A GLOBAL LEADER IN EPIGENETICS

INVESTOR PRESENTATION
MADX: ORY
1Q 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

✓ Raised **€40M** (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

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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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<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>
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<td>256</td>
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<tr>
<td>Total Assets</td>
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<td>73,210</td>
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<tr>
<td>Deferred revenue</td>
<td>0</td>
<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

- **A Productive Epigenetic Platform**
  - A strong focus on LSD1
  - 3 Different LSD1 inhibitors in development
  - Additional programs on other targets

### Pipeline Summary

<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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<tr>
<td><strong>VAFIDEMSTAT (ORY-2001) - dual LSD1-MAO B Inhibitor</strong></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>
<td>SATEEN monotherapy</td>
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<td>CNS Basket Trial Aggression</td>
<td>REIMAGINE monotherapy</td>
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<td><strong>IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor</strong></td>
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<td>AML (Elderly Unfit)</td>
<td>ALICE Combo w Aza</td>
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<td>SCLC (First Line Relapsed)</td>
<td>CLEPSIDRA Combo w Platinum/Etoposide</td>
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<tr>
<td><strong>ORY-3001 - selective LSD1 inhibitor</strong></td>
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<tr>
<td>Non Oncological</td>
<td>Preclinical finished</td>
<td></td>
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</table>

**OTHER PROGRAMS**

| Undisclosed | | | | | | |

[ORYZON logo]
Solid evidence of an epigenetics axis in CNS diseases

**In Neurodegenerative disorders**

- Historic results with HDACi’s
  - HDACi improves HD symptoms in animal models
  - HDAC2 inhibition recovers memory on the AD bi-tg CK-p25 Tg mouse model
  - HDAC inhibition improves FTD
  - HDAC inhibition improves MS in EAE models


**In Psychiatric disorders**

- HDAC inhibition appears to play a role in major depression
- Histone methylation is also implicated in depression
- More than 40 years of clinical use of valproate in human clinics in CNS disorders: epilepsy, bipolar disorder and others

Vafidemstat (ORY-2001)

A Phase II stage clinical compound

- A small molecule that selectively inhibits LSD1 and MAO-B (IC50s of 100nM in LSD1 / 75nM 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
  - 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
- 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) induced expression changes in Inflammatory genes

Several inflammatory biomarkers were reduced in the model

**S100A9 as a biomarker for treatment with ORY-2001**

- S100A9 is an alarmin, amplifier of inflammation, innate immune system, activates TLR4
- Amyloidogenic
- Up-regulated in the hippocampus of SAMP8 mice
- Modulated by ORY-2001 treatment
- S100A9 KO or KD is beneficial in Tg2576 and APP/PS1 transgenic models for AD → functional implication
- **Upregulated in the human AD brain**, and may contribute to plaque formation
- Involved in neuroinflammatory processes, not limited to AD but also found in:
  - Traumatic Brain Injury
  - Post-Operative Cognitive Decline
  - Multiple Sclerosis
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.

**Therapeutic treatment (p.o.)**
Vafidemstat (ORY-2001), a “Neuron fixer”: Preclinical Summary

- Positive results in 7 different animal models/test paradigms and in *in-vitro* models
- Anti LSD1 activity is the driving effector
- Does not reduce basal activity nor provokes sedation
- Capable of acting in most of the processes that manifest in patients with different neurodegenerative and psychiatric diseases
- Biomarkers identified in animals that show promise for use in human

### ORY-2001 Results in PC models

<table>
<thead>
<tr>
<th>+</th>
<th>Cognition / Memory</th>
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<tbody>
<tr>
<td>+</td>
<td>Neuroprotection</td>
</tr>
<tr>
<td>+</td>
<td>Neuroinflammation</td>
</tr>
<tr>
<td>+</td>
<td>Social Withdrawal / Apathy</td>
</tr>
<tr>
<td>+</td>
<td>Sociability</td>
</tr>
<tr>
<td>+</td>
<td>Aggression/Agitation</td>
</tr>
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</table>

### Relevance in some CNS disorders

<table>
<thead>
<tr>
<th>Neurodegenerative space</th>
<th>Psychiatric space</th>
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</thead>
<tbody>
<tr>
<td>AD</td>
<td>MS</td>
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<td>+</td>
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<td>+</td>
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</tbody>
</table>

These data may substantially broaden the potential clinical development of ORY-2001 beyond the current indications of AD and MS that the company is initially advancing in clinical trials.
Vafidemstat (ORY-2001)

CLINICAL DEVELOPMENT
Vafidemstat (ORY-2001) Phase I: Safety and hematology

- **Safe and well tolerated** in a +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 \(\text{CSF/plasma}_{u}\text{ ratio} \approx 0.7-0.9\)
- **ORY-2001 efficiently inhibits the brain human LSD1**
- **PK** Oral PK T1/2 \(\approx 22\)h 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

- **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 in EU. 17 sites
- Spain, France & UK actively recruiting
- 68 randomized as per mid February

A Twin study in US: around 25 patients
- IND 1Q2019
- FPI expected 1Q2019
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

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): Phase IIa study in MS

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

**SAfety, Tolerability 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 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 +1year on treatment
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
  - DLB
  - BPD
  - ADHD
  - ASD
- Approved September 2018
- FPI 4Q 2018
- Expected LPO 1Q 2019

Conferences where preliminary data are expected to be presented:
Iadademstat (ORY-1001)

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

- A small molecule that selectively inhibits LSD1
- Covalent binder. Active in cells at subnanomolar levels
- Preclinical in-vivo positive results in xenografts of AML, SCLC and in PDX of SCLC
- Characterized in PC regulatory toxicological studies
- First LSD1 drug to enter into clinical trials
- Best in Class
- MoA identified in Leukemia, SCLC and medulloblatoma
- Produces positive results in a Acute Leukemia Phase I/IIa trial (manuscript submitted):
  - Safe and 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
- 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

In Phase IIa in two different clinical studies
Iadademstat (ORY-1001) is a clean and safe LSD1 inhibitor

- Iadademstat is a First & Best in Class selective LSD1 inhibitor in oncology
- The most advanced LSD1 inhibitor in clinical development in solid and hematological tumors

**ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia**

Tamara Maes,1,6,7 Cristina Mascaro,7 Irigo Tirapu,7 Angels Estiarte,7 Filippo Ciceri,7 Serena Lunardi,7 Nathalie Guibourt,1 Alvaro Perdone,7 Michele M.P. Lufino,7 Tim C.P. Somerville,8 Dan H. Wiseman,9 Qiangqiang Duy,4 Ari Melnick,9,10 Christophe Willekens,6 Alberto Ortega,1 Marc Martinell,1 Nuria Valls,1 Guido Kurz,1 Matthew Frye,7 Julio Cesar Castro-Palomino,1 and Carlos Buesa1

1Oryzon Genomics, S.A, Carrer Sant Ferran 74, 08940 Cornellà de Llobregat, Spain
2Leukaemia Biology Laboratory, Cancer Research UK Manchester Institute, The University of Manchester, Manchester M20 4BX, UK
3Department of Medicine, Division of Hematology & Medical Oncology, Weill Cornell Medicine, New York, 10065 NY, USA
4Department of Pharmacology, Weill Cornell Medicine, New York, 10065 NY, USA
5Drug Development Department (DITEP) and Hematology Department, Gustave Roussy, Université Paris-Saclay, 94805 Villejuif, France
6Lead Contact
7Correspondence: tmaes@oryzon.com
8https://doi.org/10.1016/j.ccell.2018.02.002

**ORY-1001: Overcoming the Differentiation Block in AML**

Prithviraj Bose1 and Marina Y. Konopleva1,2
1Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
2Correspondence: mkonopleva@mdanderson.org
3https://doi.org/10.1016/j.ccell.2018.02.014

In this issue of Cancer Cell, Maes and colleagues report *in vitro* and *in vivo* findings with ORY-1001—an oral, highly potent and selective covalent small-molecule inhibitor of lysine-specific demethylase 1 (LSD1)—in development for acute myeloid leukemia (AML), as well as correlative data from two AML patients receiving ORY-1001.
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

SCLC
- Second Line Combination with SOC
- ORY-1001 Biomarkers
- Relapsed/Refractory SCLC

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
Iadademstat 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.
- 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 is ~2 orders of magnitude more potent in sensitive cell lines than GSK’s clinical LSD1 inh. GSK2879552 (side by side comparison).
Ladademstat (ORY-1001) is efficient in PDX- SCLC

- Response to ORY-1001 in PDX models of SCLC is variable, but some are very strong.

  - FHSC04 model: derived from a SCLC patient who relapsed after first line therapy.

  - 6/10 FHSC04 mice treated with ORY-1001 did not show relapse after 300 days.

- Data from David MacPherson Lab.
Iademstat (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 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 cycle of combo iada+SoC and has started cycle 2.
- Satisfactory and dynamic recruitment pace: 3 more patients enrolled 2nd week of February
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
**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: 2\textsuperscript{nd} cohort started by February
POTENTIAL ADDITIONAL ONCOLOGICAL INDICATIONS AND NEW COMBO APPROACHES:

Possible combinations with I-O check point inhibitors

Studies listed on clinicaltrials.gov involving combinations of PD-1 or PD-L1 agents
Source:“PD-1/PD-L1 Combination Therapies” report, 2017, Evaluate Ltd
POTENTIAL ADDITIONAL ONCOLOGICAL INDICATIONS AND NEW COMBO APPROACHES:

Brain Tumors
- Medulloblastoma
- Glioblastoma

**Lsd1 as a therapeutic target in Gfi1-activated medulloblastoma**

Catherine Lee¹,², Vasilisa A. Rudneva³, Serap Erkek⁴,⁵,⁶, Marc Zapatka⁷, Lianne Q. Chau¹, Silvia K. Tacheva-Grigorova¹, Alexandra Garancher¹, Jessica M. Ruset¹, Ozlem Aksoy⁸, Robin Lea⁹, Helal P. Mohammad⁹, Jianxun Wang¹⁰, William A. Weiss⁸, H. Leighton Grimes¹¹, Stefan M. Pfister³,¹², Paul A. Northcott³ & Robert J. Wechsler-Reya¹,²

Drugs that modify the epigenome are powerful tools for treating cancer, but these drugs often have pleiotropic effects, and identifying patients who will benefit from them remains a major clinical challenge. Here we show that medulloblastomas driven by the transcription factor Gfi1 are exquisitely dependent on the enzyme lysine demethylase 1 (Kdm1a/Lsd1). We demonstrate that Lsd1 physically associates with Gfi1, and that these proteins cooperate to inhibit genes involved in neuronal commitment and differentiation. We also show that Lsd1 is essential for Gfi1-mediated transformation: Gfi1 proteins that cannot recruit Lsd1 are unable to drive tumorigenesis, and genetic ablation of Lsd1 markedly impairs tumor growth in vivo. Finally, pharmacological inhibitors of Lsd1 potently inhibit growth of Gfi1-driven tumors. These studies provide important insight into the mechanisms by which Gfi1 contributes to tumorigenesis, and identify Lsd1 inhibitors as promising therapeutic agents for Gfi1-driven medulloblastoma.
LSD1 inhibition is key in medulloblastoma

Gfi1 SNAG domain is required for transformation of NSCs

LSD1 is required for tumorigenic potential of Myc-Gfi1-transformed NSCs

LSD1i is effective in vitro and in vivo against Gfi1-driven MB

MoA:

Gfi1 is a key driver of medulloblastoma initiation and maintenance and Lsd1 is a critical mediator of its effects. Gfi1 and Lsd1 act by repressing genes important for neuronal fate commitment and differentiation. Pharmacological targeting of Lsd1 may be effective for treatment of Gfi1-activated medulloblastoma.
Recent & Anticipated Oryzon main catalysts

**IADADEMSTAT (ORY-1001): lead CANCER asset**

- **FPI Phase IIa in elderly unfit AML**
  - **ALICE**
  - **CLEPSIDRA**

- **FPI Phase IIa in SCLC**

**Period of Preliminary Clinical Read Outs**

- **2019**
  - **2019 ASCO ANNUAL MEETING**
  - **Chicago; June**

- **2020**
  - **BARCELONA 2019**
  - **ESMO congress**
  - **BCN; Sept**
  - **Orlando; Dec**

**Potential Conferences where data may be presented**

- **EHA EUPEAN HEMATOLOGY ASSOCIATION**
- **Amsterdam; June**

**Open Label Studies**
Recent & Anticipated Oryzon main catalysts

VAFIDEMSTAT (ORY-2001): lead CNS asset

★ Conferences where preliminary data are expected to be presented

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<th>Year</th>
<th>Conference</th>
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<td>REIMAGINE</td>
<td>Warsaw</td>
<td>Apr</td>
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<td>12m read outs in AD-EU</td>
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Phase Ia Interim 6m read outs in AD-EU
Phase Ia in MS Prelim Safety read outs
Phase Ia in AD Prelim read outs
Basket trial Prelim read outs
FPI in a Basket trial in Aggression

Period of Preliminary Clinical Read Outs