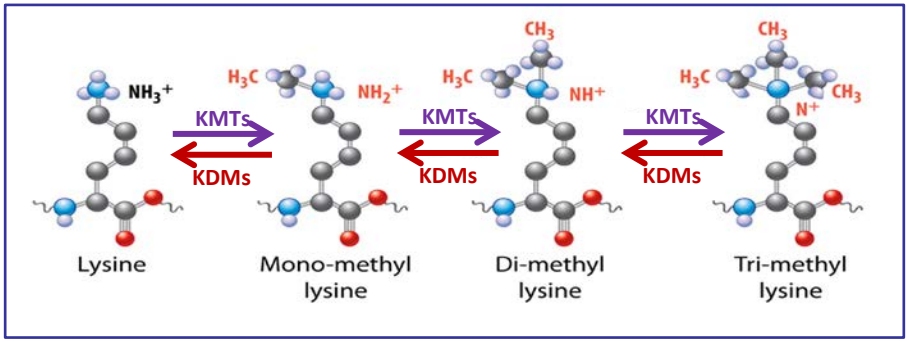
Epigenetics: The critical role of Histone coding



http://www.resverlogix.com/imageviewer.php?pic=/upload/body_image/74/02/rvx_epigenetics.jpg&alt=



- **Epigenetics** – the study of heritable changes in genome function that occur without a change in DNA sequence
- These changes mainly occur due to variations in the structure of **chromatin** that silence or activate whole regions of the chromosome and all the genes that reside in this region
- These variations are caused by post-translational modifications on **histones**, the proteins that serve as scaffold for the DNA to conform the chromatin
- Lysine methylation and demethylation is one of the key epigenetic modifications of the Histone tails

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The epigenetic products

			Deacetylases	Methyltransferases	Demethylases	Bromodomain
Launched			Celgene ISTODAX (romidepsin) for injection	Vidaza azacitidine for injection		
			Johnson & Johnson Eisai	DACOGEN decitabine for injection		
			MERCK Zolinza [vorinostat] capsules			
			NOVARTIS FARYDAK (panobinostat) capsules			
			ONXEO SPECTRUM PHARMACEUTICALS Beleodaq (belinostat) for injection			
R&D	Phase III	1				
	Phase II	5		1		
	Phase I	5		4	2	6
	Preclinical	5		3	3	3
	Discovery-HtL	2		3	3	4

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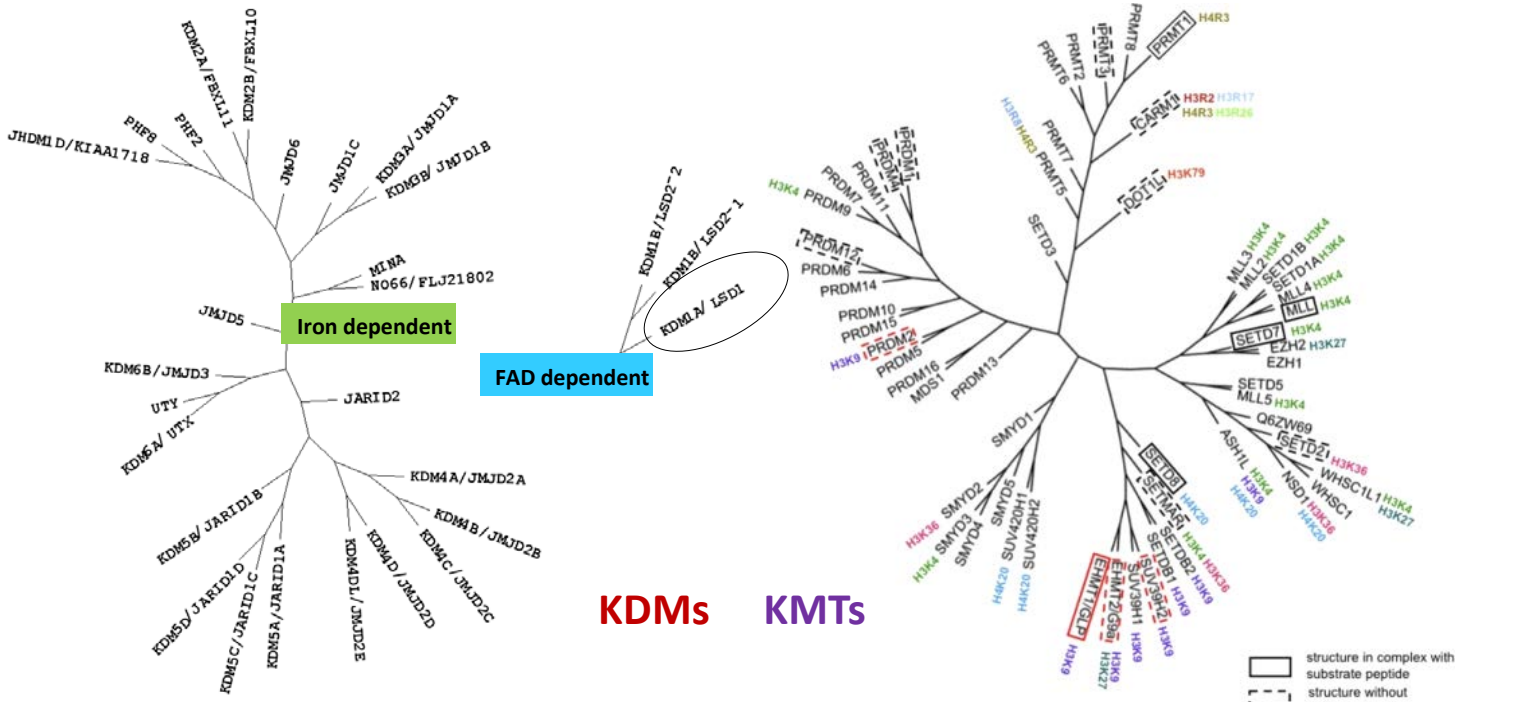
Oryzon is exploring a wide field in epigenetics

Histone lysine methylation and demethylation is performed by a plethora of different enzymes. A number of targets are being preferentially explored by Oryzon.



http://apps.thesgc.org/resources/phylogenetic_trees

Structural Biology of Human H3K9 Methyltransferases
Wu H, et al PLoS ONE (2010)

To explore such a vast domain, Oryzon relies on its epigenentic technological platform. More than 1500 NCEs designed and tested in different screening cascades

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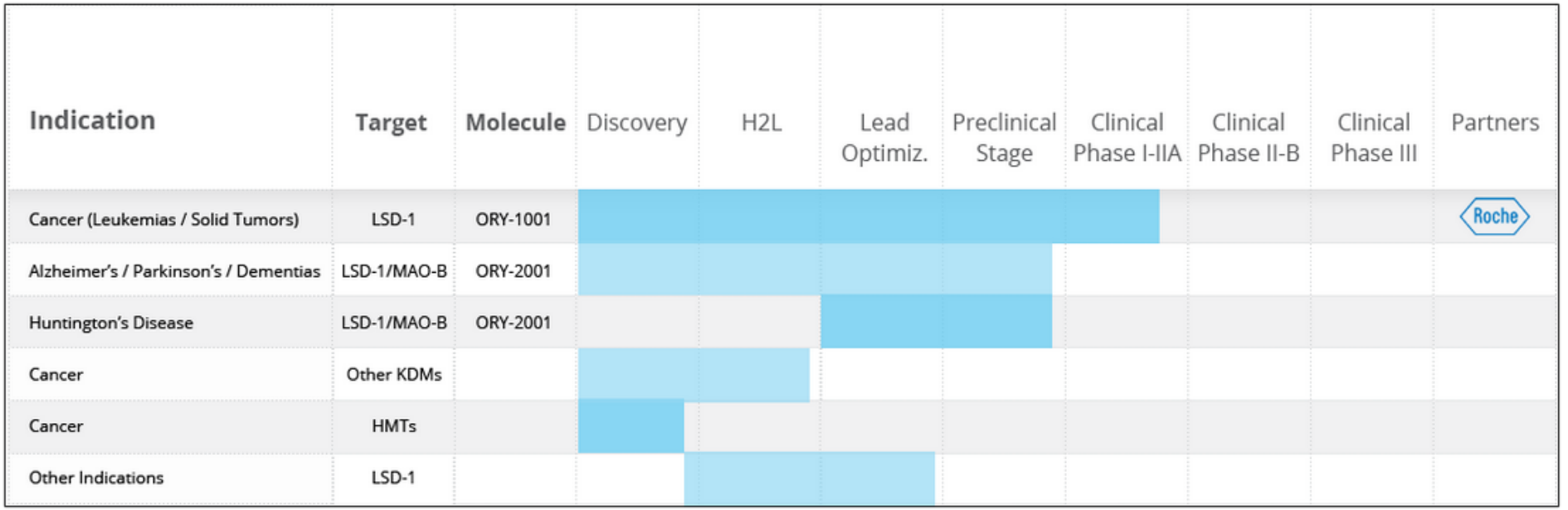
Current Pipeline



Indication	Target	Molecule	Discovery	H2L	Lead Optimiz.	Preclinical Stage	Clinical Phase I-IIA	Clinical Phase II-B	Clinical Phase III	Partners
Cancer (Leukemias / Solid Tumors)	LSD-1	ORY-1001								Roche
Alzheimer's / Parkinson's / Dementias	LSD-1/MAO-B	ORY-2001								
Huntington's Disease	LSD-1/MAO-B	ORY-2001								
Cancer	Other KDMs									
Cancer	HMTs									
Other Indications	LSD-1									

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ORY-1001 LEUKEMIA

A product patent license from Oryzon to Roche in April 2014

- A global licensing agreement for the use of ORY-1001 and backups for oncology and other therapeutic indications.
- The license compound is covered by two patents in the Oryzon IP portfolio (1).
- Oryzon is responsible for completing the ongoing Phase I and IIA, after which Roche continues the clinical development covering all additional investments.
- The two companies are collaborating on R&D of the compound through the Roche Translational Clinical Research Center (TCRC) based in NYC

- ***Payment** at contract signing plus near term milestone totals **$21 M***
- ***Development and Sales milestones total >>$500 M***
- ***Sales royalty rates tiered up to mid-teens***

(1) The remaining 17 patents families of Oryzon's LSD1 portfolio are not part of the Roche agreement.


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ORY-2001 in CNS

Epigenetic players in CNS

	Compound	Target	Target Indications	Status
FORUM PHARMACEUTICALS™	FRM-0334	HDAC	FTD	Phase II
RESVERLOGIX	RVX-208	BRD	AD	Phase IIa (planned) It is in Phase III in secondary prevention of MACE with diabetes and low HDL
ORYZON	ORY-2001	LSD1+MAOB	AD, other dementias and neuroinflammatory disorders	Phase I in Q1/2016
rodin THERAPEUTICS	BRD668	HDAC	AD, PD	LO

ORY-2001 Target Indications

Alzheimer's Disease (AD)

LSD1 inhibition is a potential disease-modifying therapy for AD, a highly differentiated profile according to the international AD current pipeline

other dementias and neuroinflammatory disorders

Oryzon's research has been partly funded by competitive grants

ORY-2001 Mechanism of action

- LSD1 is involved in neural stem cell proliferation and cell specification.
- Terminal differentiation in neurons requires down-regulation of LSD1 activity, a process achieved at the transcriptional, post-transcriptional and post-translational level.
- ORY-2001 completely rescues the memory and learning defects of SAMP8 mice as determined by the performance of treated vs non-treated animals in the NOR test..
- Treatment with ORY-2001 up-regulates the hippocampal expression of genes related to improved cognitive function, neuroplasticity and memory, and down-regulate genes overexpressed in SAMP8 mice and in AD patients. Therefore, inhibition of LSD1 may result in beneficial effects on memory.

ORY-2001 Mechanism of action

- The LSD1 enzyme is structurally related to MAO-A and MAO-B, targeted by tranylcypromine (TCP, Parnate™) and Rasagiline (Azylect™), drugs used to treat depression and PD.

- MAO-B is a well characterized target for Parkinson's disease (PD), and it is also being reconsidered in the context of Alzheimer's Disease. Here, the protein is over-expressed in reactive astrocytes around amyloid plaques, and mediates the aberrant and abundantly production of the inhibitory gliotransmitter GABA, which negatively affects synaptic plasticity, learning and memory.

- Dual inhibitors targeting MAO-B in addition to LSD1 thus incorporate a potential plus for the treatment of neurodegenerative disease.

- Oryzon's ORY-2001 is the only dual LSD1/MAO-B inhibitor currently being moved forward to Phase I studies. It is also the only LSD1 inhibitor publicly in development for the treatment of neurodegenerative disease.

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ORY-2001, a Preclinical Candidate for AD and other CNS disorders

MOLECULE	MW <350. Stereochemically pure compound Covalent binder to the FAD cofactor
POTENCY	Balanced LSD1/MAOB activity, with IC50s in the range 70-100 nM
SELECTIVITY	>70 fold on MAOA (>5 microM IC50) >100 fold on LSD2 (>10 microM IC50)
In-VITRO	induces cell differentiation with an EC50 26 nM
In-VIVO	Dose-dependent PD effects in the range 0,1-3mg/kg Proven Target engagement for LSD1 and MAOB activity
PK	Half -life suitable for once-a-day administration; orally bioavailable High Brain exposure: Brain /plasma ratio >1
PHARMACOLOGY	No relevant Cyp inhibition, no induction of Cyp1B1 No hERG inhibition. No mutagenicity
ADMET	Good LM stability in human, dog, rat and mice microsomes

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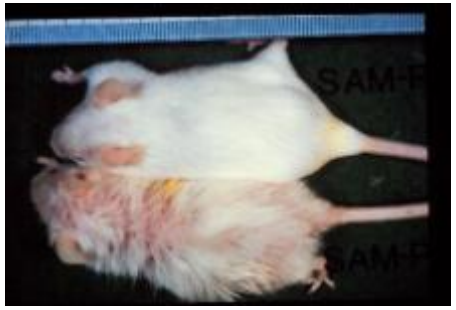
SAMP8 : a non transgenic mouse model for AD

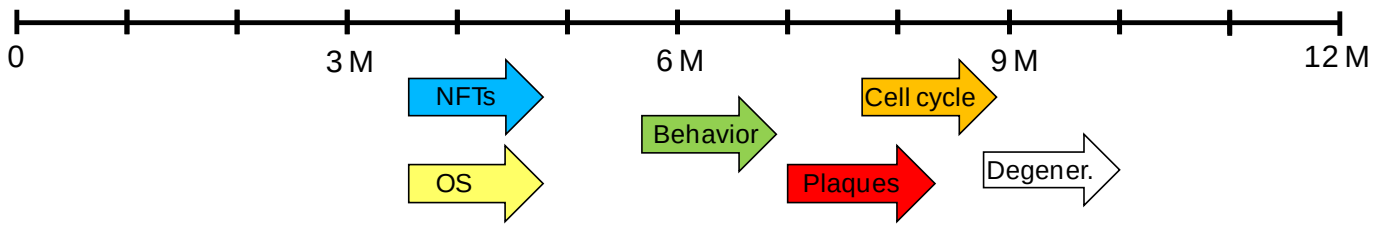
The Senescence-Accelerated Mouse-Prone 8 (SAMP8) was developed by Dr. Toshio Takeda (Kyoto University) from AKR/J mice.

- Develops deficits in learning and memory relatively early in its lifespan.
  - Impairments in avoidance tasks
  - Impairment of their spatial memory task ability

- Pathological similarities to Alzheimer Disease
  - Abeta deposition becomes clear from 7-8 months

- Profound disorder of their circadian rhythms of spontaneous motor activity and drinking behaviors.
- Histopathology: spongiform degeneration, astrogliosis, clusters of activated microglia, impaired blood-brain barrier function…
- Decline in immune responsiveness.





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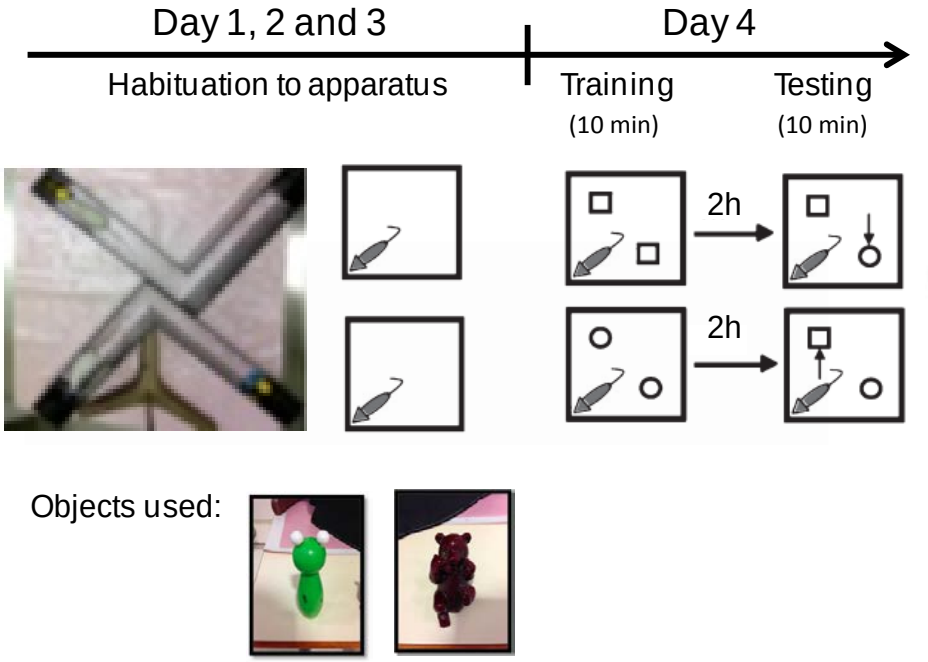
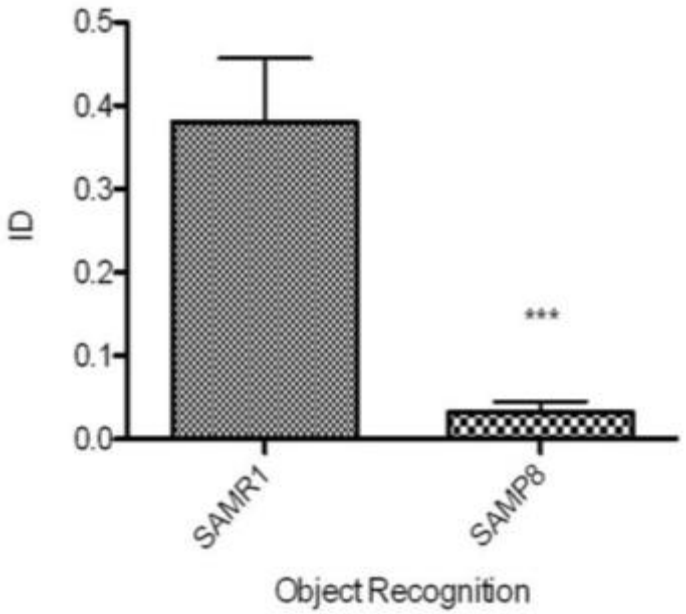
SAMP-8 mice and the novel object recognition test (memory)

Concept: mice are trained by confronting them with an object, which they tend to explore. After 2h (mid term memory) or 24h (long term memory) they are confronted with 2 objects, the old one, and a new one. The SAMR1 reference strain remembers the old object and preferentially explores the new object. The SAMP8 strain has forgotten all about the old object and makes no distinction.





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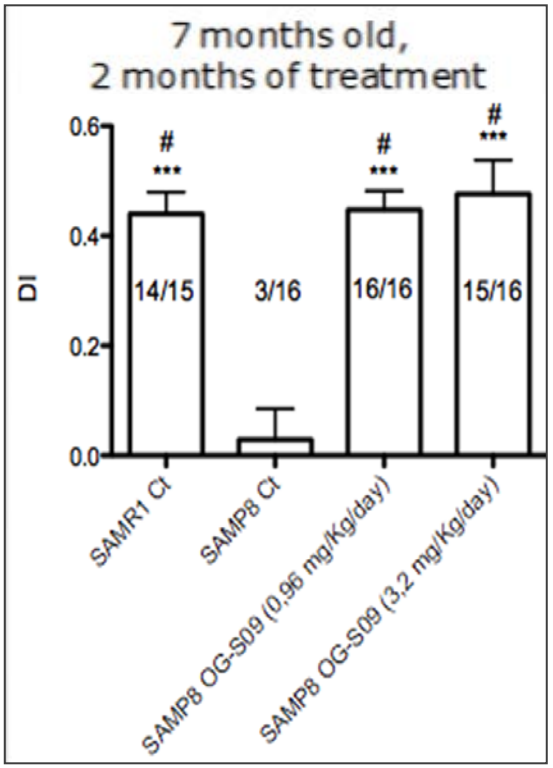
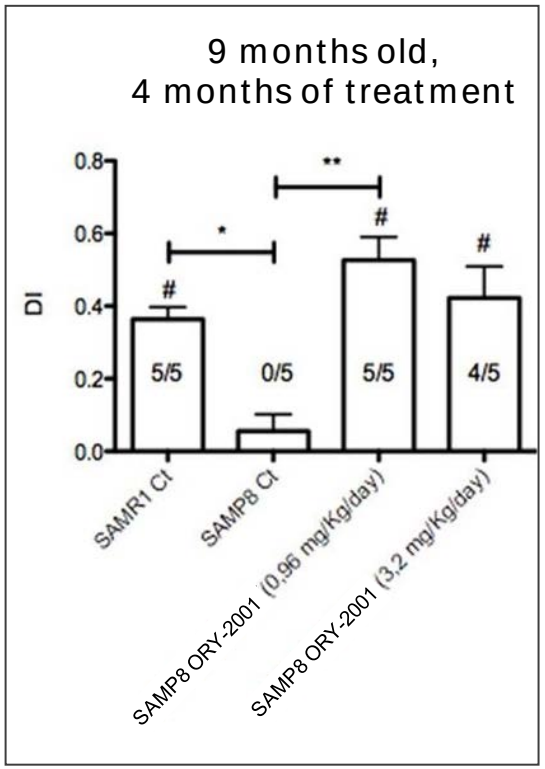
PoC studies in SAMP8 mice: STUDY # 1

SAMP8 female animals treated with ORY-2001 (0.96 and 3.2 mg/kg)

- Provides a protective effect in the memory of female mice, compared to age-matched SAMP8 mice.
- Some toll on the mice at the highest dose → adapt dose in male Study #2



Retested 2h after training



Retested 2h after training

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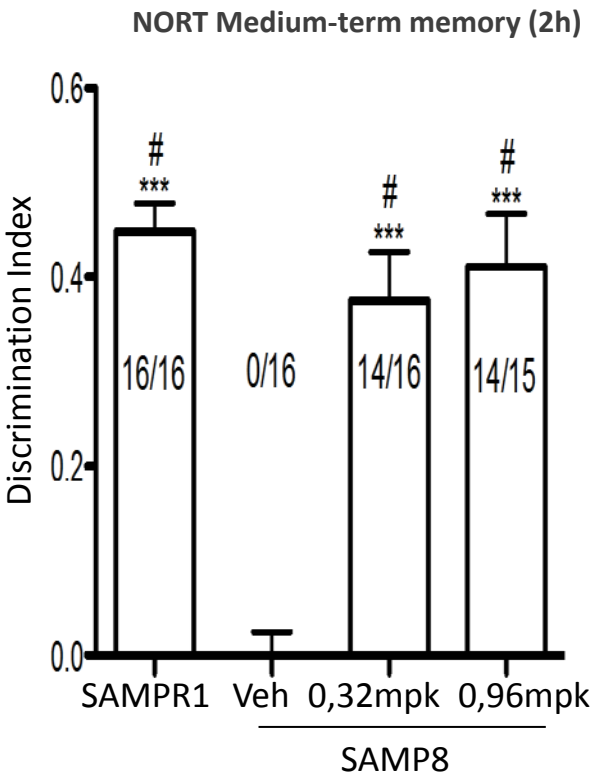
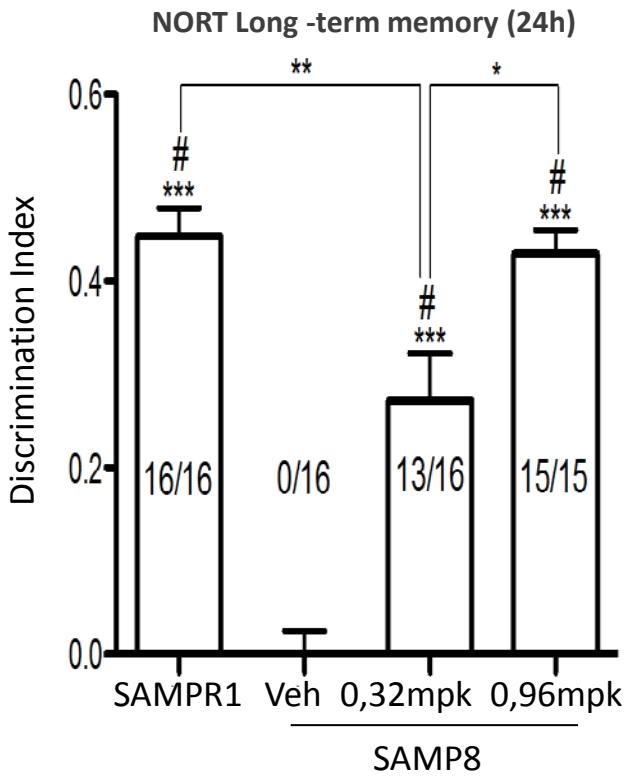
PoC studies in SAMP8 mice: STUDY # 2

SAMP8 male animals treated with ORY-2001 (0.32 mg/kg; 0.96 mg/kg)

- provides a protective effect in the medium- and long-memory of male mice, compared to age-matched SAMP8 mice.





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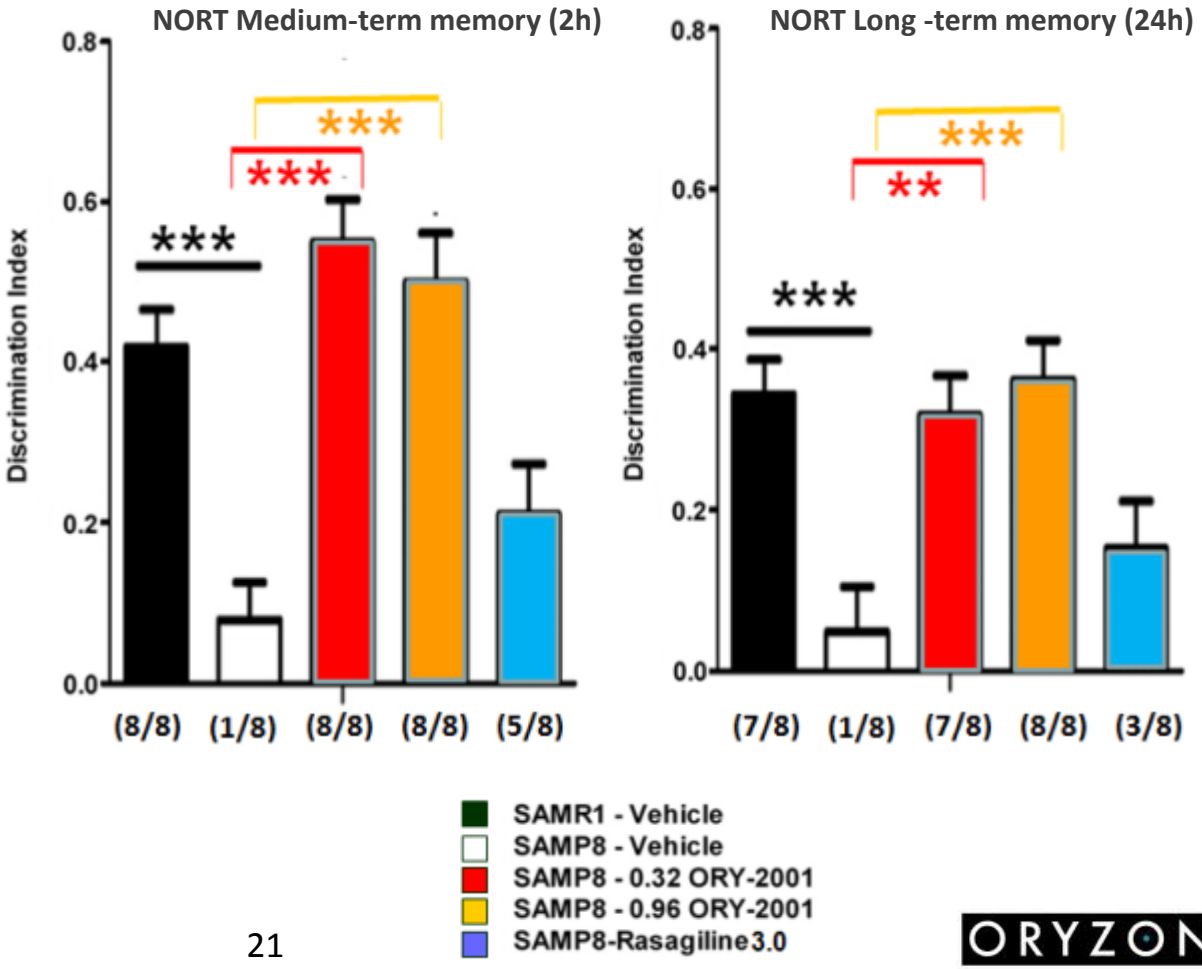
PoC studies in SAMP8 mice: STUDY # 3

SAMP8 male animals (n=8 per group) treated with ORY-2001 (0.32 mg/kg; 0.96 mg/kg)

- Provides a protective effect in the medium- and long-memory of male mice, compared to age-matched SAMP8 mice.
- MAOB inhibition alone shows a trend on cognitive improvement on the SAMP8 animals however it is not significant; (p=0,12 at 2h and p=0,22 at 24 h.)
- LSD1 inhibition is therefore crucial to obtain the recovery on cognitive improvement on the SAMP8 animals.



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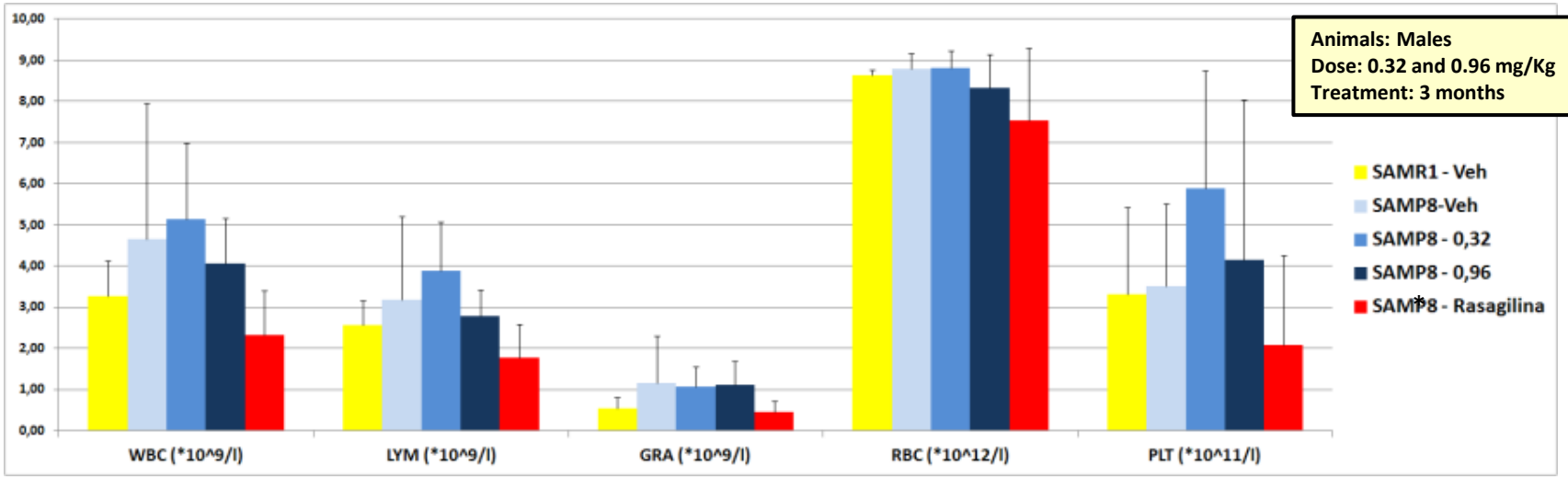
ORY-2001 provides a high therapeutic window

PoC studies in SAMP8 mice: STUDY # 3

HEMOGRAM: No differences between animals treated with ORY2001 and control



**Blood samples from rasagiline treated animals was coagulated, that might affect the hemogram results of this group.*

- At 0,32 mpk and 0,96 mpk oral daily chronic doses on SAMP8 animals do not show any hematological effect.
- At 3.0-3,2 mpk, SAMP8 and other mice strains showed a mild reduction of Platelet level (NOAEL) suggesting that a dose close to 3mpk is the maximal one compatible with a chronic treatment

That means that the therapeutic window is, at very least, 10 fold.

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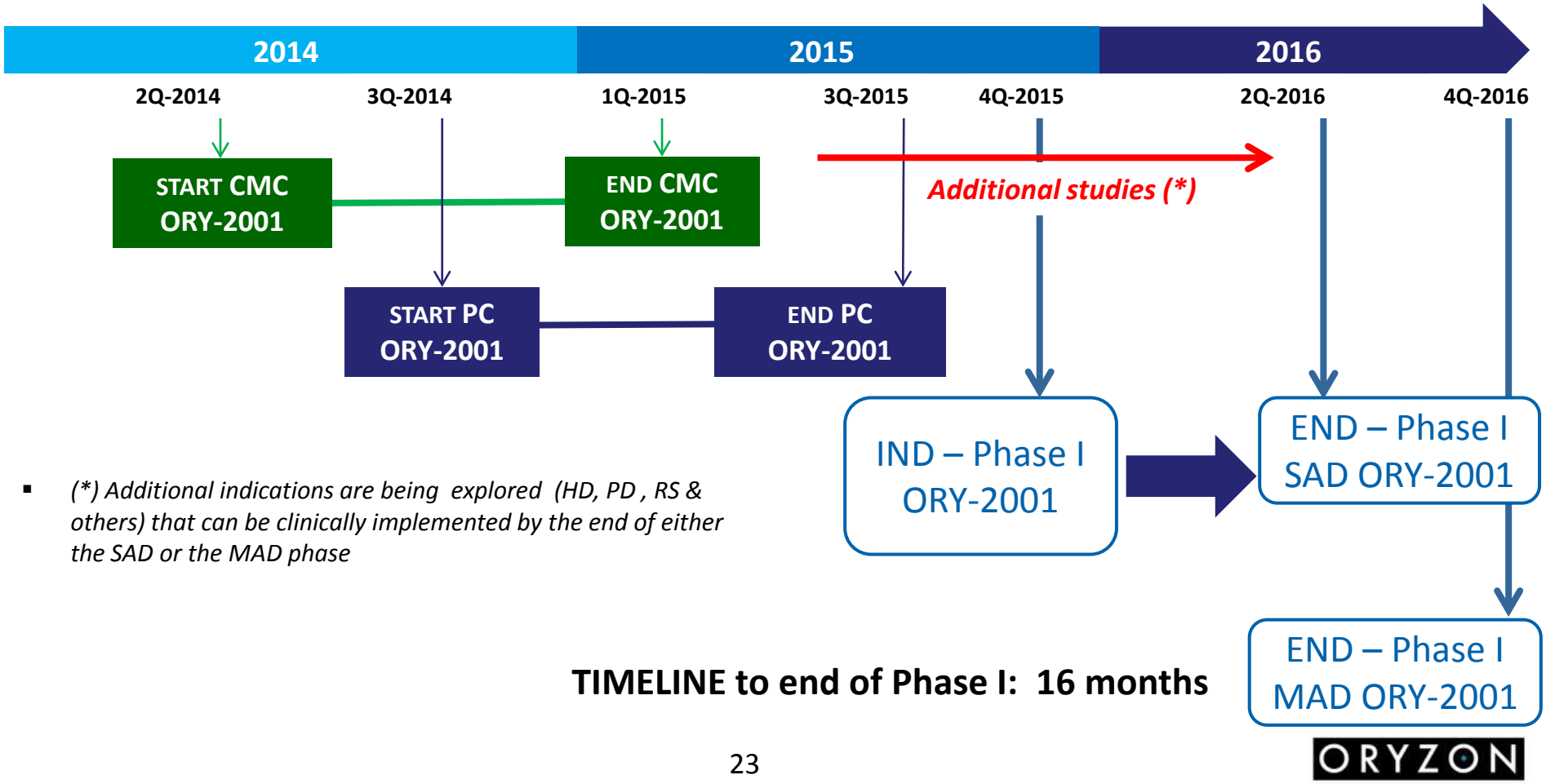
Development Timeline for ORY-2001

ORY-2001 clinical candidate has successfully finished PC regulatory toxicity studies and will be ready for clinical testing in humans by Q4/2015



- *(*) Additional indications are being explored (HD, PD , RS & others) that can be clinically implemented by the end of either the SAD or the MAD phase*

TIMELINE to end of Phase I: 16 months

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ORY-2001 preferential partnering scenario

The split of commercial territorial rights with the partner in return to a significant contribution in the clinical development is considered the preferential collaboration scenario.


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Thank you !
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