ORYZON

Pioneering personalized medicine with epigenetics

Corporate Presentation
1Q 2026
ORY:SM / ORY.MC

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Oryzon Develops Potent and Selective Epigenetic Drugs

Epigenetics experts specializing in LSD1 Biology

Vafidemstat: Phase III ready. LSD1i CNS asset geared toward ameliorating aggression and agitation in borderline personality disorder. **Phase II in schizophrenia**

Iadademstat: in Phase II. 2nd LSD1i asset developed in multiple hematology and oncology indications

Experienced management **team**, Board of Directors and world-renowned clinical regulatory and industry experts

Robust financial position with > $60m raised in 2025; cash runway through 1H 2027

Oryzon: a Specialist in Epigenetics Developing New Targeted Therapies in CNS and Oncology

Developing potent and selective epigenetic drugs with well-defined registrational pathways

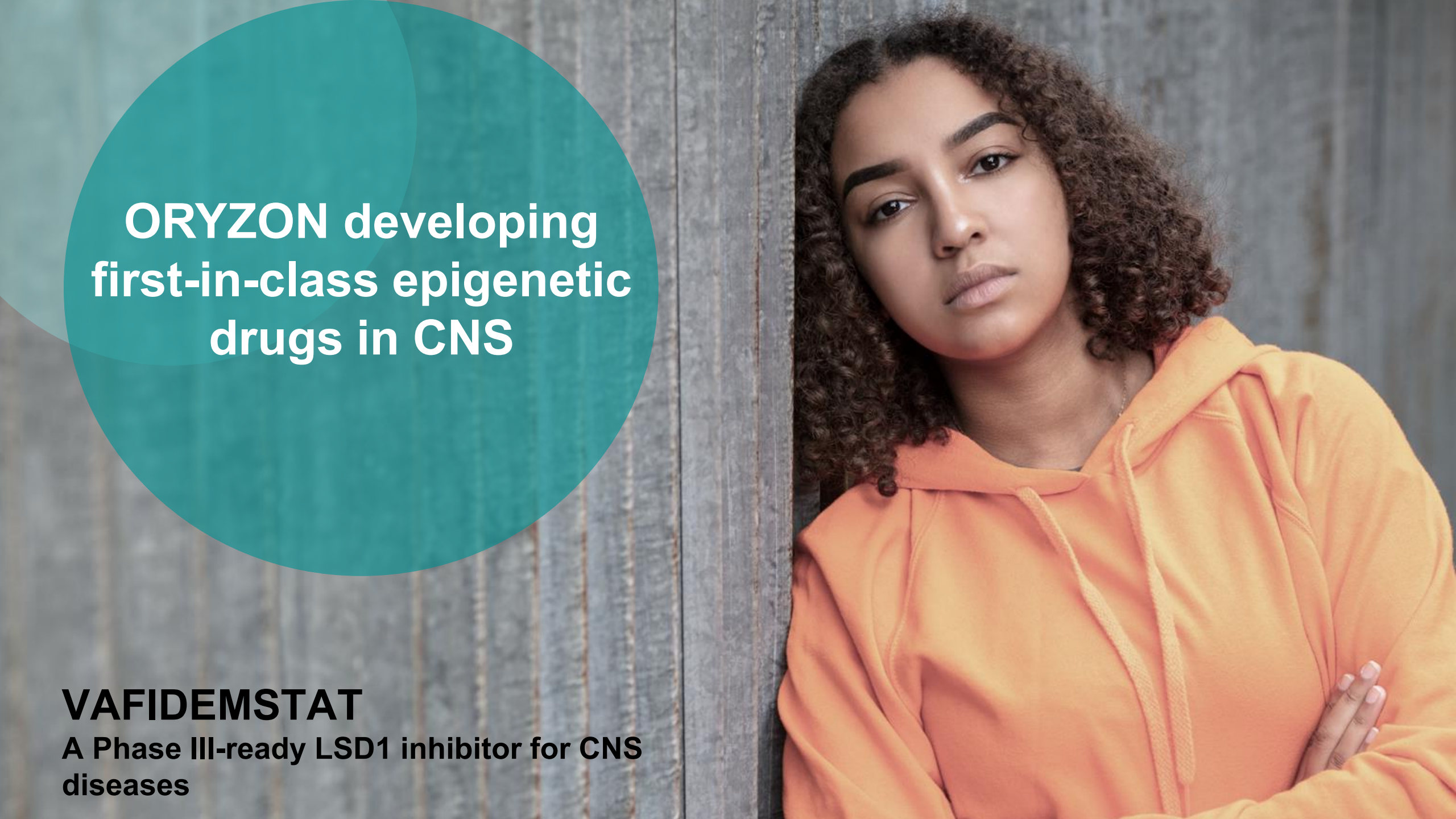
Vafidemstat

- Phase III-ready asset in aggression in Borderline Personality Disorder (BPD)
- Phase II in Schizophrenia
- Phase II in aggression in ASD to start in 2026

Iadademstat

- Strong clinical data
- Leverages CRADA-NCI agreement; requires only modest investment
- In Phases Ib and II in:
  - Oncology: AML, MDS, MPN and SCLC
  - Hematology: Sickle Cell Disease. Phase II in ET to start in 2026

ORYZON developing first-in-class epigenetic drugs in CNS



VAFIDEMSTAT

A Phase III-ready LSD1 inhibitor for CNS diseases

LSD1 inhibition, a novel therapeutic option in CNS disorders

ORYZON is the only company to have developed an LSD1i for CNS: vafidemstat

Currently ready for Phase III clinical development

Vafidemstat pharmacology supports use in different mental diseases

Vafidemstat (aka ORY-2001) and other LSD1i induce expression of genes **involved in neuronal plasticity**, restoring neuronal morphology, branching and axonal navigation

Vafidemstat **restores the response to stress** by regulating genes involved in control of stress cues in the PFC-amygdala axis, as IEG, SRF, and others

LSD1i is able to **rescue glutamatergic NMDA-R hypofunction** in prefrontal cortex in different ASD and SCZ models

Vafidemstat improves sociability

Vafidemstat reduces aggression

Vafidemstat improves memory

Borderline Personality Disorder, Schizophrenia, Autism, ADHD, others

Vafidemstat is Safe and Well Tolerated

A very robust safety package. +425 treated subjects

Oral & Brain Penetrant

Oral, once daily
1.2 mg /day (RP2D)

An optimal CSF: plasma ratio of 0.9

Safe, No DDIs

Comparable SARs between placebo and vafidemstat arms in 6 Phase II trials

No side effects

No weight gain

No sedation / somnolence

No sexual dysfunction

No extrapyramidal signs

Aggression, a Huge Medical Need in CNS Diseases

Agitation and aggression are common in most psychiatric and neurodegenerative diseases

Clinical data with vafidemstat

AD	Up to **52%** of **Alzheimer's disease** patients show agitation & aggression
ADHD	Up to 50% of Attention Deficit & Hyperactivity patients show agitation & aggression
BPD	**73%** of **Borderline personality disorder** patients engaged in violent behavior in last 1 yr
ASD	**Up to 68%** of **Autistic Spectrum disorder** patients may show agitation & aggression
SCZ	Up to 43% of **Schizophrenia** pooled patients show agitation & aggression

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Vafidemstat Current Clinical Development

- Exploring large multifactorial indications (Borderline Personality Disorder, Schizophrenia and Autism)
- Exploring also feasibility in some rare genetically-driven neurodevelopmental disorders (Phelan McDermid, Fragile X, Kabuki, etc)

Indication	Sponsor	Preclinical	Phase I	Phase II	Phase III	Status/upcoming catalysts
Borderline Personality Disorder (BPD) Agitation/Aggression	Oryzon			PORTICO-2	Submitted	Phase III in preparation
Schizophrenia Negative Symptoms / Positive Symptoms / CIAS	Oryzon			EVOLUTION		EU expansion in 2026; readout in 2H2027
Autism Spectrum Disorder (ASD) Aggression / Repetitive Behavior	Oryzon			HOPE-2		PhII in preparation; to initiate in 1H2026

Vafidemstat Demonstrated a Relevant Clinical Benefit in Reducing Agitation /Aggression across ASD, ADHD and BPD Patients in PoC Phase IIa Study

PCN Psychiatry and Clinical Neurosciences

Regular Article | Open Access

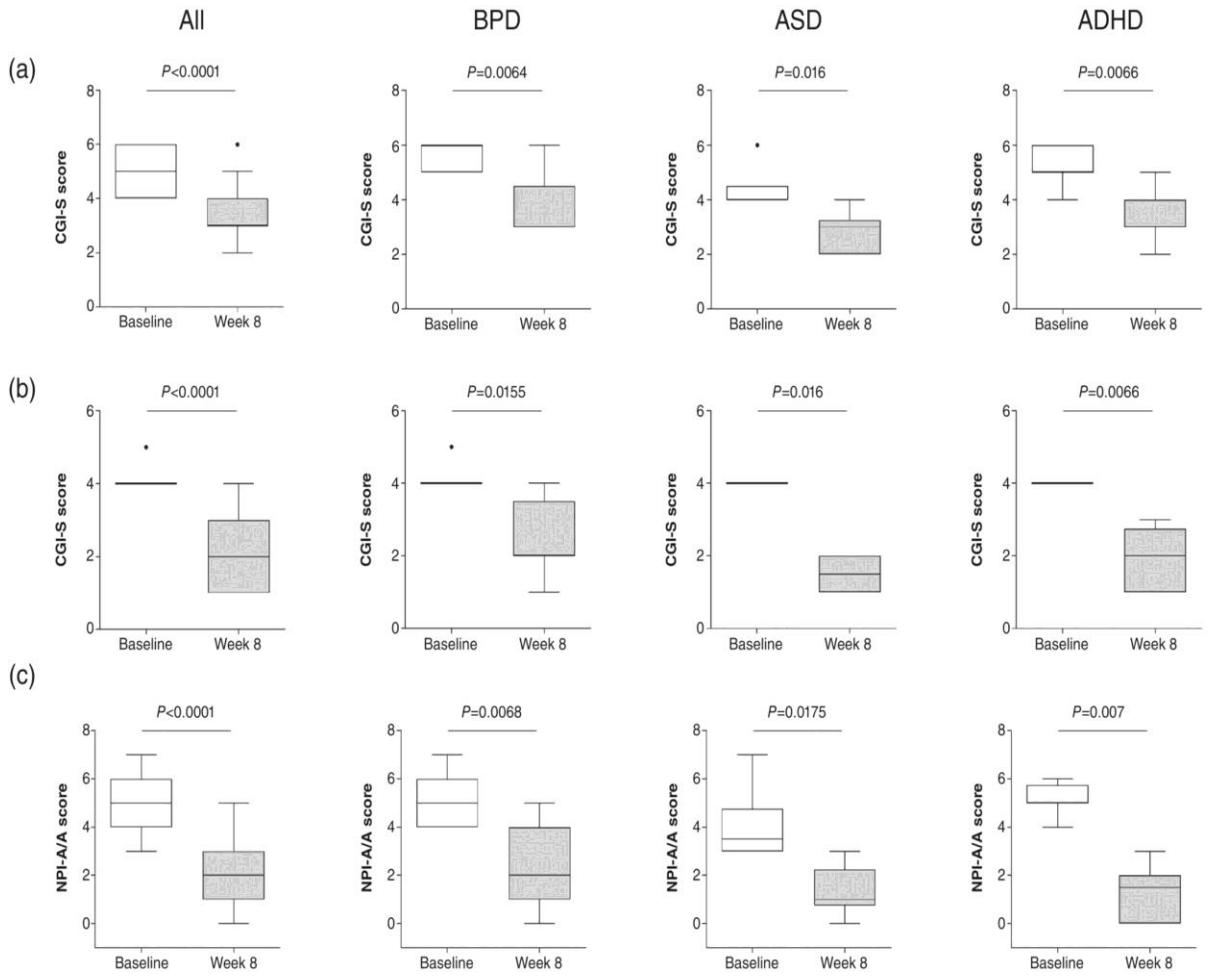
REIMAGINE: A central nervous system basket trial showing safety and efficacy of vafidemstat on aggression in different psychiatric disorders

Marc Ferrer MD, PhD, Vanesa Richarte MD, PhD, Laura Gisbert MD, PhD, Jordi Xaus PhD, Sonia Gutierrez BSc, MSc, Maria Isabel Arevalo PhD, Michael Ropacki MA, PhD, Roger Bullock MD, Carlos Buesa PhD, Josep Antoni Ramos-Quiroga MD, PhD

First published: 12 February 2025 | https://doi.org/10.1111/pcn.13800

Clinical Trial Registration: REIMAGINE EudraCT#: 2018-002140-88.

Eight-week vafidemstat treatment led to a statistically significant reduction in agitation/aggression compared with baseline across all assessments (all participants, $p < 0.0001$)



ASD: Autism Spectrum Disorder ADHD: Attention deficit & Hyperactivity Disorder
BPD: Borderline Personality Disorder

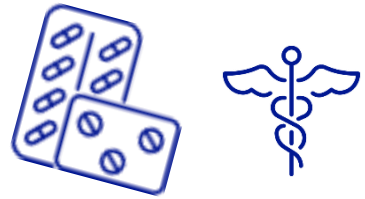
Borderline Personality Disorder: an Unmet Medical Need & Vast Commercial Opportunity (+$3Bn)

Prevalent & impairing disease

9 million in US & EU

Two main types of symptoms

Psychiatric symptoms
+
Agitation/Aggression
(including self-aggression)



No approved drugs yet

Patients on off-label anti-psychotics

Vafi improves these symptoms in:
- BPD patients
- PC models

Oryzon is leading the BPD field ahead of the competition

PORTICO: a Global Phase IIb Randomized, Placebo-Controlled, Double Blinded Trial in BPD to Inform Subsequent Development

Key inclusion criteria

Men and women 18-65 years of age

DSM-5 BPD diagnostic criteria, at least 3 months before the Screening visit.

Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR) Agitation & Aggression (A/A) subscale score of ≥ 16 (severity x frequency) summed across the 4-items comprising the A/A subscale, and the sum of the A/A subscale severity scores ≥ 6

Stable regimen of background pharmacotherapy at Screening, Baseline and throughout the trial

Maintenance of pre-screening psychotherapy schedule throughout the trial

Willing and able to adhere to the protocol prohibitions, restrictions and requirements

N=211
Randomized
1:1

Vafidemstat, 1.2mg
Once daily (5 ON, 2 PBO), N=106

Placebo
Once daily, N=105

14-week trial

Endpoints

Primary:

Agitation/Aggression (CGI-S A/A) from baseline to weeks 8-12

Improvement in Borderline Personality Disorder Checklist (BPDCL) from baseline to weeks 8-12

Secondary (efficacy):

To evaluate the change over time on the CGI-S A/A

To evaluate the change over time on the BPDCL

To evaluate the difference on the following measures, from baseline to weeks 8-12, as well as change over time, between the active treatment arm and the placebo arm:

- Borderline Evaluation of Severity over Time (BEST)
- State-Trait Anger Expression Inventory 2 (STAXI-2)
- State-Trait Anxiety Inventory (STAI)
- Beck Depression Inventory – II (BDI-II)

PORTICO final results presented at **ECNP-2024**

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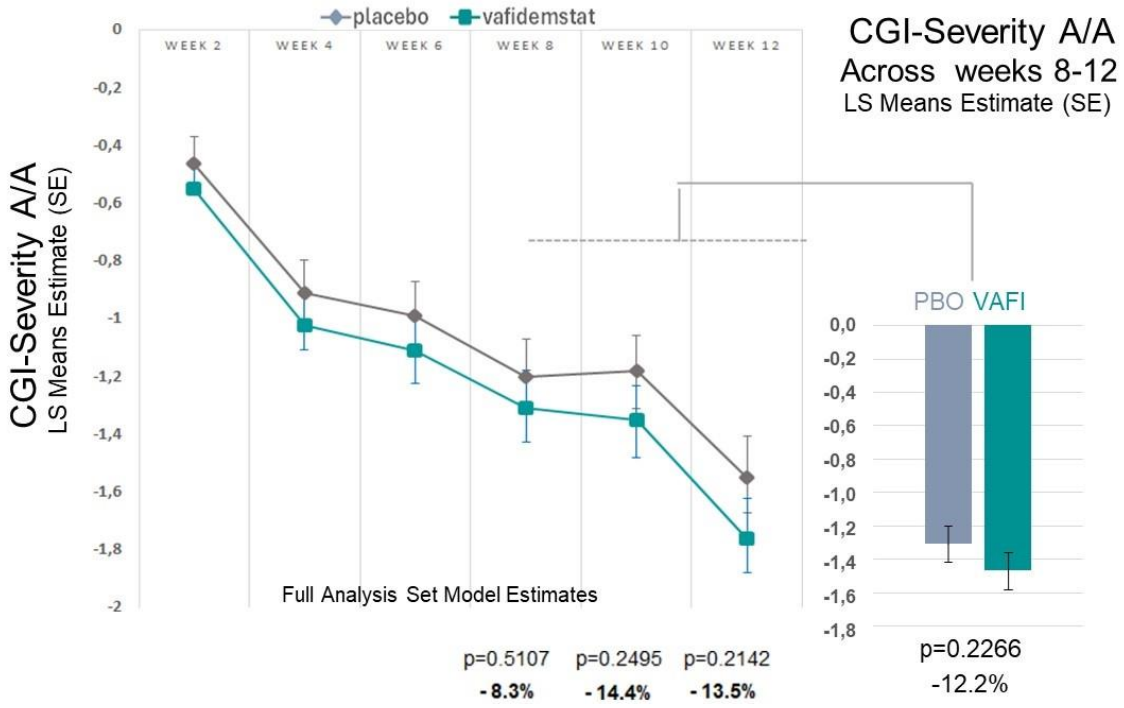
PORTICO: Vafidemstat Improves Aggression Over Placebo (Secondary Endpoint)

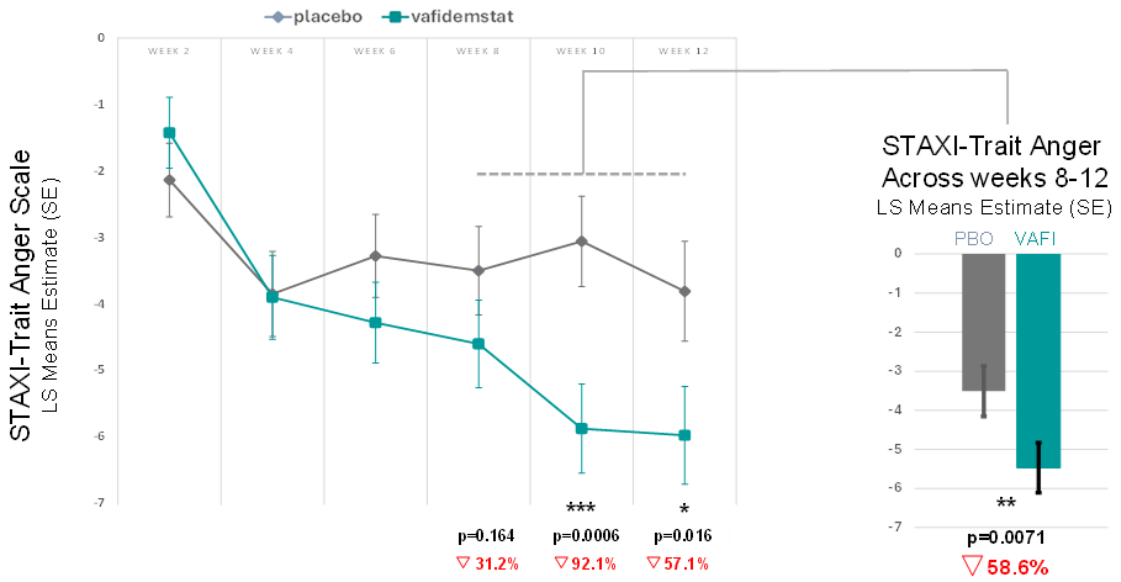
"STAXI allows us to effectively and efficiently know if someone is getting better over the course of the trial and in ways that are highly relevant to the clinical work with BPD" - Sarah Fineberg, M.D., Ph.D.

Yale University School of Medicine

Primary endpoint
CGI-S A/A (Clinician rated)



Secondary endpoint
STAXI-2 Trait Anger (Patient rated)



PORTICO: Vafidemstat was Safe and Well Tolerated

Vafidemstat-treated patients showed a reduced inclination towards self-harm

Treatment-Emergent Adverse Events by Preferred Term Occurring in > 5% of Subjects	Placebo (N=104) N (%), e	Vafidemstat (N=106) N (%), e
TEAEs by Preferred Term	68 (65.4%), 214	61 (57.5%), 192
Headache	17 (16.3%), 18	13 (12.3%), 16
Nasopharyngitis	18 (17.3%), 22	9 (8.5%), 11
Tension Headache	6 (5.8%), 17	5 (4.7%), 11
Platelet Count Decreased	1 (1.0%), 1	8 (7.5%), 8*
Nausea	2 (1.9%), 2	6 (5.7%), 6
Intentional Self-Injury	6 (5.8%), 10	1 (0.9%), 2

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* *7 cases of numerical, clinically insignificant, and transient platelet (PLT) reductions & 1 transient and rapidly self-resolved thrombocytopenia (TP) grade 1*

Vafidemstat: Summary and Next Steps

End-of-Phase II Meeting with FDA resulted in positive feedback:

- Agitation-Aggression in BPD acknowledged as a possible therapeutic indication
- FDA feedback supports initiation of a Phase III trial (PORTICO-2) using STAXI-2 Trait Anger as a primary efficacy endpoint measure, but additional information was requested regarding the face validity of the proposed endpoints.
- Secondary endpoints will include patient-rated and clinician-rated scales to assess agitation/aggression and overall BPD improvement

Phase III Protocol submitted after further constructive interactions with the agency:

- In response, the company convened a panel of renowned U.S. experts (including Dr Alan F. Schatzberg, Dr. Eric Hollander, Dr Emil F. Coccaro and Dr Sarah Finneberg) to contribute to the design of the Phase III protocol.
- As per FDA suggestions, the initial design was modified to incorporate a key secondary endpoint, the Overt Aggression Scale-Modified, OAS-M, a well-validated ClinRO shown to reliably measure reductions in aggression in patients receiving pharmacological treatment. Importantly, this scale has a strong psychometric correlation with the proposed primary endpoint, the STAXI-2 Trait Anger scale.
- Phase III protocol also included Qualitative research and Psychometric analyses following FDA recommendations
- **FDA's feedback received on Oct 16th**

Next Step:

Company to address FDA's comments and resubmit protocol

New and Prestigious US-centric Clinical Advisory Board for CNS

Alan F. Schatzberg

Stanford MEDICINE

Alan F. Schatzberg renowned American psychiatrist. Since 1991, he has been the Kenneth T. Norris Jr . Professor of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. He was chair of the department Psychiatry and Behavioral Sciences at Stanford from 1991 to 2010. He is also the co-editor-in-chief of the Journal of Psychiatric Research. Alan Schatzberg, was the principal investigator for mifepristone for use as an antidepressant developed by Corcept Therapeutics, a company Schatzberg had founded.

Eric Hollander, M.D.

EINSTEIN
Albert Einstein College of Medicine

Eric Hollander, M.D. is Professor, Department of Psychiatry and Behavioral Sciences at Albert Einstein College of Medicine in NYC. Director, of the Autism and Obsessive Compulsive Spectrum Program, Department of Psychiatry and Behavioral Sciences.

Dr. Emil F. Coccaro

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Dr. Emil F. Coccaro is a psychiatrist in Columbus, Ohio and is affiliated with Ohio State University Wexner Medical Center. He received his medical degree from New York University Grossman School of Medicine and has been in practice for more than 20 years. He is an expert in Aggression and has contributed to The Overt Aggression Scale Modified (OAS-M) for clinical trials targeting impulsive aggression and intermittent explosive disorder.

Dr. Sarah Fineberg

Yale University
School of Medicine

Dr. Sarah Fineberg is Assistant Professor of Psychiatry at Yale University investigating the neurobiological mechanisms behind borderline personality disorder (BPD) and related mental health conditions. She has participated in several BPD clinical trials.

New Senior Advisory Board to Strengthen our CNS Program

Iman Barilero

Senior Regulatory Affairs Advisor

Dr Iman Barilero is a biopharmaceutical executive with over 30 years of global leadership in regulatory affairs and drug development.

She served as **Vice President, Head of Global Regulatory Science for CNS at Lundbeck,** where she led global regulatory strategies for breakthrough therapies targeting **depression, bipolar disorder, schizophrenia, stroke,** and other.

She had previous regulatory responsibilities at **J&J and Roche.** Her expertise includes direct engagement with major health authorities such as the FDA, EMA, and other.

Raymond Sanchez

Senior Strategy & Clinical Development Advisor

Dr. Raymond Sanchez is a psychiatrist and Pharma executive with more than twenty years of industry experience in psychiatry.

Dr Sanchez has played a key role in the development and **global approval of drugs such as *Abilify, Abilify Maintena, Rexulti*** among others.

Dr Sanchez was the **Chief Medical Officer of Cerevel Therapeutics**, focused on the development of novel treatments in Neuro-Psychiatry, until August 2024 when Cerevel was acquired by AbbVie for $8.7 billion.

He is now a Senior Advisor at Bain Capital Life Sciences as well as a Board member for several organizations**.**

Christopher Breder

Senior Strategy & Clinical Development Advisor

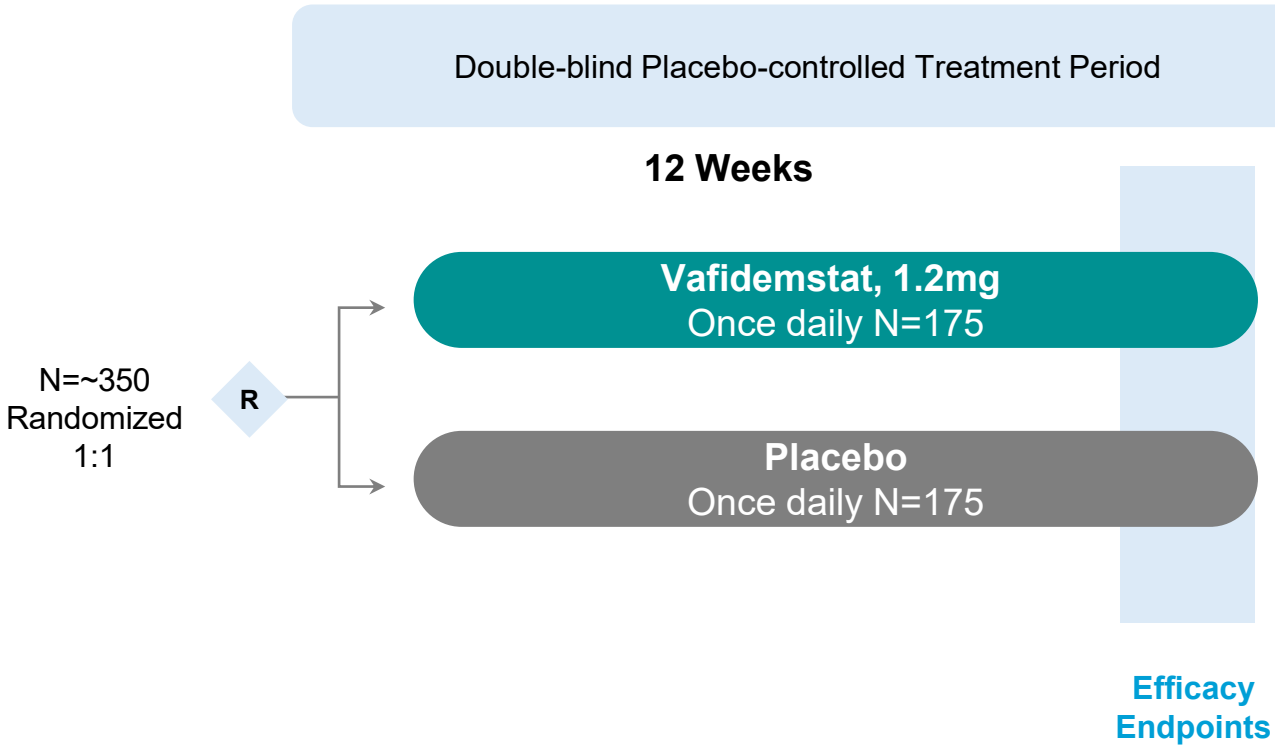
Dr Christopher Breder is a physician-scientist with extensive experience in both the pharmaceutical industry and the FDA, spanning drug development, regulatory affairs, and clinical research across neurology, psychiatry and rare diseases.

As **a Medical Officer at the FDA (2009-2019), he contributed to the review of numerous INDs and new drug and biologic application approvals in neurology, anesthesiology and rare diseases**.

He has held senior clinical development and strategic leadership roles at **Sunovion, Supernus and Bristol Myers Squibb,**

Vafidemstat: PORTICO-2 Phase III Study Proposed Design

Aggression: Primary endpoint (STAXI-2 Trait Anger) + Key Secondary endpoint (OAS-M)



Endpoints

Primary:
Efficacy in Agitation-Agression by STAXI-2 Trait Anger

Key Secondary:
Efficacy in Agitation-Aggression by OAS-M (ClinRO FDA accepted scale)

Secondary:
Efficacy improvements in:

- Overall improvement by BEST
- Overall improvement by CGI-S
- Depression by BDI-II

Safety

Exploratory:

- PK
- Target Engagement
- Exploratory biomarkers
- Genetic Polymorphisms

Expanding Aggression Program: New Trials Under Preparation in ASD

To be conducted initially in Spain financed through the EU-IPCEI grant (13.1 Million Euros)

Phelan-McDermid Syndrome (PMS)

A rare genetic condition (prevalence estimate 1/30,000 births) primarily caused by a terminal deletion on chromosome 22q13.

Aggressive behavior is seen in approximately 25% of affected individuals.

Idiopathic ASD

Up to 68% of ASD patients may show agitation & aggression

Aggression is one of the reasons why young patients with ASD are institutionalized as adults

Exploring strategic collaborations with biotech companies to leverage AI platforms to select patients most likely to benefit from vafidemstat

Schizophrenia Still an Enormous Unmet Medical Need

Despite the approval of Cobenfy (BMS) for positive symptoms, addressing negative or cognitive symptoms, as well as treatment-resistant schizophrenia, remains a significant challenge in managing this disease

A prevalent & impairing disease
20 million ww.

~5 million in
US & EU

Three main types of symptoms

Positive or Negative +
Cognitive Impairment

No approved drugs yet for Negative Symptoms or Cognitive Impairment

Vafi improves these
symptoms in PC models

Total Addressable Market in 2024

US$ +10
billion

Highest Revenue Drug Category long-acting injectable (LAI) antipsychotics

Single Best seller: + $4.1 Billion
Cobenfy expected peak sales + 6 Bn

Moderate competition

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Vafidemstat in Schizophrenia (SCZ)

Genetic link between LSD1 and SCZ

Preclinical in-vitro and animal models data supporting LSD1 inhibition as a new MoA in SCZ

No approved drugs yet in negative symptoms or Cognitive Impairment symptoms

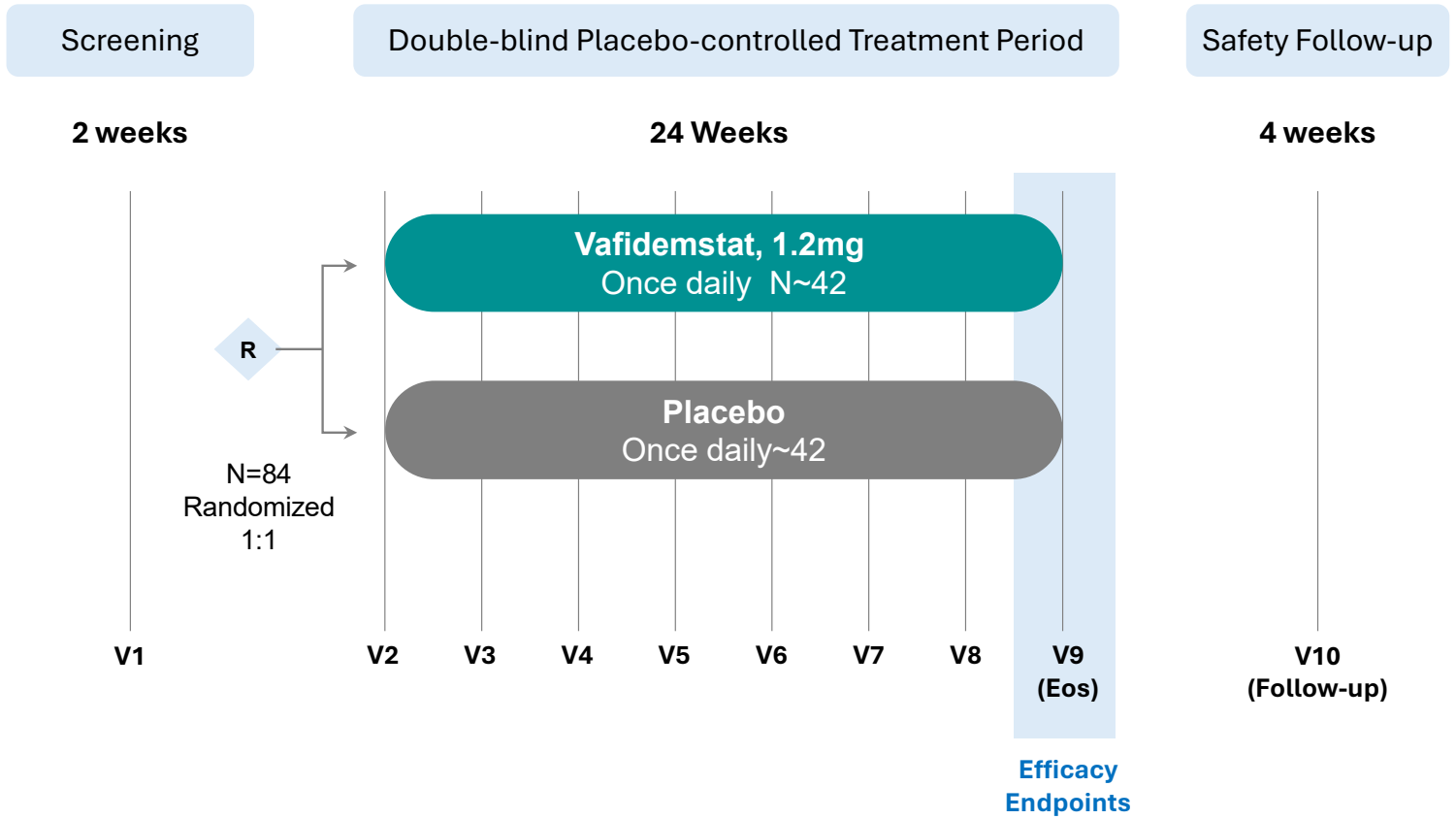
Strong market interest in Schizophrenia

EVOLUTION Phase IIb – a Real-World Trial

- **EVOLUTION** is designed as a **real-world trial**, with inclusion and exclusion criteria crafted to permit comorbidities, provided they are stable and/or under treatment.
    - Participants must present with predominant negative symptoms (PNS) of schizophrenia.
    - All enrolled subjects must be on stable treatment for schizophrenia, receiving no more than one atypical antipsychotic to manage psychotic symptoms. Long-acting injectable (LAI) formulations are permitted. The concomitant use of a second antipsychotic is not allowed.
    - 24 weeks of treatment to assess possible variation on CIAS
- A high-quality trial designed to meet the standards of registrational studies in the indication: multicenter, double-blind against a control arm, with regulatory-accepted endpoints

EVOLUTION: A Phase II Study to Measure Negative Symptoms in SCZ

Recruitment ongoing in Spain. Trial expansion unfolding in Eastern Europe countries



Readout: expected in 2027

Endpoints

Primary:
Improvement in Negative Symptoms

Secondary - Efficacy
Improvements in:

- Cognitive impairment associated with SCZ (CIAS)
- Positive symptoms for SCZ
- Positive and Negative Syndrome Scale (PANSS) Total Score
- Functional impairment in adult SCZ patients

Secondary - Safety:
To evaluate vafidemstat safety in adult SCZ patients

IADADEMSTAT

A Phase II LSD1 inhibitor for oncological and hematological diseases

Iadademstat: First and Potentially Best-in-Class LSD1 Inhibitor for Hematological Diseases

The Asset

- The most potent (nM) oral LSD1 inhibitor in clinical development
- Safety profile well-established: ~200 pts treated with iadademstat in multiple Phase I/II trials

Mechanism of Action

- LSD1 is required for leukemic stem cell survival and blocking leukemic cell differentiation
- Iadademstat prevents leukemic stem cell survival and promotes rapid differentiation/death of leukemia cells

Cancer Cell
A Cell Press journal

ARTICLE · Volume 33, Issue 3, P495-511.E12, March 12, 2018 · *Open Archive* Download Full Issue

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

Tamara Maes [1,6] · Cristina Mascaró [1] · Iñigo Tirapu [1] · … · Matthew Fyfe [1] · Julio Cesar Castro-Palomino [1] · Carlos Buesa [1] …
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First-in-Human Phase I Study of Iadademstat (ORY-1001): A First-in-Class Lysine-Specific Histone Demethylase 1A Inhibitor, in Relapsed or Refractory Acute Myeloid Leukemia

Authors: Olga Salamero, MD, Pau Montesinos, MD, Christophe Willekens, MD, José Antonio Pérez-Simón, MD, PhD, Arnaud Pigneux, MD, PhD, Christian Récher, MD, PhD, Rakesh Popat, MB, BS, PhD, … SHOW ALL … , and Tim C. P. Somervaille, MBBS, PhD | AUTHORS INFO &

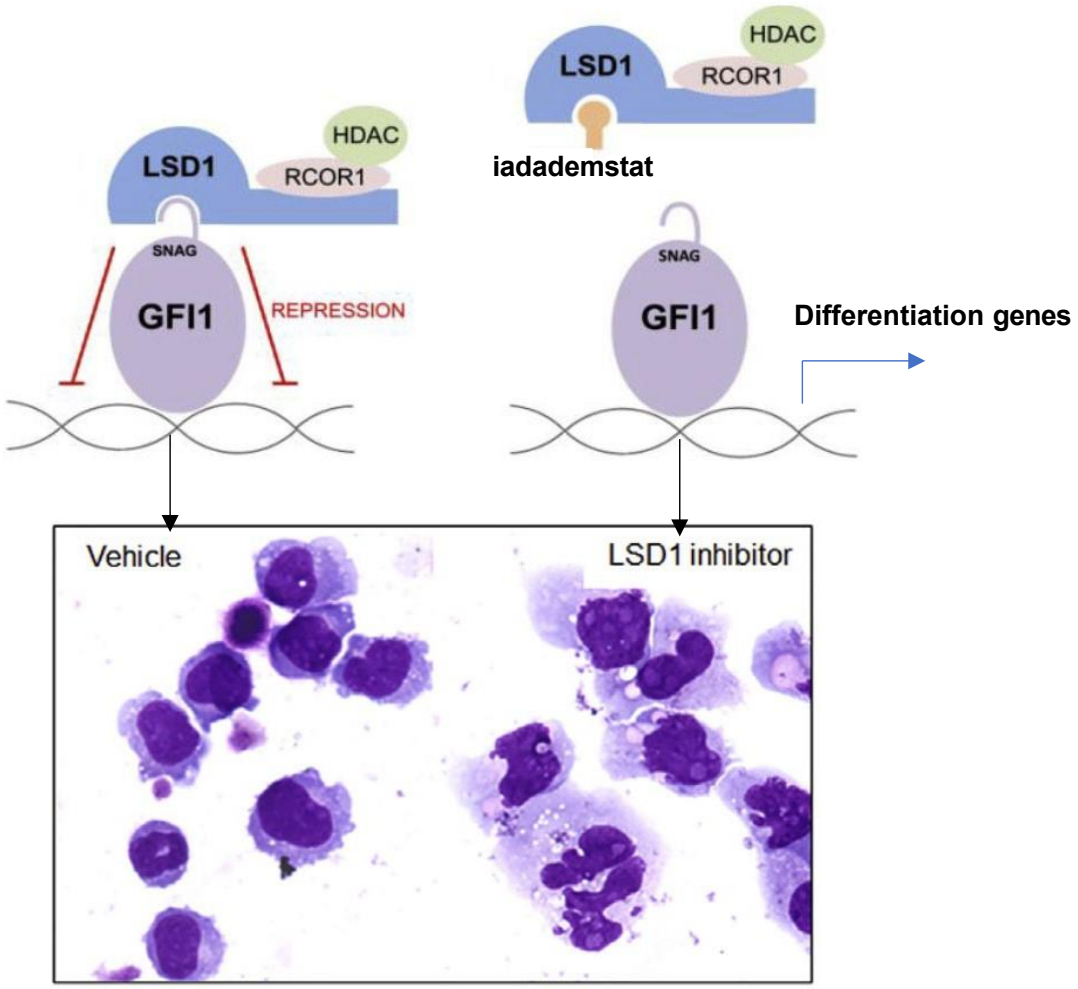
THE LANCET
Haematology

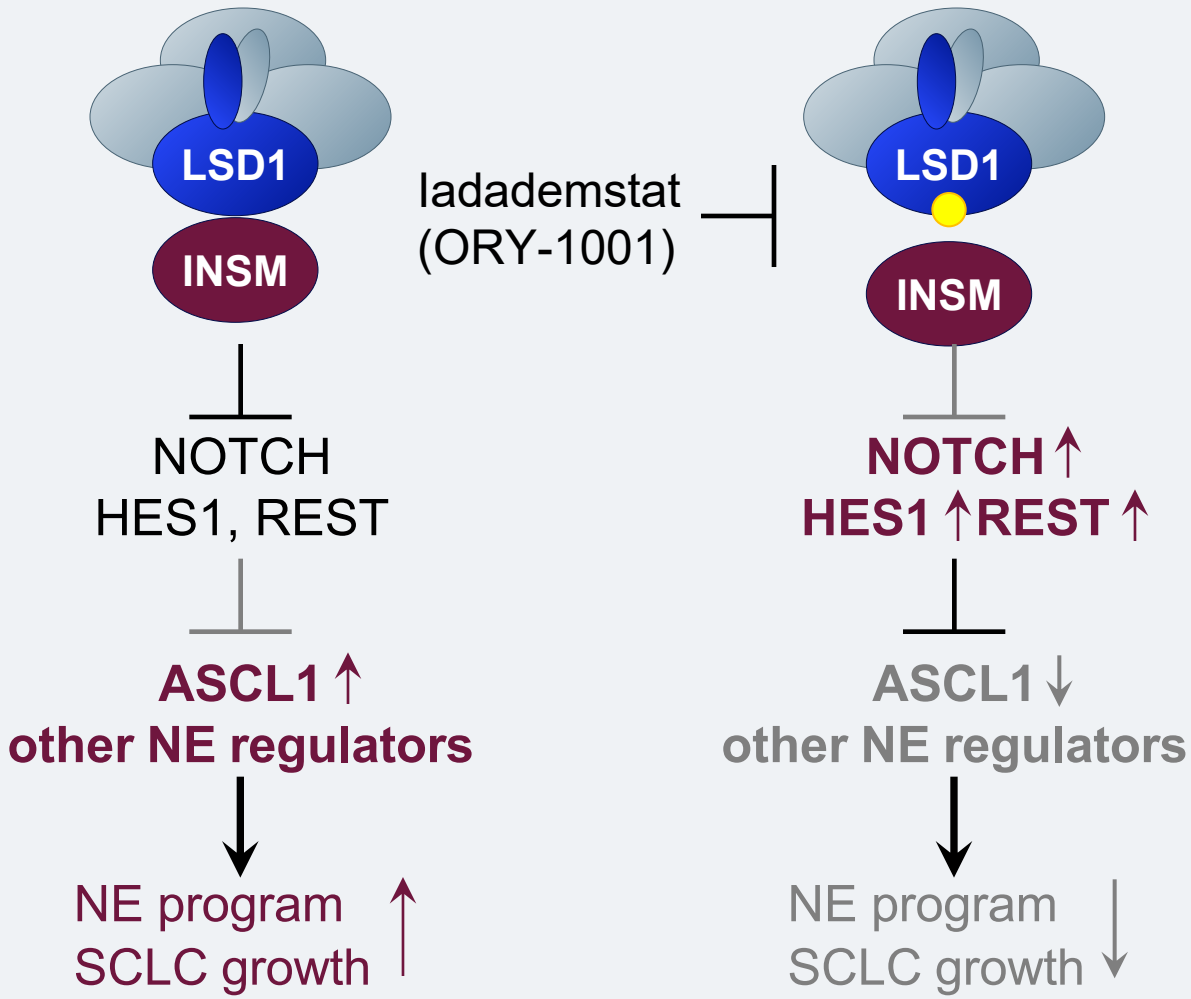
ARTICLES · Volume 11, Issue 7, E487-E498, July 2024 Download Full Issue

Iadademstat in combination with azacitidine in patients with newly diagnosed acute myeloid leukaemia (ALICE): an open-label, phase 2a dose-finding study

Olga Salamero, MD [a] · Antonieta Molero, MD [a] · José Antonio Pérez-Simón, MD [b] · Montserrat Arnan, MD [c] · Rosa Coll, MD [d] · Sara Garcia-Avila, MD [e] · et al. Show more

MoA is Well Characterized and Understood





Modified from:
Maiques-Díaz et al. 2018, Cell Reports

Iadademstat in Oncology and Hematology: Multiple Opportunities Leveraging CRADA-NCI Agreement

Indication	Sponsor	Preclinical	Phase I	Phase II	Phase III	Status/Upcoming catalysts*
Acute Myeloid Leukemia (AML) 1L unfit patients: combination w/ azacitidine	Oryzon	ALICE				Completed. Published (Lancet Hematol)
1L AML unfit patients: combination w/ azacitidine + venetoclax	OHSU	IIS-ALICE-2				EHA-ASH 2026
1L AML unfit patients: combination w/ azacitidine + venetoclax	NCI	CRADA-AML				
Refractory/Relapsed AML FLT3 mutation+ pts, combination w/ gilteritinib	Oryzon	FRIDA				Fully accrued. EHA-ASH 2026
Myelodysplastic Syndrome (MDS) combination w/ azacitidine	MCW	IIS-X005				EHA-ASH 2026
MPN: combination w/ ASTX727	NCI	CRADA-MPN				EHA-ASH 2026
Extensive-Disease Small Cell Lung Cancer (ED-SCLC) 1L patients: combination w/ ICI	NCI	CRADA-SCLC				ESMO 2026
Sickle Cell Disease (SCD)	Oryzon	RESTORE				EHA-ASH 2026
Essential Thrombocythemia (ET)	Oryzon	IDEAL				PhII protocol submitted. ASH 2026

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IIS: investigator-initiated study
MPN: myeloproliferative neoplasm

**Tentative meetings listed*

Hematology Program: Malignant and Non-Malignant Indications Investigated

AML 1L

- Encouraging data in Unfit population in combo with azacitidine
- Efficacy in unfit populations poorly responding to Ven-Aza
- **Safe** and preliminary **strong data** in triple combo Ven-Aza-Iada (ASH-2025)

AML R/R Flt3+

- Phase Ib ongoing US
- **Encouraging data** in combination with gilteritinib (ASH-2025)
- **Fully accrued**

Presented at ASH-2025

HR MDS

- Phase I ongoing US (single Institution)
- **Encouraging preliminary data**

MPNs and ET

- Phase II in combination with ASTX727 in proliferating MPNs (CRADA). **Recruiting**
- Phase II in HU-resistant /intolerant ET. **Submitted to EMA**

ET: Fast Follower strategy

SCD

- Phase Ib in SCD approved by EMA; **recruiting**
- PoM & superiority demonstrated in the most relevant and predictive animal model
- Potential for accelerated development*

SCD: PoC clinical activity in 1H2026

**Potential for accelerated approval based on biomarker (HbF)*

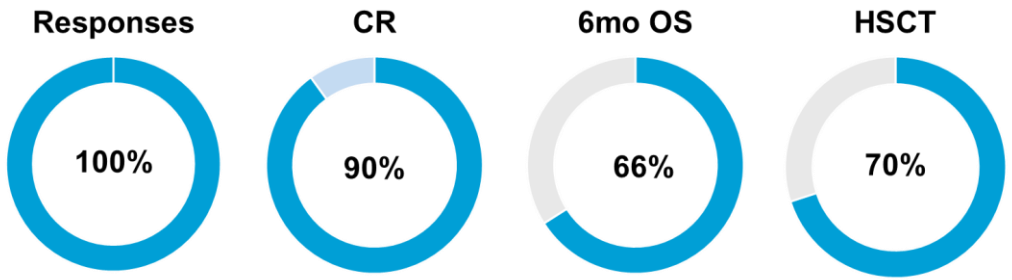
Iadademstat, a pipeline in a single asset

Iadademstat Combinations in AML are Highly Encouraging

IADADEMSTAT

+ Venetoclax and Azacitidine	+ Gilteritinib	+ Azacitidine	+ ASTX727 (decitabine+ cedazuridine)	+ Venetoclax and Azacitidine
1L Unfit AML	R/R AML flt3+	HR MDS	MPN	**1L Unfit AML**
OHSU-sponsored study (ALICE-2). Enrolling, 10 patients (ASH poster). 2 iada doses tested. Safe (1 DLT of colitis)	FRIDA. 4 iada doses tested in escalation phase. Ongoing in expansion, fully accrued	MCW-sponsored study. Enrolling. Safe, no DLTs; Signs of efficacy	NCI-NIH CRADA study. Enrolling	NCI-NIH CRADA study. Enrolling

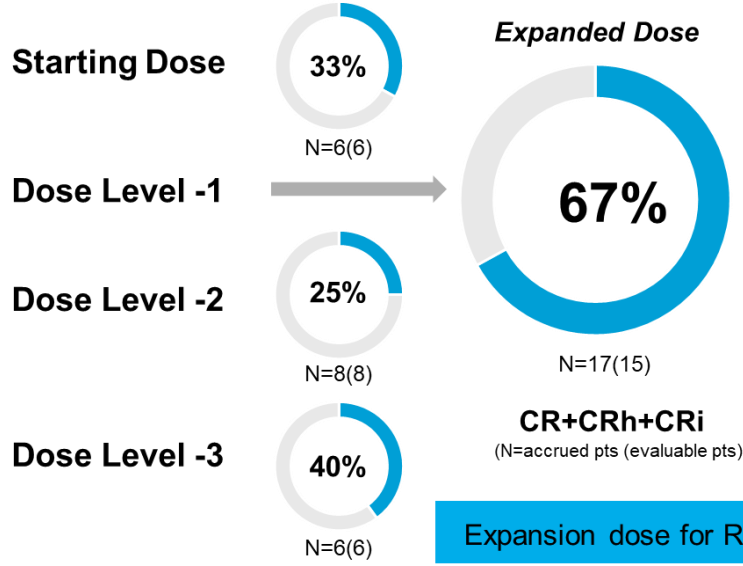
Triple Combo Iada-Ven-Aza in First Line AML



ALICE-2

C. Lachowiez et al ASH 2025

FRIDA

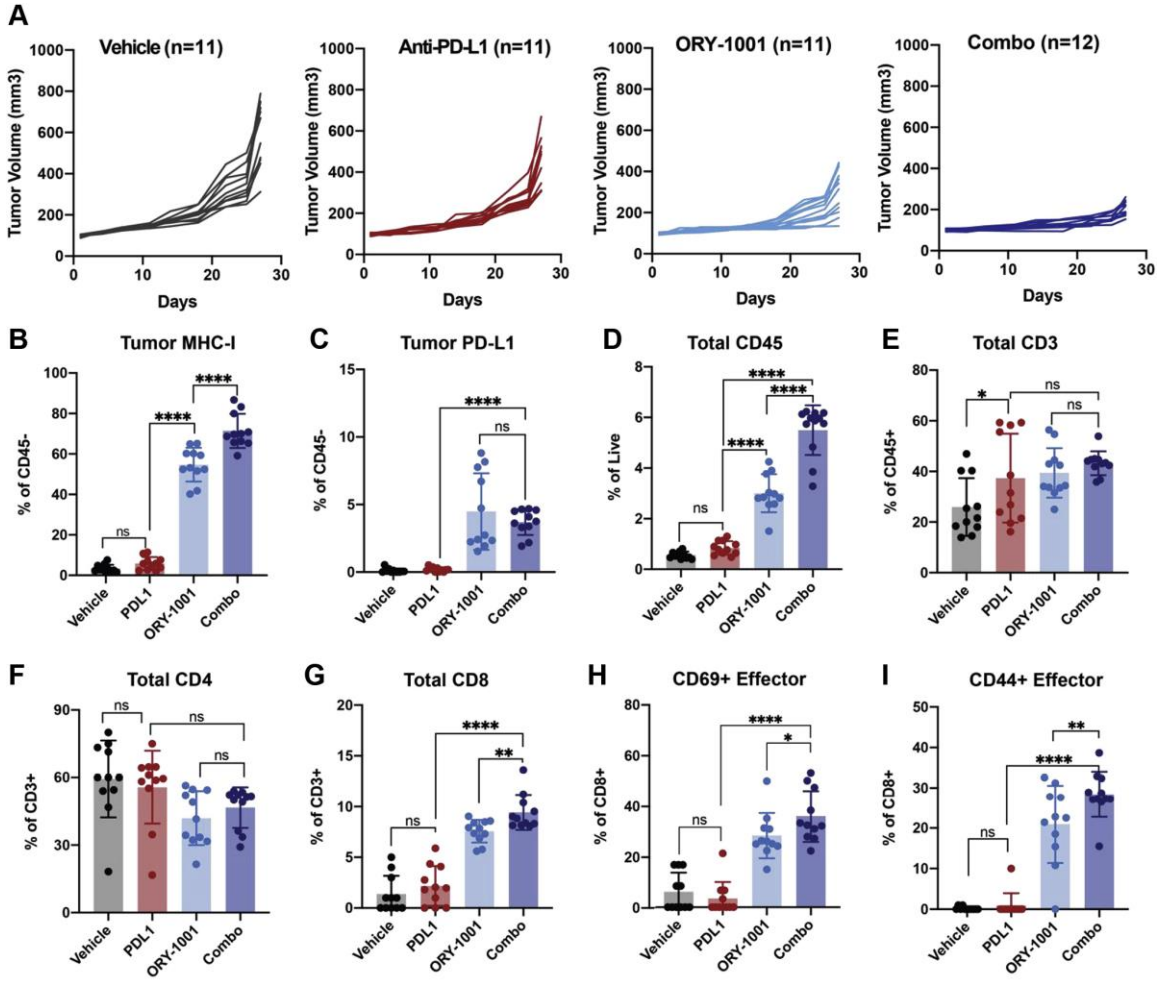


Expansion dose for RP2D selected

S. Venugopal et al, ASH2025

SCLC: Iadademstat and anti-PD-L1 Combination Inhibits SCLC Progression in Preclinical Model

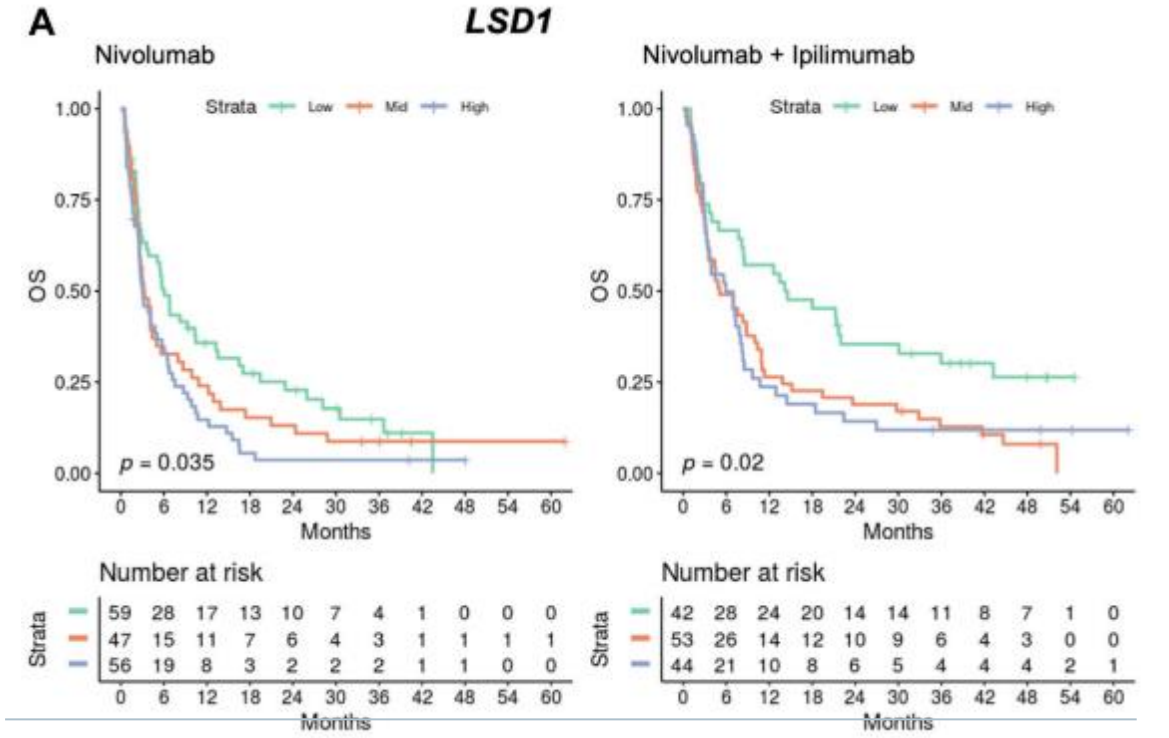
- Iadademstat renders the SCLC cells visible to the immune system
- Iadademstat synergizes with ICIs and boosts the host immune system by increasing T cell infiltration and preventing T-cell exhaustion



ORYZON

Nguyen et al., 2022

Memorial Sloan Kettering Cancer Center



Analysis of epigenetic determinants of antigen presentation identified LSD1 gene expression as a correlate of worse survival outcomes for patients treated with either nivolumab or the combination of nivolumab and ipilimumab

Rudin et al., 2023

Memorial Sloan Kettering Cancer Center

CRADA-NCI: Ongoing Phase I/II SCLC Trial in Combination with ICI

Testing the Combination of an Anti-cancer Drug, Iadademstat, With Other Anti-cancer Drugs (Atezolizumab or Durvalumab) at Improving Outcomes for Small Cell Lung Cancer

ClinicalTrials.gov ID: NCT06287775

Sponsor: National Cancer Institute (NCI)

Led by Dr. Charles Rudin

Memorial Sloan Kettering Cancer Center

RECRUITING

More than 30 sites accross the U.S., including:

- MSKCC
- JHU/ Sidney Kimmel Comprehensive Cancer Center at the John Hopkins
- Ohio State Univ Cancer Center
- City of Hope Cancer Center
- UPCI (University of Pittsburgh)
- Yale University

Enrollment (Estimated)

45-50 pts

Primary Objective

To compare the progression-free survival (PFS) between the combination of iadademstat plus immune checkpoint inhibitor (ICI) versus ICI maintenance alone.

Secondary Objectives

- To compare objective response rate (ORR) and overall survival (OS) between treatment arms.
- To evaluate the safety of combination iadademstat plus ICI.

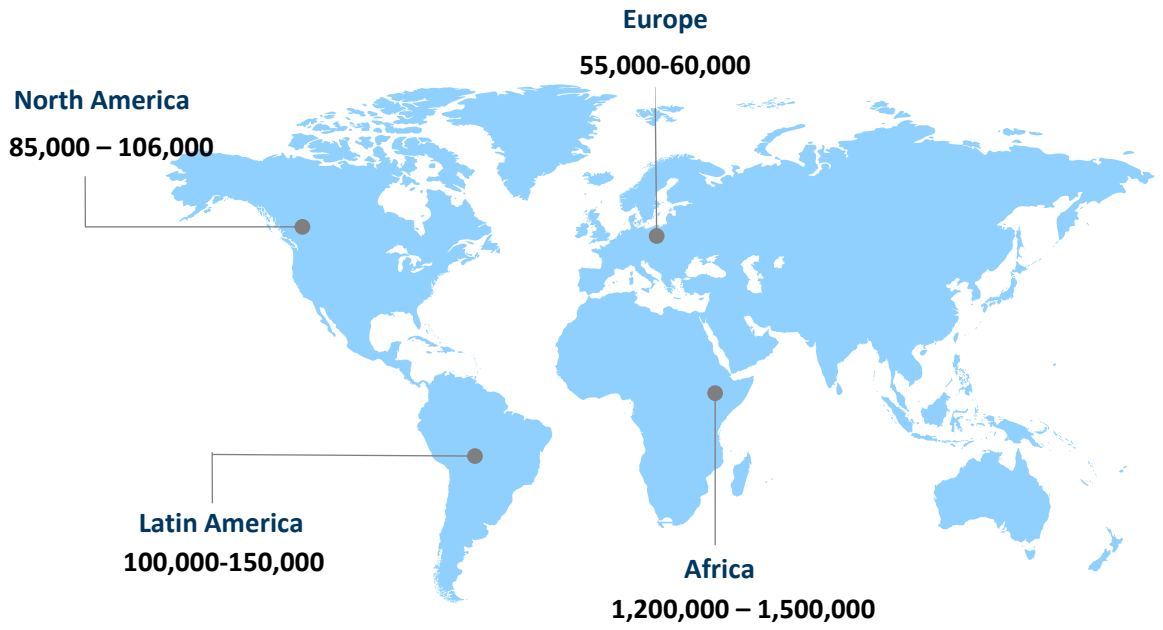
NIH NATIONAL CANCER INSTITUTE
DCTD Division of Cancer Treatment & Diagnosis

Non oncological hematological disorders: SCD and ET

Sickle Cell Disease Prevalence

Around 20-25 million people are living with SCD across the globe and the number is anticipated to increase by 30% by 2050. SCD accounts for approximately 305,773 births per year worldwide

Prevalence of Sickle Cell Disease	
Country	**Prevalence**
U.S.	80,000-100,000
Canada	5,000-6,000
U.K.	14,000-15,000
Italy	2,000-2,500
Brazil	30,000-35,000
Saudi Arabia	145,000-150,000
Kingdom of Bahrain	17,000-18,000



Number of Sickle Cell Births Per Year	
Country	**No. of SCD Birth/Year**
U.S.	3,000
India	5,200
U.K.	270
Nigeria	91,011
Tanzania	11,877
Angola	9,017
Uganda	10,877
Ghana	5,815
Niger	5,310
Zambia	6,039
Cameroon	7,712
Global	305,773

Source: United Nations, CDC, Sickle Cell Society, NCBI, MTS Sickle Cell Foundation, Inc., Fortune Business Insights Analysis

Strong Activity and High Interest from Leading Pharma Companies

USA average annual direct healthcare costs per adult patient year is > $100,000, Annual US healthcare costs are > $2 B

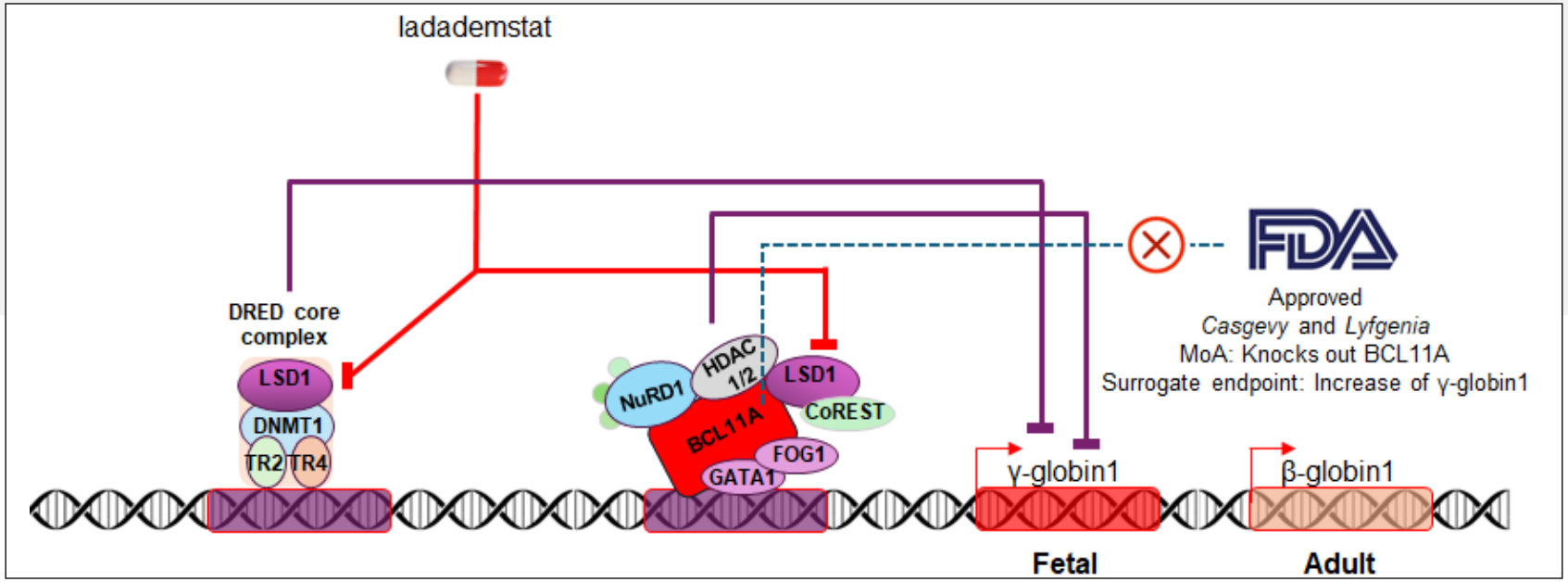
- 2019: Oxbryta received accelerated FDA approval
- 2022: Oxbryta achieved $328 million in U.S. sales
- Pfizer demonstrated in 2yr a significant market opportunity in sickle cell disease (SCD)

Global Addressable Patient Population In Developed Countries
~320,000

Bristol Myers Squibb
NOVARTIS
Pfizer
AMGEN
novo nordisk
Roche

Iadademstat MoA in Sickle Cell Disease: An FDA-approved MoA

LSD1 is a component of the protein complexes that repress *HBG1/2* transcription. Iadademstat may restore *HBG1/2* expression by inhibiting these repressive complexes



Strong Preclinical Data

- In rodents
- In Baboons in single dose
- In Baboons in long term dosing
- In ex-vivo human blood

Modified from:

- Suzuki et al.. *Fetal globin gene repressors as drug targets for molecular therapies to treat the β-globinopathies*. Molecular and Cellular Biology. 2014 Oct;34(19):3560-3569. DOI: 10.1128/mcb.00714-14.
- *Paikari, A., Sheehan, V. Fetal haemoglobin induction in sickle cell disease*. Br J Haematol 2018, 180(2): 189-200. *DOI 10.1111/bjh.15021*

An Open-label Phase Ib in SCD (RESTORE Trial) Approved by EMA

First patient enrolled in Q3 2025; PoC clinical activity expected in 2026

RESTORE

Sponsor: Oryzon

n~24-30, escalation up to n=18, expansion n=12

Open-label, up to 24 weeks treatment

Dose escalation, followed by dose expansion at RP2D

Endpoints

Primary:
Safety and tolerability, RP2D

Secondary:
HbF induction, PK/PD, hemolysis markers

Exploratory:
Vaso-occlusive crisis frequency and duration, effect on transfusion, PROs, pharmacogenomics

Status

- Recruiting
- By 1H 2026, we expect to establish safety in this population and obtain Biomarker (HbF) data indicating clinical activity
- By 2H 2026, we expect to have a first assessment of therapeutic efficacy in SCD

Essential Thrombocythemia (ET): A Fast Follower Strategy

Essential Thrombocythemia Overview

- ET is the most common type of myeloproliferative neoplasm (MPN) and increases the risk of serious complications such as stroke, heart attack, and pulmonary embolism.
- The disease affects **~200,000 people in the U.S.**

Mechanism of Action

- LSD1 inhibition blocks the terminal differentiation of megakaryocytes into platelets, leading to a steady reduction in circulating platelet counts.

Competitive Landscape

- MSD published positive Phase II results with bomedemstat, another LSD1i
- MSD initiated a Phase III trial (Shorespan-007) in 2024, with results expected in 2026–2027

Iadademstat Positioning

- Iadademstat is the only advanced LSD1 inhibitor in development across oncology and hematology (Phase Ib and II), with 200+ patients treated.
- A Phase II clinical trial (IDEAL) has been submitted to EMA and is planned to start in 1Q2026 to provide PoC.

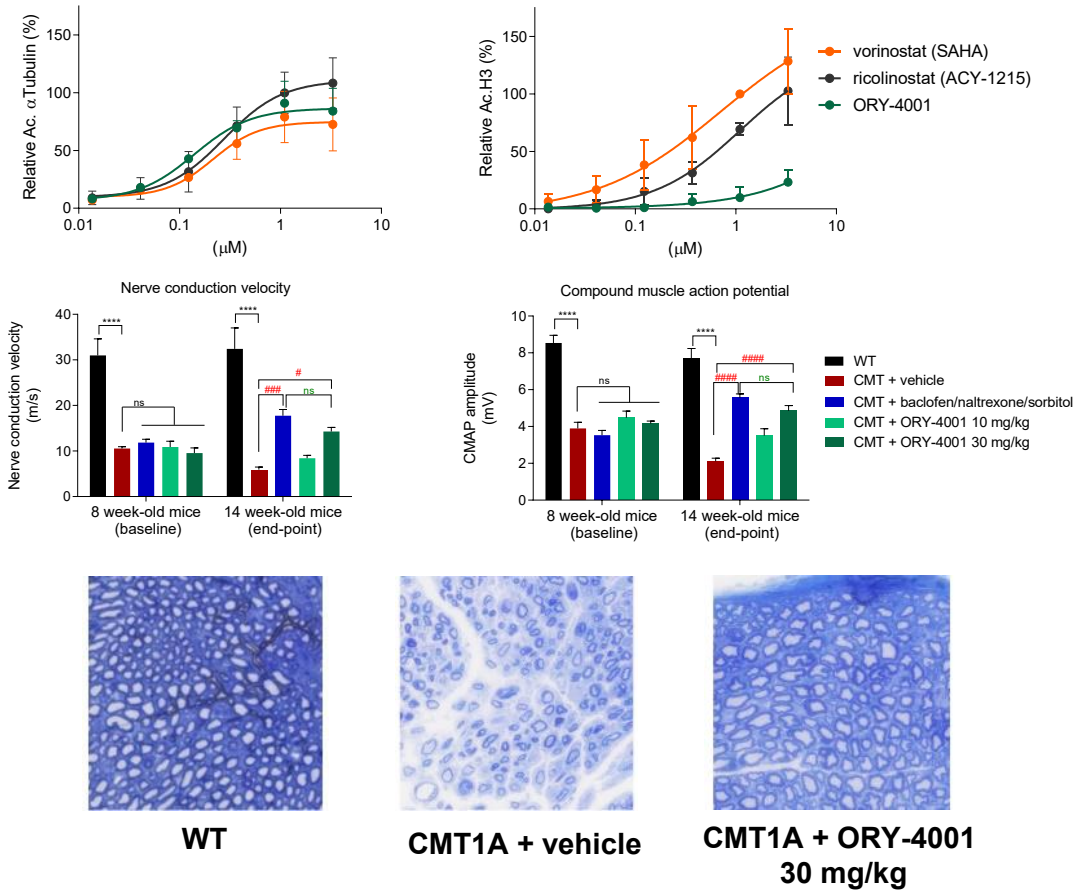
ORY-4001

A selective HDAC6 inhibitor for ALS, CMT and other CNS diseases

ORY-4001 is a highly potent and selective HDAC6 inhibitor

HDAC6 has been suggested as a therapeutic target for Amyotrophic Lateral Sclerosis (ALS), Charcot-Marie-Tooth (CMT), and other CNS diseases

- **Highly potent and selective** HDAC6 inhibitor with good pharmacology
- **Efficacy in a CMT1A model**:
  - increases nerve conduction velocity and CMAP
  - increases axonal number and myelination
- **Efficacy in ALS models** in mice, zebrafish, nematodes, and ALS patient-derived lymphoblasts
- 0.5M USD grant received from the U.S. ALS Association to support regulatory preclinical development in ALS
- First-in-Man readiness expected in 2026
- Available for partnering



Sacilotto N et al. ORY-4001, a novel potent and selective oxadiazole-based HDAC6 inhibitor shows pre-clinical therapeutic efficacy in CMT1A. PNS 2023 annual meeting

Oryzon Uniquely Positioned to Pioneer Epigenetic Drugs

Epigenetics experts specializing in LSD1 Biology

Vafidemstat: Phase III ready LSD1 CNS asset geared toward ameliorating aggression and agitation

Iadademstat: 2nd LSD1 asset developed in multiple hematology and oncology indications

Experienced management team, Board of Directors and world-renowned clinical experts

Robust financial position; cash runway through 1H2027

Upcoming clinical development milestones

- FDA final approval of PhIII **Borderline Personality Disorder** trial expected in 2026
- **Schizophrenia** EU expansion in 2026; readout expected in 2027
- **Autism Spectrum Disorder** PhII to initiate in 1H2026
- **Multiple Hematological Oncology:**
  - **AML** 1L w/ azacitidine + venetoclax PhI data update at EHA/ASH-2026;
  - **Refractory/Relapsed AML FLT3+** w/ gilteritinib PhI data update at EHA/ASH-2026
  - **Myelodysplastic Syndrome** PhI data update at EHA/ASH-2026
- **Sickle Cell Disease** PoC clinical activity in 1H2026
- **ET** PhII to start in 1Q2026

ORYZON

Pioneering personalized medicine in epigenetics