# Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

January 2022

ORY:SM / ORY.MC

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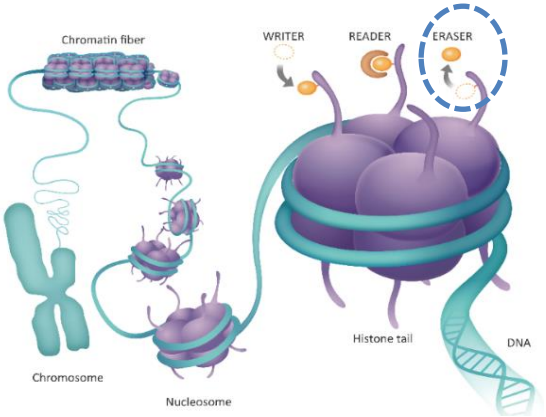
# Oryzon: Epigenetic Champion Developing New Therapies in Oncology and CNS

*LSD1 is an "eraser"*




***Histones are modified by epigenetic enzymes resulting on the unfolding or folding of chromatin and allowing or silencing gene expression***

- Growing epigenetic platform with an expanding pipeline
- Developing highly potent and selective LSD1 inhibitors with best-in-class potential
- Two programs with positive Phase IIa data in AML and SCLC, and in aggression/agitation in CNS disorders
- Potential for expedited development in 2L AML and 1L ED-SCLC, and Kabuki Syndrome
- Listed in Europe (Madrid) since 2015. Cash & Cash equivalents of $36m as per Sept30th 2021. Runway expected till 1Q2023

# Potentially Best-in-Class LSD1i Addressing Unmet Medical Needs in Oncology and CNS

**Epigenetic personalized medicine with a marked orphan disease approach**

## ONCOLOGY

**Iadademstat (ORY-1001)**
***MoA: Pro-Differentiation***
***Anti-cancer stemness***

- Potential first & best-in-class LSD1i in Oncology
- In development for AML and SCLC
- 4 Phase I/IIa clinical trials: 100+ patients dosed
- Robust and consistent responses in AML (78% ORRs)
- Two new Phase Ib/II trials with registrational potential
  - FRIDA, a study in 2L in AML
  - STELLAR, a study in 1L in ED-SCLC

## CNS

**Vafidemstat (ORY-2001)**
***MoA: Prosynaptic***
***Anti-neuroinflammatory***

- Potential first-in-class LSD1i in CNS
- 8 Phase I/II clinical trials: 300+ subjects dosed
- Positive Phase IIa data in agitation and aggression in a basket trial in multiple psychiatric disorders
- Two ongoing Phase IIb studies in BPD and SCZ initiated in 2021
- New HOPE Phase I/II trial in Kabuki syndrome has potential to support registration

# Deep Pipeline with Multiple Upcoming Milestones

| INDICATION | STUDY | PRECLINICAL / PHASE I / PHASE IIA / PHASE IIB / PHASE III | Next anticipated milestones |
|---|---|---|---|
| **IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor** | | | |
| AML (1L Elderly/Unfit) | ALICE (Combo w azacitidine) | ongoing (fully enrolled) | 2H2022 EHA/ASH Final Data |
| AML (R/R-Flt3mut+) | FRIDA (Combo w gilteritinib) | in preparation | IND 1Q2022 /FPI 1H2022 |
| ED-SCLC (1L) | STELLAR (Combo w ICI) | in preparation | IND 1H2022 /FPI 2H2022 |
| NETs (R/R) | NET Basket (Combo w other agents) | in preparation | IND 1H2022 /FPI 2H2022 |
| **VAFIDEMSTAT (ORY-2001) - CNS optimized LSD1 inhibitor** | | | |
| Borderline Personality Disorder | PORTICO | recruiting | Study updates 2022 |
| Schizophrenia (Negative symptoms & Cognition) | EVOLUTION | recruiting | Study updates 2022 |
| Kabuki Syndrome | HOPE | in preparation | IND 1H2022 /FPI 1H2022 |
| SetD1A Compass related SCZ | | under study | |
| Aggression in AD | New Study (Continuation of REIMAGINE-AD) | under study | |
| **OTHER PROGRAMS** | | | |
| COVID-19 Prevention of ARDS | ESCAPE | study finalized | |

Note: Other finalized clinical trials for iadademstat and vafidemstat are not shown. See www.oryzon.com for more details

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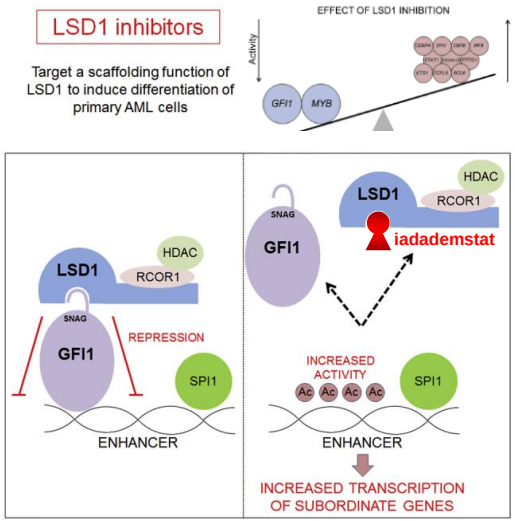
# IADADEMSTAT
# A Phase II LSD1 inhibitor in Oncology

# Iadademstat: Potentially Best-in-Class LSD1 Inhibitor for Oncology




***In leukemia, LSD1 is a building-block of some multiprotein complexes that impair normal differentiation. LSD1 inhibition collapses these complexes and allows blasts to continue normal differentiation***

LSD1 plays a key role in numerous cancers; elevated levels often correlate with more aggressive forms or poor prognosis

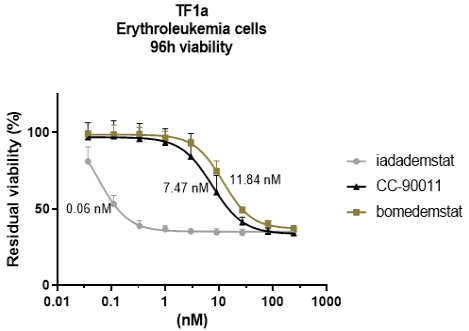
Iadademstat is a potent and highly selective, investigational oral LSD1i with best-in-class potential

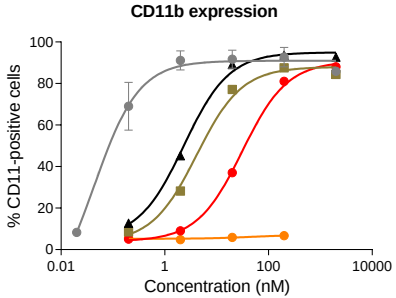
Encouraging signals of clinical efficacy in Phase IIa trials in elderly/unfit AML patients and in ED-SCLC

New Phase Ib/II trials with registrational potential in 2L AML and 1L ED-SCLC starting in 2022

# Iadademstat: Potentially Best-in-Class LSD1 inhibitor for Oncology

- The most potent LSD1 inhibitor in clinical development
- The most efficient in disrupting LSD1-transcriptional complexes



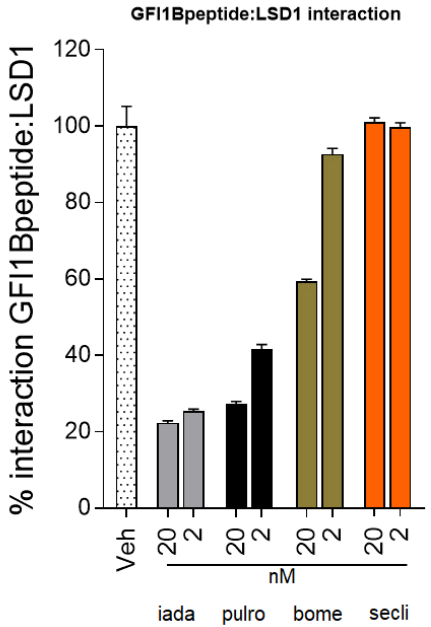

| cell assay | Iada vs Bome | Iada vs Pulro (CC-90011) |
|---|---|---|
| MOLM13 | 45-fold more potent | 22-fold more potent |
| MV(4,11) | 15-fold more potent | 8-fold more potent |
| TF1a | 197-fold more potent | 124-fold more potent |
| THP1 | 122-fold more potent | 68-fold more potent |

ACS Pharmacology & Translational Science
pubs.acs.org/ptsci
Article

**Comprehensive *in Vitro* Characterization of the LSD1 Small Molecule Inhibitor Class in Oncology**

*Published as part of the ACS Pharmacology & Translational Science special issue "Epigenetics 2022".*

Natalia Sacilotto,[⊥] Paola Dessanti,[⊥] Michele M. P. Lufino, Alberto Ortega, Alejandra Rodríguez-Gimeno, Jordi Salas, Tamara Maes, Carlos Buesa, Cristina Mascaró,* and Robert Soliva*



## Orphan Drug Designation granted for AML in US and EU

- **Clear PoC in ongoing AML Phase II study (ALICE)**
- **Registrational strategy:** Potential for expedited development in AML and SCLC in two indications
  - 2L in AML with FLT3 mutations
  - 1L in ED-SCLC

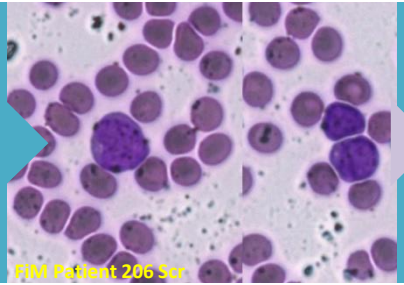
} ***Patient populations with high medical need & Significant market opportunity***

- Additional trial in NETs (collaborative) in preparation and other trials in study

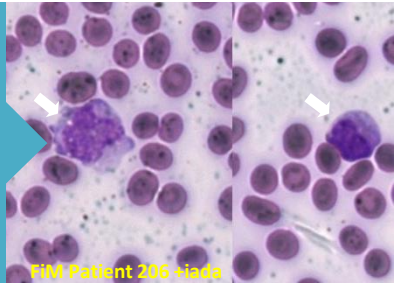
# Iadademstat MoA and Antileukemic Activity Observed in AML

**AML is the most common type of acute leukemia in adults**

**LSD1 interacts with GFI1/1B causing a block in leukemia cell differentiation**




**LSD1 inhibition modulates the GFI1/1B axis to induce terminal differentiation and control leukemia stem cell proliferation**



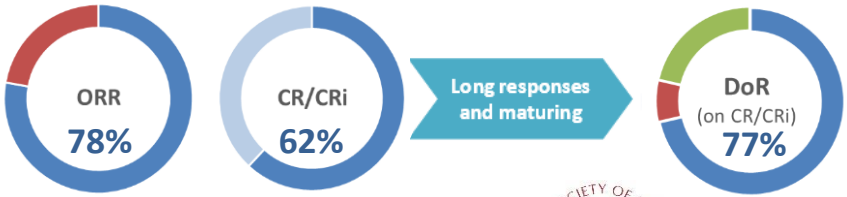

- LSD1 is **crucial for the function and maintenance of leukemic stem cells**
- Iadademstat **reduces leukemic stem cell** proliferation and **induces differentiation**
- Iadademstat has shown **clinical efficacy and safety** in combination with standard of care in **AML**

- **Clinical Status**:
  - Completed FiM Phase I (41 patients) → Generally well tolerated with antileukemic activity (1CRi) and with reductions in blood and bone marrow blast percentages and induction of blast differentiation
  - **Ongoing Phase IIa (ALICE)** (fully enrolled, 36 patients) → Encouraging signals of clinical activity (78% ORR) and generally well tolerated
    - **Last update ASH-2021**

# ALICE: a PoC Phase IIa in AML

## Trial Design / Overview

- Open label, multicenter, single arm study
- Newly diagnosed elderly or unfit AML patients
- Iadademstat in combination with azacitidine
- 36 patients (fully enrolled)
- Preliminary data (ASH-2021) with 27 evaluable patients




*Last public report presented at ASH2021*

https://www.oryzon.com/sites/default/files/events/20211213_ASH2021_poster.pdf

## Results Highlights

- **78% ORR** (21 out of 27 evaluable patients):
  - **62% CR/CRi** (13/21): 6 CR & 7 CRi (3 still evolving); 8 PR
  - 5 MRD negative patients
- Median Time to Response (TTR) of 55 days
- **Lasting responses**:
  - **77% CR/CRi with lasting responses (≥ 6 months)**
  - Longest EFS response of **+1,000 days** (still ongoing)
- 67% transfusion independence in CR/CRi patients
- Iadademstat/azacitidine combo was generally well tolerated

## Key Conclusions / Next Steps

- Data strongly support iadademstat activity – azacitidine monotherapy historically yielded ~28% ORR in the same population
- Expand into R/R AML trials where clear and significant unmet medical need remains

# Next Steps: A Phase Ib/II trial in 2L AML with registrational potential

*Phase Ib/II in FLT3 mut+ R/R AML patients combining iadademstat and gilteritinib (Xospata®)*

**FRIDA: FLT3 mutated Relapsed/Refractory AML treatment with IaDAdemstat**

- 2L AML is an underserved population: 50% of AML patients relapse
- FLT3 is the most common mutation in AML (30%) and patients have adverse prognosis. 2L R/R FLT3 mutated patients are now treated with gilteritinib, yet it remains a subpopulation with high medical need (mEFS 2.8 months & CR+CRi 34%)
- Strong rationale: preclinical synergies between iadademstat and gilteritinib
- Open label, multicenter (around 20 sites in US). 120 patients to be included
- Phase Ib objectives are to evaluate safety/tolerability, and to determine the RP2D and MTD
- Phase II objective is to evaluate efficacy of the drug at the RP2D
- IND submission 1Q2022 / FPI 1H2022

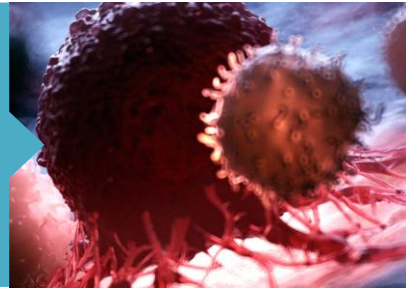
**FRIDA study could potentially support an application for accelerated approval if a significant clinical benefit in the population is demonstrated over the efficacy of gilteritinib monotherapy as determined by a matched contemporary synthetic control study**

# Iadademstat is a Therapeutic Approach for SCLC With a Well-Defined MoA

**SCLC is very aggressive and represents 15% of all lung cancers**

**LSD1i acts in SCLC by enhancing Hes1 and Notch1 pathways**

**LSD1i synergizes with ICIs and boosts the host immune system**



- Iadademstat produces **complete and durable tumor regression** in different **chemoresistant SCLC PDX models**
- Preclinically, iadademstat is **efficacious in combos with platinum/etoposide and other agents such as Immune Checkpoint Inhibitors (ICIs)**
- Oryzon has identified and patented **biomarkers** that differentiate SCLC tumors by their sensitiveness to LSD1i

- **Clinical Status**:
  - Phase I study (NCT02913443) (18 patients) → RP2D in monotherapy
  - Phase IIa (CLEPSIDRA) (14 patients) → Signs of clinical activity & Generally well tolerated in monotherapy

# Iadademstat SCLC Phase IIa CLEPSIDRA Trial Overview

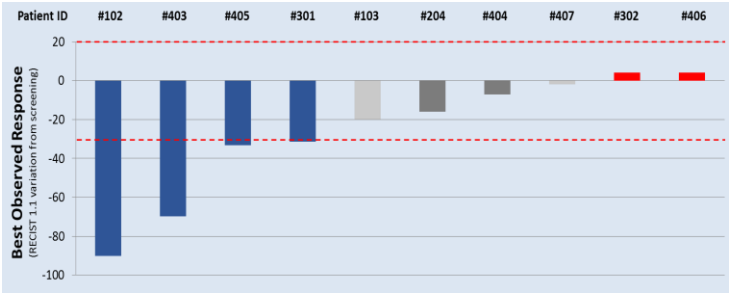
## Trial Design / Overview

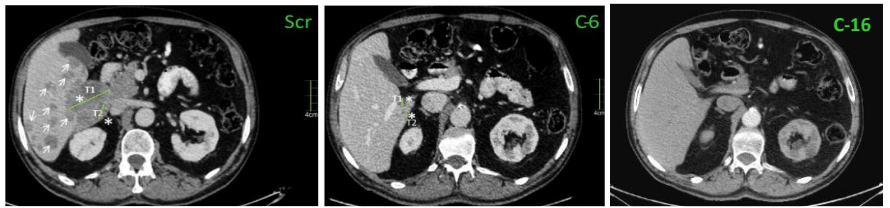
- Open label, multicenter, single-arm study
- Biomarker selected, platinum sensitive 2L ED-SCLC patients
- Iadademstat in combination with 4-6 cycles carboplatin/etoposide (21 d/cycle). After chemo, iada could be administered alone
- 14 patients enrolled; 12 biomarker-positive patients; 10 evaluable patients
- Data presented at ESMO 2020

## Results Highlights

- Platinum/etoposide in combo with iadademstat showed hematotoxicity
- Iada alone was generally well tolerated. Toxicity disappeared when treated with iada alone
- Activity signals were encouraging with **40% OR** and **mean DoR of 4.5 months** compared to SoC 15-35% OR
- **60% clinical benefit rate** (6/10 evaluable patients): 4 PRs + 2 long-term SD
- One patient had 15 cycles in monotherapy, with a total tumor size reduction of 90% and a relative tumor size reduction during iadademstat monotherapy of 53%

**2020 ESMO Conference Data Release**




## Key Conclusions / Next Steps

- Potential improvement over historical ORR of 15-35% for SoC
- Expand into 1L SCLC in combination with ICI given strong rationale for synergies

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# Next Steps: A Phase Ib/II Trial in 1L ED-SCLC with registrational potential

*A randomized Phase Ib/II study of iadademstat plus a checkpoint inhibitor in 1L patients with metastatatic SCLC*

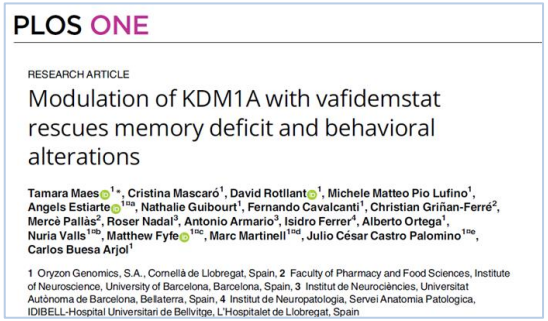
**STELLAR: Synergistic Treatment with Epigenetics in front line small celL Lung cAnceR**

- High unmet medical need and a relative low bar for improving efficacy due to the modest efficacy improvements shown in the IMPower-133, CASPIAN and Keynote-604 trials
- Strong rationale for combination: preclinical proof of strong synergies between iadademstat and ICI
- Randomized, multicenter (15-20 sites in US). 120 patients to be included
- Phase Ib objectives are to evaluate safety/tolerability, and to determine the RP2D and MTD in combination with ICIs
- Phase II objective is to evaluate efficacy of the drug measured as PFS in randomized trial against an ICI-only arm
- IND submission 1H2022 / FPI 2H2022

**STELLAR can potentially support an application for accelerated approval if a significant clinical benefit in the population is demonstrated over the efficacy of ICI+CbEt**

# VAFIDEMSTAT
# A Phase II LSD1 inhibitor for CNS diseases

# Vafidemstat: “Neuron-resetting” LSD1 Inhibitor in Phase II for Multifactorial and Monogenic CNS Disorders



PLOS ONE

RESEARCH ARTICLE

Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations

Tamara Maes[1]*, Cristina Mascaró[1], David Rotllant[1], Michele Matteo Pio Lufino[1], Angels Estiarte[1ne], Nathalie Guibourt[1], Fernando Cavalcanti[1], Christian Griñan-Ferré[2], Mercè Pallàs[2], Roser Nadal[3], Antonio Armario[3], Isidro Ferrer[4], Alberto Ortega[1], Nuria Valls[1ne], Matthew Fyfe[1nc], Marc Martinell[1nd], Julio César Castro Palomino[1ne], Carlos Buesa Arjol[1]

1 Oryzon Genomics, S.A., Cornellà de Llobregat, Spain, 2 Faculty of Pharmacy and Food Sciences, Institute of Neuroscience, University of Barcelona, Barcelona, Spain, 3 Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain, 4 Institut de Neuropatologia, Servei Anatomia Patologica, IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain

CNS Drugs
https://doi.org/10.1007/s40263-021-00797-x

ORIGINAL RESEARCH ARTICLE

First-in-Human Randomized Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the KDM1A Inhibitor Vafidemstat

Rosa María Antonijoan[1,2] · Juan Manuel Ferrero-Cafiero[1] · Jimena Coimbra[1] · Montse Puntes[1] · Joan Martínez-Colomer[1] · María Isabel Arévalo[3] · Cristina Mascaró[3] · Cesar Molinero[3] · Carlos Buesa[3] · Tamara Maes[3]

Accepted: 12 February 2021

Oryzon is the first and only company pursuing LSD1i in CNS diseases

Vafidemstat is an investigational LSD1 inhibitor with high BBB penetration, optimized for the CNS

SAFETY FIRST

Vafidemstat has been administered to more than 300 subjects across the multiple Phase I and II clinical trials completed or ongoing, and has shown to be well tolerated

Significant reduction in Aggression and Agitation in BPD, ADHD, ASD and AD patients

Multiple value-driving catalysts with Phase IIb trials ongoing in BPD and SCZ, and an IND submission for Kabuki Syndrome expected by 1H2022

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# LSD1 Inhibition and Multifactorial CNS Disorders

- LSD1 is expressed in the developing and adult nervous system
- LSD1 plays a critical role in neurogenesis, in neuronal differentiation, axonal navigation and regulating expression of key genes
- Regulation of methylation has emerged as a top pathway significantly correlated with adult psychiatric disorders
- LSD1 is the most abundant KDM in the cortex and controls gene expression through methylation and scaffolding
- Detailed topographic analysis indicates that LSD1 interacts with enhancers and promoters of important CNS genes, including some confirmed CNS disease risk genes, controlling their expression
- There is significant evidence of additional pathways where LSD1 could have an impact on multifactorial CNS disorders

***LSD1 Inhibition can compensate complex phenotypes caused by multifactorial CNS disorders***

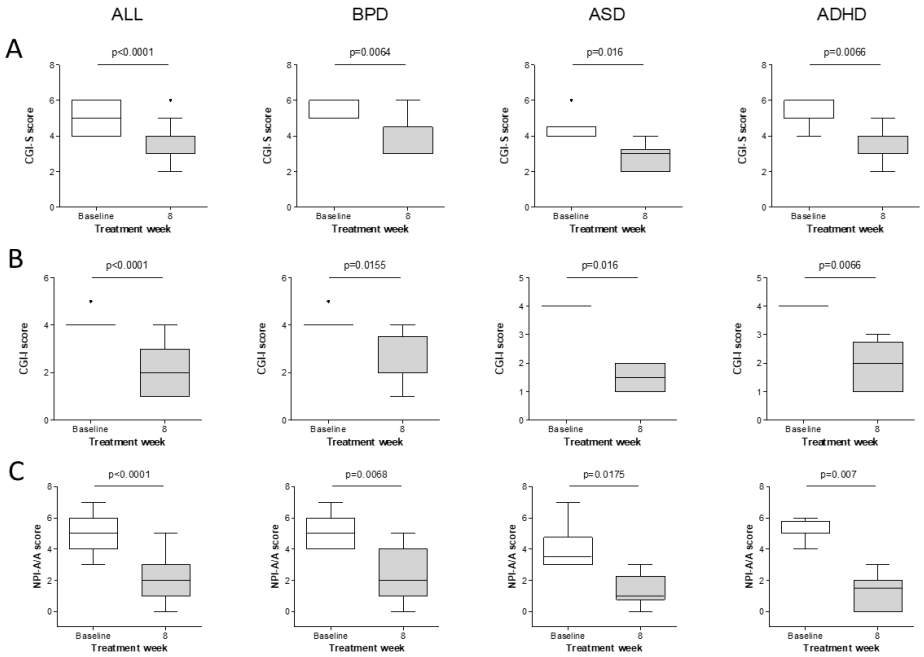
# Vafidemstat: Aggression / Agitation Phase IIa REIMAGINE Trial Overview

## Trial Design / Overview

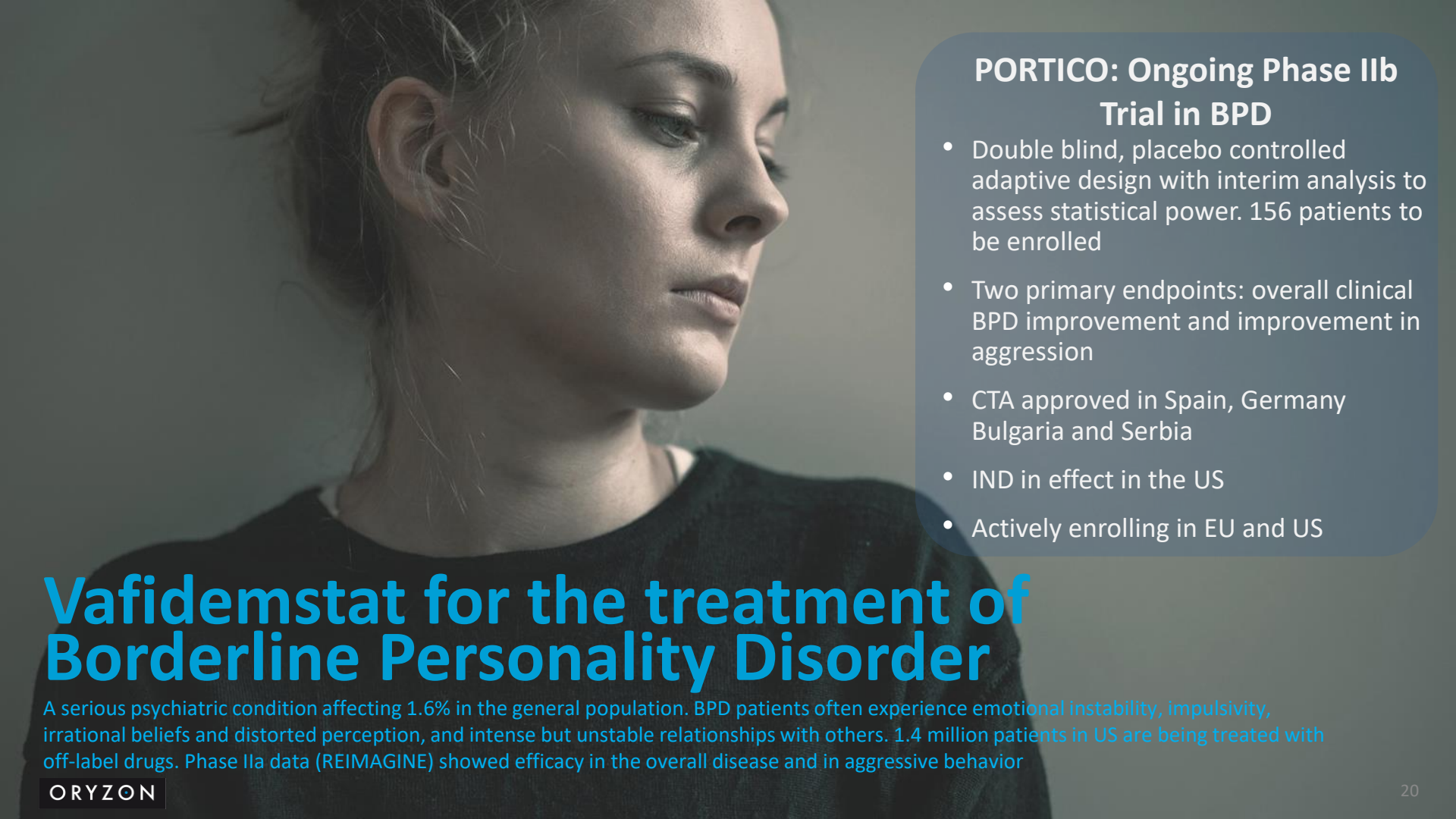
- Open label, single-center, Phase IIa study
- Adult patients with BPD, ADHD and ASD with significant agitation and aggression
- Received vafidemstat 1.2mg/day, 5 days per week for 8 weeks
- 30 patients enrolled (12 BPD, 11 ADHD, 7 ASD)

## Results Highlights

- Observed statistically significant improvements in aggression on the aggregated data as well as for each of the three disease groups, BPD, ASD and ADHD, independently
- Vafidemstat resulted in a 64% reduction of aggressiveness measured by the neuropsychiatric inventory - agitation and aggression ("NPI-A/A") scale
- Aggressiveness reduction was observed in 96% patients treated with vafidemstat for a period of two months
- Improvements also observed in overall patient functioning, particularly in BPD patients




***Effect of vafidemstat on aggression assessed by the CGI-S (A), CGI-I (B) and NPI-A/A (C) scales. Baseline and end of treatment (week 8) data are presented as Tukey whisker plots with outliers***



## PORTICO: Ongoing Phase IIb Trial in BPD

- Double blind, placebo controlled adaptive design with interim analysis to assess statistical power. 156 patients to be enrolled
- Two primary endpoints: overall clinical BPD improvement and improvement in aggression
- CTA approved in Spain, Germany Bulgaria and Serbia
- IND in effect in the US
- Actively enrolling in EU and US

# Vafidemstat for the treatment of Borderline Personality Disorder

A serious psychiatric condition affecting 1.6% in the general population. BPD patients often experience emotional instability, impulsivity, irrational beliefs and distorted perception, and intense but unstable relationships with others. 1.4 million patients in US are being treated with off-label drugs. Phase IIa data (REIMAGINE) showed efficacy in the overall disease and in aggressive behavior

## EVOLUTION: Ongoing Phase IIb Trial in SCZ

- Double blind, placebo controlled adaptive design with interim analysis to assess statistical power. 100 patients to be enrolled in two arms
- 2 arms, vafidemstat as add-on to SoC. 6 months of treatment
- Primary endpoints: efficacy to address SCZ Negative and Cognitive Symptoms
- 6-10 sites. CTA approved in Spain
- Currently recruiting patients

# Vafidemstat for the treatment of Schizophrenia

Prevalence of schizophrenia (SCZ) and related psychotic disorders in the US range between 0.25% and 0.64%.
No current approved treatments for the cognitive impairment or the negative symptoms of schizophrenia.
Abnormalities of GABAergic neurons believed to play a key role in the pathophysiology of schizophrenia. Vafidemstat upregulates GABAergic genes in PFC neurons in response to stress. LSD1i restores phenotypes in various SCZ mice models.

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# LSD1 and Precision Medicine in CNS

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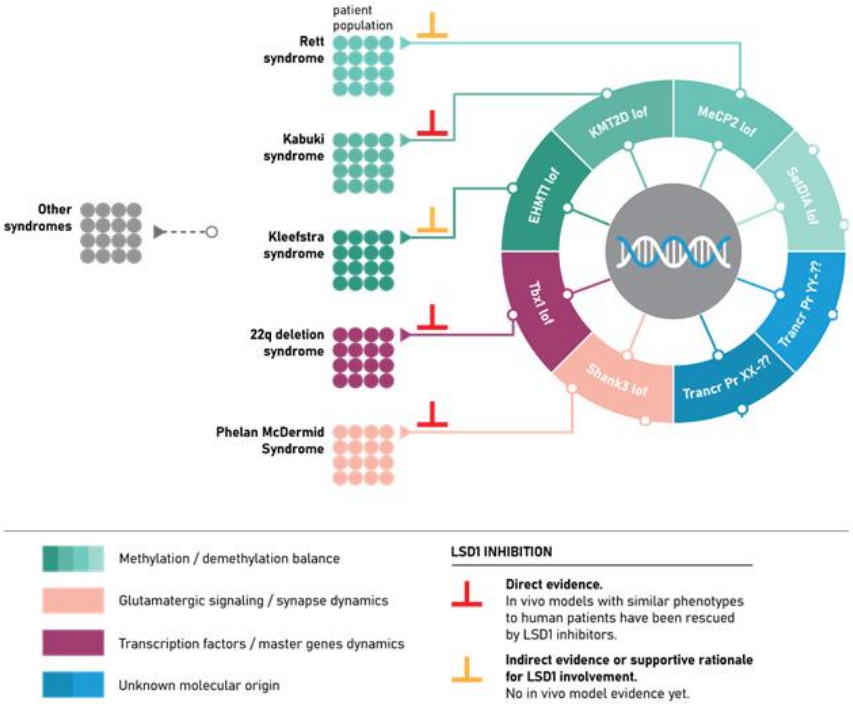
# LSD1 Inhibition: Personalized Medicine in Rare Monogenic CNS Disorders

- Dysregulated methylation plays an important role in the onset of certain neurodevelopmental disorders
- Genetic single defects or loss of alleles can cause CNS disorders with complex phenotypes
- Preclinical data has shown that excessive LSD1 activity may be a key part of specific monogenic neurodevelopmental syndromes
- LSD1 inhibition can correct distinct independent deficiencies occurring upstream by resetting the appropriate transcriptional program

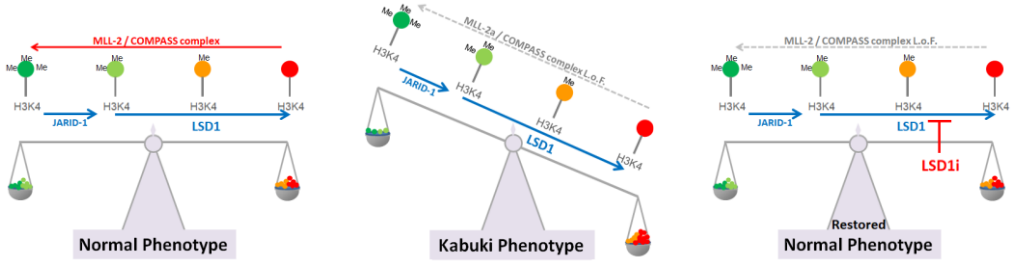



***LSD1 Inhibition can compensate complex phenotypes caused by single gene deficiencies that are the cause of some rare neurodevelopmental syndromes***

# Methylation is involved in Kabuki Syndrome and LSD1 inhibition rescues phenotypes in genetic models

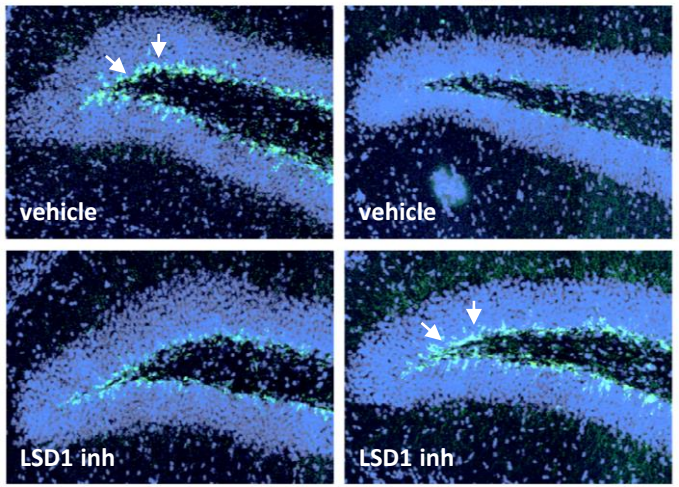
Kabuki syndrome (KS) is a congenital disorder characterized by intellectual disability, growth retardation, dysmorphic facial features and immune defects

Mutations of *MLL2 (KMT2D)* cause Kabuki syndrome in >70% of cases (known as KS type I)




- **Effects of LSD1i in the phenotype of KO Kabuki mice***
  - **LSD1i restored methylation balance in the hippocampus**
  - **LSD1i rescued adult neurogenesis and memory deficits**
  - **LSD1i restored normal neuronal morphology**
  - **LSD1i rescued global gene expression changes**
  - **LSD1i rescued the visuospatial learning and memory defects**
  - **LSD1i rescued immune defects**

**LSD1i rescued neurogenesis defects in hippocampus of Kmt2d$^{+/\beta Geo}$ mice**




*Modified from Zhang et al, Molecular Therapy: Methods & Clinical Development ,Vol. 20 , 779-791 (March 2021)

# HOPE: an adaptive Phase I/II trial with vafidemstat in Kabuki Syndrome patients

- A randomized, double blinded, multicenter study in KS type I (MLL defective) patients. 6-8 US centers to be included
- **Lead investigator**: **Dr. Jaqueline Harris**, director of the **Epigenetics Clinic at Kennedy Krieger Institute** and an assistant professor in pediatrics, neurology and genetics at The **Johns Hopkins University School of Medicine**.
- A Network of Epigenetic clinics and KOLs nucleated around the Kabuki Syndrome Foundation
- IND submission 1H2022 / FPI 1H2022. 50-60 patients to be included
- Oryzon received $1 million grant from KS philanthropists to support the HOPE trial

KABUKI SYNDROME FOUNDATION


JOHNS HOPKINS SCHOOL of MEDICINE

Boston Children's Hospital
Where the world comes for answers

Cincinnati Children's

**HOPE can potentially support an application for an accelerated approval if a significant clinical benefit in the population is demonstrated over placebo**

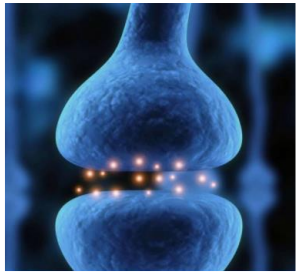
- The pool of KS type 1 patients <25 yr old is +6,000 in the developed countries
- An active patient community that allows an efficient market outreach with a limited sales force
- Initial target population will be ~3,000 patients w.w.

# Vafidemstat has a growing avenue for personalized therapy in CNS

## COMPASS-related Pathologies

SET1 (COMPASS)-like complex methylates histone H3 lysine 4 to activate promoters & define the boundaries of enhancers and superenhancers. LoF produces a variety of syndromes:

- **KMT2D (MLL2) – Kabuki Syndrome**
- **KMT2F (SetD1a) - Schizophrenia susceptibility**
- KMT2A (MLL1) - Wiedemann–Steiner syndrome
- KMT2B - Dystonia 28, Childhood-Onset
- KMT1D - Kleefstra syndrome –ASD
- KMT2C- KMT2C Syndrome -ASD
- KMT2G (SetD1b) - Syndromic intellectual disability



## Glutamatergic pathway-related Pathologies

- **Shank3 : Shankopaties – PMS / ASD**
- NMDA-R hypofunction SCZ

## Other yet unknown genetic relationships

- Rett Syndrome
- ASD syndromes
- Other schizophrenia subpopulations

**Beyond monogenic syndromes, LSD1 is also involved in the direct or indirect regulation of genes or regulators of specific pathways involved in CNS diseases, e.g. miR137, whose targets are genes involved in schizophrenia and Huntington's disease, opening the door for targeting subpopulations of large CNS indications**

# ORYZON

**A unique dual EPIGENETIC proposition in ONCOLOGY and CNS**

- A validated approach with multiple shots on goal
- 2 Phase II programs
- Differentiated pipeline of first- and potentially best-in-class LSD1 therapies
- Safety proven in 400+ subjects dosed

# Value Creation in 2022

**Multiple inflection points**

- Final data for 1L AML PoC ALICE
- New AML & SCLC trials to start in 2022 with potential to support registration
- New Kabuki Syndrome Phase I/II trial to start in 2022 with potential to support registration
- Additional trial initiations in Oncology
- CNS Phase IIb trials updates


# Pioneering personalized medicine in epigenetics