



Pioneering personalized medicine in epigenetics

For Oncology and CNS

CORPORATE PRESENTATION
4Q 2026

ORY:SM / ORY.MC

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Oryzon Develops Potent and Selective Epigenetic Drugs

A lead asset in AML and a second clinical asset in CNS

IADADEMSTAT | AML

A clinical LSD1 inhibitor being evaluated with venetoclax / azacitidine in newly diagnosed, unfit AML

100%

Overall response

18 / 18 patients

89%

Composite CR

16 / 18 patients

50%

Proceeded to HSCT

9 / 18 patients

Near-term AML milestones:

Final AML Phase II (ALICE-2) data in Q4 2026

Phase III initiation (ALICE-3) planned in 2027, subject to regulatory alignment

VAFIDEMSTAT | CNS

A second clinical asset being evaluated in schizophrenia and BPD

Randomized Phase II schizophrenia study; readout targeted for Q4 2027

BPD Phase III protocol resubmission in preparation

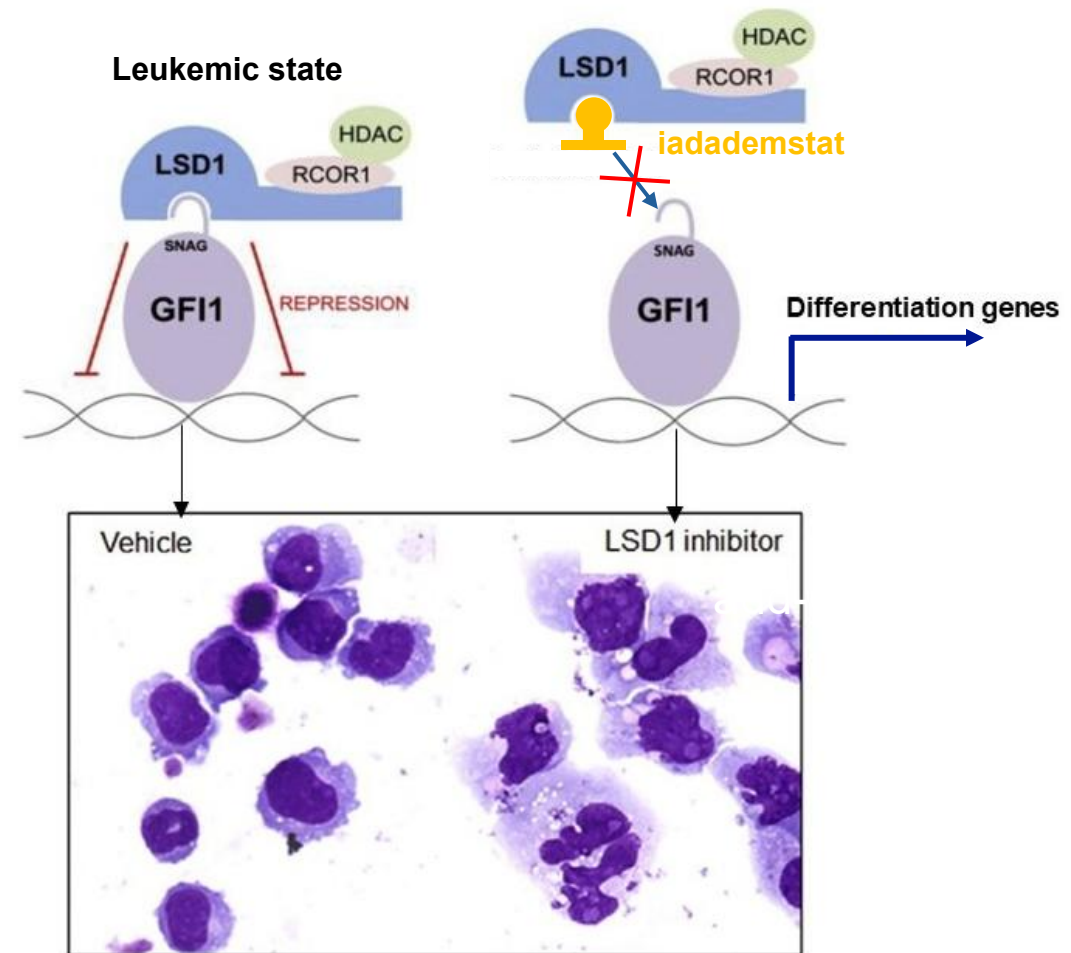
Near-term CNS milestone:

Final schizophrenia Phase II (EVOLUTION) data in Q4 2027

LSD1 Inhibition MoA in AML and Other Malignancies is Well Characterized and Understood

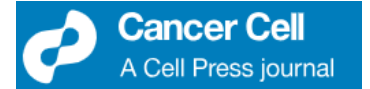
LSD1 is required for leukemic stem cell survival and blocking leukemic cell differentiation

- Iadademstat prevents leukemic stem cell survival¹
- Promotes rapid differentiation/death of leukemia cells²
- Boosts the immune system³



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

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



ARTICLE · Volume 33, Issue 3, P495-511.E12, March 12, 2018 · [Open Archive](#)

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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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Journal of Clinical Oncology[®]
An American Society of Clinical Oncology Journal

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 &](#)

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

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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 García-Avila, MD](#) ^e · et al. [Show more](#)

The Asset

- The most potent (nM) oral LSD1 inhibitor in clinical development
- Safety profile well-established: +225 pts treated with iadademstat in multiple Phase I/II trials
- Orphan Drug Designation for AML (US and EU)



ALICE-2 Responses Highly Encouraging and Pave the Way to Phase III

Maturing data continues to support iadademstat in ND-AML in combination with Ven/Aza

18/18

Overall response
100%

16/18

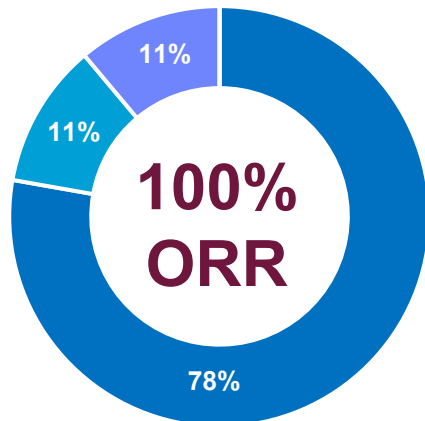
Composite CR
89%

9/18

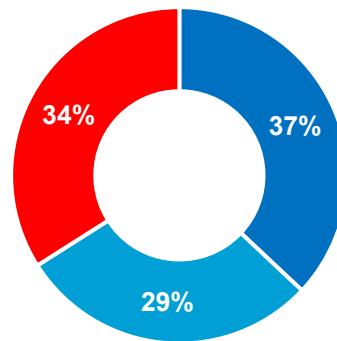
Proceeded to HSCT
50%

Response Composition

ALICE-2 (EHA 2026)¹

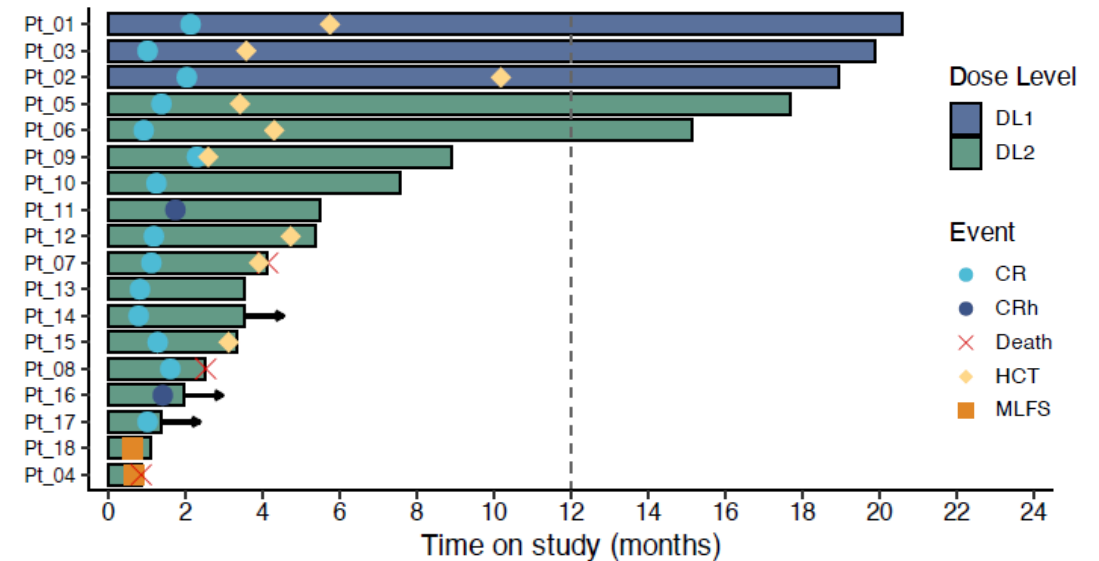


VIALE
Ven / Aza²



■ Pure CRs ■ CRh ■ MLFS ■ No Response

Responses are fast, occurring at C1 or C2



Median follow-up: 8 months

Median overall and event-free survival: not reached

Iadademstat / Venetoclax / Azacitidine Combination Continued to Demonstrate a Favorable Safety Profile

Reported adverse events, dose-limiting toxicities and early mortality

EARLY MORTALITY

0%
30-day mortality

6% (n=1)
60-day mortality (unrelated)

Findings

Common grade ≥ 3 AEs	Thrombocytopenia and neutropenia
3 DLTs at DL2	Neutropenia; <i>C. difficile</i> colitis; differentiation syndrome
2 grade 5 sepsis events	Deemed unrelated to study medications
TLS and differentiation syndrome	Occurred in separate patients and were managed with medical therapy

The triple regimen does not add safety signals to the standard Ven / Aza therapy

A Strong Biological Rationale for Higher Need AML Populations

TARGET BIOLOGY

LSD1 inhibition

Mechanistic evidence links LSD1 to leukemic-cell survival, blocked differentiation and immune system boosting.

Preclinical / mechanistic rationale

PATIENT SELECTION STRATEGY

High-need groups

The Phase III development plan focuses on high- and intermediate-risk AML, including TP53 and RAS-related biology.

Proposed clinical-development focus

CLINICAL OBSERVATIONS

Early subgroup signals

CRs reported across TP53 / RAS categories in ALICE-2; mOS increased in TP53 patients in ALICE-1 Phase II trial.

Convergent evidence in ALICE-1 and ALICE-2

Iadademstat ALICE-3 Phase III Trial Planned to Initiate in 2027

Subject to regulatory agreement and financing; accrual estimated at 24 months

High-risk cohort

TP53-mutated AML

~100 patients

Iadademstat + Venetoclax / Azacitidine

An external / real-world control is proposed
(if accepted by the FDA)

Intermediate-risk cohort

~200 patients

Proposed randomization 1:1

~100
Iada + Ven / Aza

~100
Ven / Aza

**Proposed Endpoint
Strategy**

- CR-based endpoints for potential accelerated approval
- Overall survival for full approval

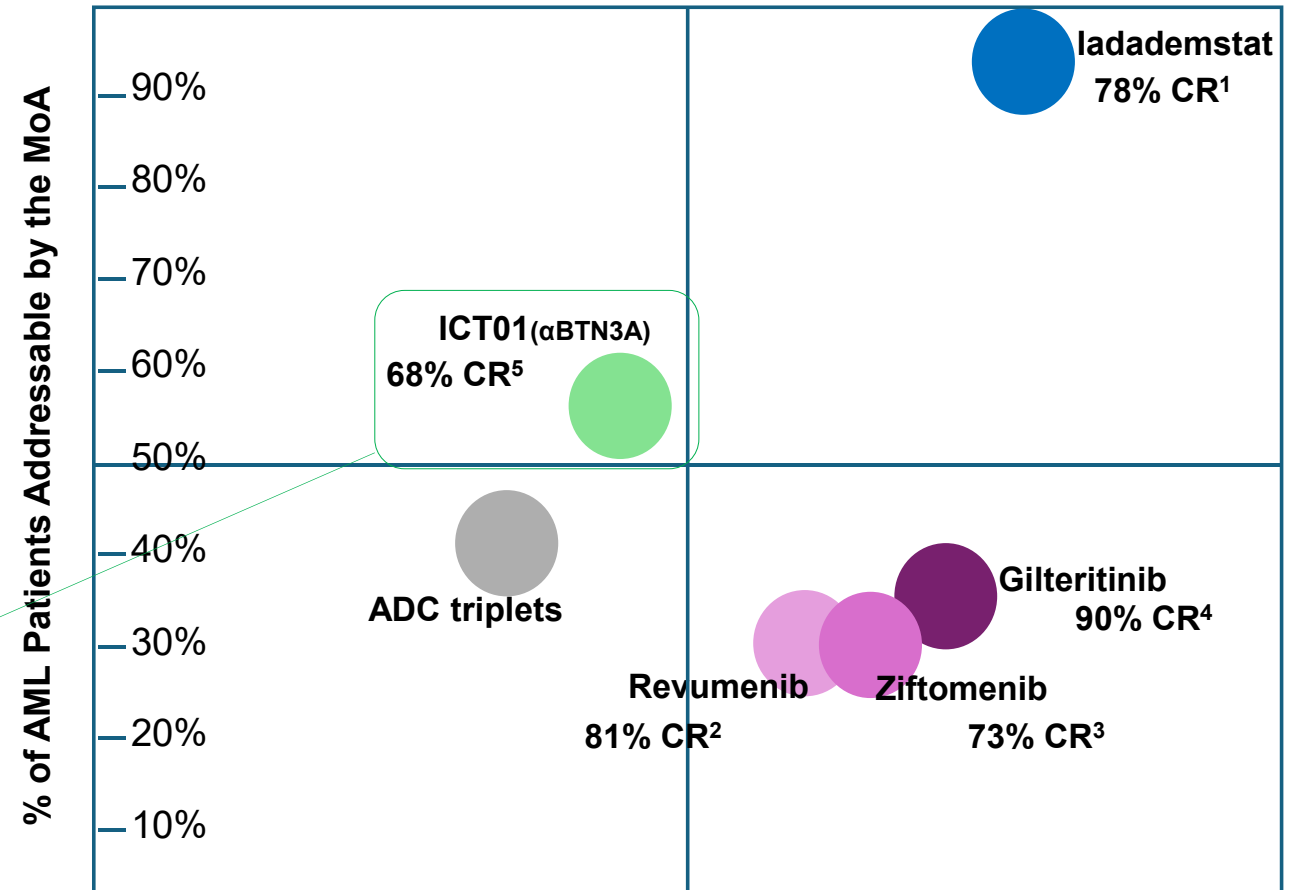
Iadademstat is Well Positioned vs Emerging 1L AML Triplets

A mutation-agnostic agent among emerging triplets:

- **Menin inhibitors** (Revumenib / Ziftomenib): Mutation restricted to NPM1/KMT2A
- **FLT3 inhibitors**: Mutation-restricted
- **ADC triplets**: Potency with logistical/toxicity complexity. Early clinical development
 - pivekimab + Ven / Aza
 - (CD123/CD70)
 - (CD277 aka α BTN3A)



Strong market appetite in the field



Tolerability / Feasibility

NPM1-mutated AML comprises about 30% of ND AML

FLT3-mutated AML comprises about 35-40% of ND AML

CD123/CD70 expressing AMLs in levels subject to therapeutic intervention may be about 40% of ND AML

Iadademstat is assuming ALL but NMP1m ND AML (70%), if only HR+IntermR that would be approx 40%

RESTORE and IDEAL: Additional Clinical Development Programs in Hematology

RESTORE | SICKLE-CELL DISEASE

Open-label Phase Ib

~24-30 patients
Dose escalation and expansion
Up to 24 weeks of treatment

Primary: safety, tolerability and RP2D.
Secondary: HbF, PK/PD and hemolysis markers.

First two cohorts enrolled; final data targeted Q2 2027

IDEAL | ESSENTIAL THROMBOCYTHEMIA

Phase II proof of concept

Recruitment ongoing in the development plan

Rationale: LSD1 inhibition affects megakaryocyte differentiation and platelet production.

First cohort dosed

Vafidemstat Pharmacology Supports Use in Different Psychiatric Disorders

The only LSD1 inhibitor in clinical development for CNS

Vafidemstat and other LSD1 inhibitors upregulate 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

LSD1 inhibition 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

Focusing on schizophrenia, borderline personality disorder and autism



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

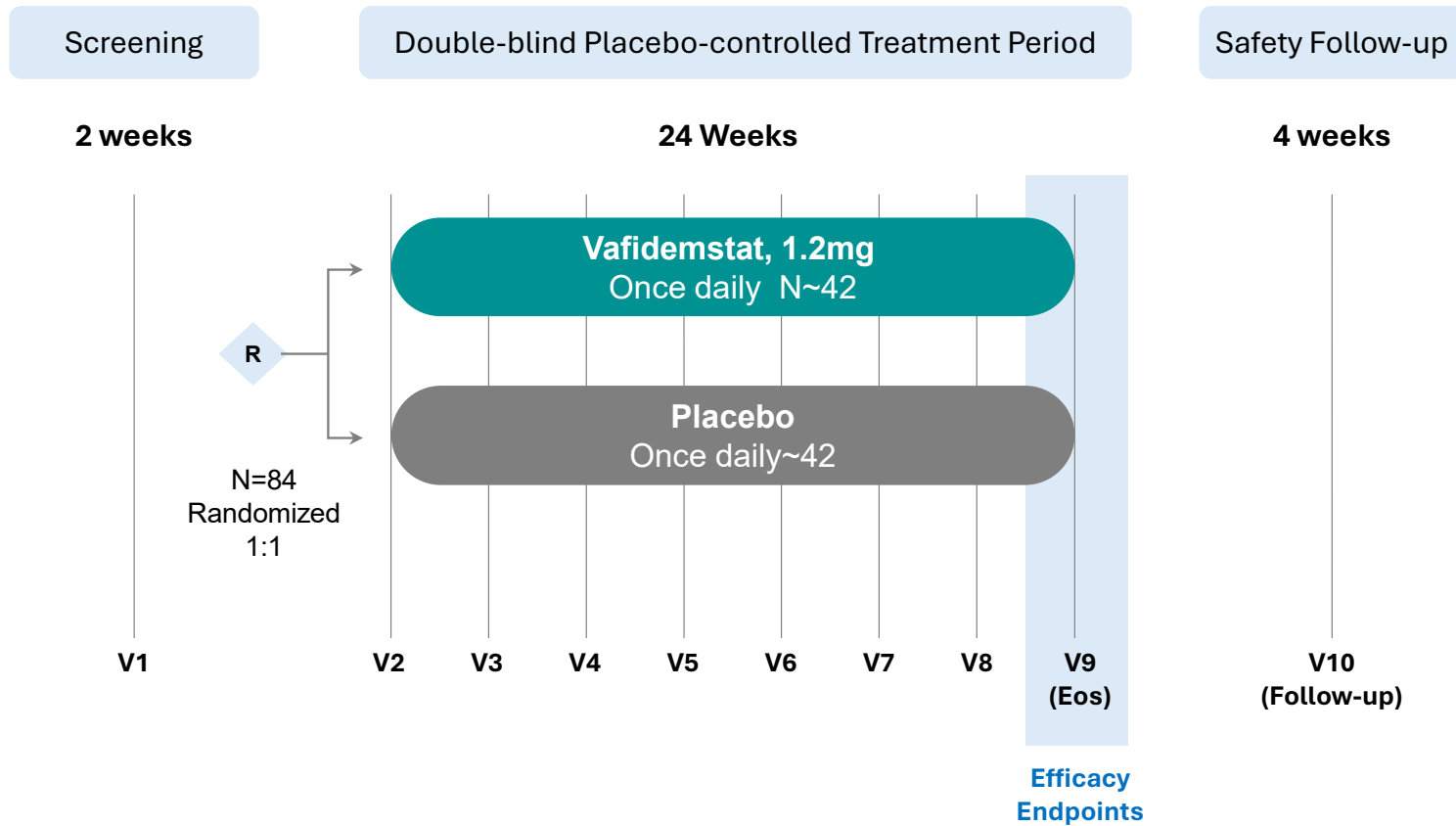


No side effects

No weight gain
No sedation / somnolence
No sexual dysfunction
No extrapyramidal signs

Randomized Phase II Study to Measure Negative Symptoms in Schizophrenia

EVOLUTION Trial Design



Primary Endpoint

Improvement in negative symptoms

Secondary assessments

Cognition, positive symptoms, PANSS total score, functional impairment and safety

Targeted readout:

Q4 2027

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

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](#) | [CC](#) [i](#)

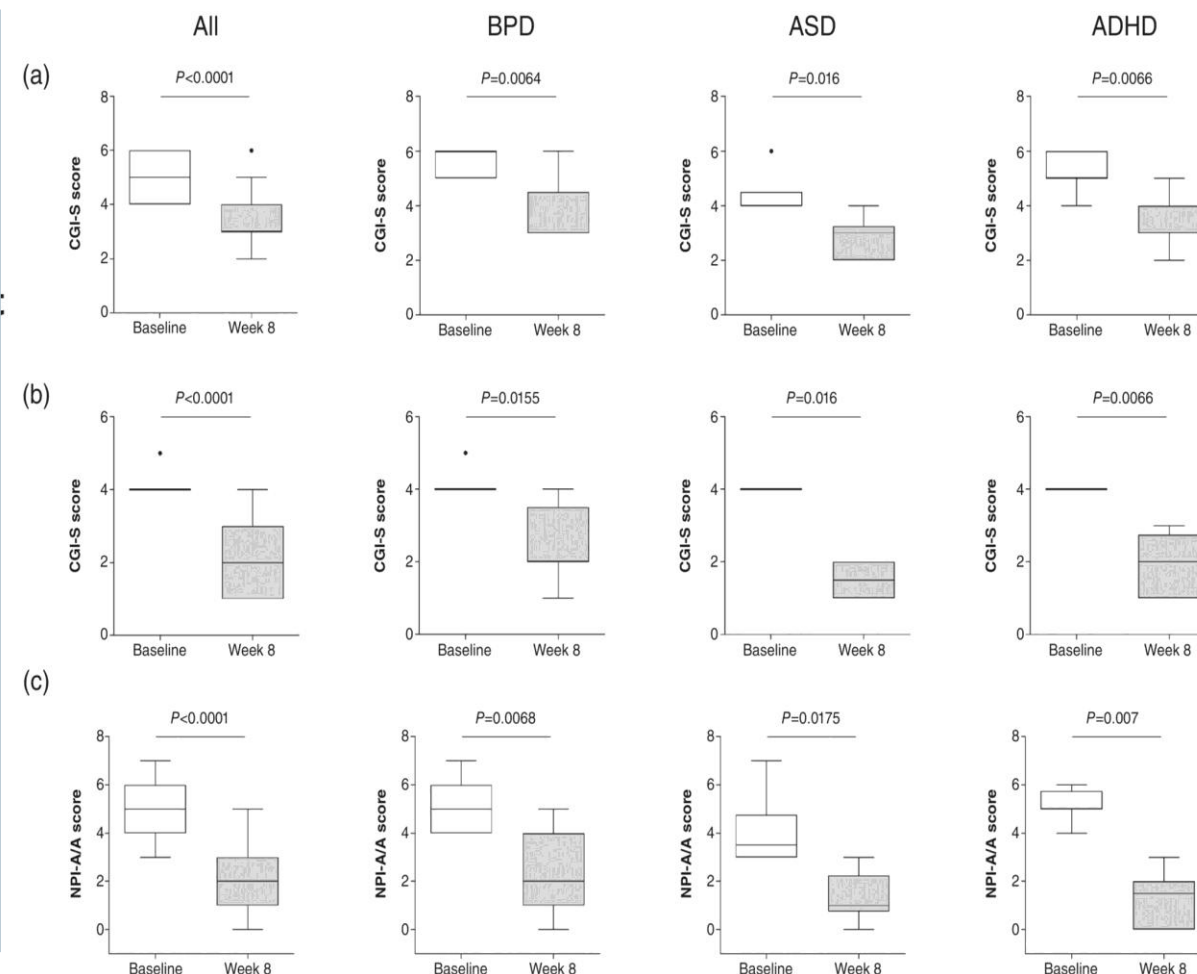
REIMAGINE: A central nervous system basket trial showing safety and efficacy of vafidemstat on aggression in different psychiatric disorders

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, $p < 0.0001$)

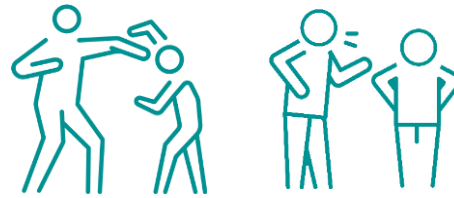


Borderline Personality Disorder: An Unmet Medical Need



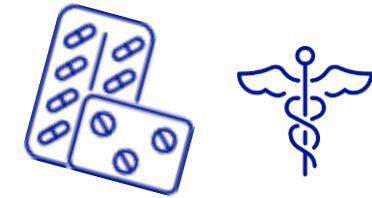
Prevalent & impairing disease

5 million in U.S.



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
- Preclinical models

Phase III Trial in Preparation for Borderline Personality Disorder

Vafidemstat reduced aggression over placebo (secondary endpoint) in PORTICO Phase II study

PORTICO: Global randomized, placebo-controlled Phase IIb study | 211 patients

Primary Aggression Endpoint

CGI-S A/A

p = 0.2266

Did not reach statistical significance

Secondary Aggression Endpoint

STAXI-2 Trait Anger

p = 0.0071

~60% of improvement over placebo in the last month of treatment

FDA Requested Additional Info on Clinical Endpoints in the Initial Phase III Protocol

Supporting evidence

Qualitative research and endpoint-validation work ongoing

Protocol refinement

Proposed ~350 patients; 12 weeks; U.S. + E.U.

Next steps

Request type C meeting + briefing package by end-2026

Additional Clinical Development Provides Expanded Opportunity

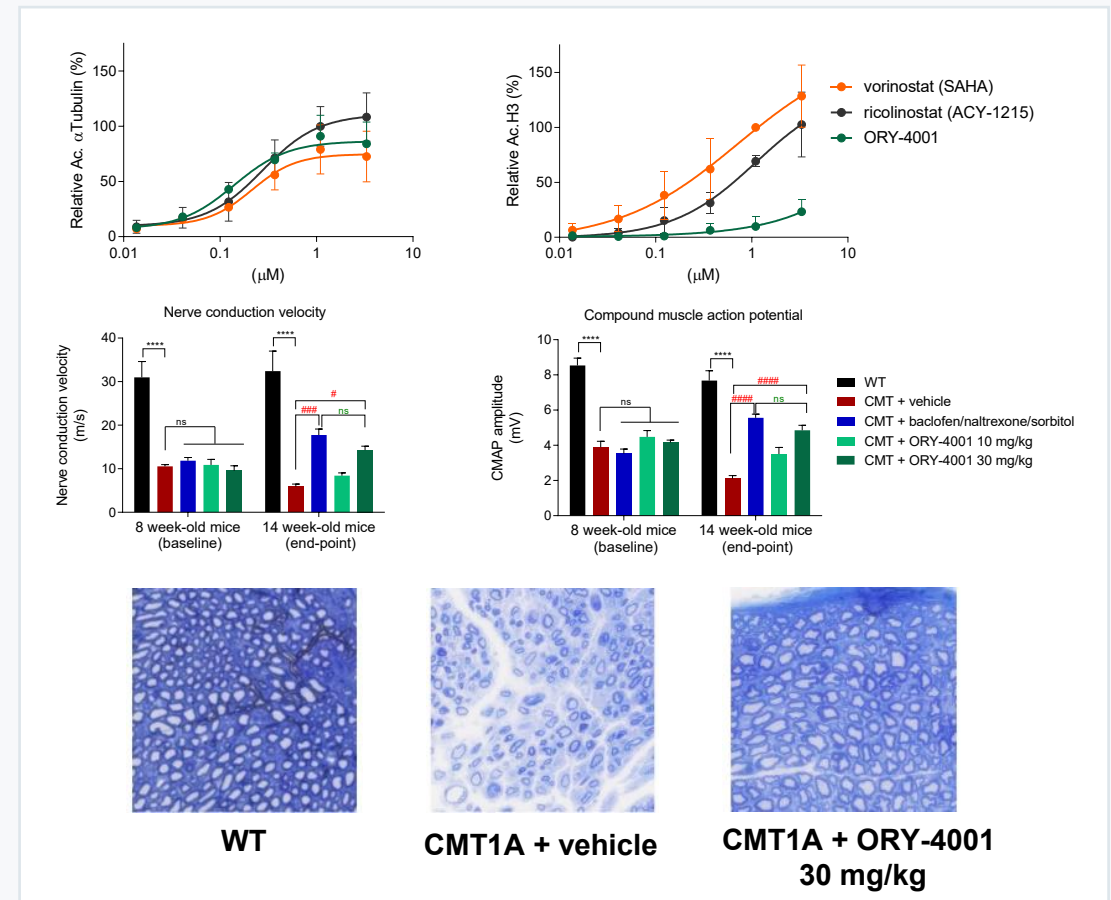
Program / indication	Sponsor	Development status	Next focus
FRIDA R/R FLT3-mutated AML	Oryzon	Phase Ib; fully enrolled; EHA 2026 update	ASH-2026 Final data updates
RESTORE Sickle-cell disease	Oryzon	Phase Ib; first two cohorts enrolled	Final readout targeted Q2 2027
IDEAL Essential thrombocythemia	Oryzon	Phase II; recruiting	Clinical proof of concept
Small-cell lung cancer (2 trials)	NCI / Yale	CRADA-SCLC and IIS-TIARA programs	Externally led clinical evaluation
MDS / Myeloproliferative neoplasms	MCW / NCI	Investigator-initiated / CRADA programs	Exploratory clinical evidence
Autism spectrum disorder	Oryzon	Phase II (PMS); recently approved by EMA	Grant-supported development work

Oryzon-funded obligations are limited thanks to CRADA Agreement with NCI, external sponsorships and grant-supported activities

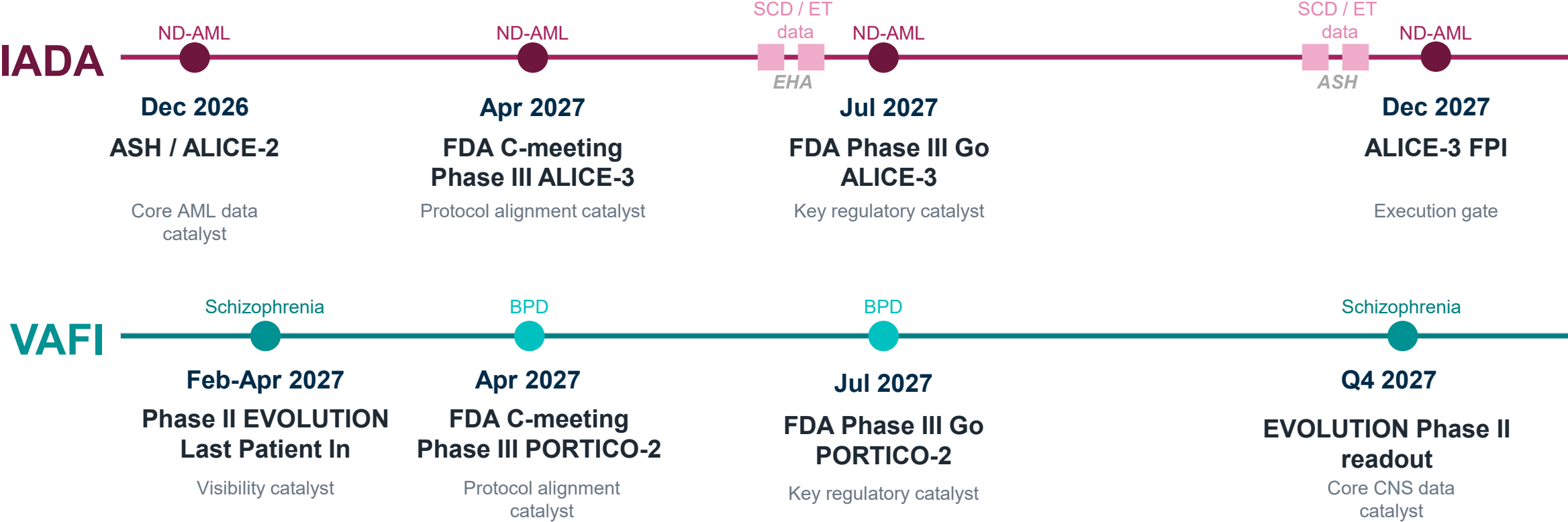
ORY-4001 is a Highly Potent and Selective HDAC6 Inhibitor

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 grant received from the U.S. ALS Association to support regulatory preclinical development in ALS
- **Available for partnering**



Advancing Toward Multiple Clinical and Regulatory Milestones



Oryzon Leadership and Advisers Bring Together Experienced Talent for Late-Stage Development in AML and CNS

Oncology



Experienced Boston-Based Medical Oncology Team | Strong Track Record of Clinical Collaborations with NCI and Leading U.S. Institutions

Ana Limon, PhD

Senior VP Medical Oncology



Douglas Faller MD, PhD



Lori Kunkel MD, PhD



Leon Hooftman MD, PhD



Felipe Prosper MD, PhD



CNS



CNS | Clinical and Regulatory Leadership

Rolando Gutierrez-Esteinou, MD

Chief Medical Officer, CNS



Raymond Sanchez
Former Chief Medical Officer of Cerevel Therapeutics



Christopher Breder
Ex-Medical Officer at the FDA (2009-2019)



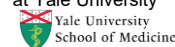
Alan F. Schatzberg
Former Head of Psychiatry Department at Stanford



Eric Hollander, M.D.
Director of the Autism and Obsessive-Compulsive Spectrum Program



Dr. Sarah Fineberg
Professor of Psychiatry at Yale University



Dr. Emil F. Coccaro
Expert in Aggression, Created the Overt Aggression Scale Modified (OAS-M)



A photograph of a modern glass skyscraper, the Oryzon building, with the company name 'ORYZON' and a globe logo on its upper facade. The building's glass reflects the sky and clouds.

ORYZON

Pioneering personalized medicine in **epigenetics**