A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION
MADX: ORY
July 2019
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Company Highlights

- A clinical stage biopharmaceutical company developing innovative therapies in the field of Epigenetics
- Large IP portfolio with technology fully developed in-house
- MADX: ORY - A publicly traded company on the Spanish Stock Exchange
- Integrated in the IBEX Small Cap Index

- Cash runway expected till 4Q2020
- Loss/Earnings from Operations 1Q2019: -$1.0M
- 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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<table>
<thead>
<tr>
<th>ORYZON GENOMICS SA</th>
<th>BALANCE SHEET DATA (UNAUDITED)¹</th>
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<tr>
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<td>(Amounts in thousands US $)</td>
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<tr>
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<td>March 31st</td>
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<td></td>
<td>2019</td>
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<td>Marketable securities</td>
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<td>Deferred revenue</td>
<td>0</td>
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<tr>
<td>Total Stockholders’ equity</td>
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¹ Spanish GAAPs
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 important in cancer, CNS, inflammatory and viral diseases

LSD1 currently being explored in CNS by Oryzon (3 Phase IIs) and Takeda (Phase I)*. No other players yet

In onco/hemonc, other players in LSD1 are Celgene, GSK, Incyte, Salarius, Imago

* Takeda is developing its CNS LSD1 inhibitor in Kabuki syndrome and, probably, Autistic Spectrum Disorder (ASD)
VAFIDEMSTAT a Phase II Clinical Stage Compound with a broad developability in CNS diseases

- LSD1 is the most abundant histone demethylase in the human frontal cortex
- Vafidemstat is a small molecule that selectively inhibits LSD1 and MAO-B
- Excellent Pharmacology. High oral bioavailability
- Positive results in 7 different animal models and in in-vitro models
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Aggression / Agitation
  - Others
- Epigenetic MoA that modulates neuroinflammation and expression of key plasticity neuronal genes
- Biomarkers identified
- Good Safety in humans in Phase I+II trials with +220 participants so far
- BBB penetrance and (indirect) human brain target engagement established
- Pharmacologically active in humans

In Phase IIa in three different clinical studies
Vafidemstat, and LSD1 inhibition, improves cognition

- vafidemstat (ORY-2001) restores memory in the SAMP8 AD model by the NORT model
- vafidemstat (ORY-2001) improves memory in the R6/1 HD model by the NORT model
- iadademstat (ORY-1001) improves working memory in the SETD1a +/- schizophrenia model
- T-448 (TAKEDA) improves memory in the NMDA receptor-hypofunction mice
Vafidemstat produces significant behavioral changes

- vafidemstat reduces aggression in the Resident Intruder test in the SAMP8 AD mice model
- vafidemstat enhances sociability in the Three-Chamber test in SAMP8 AD mice
- vafidemstat reduces social withdrawal in the rat isolation model

**VIDEO**

![Images of mice in a test environment](image)

**Graphs**

- TCT - Females 12M age
- 4 week treatment
- Chamber Preference

- Number of evasions

- Comparison of treatments:
  - Veh Veh 0.160.48
  - ORY-2001
  - Control
  - Isolated

![Graph legend and data points](image)
Vafidemstat reduces neuroinflammation and confers neuroprotection

- vafidemstat **improves clinical score in MS models that have a component of chronic and progressive disease**
- vafidemstat **reduces chronic demyelination** in chronic EAE and TMEV models
- vafidemstat **inhibits the local neuro-inflammation** in EAE and TMEV models but also blocks the inflammatory infiltration
- vafidemstat **is neuroprotective**, restoring axonal integrity in TMEV model and also in a glutamate excitotoxicity in vitro model

A broad preclinical evidence in different models supports vafidemstat activity in the MS paradigm

- **Vehicle**
- **Vafidemstat**

- (EAE mice model) therapeutic treatment (p.o.)
MoA: an upstream epigenetic mechanism producing a dual activity, antinflammatory and prosynaptic

- LSD1 localizes *in vivo* to enhancers and promoters of confirmed CNS disease risk genes
- LSD1 binds to TFs that control IEG expression and stress in the PFC-amygdala axis, including SRF
- vafidemstat potentiates the response capacity of IEGs to stress
- vafidemstat reduces the expression of inflammatory genes including S100A9 and others
- vafidemstat up-regulates genes associated with:
  - **Cognition**, notably memory and executive functioning
  - **Neuroplasticity**

LSD1 inhibition rescues the axon branching deficits in the Setd1a +/- mice

Vafidemstat potently down-regulated the expression of a subset of genes related to immune reaction and inflammation as S100A9 involved in OPC defective remyelination

- Genes up-regulated in SAMP8 mice by vafidemstat included
- Baiap3: involved in retrograde trafficking
- Prph: mutated in Amyotrophic Lateral Sclerosis (ALS),
- Fabp7: upregulation in drosophila favors long term memory consolidation
- Doc2a: activity-dependent modulator of excitatory synaptic transmission, relevant to memory formation
- Kremen2 and Rspo1, regulators of the WNT pathway

Recapitulation and reversal of schizophrenia-related phenotypes in Setd1a-deficient mice

Mukai et al 2019 [http://dx.doi.org/10.1101/529701]

In invivo axon branching rescue assays ORY-1001 was 1000-fold more potent than TCP

WT + PBS  Setd1a+/- + PBS  Setd1a+/- + TCP

SAMP8 Vehicle SAMP8 0.96 mg/kg SAMP8 3.20 mg/kg SAMP8 3.20 mg/kg SAMR1

S100a9 Inflammation signature genes Cognitive function, neuroplasticity and memory
Vafidemstat: Safety demonstrated in a Phase I study

- **Safe and well tolerated** in a +100 healthy volunteers Phase I (MAD+SAD) study
- No hematological impact at the planned doses
- Efficiently crossed the BBB (70-90%)
- Vafidemstat efficiently inhibits the brain human LSD1 in vitro
- Oral PK. **Half Life of 22h** allowing once daily oral
- PK/PD data allowed to select Phase II doses
- Vafidemstat has been already administered to **+220 volunteers and patients**
- **Phase IIs with no safety signals till now. Longest exposure to date: 15 months**
Vafidemstat: REIMAGINE - a Basket trial in aggression

REIMAGINE: A Phase II Basket trial in Aggression with vafidemstat

<table>
<thead>
<tr>
<th>Study type</th>
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<td>Allocation</td>
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<tr>
<td>Masking</td>
<td>Open Label</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>vafidemstat 1.2 mg/day</td>
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<tr>
<td>Duration</td>
<td>8 weeks + 4 weeks of follow up</td>
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</tbody>
</table>

Cohorts to be recruited

- Alzheimer’s disease: 12 patients - Starting
- Borderline Personality Disorder: 6 patients - Done
- Attention Deficit and Hyperactivity disorder: 6 patients - Done
- Autism Spectrum Disorder: 6 patients - Under analysis

Primary End Point

- Safety

Secondary End Points

- Aggression / Agitation measured by CGI-S
- Aggression / Agitation measured by CGI-I
- Aggression / Agitation measured by NPI A/A 4 items
- Psychiatric status measured by NPI Global assessment (12 Items)
- Change of BPD symptomatology measured by BPD Check List (BPDCL)
- Change of ADHD symptomatology measured by ADHD-RS
- Change of ASD symptomatology measured by ASD rating scale

when appropriate to the cohort
REIMAGINE the first proof of concept for vafidemstat in human patients

Borderline Personality Disorder (BPD) and Attention Deficit and Hyperactivity Disorder (ADHD) patients treated with vafidemstat showed a reduced aggressivity

Secondary endpoints: Efficacy

✔ Significant improvements on the Neuropsychiatric Inventory (NPI) 4-item agitation/aggression score

✔ Significant improvements in aggression evaluated using the Clinical Global Impression (CGI) CGI-S and CGI-I scales
The significant improvements in the NPI global score and overall specific scales for BPD and ADHD suggest that vafidemstat has a **broader psychiatric effect beyond aggression**

**Vafidemstat also produced significant improvements on the global NPI score (12 items) in BPD and ADHD patients**

**Remarkably, vafidemstat not only improved aggression but also produced significant improvements on the GLOBAL Borderline Personality Disorder Checklist (BPDCL) scale**
Next steps: Vafidemstat, a meaningful therapeutic option for BPD

"I find myself able now to control my negative emotions and my frustration"

Patient with severe borderline personality disorder during treatment with vafidemstat. Testimony to her psychiatrist Dr. Marc Ferrer

The company recognizes a significant development potential for vafidemstat in psychiatric indications

✓ Vafidemstat may be a disease modifying therapeutic option for BPD: reduces aggression and produces an overall improvement of the core features of the disease, with no sedation and no weight gain.
✓ BPD prevalence ranges between 0.5%-1.4% of the total population (≤ 9.1M in US+EU5)
✓ The treatment of BPD is now based on psychotherapeutic interventions. No drugs currently approved for this condition.
✓ A significant unmet medical need
✓ Global BPD Market, 2018-2027 (US$), $2,6B expected in 2027.

The company is preparing an additional Phase II/III trial in BPD and considering a Phase IIb in adult aggressive ADHD
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 the amyloid drugs have moved the industry to look for other MoAs

Vafidemstat proposition in AD

- Vafidemstat is safe and highly brain-penetrant in humans
- Brain target engagement in humans established (indirectly)
- Positive effects in different preclinical models on memory, aggression, sociability and apathy, all core features in Mild and Moderate AD patients
- Biomarkers identified that may be surrogate pharmacological biomarkers
- Vafidemstat is pharmacologically active in BPD and ADHD patients.
- Data on aggressiveness in AD to come in a few months.
- Vafidemstat may also provide clinical benefit in AD either as a single or multi-symptomatic drug or as a disease modifier
ETHERAL: Epigenetic THERapy in Alzheimer’s Disease

Besides aggression, vafidemstat may provide also further benefits

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

✓ 150 Mild to Moderate AD patients (6+6 months)
✓ Primary Objective: Safety & Tolerability
✓ Secondary Objectives:
  ✓ Cognition/Agitation/Apathy/Depression/QoL
  ✓ Volumetric MRI
✓ Biomarker guided study (with 8 CSF Biomarkers)

✓ 125 patients in EU. 17 sites
✓ Spain, France & UK actively recruiting
✓ +100 randomized as per e.o. May

✓ A Twin study in US: around 25 patients
✓ IND approved mid March
✓ US Sites (3) opened
✓ FPI recruited in May

MMSE 16-26
CSF analysis:
Abeta+
P-Tau+
Randomization
MRI at baseline
Cogstate at baseline

MRI at 6 months
Cogstate at 6 months
Cognition at 6 months
Behaviour at 6 months
Biomarkers at 6 months

1.2 mg ORY-2001
0.6 mg ORY-2001
placebo
6 months

MRI at 6 months
Cogstate 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

Interim Report
Iadademstat

A Phase II stage clinical compound
ladademstat (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**
- ladademstat is a small molecule that selectively inhibits LSD1. Preclinical positive *in vivo* results in different xenograft models. Best in Class. Full characterization published in top-rank journal.
- First LSD1i drug to enter into clinical trials. Encouraging results in a FiM Acute Leukemia Phase I/IIa trial

**Phase I/IIa acute leukemia - 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
Iadademstat a flexible CDP for a Large Market Opportunity

POTENTIAL ONCOLOGICAL INDICATIONS:

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

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

**Brain/rare Tumors**
- Medulloblastoma
- Glioblastoma

MoA well characterized in SCLC, AML and Medulloblastoma
Iadademstat in AML: Current Clinical Development Plan

**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 endpoint:** Safety and tolerability of the combo with hypomethylating agent Azacitidine
- **Secondary endpoints:** Responses; time to responses; duration of response; and overall survival

**Preliminary Results**

- Part 1 (Dose finding of the combo) Completed
- Preliminary Part 1 data with 6 patients reported at EHA-2019
- Extension Cohort with up to 18 more patients ongoing (next data set expected at ASH-2019)
- Additional reports to be presented in future Medical Conferences to be announced in 2020

Amsterdam 13-16 June 2019
Preliminary Results (5 evaluable patients out of 6)

- Combo **well tolerated**
- Fast responses (median time to response 1.5 months)
- **80% OR** (4/5 evaluable patients): **75% CRi** and **25% PR**
- 1 patient in CRi with decreasing need of transfusions
Peripheral differentiation

Potent early differentiation in responding patients
Iadademstat opportunity in SCLC

- LSD1 is a **target well characterized in SCLC** and validated in preclinical models. LSD1 inhibitors are effective in several in-vitro and in-vivo models of SCLC.
- Iadademstat produces **complete and durable tumor regression** in different chemoresistant PDX models.
- Characterized MoA.
- Identified and patented Biomarkers that are differential in sensitive cell lines, tumors and plasma from patients.
- Phase II trial ongoing in second line SCLC patients using these **biomarkers to stratify patients and identify super-responders**.
Analysis of sensitive versus resistant cell lines

GE candidates were confirmed by qRT-PCR and IHC

IHC against RNAseq

Correlation of X1 (left) and X2 (right) in PDX models:
Iadademstat: 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**

- 6 Patients enrolled. One patient at cycle 7.
- Satisfactory and dynamic recruitment pace
Anticipating a rich flow of catalysts / clinical data

Iademstat Phase IIs in oncology

2019

CLEPSIDRA
ALICE

2020

Amsterdam; June
AML data

Barcelona; Sept
SCLC data

Orlando; Dec.
AML data

Potential Conferences where data may be presented.

Vafidemstat Phase IIs in CNS

2019

REIMAGINE
ETHERAL
SATEEN

2020

Sept. Copenhag.
Psychiatry Aggression

Oct. Athens
Psychiatry Aggression

Dec. San Diego
AD aggression

April Vienna
AD Global EU 6m data

July Amsterdam
AD Global US 6m data
ORYZON – a unique investment opportunity in an epigenetic platform

- A differential proposition in **EPIGENETICS** drugs in **CNS and ONCOLOGY** around one of the most interesting targets in the field: **LSD1**
- **2 molecules** already in **Phase II** with promising clinical signals in human patients
- **Pioneers in CNS epigenetics**
  - Vafidemstat is efficacious in Psychiatric disorders (BPD and ADHD)
  - **Phase II/III in Borderline personality disorder under preparation.** Additional options in ASD or ADHD
  - Vafidemstat may be also clinically relevant in neurodegenerative disorders (Phase IIs in MS and AD ongoing)
- **Most advanced LSD1i (iadademstat) in Oncology**
  - 2 Phase II trials ongoing in combo with respective SoC in AML and SCLC
  - **Positive preliminary efficacy results** reported in dose finding part of AML trial
  - SCLC trial is a biomarker-guided study to stratify responsive patients
- **Rich pipeline** of clinical **news** expected in the next 2-4 Qs
- Clinical Operations in US started and under expansion
- A **cash efficient** company with a seasoned international management team
- **160m Euros market cap.** Highest liquid stock in the microcap group in MadridSEXC
- Perseverant **presence in the US market in the last 4 years.** Two successful PIPEs executed in 2017-18 led by US Investment Banks and with participation of US investors
- A public company in Europe with **plans to get dual listed in NASDAQ**
EXPERIENCED MANAGEMENT TEAM

CARLOS BUESA: CEO & President. Spain/US
PhD in Biochemistry and Molecular Biology. Founder and CEO since inception. Advanced programs on finance, business development, negotiation skills and human resources. He is also PADE at the IESE Business School. He is Board Member of the VC Fund Inveready and Deputy President of the Spanish BioIndustry Association.

TAMARA MAES: CSO & VicePresident. Spain
PhD in Biotechnology. Founder and Chief Scientific Officer since inception. Responsible of the creation of the whole pipeline of the company and the biological target validation programs. She is SAB member on several public institutions as CSIC and private companies. Since 2016 Scientific Advisor of the ADDF

MICHAEL T. ROPACKI: US
Vice President of Clinical Development
PhD in Clinical Neuropsychology. Dr. Ropacki has held roles of increasing responsibility for +10y at Johnson & Johnson, his last as Director of Clinical Development, Neuroscience, Research and Development, for Janssen R&D serving as the Clinical Lead responsible for developing and leading the Cognitive Health in Aging Registry. Prior to that role he served as Global Medical Affairs Leader, Head of Late-Stage Development at Janssen AD Immunotherapy, LLC.

ROGER BULLOCK: UK/PT/Spain
Chief Medical Officer
Graduated in Physiological Sciences at Keble College in Oxford University and got his MBBBS at London University
Extensive experience as clinical researcher, having participated in more than 70 clinical trials in Alzheimer’s disease and other CNS conditions
30-year research career, + than 100 peer-reviewed publications and book chap
He has worked as a consultant for companies active in the CNS space, including Lilly and Merck

SONIA GUTIERREZ: /Spain
Chief of Clinical Operations
BSc. Pharm. & MSc. & PDD in IESE Business School.
More than 20 years of experience in the clinical research and operations area at different Intral. Pharma & Biotech companies.
CNS: +13y in Lundbeck involved in + 40 Clinical Trials in CNS. Experience in oncology and other indications in Regeneron and other companies.

NEUS VIRGILI: /Spain
Chief IP Officer
B.Sc. in Organic Chemistry from the University of Barcelona
Qualified European Patent Attorney
She has over 20 years experience in pharmaceutical IP
Since 2011 IP Officer at Oryzon

ENRIC RELLO: / Spain
Chief Financial Officer
J.D.; PhD in Economics & Business Administration.
BSc & MSc in Business Administration & Laws,
From 1997 till 2007 CFO of SANDOZ (NOVARTIS), Spanish Arm.
CFO at Oryzon since 2011

EMILI TORRELL: /Spain
Chief BD Officer
B.Sc. in Sciences, Autonomous University of Barcelona
MBA at ESADE and PDG at IESE Business School
In the business development area from 1990 in the most relevant Spanish companies Prodesfarma, Almirall and Laboratorios Esteve
From 2007 BD Director at Oryzon

• An experienced and respected managerial team in the Biopharmaceutical industry
• Team members have a track record in product discovery & in advancing successfully through product development phases
• Demonstrated ability to close world class deals and to lead, and participate in international consortia