A breakthrough epigenetic approach in Alzheimer’s disease and other neurodegenerative disorders
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Business Summary

- **EPIGENETICS**: One of the world leading companies in epigenetics, as a novel way to approach oncology and CNS diseases and personalized medicine

- **PIPELINE**: 2 programs in clinic by year’s end
  - Clinic Programs can expand in multiple indications
  - Other Programs in Discovery that are progressing fast

- **PROVEN TRACK**: Cutting edge science endorsed by a world class deal in 2014 with ROCHE
  - Management team with demonstrated track record on creating innovative molecules and developing clinical assets in a cost-efficient manner

- **SOLID IP**: Excellent IP protection with a broad patent portfolio and FTO
  - 19 patent families, 8 granted in US + 2 with notice of allowance in US
  - All patented technology developed in-house, no owed royalties

- **WELL FUNDED**: Recently completed mezzanine financing in Europe raising above €15M
  - A plan to transition to a public company
Headquartered in Spain and the US

30 experienced and committed people

ORYZON Corp.
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Suite 1800
Cambridge, MA 02142

**Boston – US**
- Investor Relations
- Clinical Operations
- BD

ORYZON
Carrer Sant Ferran, 74
08940 Cornellà de Llobregat
Barcelona

**Barcelona – Spain**
- Pre-Clinical R & D
- Clinical Operations
- Investor Relations
- IP/BD/Finance
International Research Network
Epigenetics: The critical role of Histone coding

- **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
## The epigenetic products

### Launched

<table>
<thead>
<tr>
<th>Deacetylases</th>
<th>Methyltransferases</th>
<th>Demethylases</th>
<th>Bromodomain</th>
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<tbody>
<tr>
<td>Celgene</td>
<td>ISTODAX (romidepsin) for injection</td>
<td>VIDAZA (azacitidine for injection)</td>
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<tr>
<td>Johnson &amp; Johnson</td>
<td>Eisel</td>
<td>DACOCGEN (decitabine for injection)</td>
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<td>Zolinza (vorinostat) capsules</td>
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<td>Novartis</td>
<td>FARYDAK (panobinostat) capsules</td>
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<td>ONXEO SPECTRUM</td>
<td>Beleodaq (belinostat) for injection</td>
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### R&D

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</table>
Oryzon is exploring a wide field in epigenetics

Histone lysine methylation and demethylation is performed by a plethora of different enzymes. A number of targets are being preferentially explored by Oryzon.

To explore such a vast domain, Oryzon relies on its epigenetic technological platform. More than 1500 NCEs designed and tested in different screening cascades

http://apps.thesgc.org/resources/phylogenetic_trees

Structural Biology of Human H3K9 Methyltransferases
## Current Pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target</th>
<th>Molecule</th>
<th>Discovery</th>
<th>H2L</th>
<th>Lead Optimiz.</th>
<th>Preclinical Stage</th>
<th>Clinical Phase I-IIA</th>
<th>Clinical Phase II-B</th>
<th>Clinical Phase III</th>
<th>Partners</th>
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<tbody>
<tr>
<td>Cancer (Leukemias / Solid Tumors)</td>
<td>LSD-1</td>
<td>ORY-1001</td>
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<td>Roche</td>
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<tr>
<td>Huntington’s Disease</td>
<td>LSD-1/MAO-B</td>
<td>ORY-2001</td>
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<td>Cancer</td>
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<td>Other Indications</td>
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</table>
A global licensing agreement for the use of ORY-1001 and backups for oncology and other therapeutic indications.

The license compound is covered by two patents in the Oryzon IP portfolio (1).

Oryzon is responsible for completing the ongoing Phase I and IIA, after which Roche continues the clinical development covering all additional investments.

The two companies are collaborating on R&D of the compound through the Roche Translational Clinical Research Center (TCRC) based in NYC.

Payment at contract signing plus near term milestone totals $21 M

Development and Sales milestones total >>$500 M

Sales royalty rates tiered up to mid-teens

(1) The remaining 17 patents families of Oryzon’s LSD1 portfolio are not part of the Roche agreement.
ORYZON

ORY-2001 in CNS
# Epigenetic players in CNS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Target Indications</th>
<th>Status</th>
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<tr>
<td>FRM-0334</td>
<td>HDAC</td>
<td>FTD</td>
<td>Phase II</td>
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<tr>
<td>RVX-208</td>
<td>BRD</td>
<td>AD</td>
<td>Phase IIa (planned)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>It is in Phase III in secondary prevention of MACE with diabetes and low HDL</td>
</tr>
<tr>
<td>ORY-2001</td>
<td>LSD1+MAOB</td>
<td>AD, other dementias and neuroinflammatory disorders</td>
<td>Phase I in Q1/2016</td>
</tr>
<tr>
<td>BRD668</td>
<td>HDAC</td>
<td>AD, PD</td>
<td>LO</td>
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</table>
Alzheimer’s Disease (AD)
LSD1 inhibition is a potential disease-modifying therapy for AD, a highly differentiated profile according to the international AD current pipeline

other dementias and neuroinflammatory disorders

Oryzon’s research has been partly funded by competitive grants
ORY-2001  Mechanism of action

• LSD1 is involved in neural stem cell proliferation and cell specification.

• Terminal differentiation in neurons requires down-regulation of LSD1 activity, a process achieved at the transcriptional, post-transcriptional and post-translational level.

• ORY-2001 completely rescues the memory and learning defects of SAMP8 mice as determined by the performance of treated vs non-treated animals in the NOR test.

• Treatment with ORY-2001 up-regulates the hippocampal expression of genes related to improved cognitive function, neuroplasticity and memory, and down-regulate genes overexpressed in SAMP8 mice and in AD patients. Therefore, inhibition of LSD1 may result in beneficial effects on memory.
The LSD1 enzyme is structurally related to MAO-A and MAO-B, targeted by tranylcypromine (TCP, Parnate™) and Rasagiline (Azylect™), drugs used to treat depression and PD.

MAO-B is a well characterized target for Parkinson’s disease (PD), and it is also being reconsidered in the context of Alzheimer’s Disease. Here, the protein is over-expressed in reactive astrocytes around amyloid plaques, and mediates the aberrant and abundantly production of the inhibitory gliotransmitter GABA, which negatively affects synaptic plasticity, learning and memory.

Dual inhibitors targeting MAO-B in addition to LSD1 thus incorporate a potential plus for the treatment of neurodegenerative disease.

Oryzon’s ORY-2001 is the only dual LSD1/MAO-B inhibitor currently being moved forward to Phase I studies. It is also the only LSD1 inhibitor publicly in development for the treatment of neurodegenerative disease.
ORY-2001, a Preclinical Candidate for AD and other CNS disorders

MOLECULE
MW <350. Stereochemically pure compound
Covalent binder to the FAD cofactor

POTENCY
Balanced LSD1/MAOB activity, with IC50s in the range 70-100 nM
>70 fold on MAOA (>5 microM IC50)
>100 fold on LSD2 (>10 microM IC50)

SELECTIVITY
induces cell differentiation with an EC50 26 nM

In-VITRO
Dose-dependent PD effects in the range 0.1-3mg/kg
Proven Target engagement for LSD1 and MAOB activity

In-VIVO
Half-life suitable for once-a-day administration; orally bioavailable
High Brain exposure: Brain/plasma ratio >1

PK
No relevant Cyp inhibition, no induction of Cyp1B1
No hERG inhibition. No mutagenicity

PHARMACOLOGY
Good LM stability in human, dog, rat and mice microsomes

ADMET
High Brain exposure: Brain/plasma ratio >1
The Senescence-Accelerated Mouse-Prone 8 (SAMP8) was developed by Dr. Toshio Takeda (Kyoto University) from AKR/J mice.

- Develops deficits in learning and memory relatively early in its lifespan.
  - Impairments in avoidance tasks
  - Impairment of their spatial memory task ability

- Pathological similarities to Alzheimer Disease
  - Abeta deposition becomes clear from 7-8 months

- Profound disorder of their circadian rhythms of spontaneous motor activity and drinking behaviors.
- Histopathology: spongiform degeneration, astrogliosis, clusters of activated microglia, impaired blood-brain barrier function...
- Decline in immune responsiveness.
Concept: mice are trained by confronting them with an object, which they tend to explore. After 2h (mid term memory) or 24h (long term memory) they are confronted with 2 objects, the old one, and a new one. The SAMR1 reference strain remembers the old object and preferentially explores the new object. The SAMP8 strain has forgotten all about the old object and makes no distinction.
SAMP8 female animals treated with ORY-2001 (0.96 and 3.2 mg/kg)

- Provides a protective effect in the memory of female mice, compared to age-matched SAMP8 mice.
- Some toll on the mice at the highest dose → adapt dose in male Study #2
SAMP8 male animals treated with ORY-2001 (0.32 mg/kg; 0.96 mg/kg)

- provides a protective effect in the medium- and long-memory of male mice, compared to age-matched SAMP8 mice.

**PoC studies in SAMP8 mice: STUDY # 2**

**NORT Medium-term memory (2h)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Discrimination Index</th>
</tr>
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<tbody>
<tr>
<td>SAMPR1 Veh</td>
<td>0.40 ± 0.05</td>
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<tr>
<td>SAMP8 0.32mpk</td>
<td>0.45 ± 0.05</td>
</tr>
<tr>
<td>SAMP8 0.96mpk</td>
<td>0.50 ± 0.05</td>
</tr>
</tbody>
</table>

**NORT Long-term memory (24h)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Discrimination Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMPR1 Veh</td>
<td>0.42 ± 0.06</td>
</tr>
<tr>
<td>SAMP8 0.32mpk</td>
<td>0.47 ± 0.06</td>
</tr>
<tr>
<td>SAMP8 0.96mpk</td>
<td>0.52 ± 0.06</td>
</tr>
</tbody>
</table>

Significance levels:
- *p < 0.05
- **p < 0.01
- ***p < 0.001
PoC studies in SAMP8 mice: STUDY # 3

SAMP8 male animals (n=8 per group) treated with ORY-2001 (0.32 mg/kg; 0.96 mg/kg)

- Provides a protective effect in the medium- and long-memory of male mice, compared to age-matched SAMP8 mice.

- MAOB inhibition alone shows a trend on cognitive improvement on the SAMP8 animals however it is not significant; (p=0.12 at 2h and p=0.22 at 24 h.)

- LSD1 inhibition is therefore crucial to obtain the recovery on cognitive improvement on the SAMP8 animals.
ORY-2001 provides a high therapeutic window

PoC studies in SAMP8 mice: STUDY # 3

HEMOGRAM: No differences between animals treated with ORY2001 and control

- At 0.32 mpk and 0.96 mpk oral daily chronic doses on SAMP8 animals do not show any hematological effect.
- At 3.0-3.2 mpk, SAMP8 and other mice strains showed a mild reduction of Platelet level (NOAEL) suggesting that a dose close to 3mpk is the maximal one compatible with a chronic treatment.

That means that the therapeutic window is, at very least, 10 fold.
ORY-2001 clinical candidate has successfully finished PC regulatory toxicity studies and will be ready for clinical testing in humans by Q4/2015

- (*) Additional indications are being explored (HD, PD, RS & others) that can be clinically implemented by the end of either the SAD or the MAD phase

**Development Timeline for ORY-2001**

**IND – Phase I**

ORY-2001 clinical candidate has successfully finished PC regulatory toxicity studies and will be ready for clinical testing in humans by Q4/2015

**TIMELINE to end of Phase I: 16 months**
The split of commercial territorial rights with the partner in return to a significant contribution in the clinical development is considered the preferential collaboration scenario.
Thank you!

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