ORYZON

Pioneering personalized medicine in epigenetics

Corporate Presentation
September 2025
ORY:SM / ORY.MC

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Epigenetic champion developing new therapies in CNS and Oncology with an advanced pipeline

Growing epigenetic platform with an expanding pipeline to bring treatments to high unmet medical needs in CNS and Oncology

2 Programs with well-defined registrational pathways:

- iadademstat in Oncology/Hematology (Phase I-II)
- vafidemstat in CNS (Phase III-ready)

Listed in Europe (Madrid)

- Highly liquid company
- €150M raised in equity(1) since listing in 2015
- Runway 1H2027

(1) including convertible notes

LSD1 inhibition is a validated epigenetic approach for targeted therapies in Oncology/Hematology and CNS

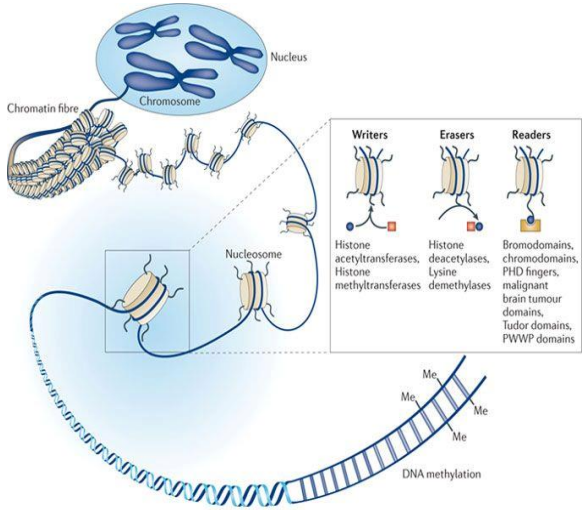


Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* **Volume 11** (2012)

Lysine specific histone demethylase 1 (LSD1): removes methyl groups from histones and scaffolds key TFs in enhancer & promoter regions

LSD1 expression and activity can block and promote gene expression

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

- In ONCOLOGY/HEMATOLOGY, an exquisitely well-defined MoA
- Class Validation: competitor LSD1i acquired for $1.4B by MERCK
- Endorsed by CRADA agreement signed with NCI-NIH: trials ongoing in AML and SCLC

- In CNS, phenotypic rescues in different genetically-defined neurodevelopmental syndromes
- Ample evidence of neurological benefits in different animal / disease models
- A unique competitive position. A Phase IIb in BPD completed (preparing Phase III) and another in SCZ ongoing

AML: acute myeloid leukemia; SCLC: small cell lung cancer; SCZ: Schizophrenia; BPD: Borderline Personality Disorder

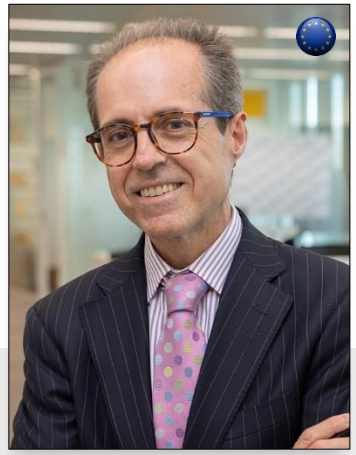
New BOD with US and EU Independent Directors Experienced in M&A

Carlos Buesa PhD
Chairman

Manuel López-Figueroa, PhD

President of the RemComm Committee

Konstantinos Alataris PhD



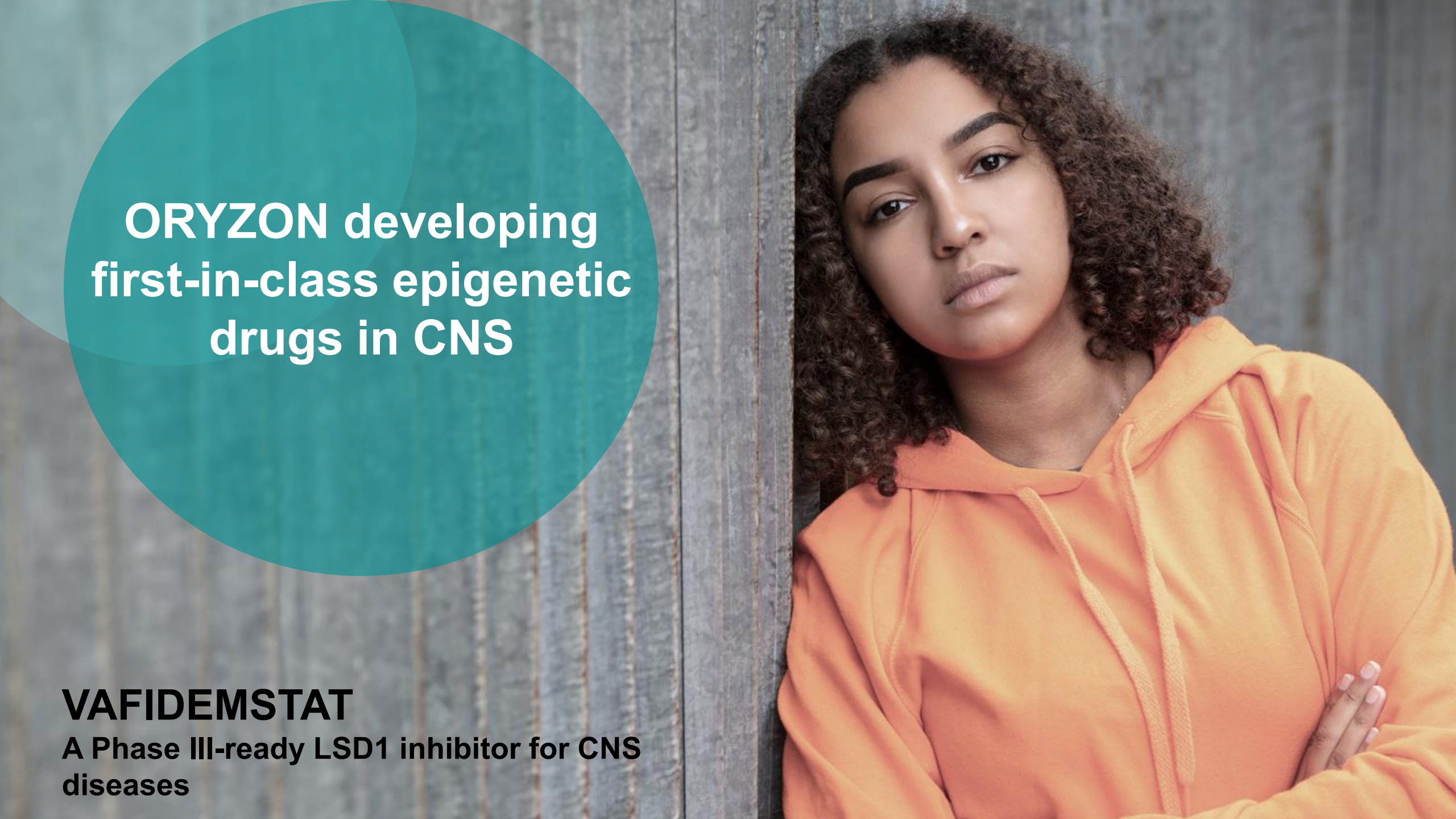
Luis Sanchez Quintana

President of the Audit and Compliance Committee

Montserrat Vendrell PhD

Pierre Beaurang PhD

ORYZON developing first-in-class epigenetic drugs in CNS



VAFIDEMSTAT

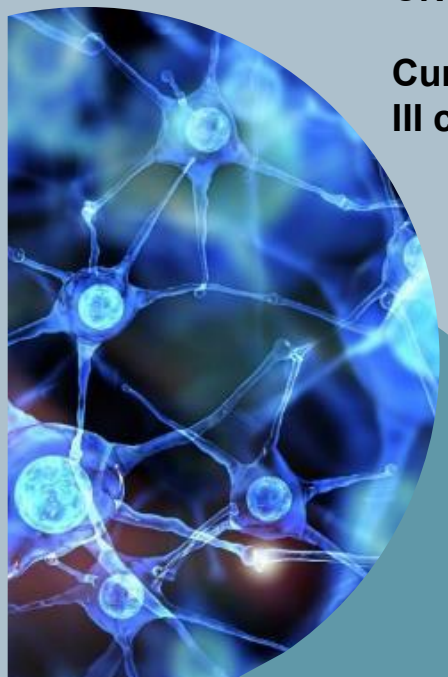
A Phase III-ready LSD1 inhibitor for CNS diseases

LSD1 inhibition, a therapeutic option in CNS disorders

LSD1 inhibition represents a novel MoA for 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

BPD: ✓

73% of **Borderline personality disorder** patients engaged in violent behavior in the last 1 yr

ADHD: ✓

Up to **50%** of **Attention Déficit & Hyperactivity** patients show agitation & aggression

ASD: ✓

Up to 68% of **Autistic Spectrum disorder** patients may show agitation & aggression

AD: ✓

Up to **52%** of **Alzheimer's disease** patients show agitation & aggression

SCZ:

Up to 43% of **Schizophrenia** pooled patients show agitation & aggression

✓ ***Clinical data with vafidemstat***

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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)

VAFIDEMSTAT	Study	Preclinical	Phase I	Phase II	Phase III	FILED
Vafidemstat (ORY-2001) - the only CNS optimized LSD1 inhibitor in clinical development						
Borderline personality disorder Agitation/Aggression & Overall Improvement	**PORTICO (Phase II)** **PORTICO-2 (Phase III)**				*submitted*	
Schizophrenia Negative Symptoms / Positive Symptoms / CIAS	**EVOLUTION**					
Autistic Spectrum Disorder Aggresion / repetitive behaviour	**HOPE-2** **(Phase II In prep)**					

- PORTICO-2 Phase III protocol submitted to FDA, awaiting FDA feedback
- Country expansion ongoing for the Phase II in Schizophrenia

Oryzon’s Proposal in BPD: Vafidemstat as a First-in-Class Agent for Aggression Control

Vafidemstat demonstrated a relevant clinical benefit in reducing agitation /aggression across ASD, ADHD and BPD patients in PoC Phase IIa study

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

PCN Psychiatry and Clinical Neurosciences

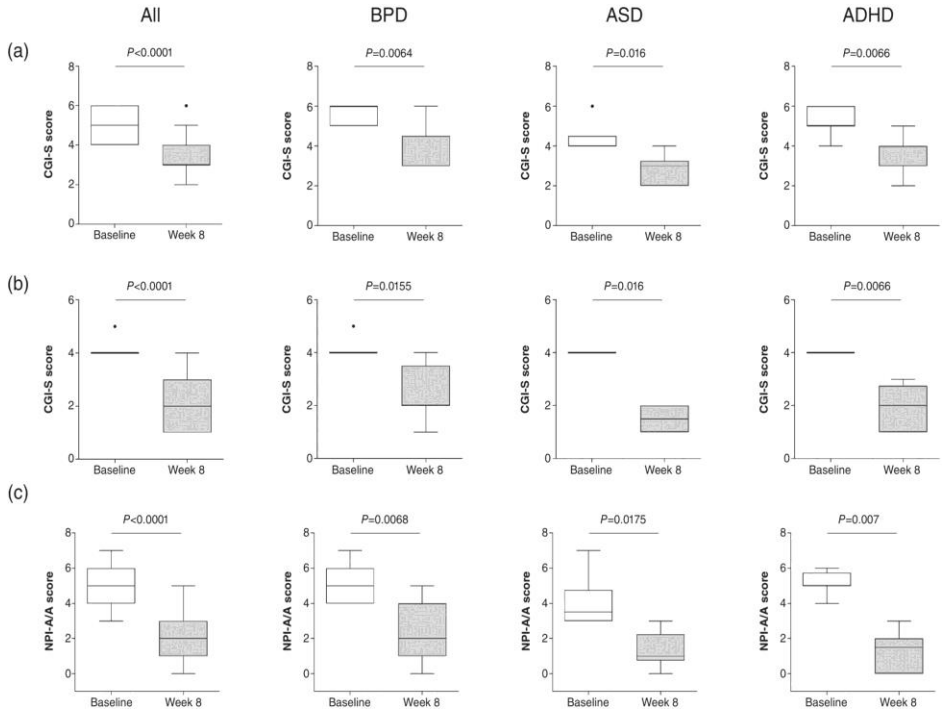
Regular Article | Open Access

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

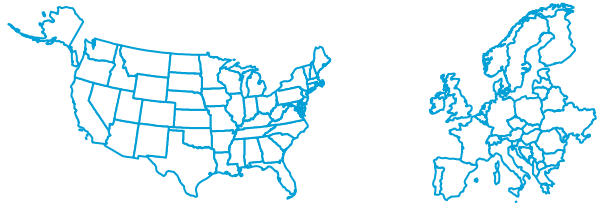
First published: 12 February 2025 | https://doi.org/10.1111/pcn.13800

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



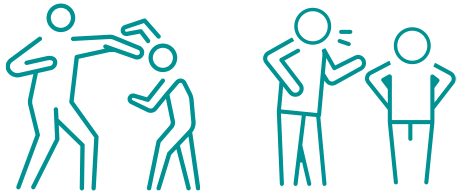
Eight-week vafidemstat treatment led to a **statistically significant reduction in agitation/aggression** compared with baseline across all the assessments (all participants, $p < 0.0001$)

Borderline personality disorder: an unmet medical need & vast commercial opportunity



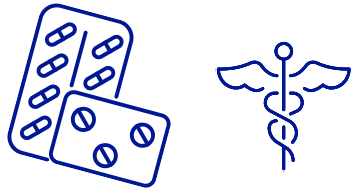
Prevalent & impairing disease

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 the 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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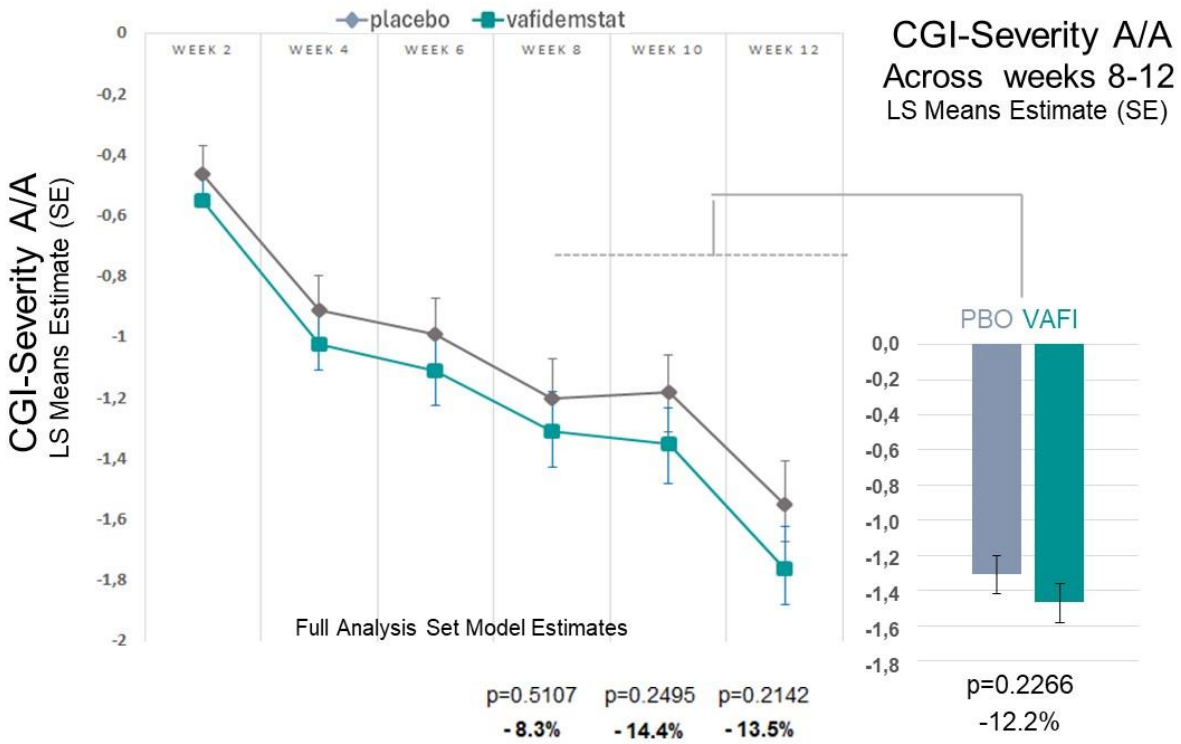
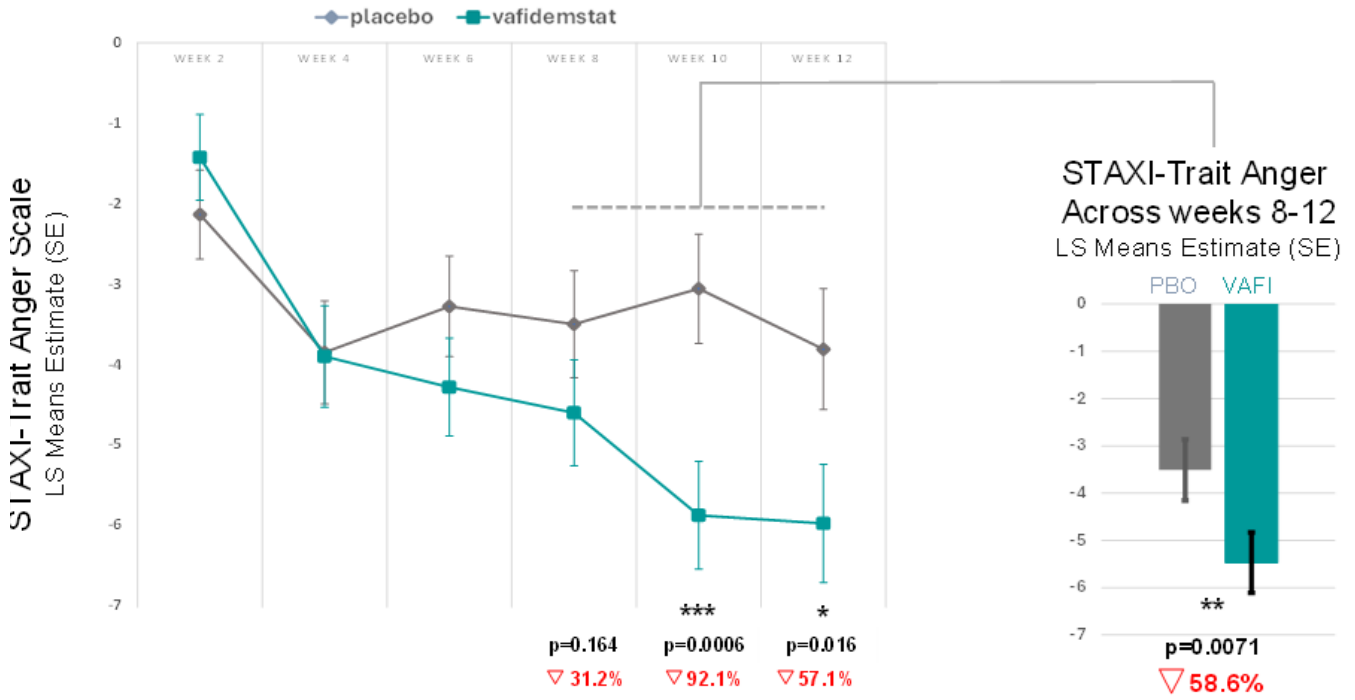
PORTICO: Treatment improves aggression over placebo (Secondary endpoint)

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



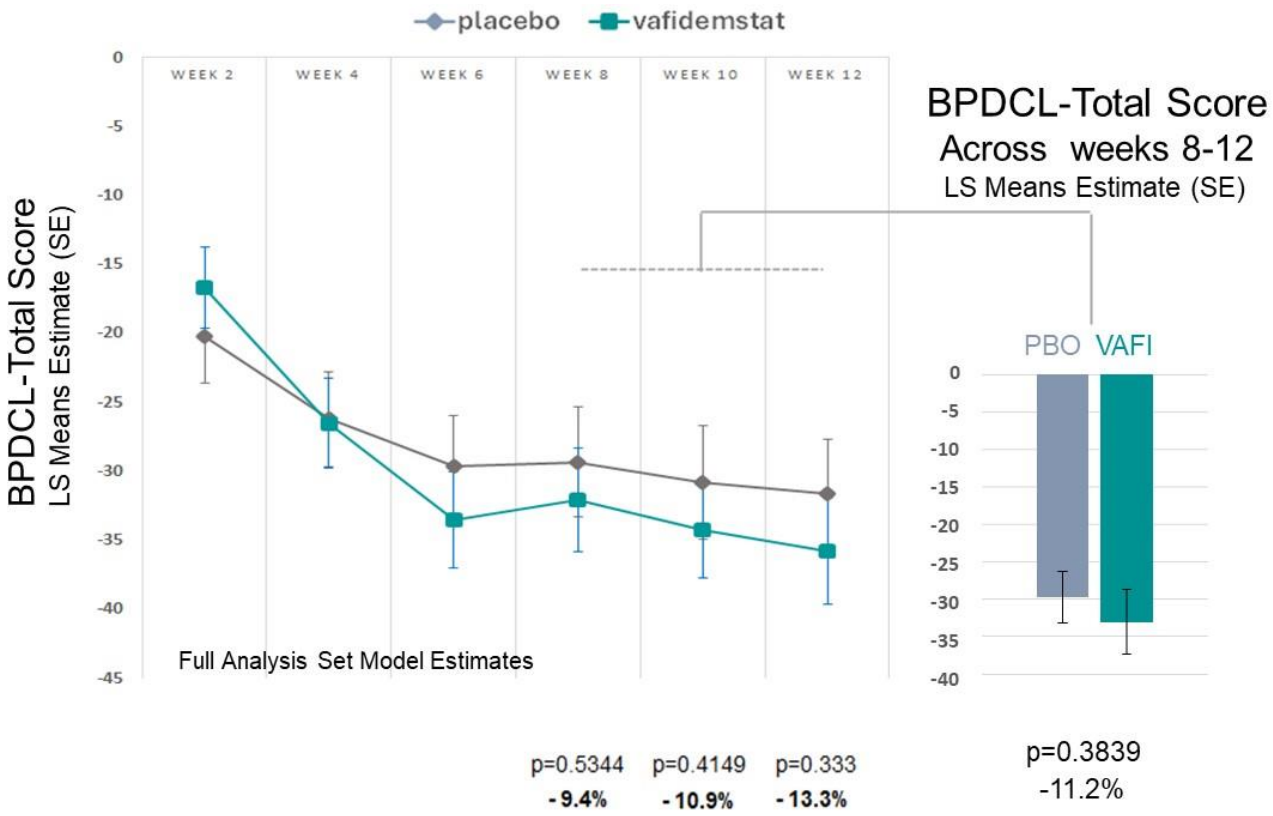
Secondary endpoint
STAXI-2 (Patient rated)



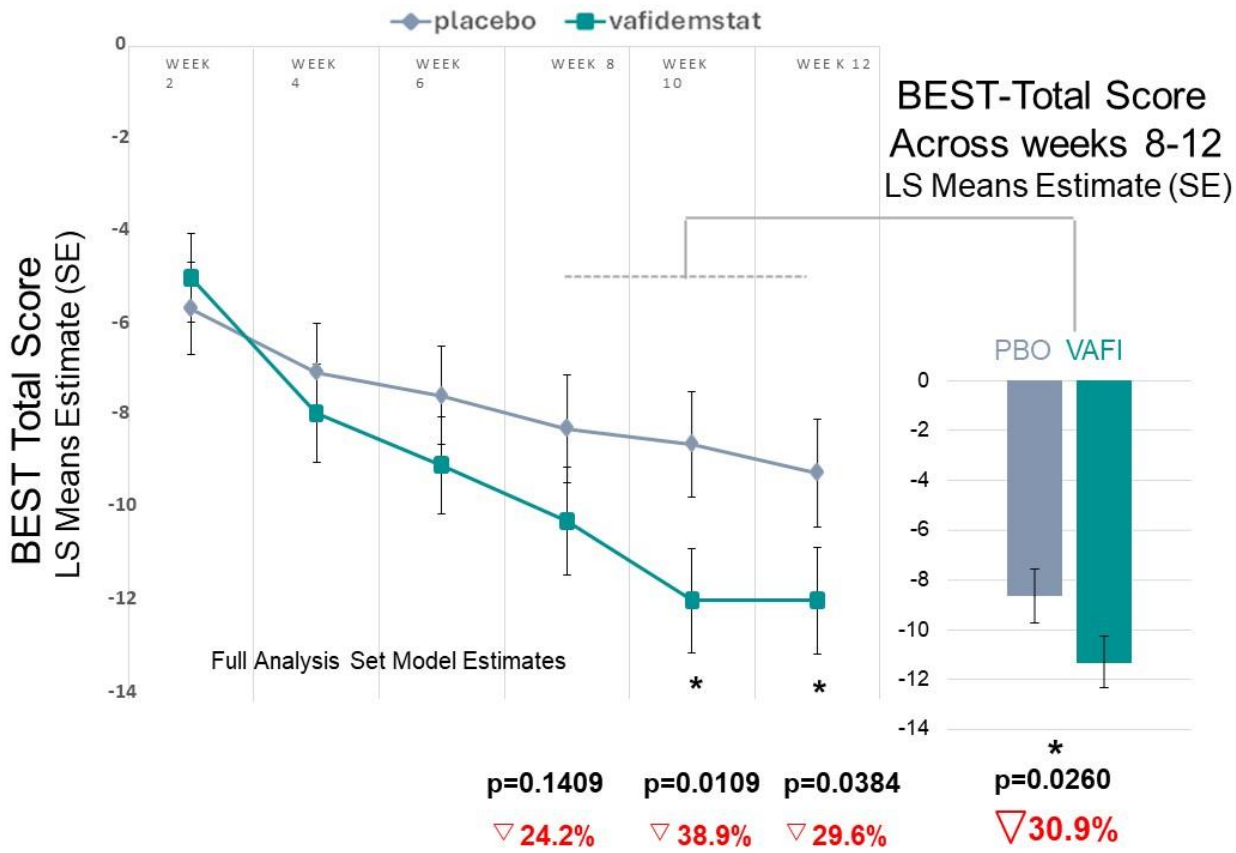
Data presented as oral comm at ECNP-2024

PORTICO: Treatment improves overall severity over placebo (Secondary endpoint)

Primary endpoint
BPDCL (Patient rated)



Secondary endpoint
BEST (Patient rated)



Data presented as oral comm at ECNP-2024

PORTICO: good safety 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

Serious Adverse Events

- There was 1 serious AE, a kidney infection, in a vafidemstat treated subject
- Case was independently judged by the PI as 'Unlikely Related' to treatment (started before treatment)
  - Subject's dose was not changed, the condition 'Recovered/Resolved' within 7 days, and the subject completed the trial

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

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 supported 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
- **Currently awaiting FDA's feedback**

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.

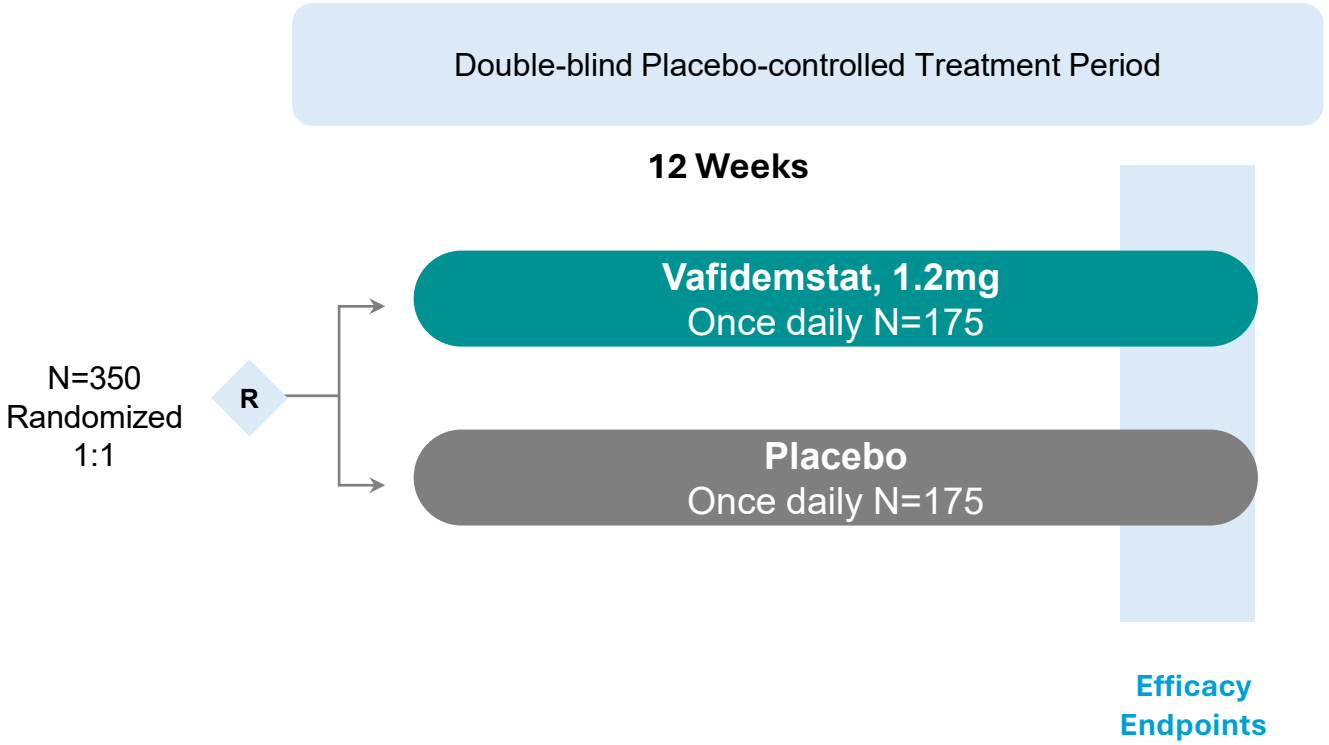
Dr. Sarah Fineberg

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.

PORTICO-2 Phase III: a 350-patients study

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

Expansion of Aggression program: new trials under evaluation in ASD

To be conducted initially in Spain at reduced cost through the EU-IPCEI grant

Phelan-McDermid Syndrome (PMS)

A rare genetic condition (prevalence estimate 1/30,000 births) primarily caused by a terminal deletion on the 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 for the selection of patients most likely to benefit from vafidemstat

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Vafidemstat in Schizophrenia

Genetic and physiological connections between LSD1 and schizophrenia pathology

Vafidemstat in Schizophrenia

Genetic link between LSD1 and SCZ

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

No approved drugs yet in negative symptoms or Cognitive Impairment symptoms

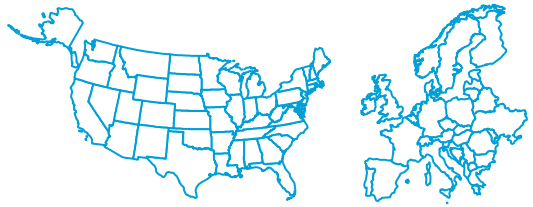
Strong market interest & huge M&A activity

Schizophrenia, still an enormous unmet medical need

Despite the recent approval of Cobenfy (BMS) for treating 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 (60%)
Cognitive Impairment (70%)

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 +6Bn

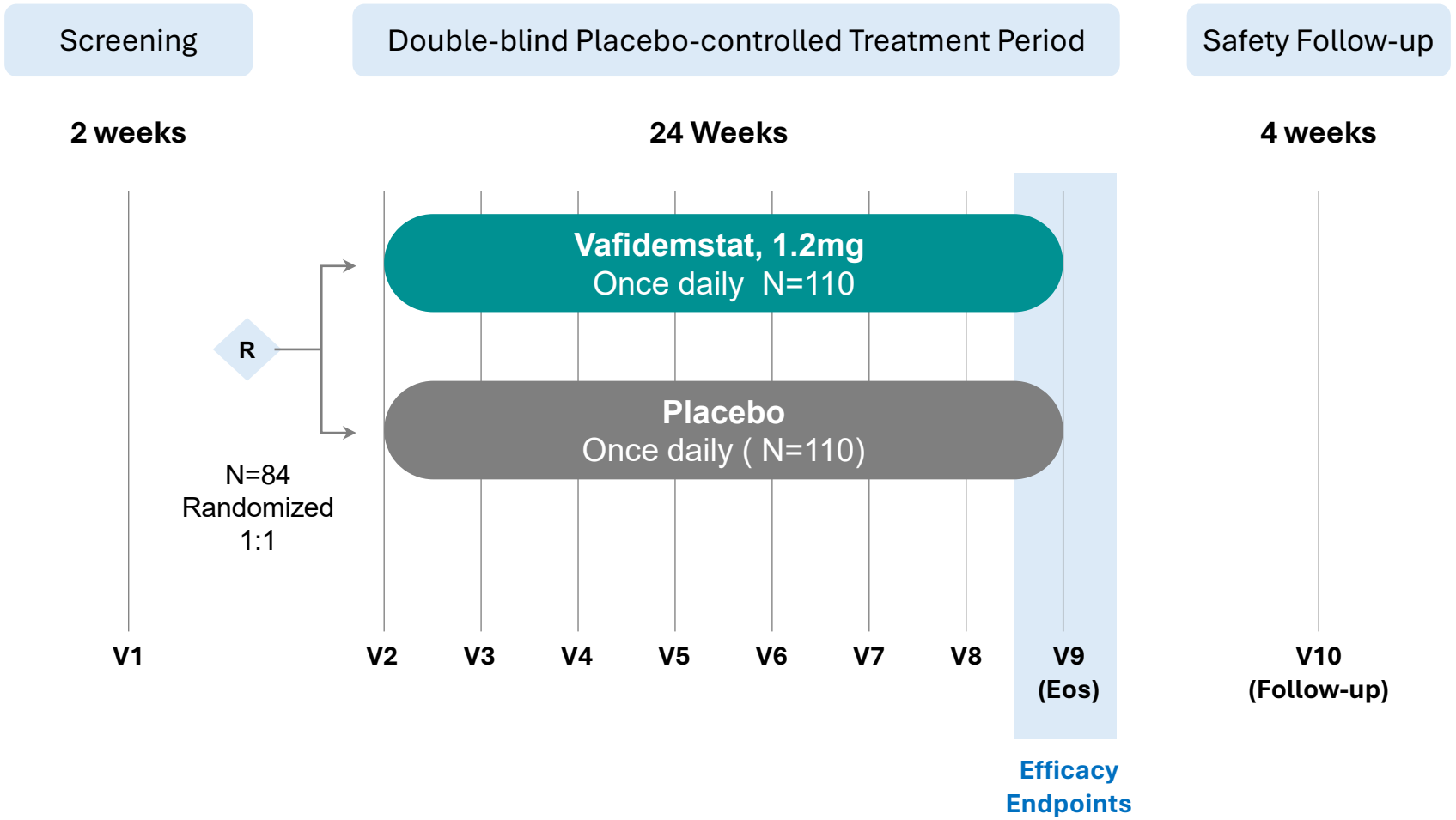
Moderate competition

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: Study In Expansion to Additional EU Countries

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



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

Readout: expected in 1H 2027

IADADEMSTAT

A Phase II LSD1 inhibitor for oncological and hematological diseases

LSD1 inhibition in oncology and hematology

- **In AML**
  - LSD1 maintains leukemic stem cells and represses differentiation; LSD1i promotes myeloid maturation and apoptosis.
  - LSD1i synergizes with other agents in AML as azacitidine, gilteritinib, and venetoclax amongst others
  - Clinical activity: In early-phase trials (e.g., iadademstat), ORR up to 55–70% in combo with azacitidine in treatment-naive AML (esp. in elderly/unfit patients).
- **In SCLC and other neuroendocrine tumors**
  - INSM1 / HMG20A and other TFs decoupled
  - ASCL-1 oncogenic program is deactivated by reinducing Notch-1
  - LSD1i induces the tumor cells to produce MHC-1 and PDL-1 receptor and boosts immune system
  - Strong preclinical evidence of benefits
- **In epithelial cancers** → Strong preclinical evidence of benefits
- **In Myelofibrosis** → Preliminary clinical evidence of benefits
- **In Polycythemia Vera** → Preliminary clinical evidence of benefits
- **In Essential Thrombocythemia** → Preliminary clinical evidence of benefits
- **In Sickle Cell Disease** → Strong preclinical evidence of benefits

ONCOLOGY-HEMATOLOGY PROGRAM (iadademstat)

program ready to be licensed

Iadademstat is the most potent LSD1 inhibitor in clinical development

AML 1L

- Encouraging data in Unfit population in combo with azacitidine
- Special efficacy in unfit populations poorly responding to Ven-Aza
- Preliminary encouraging data in triple combo Iada-Ven-Aza (ASH-2025)

AML R/R Flt3+

- Phase Ib ongoing US
- Encouraging data in combination with gilteritinib
- In a dose expansion
- New data at ASH-2025

HR MDS

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

SCLC 1L-ED

- Phase Ib-II randomized trial sponsored by NCI under our CRADA.
- FPI April 2025. Recruiting
- 40 pt to be recruited
- Led by MSKCC.
- +30 sites in the US

MPNs and ET

- Phase II in combination with ASTX727 in proliferating MPNs (CRADA; FPI Q4'25)
- Phase II in ET HU-resistant /intolerant in preparation; submission to EMA on Q4'25

SCD

- Commercially-validated MoA (HbF induction)
- Superior to current SoC and other agents in development
- Phase Ib in SCD approved by EMA, FPI Q4'25

AML: acute myeloid leukemia; ET: essential thrombocythemia; MDS myelodysplastic syndrome; MPN: myeloproliferative neoplasm; SCD: sickle cell disease; SCLC: small cell lung cancer;

Iadademstat in Oncology: multiple shots on goal & leverage on CRADA-NCI agreement

The oncology program represents a significant upside and requires only a modest investment, as most studies are funded through the CRADA agreement with the NCI-NIH

Program	Study	Preclinical Phase	Phase I		Phase II		Status	Expected Milestone(s)
			Phase Ia	Phase Ib	Phase IIa	Phase IIb		
Oncology: Iadademstat (ORY-1001) – Selective LSD1 inhibitor								
AML 1L Unfit Patients Combination with azacitidine	**ALICE**						**Completed** Study has results	Final positive results published May 2024 (Lancet Haematology)
AML 1L Unfit Patients Combination with azacitidine and venetoclax	**ALICE-2 (IIS-X002)**			**Phase Ib**			**Recruiting** Sponsor: OHSU	2nd cohort enrolled
AML 1L Unfit Patients Combination with azacitidine and venetoclax	**ALICE-3 (CRADA-AML)**			**Phase Ib**			**Recruiting** Sponsor: NCI Led by UPMC	1st patient dosed
AML R/R-Flt3mut+ Combination with gilteritinib	**FRIDA**			**Phase Ib**			**Recruiting**	Initial data presented at EHA-2024 Next data update ASH-2025 ★
MDS Combination with azacitidine	**IIS-X005**			**Phase I**			**Recruiting** Sponsor: MCW	1st patient dosed
ED-SCLC 1L Combination with ICI	**STELLAR-0 (CRADA-SCLC)**				**Phase I / II**		**Recruiting** Sponsor: NCI, Led by MSKCC	1st patient dosed ★

CRADA: Cooperative Research and Development Agreement; ICI: immune checkpoint inhibitor; IIS: investigator-initiated study; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; OHSU: Oregon Health & Science University; SCLC: small cell lung cancer; UPMC: University of Pittsburgh Medical Center.
Note: Study names indicated for IIS or CRADA trials correspond to Oryzon's internal names for these trials

FRIDA: a Phase Ib trial in R/R AML under OPTIMUS FDA rules as a foundation for an accelerated development

Inclusion Criteria

Adult pts with Relapsed/ Refractory FLT3m$^+$ AML

- Refractory or relapsed to first- or second-line treatment
- ECOG 0-2
- Normal liver and renal function
- Prior frontline midostaurin or sorafenib or quizartinib or gilteritinib under specific circumstances

Approximately 15 sites

Escalation

Up to ~6 pts/dose level

Pharmacologically active dose/s

	Iadademstat PO	Gilteritinib PO
Dose level +1	150 µg, 4 weeks	120 mg
Starting dose	100 µg, 4 weeks	120 mg
Dose level -1	75 µg, 4 weeks	120 mg
Dose level -2	75 µg, 3 out of 4 weeks	120 mg

3+3 design

Expansion

Up to ~ 14 pts/dose cohort

Dose C1:
Iadademstat + Gilteritinib

Dose C2:
Iadademstat + Gilteritinib

Bayesian Monitoring

Final Analysis

(Selected endpoints)

Primary
- Safety
- RP2D

Secondary
- Efficacy: CR/CRh,
- Efficacy: OS
- Efficacy: EFS,ORR
- Efficacy: DoR
- Transfusion rates

Exploratory
- MRD
- Gene mutation status
- Biomarkers

Expansion DL-1	**DL-1: 14 pts accrued (2 non evaluable)**

Abstract accepted - ASH-2025

ORYZON

ALICE-2: Iadademstat in 1L unfit AML

Triple combination iadademstat-venetoclax-azacitidine

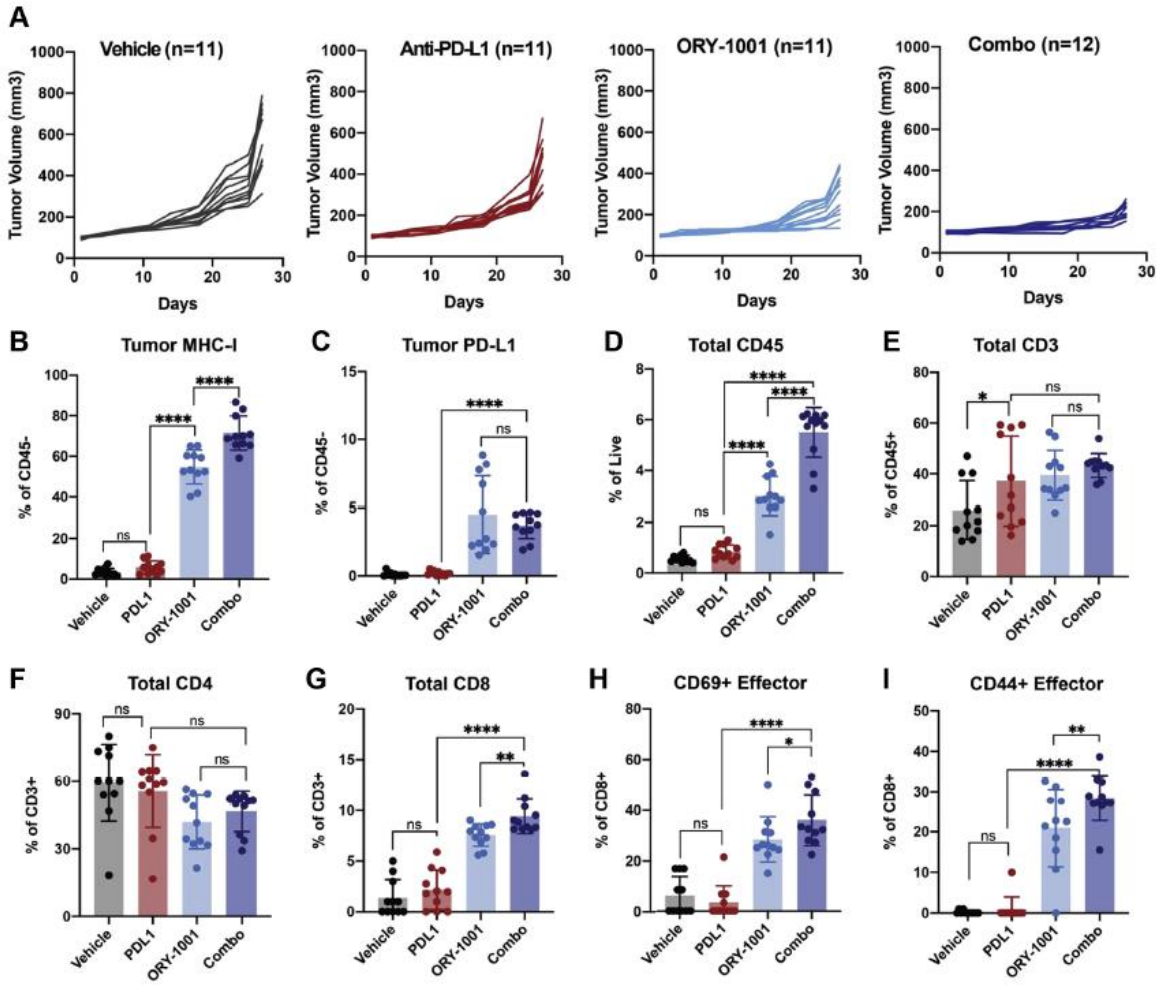
- NCT06357182
- Investigator-initiated study (IIS)
- Sponsor: Oregon Health and State University (OHSU)
- Principal Investigator: Dr. Curtis Lachowiez, OHSU Knight Cancer Institute
- N = 24

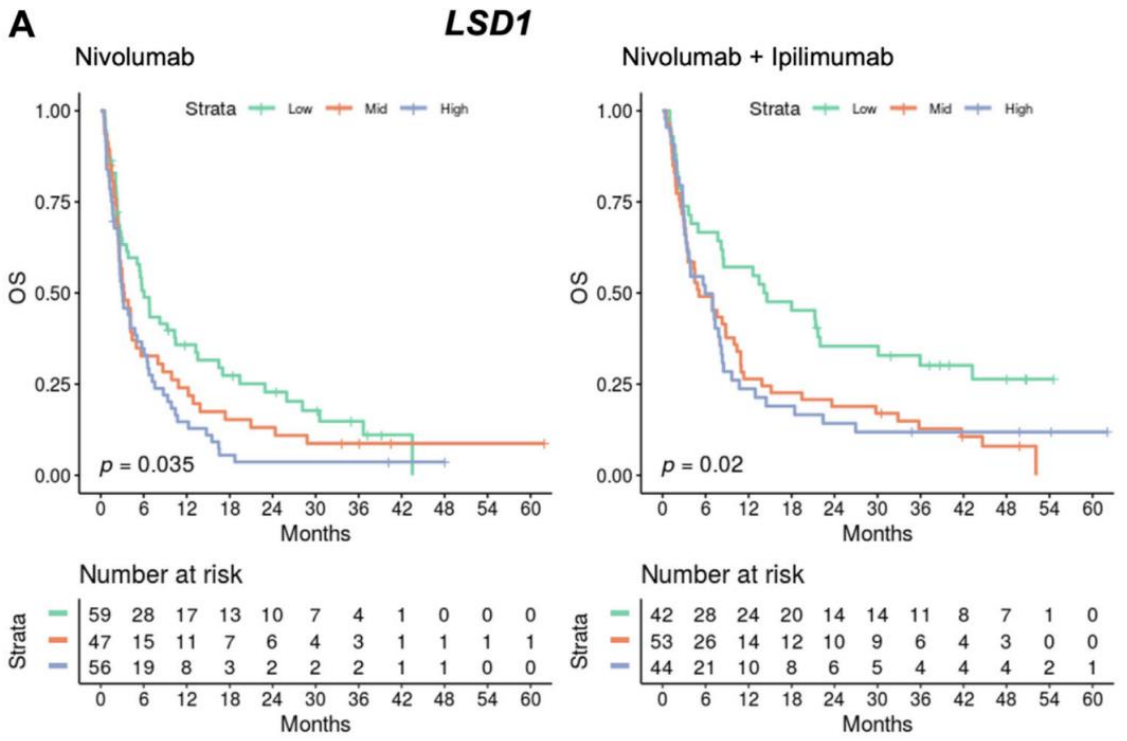
Status:

- FPI: August 2024
- Recruiting
- Expected completion: May 2026
- No DLTs . Safe combination
- Promising efficacy

Abstract accepted ASH-2025

Iadademstat and anti-PD-L1 combination inhibits SCLC progression





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

Nguyen et al., 2022 and Rudin et al., 2023

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

ORYZON to provide drug
FPI April 2025, enrolling

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

- MSKCC
- John Hopkins
- City of Hope Cancer Center
- University of Chicago
- Yale University

Enrollment (Estimated)

45-50 pts

Primary Objective

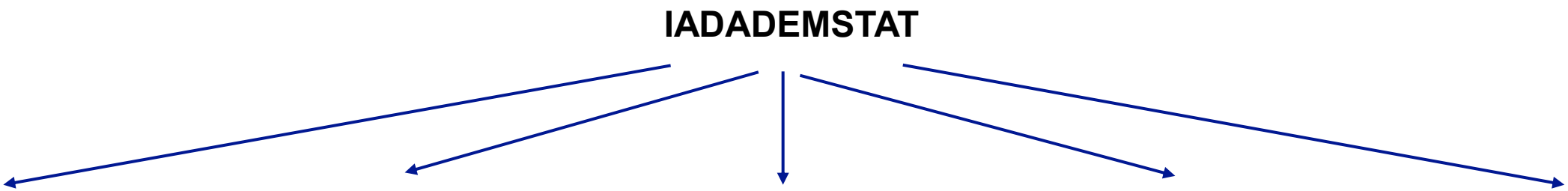
To compare the progression-free survival (PFS) between the combination of iadademstat plus immune checkpoint inhibitor (ICI) versus ICI maintenance alone.

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

Iadademstat combinations are highly encouraging in different settings



+ Gilteritinib	+ Venetoclax and Aza	+ ASTX727 (decitabine+ cedazuridine)	+ Azacitidine	+ Atezolizumab or Durvalumab
R/R AML flt3+	1L unfit AML	MPN	HR MDS	1L SCLC maintenance
FRIDA: highly promising response rate in the dose expansion **Abstract accepted ASH-2025**	OHSU Study: 9 patients recruited. No DLTs. Promising efficacy. **Abstract accepted ASH-2025** Additional trial ongoing in same space (NCI-NIH CRADA study)	NCI-NIH Study FPI expected Q4'25 TIP abstracts submitted ASH-2025	MCW-sponsored Study Promising preliminary data. Space of high interest after failure of Phase III with Ven+Aza	NCI-NIH CRADA study

IADADEMSTAT

in non-malignant hematological diseases

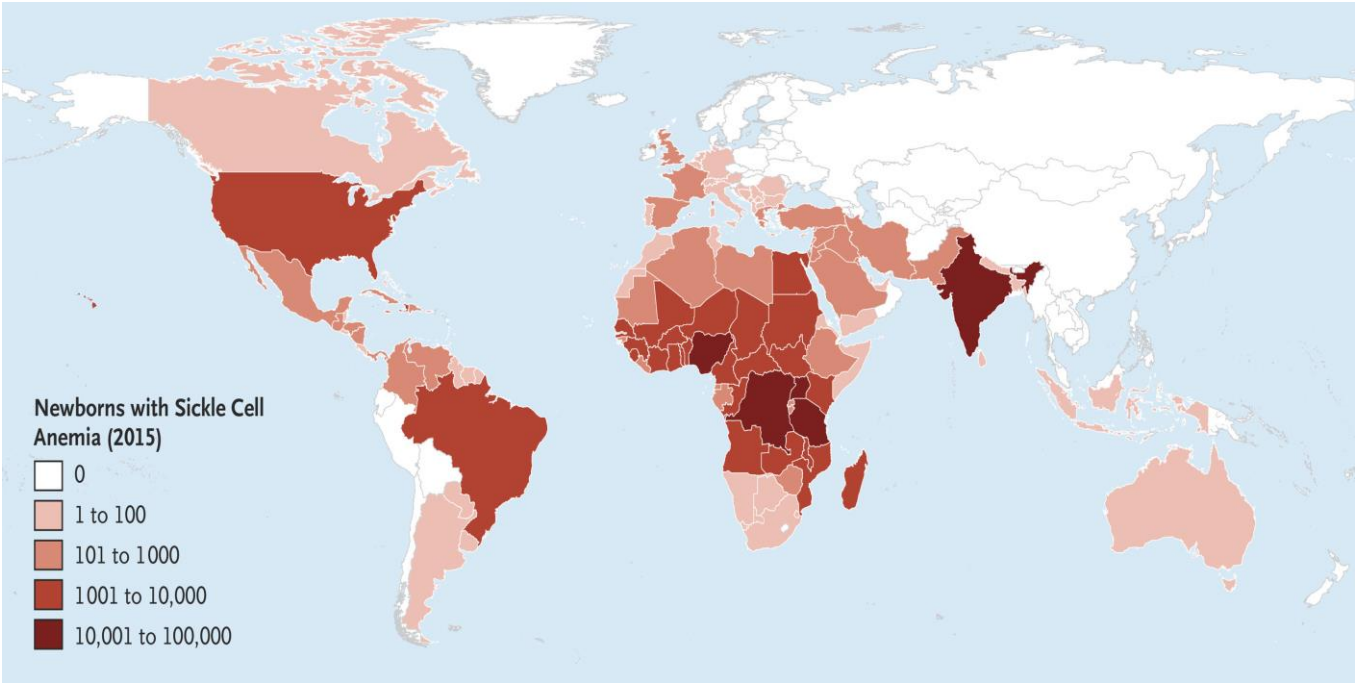
New non-malignant hematology program: Sickle Cell Disease (SCD)

Caused by a genetic mutation in the beta globin gene causing abnormal sickle-shaped red Blood cells (RBC) rigid and sticky that block blood flow and oxygen delivery to all parts of the body. Producing painful VOCs (vaso-occlusive events), which can also cause Acute Chest Syndrome and stroke, organ damage, kidney failure and early mortality

Most common inherited blood disorder in the US (US Prevalence 80,000-100,000)

Approved Treatments
Curative: HSCT (and potentially gene therapies)
Supportive: Blood transfusions, hydroxyurea (HbF inducer), crizanlizumab (P-selectin inhibitor), L-glutamine (antioxidant)

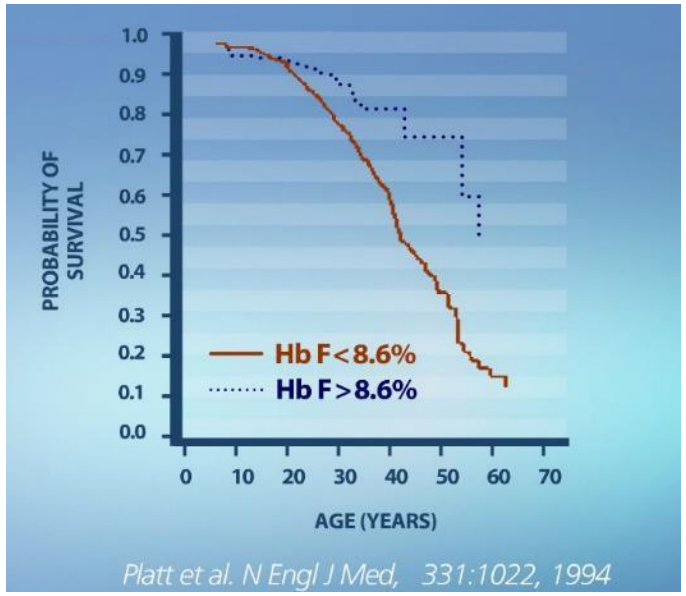
Market Opportunity
The US market is valued at $4.8B by 2030



Fetal (Ɣ) globin inhibits polymerization of HbS (SCD mutated Hb) addressing the specific pathophysiology of the disease

Any increment of fetal Hb (HbF) reduces severity of SCD; HbF > 8.6% or absolute 0.5 g HbF/dl normalizes survival

Natural History



NIH Landmark study In SCD (1978-1998)
~4000 subjects

HbF > 8.6% improves survival to normal range for race

Increases in HbF to a level of ≥ 8.6% or absolute HbF to ≥ 0.5 gm/dl correlate with survival and may serve as surrogate endpoints for potential accelerated approval

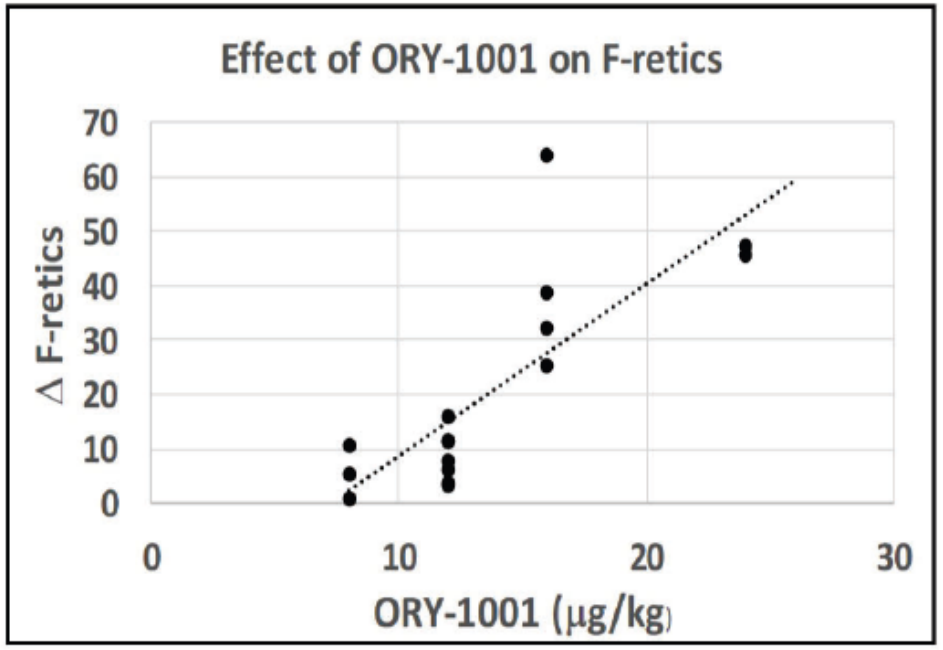
Hydroxyurea

Current Standard of Care

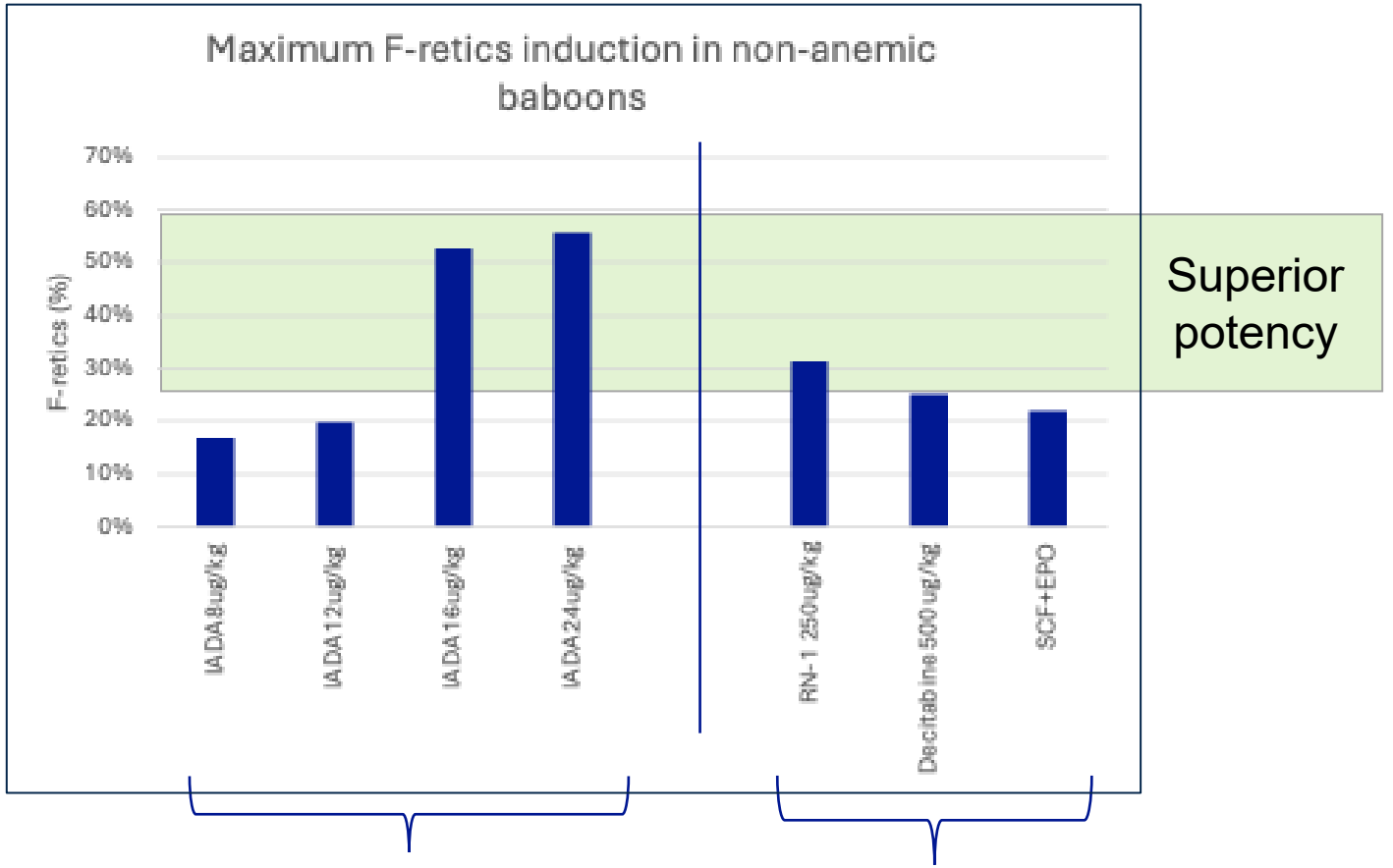
- \+ Potential to ameliorate disease pathology
- − Non-responders
- − Waning efficacy
- − Safety and tolerability issues

Proof-of-mechanism with iadademstat in non-anemic baboon model

Iadademstat effective and superior at inducing F-retics (young red cells expressing HbF)



Ibanez V. et al., Blood (142) Supp 1,2023.



Single dose was effective in increasing F-retics within 8 days in most relevant animal model without any associated neutropenia, thrombocytopenia or consistent effects on reticulocyte counts

HbF: fetal hemoglobin

RESTORE - new Phase Ib clinical trial with iadademstat in SCD

Approved by EMA, FPI expected in October 2025

RESTORE (***RE***gulation of ***S***ickling ***T***hr***O***ugh **R**eprogramming **E**pigenetics)

- N = 24-30
- Conducted in Spain
- Treatment: up to 24 weeks
- Endpoints:

Primary:
- Safety and Tolerability of iadademstat
- RP2D selected

Secondary:
- Activity inducing HbF
- PK/PD profile
- Effect on Lab markers of Hemolysis

Exploratory
- VOC frequency and duration
- Effect on RBV transfusions
- PROs
- Pharmacogenomics

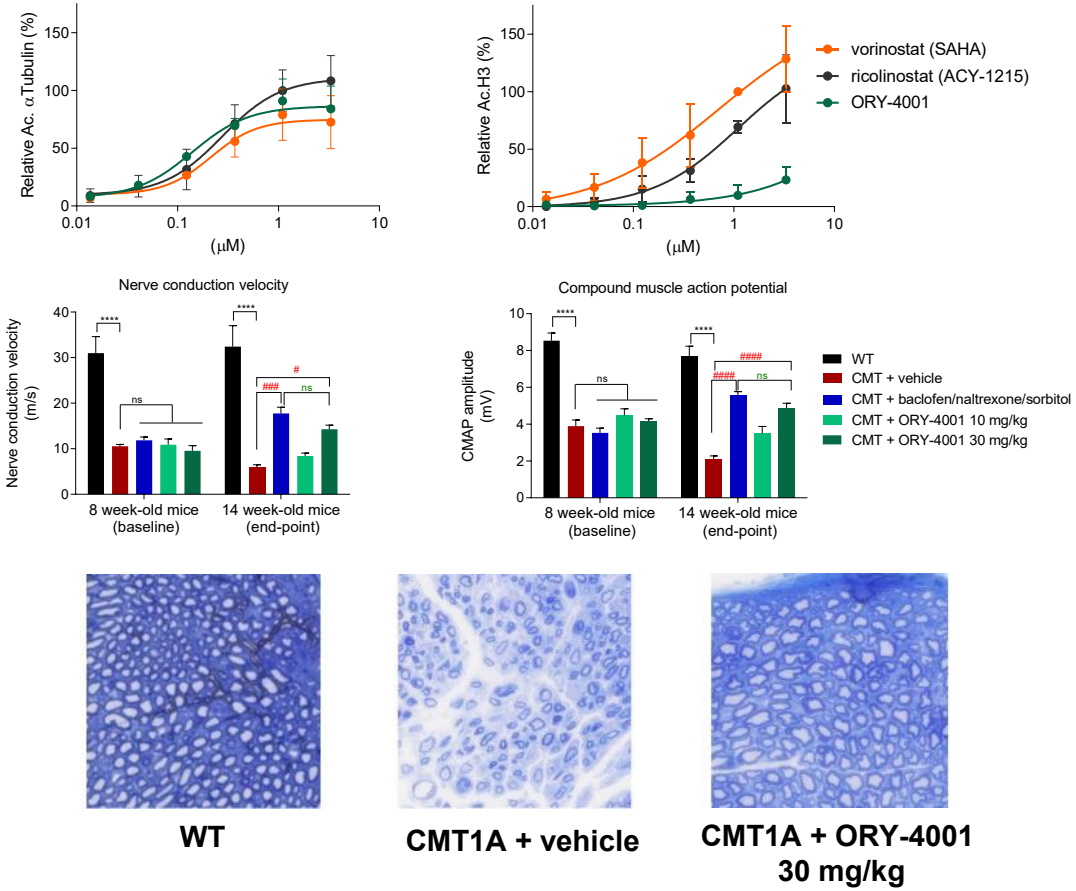
ORY-4001

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 1H2026
- Available for partnering



WT | **CMT1A + vehicle** | **CMT1A + ORY-4001 30 mg/kg**

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

Pioneering personalized medicine in epigenetics