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COMPANY HIGHLIGHTS

✔ MADX: ORY  A **publicly traded** company on the Spanish Stock Exchange

✔ A **clinical stage** biopharmaceutical company developing innovative therapies in the field of Epigenetics

✔ A competitive **EPIGENETIC Platform** with a first program that validates the platform scientifically and clinically
  ✔ Two therapeutic programs in clinical development with multiple indication opportunities
  ✔ Additional assets in preclinical development to be progressed quickly

✔ Signed global **strategic partnership with ROCHE** valued up to $500M(*)

✔ IP portfolio with technology developed in-house (+20 patent families)

✔ Raised **€32M** (in 2015-2016). **Cash runway** expected till **mid 2018**

(*) Aggregate contingent milestone payments. See SLIDE 8
**MANAGEMENT TEAM**

**CARLOS BUESA**: CEO  
PhD in Biochemistry and Molecular Biology. Author of more than thirty papers and patents internationally. In 2000, he founded Oryzon Genomics, and since 2001 he has served as Chief Executive Officer and Chairman of the Board of Directors. He has taken several 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**:  
Founder and Chief Scientific Officer  
PhD in Biotechnology from the University of Ghent, Belgium. She has produced over twenty scientific papers and patents internationally and has developed innovative HTS methods for functional genomics. She is SAB member on several public institutions as CSIC and private companies. Since 2016 Scientific Advisor of the ADDF.

**NEUS VIRGILI**:  
Intellectual Property Director  
B.Sc. in Organic Chemistry from the University of Barcelona (1990).  
Qualified European Patent Attorney  
She has got over 20 years experience in pharmaceutical IP  
From 2011 IP Officer at Oryzon.

**ENRIC RELLO**:  
Chief Financial Officer  
B.Sc. in Business, University of Barcelona  
HBS Finance Excellence Program, Harvard Business School (Executive Education) USA.  
1993-1997 Biochemie SA (Novartis) Financial Controller / Controller Manager  
From May 2011 CFO at Oryzon.

**CESAR MOLINERO**:  
Medical and Clinical Operations Director  
PhD in Medicine from the University of Barcelona & AMP at ESADE Business School and Babson  
In 1992 he joined the Medical Department of KabiPharmacia  
In 1994, he joined the Department of Clinical Research at Laboratorios Esteve where, in 1998, he assumed responsibilities as Medical Adviser  
In 2002 he joined Madaus S.A. (Barcelona) as Medical and Regulatory Affairs Director, and later with responsibility as Group VP for Medical, R&D and Regulatory Affairs  
Joined Oryzon in January 2014.

**EMILI TORRELL**:  
Director of Business Development  
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.

- One of the most experienced and respected managerial teams in the Biopharmaceutical industry in Spain  
- 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
**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.
A LSD1 focused company
LSD1 is an enzyme that demethylates histones: specifically mono and dimethylated H3K4 and H3K9

<table>
<thead>
<tr>
<th>MOLECULE</th>
<th>TARGET</th>
<th>INDICATION</th>
<th>DISCOVERY</th>
<th>H2L</th>
<th>LEAD OPTIMIZATION</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE IIA</th>
<th>PHASE IIB</th>
<th>PHASE III</th>
<th>PARTNER</th>
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<td>ORY-1001 (*)</td>
<td>LSD1</td>
<td>Leukemia(***): Small Cell Lung Cancer</td>
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<td>Roche</td>
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<td>Alzheimer’s Disease Parkinson’s Disease Other Dementias</td>
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<td>LSD1-MAOB</td>
<td>Multiple Sclerosis Other CNS Autoimmune</td>
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<td>Huntington’s Disease Other Orphan Diseases</td>
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<td>ORY-3001</td>
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<td>Undisclosed Indication</td>
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<td>Other Assets</td>
<td>Other KDMs</td>
<td>Cancer Other indications</td>
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<td>Other Epigenetic Targets</td>
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</tbody>
</table>

(*) ORY-1001 is also known under Roche's ID codes R66016 and ROY051790
(***) Phase I / II A in Acute Leukemia has been done in the same trial
LSD1 is a target in some cancers

LSD1 is a key effector of the differentiation block in MLL leukemia

MLL Leukemic stem cells are addicted to LSD1 activity

ORY-1001 is a highly potent and selective LSD1 inhibitor with orphan drug status granted by the European Medicines Agency (EMA)

Finishing Data Analysis of Phase I/IIA study:

- Completed Part 1 of the study (Phase I) in acute leukemia
- Extension Arm (Phase IIA) completed

Potential for additional indications in solid tumors

A big market potential
License Agreement with Roche

- Effective from April 1st, 2014
- License of two patent families of the Oryzon IP Portfolio that Oryzon has created in its pioneering research in LSD1
- Scope of the collaboration: R&D and commercialization of Oryzon’s LSD1 inhibitor lead agent ORY-1001 (RG6016) and/or its backup compounds for oncology, haematology (e.g. AML) and non-malignant conditions
- The license also includes a 2-year collaborative R&D program, extended until March 2017, between Oryzon and Roche’s NY-based Translational Clinical Research Center (TCRC), to better understand the potential of LSD1 inhibitors in oncology and haematology
- Under the terms of the agreement, Oryzon has already received an upfront payment and near-term milestones and collaboration fees totaling $23 million, plus potential development, commercial and sales milestone payments across haematology, cancer and non-malignant indications that could exceed $500 million, together with tiered royalties on sales which range up to mid-double digits
  - $435 million in development milestones
    - $235 million for hematological and solid cancerous indications
    - $80 million for non-cancerous indications
    - $120 million for nervous system disorders
  - $90 million in sales milestones
- For complete details, please see the public-offer Prospectus of Oryzon (page 225-97) at the Spanish Stock-Exchange website.
Well tolerated and has been administered to 41 patients in total up to a maximum of three cycles. Excellent oral bioavailability in humans and excellent pharmacokinetic parameters

Pharmacodynamic biomarkers S100A12, VCAN, ITGAM, LY96, CD86, GPR65, CRISP9, ANXA2 and LYZ permit monitoring of response to ORY-1001 treatment in M4/M5 AML patients

Promising clinical responses were observed in the Phase IIA arm (14 patients, 4M6, 6MLL gene fusion and 4 MLL other mutations) mandating further clinical research and investigation

Taking the four M6 patients together, there was no significant rise in blast cell count after two cycles of therapy – suggesting disease stabilization

4/6 patients with MLL leukemia showed evidence of morphological blast cell differentiation

2 of these exhibited a differentiation syndrome

100% (5/5) of patients with MLL gene fusion with evaluable PD samples showed evidence of blast differentiation by qRT-PCR analysis in PD analyses

23% of Bone Marrow responses (3/13)
ORY-1001 (RG6016): Next Steps

☑️ ORY-1001 has demonstrated Biological Proof of Mechanism as a highly active LSD1 inhibitor with strong differentiation-inducing activity in patients with MLL leukemia. It has shown an excellent safety profile in acute leukemia patients, and also displayed excellent oral bioavailability and pharmacokinetic parameters.

☑️ ORY-1001 might be a potential combinatorial therapeutic option in the treatment of several types of acute myeloid leukemia. Pharmacodynamic biomarkers identified for M4-M5 leukemias.

☑️ As a potent and safe LSD1 inhibitor, ORY-1001 is also of potential interest in the treatment of solid tumors such as small cell lung cancer, and possibly others in the future.

☑️ In Small Cell Lung Cancer (SCLC; Milleti et al., 2016, AACR: “Neuroendocrine gene transcript expression is associated with sensitivity to lysine-specific demethylase-1 inhibitor RO7051790 in small cell lung cancer-derived cell lines”). High levels of neuroendocrine markers ASCL1, DDC, and GRP; a gene signature based on these markers predicts response to RO7051790 in SCLC cell lines (p-value 0.0055). ~50% of SCLC patients express high levels of ASCL1, DDC, and GRP, suggesting that this subpopulation may benefit from an RO7051790 based therapy.

Roche now has sole responsibility of developing ORY-1001 (Roche’s ID codes RO7051790 and RG6016) and has recently initiated its first clinical trial with ORY-1001 in extensive-stage disease SCLC (ED SCLC). The trial is an open-label, multi-centre (4 countries) study with an estimated 70 ED SCLC patients to be treated with ORY-1001. Safety/tolerability is the primary endpoint, while secondary endpoints will include preliminary efficacy (overall survival, progression-free survival, objective response) and PK/PD data. The estimated completion date is expected in 2H 2019.

ROCHE has already started a Phase I with ORY-1001 (RG6016) in Small Cell Lung Cancer (data expected in 2H 2019).
Identical twins (monozygotic)
- Same DNA with GBA risk mutation
- Disconcordant for symptoms of Parkinson’s
- Up to 20 years difference in onset
- Patient derived iPSCs: difference in MAO-B levels

Luca Lovrečić, et al., 2013 The Role of Epigenetics in Neurodegenerative Diseases
LSD1 in the CNS

✔ **LSD1 is a key component of different CNS transcriptional complexes** interacting with different transcription factors and very often with HDAC1 and HDAC2

✔ In the brain one of these TFs is REST. The LSD1-REST-CoREST-HDAC1/2 repressor complex is involved mainly in controlling developmental programs and modulating neuronal morphology in the CNS. Different to what happens in HDACs, it has been proven that it is possible to develop extremely selective LSD1 inhibitors with excellent pharmacological properties

✔ LSD1 is known to be an important regulator in the maintenance of pluripotency and in specification of neuronal commitment of pluri- or multipotent cells

✔ In C. elegans, Drosophila and mammalian cells LSD1 suppression has been reported to significantly enhance the removal of misfolded proteins with a critical role on neurodegeneration like SOD1, TDP-43, FUS, and polyglutamine-containing proteins, indicating a general improvement in protein quality control
ORY-2001 – A COMPOUND FOR CNS expected to be ready for Phase II in 2H2017

✔️ Pharmacological Properties
  ✔️ A selective dual LSD1-MAO-B inhibitor
  ✔️ Optimal ADMET and PK profiles
  ✔️ Crosses efficiently the BBB
  ✔️ Once daily oral bioavailable
  ✔️ Selectivity against MAO-A demonstrated in-vitro and in-vivo
  ✔️ High therapeutic window in animals: a safe drug for chronic settings
  ✔️ Target engagement demonstrated in vivo

✔️ Biomarkers identified

✔️ Exclusively owned by Oryzon

✔️ Preclinical Proof of Concept Achieved in different animal models of:
  ✔️ Alzheimer’s Disease
  ✔️ Huntington’s Disease
  ✔️ Multiple Sclerosis
  ✔️ 2 Additional CNS disorders

✔️ Additional indications being explored preclinically

✔️ Clinical development → In Phase I:
  LVO expected in early 2017
  ✔️ Alzheimer’s Disease is lead indication → Phase IIB Planned
  ✔️ Additional indications: MS and HD → Phase IIA Planned
The senescence accelerated mouse (SAMP8) as a model for oxidative stress and Alzheimer's disease

John E. Morley, Harvey James Ambrichter, Susan A. Farr, Vijaya B. Kumar

ARTICLE INFO

The senescence accelerated mouse (SAMP8) is a spontaneous animal model of senescence associated protein expression (SAGE) in oxidative stress. It develops early memory and memory-related changes in the brain, including cellular and molecular changes in the brain that are linked to oxidative stress. The senescence accelerated mouse is a model for studying the relationship between oxidative stress and Alzheimer's disease. This article provides a detailed review of the model and the mechanisms underlying age-related neurodegeneration in Alzheimer's disease.

Table 1
Comparison of Alzheimer's disease, SAMP8 mouse and transgenic models.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Alzheimer's disease</th>
<th>SAMP8</th>
<th>Transgenic models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overproduction of amyloid-β</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Amyloid plaques</td>
<td>Yes</td>
<td>Late*</td>
<td>Yes</td>
</tr>
<tr>
<td>Phosphorylated tau</td>
<td>Increased</td>
<td>Increased</td>
<td>In some models</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuron loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Synaptic dysfunction</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dendritic spine loss</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Glossis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cholinergic deficit</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Learning and memory impaired</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiac rhythm disturbances</td>
<td>Yes</td>
<td>Yes</td>
<td>4 months</td>
</tr>
<tr>
<td>Oxidative damage</td>
<td>Yes</td>
<td>Yes</td>
<td>8 months</td>
</tr>
</tbody>
</table>

* = uncertain.

* Occur at 16 to 18 months.
ORY-2001: A possible disease modifier drug

- 2 or 4 months of oral treatment with ORY-2001 produce a marked cognitive improvement in SAMP8 animals measured by NORT memory tests
- 9 studies in the last 5 years +150 animals tested
- Other +readouts in animal models of MS, HD, PD and other human CNS disorders

ORY-2001 restores the discrimination index in SAMP8 mice

Meta-analysis of cognitive deficit of untreated SAMP8 mice (historical data)
Is ORY-2001 a disease modifying drug?

Cross over Experiment

- The drug restored memory function after the deficit had developed
- The delayed start cohort (0+1) experienced the full benefit
- The early start (1+0) cohort continued to show significant benefit 1 month after treatment interruption

→ Disease modifying potential
PoC studies in SAMP8 mice

- The effect is driven by LSD1 but there is an additive / synergistic effect provided by the MAOB component.

- ORY-2001 provides a 
  **dose dependent**  protective effect in the medium-term memory of mice, compared to age-matched SAMP8 mice.
LSD1 function in the brain: LSD1-8a KO mice

LSD1-8a KO mice (Zibetti et al, Wang et al)
- Neuronal differentiation ↓, Neurite extension ↓
- Long Term Memory ↓
- Induction of Egr ↓, Fos ↓, Npas4 ↓, Arc ↓


Shelly Berger: ACSS2 deficit leads to memory defect and defect in up-regulation of similar gene set

LSD1 function in the brain: LSD1-8a KO mice

LSD1-8a KO mice (Zibetti et al, Wang et al)
- Neuronal differentiation ↓, Neurite extension ↓
- Long Term Memory ↓
- Induction of Egr ↓, Fos ↓, Npas4 ↓, Arc ↓

**Hippocampal gene expression changes induced by ORY-2001**

- ORY-2001 potently down-regulated the expression of a subset of genes related to immune reaction and inflammation, including S100A9 and T-cell receptor b chains in SAMP8 mice.

- ORY-2001 up-regulated genes associated with improved cognitive function, neuroplasticity and memory, including: Egr, Fos, Nr4a1, Npas4, Arc... i.e. the pharmacological intervention mimicks the stimulation of LSD1-8a, supports the observation of improved memory.
S100A9 and Alzheimer’s disease

- S100A9 downregulation improves memory in different AD Tg mice models
- S100A9 has been involved in the A-Beta deposition dynamics

CT-Tg mice
Mutant APP(V717I)
CT100 (London mutation)

Tg2576 mice
mutant APP (isoform 695);
Swedish mutation (KM670/671NL)

Tg2576 mice
mutant APP (isoform 695);
Swedish mutation (KM670/671NL)

sh S100a9 RNA
lentiviral brain injection

S100a9 knockedown attenuates learning and memory impairment in Tg2576 mice / reduces amyloid plaques in Tg2576 brains

S100a9 markedly increased in cortex and hippocampus, memory impairment

S100a9 upregulated in hippocampus, memory impairment

S100a9 upregulated in hippocampus, memory impairment, amyloid pathology

S100a9 -/- knock-out mice

Tg2576 S100a9 -/- mice have improved memory, reduces amyloid pathology

APP/PS1 mice
mutant APPswe
PSEN1dE9

APP/PS1 mice
mutant APPswe
PSEN1dE9

S100a9 -/- knock-out mice

APP/PS1 S100a9 -/- mice have increased phagocytosis of fibrillar amyloid β (Aβ) in microglia cells, improved memory

S100a9 markedly increased in cortex and hippocampus, memory impairment

S100a9 upregulated in hippocampus, memory impairment

S100a9 upregulated in hippocampus, memory impairment, amyloid pathology

(Kummer et al., 2012)

(Kummer et al., 2012)

(Kim et al., 2014)
ORY-2001 also a possible approach to treat Multiple Sclerosis?

- ORY-2001 downregulates S100A9 in the Hc of SAMP8 animals
- Complexes of S100A8 and S100A9 (S100A8/A9) are expressed and released at inflammatory sites
- A correlation between serum levels of S100A8/A9 and disease activity has been observed in many inflammatory disorders
- Quinoline-3-carboxamides (Q compounds) that target S100A9 have been explored as treatments for autoimmune/inflammatory diseases in humans. And one of these, Laquinimod is being currently explored for Multiple Sclerosis treatment
- There are additional models/diseases in which S100A9 has been found to be both overexpressed and deleterious. One of these models is EAE, a Multiple Sclerosis model
**ORY-2001 in Experimental Autoimmune Encephalomyelitis (EAE)**

- Model for multiple sclerosis
  - C57BL/6 mice immunized s.c. with 100 μg of MOG35–55 emulsified in CFA containing 4 mg/ml M. tuberculosis H37 RA and i.p. injections of 200 ng of pertussis toxin on days 0 and 2

- Treatment after onset of EAE symptoms (d11) during 2 weeks with

- ORY-2001 clearly reduced the Mean Clinical Score, ORY-LSD1 was less effective, Rasagiline appeared to marginally delay onset but effects were not significant.

- Increased cellularity in lymph nodes, spleen may indicate reduced egress of lymphocytes

- Lower doses of ORY-2001 were also effective (not shown), MoA to be presented at ACTRIMS, Orlando

  → Cytokine profiling, gene expression in brain/spinal cord, immune cell proliferation
LSD1 plays a role in expression of neuronal genes thru demethylation of H3K4 and H3K9
A Phase I study with 88 healthy volunteers, young and elderly

- **Single Ascending Dose (SAD):** all cohorts were safe. **No hematological effects** nor any other relevant/significant side effects observed in any cohort.

- **Additional arm** to determine CSF ORY-2001 levels after a single dose.

- **Multiple Ascending Dose (MAD):** five dose levels tested so far in young volunteers, **no hematological effects** nor any other relevant/significant side effects observed.
ORY-2001 DEVELOPMENT TIMELINE

- ORY-2001 expected to be ready for Phase II in 2H-2017
- The Phase I in healthy volunteers enables us to go for Phase IIIs in different indications
- The company envisages to perform three different Phase IIIs in AD, MS and HD

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<th>2015</th>
<th>2016</th>
<th>2017</th>
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<tr>
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<tr>
<td>1H2017</td>
<td>2H2017</td>
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PLANNED ORY-2001 CDP

- Phase II-B in AD
- Phase II-A in MS
- Phase II-A in HD

A multibillion market potential (*)

ORYZON, A UNIQUE OPPORTUNITY

Corporate Strategy: Epigenetics Momentum, IP & First in Class Clinical Assets

✓ Epigenetics is an emerging field with high interest from Pharma (select acquisitions: Roche/Tensha; Celgene/Acetylon; Merck/OncoEthix) and from Specialized Investors (Imago, Constellation)
✓ High quality science and a broad patent portfolio on LSD1, one of the hottest targets in this area (GSK, Celgene, Incyte, Takeda). Competitive Patent portfolio with +20 patent families, many already granted in USA
✓ ORYZON is a pioneer in epigenetics

Platform + Broad Product Pipeline: Aim for three different assets in Clinic (5-6 trials) by 2017

✓ We developed the first ever LSD1 inhibitor reaching clinical trials in the world. We have reported the first human data in oncology with ORY-1001 (RG-6016)
✓ A dual LSD1-MAOB inhibitor finishing Phase I and with PoC in several human disease animal models
✓ Three Phase IIA-IIB clinical trials expected to start in 2H 2017
✓ A third LSD1 inhibitor being developed for an orphan disease and Phase I expected in 2017
✓ Other epigenetic programs in development

Financials and Governance: Strong balance sheet

✓ A dynamic and capital efficient company with excellent know-how (40 people)
✓ €29M in cash at the end of 3Q-2016: Cash runway expected until mid 2018, but wanting to invest more to capture the upside of our Phase IIB in ORY-2001 and other clinical programs
✓ An experienced public company board with experienced executives with proven track record in the industry
✓ Top governance according to public company standards
## Financial Overview – September 30th 2016

<table>
<thead>
<tr>
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<td>Short-term financial assets</td>
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<td>5,104,884</td>
</tr>
</tbody>
</table>

New Financial bank loans in 2016
15,750 Mio €
2,68% Average Interest Rate
On January 2nd 2017, Oryzon Genomics had 1,301 shareholders.

- The 54.55% of the shares are owned by the reference shareholders.

All the Company shares are common shares, without any additional options or warrants.
**ANTICIPATED ORYZON CATALYSTS**

**2014**
- Transformational deal with Roche ($21M) on ORY-1001

**2015-16**
- CONSOLIDATION PERIOD
  - Public in Europe ($36M raised June-2015-June 2016 )
  - ORY-1001: Clinical Data Presented at ASH-2016
  - Second Asset (ORY-2001 in clinic development)

**2017**
- ORY-1001: LEAD CANCER ASSET
  - FPI in Phase I SCLC by Roche 1Q
    - Phase I-IIA study expected to formally close 2Q
- ORY-2001: LEAD CNS ASSET
  - Anticipated Top Line Phase I (ADPD-2017 Conference) 1Q
  - Anticipated demonstration of human target engagement 2Q
  - Anticipated Phase I Completion 2Q
  - Anticipated filing CTA / IND for Phase II-A in MS 2H
  - Anticipated filing CTA / IND for Phase II-A in AD 2H
  - Anticipated filing CTA / IND for Phase II-A in HD 2H
  - Anticipated FPI in a Phase II-A study in MS 2H
- ORY-3001:
  - Anticipated filing CTA / IND for Phase I study on an orphan indication yet to be disclosed 2H

**2018**
- ORY-2001: LEAD CNS ASSET
  - Anticipated FPI in a Phase II-A study in AD 1Q
  - Anticipated FPI in a Phase II-A study in HD 1Q
THANK YOU VERY MUCH!

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