A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION

MADX: ORY

JANUARY 2017

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COMPANY HIGHLIGHTS

- MADX: ORY A **publicly traded** company on the Madrid 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 at $500M
- Strong IP portfolio with technology developed in-house (+20 patent families)
- **Raised €32M** in the last 12 months. **Cash runway till 2018**
- **+32%** stock evolution on the last 12 months

BOLSA DE MADRID

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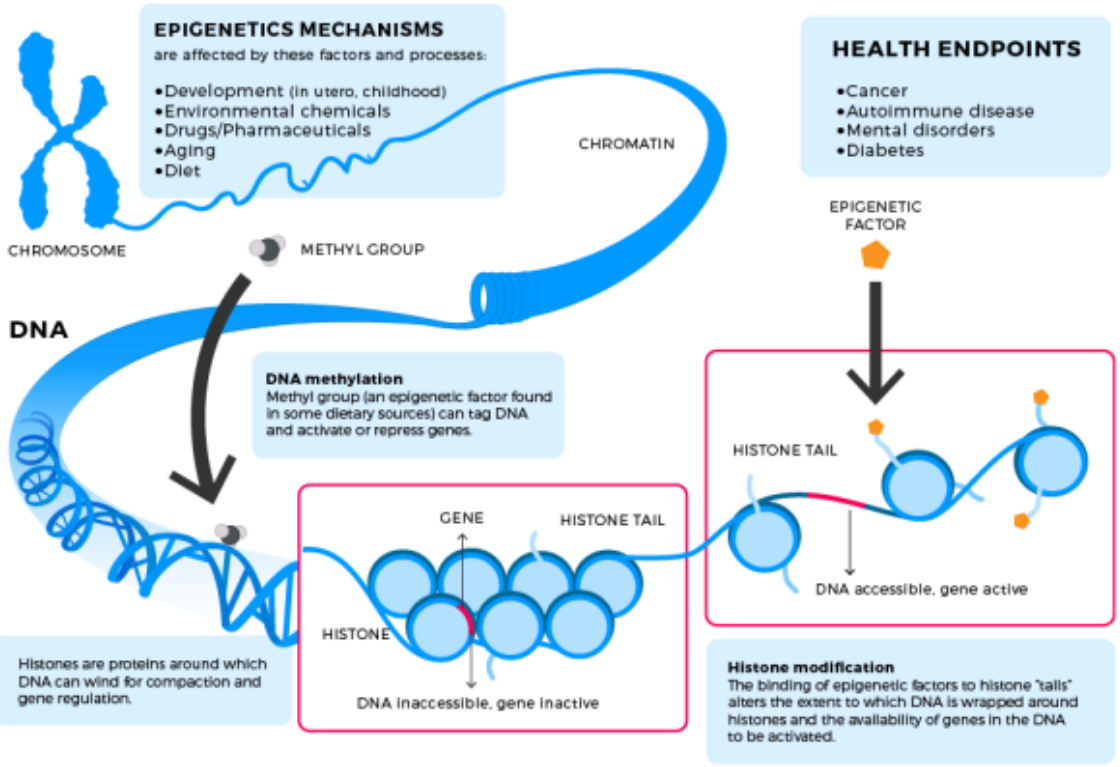
EPIGENETICS: THE CRITICAL ROLE OF HISTONE CODING

- **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

INDICATION	TARGET	MOLECULE	DISCOVERY	H2L	LEAD OPTIMIZATION	PRECLINICAL	PHASE I	PHASE IIA	PHASE IIB	PHASE III	PARTNER
CANCER Leukemia	LSD1	ORY-1001 (*) (RG6016)									Roche
CANCER Small Cell Lung Cancer	LSD1	ORY-1001 (RG6016)									Roche
CNS DEMENTIAS Alzheimer's Disease Parkinson's Disease Other Dementias	LSD1-MAOB	ORY-2001									
CNS INFLAMMATION Multiple Sclerosis Other Autoimmune	LSD1-MAOB	ORY-2001									
CNS ORPHAN Huntington's Disease Other Orphan Diseases	LSD1-MAOB	ORY-2001									
OTHER INDICATIONS	LSD1	ORY-3001									
CANCER	Other KDMs										
CANCER	Other Epigenetic Targets										

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

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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 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 $2+ billion 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**

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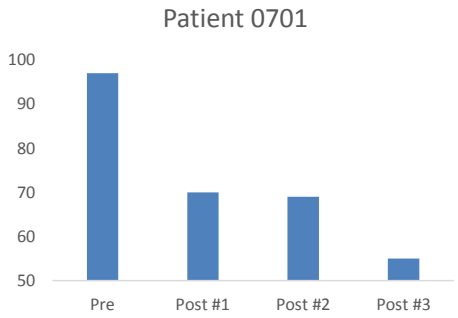
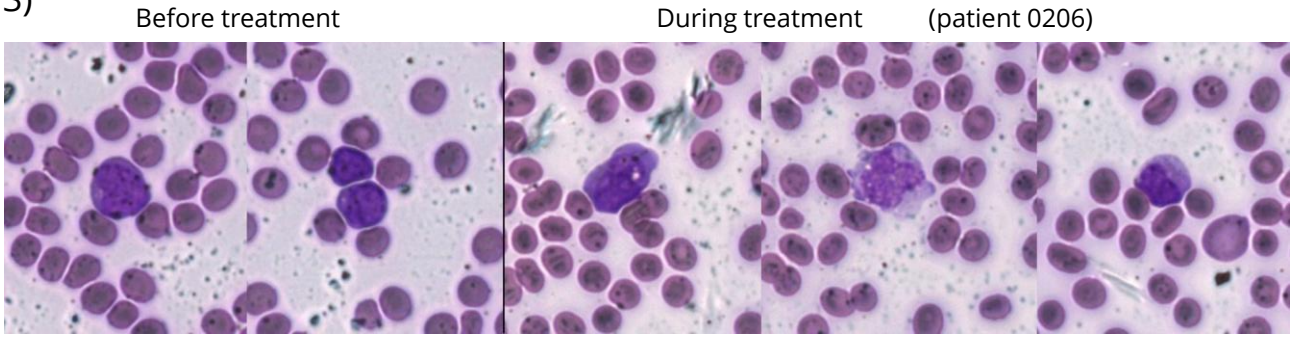
PHASE I/IIA HIGHLIGHTS: ORY-1001 IN ACUTE LEUKEMIA

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

- *See ASH Ancillary **Investor / Analyst luncheon event webcast** at https://www.oryzon.com*

- 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 BM responses (3/13)





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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
- Pharmacodynamic biomarkers identified for M4-M5 leukemias, as well as for Small Cell Lung Cancer (SCLC; Milleti et al., 2016, AACR: "Neuroendocrine gene transcript expression is associated with efficacy to lysine-specific demethylase-1 inhibitor RG6016 in small cell lung cancer-derived cell lines") and other subtypes of malignancies
- ORY-1001 might be a potential combinatorial therapeutic option in the treatment of several types of acute myeloid leukemia
- 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

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 H2 19. *See https://clinicaltrials.gov/ for more details (Study identifier NCT02913443)*

ROCHE has already started a Phase I with ORY-1001 (RG6016) in Small Cell Lung Cancer

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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

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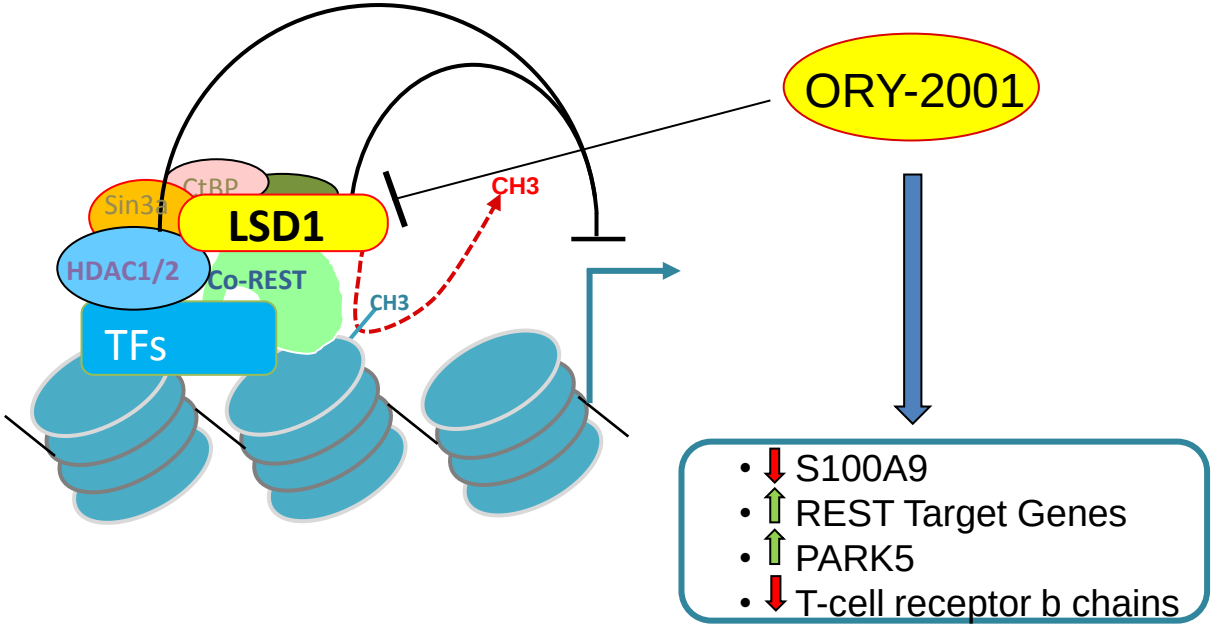
LSD1 in the CNS

- **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 ready for Phase II in 1H2017

- **Pharmacological Properties**
  - A selective dual LSD1-MAO-B inhibitor
  - Optimal ADMET and PK profiles
  - Crosses efficiently the BBB
  - Once daily oral bioavailable
  - Good pharmaceutical properties
  - 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

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SAMP8 mouse: A model for Alzheimer's Disease

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

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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.

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Review Article

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

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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
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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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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.

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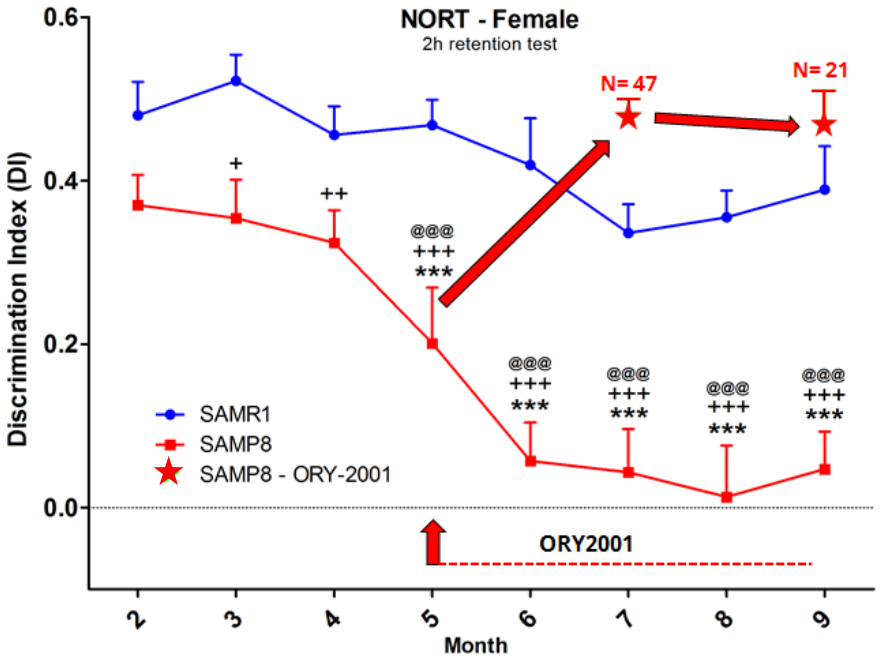
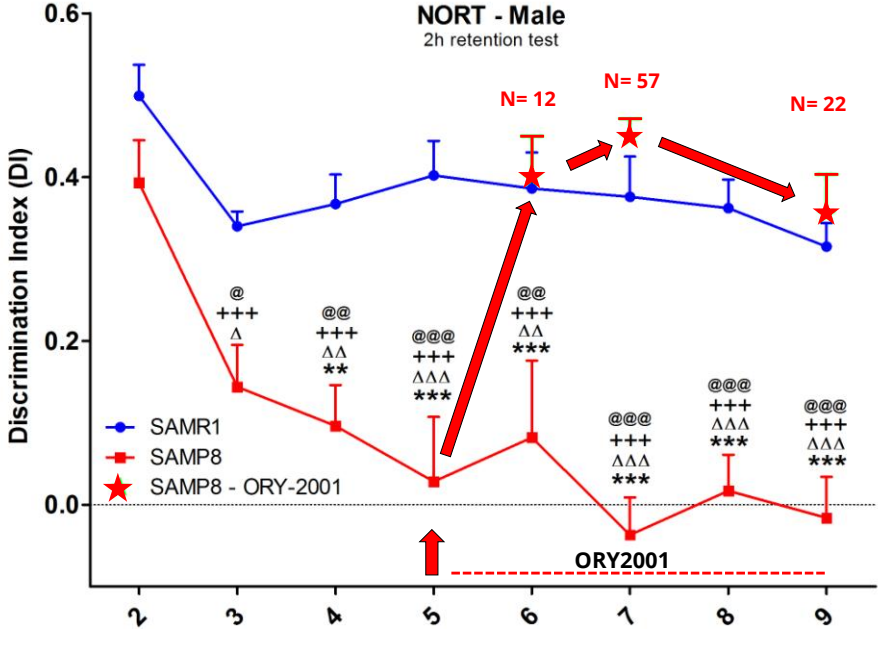
ORY-2001: A possible disease modifier drug

- ✓ 2 or 4 months of oral treatment with ORY-2001 produce a marked cognitive improvement in SAMP8 animals measured by NORT memory tests
- ✓ +150 animals tested





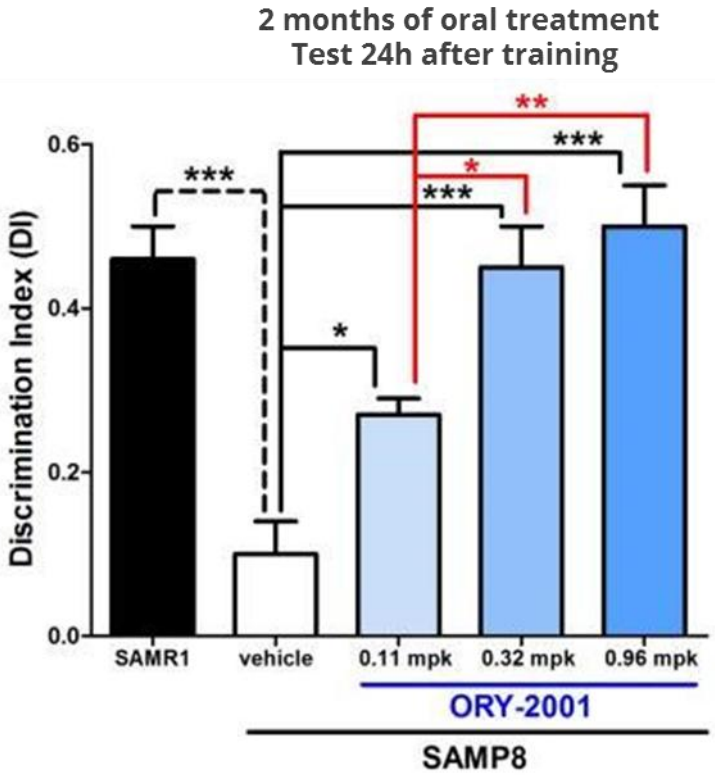
ORY-2001 restores the discrimination index in SAMP8 mice

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

PoC studies in SAMP8 mice

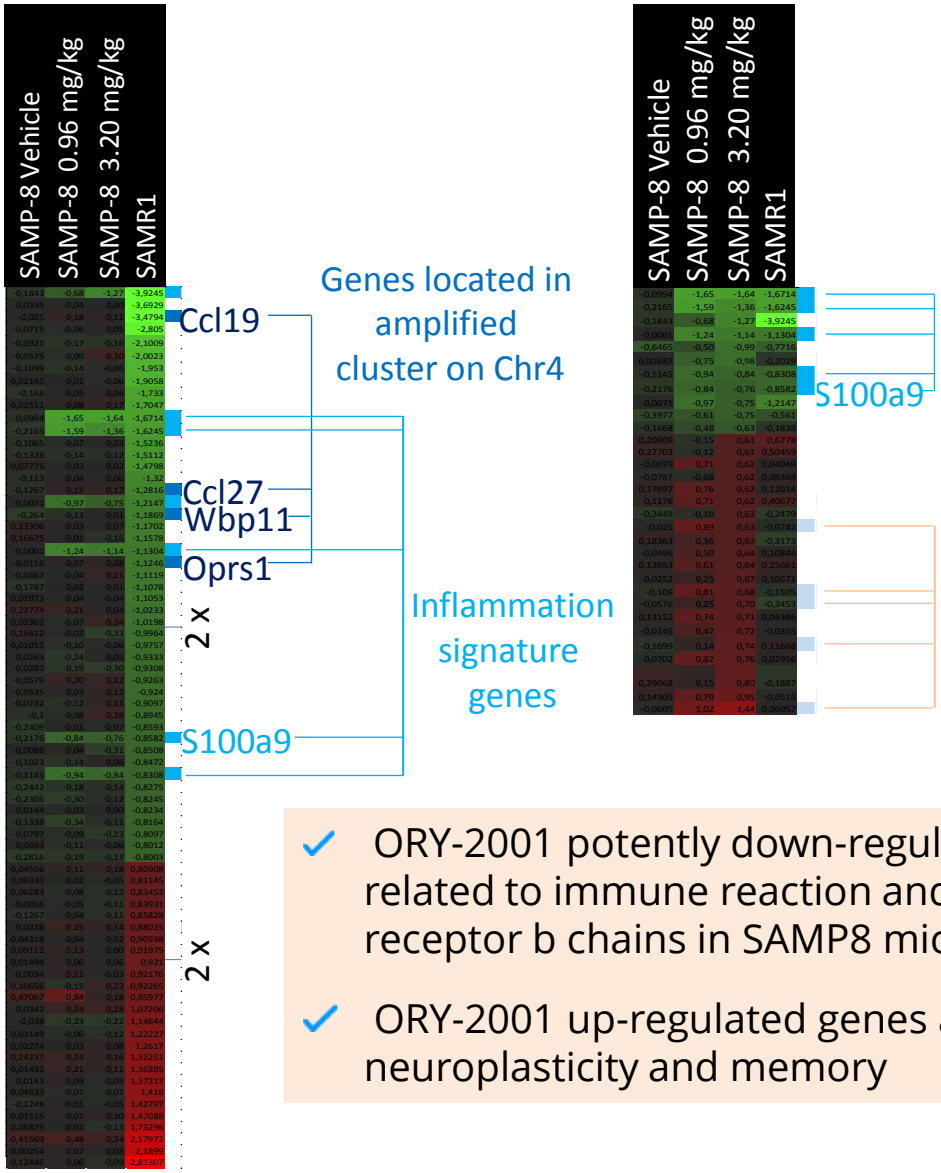
- ✓ 2 or 4 months of oral treatment with ORY-2001 produce a marked cognitive improvement in SAMP8 animals measured by NORT memory tests

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



PoC studies in SAMP8 mice - **BIOMARKERS**

We have identified different Hippocampal **biomarkers** upon ORY-2001 treatment:



<50 genes up or down-regulated by > 2-fold female SAMP8 vs SAMR1 (see also Carter *et al.*)

Chr 4 cluster incuding *Ccl19* and *Ccl27* is amplified and over-expressed SAMP8 vs SAMR1 mice

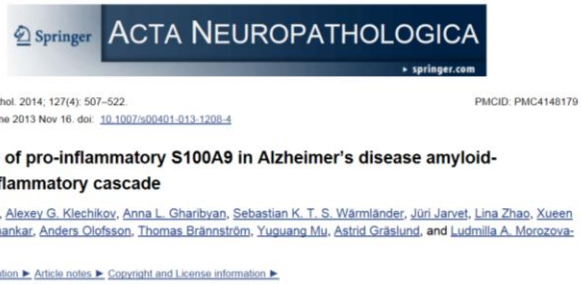
Inflammation genes upregulated in SAMP8 vs SAMR1 mice

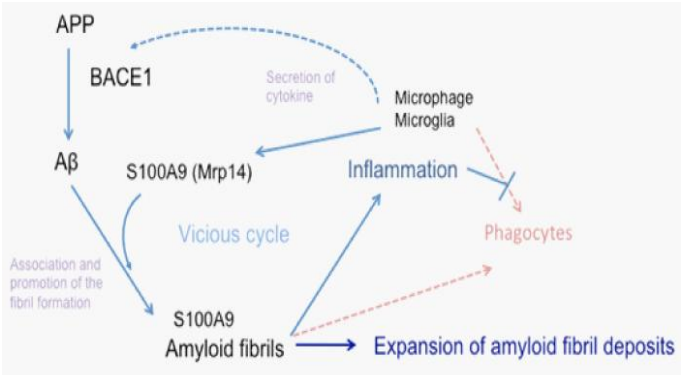
- ✓ ORY-2001 potently down-regulated the expression of a subset of genes related to immune reaction and inflammation, including S100A9 and T-cell receptor b chains in SAMP8 mice
- ✓ ORY-2001 up-regulated genes associated with improved cognitive function, neuroplasticity and memory

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 a possible approach to treat Multiple sclerosis?

Experimental Autoimmune Encephalitis (EAE) mice model is a model in which S100A9 has been described to be upregulated

This model is considered a meaningful model for Multiple Sclerosis

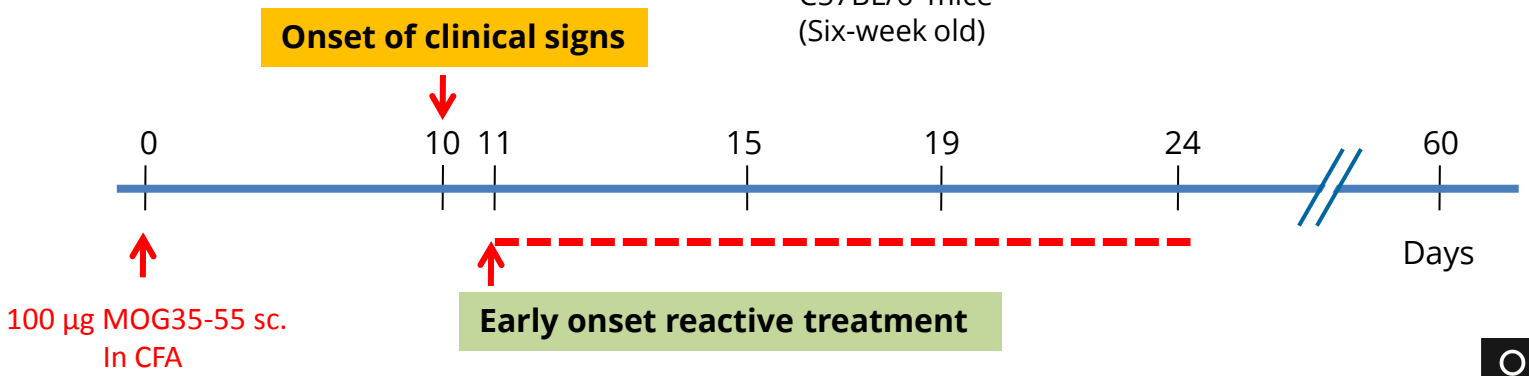
To determine the efficacy of ORY-2001 following oral gavage administration for 2 consecutive weeks in mice.

Method:
Female C57BL/6 mice
G1 : Vehicle Control
G2 : ORY-2001 1.0 mg/Kg , p.o.
G3 : ORY-2001 3.0 mg/Kg , p.o.

Parameter to asses:
Body weight
Clinical score
Inflammatory response
Autoimmune response

Clinical score:
0.0, no clinical signs
0.5, partial loss of tail tonicity
1.0, complete loss of tail tonicity
2.0, flaccid tail and abnormal gait
3.0, hind leg paralysis
4.0, hind leg paralysis with hind body paresis
5.0, hind and fore leg paralysis
6.0, death

C57BL/6 mice
(Six-week old)



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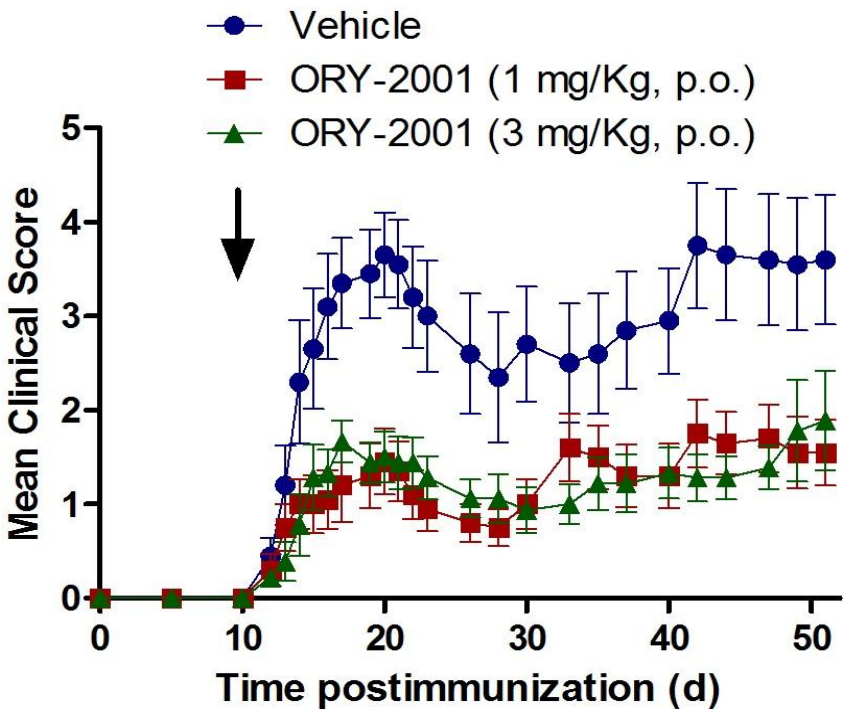
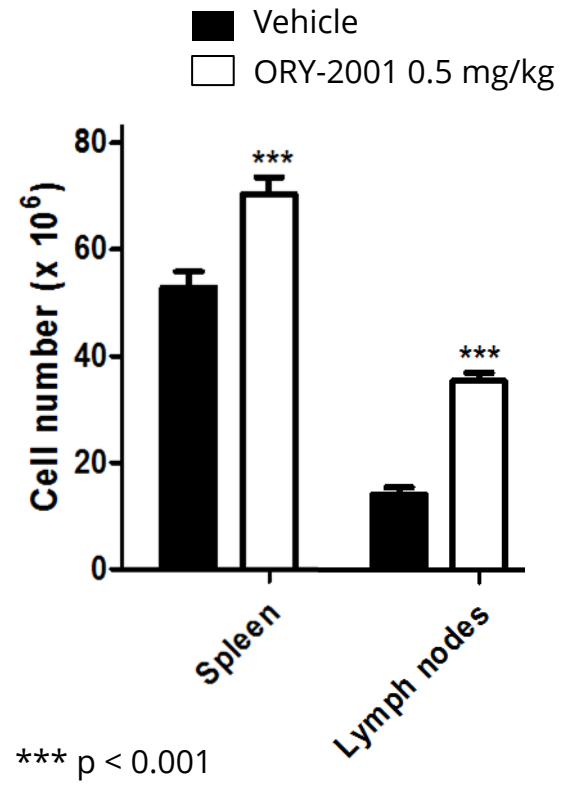
Multiple Sclerosis (Experimental Autoimmune Encephalitis (EAE) mice model)

- ✓ Treatment with ORY-2001 during the effector phase of the disease greatly inhibited the development of EAE and reduced disease incidence and severity
- ✓ Animals treated with ORY-2001 show more cellularity on the lymphoid organs indicating that the T cell immune response against oligodendrocytes did not occur



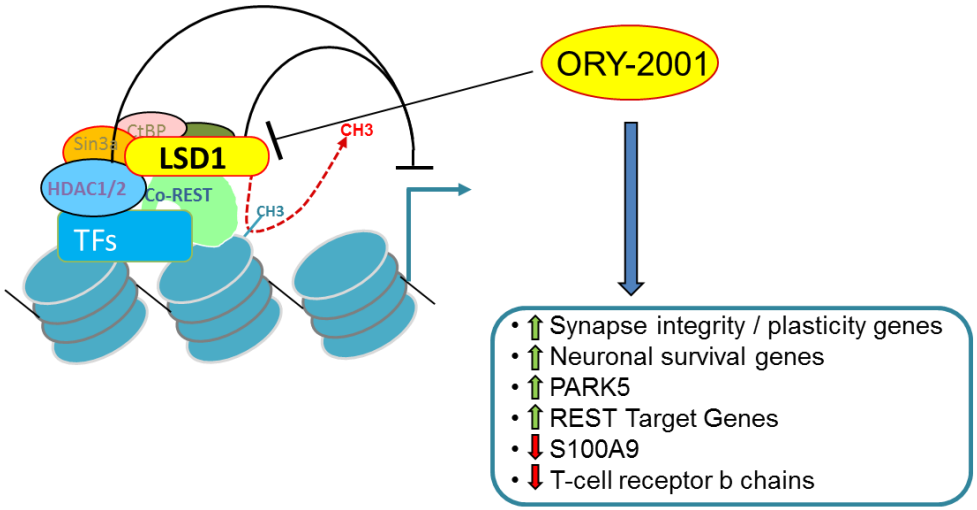


*** p < 0.001

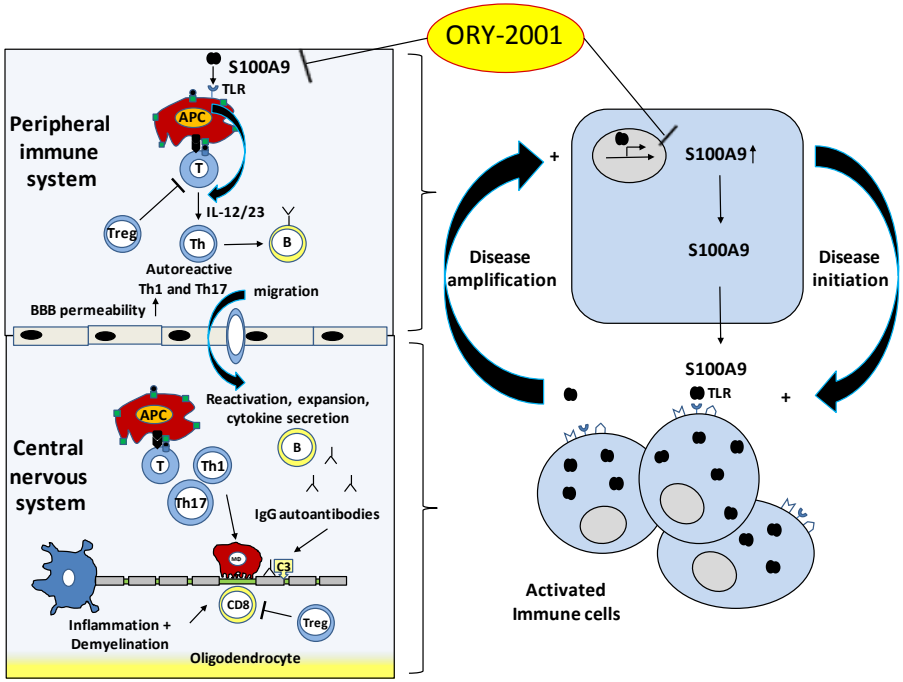
ORY-2001 is protective in the EAE model

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



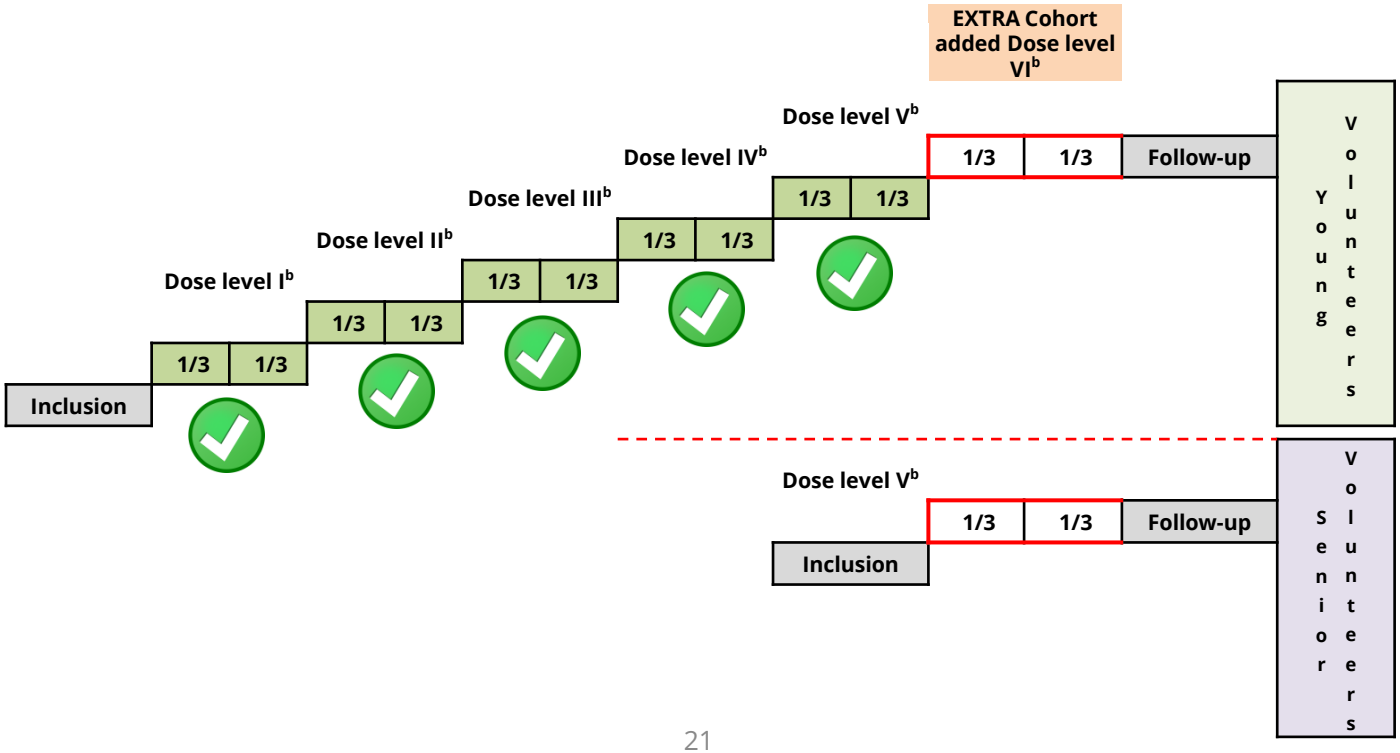
ORY-2001 Phase I Clinical Trial - SAFETY

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

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

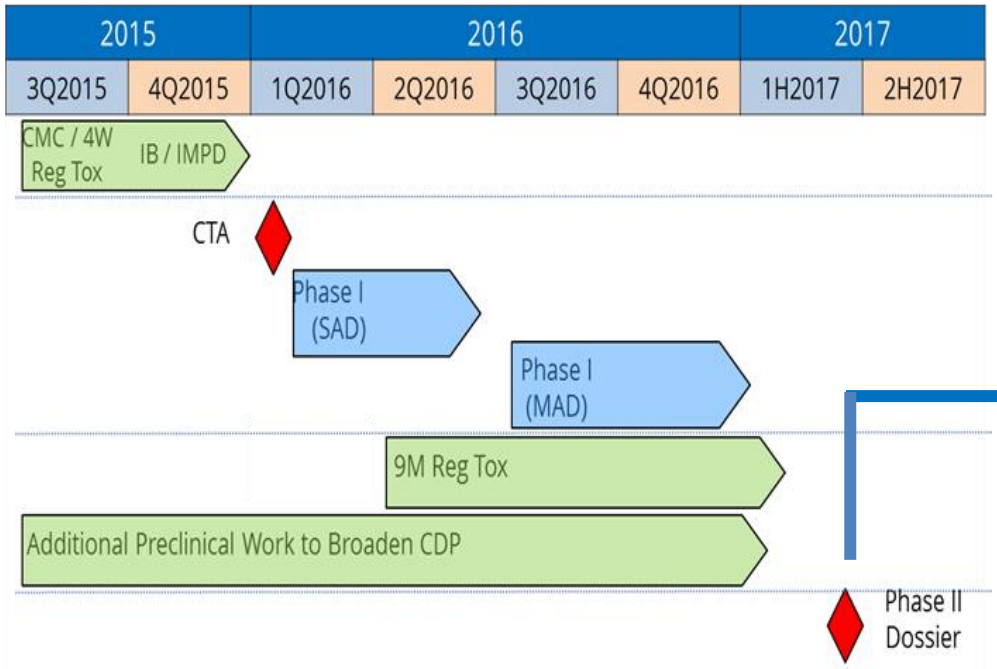
TITLE: A Study to Assess the Safety, Tolerability and Pharmacokinetic of Single and Multiple Oral Doses of ORY-2001 in Healthy Male, Female Subjects and Elderly Population
STUDY CODE: CL01-ORY-2001
EUDRACT NUMBER: 2015-003721-33

- ✓ **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-2001levels 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 will be Phase II ready in 2Q-2017
- The Phase I in healthy volunteers enables us to go for Phase II's in different indications
- The company envisages to perform three different Phase II 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

ORYZON, A UNIQUE OPPORTUNITY

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

- ✓ Epigenetics is one of the hottest spots in the Pharma Industry with high appetite from Pharma Companies (2016 acquisitions Roche –Tensha; Celgene –Acetylon) and from Specialized Investors (Imago, Constellation)
- ✓ ORYZON has World class Science and a broad patent portfolio on LSD1, one of the hottest targets in this area (GSK, Celgene, Incyte, Takeda…). Excellent Patent Position and FTO. +20 patent families, many already granted in USA
- ✓ ORYZON is a Global Champion in Epigenetics: We pioneer

Platform + Broad Product Pipeline: 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 in several human disease animal models
- ✓ Three Phase IIA-IIB clinical trials ready to start in 2H 2017
- ✓ A third LSD1 inhibitor being developed for an Orphan disease and Phase I ready 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 until 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 Top Executives with proven track record in the industry
- ✓ Top Governance according to Public Company standards

ORYZON

2017 CATALYSTS

2014

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

2015-16

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

2017

- ✓ **ORY-1001: LEAD CANCER ASSET**
  - Phase I-IIA study formally closed
  - FPI in Phase I SCLC by Roche
- ✓ **ORY-2001: LEAD CNS ASSET**
  - Complete Phase I finalized
  - Human Target Engagement demonstrated
  - CTA / IND for Phase II-A approved for MS
  - CTA / IND for Phase II-B approved for AD
  - CTA / IND for Phase II-A approved for HD
  - FPI in a Phase II-A study on MS
- ✓ **ORY-3001:**
  - CTA / IND approved for a Phase I study on an orphan indication yet to be disclosed
- ✓ **CORPORATE**
  - Prepare to Dual List on the NASDAQ in the near future

2018

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

ORYZON


THANK YOU VERY MUCH!
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