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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

A competitive EPIGENETIC Platform with a first program that validates scientifically and clinically the platform.

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 for ORY-1001 valued at 500M USD

Strong IP portfolio with technology developed in-house

Raised €27m in the last 12 months. Cash runway till 1H2018
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
LSD1 is an enzyme that demethylates histones: specifically mono and dimethylated H3K4 and H3K9.

LSD1 belongs to the family of FAD–dependent amine oxidases, which include known CNS drug targets, such as MAO-A and MAO-B.

The general MAO inhibitor tranylcypromine is a chemical starting point to design LSD1 inhibitors.

Oryzon’s LSD1 program

Selective LSD1 i

- Extremely Potent
- ORY-1001
  - Cancer Hematological & Solid Tumors
  - Phase I/IIA

Potent

- ORY-3001
  - Other Indications Orphan / Non onco...
  - In process of nomination as Preclinical Candidate

Dual Selective LSD1-MAOB i

- Mildly Potent
- ORY-2001
  - Neurodegeneration / Neuroinflammation
  - Phase I
## Extensive Pipeline: 2 Programs in Clinic with Multiple Indications

<table>
<thead>
<tr>
<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>
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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)

Currently in Phase I/IIA

• Completed Part 1 of the study (Phase I) in acute leukemia

• Extension Arm (Phase II-A) ongoing

Potential for additional indications in solid tumors
**Phase I Highlights: ORY-1001 Leukemia**

Licensed to ROCHE in 2014

- $23m received in 2014-15
- $+500m in future contingent milestones
- Tiered royalties up to double digit.
- Clinical development and all related investments beyond the ongoing Phase I/IIA trial are the responsibility of ROCHE

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**Trial Design**

<table>
<thead>
<tr>
<th>Refractory &amp; Relapsed Acute Leukemia</th>
<th>Multi-Center (5)</th>
<th>Multiple Ascending Dose (8 Cohorts)</th>
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**Primary Endpoint**

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

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**Secondary Endpoints**

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<tr>
<th>Characterize PK</th>
<th>Assess Responses (CR/Cri/PR), particularly for rMLL gene</th>
<th>Evaluate surrogate PD markers for target engagement</th>
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</thead>
</table>

**Preliminary Results**

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

Licensed to ROCHE in 2014

$23m received in 2014-15

+$500m in future contingent milestones

Tiered royalties up to double digit.

Clinical development and all related investments beyond the ongoing Phase I/IIA trial are the responsibility of ROCHE
After the MRD, an Expansion arm (Phase II-A) to include patients with target mutations (MLL and others) to evaluate preliminary signs of efficacy

14 Patients enrolled
Status: Enrollment closed. 3 patients still under treatment
Completion Date: 3Q16

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 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
- Global Mk Potential of $932 million in 2024, CAGR of 10.5%

### Small Cell Lung Cancer
- 15% of all Lung Cancers
- 32,420 new cases in US in 2014
- Global Mk Potential of $684 million in 2017

### 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](http://www.hematology.org)
3. [www.lungcancer.org](http://www.lungcancer.org)
4. Global Data 2015
5. Decision Resources 2015
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

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

LSD1 is known to be an important regulator in the maintenance of pluripotency and in specification of neuronal commitment of pluripotent or multipotent cells.

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 ready for Phase II in 1H2017

- Highly selective dual LSD1-MAO-B inhibitor
- Preclinical Proof of Concept: LSD1 Against AD and HD
- A third indication (still confidential)
- Other additional indications being explored preclinically
- Clinical development: In Phase I - LPO expected in Dec2016
  - 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
PoC studies in SAMP8 mice

ORY-2001 provides a dose dependent protective effect in the medium-term memory of female mice, compared to age-matched SAMP8 mice.
ORY-2001: A possible disease modifier drug

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

ORY-2001 restores the discrimination index in SAMP-8 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 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
BIOMARKERS: We have identified different biomarkers upon ORY-2001 treatment:

- Down-regulation of the pro-inflammatory S100A9 protein by ORY-2001 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)
  - and traumatic brain injury (TBI).

- Knockout or knockdown of S100A9 has been shown to be beneficial to memory in APP/PS1 and Tg2576 models of Alzheimer's disease.
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.

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**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

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**Phase I Clinical Trial** in young and elderly healthy volunteers
## ORY-2001 DEVELOPMENT TIMELINE

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<thead>
<tr>
<th>2015</th>
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<tr>
<td>4Q2016</td>
<td>1H2017</td>
<td>2H2017</td>
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**CMC / 4W**  
**Reg Tox**  
**IB / IMPD**  

**CTA**

**Phase I**  
(SAD)  

**Phase I**  
(MAD)  

**9M Reg Tox**

**Additional Preclinical Work to Broaden CDP**

**Phase II**  
Dossier  

**Phase II AD**

**Phase II Additional Indications: HD...**
ORY-2001 CLINICAL & MARKET POTENTIAL

**ORY-2001 market capture opportunity above $3 billion.**
Further development may include Neuro-inflammatory disorders

**ALZHEIMER’S DISEASE**
5.4 M people currently affected in US. By 2025 the number of patients will rise to 7.1 million in USA
8.7 million Europeans are also affected and in Asia another potential 10 to 12 million people are diagnosed or suspected to suffer AD.

**Drug market projected to reach US $9.5 billion by 2017**

**PARKINSON’S DISEASE**
Around 6.3 million people have the condition worldwide
It affects over 1 million people in the US, with nearly 60,000 people newly diagnosed every year.

**Drug market projected to reach US $2.6 billion in 2020 in the 7MM**

**HUNTINGTON’S DISEASE**
Worldwide prevalence of HD is 5-10 cases per 100,000 persons. There are around 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease
Up to 71,000 patients in Europe.

**Drug market projected to reach US$1.3 billion by 2020**

1. Alzheimer’s association [www.alz.org](http://www.alz.org)
7. [http://www.strategyr.com](http://www.strategyr.com)
FINANCIAL HIGHLIGHTS

✓ €27m raised in the last 12 months (equity+debt)
✓ Strong balance sheet with €+29m in cash at the end of Q1-2016
✓ $5 million payment from ROCHE in 2015 ($23m total in the period 2014-15)
✓ Secured €2.6M in public aids in 2015
✓ €20M in debt with low interest rates
  • Repayment terms over either 3-4y or 8-10y (commercial loans or Public R&D loans)
  • Rates from 0-3% (average cost of debt 1.3%)
  • 1Q-2016: 10.5M non-senior, non-secured debt in 1Q 2016 4-5y term at rates between 1.5%-3.5%
✓ Expected cash burn of €10-12M annually for next 2 years
✓ Raised €31 M since inception
✓ Spanish GAAP rules adapted to IFRS and ready for Nasdaq
✓ Accounts audited by Grant Thornton since 2003
✓ 35 employees (40 expected by the year’s end)
ORY-1001: LEAD CANCER ASSET
- Complete Phase IIA and report target efficacy
- Roche execute ongoing clinical development plan

ORY-2001: LEAD CNS ASSET
- Begin Phase I patient enrolment
  - Complete Phase I dosing safety study in healthy volunteers
  - Layout of a multiple Phase II clinical study including potential additional indications

ORY-3001: Nomination of Preclinical Candidate

CORPORATE
- Prepare to Dual List on the NASDAQ in the future
THANK YOU VERY MUCH!

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