
ORYZON
Pioneering personalized medicine in epigenetics
Junta General Extraordinaria
Corporate Presentation
12 Diciembre 2025
ORY:SM / ORY.MC

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 2027
Autism Spectrum Disorder (ASD) Aggression / Repetitive Behavior	Oryzon			HOPE-2		PhII in preparation; to initiate in 1Q2026

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			ASH 2025
Refractory/Relapsed AML FLT3 mutation+ pts, combination w/ gilteritinib	Oryzon			FRIDA		ASH 2025 & EHA 2026
Myelodysplastic Syndrome (MDS) combination w/ azacitidine	MCW		IIS-X005			EHA 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 in preparation. EHA & ASH 2026

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IIS: investigator-initiated study
MPN: myeloproliferative neoplasm

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 ET HU-resistant /intolerant; **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

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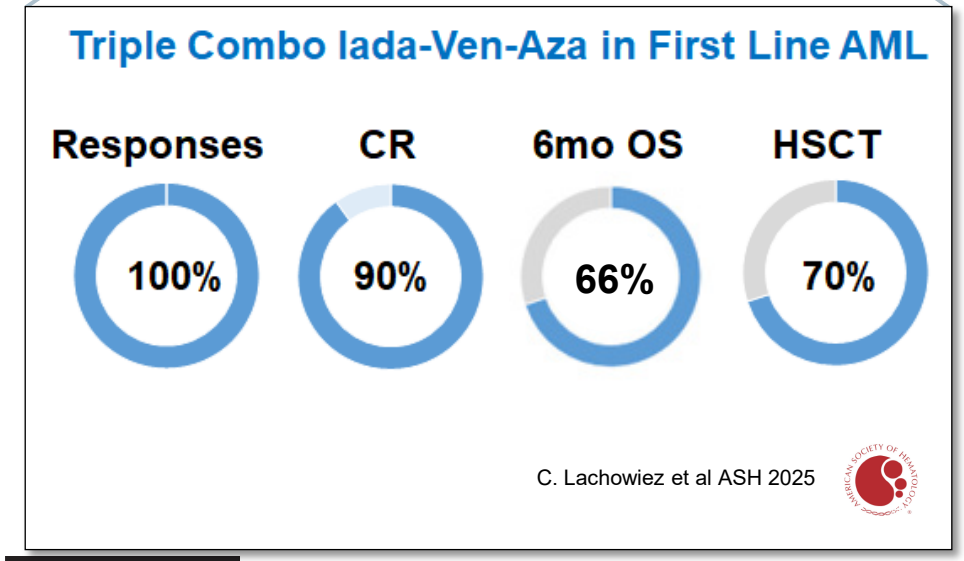
**Potential for accelerated approval based on biomarker (HbF)*

Iadademstat Combinations in hematologic malignancies

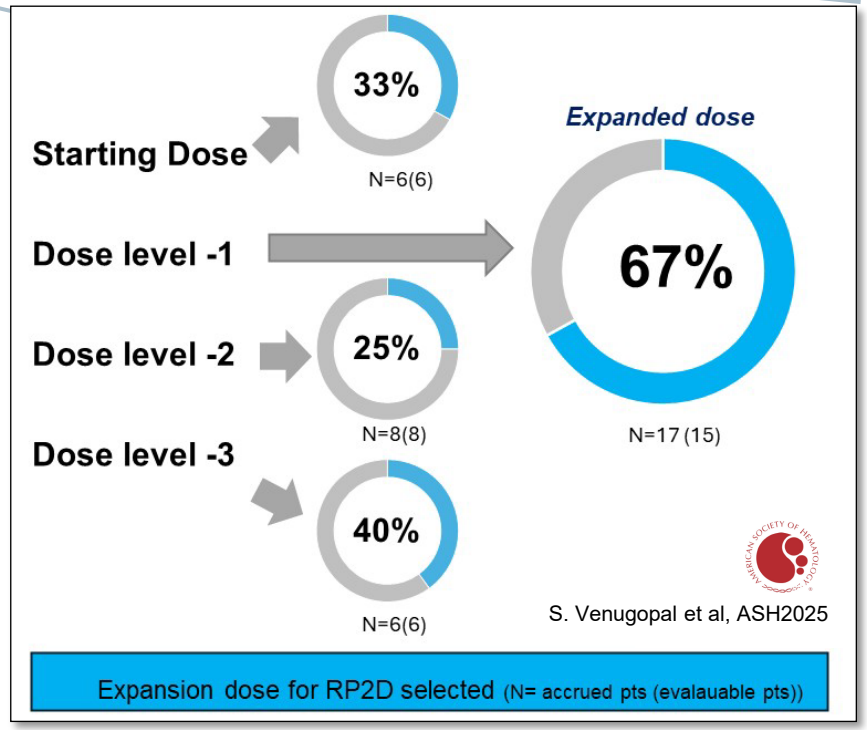
New Data: Iadademstat Combinations in AML are Highly Encouraging

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**
Enrolling, currently 10 patients. 2 iada doses tested. Safe (1 DLT of colitis)	Ongoing in expansion, not further accruing.	Enrolling. Safe, no DLTs; Signs of efficacy	Enrolling	Enrolling



ALICE-2

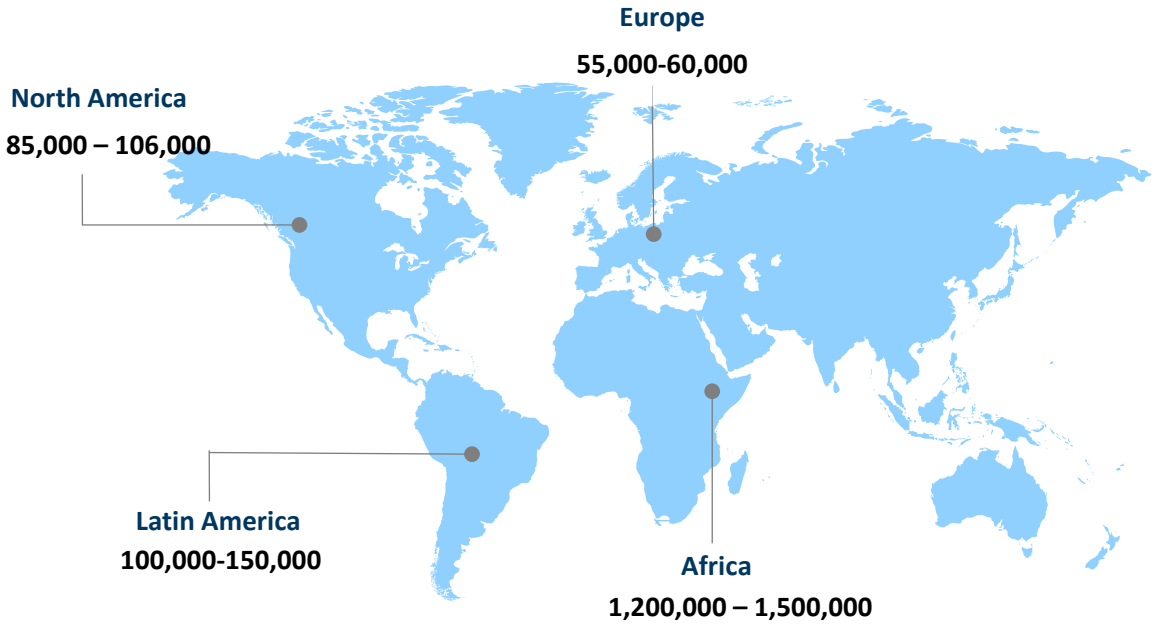


FRIDA

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

SCD 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

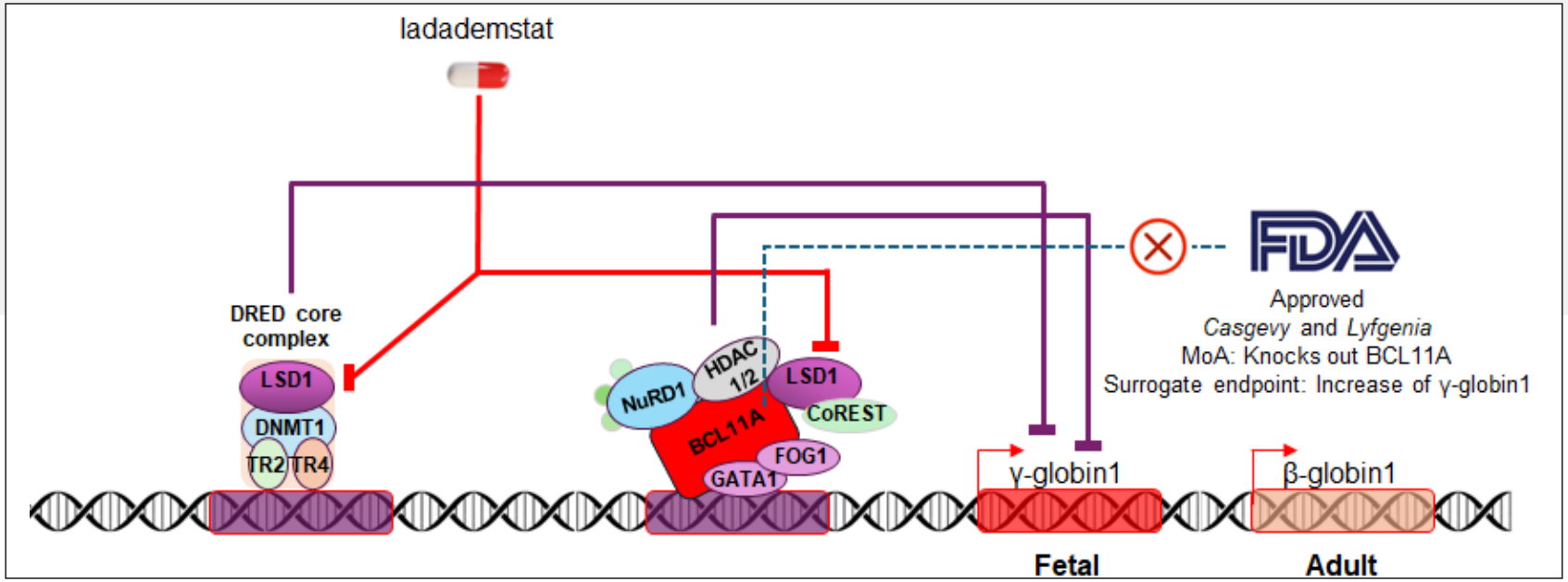
- 2019: Oxbryta received accelerated FDA approval
- 2022: Oxbryta achieved $328 million in U.S. sales
- Pfizer demonstrated in 2yr a significant market opportunity in sickle cell disease (SCD)

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. (2017) Fetal haemoglobin induction in sickle cell disease*. British Journal of Haematology *DOI 180.10.1111/bjh.15021*
- Xu J, et al .(2013) *Corepressor-dependent silencing of fetal hemoglobin expression by BCL11A*. Proc Natl Acad Sci U S A. Apr 16;110(16):6518-23. doi: 10.1073/pnas.1303976110.

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An Open-label Phase Ib in SCD (RESTORE trial) approved by EMA

FPI enrolled on Nov 3rd

	RESTORE
Expected Accrual 24-30 pts	Escalation: 18 Expansion: total of 12 at RP2D
Treatment duration:	Up to 24 wks.
Sites:	6 (all in Spain)
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

By 1H 2026:

- **We expect to establish safety in this population**
- **Biomarker (HbF) data indicating clinical activity**

By 2H 2026:

- **We expect to have a first assessment of the therapeutic efficacy of iadademstat in SCD**