A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION

MADX: ORY

JANUARY 2018

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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** validated scientifically and clinically
- Three therapeutic programs in LSD1 in development with multiple indication opportunities
  - 1 In CNS → in Phase IIA
  - 1 in Oncology → ready to start Phase II
  - 1 in an orphan disease → ready to start Phase I
- Large IP portfolio with technology fully developed in-house

- **Raised €32M** (in 2015-2016). Additional **18.2M€** raised from blue chip investors in the US and Europe **in March 2017**
- 33.48M Shares outstanding. Fully diluted. No warrants, no options
- **Cash runway** expected till **1Q2020**

ORYZON GENOMICS SA
BALANCE SHEET DATA (UNAUDITED)
(Amounts in thousands US $)

	September 30th, 2017	September 30th, 2016
Cash and cash equivalents	39.841	25.900
Marquetable securities	200	6.248
Total Assets	69.741	56.564
Deferred revenue	0	0
Total Stockholders' equity	42.049	26.774

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EXTENSIVE PIPELINE : 2 PROGRAMS IN CLINIC WITH MULTIPLE INDICATIONS

- ✓ A LSD1 focused company
- ✓ 3 Different LSD1 inhibitors in development

MOLECULE	TARGET	INDICATION	DISCOVERY	H2L	LEAD OPTIMIZATION	PRECLINICAL	PHASE I	PHASE IIA	PHASE IIB	PHASE III
ORY-1001	LSD1	Leukemia (*)								
		Small Cell Lung Cancer								
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 KDMs	Cancer Other indications								
	Other Epigenetic Targets	Cancer Other indications								

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

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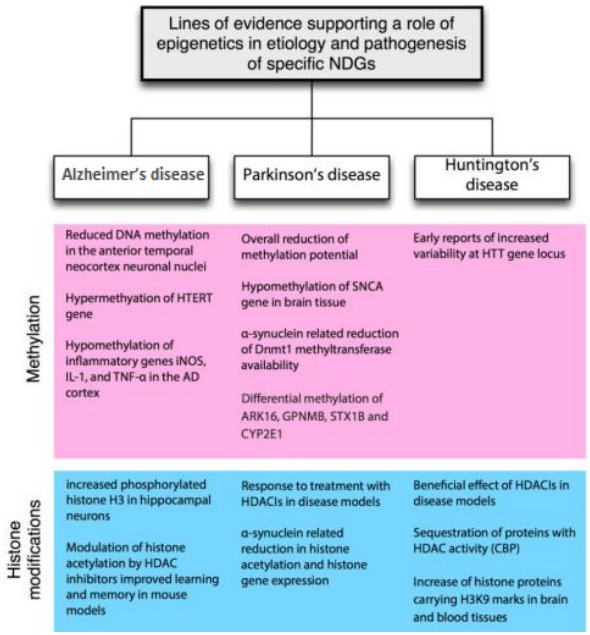
SOLID EVIDENCES OF AN EPIGENETIC ROLE IN NEURODEGENERATIVE DISORDERS

- ✓ HDACi improves HD symptoms in several animal models
- ✓ HDAC2 inhibition recovers memory on the AD bi-tg CK-p25 Tg mouse model
- ✓ HDAC inhibition improves FTD
- ✓ HDAC inhibition improves MS in EAE models
- ✓ HDAC2 cooperates with TFs as Sp3 in regulating Synaptic Function and Plasticity in Neurons



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

- → 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

- ✓ **LSD1 is a key component of different CNS Transcriptional complexes** interacting with different Transcription Factors and very often with HDAC1 and HDAC2
- ✓ **Different to what happens in HDACs, it has been proven that it is possible to develop extremely selective LSD1 inhibitors with excellent pharmacological properties**

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ORY-2001 Summary

- A small molecule that selectively inhibits LSD1 and MAO-B
- Excellent Pharmacology. Safe in 9 months PC regulatory toxicological studies.
- Oral and Safe in humans in a Phase I trial with 106 healthy volunteers
- Crosses the BBB and engages the target in humans
- In Phase IIA (in a MS trial), other trials planned (AD)
- Biomarkers identified in animals that may be of use in human clinics
- Positive results in 7 different animal models and in many in-vitro models
- Produces positive results in:
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal
  - Aggression/Agitation
  - Others
- Capable of acting in all the processes that manifest in neurodegenerative disease patients

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ORY-2001 restores cognition in mid age and old SAMP8 AD animals

More than 200 SAMP8 mice treated with ORY-2001 in 10 different experiments showed memory rescue, a schematic overview below

MILD

MODERATE

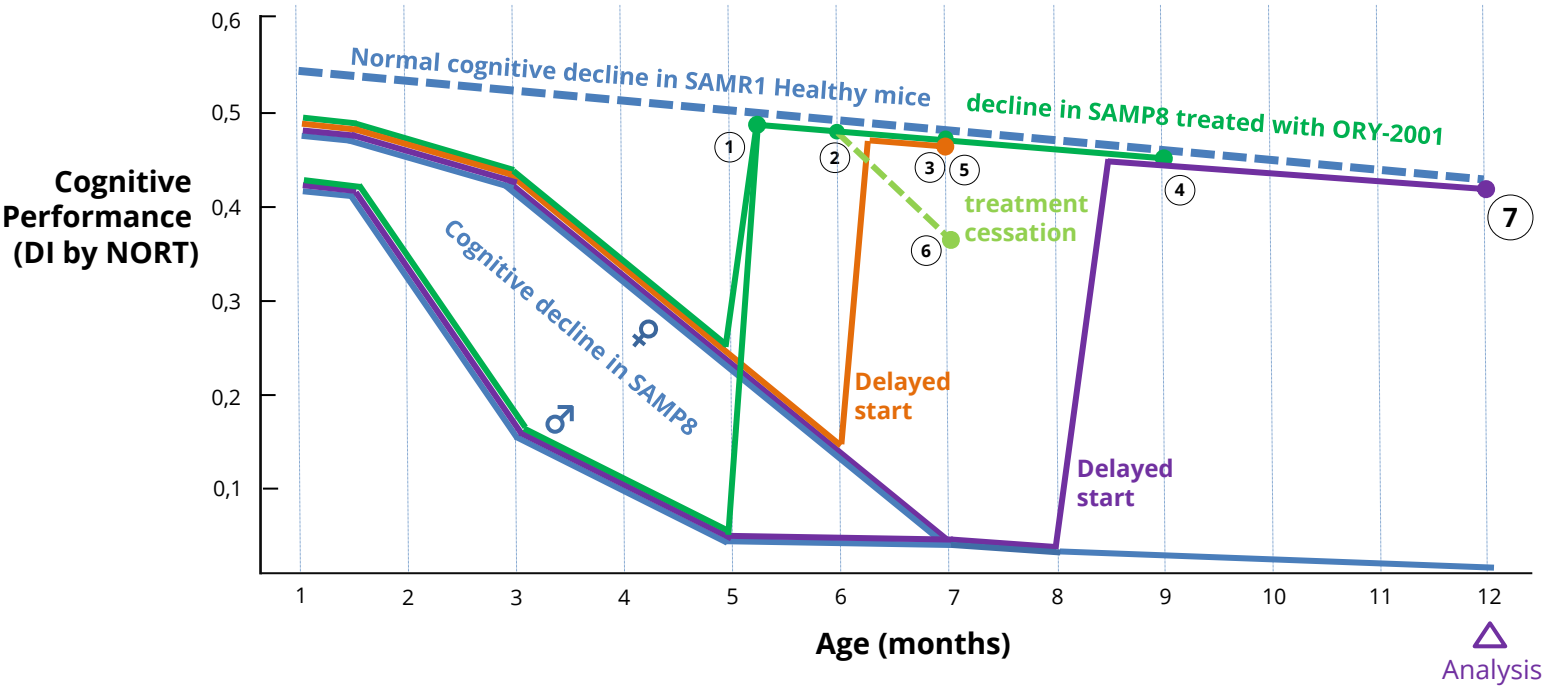
SEVERE

Treatment from month 5 during 1 week (1), 1 month (2), 2 months (3), 4 months (4)

Treated from month 6 during 1 month (Delayed start-1) (5)

Treatment from month 5 during 1 month, tested at month 7 (1 month after treatment cessation) (6)

Treatment from month 8 during 4 months (Delayed start-2) (7)



Results suggestive of Disease modifying potential

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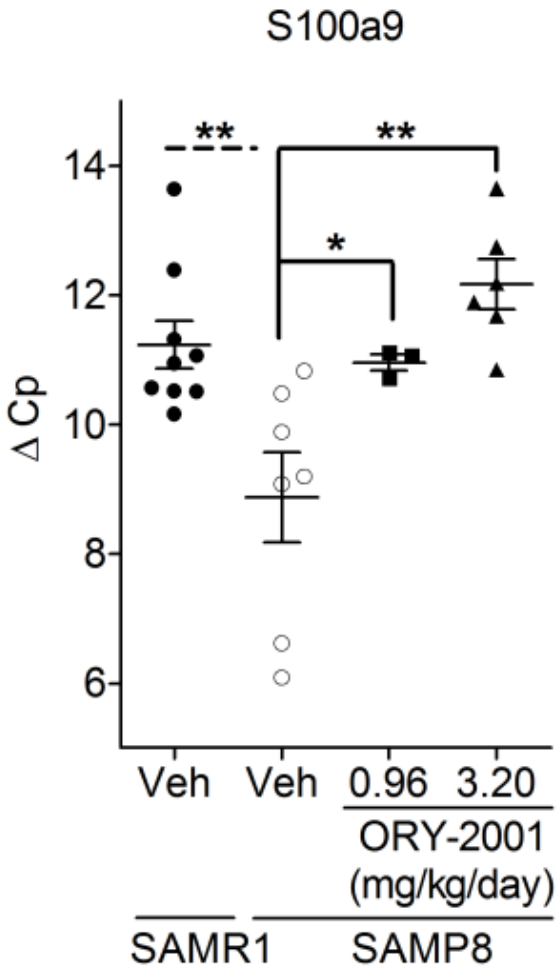
BIOMARKERS: Synaptic Plasticity and Neuroinflammation

- Up-regulation of the synaptic plasticity genes in hippocampus by ORY-2001
- Down-regulation by ORY-2001 of the pro-inflammatory genes as **S100A9.** This protein in hippocampus is particularly interesting, since S100A9 is emerging as an important contributor to inflammation-related neurodegeneration
- S100A9 was found to be increased in
  - patients with AD
  - postoperative cognitive dysfunction (POCD)
  - traumatic brain injury (TBI)
  - In neuroinflammatory diseases like MS and others



Anti-neuroinflammatory results are not constrained to this experimental model

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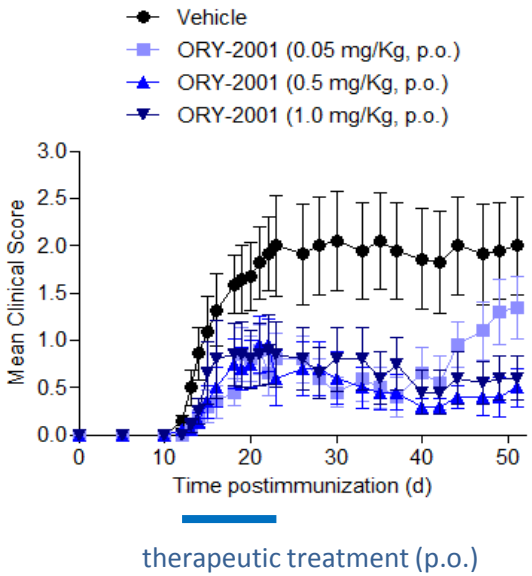
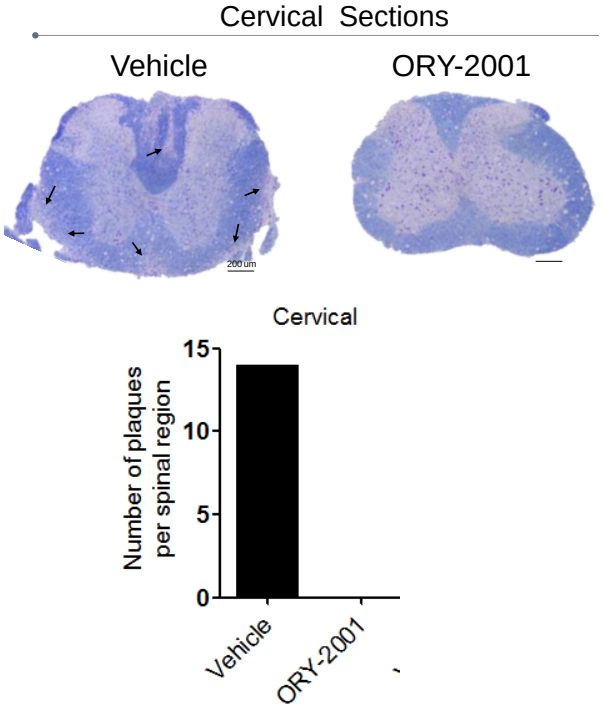
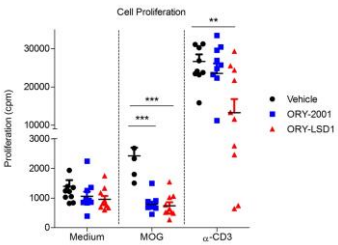
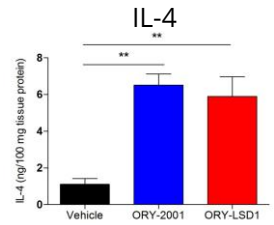
ORY-2001 reduces the expression of genes involved in neuroinflammation

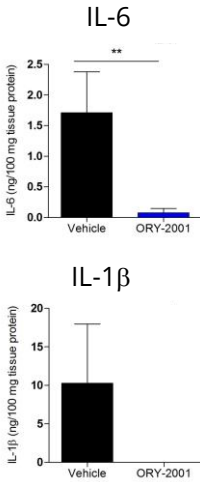
- ORY-2001 down-regulates genes associated with inflammation including S100A9 and T-cell receptor b chains that can be found over-expressed in SAMP-8 mice
- In more specific models of inflammation, ORY-2001 protects the brain and CNS from acute inflammatory stress, as shown in the EAE model where immune infiltration in the spinal cord is greatly reduced, demyelination is avoided and the clinical score is greatly reduced
- ORY-2001 also provides protection in other murine models with induced demyelinating disease





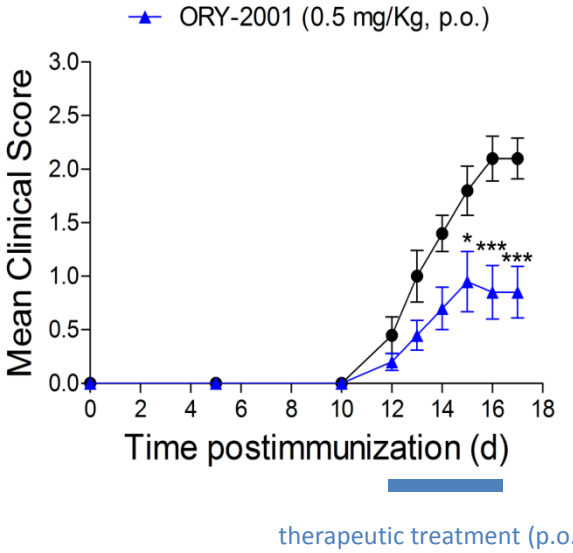


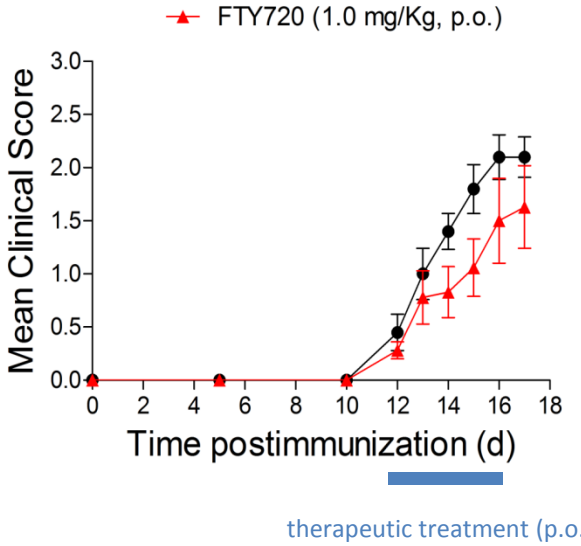


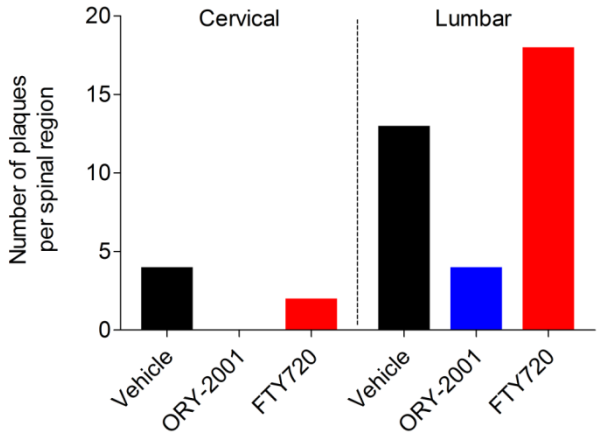


ORY-2001 is more protective and/or acts faster than Fingolimod in the effector phase of the EAE model

Effects of ORY-2001 and FTY720 (fingolimod) in the **EAE effector phase** (therapeutic setting):





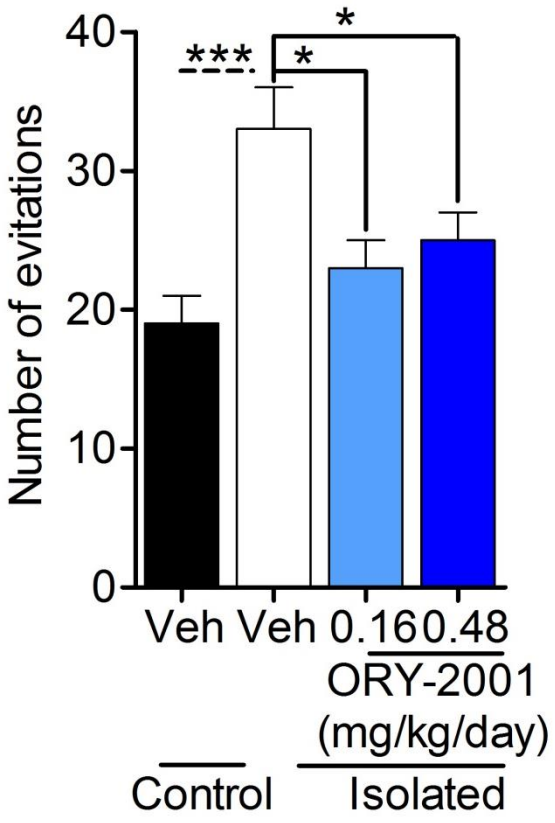


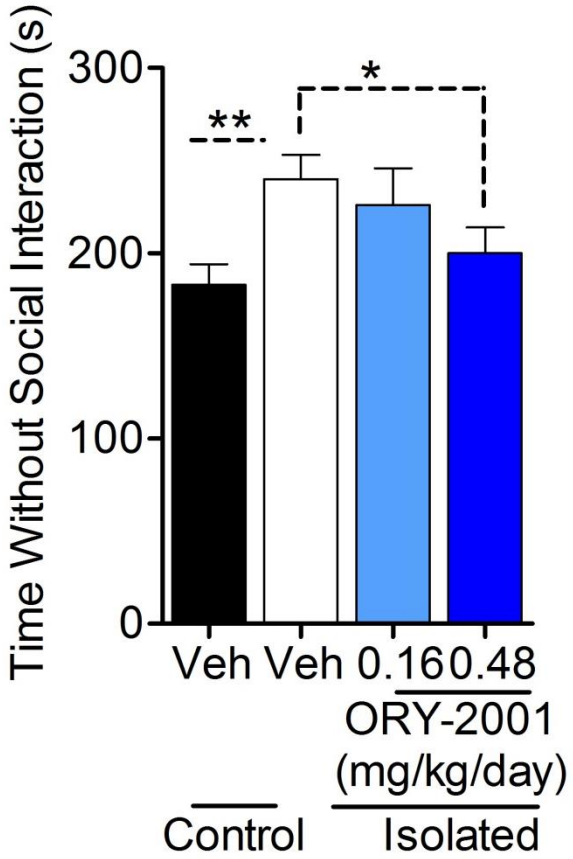
- ORY-2001 clearly reduced the mean clinical score, FTY720 exhibited only a tendency
- ORY-2001 is more effective and/or faster acting than FTY720 in the effector phase

ORY-2001 reduces social withdrawal in rats

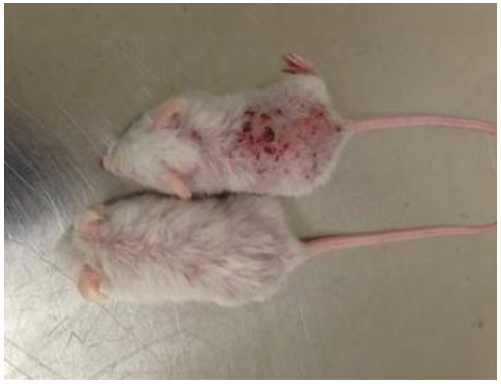
- In Alzheimer's and other neurodegenerative disorders, cognitive decline is often accompanied by aggressiveness, agitation, psychosis, depression, social withdrawal and apathy
- The post-weaning social isolation rat model of neurodevelopmental deficits was used to further assess ORY-2001 effects on behavior

In this rat model, isolation after the weaning resulted in higher social avoidance. Treatment with **ORY-2001 reverted this effect, normalizing the social interaction behavior**





ORY-2001 reduces aggression in mice Alzheimer's Disease model

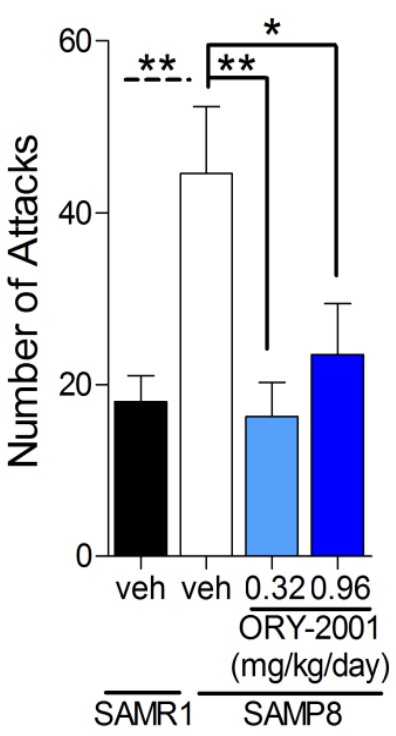


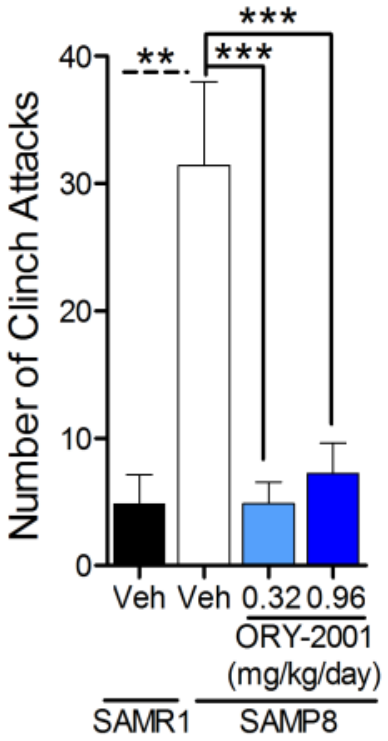
Unplanned observations revealed that SAMP8 male mice treated with ORY-2001 (bottom mouse) presented a better condition than untreated animals (top mouse) suggesting that ORY-2001 might reduce the aggressions between males caged together.

In AD patients, cognitive decline is often accompanied by **aggressiveness**

Using the Resident-Intruder test, social behavior was evaluated in SAMP8 mice:

- ✓ SAMP8 animals showed higher aggressive behavior than SAMR1 animals, and ORY-2001 treatment **significantly reduced aggression parameters** and restored to levels equivalent to control SAMR1 mice





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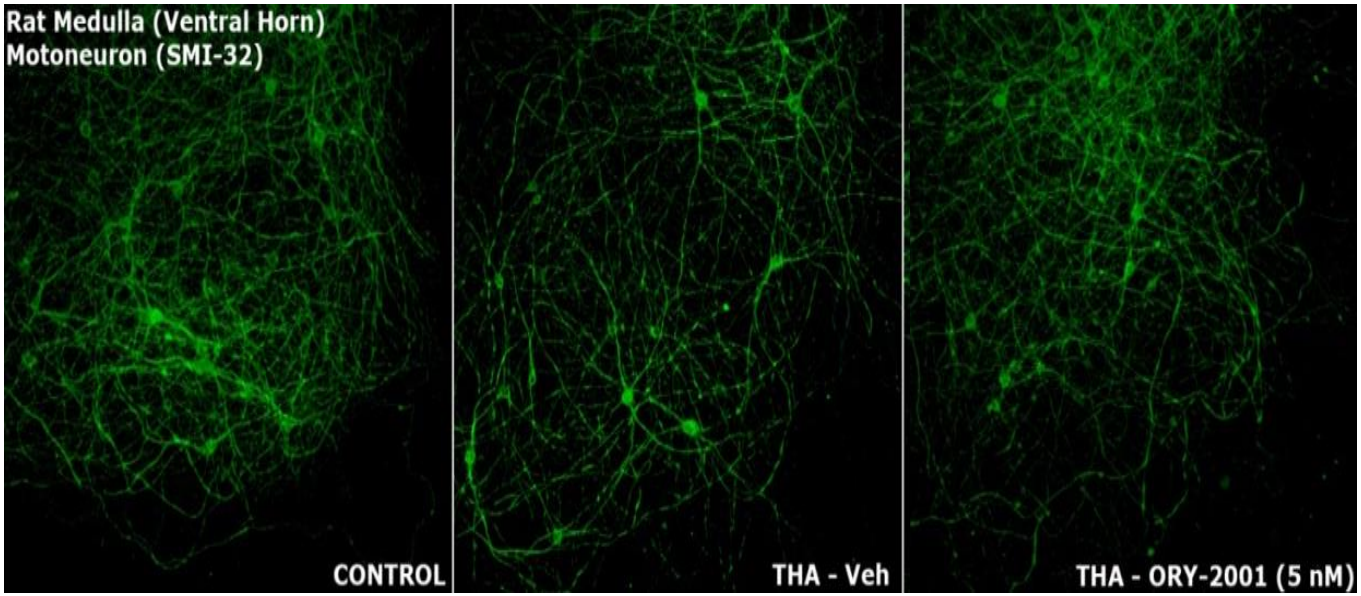
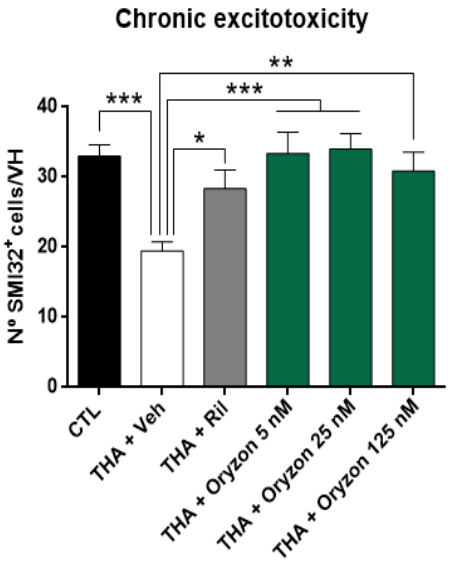
ORY-2001 confers neuroprotection

Glutamate excitotoxicity

- ORY-2001 treatment protects against chronic glutamate excitotoxicity in organotypic spinal medulla explants exposed to THA, a potent glutamate transporter inhibitor, a classical model of Amyotrophic Lateral Sclerosis (ALS).
- There is evidence for chronic excitotoxicity in human patients of AD which may be driven by multiple factors including the sensitization of NMDA receptors, a decrease in L-glu and L-asp reuptake capacity and an increase in glutamate release via system x_c-





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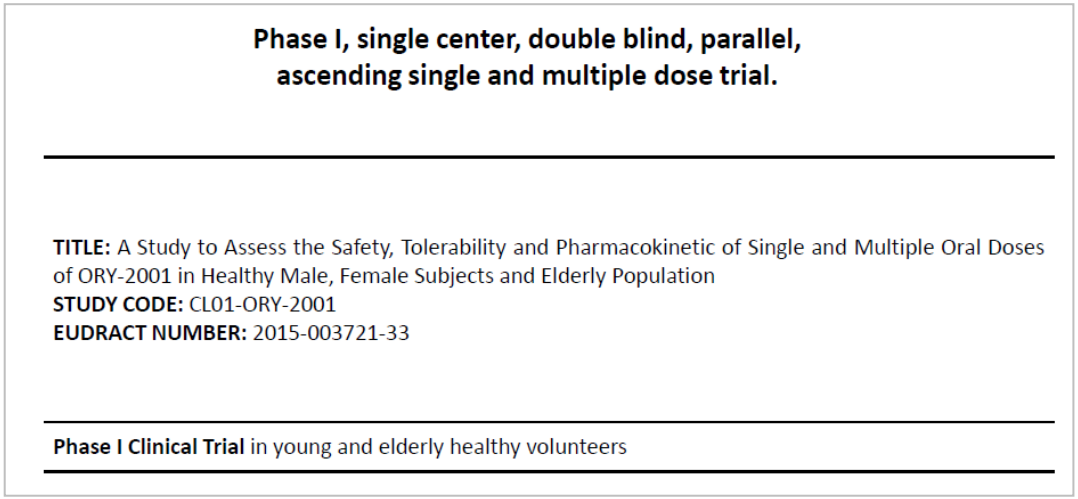
ORY-2001 Phase I CLINICAL TRIAL: Satisfactory answers

The Questions we wanted to answer

1. Epigenetic drugs often have pleiotropic effects resulting in side effects
2. Epigenetic drugs often have a hematological impact, eventually producing neutropenia and thrombocytopenia
3. Drugs for CNS need to demonstrate brain penetrance and target engagement

The Clinical Trial CL01-ORY-2001 was designed to address all these concerns



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

Phase I Clinical Trial in young and elderly healthy volunteers

A Phase I study with 106 healthy volunteers, young and elderly

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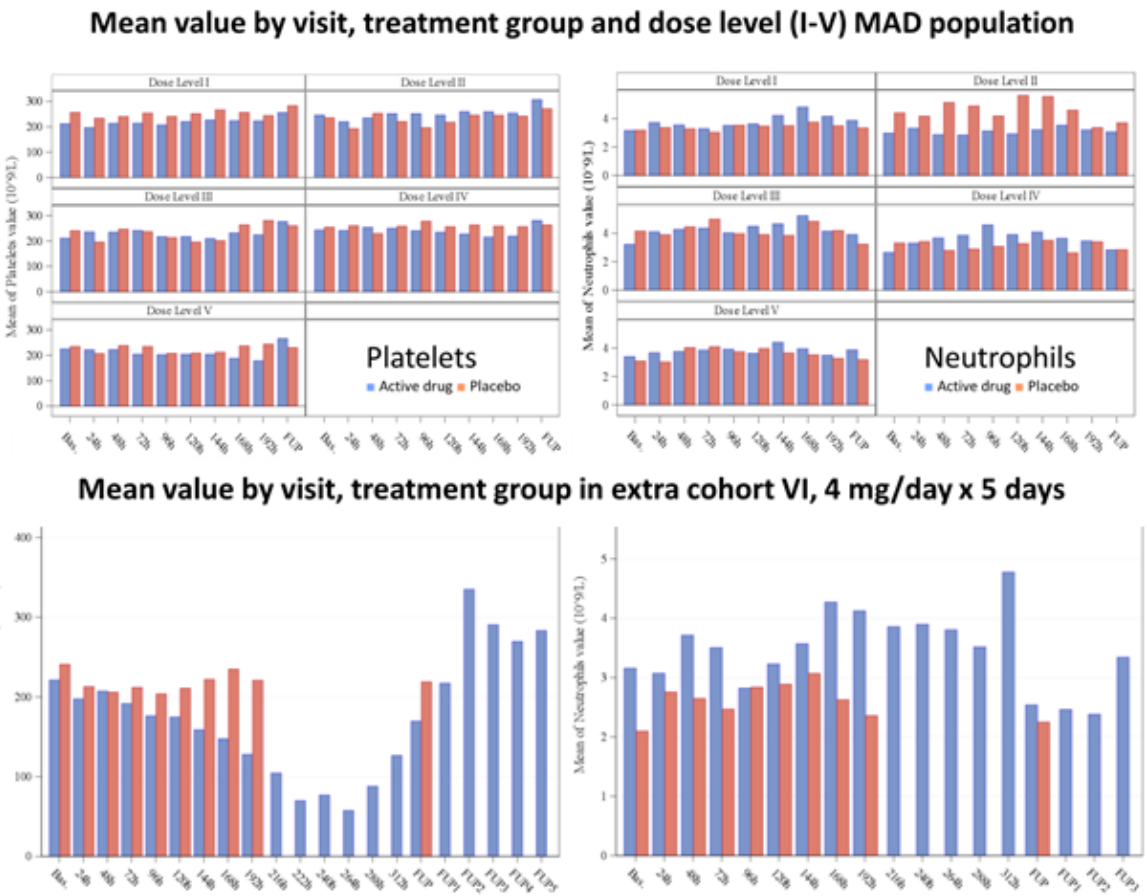
CL01-ORY-2001 Phase I: Safety and hematology

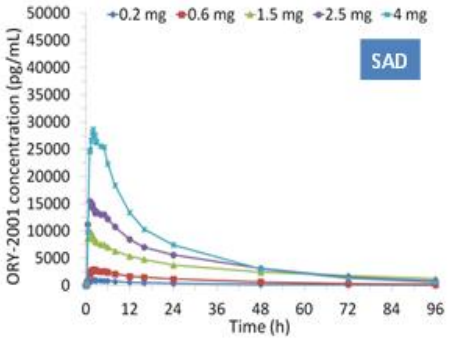
- Orally administered ORY-2001 is safe and well tolerated
- ORY-2001 did not provoke significant clinical or laboratory changes or adverse events in the MAD up to 2.5 mg. Single and Multiple ascending doses were hematologically safe.
- An additional cohort was requested in an amendment to model the PK/PD ratios.
- PK-PD modelling allows us to establish a safe administration scheme for long term efficacy studies of ORY-2001 in Phase II trials

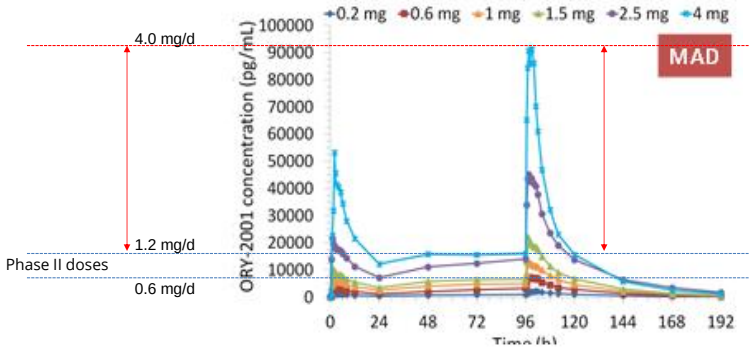


FINAL DATA of Phase I on ORY-2001 were presented at AAIC-2017 London (July-2017)

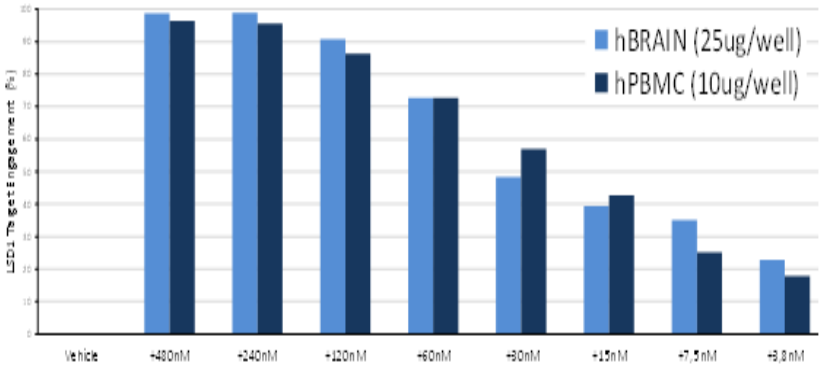
ORY-2001 PHASE I CLINICAL TRIAL CONCLUSIONS

- **Elderly cohort** Safety data comparable to young healthy volunteers
- **PK** Oral PK T1/2 ≈ 22h allowing once daily oral
- **ORY-2001 efficiently crosses the BBB**:
  - ORY-2001 concentrations measured in CSF at 2, 6 and 12 h after a single oral 2 mg or 4 mg dose
  - CSF levels comparable to corresponding unbound plasma concentrations (CSF/plasmau ratio ≈ 0.7-0.9)
- **ORY-2001 efficiently inhibits the brain human LSD1**





Time	CSF/plasma$_u$ ratio	
	SAD 2 mg	SAD 4mg
2 h	0.78	0.69
6 h	0.74	0.83
12 h	0.92	0.91
Cmax	0.64	0.78



ORY-2001: next two Phase IIa studies ready to start

SATEEN A pilot study in MS

SAfety, **T**olerability and **E**fficacy in an **E**PIGE**N**ETIC approach to treat Multiple Sclerosis

Randomised, double-blind, placebo-controlled, 3-arm, 36 weeks parallel-group study to evaluate the safety and tolerability of ORY-2001 in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS)

APPROVED by the AEMPS (October 30th)

Spain only; 4 Hospitals; 24 patients (RR & SP);

FPI expected Jan 2018; LPO December 2018

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A multicenter, multinational, randomized, double-blind, placebo-controlled, 3-arm, 26 weeks parallel-group study to evaluate the safety, tolerability of ORY-2001 in patients with mild-moderate AD

Design: This Phase IIa study is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in 90 patients (male and female, aged 50 to 85 years) with mild to moderate AD. The safety, tolerability and clinical effects of two doses of ORY-2001 *vs* placebo, in a 2:2:1 ratio (36/36/18), will be evaluated in these patients. The study will consist of a screening period and a 26 week double-blind, placebo-controlled treatment period with an open-label extension period of 26 weeks.

Population: No. of patients: **90**
Randomization : 2/2/1
2 dose ORY-2001 arms (36/36) and one placebo(18)

Sites: 12-15 Sites

Clinical Study Time Frame:

- **First patient in: 1Q 2018**
- **Last patient last visit: 1Q 2019**
- **Study end: 4Q 2019**

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ETHERAL

Outcome measures:

Primary endpoint:

Frequency and severity of adverse events

Exploratory endpoints:

Cognitive: MMSE, ADAS-cog 14, Cogstate battery
Functional: CDR-SB, Dependence scale
Other Functional and behavioural Tests
Biomarkers: MRI, CSF (AD, Novel e.g. S100A9, YKL40) and other CSF and peripheral biomarkers

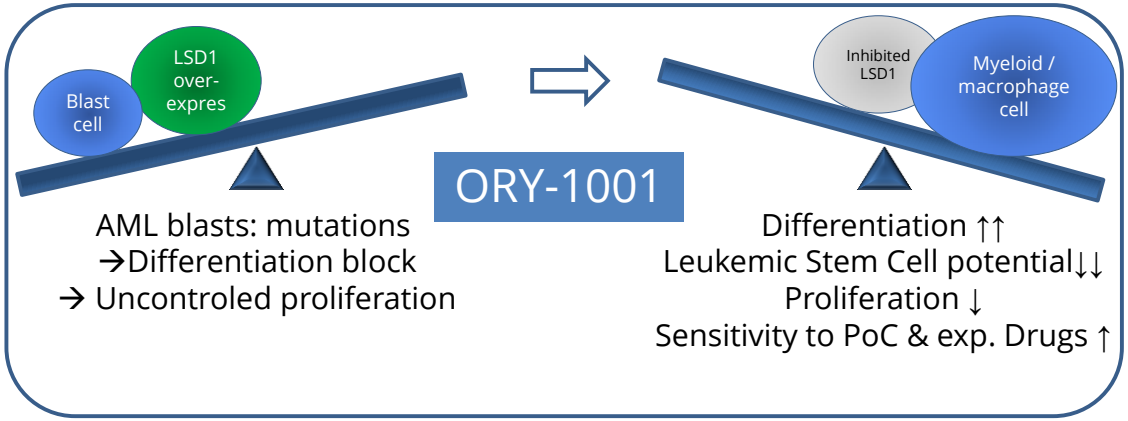
ORY-1001

LSD1 inhibitors in Cancer

SUMMARY

LSD1 IS A TARGET IN SOME CANCERS

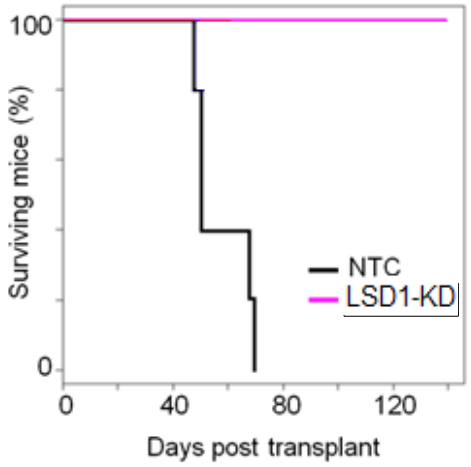
- ✓ LSD1 is a key effector of the differentiation block in MLL leukemia
- ✓ MLL Leukemic stem cells are addicted to LSD1 activity



23 murine MLL leukemias
Known AML-CFC
% blast-like (Type 1) ≈ LSC potential

GE analysis

Top epigenetic factor: LSD1



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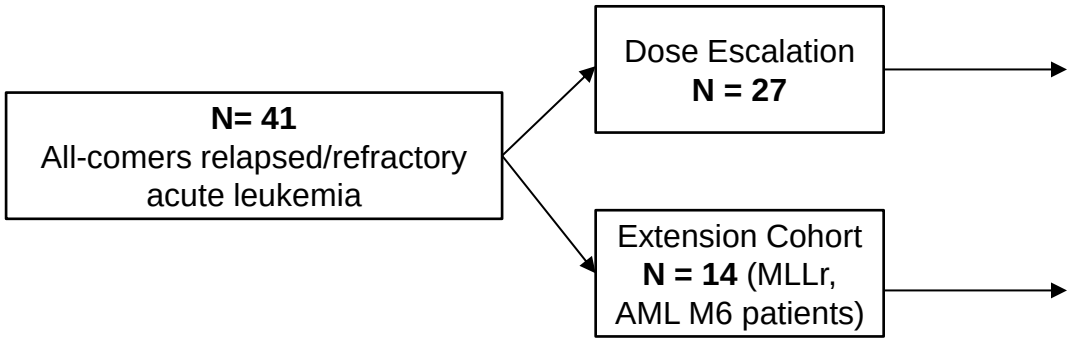
First Phase I/IIA clinical trial with ORY-1001 in AL (I)

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

Phase I (Dose escalation summary)

- ✓ ORY-1001 was well tolerated. Predicted toxicities were thrombocytopaenia & anaemia. The great majority of AEs and SAEs were likely related to the underlying disease and not to drug
- ✓ AEs observed at the MTD were: Lung infections, Severe fatigue, Erythema nodosum
- ✓ Results of the study suggest a maximum tolerated dose of 220 µg/m²/d, the SMC recommended a dose of 140µ/m²/d for future studies.
- ✓ Excellent oral bioavailability in humans and pharmacokinetic parameters well established
- ✓ **1 CRi** and 5 patients showed hints of clinical response at cohorts 3, 5, 6 and 7

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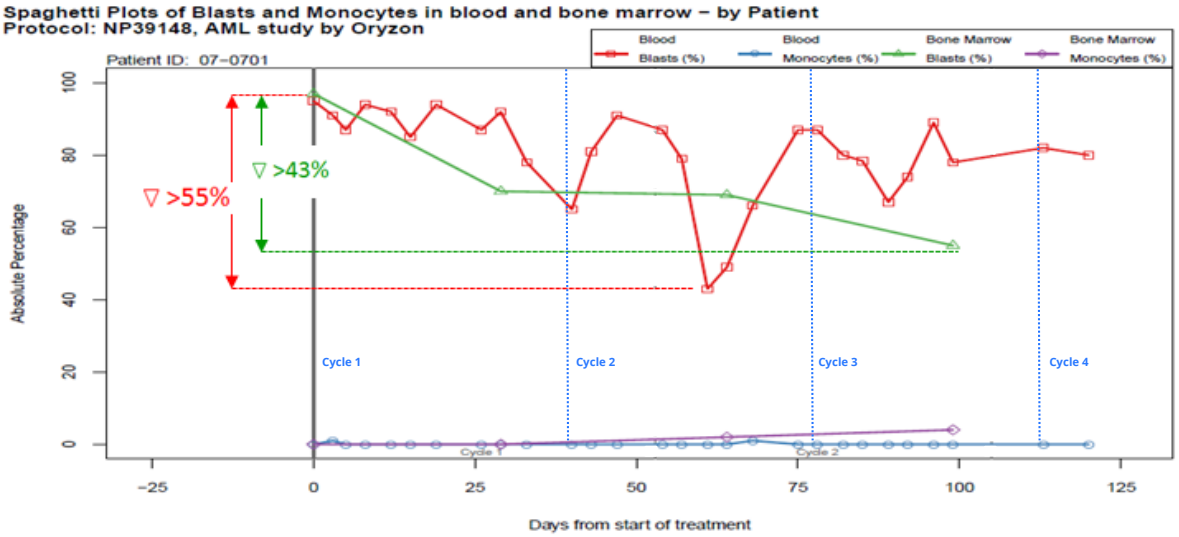
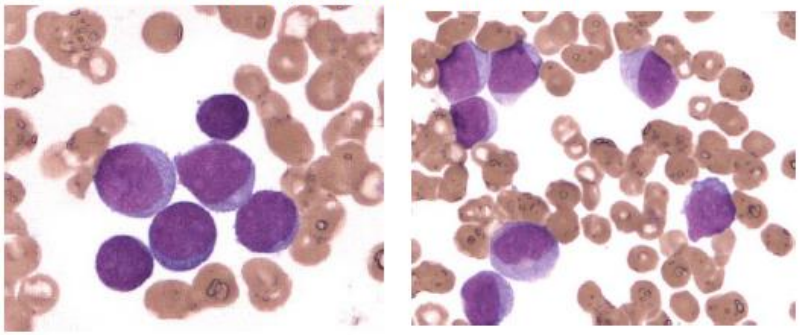
ORY-1001 Phase IIa: extension arm – Therapeutic effects

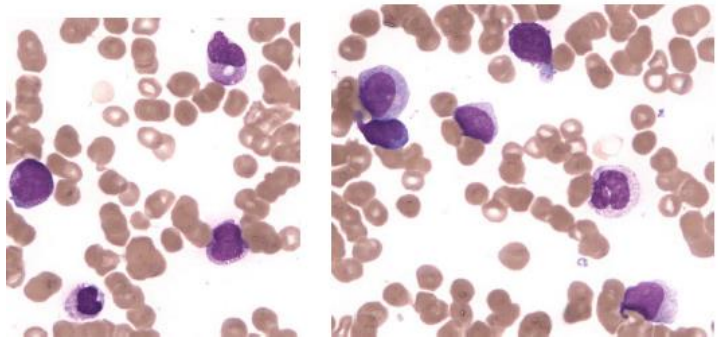
- ✓ 55% blast reduction from baseline in patient 0701 (MLL-AF M4)



Bone marrow 12/15/2015 = baseline



Bone marrow 03/24/2016 = C3D29



- ✓ Baseline = 97% BM blasts
- ✓ Post ORY-1001 2 cycle treatment **= 55% blast reduction**
- ✓ **Granulocytic differentiation = 28%**

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PHASE I/IIA CONCLUSION HIGHLIGHTS:

58th ASH® Annual Meeting and Exposition
San Diego Convention Center • San Diego, California
MEETING: DECEMBER 3-6, 2016
EXPOSITION: DECEMBER 3-5, 2016

- ✓ *Preliminary data presented at ASH 2016.*

- ✓ ORY-1001 was administered to **41 patients**
- ✓ **Excellent oral bioavailability** in humans and excellent PK parameters
- ✓ **Pharmacodynamic biomarkers (MLLr)** permit monitoring of response to ORY-1001 in M4/M5 AML patients
- ✓ **22% (6/27) response rate in the phase 1 portion, including one CRi** (complete remission with incomplete blood count recovery)
- ✓ **46% (6/13) of relapsed/refractory AML patients showed anti-leukemic clinical activity** in extension arm
- ✓ Partial bone marrow remission in 50% (2/4) M6 patients, **suggesting disease stabilization**
- ✓ 100% (5/5) of MLL gene fusion patients with evaluable PD samples showed evidence of blast differentiation by qRT-PCR analysis
- ✓ 67% (4/6) of MLL leukemia patients showed evidence of morphological blast cell differentiation (2 patients experienced a differentiation syndrome)
- ✓ 15% (2 (M6)/13) partial bone marrow responses and 1 MLL patient with 3 month hematologic improvement
- ✓ **From all patients in the phase 1/2a study, antileukemic activity observed in 29% of patients (12/41), including one CRi**

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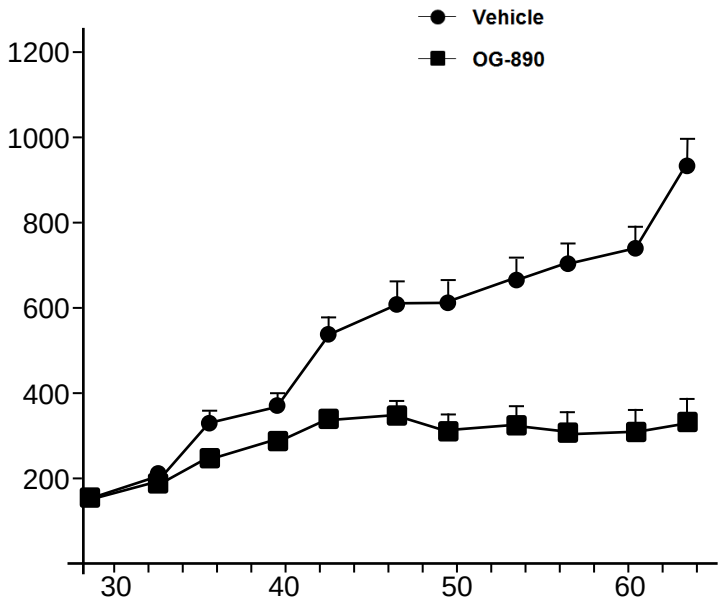
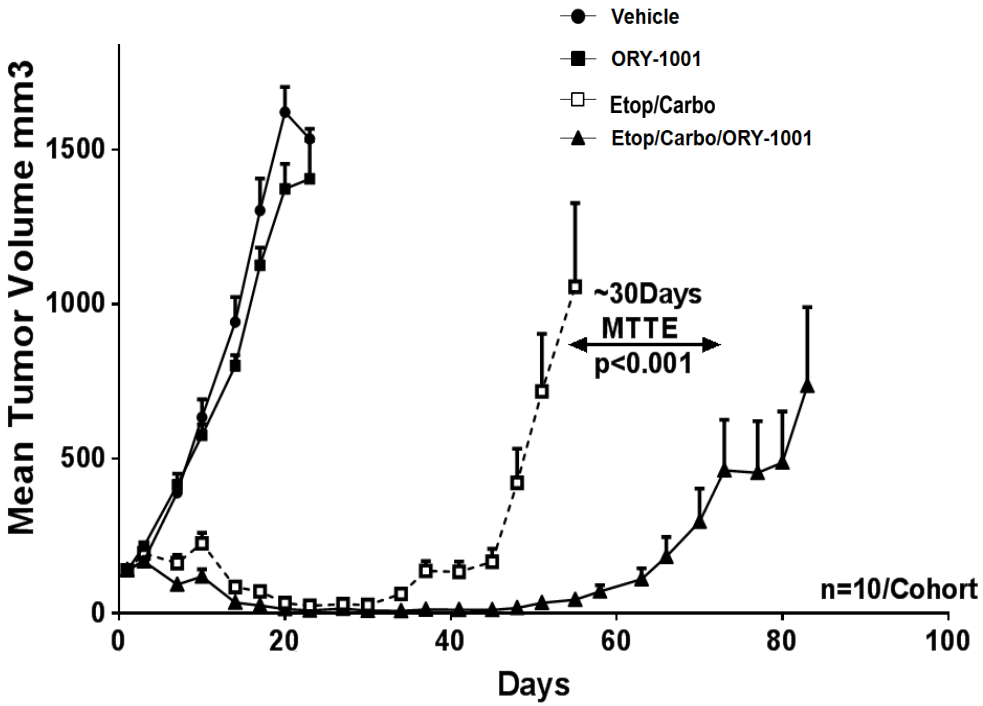
LSD1 in Small Cell Lung Cancer (SCLC)

- LSD1 inhibition alone can stop tumor progression in NCI-H1417 SCLC xenograft



- Combination of ORY-1001 with SOC Improves Potency and Duration Response in H526 Model



MTTE- Median Time to Endpoint

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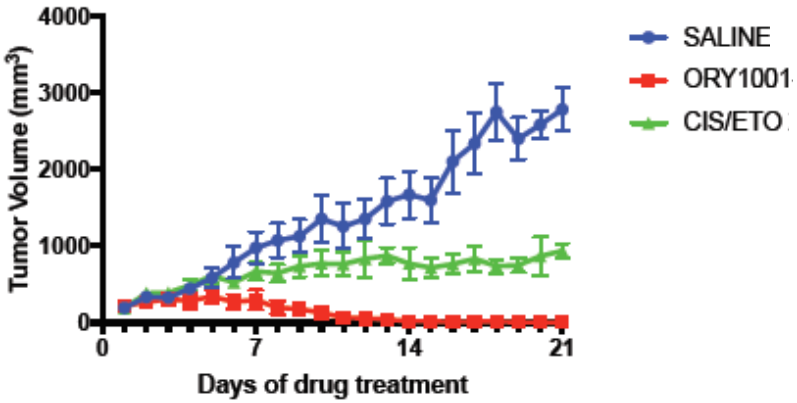
ORY-1001 PDX-SCLC xenografts

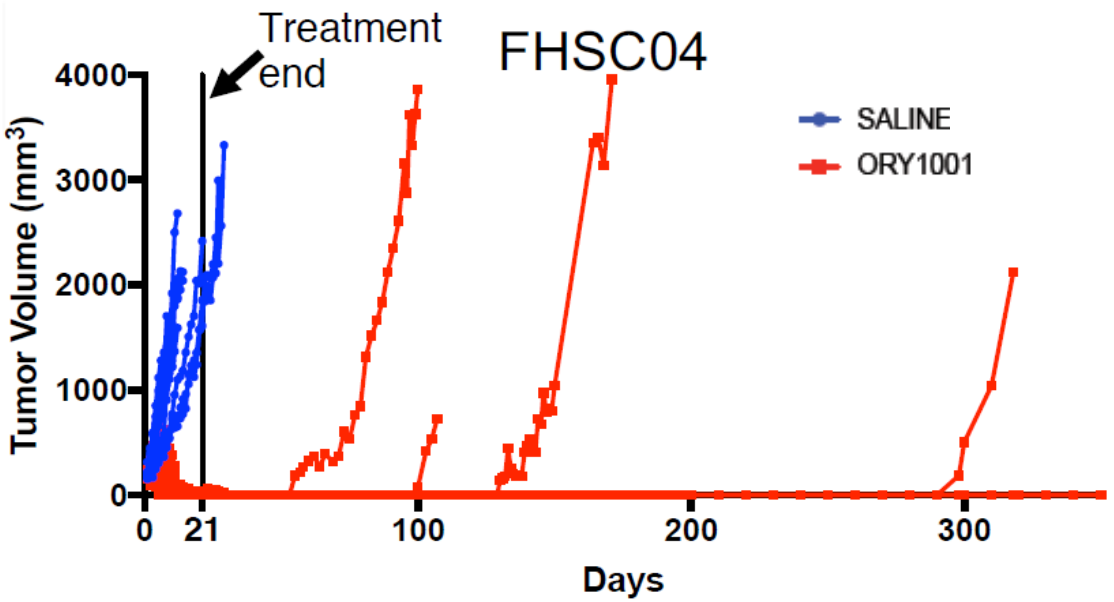
- Response to ORY-1001 in PDX models of SCLC is variable, but some are very strong

- FHSC04 model: derived from a SCLC patient who relapsed after first line therapy
- **6/10 FHSC04 mice treated with ORY-1001 did not show relapse after 300 days**



Data from
David MacPherson Lab

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE



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ORY-1001 in SCLC and next clinical development

- ✓ Oryzon licensed ORY-1001 global rights to Roche (2014)
- ✓ In January 2017 an exploratory Phase I study of RG6016 (ORY-1001) was started in small cell lung cancer (SCLC). This clinical trial has been executed by ROCHE
- ✓ ORYZON has regained rights on ORY-1001 in January 2018 as a consequence of Roche's reprioritization portfolio
- ✓ Oryzon to continue clinical development of ORY-1001
- ✓ In SCLC, we anticipate to introduce stratification of patients using biomarkers

- ➢ **A new Phase I/IIa in SCLC is in preparation**
- ➢ **A follow on Phase IIa in AML- MDS in combination with other agents is under preparation**

Anticipated Start for both 1H 2018

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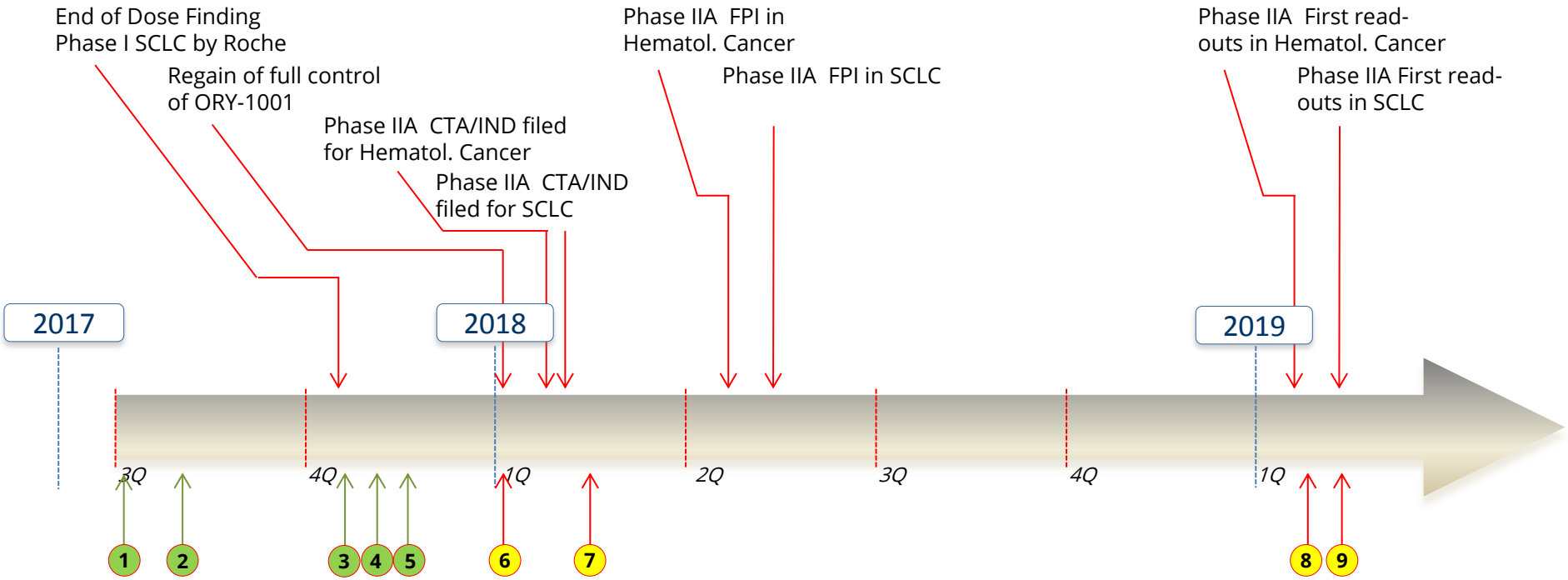
ANTICIPATED ORYZON MAIN CATALYSTS

ORY-1001: LEAD CANCER ASSET

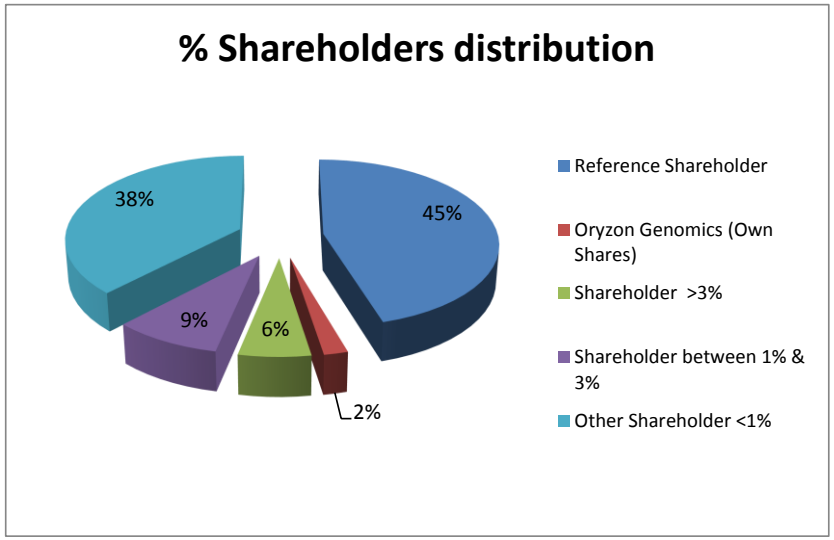


1. Phase I Final Data (AAIC-2017 London)
2. Filing CTA / IND for Phase IIA in MS
3. Additional Preclinical Data of ORY-2001 in MS (ECTRIMS-ACTRIMS-2017 Paris)
4. Presentation of Phase IIA plans in AD (CTAD-2017 Boston)
5. Additional Preclinical Data of ORY-2001 in animal models of other human CNS conditions (SFN2017)
6. Anticipated FPI in a Phase IIA study in MS
7. Anticipated FPI in a Phase IIA study in AD
8. Phase IIA Prelim read outs in MS
9. Phase IIA Prelim read outs in AD

ORY-2001: LEAD CNS ASSET

Capitalization and ownership summary

TOP 10 ORYZON SHAREHOLDER	by October 31st 2017	
NAJETI CAPITAL SA	7.017.799	**20,54%**
TAMARA MAES	3.742.530	**10,96%**
CARLOS MANUEL BUESA	3.742.530	**10,96%**
ARRIENDOS VENFERCA, SL	2.004.723	**5,87%**
JOSE MARIA ECHARRI	1.026.928	**3,01%**
MINORITY SHAREHOLDERS	16.626.881	**48,67%**
TOTAL COMPANY SHARES	**34.161.391**	



	Shareholder	Shares	%
Reference Shareholder	4	15.529.787	45,46%
Oryzon Genomics (Own Shares)	1	668.587	1,96%
Shareholder >3%	1	2.004.723	5,87%
Shareholder between 1% & 3%	6	3.008.833	8,81%
Other Shareholder <1%	2229	12.949.461	37,91%
TOTAL	**2241**	**34.161.391**	**100%**

On October 31st 2017, Oryzon Genomics had 2.241 shareholders.

- The 45.46% of the shares are owned by the reference shareholders.

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

ORYZON

ORYZON
A GLOBAL LEADER
IN EPIGENETICS

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