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Company Highlights

✅ MADX: ORY  A publically traded company on the Spanish Stock Exchange

✅ Integrated in the IBEX Small Cap Index

✅ 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

✅ Large IP portfolio with technology fully developed in-house

✅ Raised €50M (in 2015-2017). Additional €13M raised from investors in the US and Europe in October 2018

✅ Cash runway expected till 4Q2020

✅ Loss/Earnings from Operations 2018: -3.3M€

✅ One of the MOST LIQUID companies in the MicroCap group in the Spanish Stock Market
  
  ✅ 39.1 M Shares outstanding. Fully diluted
  ✅ 350,000 daily volume (Avg Traded Volume in 2018)
  ✅ +88M shares negotiated in 2018 / ≈5 months for share full turnover

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

<table>
<thead>
<tr>
<th></th>
<th>December 31st, 2018</th>
<th>December 31st, 2017</th>
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</thead>
<tbody>
<tr>
<td>Cash and cash equivalents</td>
<td>39,296⁽¹⁾</td>
<td>41,916</td>
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<tr>
<td>Marketable securities</td>
<td>162</td>
<td>256</td>
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<tr>
<td>Total Assets</td>
<td>77,231</td>
<td>73,210</td>
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<tr>
<td>Deferred revenue</td>
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<td>0</td>
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<tr>
<td>Total Stockholders' equity</td>
<td>51,668</td>
<td>41,294</td>
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</table>

⁽¹⁾ 34,5 M€
LSD1 in human diseases

Lysine specific histone demethylase 1 (LSD1), aka KDM1A, removes methyl marks at mono- and dimethyl-H3K4 (histone H3 lysine 4) and H3K9 (histone H3 lysine 9)

LSD1 is involved in different pathologies:

- Solid tumors
- HemOnc
- Hematol. disorders
- Inflammation
- Neurodegeneration
- Psychiatric disorders
- Viral Infections
- Others...

Fu et al., Future Med. Chem. 2017 9(11)
Extensive pipeline: 2 programs in clinic with multiple indications each

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>STUDY</th>
<th>RESEARCH</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE IIA</th>
<th>PHASE IIB</th>
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<tbody>
<tr>
<td>VAFIDEMSTAT (ORY-2001) - dual LSD1-MAO B Inhibitor</td>
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<td>Alzheimer's disease (Mild Moderate)</td>
<td>ETHERAL monotherapy</td>
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<td>Multiple Sclerosis (Relapse Remitting &amp; Secondary Progressive)</td>
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<td>CNS Basket Trial Aggression</td>
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<tr>
<td>IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor</td>
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<tr>
<td>AML (Elderly Unfit)</td>
<td>ALICE Combo w Aza</td>
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<tr>
<td>SCLC (First Line Relapsed)</td>
<td>CLEPSIDRA Combo w Platinum/Etoposide</td>
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<td>ORY-3001 - selective LSD1 inhibitor</td>
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<td>Non Oncological</td>
<td>Preclinical finished</td>
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<td>OTHER PROGRAMS</td>
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Vafidemstat (ORY-2001)

A Phase II stage clinical compound

- A small molecule that selectively inhibits LSD1 and MAO-B (IC50 s of 100nM in LSD1 / 75 nM in MAOB)
- Covalent binder. Excellent Pharmacology. High oral bioavailability
- Demonstrated target engagement
- Characterized in 6 and 9 months PC regulatory toxicological studies
- Positive results in 7 different animal models and in in-vitro models
- Superior performance than other LSD1 inhibitors. Produces positive results in:
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Agression / Agitation
  - Others
- Biomarkers identified in animals that show promise for use in humans
- Capable of acting in all the processes that manifest in neurodegenerative disease patients
- Safe in humans in a Phase I trial with 106 healthy volunteers
- Crosses the BBB and human target engagement

In Phase IIa in three different clinical studies
Vafidemstat (ORY-2001) restores cognition measured by NORT in SAMP8 AD model

Preclinical results suggestive of Disease modifying potential

(Similar memory restoration results observed with Vafidemstat in the R6/1 HD model. Positive effects in memory also described recently in the NMDA receptor-hypofunction mice with T-448, a selective LSD1 inhibitor from Takeda)
Vafidemstat (ORY-2001) reduces aggression in mice Alzheimer’s Disease model

In the cognition tests we noticed that SAMP8 male mice treated with vehicle aggressed cage mates while ORY-2001-treated animals did not. Later we confirmed this in proper _Resident-intruder_ aggression tests.

SAMP8 animals treated with ORY-2001 are not aggressive and have normal levels of basal activity (no sedation).
Vafidemstat (ORY-2001) also corrects the lack of sociability of aged SAMP8 mice

In the delayed start experiment, where treatment was initiated in 8 month old SAMP8 mice and behavior was evaluated at 12 months of age, treatment with ORY-2001 restored not only memory but also social interaction/sociability measured on the Three chamber test Paradigm (TCT)

TCT is widely used to evaluate drugs as a model for Autism Spectrum Disorder

Vafidemstat (ORY-2001) enhances sociability
Vafidemstat (ORY-2001) is effective in the EAE and Thyler’s models and reduces neuroinflammation

- In 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 significantly 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 reduces microglial activation in Theiler’s MS model.

- ORY-2001 is neuroprotective, restoring axonal integrity in TMEV model and also in a glutamate excitotoxicity in vitro model.

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Vehicle ORY-2001 ORY-LSD1
Vehicle ORY-2001 ORY-LSD1
A
B
Lumbar Sections
Cervical Sections

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Vehicle ORY-2001 ORY-LSD1
Vehicle ORY-2001 ORY-LSD1
A
B
Lumbar Sections
Cervical Sections
Vafidemstat (ORY-2001)
CLINICAL DEVELOPMENT
Vafidemstat (ORY-2001) Phase I: Safety and hematology

- **Safe and well tolerated** in over 100 healthy volunteers Phase I study
- **No hematological impact** at the planned doses
- **Efficiently crossed 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/plasma ratio ≈ 0.7-0.9)
- **ORY-2001 efficiently inhibits the brain human LSD1**
- **PK** Oral PK T1/2 ≈ 22h allowing once daily oral
- **PK/PD data allow to select Phase II doses**
- **ORY-2001 has been already administered to many patients in the ongoing Phase IIs with no safety issues so far**

Vafidemstat (ORY-2001) is in Phase II in humans in AD and MS where we expect to have the first read outs in 2H2019
ETHERAL: Epigenetic THERapy in Alzheimer’s Disease

An ambitious Phase IIa study to provide useful information to design future Phase II/III studies

**CLINICAL STUDY PROTOCOL**

A multicentre, multinational, randomised, double-blind, placebo-controlled, 3-arm, 24-week parallel-group study to evaluate the safety, tolerability and preliminary efficacy of ORY-2001 in patients with mild-moderate Alzheimer’s Disease. ETHERAL Study

- **Mild to Moderate AD patients**
- **Nº of patients: 150**
- **Primary Objective: Safety & Tolerability**
- **Secondary Objectives:**
  - Cognition/Agitation/Apathy/QoL
  - Volumetric MRI
  - **Biomarker guided study** with several CSF inflammatory Biomarkers

- 125 patients in EU. 17 sites
- Spain, France & UK actively recruiting
- 80 randomized as per mid March

- A Twin study in US: around 25 patients
- IND approved
- FPI expected 1H2019

**Diagram:**

- MMSE 16-26
- CSF analysis: Abeta+, P-Tau+
- Randomization
  - MRI at baseline
  - Cogstate at baseline
  - Placebo
  - 6 months
- 1.2 mg ORY-2001
- 0.6 mg ORY-2001
  - MRI at 6 months
  - Cognition at 6 months
  - Behaviour at 6 months
  - Biomarkers at 6 months
  - Interim Report
  - MRI at 12 months
  - Cognition at 12 months
  - Behaviour at 12 months
  - Biomarkers at 12 months
- 1.2 mg ORY-2001
- 0.6 mg ORY-2001
- +6 months
Vafidemstat (ORY-2001) ETHERAL Phase IIa: Biomarker strategy

**S100A9 has been characterized as one of the TOP10 up-regulated genes in LOAD dataset**

- S100A9 PROTEIN levels are significantly increased in CSF from AD patients compared to age-matched controls
- S100A9 CSF PROTEIN levels will be monitored in ETHERAL AD trial
  - S100A9 and inflammation have a correlation with the disease
  - Inflammation plays a mechanistic role in the progression of the disease
  - ORY-2001 reduces S100A9 in animals

**Human PFC (RNA)**

**Human CSF (protein)**

S100A9 CSF levels will be monitored in Phase II studies
S100A9 has the potential to be a surrogate biomarker for drug activity
S100A9 data might be part of a rationale for a fast track

Changes in S100A9 in patient’s CSF may have important clinical development implications
Vafidemstat (ORY-2001): REIMAGINE: A Basket trial in aggression

**ORY-2001 REIMAGINE Study**

✓ A single center open label exploratory basket trial to assess the effect of ORY-2001 in reducing aggression in patients with two neurodegenerative and three neuropsychiatric indications

✓ N=30, with 6 participants per condition

✓ Single arm of ORY-2001 (1.2 mg)

✓ 8 weeks treatment duration

✓ AD
✓ D LB
✓ BPD
✓ ADHD
✓ ASD

✓ Approved September 2018

✓ FPI 4Q 2018

✓ Expected LPO 1Q 2019

Conferences where preliminary data are expected to be presented
Vafidemstat (ORY-2001): REIMAGINE: A Basket trial in aggression

**REIMAGINE** the first proof of concept for Vafidemstat in human patients.

Borderline Personality Disorder (BPD) patients treated with Vafidemstat showed a reduced aggressivity and a better overall performance in the global BPDCL.

Complete data on this cohort will be presented at the Warsaw EPA 2019 Conference

- Vafidemstat was safe and well tolerated by the BPD patients
- Patients had an overall decrease in the Columbia-Suicide Severity Rating Scale
- Vafidemstat produced significant improvements in the Clinical Global Impression (CGI)
- Vafidemstat also produced significant improvements in the Neuropsychiatric Inventory, not only at the 4-item agitation/aggression NPI subscale score, but also at the global NPI score (12 items)
- Remarkably, Vafidemstat also produced significant improvements on the Borderline Personality Disease Checklist (BPDCL) both on the global scale and in the subset of domains related with agitation/aggression
- BPD prevalence ranges between 0.5%-1.4% (*) and it represents a significant unmet medical need

Iadademstat (ORY-1001)

A Phase II stage clinical compound
Iadademstat (ORY-1001): the most advanced LSD1 inhibitor in clinic

- LSD1 is involved in different cancers. High levels of LSD1 often correlate with more aggressive forms of cancer and/or bad prognosis.
- MoA identified in Leukemia, SCLC and medulloblatoma
- Iadademstat is a small molecule that selectively inhibits LSD1. Preclinical in-vivo positive results in xenografts of AML, SCLC and in PDX of SCLC
- First LSD1 drug to enter into clinical trials and still Best in Class
- Produced positive results in an Acute Leukemia Phase I/IIa trial (manuscript submitted)
- Identified Biomarkers to stratify SCLC patients
- Phase IIa ongoing in SCLC (CLEPSIDRA)
- Phase IIa ongoing in AML (ALICE)
- Preclinical / Biomarkers and new combos under constant investigation
Iadademstat a flexible CDP for a Large Market Opportunity

MoA well characterized in SCLC, AML and Medulloblastoma

Small Cell Lung Cancer is the main indication under exploration

POTENTIAL IADADEMSTAT ONCOLOGICAL INDICATIONS:

**Solid Tumors**
- Small Cell Lung Cancer
- Prostate cancer
- Colorectal cancer
- Bladder cancer
- Some breast cancers

**HemONC**
- AML
- MDS
- Myelofibrosis
- Non Hodgkin
- Lymphoma

**Brain Tumors**
- Medulloblastoma
- Glioblastoma
LSD1 is a target well characterized in SCLC and validated in preclinical models. LSD1 inhibitors are effective in vitro and in-vivo xenograft models of SCLC.

iadademstat is the best and first in class LSD1 inhibitor in clinic development.

iadademstat produces complete and durable tumor regression in different chemoresistant PDX models.

Characterized MoA (induction of Notch and repression of ASCL1).

Identified and patented Biomarkers that are differential in sensitive cell lines.

Characterization of Biomarkers in tumors and plasma from patients.

Phase II Clinical trial ongoing in second line SCLC patients using these biomarkers to stratify patients and identify super-responders.
Iadademstat (ORY-1001): SCLC Current Clinical Development Plan

**CLEPSIDRA:** A Combination trial of LSD1 and Etop-Platinum in Small Cell Lung Cancer in biomarker-ID Relapsed pAtients

A Phase IIa study to assess the safety, tolerability, dose finding and efficacy of Iadademstat (ORY-1001) in combination with platinum-etoposide chemotherapy in patients with relapsed, extensive-stage disease small cell lung cancer who are positive to candidate predictive biomarkers

- Single arm
- Open label; 4 sites in Spain
- Up to 36 patients to be enrolled
- **Primary end point:** Safety and tolerability of the combo with platinum-etoposide therapy
- **Secondary endpoints:** RECIST responses; time to responses; duration of response; and overall survival

**Preliminary Results**

- Patient 1 already completed the first two cycles of combo iada+SoC and has started cycle 3.
- Satisfactory and dynamic recruitment pace: 3 more patients enrolled as per 2nd week of February
Iadademstat (ORY-1001) MoA: a potent differentiating agent to treat Acute Leukemias

LSD1 is a target for HEMATOLOGICAL CANCERS, and in particular, for a subset of acute myeloid leukemia: mixed lineage leukemia MLL-AML

✓ Oryzon’s LSD1 inhibitors block progression of leukemia into the circulation in mice with experimentally initiated MLL-AF9 AML

✓ Oryzon’s LSD1 inhibitors target Leukemia Stem Cells but spare normal HSPCs
Iademstat (ORY-1001): AML Current Clinical Development Plan

**Phase I/IIa previous data (manuscript submitted)**

- Safe and very well tolerated and therefore a meaningful candidate for combination with other agents
- PD Biomarkers identified in different subsets of leukemia
- Antileukemic activity observed in 29% of patients (12/41), including one CRi as Proof of Biological concept

**ALICE: An AML trial with LSD1i in Combination with azacitidine in the Elderly**

A Phase IIa study to evaluate the safety, tolerability, dose finding and efficacy of Iademstat (ORY-1001) in combination with azacitidine in older patients with AML in first line therapy

- Single arm
- Open label
- Up to 36 patients to be enrolled
- **Primary end point:** Safety and tolerability of the combo with hypomethylating agent Azacitidine
- **Secondary endpoints:** Responses; time to responses; duration of response; and overall survival

**Preliminary Results**

- 3 patients have already gone through the first cycle; good tolerability
- Satisfactory and dynamic recruitment pace: 2nd cohort started by February

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*EHA* | *ORYZON*
Recent & Anticipated Oryzon main catalysts

IADADEMSAT (ORY-1001): lead CANCER asset

FPI Phase IIa in elderly unfit AML

FPI Phase IIa in SCLC

Potential Conferences where data may be presented

Period of Preliminary Clinical Read Outs

Open Label Studies
Recent & Anticipated Oryzon main catalysts

VAFIDEMSTAT (ORY-2001): lead CNS asset

Conferences where preliminary data are expected to be presented:

- **2019**
  - Copenhagen; Sept
  - Athens; Oct
  - Warsaw; Apr
  - Lisbon; Apr

- **2020**
  - Stockholm Sept
  - San Diego; Dec
  - March
  - Amsterdam; July

Period of Preliminary Clinical Read Outs

- REIMAGINE: Basket trial Prelim read outs
- SATEEN: Safety read outs
- ETHERAL: Phase Ila in AD Prelim read outs
- Phase Ila Interim 6m read outs in AD-EU
- 12m read outs in AD-EU

Recent & Anticipated Oryzon main catalysts:

- **2019**
  - REIMAGINE: Basket trial Prelim read outs
- **2020**
  - VAFIDEMSTAT (ORY-2001): lead CNS asset
  - Phase Ila in AD Prelim read outs
  - Phase Ila in MS Prelim Safety read outs
  - ETHERAL: Phase Ila in AD Prelim read outs

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