A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION

MADX: ORY

2017 BIO CEO & Investor Conference

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ORYZON

COMPANY HIGHLIGHTS

- MADX: ORY A **publicly traded** company on the Spanish Stock Exchange
- A **clinical stage** biopharmaceutical company developing innovative therapies in the field of Epigenetics
- A competitive **EPIGENETIC Platform** with a first program that validates the platform scientifically and clinically
  - Two therapeutic programs in clinical development with multiple indication opportunities
  - Additional assets in preclinical development to be progressed quickly
- Signed global **strategic partnership with ROCHE** valued up to $500M(*)
- IP portfolio with technology developed in-house (+20 patent families)
- **Raised €32M** (in 2015-2016). **Cash runway** expected till **mid 2018**

(*) Aggregate contingent milestone payments. See SLIDE 8

BOLSA DE MADRID

OPEN 4.68	DAY RANGE 4.58 - 4.76	VOLUME 29,747
PREVIOUS CLOSE 4.68	52WK RANGE 2.55 - 5.20	1 YR RETURN 33.32%
YTD RETURN 32.22%	CURRENT P/E RATIO (TTM) -	EARNINGS PER SHARE (EUR) (TTM) -0.03
MARKET CAP (M EUR) 130.440	SHARES OUTSTANDING (M) 28.468	PRICE/SALES (TTM) 31.68

ORYZON

MANAGEMENT TEAM

▪ CEO

CARLOS BUESA: CEO
PhD in Biochemistry and Molecular Biology. Author of more than thirty papers and patents internationally. In 2000, he founded Oryzon Genomics, and since 2001 he has served as Chief Executive Officer and Chairman of the Board of Directors. He has taken several advanced programs on finance, business development, negotiation skills and human resources. He is also PADE at the IESE Business School. He is Board Member of the VC Fund Inveready and Deputy President of the Spanish BioIndustry Association.

▪ CSO

TAMARA MAES:

Founder and Chief Scientific Officer

PhD in Biotechnology from the University of Ghent, Belgium. She has produced over twenty scientific papers and patents internationally and has developed innovative HTS methods for functional genomics

She is SAB member on several public institutions as CSIC and private companies. Since 2016 Scientific Advisor of the ADDF

▪ IP Director

NEUS VIRGILI :

Intellectual Property Director

B.Sc. in Organic Chemistry from the University of Barcelona (1990).

Qualified European Patent Attorney

She has got over 20 years experience in pharmaceutical IP

From 2011 IP Officer at Oryzon

▪ CFO

ENRIC RELLO:

Chief Financial Officer

B.Sc. in Business, University of Barcelona

HBS Finance Excellence Program. Harvard Business School (Executive Education) USA.

1993-1997 Biochemie SA (Novartis) Financial Controller / Controller Manager

1997- 2007 Sandoz Industrial Products S.A. (Novartis), CFO Spanish Affiliate.

From May 2011 CFO at Oryzon

▪ Clinical Director

CESAR MOLINERO:

Medical and Clinical Operations Director

PhD in Medicine from the University of Barcelona & AMP at ESADE Business School and Babson

In 1992 he joined the Medical Department of KabiPharmacia

In 1994, he joined the Department of Clinical Research at Laboratorios Esteve where, in 1998, he assumed responsibilities as Medical Adviser

In 2002 he joined Madaus S.A. (Barcelona) as Medical and Regulatory Affairs Director, and later with responsibility as Group VP for Medical, R&D and Regulatory Affairs

Joined Oryzon in January 2014

▪ BDO

EMILI TORRELL:

Director of Business Development

B.Sc. in Sciences, Autonomous University of Barcelona

MBA at ESADE and PDG at IESE Business School

In the business development area from 1990 in the most relevant Spanish companies Prodesfarma, Almirall and Laboratorios Esteve

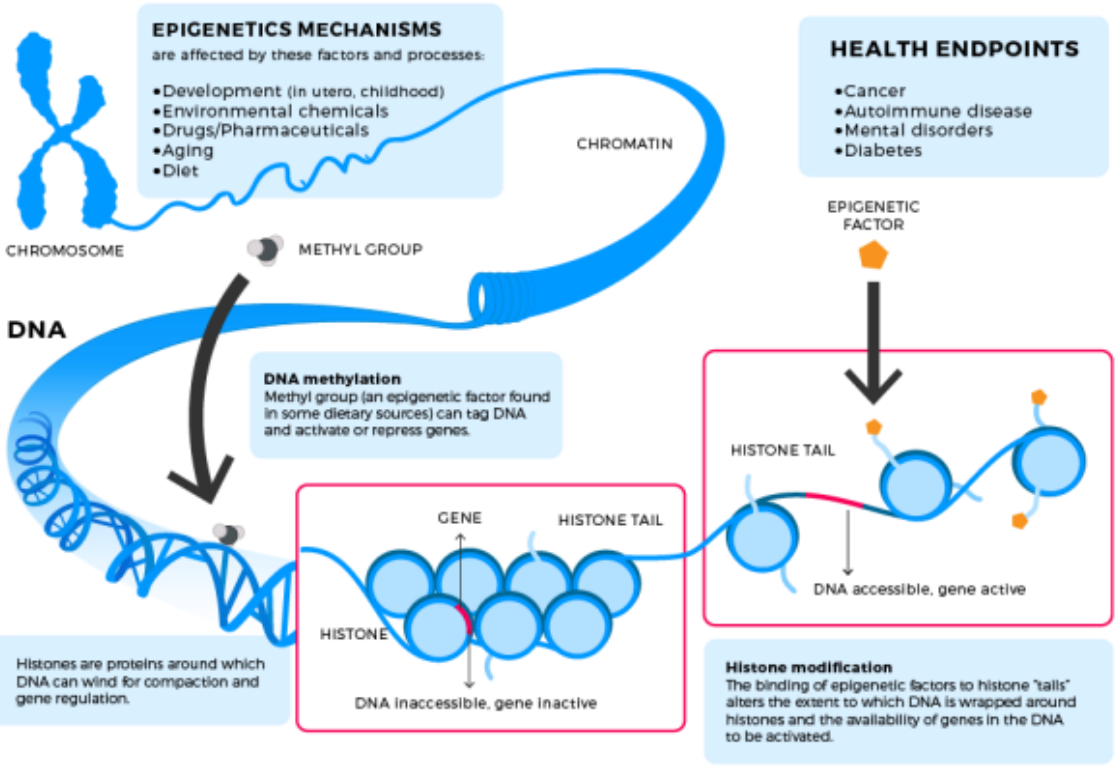
From 2007 BD Director at Oryzon

- One of the most experienced and respected managerial teams in the Biopharmaceutical industry in Spain
- Team members have a track record in product discovery & in advancing successfully through product development phases
- Demonstrated ability to close world class deals and to lead, and participate in international consortia

ORYZON

EPIGENETICS: THE CRITICAL ROLE OF HISTONE CODING

- **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**



EXTENSIVE PIPELINE : 2 PROGRAMS IN CLINIC WITH MULTIPLE INDICATIONS

- ✓ A LSD1 focused company
- ✓ LSD1 is an enzyme that demethylates histones: specifically mono and dimethylated H3K4 and H3K9

MOLECULE	TARGET	INDICATION	DISCOVERY	H2L	LEAD OPTIMIZATION	PRECLINICAL	PHASE I	PHASE IIA	PHASE IIB	PHASE III	PARTNER
ORY-1001 (*)	LSD1	Leukemia(**)									Roche
		Small Cell Lung Cancer									Roche
ORY-2001	LSD1-MAOB	Alzheimer's Disease Parkinson's Disease Other Dementias									
		Multiple Sclerosis Other CNS Autoimmune									
		Huntington's Disease Other Orphan Diseases									
ORY-3001	LSD1	Undisclosed Indication									
Other Assets	Other KDMs	Cancer Other indications									
	Other Epigenetic Targets	Cancer Other indications									

(*) ORY-1001 is also known under Roche's ID codes RG6016 and RO7051790

(**) Phase I / IIA in Acute Leukemia has been done in the same trial

ORYZON

ORY-1001: ONCOLOGY PROGRAM

- **LSD1 is a target in some cancers**
- LSD1 is a key effector of the differentiation block in MLL leukemia
- MLL Leukemic stem cells are addicted to LSD1 activity
- ORY-1001 is a highly potent and selective LSD1 inhibitor with orphan drug status granted by the European Medicines Agency (EMA)
- Finishing Data Analysis of Phase I/IIA study:
  - Completed Part 1 of the study (Phase I) in acute leukemia
  - Extension Arm (Phase IIA) completed
- Potential for additional indications in solid tumors

A big market potential

Licensed to ROCHE in 2014

- **$23M received in 2014-15**
- **$500+M in future contingent milestones**
- **Tiered royalties up to double digit**
- **Further clinical development and all related investments beyond this Phase I/IIA trial are the responsibility of ROCHE**

ORYZON

License Agreement with Roche

- Effective from April 1st, 2014
- License of two patent families of the Oryzon IP Portfolio that Oryzon has created in its pioneering research in LSD1
- Scope of the collaboration: R&D and commercialization of Oryzon's LSD1 inhibitor lead agent ORY-1001 (RG6016) and/or its backup compounds for oncology, haematology (e.g. AML) and non-malignant conditions
- The license also includes a 2-year collaborative R&D program, extended until March 2017, between Oryzon and Roche's NY-based Translational Clinical Research Center (TCRC), to better understand the potential of LSD1 inhibitors in oncology and haematology
- Under the terms of the agreement, Oryzon has already received an upfront payment and near-term milestones and collaboration fees totaling $23 million, plus potential development, commercial and sales milestone payments across haematology, cancer and non-malignant indications that could exceed $500 million, together with tiered royalties on sales which range up to mid-double digits
  - $435 million in development milestones
    - $235 million for hematological and solid cancerous indications
    - $80 million for non-cancerous indications
    - $120 million for nervous system disorders
  - $90 million in sales milestones
- For complete details, please see the public-offer Prospectus of Oryzon (page 225-97) at the Spanish Stock-Exchange website.

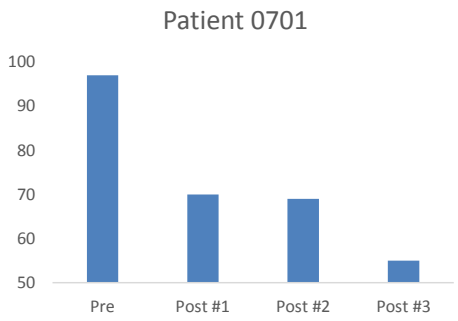
ORYZON

PHASE I/IIA HIGHLIGHTS: ORY-1001 IN ACUTE LEUKEMIA

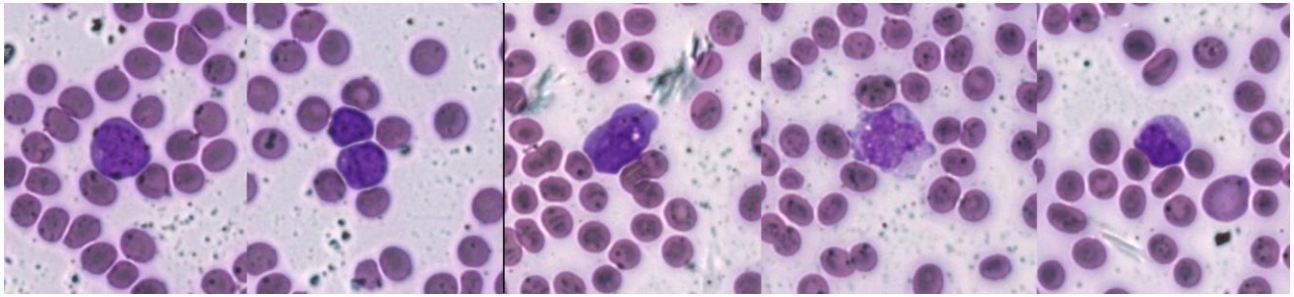
58th ASH® Annual Meeting and Exposition
San Diego Convention Center • San Diego, California

- *Preliminary data presented at ASH 2016.*

- Well tolerated and has been administered to 41 patients in total up to a maximum of three cycles. Excellent oral bioavailability in humans and excellent pharmacokinetic parameters
- Pharmacodynamic biomarkers S100A12, VCAN, ITGAM, LY96, CD86, GPR65, CRISP9, ANXA2 and LYZ permit monitoring of response to ORY-1001 treatment in M4/M5 AML patients
- Promising clinical responses were observed in the Phase IIA arm (14 patients, 4M6, 6MLL gene fusion and 4 MLL other mutations) mandating further clinical research and investigation
- Taking the four M6 patients together, there was no significant rise in blast cell count after two cycles of therapy – suggesting disease stabilization
- 4/6 patients with MLL leukemia showed evidence of morphological blast cell differentiation
- 2 of these exhibited a differentiation syndrome
- 100% (5/5) of patients with MLL gene fusion with evaluable PD samples showed evidence of blast differentiation by qRT-PCR analysis in PD analyses
- 23% of Bone Marrow responses (3/13)



Before treatment During treatment (patient 0206)



ORYZON

ORY-1001 (RG6016): Next Steps

Licensed to ROCHE in 2014

- ORY-1001 has demonstrated Biological Proof of Mechanism as a highly active LSD1 inhibitor with strong differentiation-inducing activity in patients with MLL leukemia. It has shown an excellent safety profile in acute leukemia patients, and also displayed excellent oral bioavailability and pharmacokinetic parameters
- ORY-1001 might be a potential combinatorial therapeutic option in the treatment of several types of acute myeloid leukemia. Pharmacodynamic biomarkers identified for M4-M5 leukemias
- As a potent and safe LSD1 inhibitor, ORY-1001 is also of potential interest in the treatment of solid tumors such as small cell lung cancer, and possibly others in the future
- In Small Cell Lung Cancer (SCLC; Milleti et al., 2016, AACR: "Neuroendocrine gene transcript expression is associated with sensitivity to lysine-specific demethylase-1 inhibitor RO7051790 in small cell lung cancer-derived cell lines"). High levels of neuroendocrine markers ASCL1, DDC, and GRP; a gene signature based on these markers predicts response to RO7051790 in SCLC cell lines (p-value 0.0055). ~50% of SCLC patients express high levels of ASCL1, DDC, and GRP, suggesting that this subpopulation may benefit from an RO7051790 based therapy"

Roche now has sole responsibility of developing ORY-1001 (Roche's ID codes RO7051790 and RG6016) and has recently initiated its first clinical trial with ORY-1001 in extensive-stage disease SCLC (ED SCLC). The trial is an open-label, multi-centre (4 countries) study with an estimated 70 ED SCLC patients to be treated with ORY-1001. Safety/tolerability is the primary endpoint, while secondary endpoints will include preliminary efficacy (overall survival, progression-free survival, objective response) and PK/PD data. The estimated completion date is expected in 2H 2019.

ROCHE has already started a Phase I with ORY-1001 (RG6016) in Small Cell Lung Cancer (data expected in 2H 2019)

ORYZON

ROLE OF EPIGENETICS IN NEURODEGENERATIVE DISORDERS

ORY-2001: OUR NEXT GROWTH DRIVER

Lines of evidence supporting a role of epigenetics in etiology and pathogenesis of specific NDGs

	Alzheimer's disease	Parkinson's disease	Huntington's disease
Methylation	Reduced DNA methylation in the anterior temporal neocortex neuronal nuclei Hypermethyation of HTERT gene Hypomethylation of inflammatory genes iNOS, IL-1, and TNF-α in the AD cortex	Overall reduction of methylation potential Hypomethylation of SNCA gene in brain tissue α-synuclein related reduction of Dnmt1 methyltransferase availability Differential methylation of ARK16, GPNMB, STX1B and CYP2E1	Early reports of increased variability at HTT gene locus
Histone modifications	increased phosphorylated histone H3 in hippocampal neurons Modulation of histone acetylation by HDAC inhibitors improved learning and memory in mouse models	Response to treatment with HDACIs in disease models α-synuclein related reduction in histone acetylation and histone gene expression	Beneficial effect of HDACIs in disease models Sequestration of proteins with HDAC activity (CBP) Increase of histone proteins carrying H3K9 marks in brain and blood tissues

Luca Lovrečić, et al., 2013 The Role of Epigenetics in Neurodegenerative Diseases

ENVIRONMENT

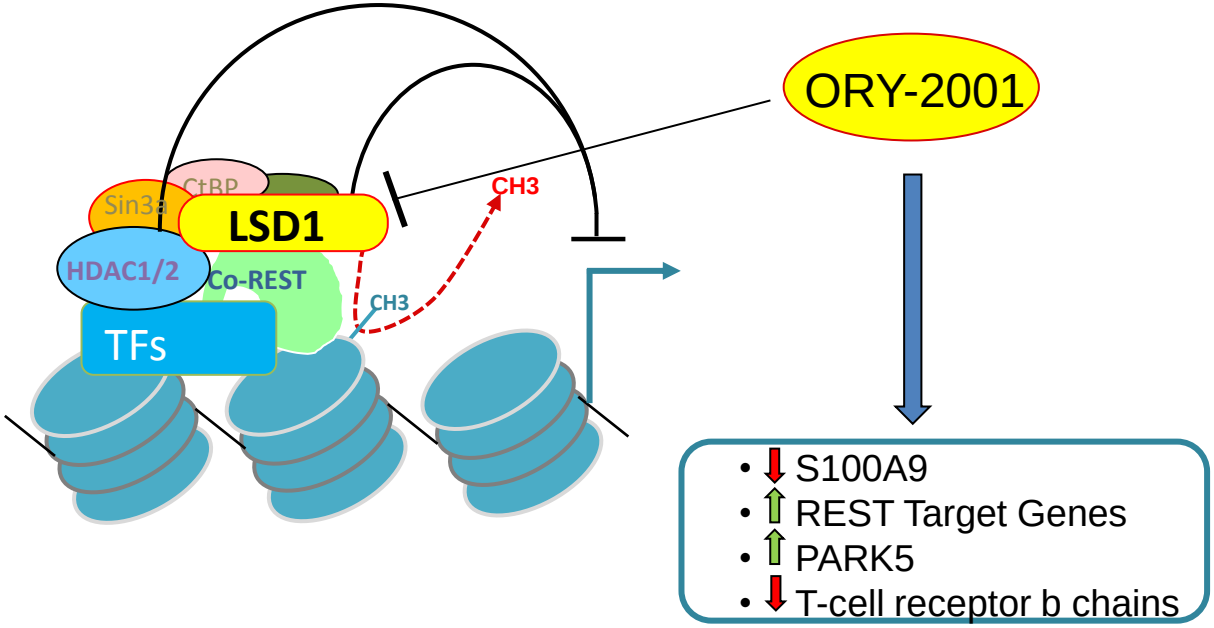
GENES EXPERIENCE

- Identical twins (monozygotic)
- Same DNA with GBA risk mutation
- Disconcordant for symptoms of Parkinson's
- Up to 20 years difference in onset
- Patient derived iPSCs: difference in MAO-B levels

ORYZON

LSD1 in the CNS

- **LSD1 is a key component of different CNS transcriptional complexes** interacting with different transcription factors and very often with HDAC1 and HDAC2
- In the brain one of these TFs is REST. The LSD1-REST-CoREST-HDAC1/2 repressor complex is involved mainly in controlling developmental programs and modulating neuronal morphology in the CNS. Different to what happens in HDACs, it has been proven that it is possible to develop extremely selective LSD1 inhibitors with excellent pharmacological properties
- LSD1 is known to be an important regulator in the maintenance of pluripotency and in specification of neuronal commitment of pluri- or multipotent cells
- In C. elegans, Drosophila and mammalian cells LSD1 suppression has been reported to significantly enhance the removal of misfolded proteins with a critical role on neurodegeneration like SOD1, TDP-43, FUS, and polyglutamine-containing proteins, indicating a general improvement in protein quality control



ORY-2001 – A COMPOUND FOR CNS expected to be ready for Phase II in 2H2017

- **Pharmacological Properties**
  - A selective dual LSD1-MAO-B inhibitor
  - Optimal ADMET and PK profiles
  - Crosses efficiently the BBB
  - Once daily oral bioavailable
  - Selectivity against MAO-A demonstrated in-vitro and in-vivo
  - High therapeutic window in animals: a safe drug for chronic settings
  - Target engagement demonstrated in vivo
- **Biomarkers identified**
- **Exclusively owned by Oryzon**

- **Preclinical Proof of Concept** Achieved in different animal models of:
  - Alzheimer's Disease
  - Huntington's Disease
  - Multiple Sclerosis
  - 2 Additional CNS disorders
- Additional indications being explored preclinically
- **Clinical development → In Phase I:**

  LVO expected in early 2017
  - Alzheimer's Disease is lead indication → Phase IIB Planned
  - Additional indications: MS and HD → Phase IIA Planned

ORYZON

SAMP8 mouse: A model for Alzheimer's Disease

Biochimica et Biophysica Acta 1832 (2013) 839–850

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The senescence accelerated mouse (SAMP8) as a model for oxidative stress and Alzheimer's disease☆

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Amyloid beta

ABSTRACT

The senescence accelerated mouse (SAMP8) is a spontaneous animal model of overproduction of amyloid precursor protein (APP) and oxidative damage. It develops early memory disturbances and changes in the blood–brain barrier resulting in decreased efflux of amyloid-β protein from the brain. It has a marked increase in oxidative stress in the brain. Pharmacological treatments that reduce oxidative stress improve memory. Treatments that reduce amyloid-β (antisense to APP and antibodies to amyloid-β) not only improve memory but reduce oxidative stress. Early changes in lipid peroxidative damage favor mitochondrial dysfunction as being a trigger for amyloid-β overproduction in this genetically susceptible mouse strain. This sets in motion a cycle where the increased amyloid-beta further damages mitochondria. We suggest that this should be termed the Inflammatory-Amyloid Cycle and may well be similar to the mechanisms responsible for the pathophysiology of Alzheimer's disease. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

International Scholarly Research Network
ISRN Cell Biology
Volume 2012, Article ID 917167, 12 pages
doi:10.5402/2012/917167

Review Article

Senescence-Accelerated Mice P8: A Tool to Study Brain Aging and Alzheimer's Disease in a Mouse Model

Mercè Pallàs

Unitat de Farmacologia i Farmacognòsia, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona y Centros de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Nuch Universitari de Pedralbes, 08028 Barcelona, Spain

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The causes of aging remain unknown, but they are probably intimately linked to a multifactorial process that affects cell networks to varying degrees. Although a growing number of aging and Alzheimer's disease (AD) animal models are available, a more comprehensive and physiological mouse model is required. In this context, the senescence-accelerated mouse prone 8 (SAMP8) has a number of advantages, since its rapid physiological senescence means that it has about half the normal lifespan of a rodent. In addition, according to data gathered over the last five years, some of its behavioral traits and histopathology resemble AD human dementia. SAMP8 has remarkable pathological similarities to AD and may prove to be an excellent model for acquiring more in-depth knowledge of the age-related neurodegenerative processes behind brain senescence and AD in particular. We review these facts and particularly the data on parameters related to neurodegeneration. SAMP8 also shows signs of aging in the immune, vascular, and metabolic systems, among others.

frontiers in AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 29 October 2013
doi: 10.3389/fnagi.2013.00065

Nodes and biological processes identified on the basis of network analysis in the brain of the senescence accelerated mice as an Alzheimer's disease animal model

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[†] These authors have contributed equally to this work.

Harboring the behavioral and histopathological signatures of Alzheimer's disease (AD), senescence accelerated mouse-prone 8 (SAMP8) mice are currently considered a robust model for studying AD. However, the underlying mechanisms, prioritized pathways and genes in SAMP8 mice linked to AD remain unclear. In this study, we provide a biological interpretation of the molecular underpinnings of SAMP8 mice. Our results were derived from differentially expressed genes in the hippocampus and cerebral cortex of SAMP8 mice compared to age-matched SAMR1 mice at 2, 6, and 12 months of age using cDNA microarray analysis. On the basis of PPI, MetaCore and the co-expression network, we constructed a distinct genetic sub-network in the brains of SAMP8 mice. Next, we determined that the regulation of synaptic transmission and apoptosis were disrupted in the brains of SAMP8 mice. We found abnormal gene expression of RAF1, MAPT, PTGS2, CDKN2A, CAMK2A, NTRK2, AGER, ADRBK1, MCM3AP, and STUB1, which may have initiated the dysfunction of biological processes in the brains of SAMP8 mice. Specifically, we found microRNAs, including miR-20a, miR-17, miR-34a, miR-155, miR-18a, miR-22, miR-26a, miR-101, miR-106b, and miR-125b, that might regulate the expression of nodes in the sub-network. Taken together, these results provide new insights into the biological and genetic mechanisms of SAMP8 mice and add an important dimension to our understanding of the neuro-pathogenesis in SAMP8 mice from a systems perspective.

Keywords: Alzheimer's disease, senescence accelerated mouse prone 8, molecular network, hippocampus, cerebral cortex, differential expressed genes, synaptic transmission, apoptosis

Table 1
Comparison of Alzheimer's disease, SAMP8 mouse and transgenic mice models.

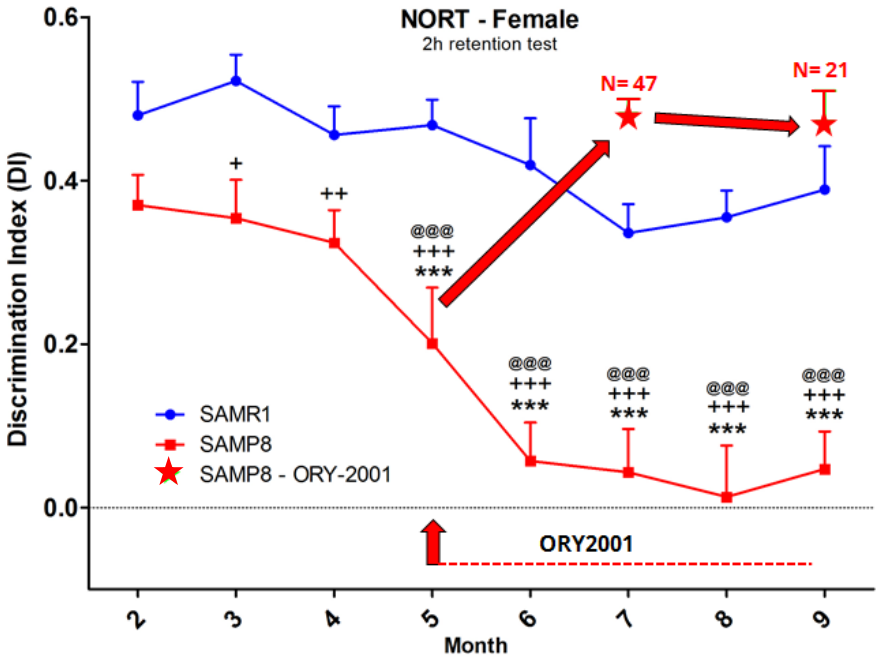
	Alzheimer's disease	SAMP8	Transgenic models
Overproduction of amyloid-β	Yes	Yes	Yes
Amyloid plaques	Yes	Late[a]	Yes
Phosphorylated tau	Increased	Increased	In some models
Cerebral amyloid angiopathy	Yes	Yes	Yes
Neuron loss	Yes	Yes	?
Synaptic dysfunction	Yes	Yes	Yes
Dendritic spine loss	Yes	Marked	?
Gliosis	Yes	Yes	Yes
Cholinergic deficit	Yes	Yes	Yes
Learning and memory impaired	Yes	Yes	Yes
Circadian rhythm disturbances	Yes	Yes	?
Oxidative damage	Yes	4 months	8 months

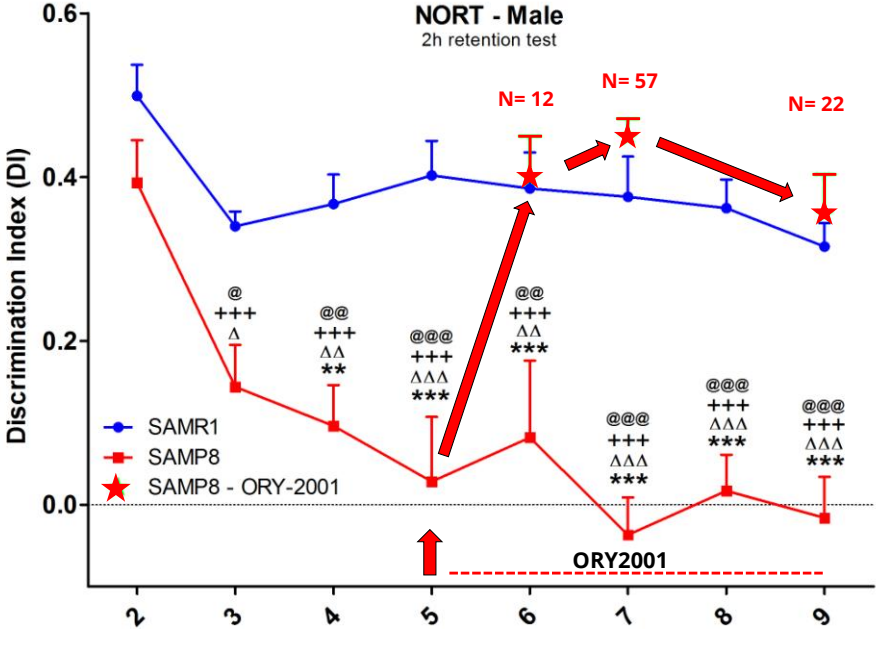
? = uncertain.
[a] Occur at 16 to 18 months.

ORYZON

ORY-2001: A possible disease modifier drug

- 2 or 4 months of oral treatment with ORY-2001 produce a marked cognitive improvement in SAMP8 animals measured by NORT memory tests
- 9 studies in the last 5 years +150 animals tested
- Other +readouts in animal models of MS, HD, PD and other human CNS disorders





ORY-2001 restores the discrimination index in SAMP8 mice

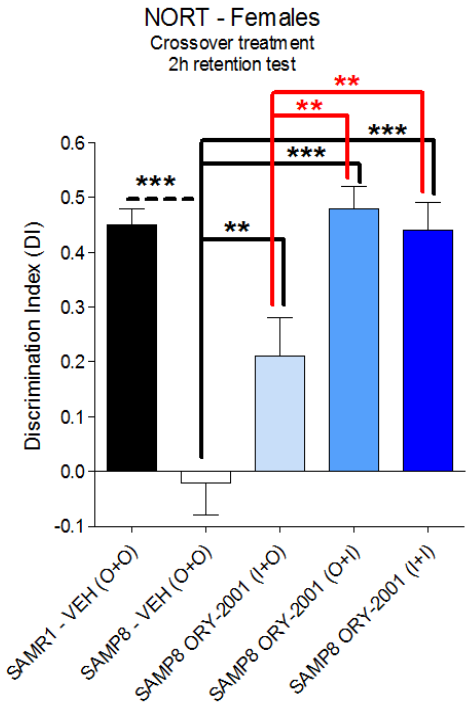
Meta-analysis of cognitive deficit of untreated SAMP8 mice (historical data)

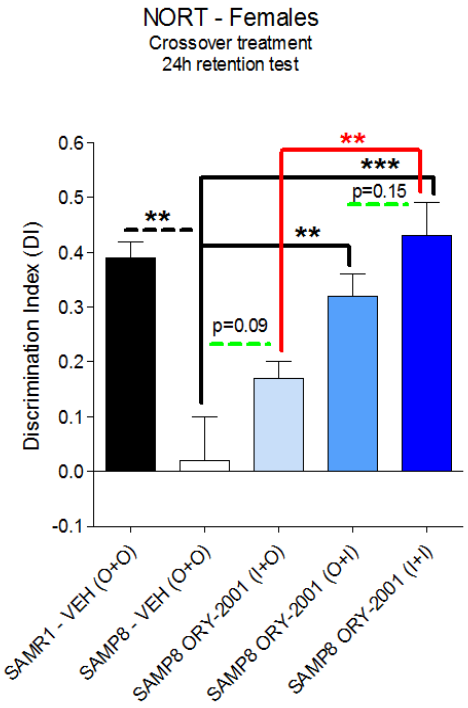
Is ORY-2001 a disease modifying drug?

ongoing

- Cross over Experiment

Month	Treatment		
	6	7	Code
SAMR1	Vehicle	Vehicle	0+0
SAMP8	Vehicle	Vehicle	0+0
SAMP8	ORY-2001	ORY-2001	1+1
SAMP8	ORY-2001	Vehicle	1+0
SAMP8	Vehicle	ORY-2001	0+1





- The drug restored memory function after the deficit had developed
- The delayed start cohort (0+1) experienced the full benefit
- The early start (1+0) cohort continued to show significant benefit 1 month after treatment interruption

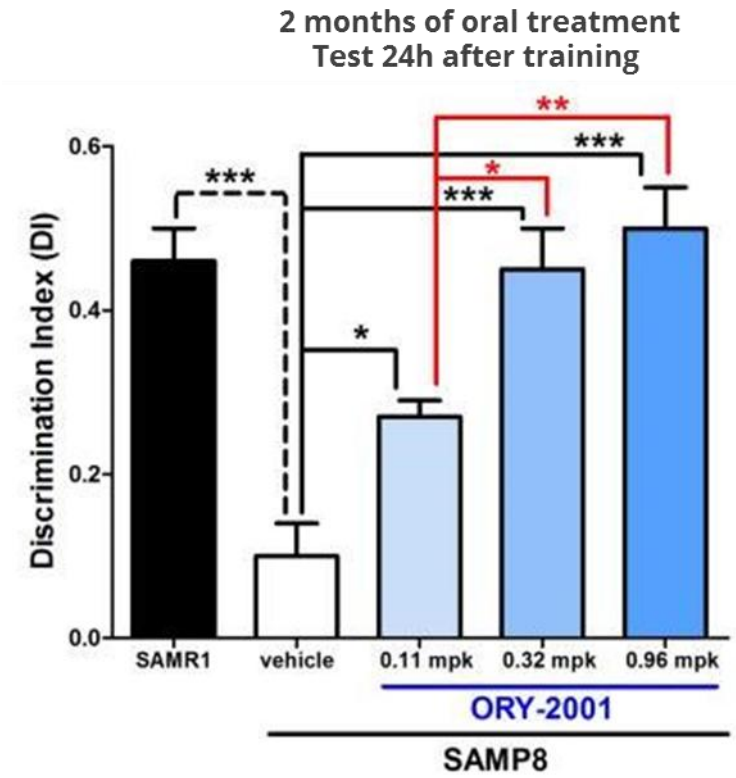
→ Disease modifying potential

ORYZON

PoC studies in SAMP8 mice

- ✓ The effect is driven by LSD1 but there is an additive / synergistic effect provided by the MAOB component

- ✓ ORY-2001 provides a **dose dependent** protective effect in the medium-term memory of mice, compared to age-matched SAMP8 mice



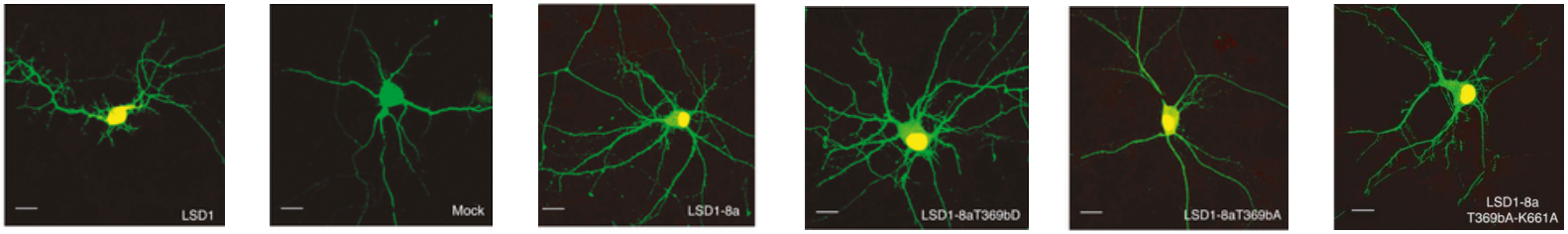
LSD1 function in the brain: LSD1-8a KO mice

LSD1-8a KO mice (Zibetti et al, Wang et al)

- Neuronal differentiation ↓, Neurite extension ↓
- Long Term Memory ↓
- Induction of Egr ↓, Fos ↓, Npas4 ↓, Arc ↓

Shelly Berger: ACSS2 deficit leads to memory defect and defect in up-regulation of similar gene set

How LSD1-8a works? Rat cortical neuron differentiation (Toffolo et al. J Neurochem. 2014)



LSD1 | mock | LSD1-8a | LSD1-8a Thr369bAsp | LSD1-8a Thr369bAla | LSD1-8a Thr369bAla + Lysine661Ala

↓

"phosphorylated"

↓

"unphosphorylated"

↓

"unphosphorylated" catalytically dead

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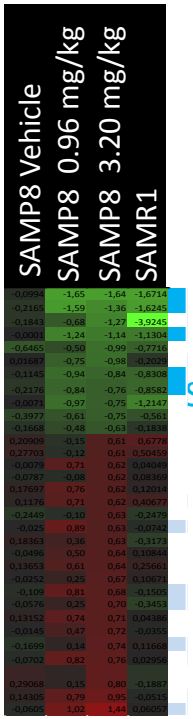
Hippocampal gene expression changes induced by ORY-2001

Genes located in amplified cluster on Chr4

Inflammation signature genes



Inflammation signature genes

Cognitive function, neuroplasticity and memory

	SAMP8		SAMR1
	vehicle	DUAL 0,96 mg/kg	vehicle
Junb	0,01	0,47	0,35
Egr4	-0,03	0,39	0,38
Arc	0,11	0,33	0,40
Npas4	0,05	0,48	0,43
Egr2	0,13	1,10	0,52
Nr4a1	0,11	0,45	0,52
Fos	-0,13	0,79	0,54

- ✓ ORY-2001 potently down-regulated the expression of a subset of genes related to immune reaction and inflammation, including S100A9 and T-cell receptor b chains in SAMP8 mice.
- ✓ ORY-2001 up-regulated genes associated with improved cognitive function, neuroplasticity and memory, including: Egr, Fos, Nr4a1, Npas4, Arc… i.e. the pharmacological intervention mimicks the stimulation of LSD1-8a, supports the observation of improved memory

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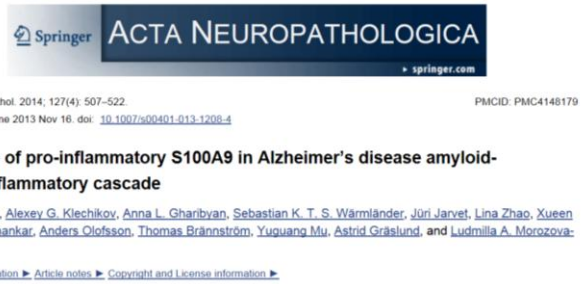
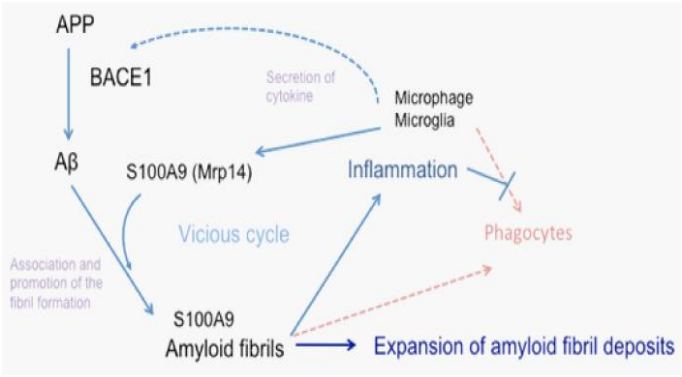
S100A9 and Alzheimer's disease

- ✓ S100A9 downregulation improves memory in different AD Tg mice models
- ✓ S100A9 has been involved in the A-Beta deposition dynamics

CT-Tg mice Mutant APP(V717I) CT100 (London mutation)			S100a9 markedly increased in cortex and hippocampus, memory impairment *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)			S100a9 upregulated in hippocampus, memory impairment *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)		sh S100a9 RNA lentiviral brain injection →	S100a9 Knockdown attenuates learning and memory impairment in Tg2576 mice / reduces amyloid plaques in Tg2576 brains *(Ha et al., 2010)*
Tg2576 mice mutant APP (isoform 695); Swedish mutation (KM670/671NL)	X	S100a9 -/- knock-out mice →	Tg2576 S100a9 -/- mice have improved memory, reduces amyloid pathology *(Kim et al., 2014)*
APP/PS1 mice mutant APPswe PSEN1dE9			S100a9 upregulated in hippocampus, memory impairment, amyloid pathology *(Kummer et al., 2012)*
APP/PS1 mice mutant APPswe PSEN1dE9	X	S100a9 -/- knock-out mice →	APP/PS1 S100a9 -/- mice have increased phagocytosis of fibrillar amyloid β (Aβ) in microglia cells, improved memory *(Kummer et al., 2012)*





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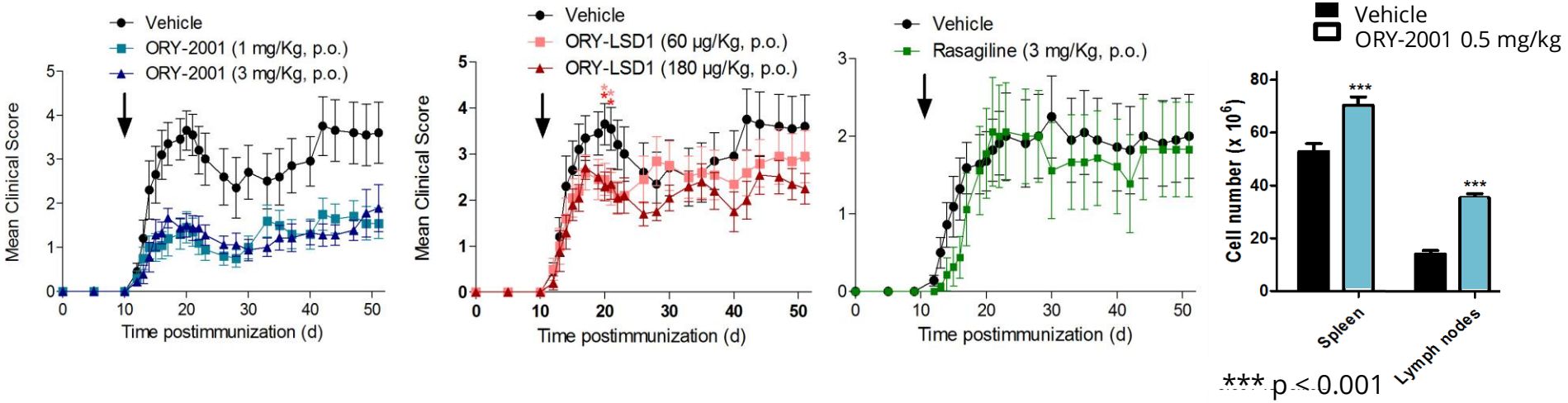
ORY-2001 also a possible approach to treat Multiple Sclerosis ?

- ORY-2001 downregulates S100A9 in the Hc of SAMP8 animals
- Complexes of S100A8 and S100A9 (S100A8/A9) are expressed and released at inflammatory sites
- A correlation between serum levels of S100A8/A9 and disease activity has been observed in many inflammatory disorders
- Quinoline-3-carboxamides (Q compounds) that target S100A9 have been explored as treatments for autoimmune/inflammatory diseases in humans. And one of these, Laquinimod is being currently explored for Multiple Sclerosis treatment
- There are additional models/diseases in which S100A9 has been found to be both overexpressed and deleterious. One of these models is EAE, a Multiple Sclerosis model

ORY-2001 in Experimental Autoimmune Encephalomyelitis(EAE)

- ✓ Model for multiple sclerosis
  - C57BL/6 mice immunized s.c. with 100 µg of MOG35–55 emulsified in CFA containing 4 mg/ml M. tuberculosis H37 RA and i.p. injections of 200 ng of pertussis toxin on days 0 and 2
- ✓ Treatment after onset of EAE symptoms (d11) during 2 weeks with
  - ORY-2001 p.o.; ORY-LSD1 p.o.; Rasagiline p.o.



- ✓ ORY-2001 clearly reduced the Mean Clinical Score, ORY-LSD1 was less effective, Rasagiline appeared to marginally delay onset but effects were not significant.
- ✓ Increased cellularity in lymph nodes, spleen may indicate reduced egress of lymphocytes
- ✓ Lower doses of ORY-2001 were also effective (not shown), MoA to be presented at ACTRIMS, Orlando

→ Cytokine profiling, gene expression in brain/spinal cord, immune cell proliferation

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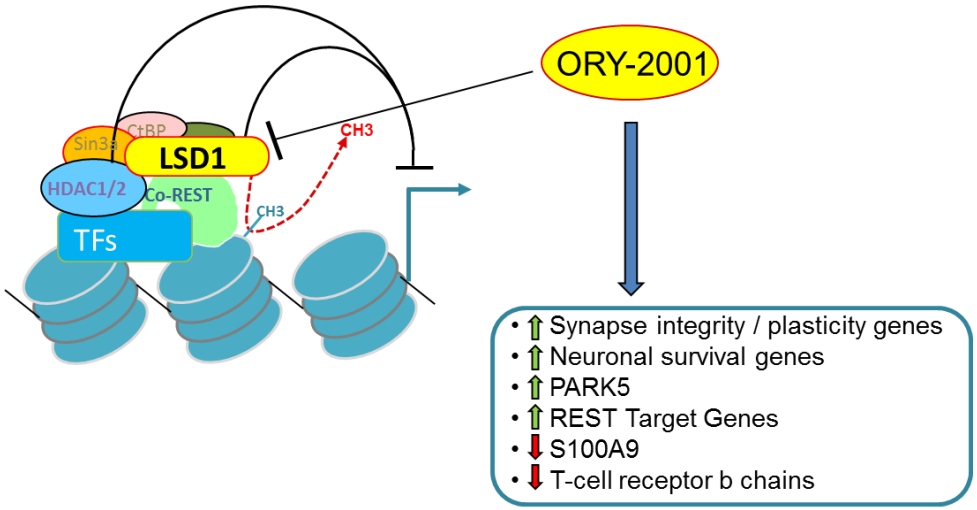
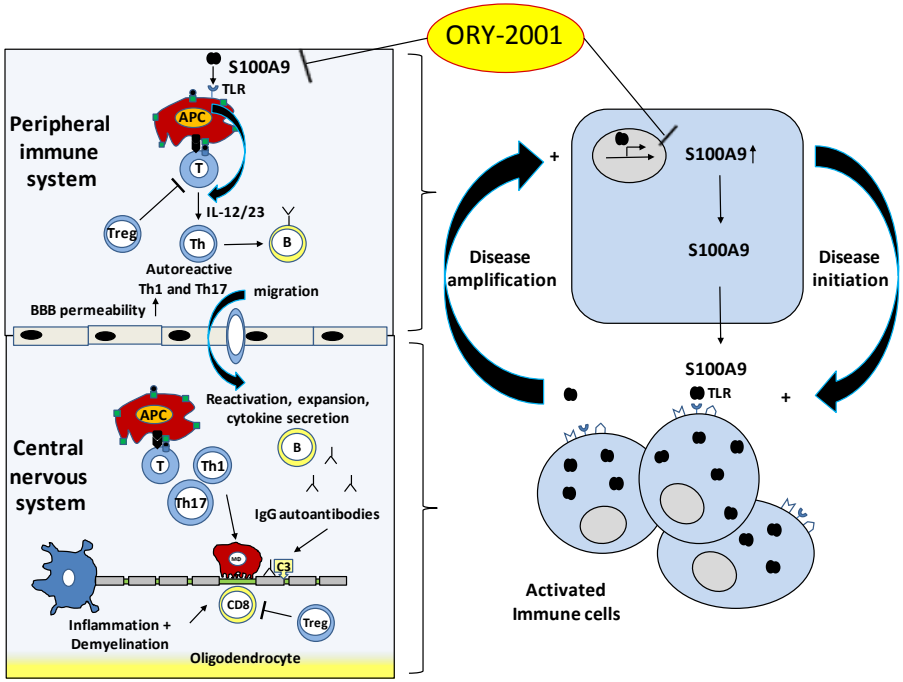
ORY-2001 has a Multi-Modal Mechanism of Action

A neuroprotective component + antiinflammatory component



LSD1 plays a role in expression of neuronal genes thru demethylation of H3K4 and H3K9



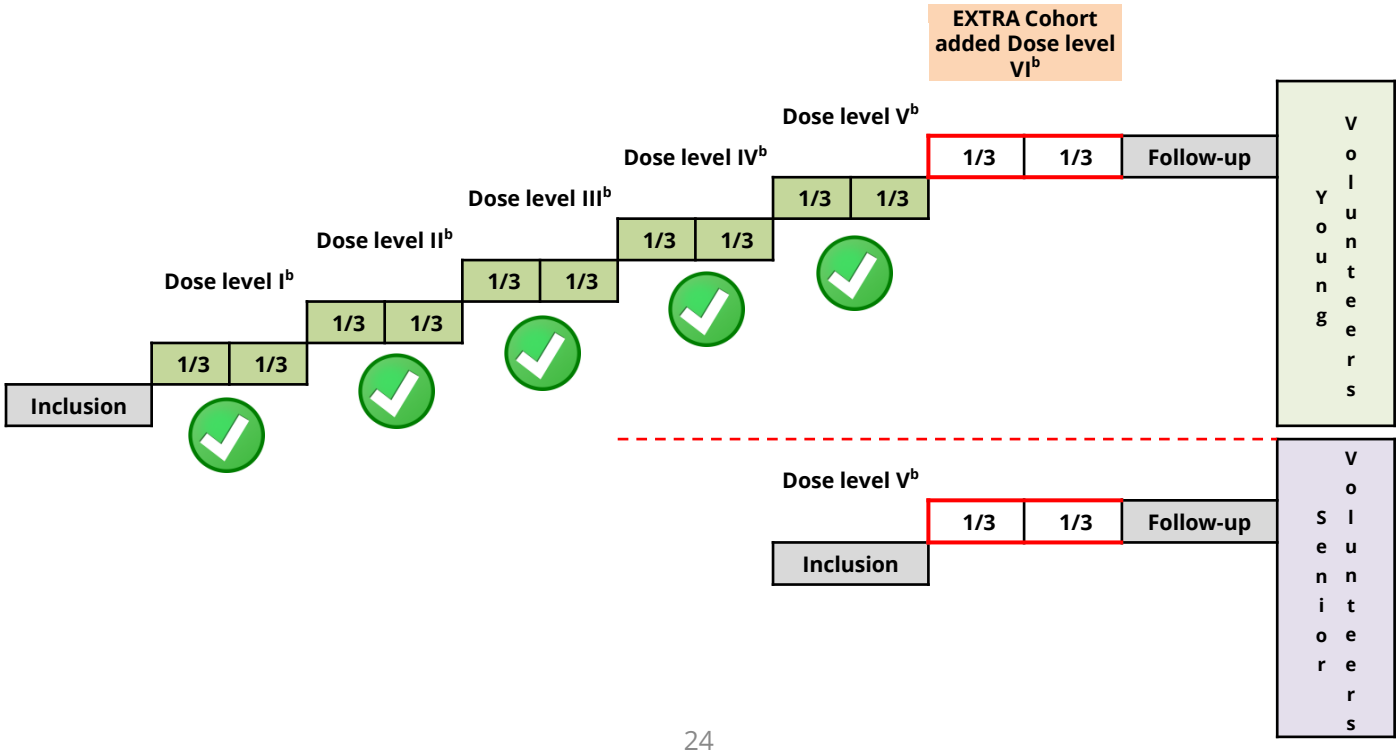
ORY-2001 Phase I Clinical Trial - SAFETY

A Phase I study with 88 healthy volunteers, young and elderly

Phase I, single center, double blind, parallel, ascending single and multiple dose trial.

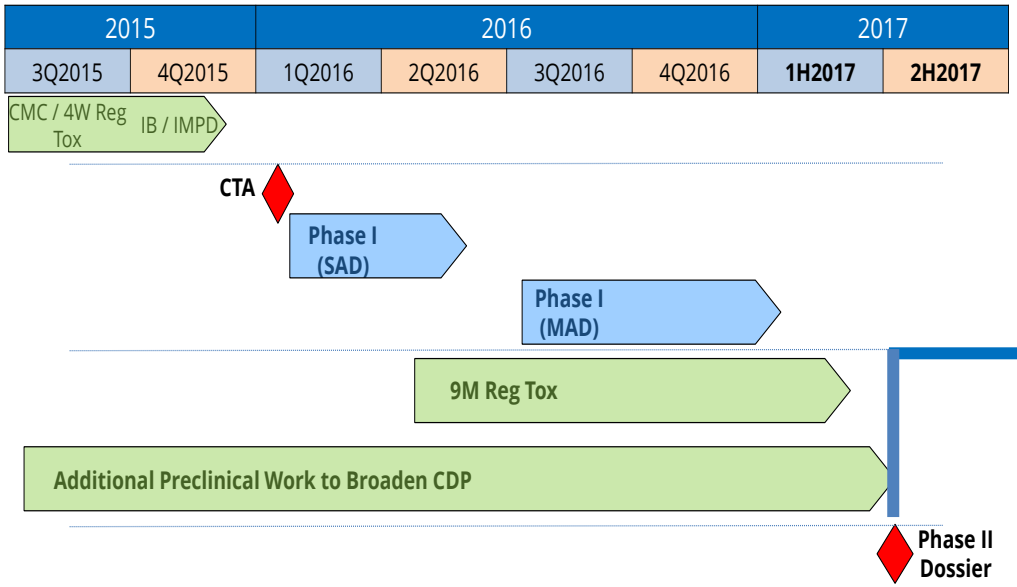
TITLE: A Study to Assess the Safety, Tolerability and Pharmacokinetic of Single and Multiple Oral Doses of ORY-2001 in Healthy Male, Female Subjects and Elderly Population
STUDY CODE: CL01-ORY-2001
EUDRACT NUMBER: 2015-003721-33

- ✓ **Single Ascending Dose (SAD):** all cohorts were **safe**. **No hematological effects** nor any other relevant/significant side effects observed in any cohort
- ✓ **Additional arm** to determine CSF ORY-2001 levels after a single dose
- ✓ **Multiple Ascending Dose (MAD):** five dose levels tested so far in young volunteers, **no hematological effects** nor any other relevant/significant side effects observed



ORY-2001 DEVELOPMENT TIMELINE

- ORY-2001 expected to be ready for Phase II in 2H-2017
- The Phase I in healthy volunteers enables us to go for Phase IIs in different indications
- The company envisages to perform three different Phase IIs in AD, MS and HD



PLANNED ORY-2001 CDP

Phase II-B in AD

Phase II-A in MS

Phase II-A in HD

A multibillion market potential (*)

(*) GlobalData Healthcare Report May 2015

ORYZON, A UNIQUE OPPORTUNITY

Corporate Strategy: Epigenetics Momentum, IP & First in Class Clinical Assets

- Epigenetics is an emerging field with high interest from Pharma (select acquisitions: Roche/Tensha; Celgene/Acetylon; Merck/OncoEthix) and from Specialized Investors (Imago, Constellation)
- High quality science and a broad patent portfolio on LSD1, one of the hottest targets in this area (GSK, Celgene, Incyte, Takeda). Competitive Patent portfolio with +20 patent families, many already granted in USA
- ORYZON is a pioneer in epigenetics

Platform + Broad Product Pipeline: Aim for three different assets in Clinic (5-6 trials) by 2017

- We developed the first ever LSD1 inhibitor reaching clinical trials in the world. We have reported the first human data in oncology with ORY-1001 (RG-6016)
- A dual LSD1-MAOB inhibitor finishing Phase I and with PoC in several human disease animal models
- Three Phase IIA-IIB clinical trials expected to start in 2H 2017
- A third LSD1 inhibitor being developed for an orphan disease and Phase I expected in 2017
- Other epigenetic programs in development

Financials and Governance: Strong balance sheet

- A dynamic and capital efficient company with excellent know-how (40 people)
- €29M in cash at the end of 3Q-2016: Cash runway expected until mid 2018, but wanting to invest more to capture the upside of our Phase IIB in ORY-2001 and other clinical programs
- An experienced public company board with experienced executives with proven track record in the industry
- Top governance according to public company standards

ORYZON

Financial Overview – September 30th 2016

Cash Balance		**28.803.492**
Short-term financial assets	5.598.006	
Cash and Equivalents	23.205.486	
Financial Debt		**23.698.609**
Long-term Debts	19.098.559	
Short-term debts	4.600.050	
Net Balance		**5.104.884**

New Financial bank loans in 2016

15,750 Mio €

2,68% Average Interest Rate

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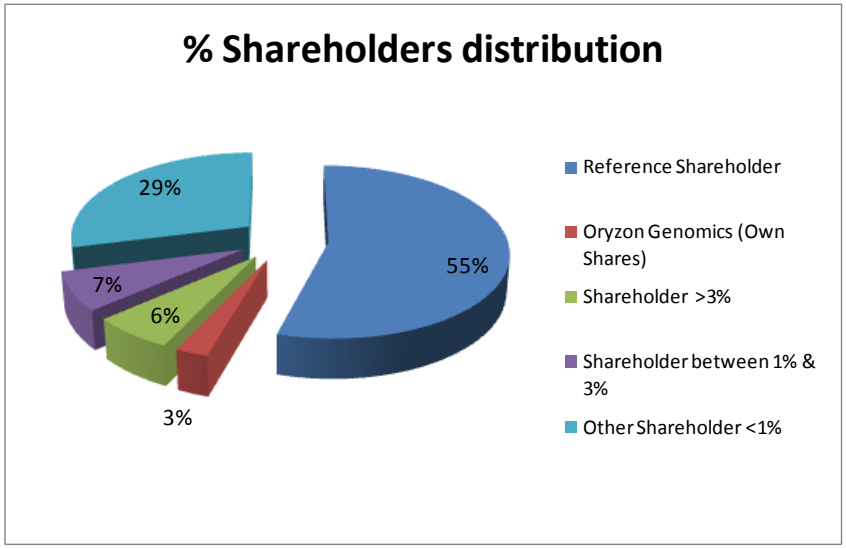
Capitalization and ownership summary

TOP 10 ORYZON SHAREHOLDER	by January 2nd 2017	
NAJETI CAPITAL SA	7.017.799	**24,65%**
TAMARA MAES	3.742.530	**13,15%**
CARLOS MANUEL BUESA	3.742.530	**13,15%**
INVERSIONES COSTEX S.L.	1.854.723	**6,52%**
JOSE MARIA ECHARRI	1.026.928	**3,61%**
MINORITY SHAREHOLDERS (free flow)	11.083.316	**38,93%**
TOTAL COMPANY SHARES	**28.467.826**	



	Shareholder	Shares	%
Reference Shareholder	4	15.529.787	54,55%
Oryzon Genomics (Own Shares)	1	743.688	2,61%
Shareholder >3%	1	1.854.723	6,52%
Shareholder between 1% & 3%	4	2.096.513	7,36%
Other Shareholder <1%	1291	8.243.115	28,96%
TOTAL	**1301**	**28.467.826**	**100%**

On January 2nd 2017, Oryzon Genomics had 1.301 shareholders.

The 54,55% of the shares are owned by the reference shareholders.

All the Company shares are common shares, without any additional options or warrants.

ANTICIPATED ORYZON CATALYSTS

2014

- ✓ **Transformational deal with Roche ($21M) on ORY-1001**

2015-16

- ✓ **CONSOLIDATION PERIOD**
- ✓ **Public in Europe ($36M raised** June-2015-June 2016 **)**
- ✓ **ORY-1001:** Clinical Data Presented at ASH-2016
- ✓ **Second Asset** (ORY-2001 in clinic development)

2017

- ✓ **ORY-1001: LEAD CANCER ASSET**
  - ✓ **FPI in Phase I SCLC by Roche** **1Q**
  - Phase I-IIA study expected to formally close 2Q
- ✓ **ORY-2001: LEAD CNS ASSET**
  - Anticipated Top Line Phase I (ADPD-2017 Conference) 1Q
  - Anticipated demonstration of human target engagement 2Q
  - Anticipated Phase I Completion 2Q
  - Anticipated filing CTA / IND for Phase II-A in MS 2H
  - Anticipated filing CTA / IND for Phase II-A in AD 2H
  - Anticipated filing CTA / IND for Phase II-A in HD 2H
  - Anticipated FPI in a Phase II-A study in MS 2H
- ✓ **ORY-3001:**
  - Anticipated filing CTA / IND for Phase I study on an orphan indication yet to be disclosed 2H

2018

- ✓ **ORY-2001: LEAD CNS ASSET**
  - Anticipated FPI in a Phase II-A study in AD 1Q
  - Anticipated FPI in a Phase II-A study in HD 1Q

ORYZON

THANK YOU VERY MUCH!

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