



**ORYZON**

Pioneering Personalized Medicine in  
**EPIGENETICS**

**CORPORATE PRESENTATION  
2Q-2020**

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## Company Highlights

- ✓ A **clinical stage** biopharmaceutical company developing innovative therapies in the field of **Epigenetics**
- ✓ **Two molecules** already with **positive data in humans**
- ✓ 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**

- ✓ **Raised an aggregate of circa €85M** (in 2015-2019)
- ✓ **Cash runway** expected till **1Q2022**
- ✓ One of the most **LIQUID** companies in the MicroCap group in the Spanish Stock Market
  - ✓ 45.7 M Shares outstanding. Fully diluted
  - ✓ +310,000 daily volume (Avg Traded Volume in 2019)
  - ✓ +78M shares negotiated in 2019 / ≈6 months for share full turnover



BOLSA DE MADRID



ORYZON GENOMICS SA  
BALANCE SHEET DATA (UNAUDITED)  
(Amounts in thousands US \$)

	March 31st, 2020	March 31st, 2019
Cash and cash equivalents	32,121	32,551
Marketable securities	155	159
Total Assets	84,301	73,158
Deferred revenue	0	0
Total Stockholders' equity	65,709	49,240

<sup>1</sup> Spanish GAAPs

# Epigenetic Modifications: New Targets for Drug Development

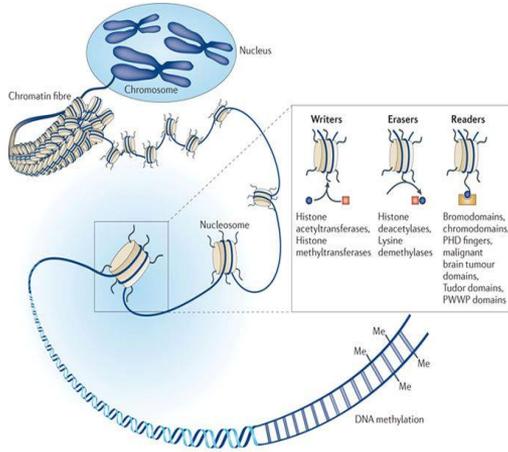


Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* volume 11 (2012)

- ❖ Heritable DNA modifications that do not alter the actual DNA sequence but change gene activity and expression
  - ❖ Histone modifications
  - ❖ DNA methylation
  - ❖ microRNAs...
- ❖ Histone modifying enzymes are “writers” or “erasers” - adding or removing epigenetic marks from histone tails
- ❖ Epigenetic dysfunctions are associated with aberrant gene expression and disease
- ❖ Epigenetic drugs can restore these transcriptional imbalances

An area of hot world class science



Lysine specific histone demethylase 1 (LSD1): an epigenetic “eraser” that removes methyl groups from histones



✓  
LSD1 expression and activity can both block and promote gene expression

✓  
LSD1 plays a important role in cancer, CNS, inflammatory and viral diseases



# Oryzon is pioneering epigenetics in CNS and active in oncology

A broad pipeline to address unmet medical needs with an attractive market opportunity

INDICATION	STUDY*	RESEARCH	PRECLINICAL	PHASE I	PHASE IIA	PHASE IIB	PHASE III
<b>VAFIDEMSTAT (ORY-2001) - CNS optimized LSD1 inhibitor (‡)</b>							
Aggression in BPD	REIMAGINE / PORTICO (†)	[Progress bar]					
Aggression in ADHD	REIMAGINE / ENTRANCE (†)	[Progress bar]					
Aggression in ASD	REIMAGINE / COLONNADE (†)	[Progress bar]					
Aggression in AD	REIMAGINE-AD / GATEWAY (†)	[Progress bar]					
Alzheimer's disease (Mild Moderate)	ETHERAL monotherapy	[Progress bar]					
Multiple Sclerosis (RR & SP)	SATEEN monotherapy	[Progress bar]					
<b>IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor</b>							
AML (Elderly Unfit)	ALICE Combo w Aza	[Progress bar]					
SCLC (First Line Relapsed)	CLEPSIDRA Combo w Platinum/Etoposide	[Progress bar]					
<b>ORY-3001 - selective LSD1 inhibitor</b>							
Non Oncological	Preclinical finished	[Progress bar]					
<b>OTHER PROGRAMS</b>							
HDAC6/Other undisclosed		[Progress bar]					
( ‡) A new Phase II in COVID-19 has been initiated recently. Trial name: ESCAPE		* IN BLUE, NEW PHASE IIB STUDIES UNDER PREPARATION OR EVALUATION					

## CNS Market Need

Aggression is a common feature in many psychiatric diseases. +50% in ADHD(\*\*)

Global BPD market expected to grow to \$2.6B in 2027

45 million people with AD worldwide; 20% shows aggressiveness

Options to accelerated approval in genetic subpopulations of schizophrenia and ASD

## Oncology Market Need

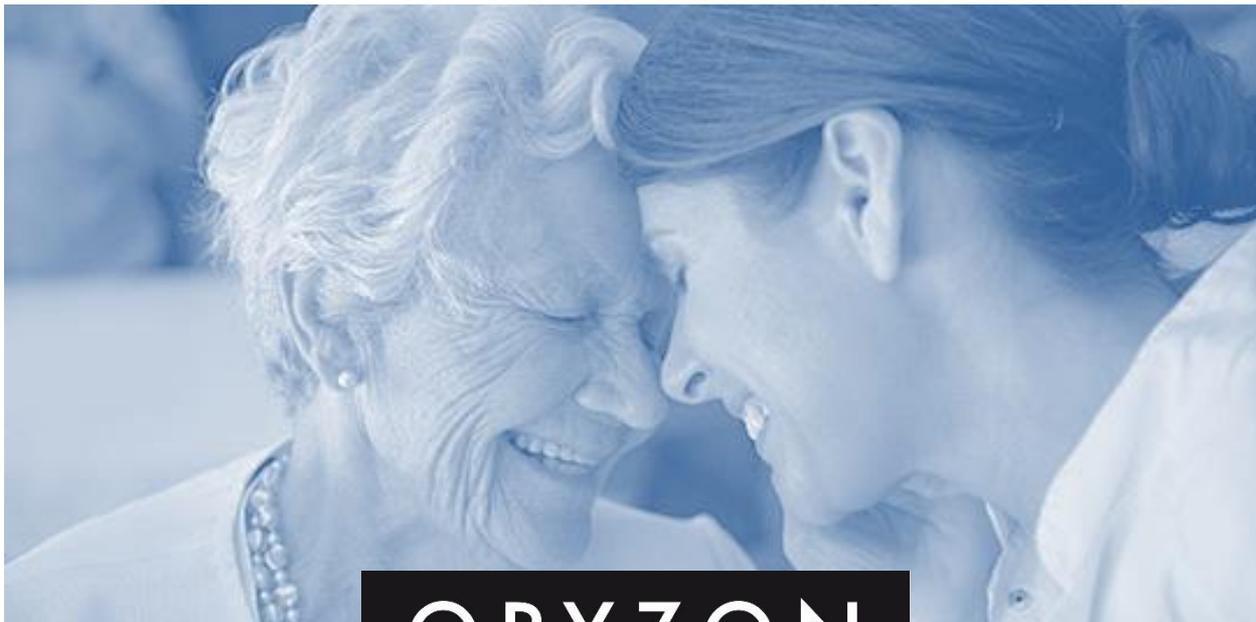
Global AML market of \$990m in 2019. Room for new Combos according to KoLs

SCLC is a serious unmet medical need, with a MOS of 8–12 months and 5% 2-year OSR

Global SCLC market +300,000 patients/y. FDA approved label extension of Pembro but only 19% of ORR (\*\*\*)

Options to accelerated approval in subpopulations of AML-MDS

(\*\*) J Child Adolesc Psychopharmacol. 2016 Feb 1; 26(1): 19–25.  
 (\*\*\*) Keynote study in 83 patients



**ORYZON**

**VAFIDEMSTAT a Phase II Clinical Stage Compound  
with a broad developability in CNS diseases**

## Vafidemstat (ORY-2001): a “Neuron-fixer” ready for Phase IIb

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- ✓ Vafidemstat is a **small molecule** LSD1 inhibitor optimized for CNS
- ✓ **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 about 250 participants** so far
- ✓ **BBB penetrance** and (indirect) human brain target engagement established
- ✓ Pharmacologically active in humans

# Vafidemstat, and LSD1 inhibition, improves cognition

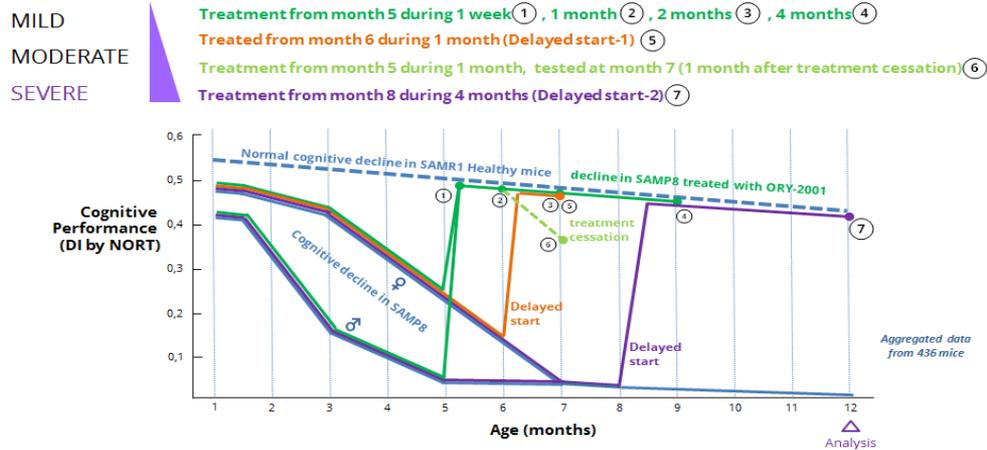
In Alzheimer's SAMP8 model vafidemstat restores memory by the NORT model

In Huntington disease R6/1 model vafidemstat improves memory by the NORT model

In Schizophrenia SETD1a +/- model iadademstat (ORY-1001) improves working memory

In Psychosis & Schizophrenia NMDA receptor-hypofunction mice model T-448 (TAKEDA) LSD1 inhibitor improves memory

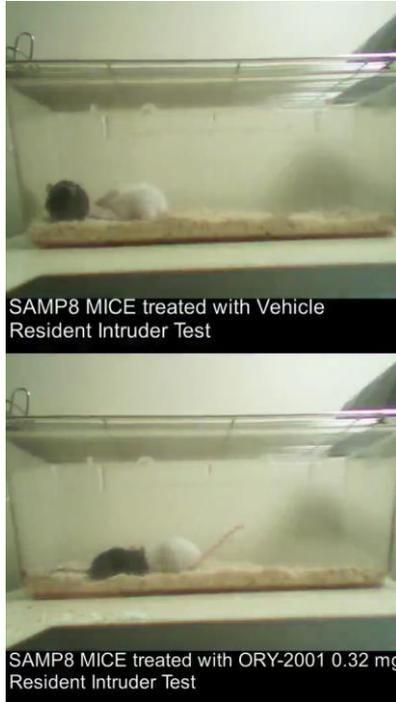
## Vafidemstat Fully Restores Memory Measured by NORT in SAMP8 AD Model



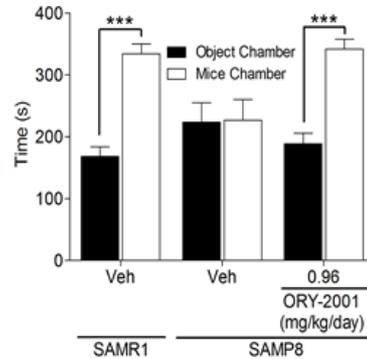
Cognition and memory impairments are found in AD and dementias but also in Autism, Schizophrenia, Depression, Bipolar disorder and other psychiatric conditions

# Vafidemstat Produces Significant Behavioural Changes

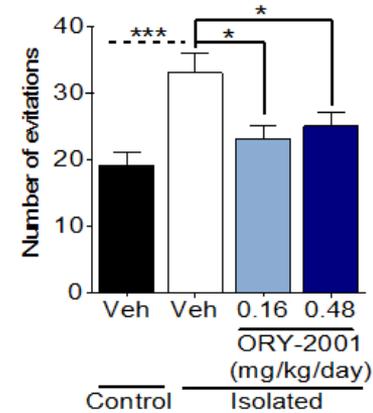
Vafidemstat Reduces Aggression in the Resident Intruder Test in the SAMP8 AD Mice model



Vafidemstat Enhances Sociability in the Three-Chamber Test in SAMP8 AD Mice



Vafidemstat Reduces Social Withdrawal in the Rat Isolation Model

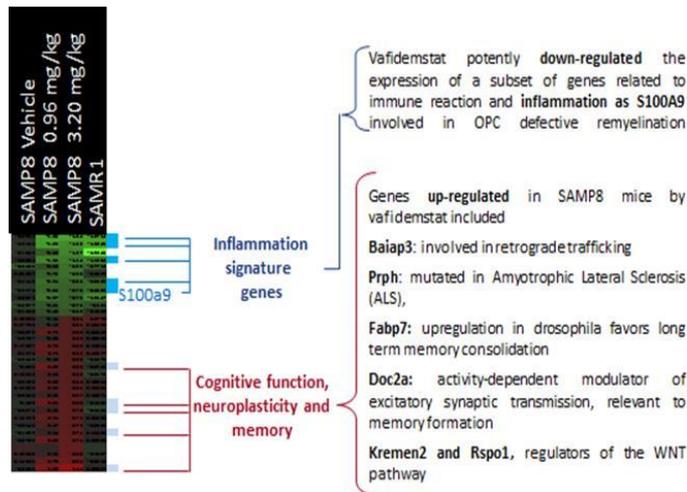


# MoA: an upstream epigenetic mechanism producing a dual activity, antiinflammatory and prosynaptic

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 **up-regulates** genes associated with **Neuroplasticity & Cognition**
- Vafidemstat **reduces** the expression of **inflammatory** genes as S100A9 and others in SAMP8 AD model and IL-6, IL-1B and many others in MS models



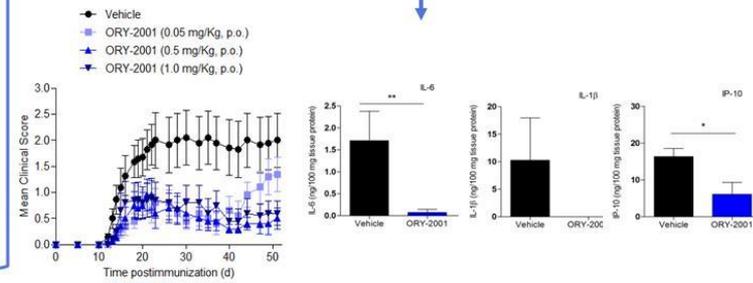
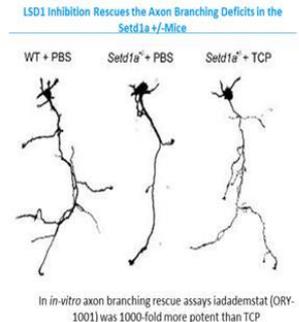
Vafidemstat potently down-regulated the expression of a subset of genes related to immune reaction and inflammation as S100A9 involved in OPC defective remyelination

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

Prosynaptic

Anti-inflammatory



# LSD1 inhibition rescues different phenotypes in genetic models of ASD and Schizophrenia

nature  
neuroscience

Article | Published: 12 March 2018

## Social deficits in *Shank3*-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition

Luye Qin, Kaijie Ma, Zi-Jun Wang, Zihua Hu, Emmanuel Matas, Jing Wei & Zhen Yan

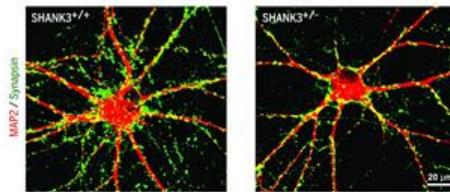
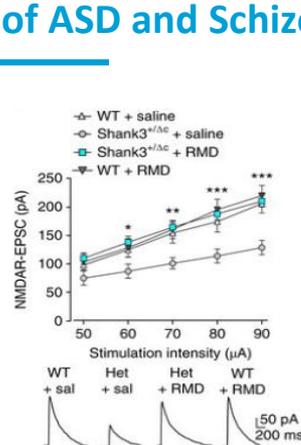


Image from Yi et al Science 06 May 2016

Mutation of *SHANK3* gene is causally linked to ASD. HDAC & LSD1 inhib rescue the mice phenotype Qin et al Nat Neurosci. 2018. & Zhen Yan Oral Comm SF-2019

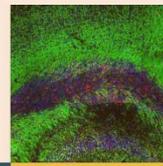


LSD1 inhibition also rescues the *Shank3* ASD phenotype

Zhen Yan Oral Comm SFN-2019



NEUROSCIENCE  
2019  
October 19-23  
Chicago, IL



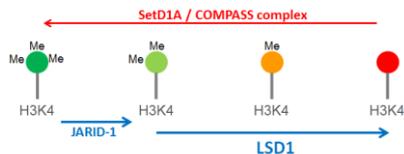
## Neuron

ARTICLE | ONLINE NOW

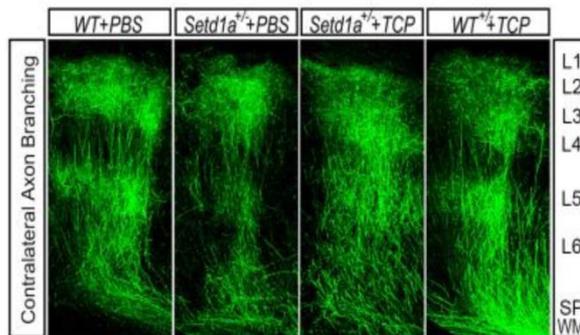
## Recapitulation and Reversal of Schizophrenia-Related Phenotypes in *Setd1a*-Deficient Mice

Jun Mukai<sup>7, 8</sup>, Enriko Cannavò<sup>7</sup>, Gregg W. Crabtree<sup>9</sup>, ... Atsushi Takata<sup>9</sup>, Bin Xu<sup>9</sup>, Joseph A. Gogos<sup>9</sup>

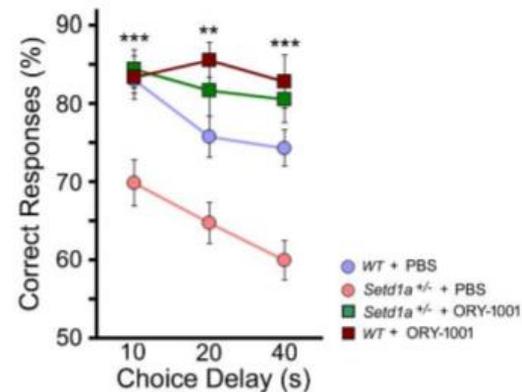
Published: October 09, 2019 • DOI: <https://doi.org/10.1016/j.neuron.2019.09.014>



## LSD1 inhibition rescues the contralateral axon branching deficits in-vivo in the *Setd1a*<sup>+/-</sup> mice

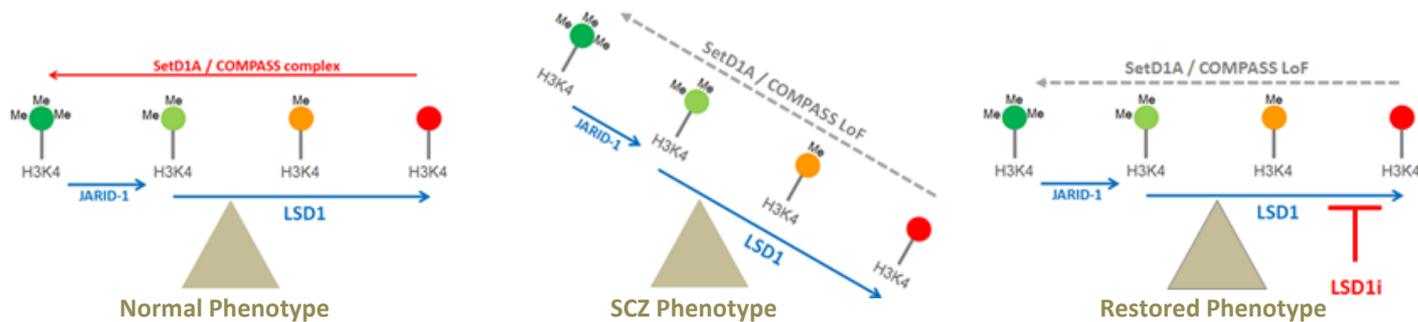


## Rescue of WM performance in *Setd1a*<sup>+/-</sup> mice treated with ORY-1001



## LSD1 inhibition paves the way for personalized medicine in psychiatry

- ❖ SETD1A is a key schizophrenia (SCZ) susceptibility gene. Mutations in SETD1A increase the risk of SCZ by 35 times, as well as a number of other neurological disorders. SETD1A is part of the Set1/COMPASS complex, mediates mono-, di-, and tri-methylation of the lysine 4 on the histone H3 protein
- ❖ In addition to SETD1A, mutations in other subunits of Set1/COMPASS complex have been reported in SCZ and other neuro-developmental disorders
- ❖ Mutant mice carrying a heterozygous loss-of-function mutation of the orthologous gene exhibit alterations in axonal branching and cortical synaptic dynamics, accompanied by specific deficits in working memory that recapitulate SCZ-related alterations
- ❖ SCZ patients carrying these mutations identified.
- ❖ Increased interest by FDA and other regulators to explore a personalized medicine approach in these hard to treat populations



## Vafidemstat : Safety demonstrated in 250 volunteers and patients

### Safe and well tolerated in a +100 healthy volunteers (young and elderly) Phase I (MAD+SAD) study

- ❖ No hematological impact at planned doses
- ❖ Efficiently crossed the BBB (70-90%)
- ❖ Oral PK - Half Life of 22h allowing once daily oral
- ❖ PK/PD data allowed definition of recommended Phase II doses

### Safe and well tolerated so far in diverse Phase II studies

- ❖ Vafidemstat has been already administered to around 250 volunteers and patients
- ❖ Phase IIs (MS, AD, ADHD, BPD and ASD patients) with no safety signals to date
- ❖ Longest exposure to date: 18 months



# Vafidemstat: REIMAGINE - a Basket trial in aggression

**Duration** 8 Weeks treatment + 4 weeks of follow up

## Cohorts to be recruited

Borderline Personality Disorder	6 patients	Done – Data reported in April 2019	Upscaled later to an aggregated of 30 patients; <b>Trial Status Completed</b> (LPO 22.10.2019)
Attention Deficit and Hyperactivity Disorder	6 patients	Done – Data reported in April 2019	
Autism Spectrum Disorder	6 patients	Done – Data reported in Sept 2019	

## Endpoints

Safety

Efficacy:

Aggression / Agitation measured by CGI-S

Aggression / Agitation measured by CGI-I

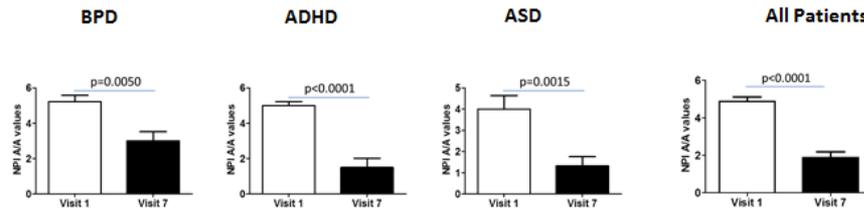
Aggression / Agitation measured by NPI A/A 4 items

Psychiatric status measured by NPI Global assessment (12 items)

Change in specific disease scales

Significant improvements in aggression evaluated using the Neuropsychiatric Inventory 4-item agitation/aggression score (NPI-A/A)

### NPI-A/A Agitation/Aggression (4 items)



**Reduced Aggressivity in patients of the three psychiatric indications: Borderline Personality Disorder (BPD), Attention Deficit and Hyperactivity Disorder (ADHD) and Autistic Spectrum Disorder (ASD) treated with vafidemstat**

REIMAGINE data  
presented at

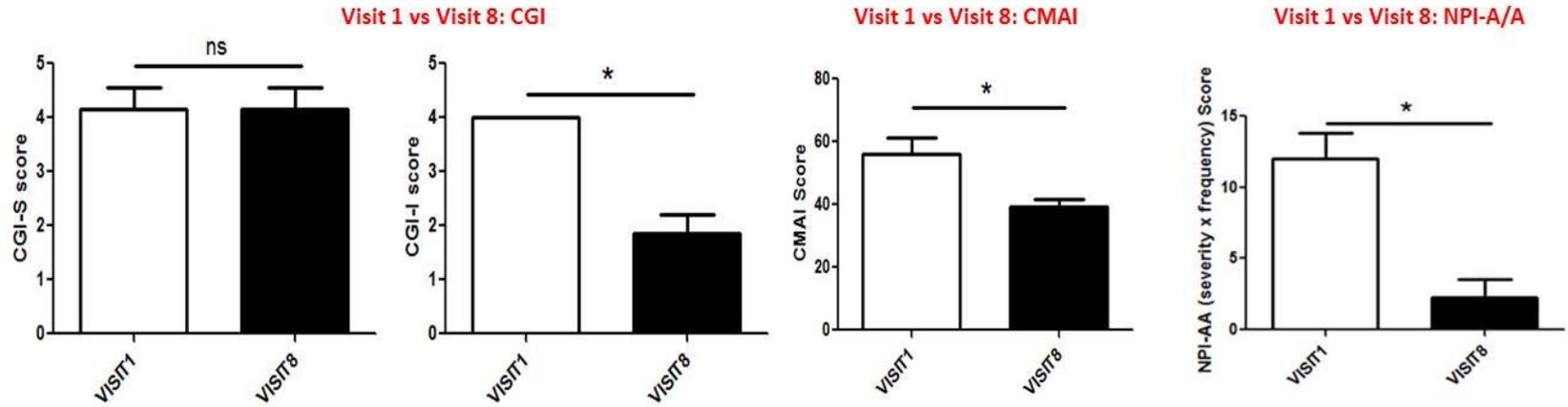


# REIMAGINE-AD: Reduction of agitation/aggression in severe and moderate AD patients after 6 months

REIMAGINE-AD: A Phase IIa trial in Moderate and Severe AD

<b>Duration</b>	<b>24 weeks treatment + 4 weeks of follow up</b>	
Open Label / Single arm (1.2mg)	12 patients	Recruitment Completed

- Statistical improvements in different Agitation/Aggression scales after 6 months of treatment: CGI-I, CMAI and NPI-A/A
- Reduction on Agitation / aggression takes longer in severe and moderate AD patients than in younger REIMAGINE patients
- Also improvements in Caregiver burden and Global NPI



Data Presented at  
APRIL 2020

**AD/PD 2020**  
The 15<sup>th</sup> International Conference on  
Alzheimer's & Parkinson's Diseases

## Next steps: The company recognizes a significant development potential for vafidemstat in psychiatric indications

### PORTICO, a Phase IIb trial with vafidemstat in all-in BPD to treat agitation-aggression

#### ❖ **PORTICO: a Phase IIb in BPD Under Preparation**

- double blind, randomized, placebo-controlled, 16-week treatment period
- Spain, US and Europe TBD
- N=100
- **Expected FPI: tbd (examining Covid-19 impact)**
- Expected LPO: tbd

❖ After positive data in REIMAGINE-AD, a Phase IIb in agitated-aggressive AD patients (GATEWAY) will be designed and prepared

❖ A personalized medicine Phase II trial in SetD1a mutant schizophrenic patients under study in collaboration with a Top US Institution

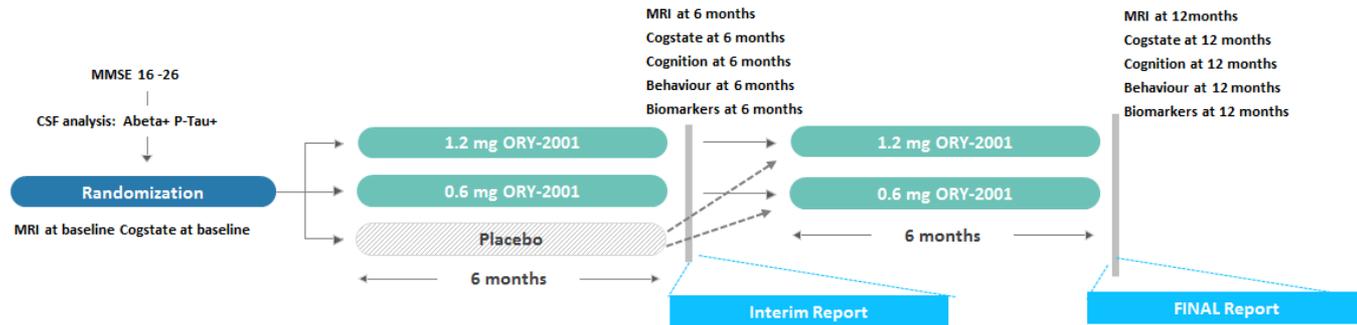
❖ A personalized medicine Phase II trial in Shank3 mutant Phelan McDermid (ASD) patients under study in collaboration with one of the most important Hospitals in Spain

OPTIONS TO ACCELERATED APPROVAL IN  
GENETICALLY DEFINED SUBPOPULATIONS  
OF SCZ AND ASD

# An ambitious Phase II trial, ETHERAL: Epigenetic THERapy in Alzheimer's Disease

Besides aggression, vafidemstat may provide also further benefits to AD patients

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 different CSF Biomarkers: Anti-inflammatory, synaptic integrity and neurodegeneration markers)



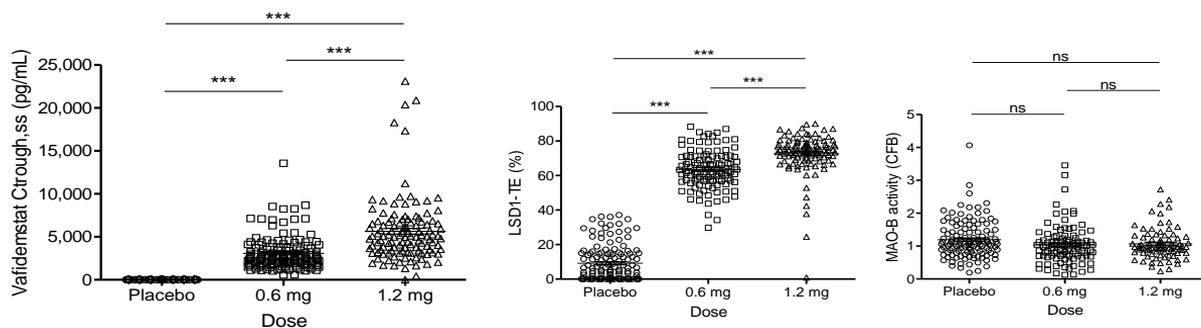
- ✓ 17 sites; 117 patients
- ✓ Spain, France & UK
- ✓ Recruitment finalized



- ✓ Twin study in US: around 25-28 patients
- ✓ FPI recruited in May
- ✓ Recruitment ongoing

## ETHERAL-EU 6m data: Safety and PK/PD Results

- Vafidemstat treatment appears to be **safe and well tolerated**
  - ▶ Similar drop-outs in all arms
  - ▶ 23 SAEs observed were randomly distributed through study arms. Most of them (78%) not related to the drug treatment
  - ▶ Platelet, neutrophils and other hematological parameters do not show clinically relevant variations due to vafidemstat treatment
  - ▶ No abnormal and clinically significant liver enzymes levels or other laboratory findings reported to date
- Pharmacokinetic results correlate with previous observations (Phase I data)
- No MAO-B inhibition detected in the PBMCs of AD patients, as expected from Phase I data
- Vafidemstat acts as a selective LSD1 inhibitor in humans at the therapeutic doses tested



One-tail Student t test (\*\*\*,  $p < 0.001$ ; ns, not significant)  
LSD1-TE: LSD1 Target Engagement

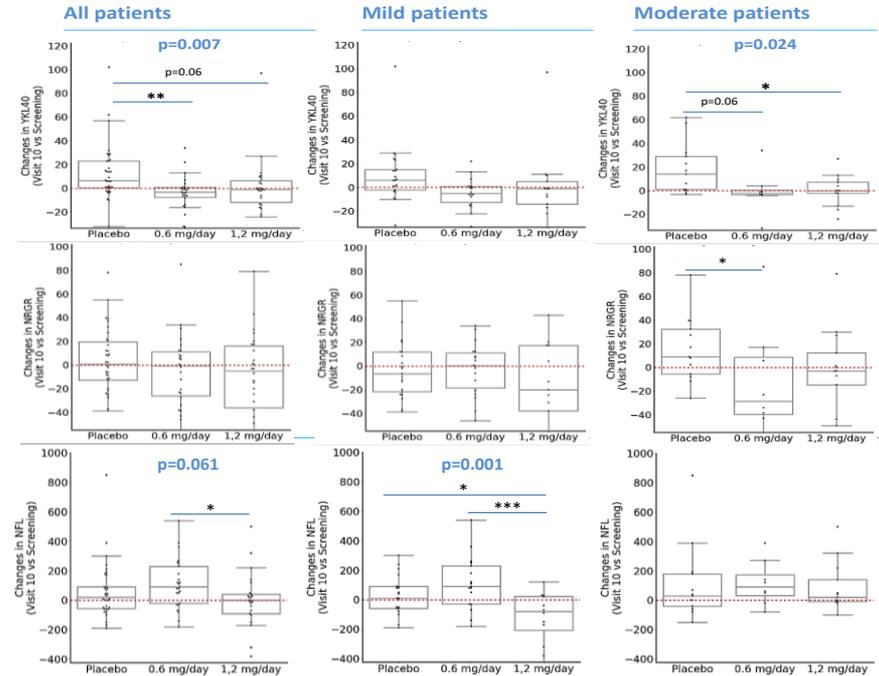
Data Presented at  
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The 15<sup>th</sup> International Conference on  
Alzheimer's & Parkinson's Diseases

# ETHERAL-EU 6m data: CSF Biomarkers – YKL40, neurogranin and NFL

## Vafidemstat treatment reduces the levels of the inflammatory CSF biomarker YKL40

- After 6 month of treatment, a treatment effect on the CSF levels of the inflammatory **YKL40 biomarker** was observed, which appears mainly driven by the effect in moderate patients
- Although no statistically differences were observed between groups, a trend to reduce CSF neurogranin (NRGR) levels was observed in vafidemstat treatment arms, **achieving statistically significance in the low dose arm in moderate patients**
- Plasma neurofilament light chain (NFL) has been proposed as a blood-based biomarker for neurodegeneration; **in mild patients, vafidemstat treatment at 1.2 mg was able to reduce the increase of NFL**

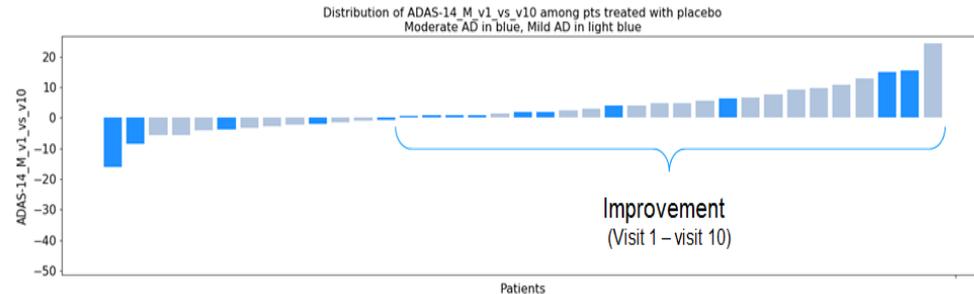
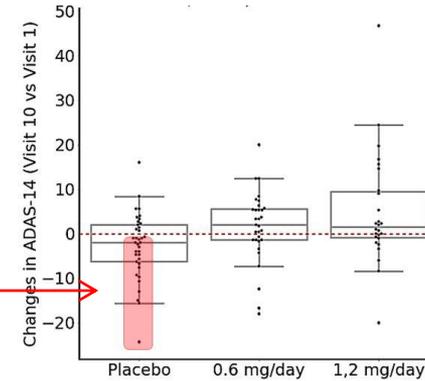


Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population) (ANOVA p value in blue, not showed when not significant) with Post-hoc multiple comparisons Tukey test (\*, p<0.05)

# ETHERAL-EU 6m data: Preliminary Cognitive Efficacy data - ADAS-Cog14

## 6 month analysis did not show cognitive improvement after vafidemstat treatment

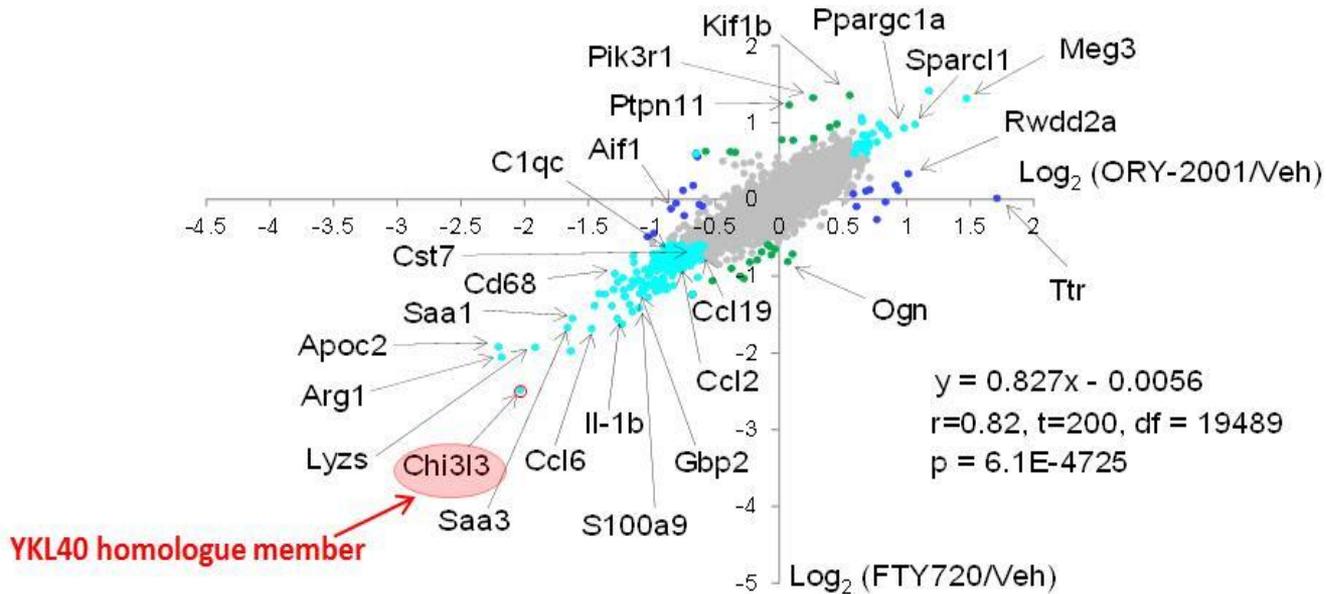
- No statistically significant differences were expected or observed in the ADAS-Cog14 at 6 months between treatment arms
- No significant progression was seen through visits (change over time) in any of the treatment arms
- An unexpected improvement in the Placebo arm was observed (with improvements >10pts) and will require further analysis. This fact will difficult additional interpretations in terms of Cognition
- **65% of the Placebo patients showed an improvement in their ADAS-Cog14 score after 6 months of study duration, some with increases of 10-20 points**



## Vafidemstat and inflammation: Decrease of YKL40 in humans in keeping with previous preclinical data

Vafidemstat treatment reduces the levels of the inflammatory marker YKL40 in brain and spinal cord in the EAE MS model

- **Chi3l3**, a member of the same family, is strongly induced during the effector phase in the EAE model and was one of the gene most strongly reduced with vafidemstat, especially in the spinal cord. The dose was 0.5 mg/kg of vafidemstat (ORY-2001).



## ETHERAL-EU: 6 month Analysis - Key Findings Summary

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- ETHERAL has met the Primary Safety Endpoint
  - ▶ *Vafidemstat was safe and well-tolerated in a mild-to-moderate AD population*
- ETHERAL has produced **interesting biomarker data** that deserve further exploration
  - ▶ *Significant reduction in the CSF levels of YKL40 (an anti-inflammatory biomarker)*
  - ▶ *Signals of Improvement in the levels of Neurogranin (a synaptic damage biomarker) and NFL*
    - ***First in human data supporting PHARMACOLOGICAL ACTIVITY IN THE BRAIN: vafidemstat treatment reducing CSF inflammatory biomarker***
- ETHERAL is not powered for efficacy analyses
  - ▶ *No differences observed between groups on the ADAS-Cog14*
  - ▶ *Unexpected improvement in the Placebo arm will hamper additional interpretation*
  - ▶ *Additional analyses of the other efficacy endpoints is currently underway*
- ETHERAL study is still ongoing and patients are to be treated up to 12 months
  - ▶ *Current analysis of all data should be considered preliminary*
  - ▶ *Final 12 month data release for the EU study expected by Q2 2021*



**ORYZON**

**IADADEMSTAT a Phase II Clinical Stage Compound  
with a broad developability in oncology**

## LSD1 and cancer

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- ✓ LSD1 is involved in different cancers and **in cancer stemness**
- ✓ **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. Positive preclinical *in vivo* results in different xenograft models. Best in Class. Full characterization published in top-rank journal.

### 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 (ORY-1001): a potent & selective differentiating agent: Summary

Cancer Cell  
Article



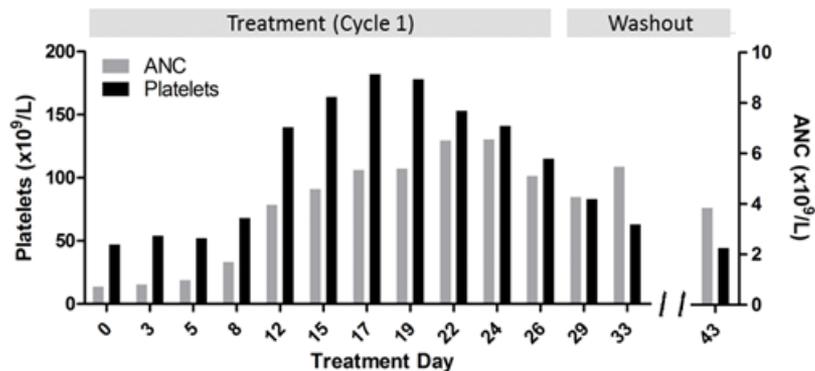
## ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia

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<https://doi.org/10.1016/j.ccell.2018.02.002>

- ❖ Irreversible, highly selective, potent, small molecule LSD1 inhibitor. Covalently binds to FAD-cofactor of LSD1
- ❖ Orally bioavailable, good pharmacologic properties, ADME, PK
- ❖ Encouraging results in a **FiM Acute Leukemia Phase I/IIa trial:**
  - ❖ Administered to 41 Relapsed Refractory Acute Leukemia patients



### Phase I/IIa acute leukemia – final data (*Manuscript submitted*)

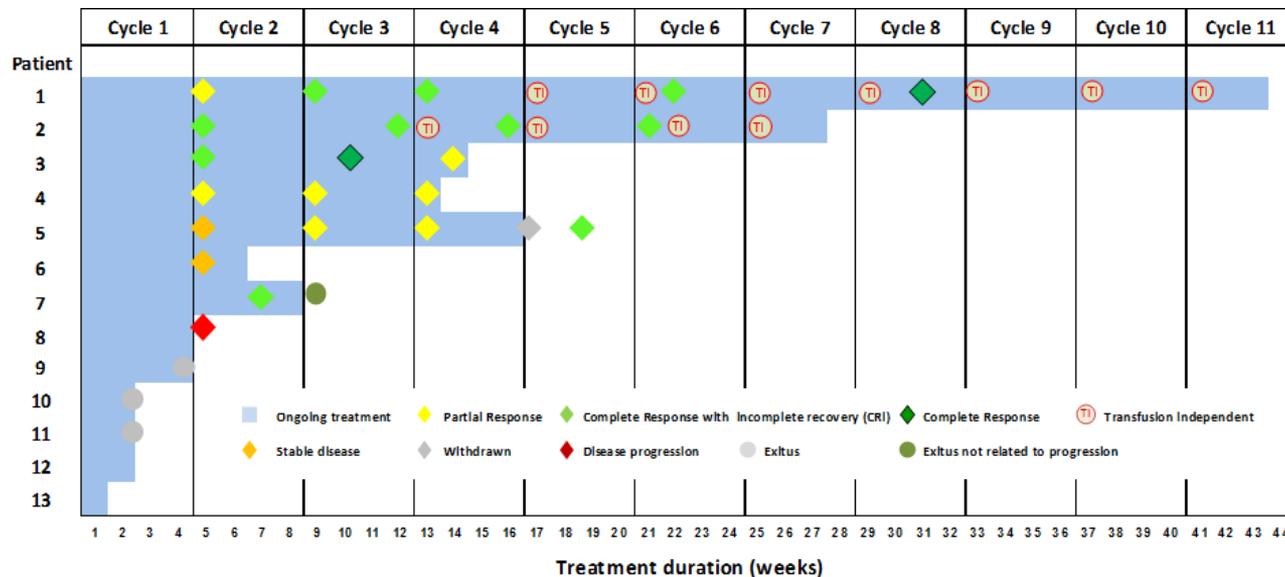
- ❖ Safe and well tolerated: a meaningful candidate for combination with other agents
- ❖ Clear differentiating activity at molecular and cellular level
- ❖ Antileukemic activity observed in 29% of patients (12/41), including one **CRi** as proof of Biological concept

## 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

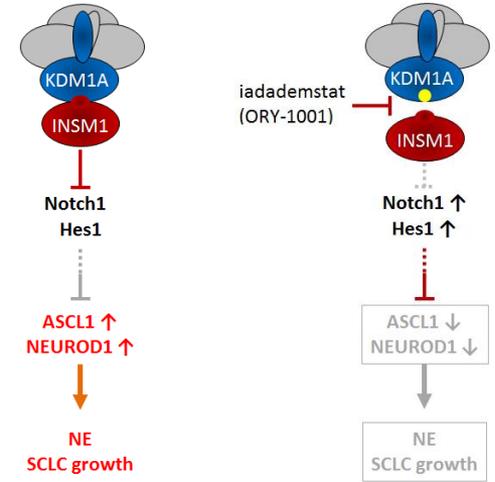
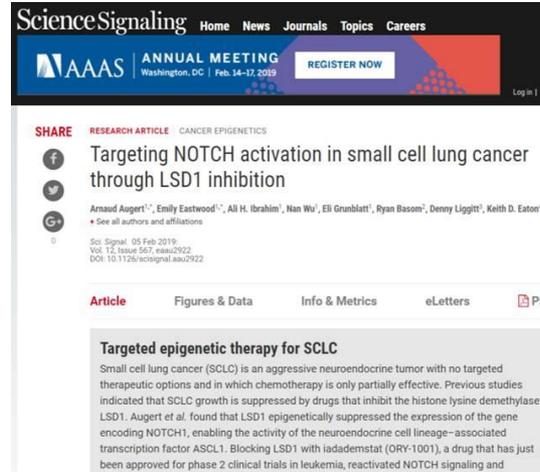
- ✓ Single arm & Open label. Up to 36 patients to be enrolled. **Primary endpoint:** Safety and tolerability of the combo with hypomethylating agent Azacitidine. **Secondary endpoints:** Responses; time to responses; duration of response; and overall survival. Preliminary data for first 6 and 12 patients reported at **EHA-2019 & ASH-2019**

- ❖ Combination of iadademstat and azacitidine shows a good safety profile in elderly AML patients
- ❖ Preliminary signals of clinical efficacy are encouraging, with 75% of ORs (6/8 evaluable patients: 2 CR, 3 CRi and 1 PR)
- ❖ Rapid clinical responses (mean time to first response is currently 32 days)
- ❖ Preliminary rate of conversion to red cell Transfusion Independence (40%) is also encouraging



# Iadademstat a therapeutic approach for SCLC with a well defined MoA

- ✓ LSD1 is a **target well characterized in SCLC**
- ✓ LSD1 inhibitors are effective in several in-vitro and in-vivo models of SCLC
- ✓ Characterized MoA
- ✓ Iadademstat produces **complete and durable tumor regression** in different chemoresistant PDX models
- ✓ Iadademstat is **efficacious in combos with CbEt and other agents**
- ✓ Identified and patented Biomarkers that are differential in sensitiveness to LSD1i
- ✓ Phase II trial ongoing in second line SCLC patients using these **biomarkers to stratify patients and identify super-responders**

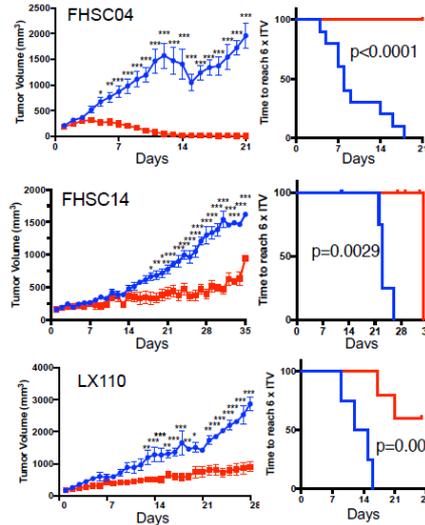


# Iadademstat is efficacious in monotherapy in some PDX-SCLC xenografts

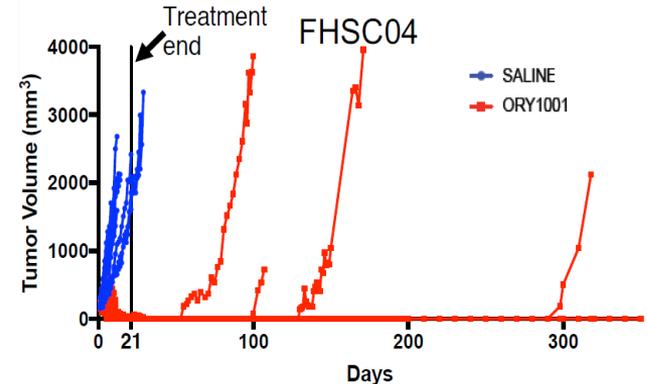
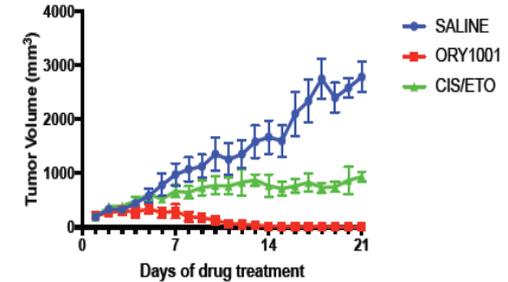
- ✓ Response to iadademstat in PDX models of SCLC is variable, but some are very strong

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

- ✓ 6/10 FHSC04 mice treated with iadademstat did not show relapse after 300 days



*Sci Signal.* 2019 Feb 5;12(567).



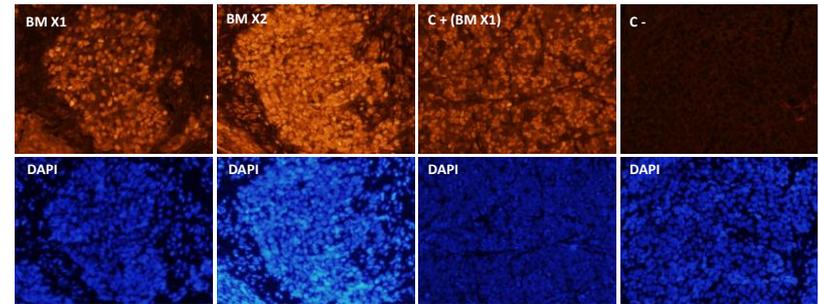
FRED HUTCHINSON  
CANCER RESEARCH CENTER  
A LIFE OF SCIENCE

## Iadademstat: SCLC - Phase II CLEPSIDRA - preliminary efficacy signals

**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; 6 sites in Spain
- ✓ **Up to 36 patients to be enrolled**
- ✓ **4-6 cycles iadademstat+platinum/etoposide, thereafter iadademstat monotherapy (at investigators' criteria)**
- ✓ **Primary endpoint:** Safety and tolerability of the combo with platinum-etoposide therapy
- ✓ **Secondary endpoints:** RECIST responses; time to responses; duration of response; and overall survival



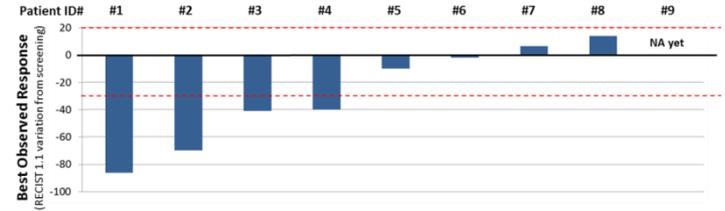
*Biomarker analysis from a CLEPSIDRA patient*

# Iadademstat: SCLC - Phase II CLEPSIDRA - preliminary efficacy signals

## Preliminary Results



- ❖ **75% response rate** (6/8 evaluable patients): 4 PRs and 2 long-term SD
- ❖ Current level of observed responses suggests that **patient selection by Biomarkers** may be effective to increase ratio of ORs



Patient 1	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	cycle 9	cycle 10	cycle 11	cycle 12	cycle 13
CbEp													
iadademstat	60	60	60	60	60	60	60	60	60	60	60	60	60
Best response		PR -43,30%		PR -71,20%		PR -78,70%		PR -86,30%		PR -86,30%		PR -86,30%	

- ❖ Main toxicity observed in the combination with carboplatin-etoposide is hematological
- ❖ **iadademstat alone is safe and shows no hematological, general or neuronal toxicity** in ED-SCLC patients, suggesting potential for monotherapy and other combos
- ❖ iadademstat alone sustains further therapeutic benefit

# Anticipating a rich flow of science catalysts / clinical data (non-comprehensive selection)

Iadademstat Phase II  
in oncology

2020

Vafidemstat Phase II  
in CNS

CLEPSIDRA

ALICE

June (virtual meeting)



ALICE AML data

Madrid – September



CLEPSIDRA SCLC data

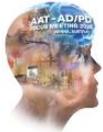
San Diego – December



ALICE AML data

2021

REIMAGINE-AD  
ETHERAL-EU 6m Interim



April

REIMAGINE-AD

ETHERAL

SATEEN

PORTICO

ETHERAL-US  
6m Interim



Barcelona - March

ETHERAL-EU+US  
12m FINAL



Boston - June

Potential Conferences where data may be presented

## ORYZON – a unique investment opportunity in an epigenetic platform

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- ✓ A differential proposition in **EPIGENETICS** drugs in **CNS and ONCOLOGY** around one of the most interesting targets in the field: **LSD1**
- ✓ **2 molecules in Phase II** with promising clinical signals of efficacy in patients
- ✓ **Pioneers in CNS epigenetics**
  - ✓ Vafidemstat shows efficacy in psychiatric disorders (BPD , ADHD, ASD)
  - ✓ **Phase IIb in Borderline personality disorder in preparation.** Additional trials in agitation in AD, ADHD or ASD under evaluation
  - ✓ Vafidemstat may be also clinically relevant in neurodegenerative disorders (Phase IIs in MS and AD ongoing)
  - ✓ Trials in genetically defined patient subpopulations in SCZ and ASD under study
- ✓ **Most advanced LSD1i (iadademstat) in Oncology**
  - ✓ **Positive preliminary efficacy results** reported in the ongoing Phase II trials in AML and SCLC
  - ✓ **SCLC trial is a biomarker-guided** study to stratify responsive patients
  - ✓ Options to get accelerated approval
- ✓ **Rich pipeline** of clinical **news** expected in the next Qs. Clinical Operations in US started and under expansion
- ✓ A **cash efficient** company with a seasoned international management team
- ✓ **€135M market cap.** One of the most liquid stocks in the microcap group in MadridSEXC with **plans to** get dual listed in **NASDAQ**
- ✓ Perseverant **presence in the US market in the last 4 years.** Three successful PIPEs executed in 2017-19 led by US Investment Banks and with participation of US-EU-IL investors

ORYZON

Pioneering Personalized Medicine in  
**EPIGENETICS**

