
ORYZON
A GLOBAL LEADER
IN EPIGENETICS
INVESTOR PRESENTATION
BIOTRINITY
London April 2016

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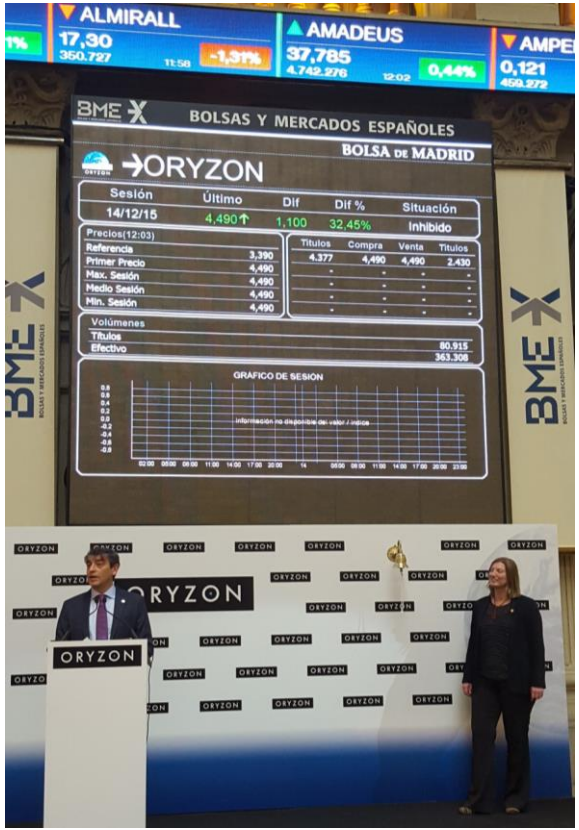
COMPANY HIGHLIGHTS



- MADX: ORY A publicly traded company in the Madrid Stock Exchange
- A clinical stage biopharmaceutical company developing innovative therapies in oncology and neurodegeneration leading the field of Epigenetics
- Two therapeutic programs in clinical development with multiple indication opportunities & additional assets in preclinical development
- Signed global strategic partnership with ROCHE for ORY-1001 valued at 500M USD
- Cash runway till 2018

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EXTENSIVE PIPELINE : 2 PROGRAMS IN CLINIC WITH MULTIPLE INDICATIONS

INDICATION	TARGET	MOLECULE	DISCOVERY	H2L	LEAD OPTIMIZATION	PRECLINICAL	PHASE I-IIA	PHASE IIB	PHASE III	PARTNER
CANCER Leukemia Solid Tumors	LSD-1	ORY-1001								Roche
DEMENTIAS Alzheimer's Disease Parkinson's Disease Other Dementias	LSD-1-MAOB	ORY-2001								
ORPHAN Huntington's Disease Other Orphan Diseases	LSD-1-MAOB	ORY-2001								
OTHER INDICATIONS	LSD-1									
CANCER	Other KDMs									
CANCER	Other Epigenetic Targets									

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ORY-1001: ROCHE PARTNERSHIP

- LSD1 is a key effector of the differentiation block in MLL leukemia and other cancers
- In April 2014, Oryzon and ROCHE entered into a global collaboration on ORY-1001, for oncology, hematology and non-malignant conditions
- Clinical development and all related investments beyond the ongoing Phase I/IIA trial are the responsibility of ROCHE
- Parties collaborate on R&D through the ROCHE Translation Clinical Research Center (TCRC)

Roche

- → Global Commercial rights of ORY-1001 to ROCHE
- → Development and sales milestones total >**500M USD**
- → Payment at contract signing plus near term milestone total **21M USD**
- → Sales royalty rates tiered up to **mid-teens**

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PHASE I HIGHLIGHTS: ORY-1001 LEUKEMIA

TRIAL DESIGN		
Refractory & Relapsed Acute Leukemia	Multi-Center (5)	Multiple Ascending Dose (8 Cohorts)

PRIMARY ENDPOINT
Evaluate Safety (hematological and non-hematological toxicities) and Tolerability

SECONDARY ENDPOINTS		
Characterize PK	Assess Responses (CR/Cri/PR), particularly for rMLL gene	Evaluate surrogate PD markers for target engagement

PRELIMINARY RESULTS
Excellent safety profile
Demonstrated impact on pharmaceutical target
PD clear readings several biomarkers
Good PK
Established maximum recommended dose

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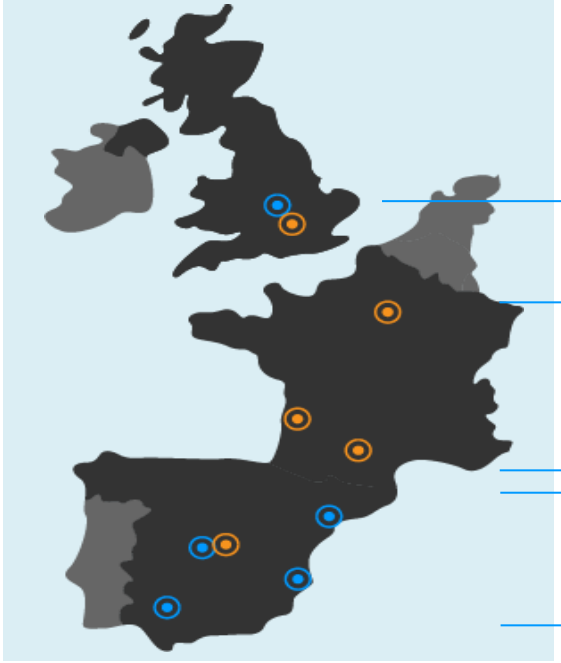
PHASE IIA: ORY-1001 LEUKEMIA

After the MRD , an Expansion arm (Phase II-A) to include patients with target mutations (MLL and others) to evaluate preliminary signs of efficacy

CENTERS



- ✓ 12-14 Patients to be included
- ✓ Status: 11 patients enrolled and actively recruiting
- ✓ Completion Date: 2Q-2016

Expected to Report Preliminary Data in ASH 2016

10 Hospitals in 3 Countries

→ **UK**
- Christie Hospital, Manchester
- University College London hospitals NHS

→ **FRANCE**
- Gustave Roussy, Paris
- CHU Hopitaux, Bordeaux
- Hôpital Purpan - (CHU), Toulouse

→ **SPAIN**
- Valle de Hebron, Barcelona
- La Fe, Valencia
- Virgen del Rocío, Sevilla
- 12 de Octubre, Madrid
- Gregorio Marañón, Madrid

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ORY-1001 CLINICAL & MARKET POTENTIAL

ORY-1001 market capture opportunity above $1.8 billion

A number of scientific reports point out the potential of LSD1 inhibition as a target in a number of solid tumors

Non oncological diseases as SCD and others may also be a CDP option

Acute Myeloid Leukemia

12% of all Blood Cancers
18.860 new cases in US in 2014 [1,2]

Global Mk Potential of $932 million in 2024,
CAGR of 10.5% [4]

Small Cell Lung Cancer

15% of all Lung Cancers
32.420 new cases in US in 2014 [1,3]

Global Mk Potential of $684 million in 2017 [5]

Sickle Cell Disease

SCD Epidemiology
US/EU Prevalence ~150K

US Mk Potential of $200 million in 2017,
(Market to grow at 17% CGAR till 2019)

NOTE: ROCHE is the sole responsible for the further Clinic Development Plan for ORY-1001. The indications and markets mentioned above are only presented on its likelihood based on the development of competitors or published scientific reports

1. ACS, Cancer Facts & Figures 2014
2. www.hematology.org
3. www.lungcancer.org
4. Global Data 2015
5. Decision Resources 2015

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ROLE OF EPIGENETICS: NEURODEGENERATIVE DISORDERS

- ✓ HDACi improves HD symptoms in animal models
- ✓ HDAC2 inhibition recovers memory on the bi-transgenic CK-p25 Tg mouse model
- ✓ HDAC inhibition improves FTD

Efforts to develop Selective HDACi

rodin THERAPEUTICS

Selective HDAC2 i in Alzheimer's Disease
Program in Preclinical

Acetylon Pharmaceuticals, Inc.

HDAC-6 i in neurodegeneration and autoimmunity.
Program in Preclinical

FORUM PHARMACEUTICALS

HDAC i in Prodromal to Moderate FTD with Granulin Mutation
Phase II

Pan-HDAC inhibitors have demonstrated preclinical proof of concept that inhibition of HDACs improves cognitive function, however, these drugs have dose limiting side effects that make them unsuitable for the chronic settings needed in neurological indications.

Developing more selective HDAC inhibitors is not an insignificant challenge as HDACs are highly conserved proteins

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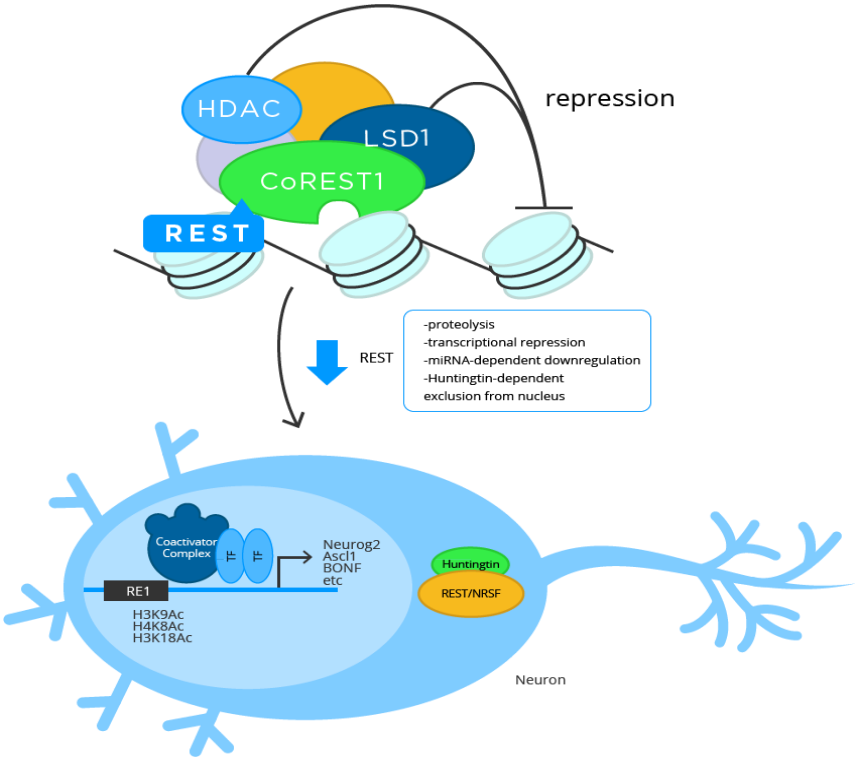
LSD1 IN THE NERVOUS SYSTEM

- Different to what happens in HDACs, we have proven that it is possible to develop extremely selective LSD1 inhibitors with excellent pharmacological properties for CNS
- LSD1 is a key component of the LSD1-REST-CoREST-HDAC1/2 repressor complex involved mainly in controlling developmental programs and modulating neuronal morphology in the CNS
- Oryzon has the wider IP portfolio in the LSD1 space with drug candidates specially suitable to be developed in neurological indications



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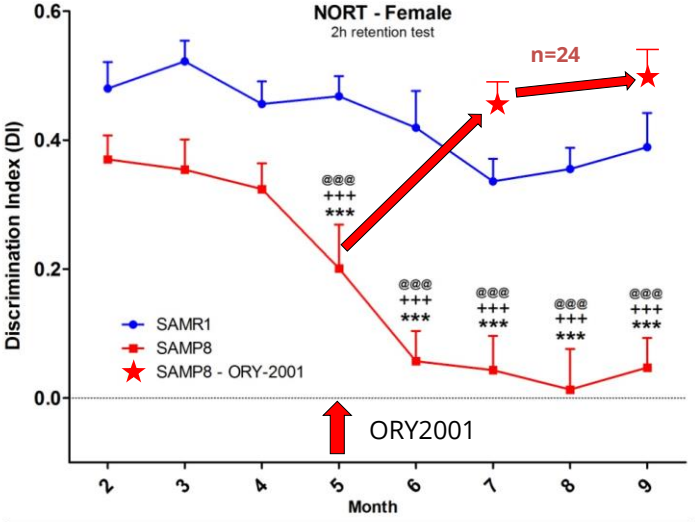
ORY-2001 – A COMPOUND FOR CNS IN PHASE I

- Highly selective dual LSD1-MAO-B inhibitor
- Preclinical Proof of Concept: LSD1 Against AD and HD and a third indication
- Clinical development : Currently In Phase I
  - Alzheimer's Disease is lead indication
  - Potential for additional indications: PD, HD and others
- Pharmacological Properties
  - 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

ORY-2001 A possible disease modifier drug

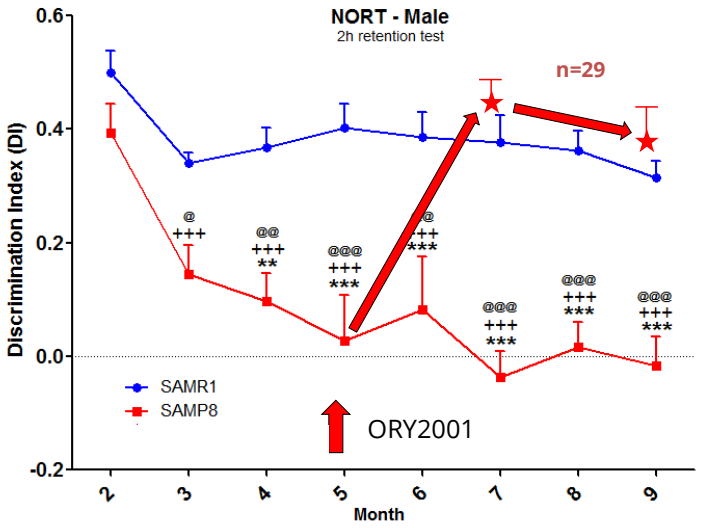
Meta-analysis of cognitive deficit of untreated SAMP-8 mice (historical data)



SAMP8 cognitive deficit compared to SAMR1 start to be significative from month 5. *** p <0.001 two-way ANOVA (Genotype vs. Age; n = 15 genotype/month)

SAMP8 animals treated with ORY-2001 for 2 months have restored cognitive function compared to control SAMP8 of 5-9 months. +++ p < 0.001 two-way ANOVA (Treatment vs control; treated group n = 24)

SAMP8 animals treated with ORY-2001 for 4 months have restored cognitive function compared to control SAMP8 of 5-9 months. @@@ p < 0.001 two-way ANOVA (Treatment vs contro; treated group n = 10)



SAMP8 cognitive deficit compared to SAMR1 start to be significative from month 4. ** p < 0.01; *** p <0.001 two-way ANOVA (Genotype vs. Age; n = 15 genotype/month)

SAMP8 animals treated with ORY-2001 for 2 months have restored cognitive function compared to control SAMP8 of 3-9 months. +++ p < 0.001 two-way ANOVA (Treatment vs control; treated group n = 29)

SAMP8 animals treated with ORY-2001 for 4 months have restored cognitive function compared to control SAMP8 of 3-9 months. @ p < 0.05; @@ p < 0.01; @@@ p < 0.001 two-way ANOVA (Treatment vs contro; treated group n = 10)

ORY-2001 restores the discrimination index in SAMP-8 mice

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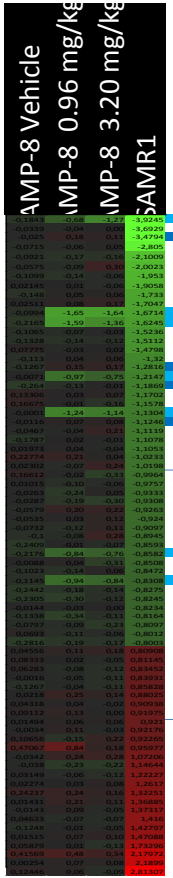
PoC studies in SAMP8 mice - **BIOMARKERS**

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



Ccl19

Ccl27

Wbp11

Oprs1

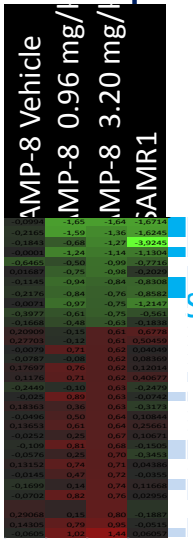
2 x

S100a9

2 x

Genes located in amplified cluster on Chr4

Inflammation signature genes



S100a9

Inflammation signature genes

Cognitive function, neuroplasticity and memory

<50 genes up or down-regulated by > 2 fold female SAMP-8 vs SAMR1 (see also Carter *et al.*).

Chr 4 cluster incuding *Ccl19* and *Ccl27* is amplified and over-expressed SAMP-8 vs SAMR1 mice.

Inflammation genes upregulated in SAMP-8 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 SAMP-8 mice.**
- **ORY-2001 up-regulated genes associated with improved cognitive function, neuroplasticity and memory.**

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ORY-2001 DEVELOPMENT TIMELINE

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

Phase I Clinical Trial in young and elderly healthy volunteers

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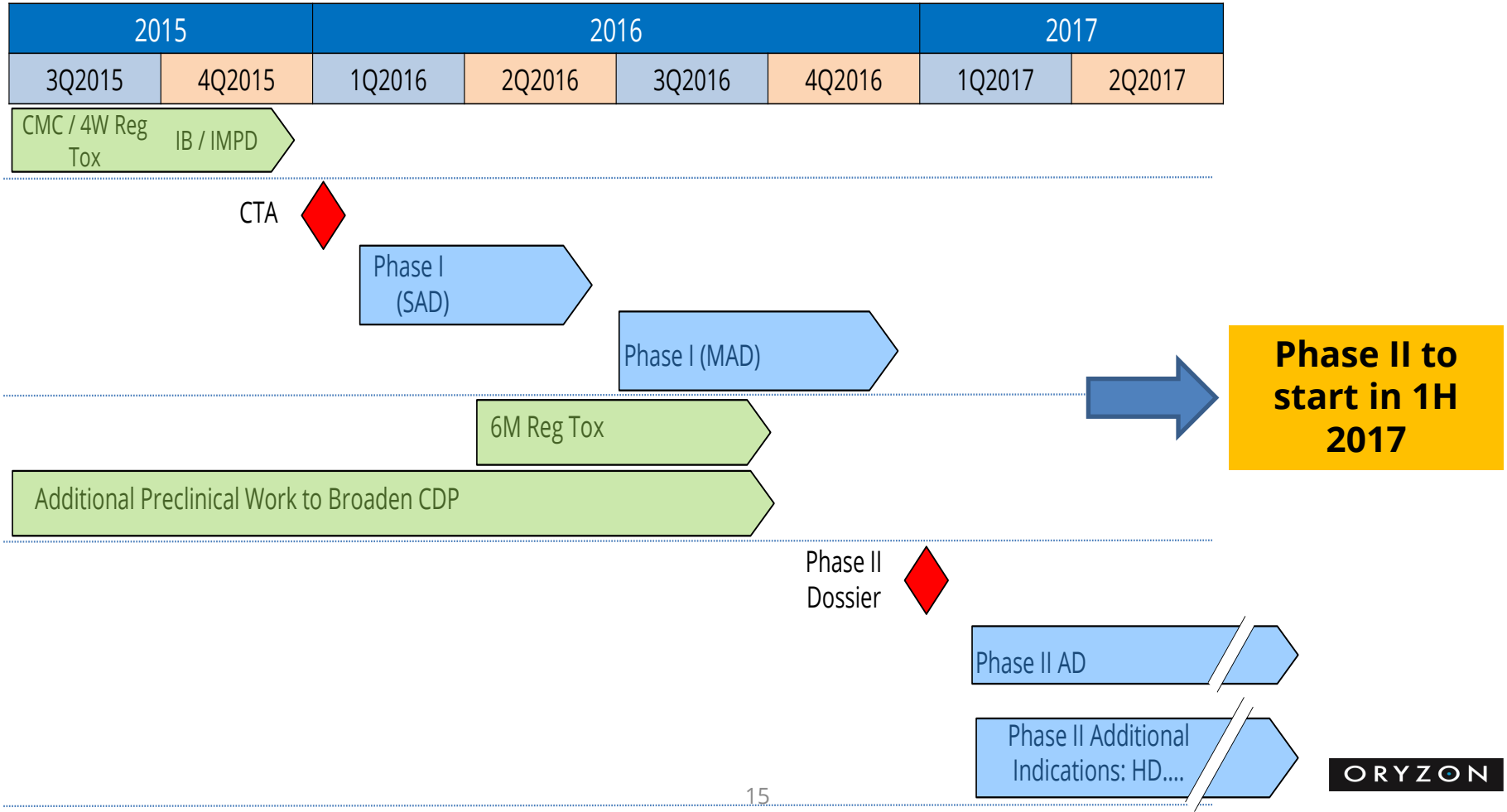
ORY-2001 DEVELOPMENT TIMELINE



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CATALYSTS 2015 - 2016

- ✓ ORY-1001: LEAD CANCER ASSET
  - Conclude Phase I dosing study
  - Receive recommended dose milestone payment from Roche
  - Phase IIA first patient-in
  - **Complete Phase IIA and report target efficacy**
  - **Roche execute ongoing clinical development plan**
- ✓ ORY-2001: LEAD CNS ASSET
  - Complete preclinical toxicology package
  - File CTA/IND
  - Begin Phase I volunt. enrolment
  - **Complete Phase I dosing safety study**
  - **Layout of a multiple Phase II clinical study including potential additional indications**
- ✓ CORPORATE
  - €16.5M cross over funding in Spain
  - List on the Spanish Main Market
  - **Prepare to List on the NASDAQ in the future**

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THANK YOU VERY MUCH!
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