A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION
MADX: ORY
April 2019
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Company Highlights

- MADX: ORY  a **publicly 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
- **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

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**Balance Sheet Data (Audited)**

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

(1) 34.5 M€
EPIGENETIC & LSD1 in human diseases

Epigenetic mechanisms regulate the function of chromosomes

Chromatin remodeling enzymes are a central component of the epigenetic regulation

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

- A Productive Epigenetic Platform
- A strong focus on LSD1

<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>VAFFIDEMSTAT (ORY-2001) - dual LSD1-MAO B inhibitor</td>
<td>Alzheimers disease (Mild Moderate)</td>
<td>ETHERAL monotherapy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Multiple Sclerosis (Relapse Remitting &amp; Secondary Progressive)</td>
<td>SATEEN monotherapy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CNS Basket Trial Aggression</td>
<td>REIMAGINE monotherapy</td>
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<tr>
<td>IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor</td>
<td>AML (Elderly Unfit)</td>
<td>ALICE Combo w Aza</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCLC (First Line Relapsed)</td>
<td>CLEPSIDRA Combo w Platinum/Etoposide</td>
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<tr>
<td>ORY-3001 - selective LSD1 inhibitor</td>
<td>Non Oncological</td>
<td>Preclinical finished</td>
<td></td>
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<tr>
<td>OTHER PROGRAMS</td>
<td>Undisclosed</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
VAFIDEMSTAT a Phase II Clinical Stage Compound with a broad developability in CNS diseases

- A small molecule that selectively inhibits LSD1 and MAO-B (IC50s of 100nM in LSD1 / 75 nM in MAOB)
- Covalent binder. Excellent Pharmacology. High oral bioavailability
- Demonstrated target engagement in various animal species
- Characterized in 6 and 9 months PC regulatory toxicological studies
- Positive results in 7 different animal models and in *in-vitro* models
- Produces positive results in:
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Aggression / 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
- BBB penetrance and human target engagement established
- Pharmacologically active in humans

*In Phase IIa in three different clinical studies*
Vafidemstat 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 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 vafidemstat-treated animals did not. Later we confirmed this in proper Resident-intruder aggression tests.

SAMP8 MICE treated with Vehicle
Resident Intruder test

SAMP8 MICE treated with ORY-2001 0,32mg
Resident Intruder test

SAMP8 animals treated with vafidemstat are not aggressive and have normal levels of basal activity (no sedation)

Vafidemstat also enhances sociability and reduces social withdrawal (data not shown)
Vafidemstat: REIMAGINE - a Basket trial in aggression

REIMAGINE Study

✓ A single center open label exploratory PhIIa basket trial to assess the effect of vafidemstat in reducing aggression in patients with two neurodegenerative and three neuropsychiatric indications
✓ N=30, with 6 participants per condition
✓ Single arm of vafidemstat (1.2 mg)
✓ 8 weeks treatment duration
  ✓ AD
  ✓ DLB
  ✓ BPD
  ✓ ADHD
  ✓ ASD

Global Analysis

Top Line Data 2019

Conferences where preliminary data are expected to be presented. Some TBC
REIMAGINE the first proof of concept for vafidemstat in human patients

The study has met the primary and secondary endpoints in BPD patients

Borderline Personality Disorder (BPD) patients treated with vafidemstat showed a reduced aggressivity and a better overall performance in the core scales of the disease.

**Primary endpoint: Safety**

- Vafidemstat was safe and well tolerated by the BPD patients
- Patients had an overall decrease in the Columbia-Suicide Severity Rating Scale (C-SSRS)

![C-SSRS score graph](image)

Demographic data BPD patients

<table>
<thead>
<tr>
<th>nº of patients</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median (years)</td>
<td>37.33</td>
</tr>
<tr>
<td>(Min., Max.)</td>
<td>(25/46)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Median (Kg)</td>
<td>60.72</td>
</tr>
<tr>
<td>(Min., Max.)</td>
<td>(52.7/89.8)</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Median (cm)</td>
<td>164.37</td>
</tr>
<tr>
<td>(Min., Max.)</td>
<td>(162/172)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22.51</td>
</tr>
<tr>
<td>(Min., Max.)</td>
<td>(19.39/33.39)</td>
</tr>
</tbody>
</table>
Vafidemstat is efficacious in aggression

Secondary endpoints: Efficacy

✓ Vafidemstat produced significant improvements on the Clinical Global Impression (CGI) CGI-S and CGI-I scales

✓ Vafidemstat also produced significant improvements on the Neuropsychiatric Inventory (NPI), not only at the 4-item agitation/aggression NPI subscale score, but also at the global NPI score (12 items)

✓ Remarkably, vafidemstat not only improved aggression but also produced significant improvements on the Borderline Personality Disorder Checklist (BPDCL), both on the GLOBAL scale and on the combined score for NON-aggression related domains
Vafidemstat: a CNS compound with broad development potential

Vafidemstat may be a therapeutic option for BPD

- BPD prevalence ranges between 0.5%-1.4%¹ of the total population (≤ 9.1M in US+EU5)
- The treatment of BPD is largely based on psychotherapeutic interventions. It represents a significant unmet medical need: No drugs currently approved for this condition
  - Anxiety & depression are usually treated with common antidepressants but do not seem to have a strong effect on other features of the disorder. Some anxiolytic (benzodiazepines) may worsen the clinical presentation.
  - Antipsychotic agents (Risperdal®, Seroquel® etc) have shown some effect to reduce anxiety, paranoid thinking, anger/hostility, and impulsivity in patients with BPD, but sedation, weight gain² and other side effects are a significant hurdle for long term treatment and adherence.
- Vafidemstat reduces aggression and social withdrawal while enhances sociability and restores memory in animals
- In BPD patients, it not only improves aggression but produces an overall improvement of the core features of the disease, with no sedation and no weight gain
- Vafidemstat may be a disease modifying therapeutic option for BPD

Vafidemstat: a new therapeutic option for Alzheimer’s disease

Alzheimer’s, the huge need

✔ 45 million people affected worldwide
✔ The Global cost of AD is $605 billion/year
✔ No therapeutic options so far
✔ The recent failures of BACE-i and mAb’s against Abeta (Aducanumab, Crenezumab and others) have finally convinced the industry about the need to look for other MoAs
✔ AMBAR study (Grifols) has demonstrated statistical improvement in ADAS-Cog, language and verbal scales and QoL after 14 months in plasmapheresis vs placebo in moderate AD, demonstrating therapeutic feasibility in this target population

Vafidemstat proposition in AD

✔ Vafidemstat is safe and highly brain-penetrant in humans
✔ We have demonstrated indirectly brain target engagement in humans
✔ In preclinical models we see positive effects on memory, aggression, sociability and apathy, all core features in Mild and Moderate AD patients
✔ We have identified biomarkers that may be surrogate pharmacological biomarkers
✔ Vafidemstat is pharmacologically active in humans
✔ The drug may provide clinical improvement in AD in both domains, symptomatic and disease modifier
ETHERAL: Epigenetic THERapy in Alzheimer’s Disease

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

- **150 Mild to Moderate AD patients**
- 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
Vafidemstat  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 are 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
  - Vafidemstat reduces S100A9 in animals

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: Phase IIa study in MS

**SATEEN** A pilot study in MS to see a proof of biological activity

SAfety, Tolerance and Efficacy in an EPIGENETIC approach to treat Multiple Sclerosis

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

Spain only; 9 sites; 24 patients (RR & SP)

Active recruitment ongoing

Excellent safety. One patient is +1 year on treatment

A broad preclinical evidence in different models supports vafidemstat activity in the MS paradigm
Iadademstat (ORY-1001)

A Phase II stage clinical compound
Iadademstat (ORY-1001): the most advanced selective 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
- 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 LSD1i drug to enter into clinical trials and still Best in Class
- Produced positive results in an Acute Leukemia Phase I/IIa trial
- 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
Ladademstat opportunity in SCLC

- 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.
- Ladademstat 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.

![Graphs showing tumor volume and time to reach 6x ITV for FHSC04.](image)

\[ P < 0.0001 \]
Iademstat: 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 iademstat (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

Clinical Preliminary Reports to be presented at several Medical Conferences to be announced in 2019-2020
Iadademstat 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
Iadademstat: AML Current Clinical Development Plan

**Phase I/IIa previous data**
- 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 iadademstat (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

Clinical Preliminary Reports to be presented at several Medical Conferences to be announced in 2019-2020
Recent & Anticipated Oryzon main catalysts

IADADEMSTAT (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

2019

2020

ALICE

CLEPSIDRA

Amsterdam; June

BCN; Sept

Orlando; Dec

BCN; Sept

26
Recent & Anticipated Oryzon main catalysts

**VAFIDEMSTAT (ORY-2001): lead CNS asset**

*Potential Conferences where data may be presented*

- **2019**
  - Warsaw; April
  - Lisbon; April
  - Stockholm; September

- **2020**
  - Athens; October
  - San Diego; December
  - March
  - Amsterdam; July
  - 12m read outs in AD-EU

**Phase Ila in MS Prelim Safety read outs**

**Phase Ila in AD Prelim read outs**

**Period of Preliminary Clinical Read Outs**

**Reimagine**

Basket trial Prelim read outs

**Etheral**

Phase Ila Interim 6m read outs in AD-EU

**Sateen**

Phase Ila in AD

**Epa**

European Psychiatric Association

**World Federation ADHD**

**Ectrims**

European Committee for Treatment and Research in Multiple Sclerosis

**CinP**

Conferences for Alzheimer's disease and Parkinson's disease

**Ad/Pd 2020**

The 18th International Conference on Alzheimer's & Parkinson's Diseases

**Aaic20**

Alzheimer's Association Conference 2020
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A GLOBAL LEADER IN CNS EPIGENETICS

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