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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
## Extensive Pipeline: 2 Programs in Clinic with Multiple Indications

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<th>Indication</th>
<th>Target</th>
<th>Molecule</th>
<th>Discovery</th>
<th>H2L</th>
<th>Lead Optimization</th>
<th>Preclinical</th>
<th>Phase I-IIA</th>
<th>Phase IIB</th>
<th>Phase III</th>
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<td>ORY-1001</td>
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Roche
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)

- 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
# 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
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

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

Expected to Report Preliminary Data in ASH 2016
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% CAGR 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](http://www.hematology.org)
3. [www.lungcancer.org](http://www.lungcancer.org)
4. Global Data 2015
5. Decision Resources 2015
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.
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.
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
Meta-analysis of cognitive deficit of untreated SAMP-8 mice (historical data)

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

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 control; 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 control; treated group n = 10)
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 SAMP-8 vs SAMR1 (see also Carter et al.).

Chr 4 cluster including 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.
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
2015 2016 2017
3Q2015 4Q2015 1Q2016 2Q2016 3Q2016 4Q2016 1Q2017 2Q2017

CMC / 4W Reg Tox IB / IMPD

CTA

Phase I (SAD)
Phase I (MAD)
6M Reg Tox

Additional Preclinical Work to Broaden CDP

Phase II Dossier

Phase II to start in 1H 2017

Phase II AD
Phase II Additional Indications: HD...
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
THANK YOU VERY MUCH!

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