Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

SEPTEMBER 2023

ORY:SM / ORY.MC

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Epigenetic Champion Developing New Therapies in **CNS** and **Oncology**

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

Focus on **developing** highly potent and selective **epigenetic drugs** against LSD1, HDAC-6 and other targets

2 Programs in Phase II with well-defined registrational pathways: **iadademstat** in Oncology and **vafidemstat** in CNS

Listed in Europe (Madrid)

MK Cap ~$130M

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

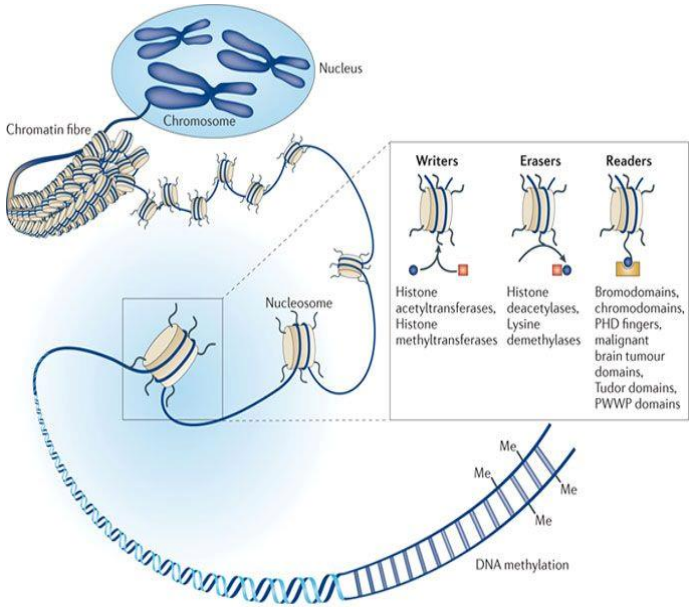

Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* **Volume 11** (2012)

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, an exquisitely well-defined MoA**
- **Class Validation: competitor LSD1i acquired for $1.4B by MERCK, and ongoing BMS's LSD1i Phase II program**
- **CRADA agreement signed with NCI-NIH**

- **in CNS, phenotypic rescues in different genetically-defined neurodevelopmental syndromes**
- **Ample evidence of neurological benefits in different animal / disease models**
- **A unique competitive position**

Two uncorrelated clinical assets with Multiple Shots on goal

	INDICATION	STUDY	PHASE	STATUS	NEXT ANTICIPATED UPDATES / MILESTONES
CNS	**VAFIDEMSTAT (ORY-2001) - CNS optimized LSD1 inhibitor**				
	Borderline Personality Disorder	**PORTICO**	**IIb**	**Recruitment Completed**	**Top Line Data 4Q23-1Q24**
	Schizophrenia (Negative symptoms & Cognition)	EVOLUTION	**IIb**	Recruiting	Study updates 2024
	Kabuki Syndrome	HOPE	**Ib/II**	IND in preparation	IND 2024
	ORY-4001 - CNS optimized HDAC6 inhibitor				
	Charcot Marie Tooth / ALS		**Clinical candidate**	Reg. Preclinical	2023 PNS Ann.Meeting June 2023
ONCOLOGY	**IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor**				
	AML (1L Elderly/Unfit)	ALICE (Combo w azacitidine)	**IIa**	Completed	Final positive results presented at ASH2022
	AML (R/R-Flt3mut+)	**FRIDA (Combo w gilteritinib)**	**Ib**	**Recruiting**	**ASCO-2024 / ASH-2024**
	NETs (R/R) *	NET Basket (Combo w paclitaxel)	**II**	Recruiting	Study updates 2H24
	ED-SCLC (1L)	STELLAR (Combo w ICI)	**Ib/II**	IND in preparation	IND 2024
OTHER PROGRAMS	**ORY-3001 - selective LSD1 inhibitor**				
	Hematological Non-Onc		**Reg. Preclinical completed**		

main investment thesis in the short-mid term

* Collaborative study with Fox Chase Cancer Center
Note: Finalized clinical trials for iadademstat and vafidemstat are not shown. See www.oryzon.com for more details
AML: acute myeloid leukemia; SCLC: small cell lung cancer; NETs: neuroendocrine tumors ; ALS: amyotrophic lateral sclerosis

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ORYZON, the only company developing epigenetic drugs in CNS

VAFIDEMSTAT
A Phase II LSD1 inhibitor for CNS diseases

Vafidemstat: an LSD1 inhibitor to treat large multifactorial CNS indications including borderline personality disorder (BPD) and schizophrenia (SCZ)

Mechanism of Action

- **LSD1i induces neuronal plasticity & downregulates neuroinflammation**
- **Modulates the glutamatergic signal**
- LSD1i improves **memory, aggressivity and sociability** and **modulates** the response to environmental stress

Key Clinical Data

- **Safety and effectiveness demonstrated as a single agent. Good Pharmacology: ORAL; no DDIs**
- **Various trials** (+400 people treated):
  - Reduction of inflammatory markers
  - Reduction in aggression (REIMAGINE basket trial; 30 BPD, ADHD, and ASD pts)
  - Improvements in overall patient functioning, particularly in BPD patients (REIMAGINE basket trial)

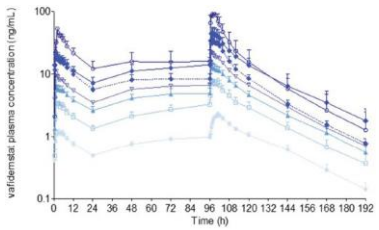
Safe & well tolerated

No differences between placebo and vafidemstat-treated patients

Excellent Brain Penetration

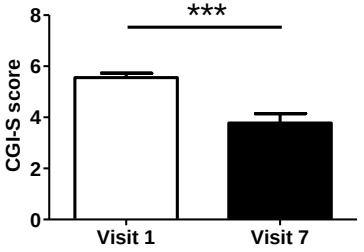
An optimal CSF : plasma ratio of 0.9

Oral, once a day



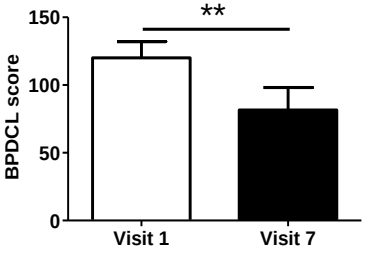
PK data supports once daily dosing in both adult and elder subjects

Reduces Aggression



Reduces Aggression in BPD, ADHD and ASD patients after 2 months of treatment

Improves BPD disease

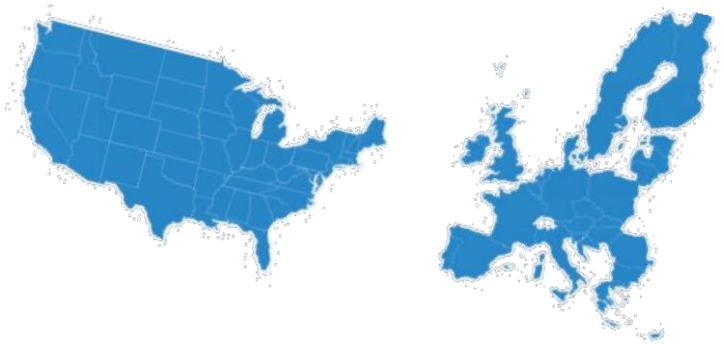


Reduces overall severity in BPD patients after 2 months of treatment

Borderline personality disorder: Unmet medical need and large commercial opportunity

A Prevalent & impairing disease

9 million in US & EU



Two main types of symptoms

Unstable-extreme interpersonal relationships

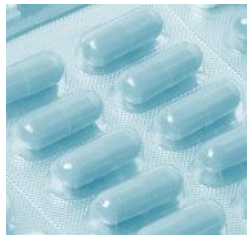
+

Agitation and Aggression*

*Including self-directed aggression

No approved drugs

Off-label antipsychotics with serious side-effects



Vafi improves BPD symptoms in:

- **BPD patients**
- **in PC models**

Highest Revenue Drug Category: Antipsychotics followed by antidepressants

Aggregated sales: ~ $1 Billion

Very low competition

0 Phase III trials

2 Phase II trials

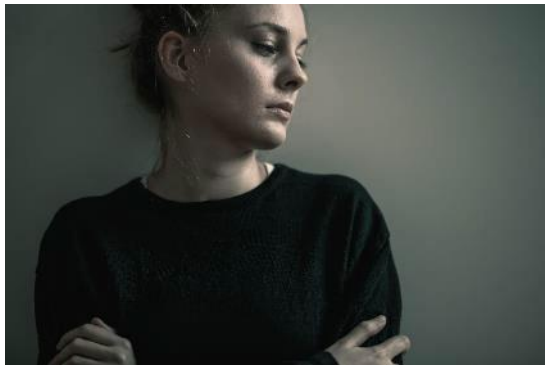
Expected peak sales for vafi

US ~ $3 billion

Ongoing Study: a Phase IIb in Borderline Personality Disorder

PORTICO:

An adaptative randomized double blind Phase IIb trial with vafidemstat in Borderline Personality Disorder patients



PORTICO (NCT04932291) Recruitment completed (210 patients enrolled in EU and US)

- With multiple independent primary endpoints:
  - Overall clinical BPD improvement: *Evaluation of the difference on the BPDCL, from baseline to specific week, between the active treatment arm and the placebo arm*
  - Improvement in aggression: *Evaluation of the difference on Agitation/Aggression (CGI-S A/A) from baseline to specific week, between the active treatment arm and the placebo arm*

Several safety analyses by the independent DMC showed safety & tolerability

A prespecified interim analysis (w 90 patients) successfully passed in 1Q23 (To assess futility & signal size)

Top Line read out 1Q24

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EVOLUTION, an ongoing PoC schizophrenia study with vafidemstat

EVOLUTION:
An adaptative randomized double blind Phase IIb trial with vafidemstat in schizophrenia patients

- Strong rationale: LSD1i restores phenotypes in various SCZ mice models
- **High Unmet Need:** No drugs approved yet for cognitive impairment or negative symptoms of SCZ
- **EVOLUTION**: Double blind, placebo controlled adaptive trial design (n=100)
- Vafidemstat as add-on to SoC. 6 months of treatment
- Primary endpoints: efficacy to address SCZ Negative and cognitive symptoms
- Actively recruiting patients in EU

A Prevalent & impairing disease
20 millio ww.

~5 million in US & EU

Market Value in 2021

US$ ~8 billion

Three main types of symptoms

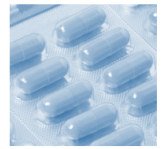
Positive or Negative
+
Cognitive Impairment

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

Single Best seller:
+ $ 3.5 Billion

No approved drugs yet for

Negative symptoms (60%)
Cognitive Impairment (70%)



Vafi improves these symptoms in PC models

Moderate competition

ORYZON is pioneering personalized medicine in CNS

VAFIDEMSTAT
A Phase II LSD1 inhibitor for CNS diseases

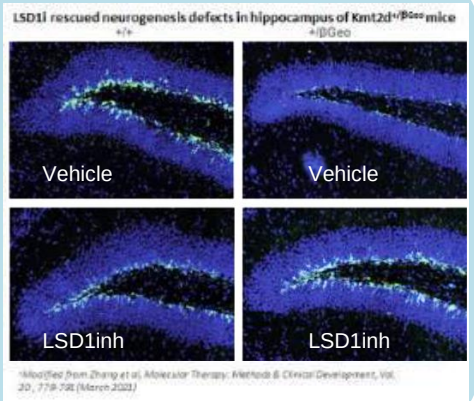
Vafidemstat: an LSD1 inhibitor targeting genetically defined neurodevelopmental syndromes, e.g., Kabuki

Mechanism of Action

- **LSD1i can compensate complex phenotypes caused by single gene deficiencies that are the cause of some rare neurodevelopmental syndromes**
- Specifically, in histone methyltransferase deficiencies like Kabuki syndrome (KS), LSD1i restores brain chromatin methylation balance and rescues multi-systemic deficits

Key Preclinical & Clinical Data

- **+400 subjects treated** with vafidemstat
- **Safety and effectiveness demonstrated as a single agent**
- In a KO mice model of KS, LSD1i produced restoration of neurogenesis, memory rescue, brain chromatin methylation rebalance and immunological rescue



Route to Market

- Initial clinical development program focused on Kabuki syndrome type 1
- **Approx. 6,000+ pts with KS type 1, with a significant market potential**
- Additional well-established genetically-defined diseases emerging **as possible label extensions**

A growing market opportunity

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

HOPE: a Phase Ib/II trial in Kabuki syndrome patients

HOPE:
An adaptative randomized double blind Phase I/II trial with vafidemstat in KS Type 1 patients

- Phase Ib objectives: evaluate safety/tolerability, and determine the RP2D
- Phase II objective: evaluate efficacy of vafidemstat at the RP2D in KS Type 1 patients
- IND 2024
- **HOPE may set the basis for an expedited development if a significant clinical benefit in the population is demonstrated over placebo**

- Kabuki syndrome (KS) is caused by **mutations in the KMT2D/MLL2 gene (KS Type 1, about 70% of cases) or the KDM6A gene (KS Type 2)**
- KS is a **congenital, rare, multisystem disorder** characterized by multiple multi-organ abnormalities including intellectual disability
- **Strong preclinical rationale for inhibiting LSD1 in KS**

JOHNS HOPKINS UNIVERSITY

Kennedy Krieger Institute

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ORYZON has an ambitious epigenetic program in Oncology

IADADEMSTAT
A Phase II LSD1 inhibitor in Oncology

AML Program:

ALICE and FRIDA trials

Iadademstat: first and potentially best-in-class LSD1 inhibitor in AML

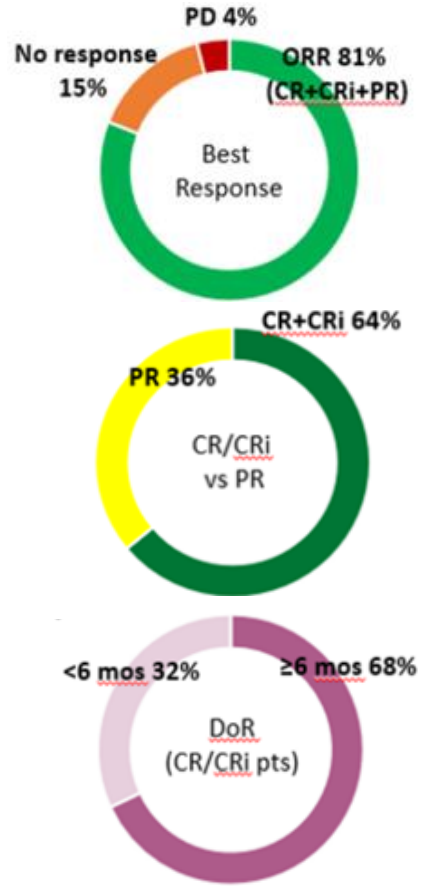
Mechanism of Action

- 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

Key Clinical Data in ALICE as PoC

- Multicenter, single arm, open label PhIIa trial in **elderly unfit AML patients** (n=36)
- **Iadademstat in combination with azacitidine**
- Primary endpoint: Dose finding, safety and tolerability of combo therapy
- Secondary endpoints: Response; time to response; duration of response; overall survival
- **Final data presented at ASH-2022**. Selected for Oral presentation.
- Shortlisted in the 25 most relevant AML comms to be considered for 2023 HIGHLIGHTS OF ASH
- **Combination is safe and effective**
- **Responses are rapid, deep and durable**
- **RP2D established**
- **Responses seen in patients with a diverse array of AML mutations**

64th ASH Annual Meeting and Exposition
December 10 – 13, 2022 • New Orleans, Louisiana

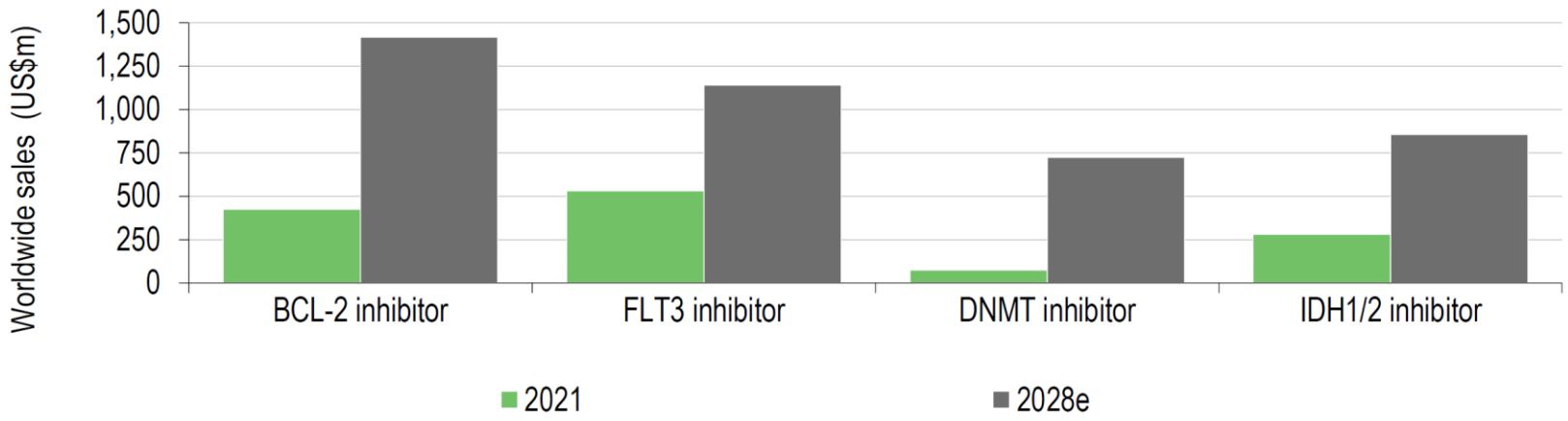


FLT3mut+ R/R AML, an interesting market opportunity

Combo w gilteritinib, best route to market

- In a competitive market, R/R AML is an underserved population: **Majority of AML patients relapse after 1L treatment and require further treatment**
- FLT3 is the most common mutation in AML (**30-40%**)
- These patients are now treated with **gilteritinib,** yet there is a **high medical need (mEFS 2.8 months & CR+CRi 34%)**
- **Global FLT3 inhibitors market expected to reach $2.06 Billion by 2032***

**https://www.bloomberg.com/press-releases/2022-08-30/bis-research-study-projects-the-global-flt3-inhibitors-market-to-reach-2-06-billion-by-2032*



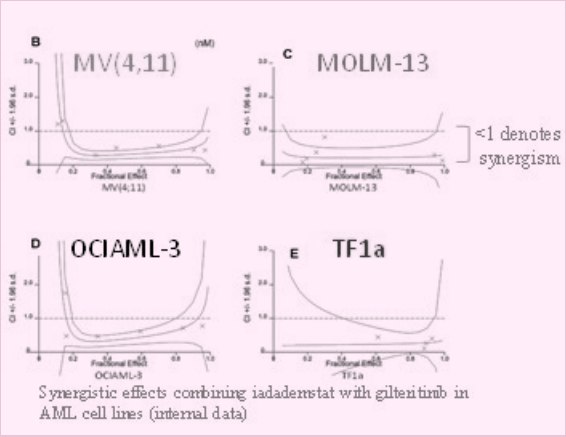
R/R-AML Flt3mut+ space is a significant market opportunity

(Source Edison Research 2023 & Evaluate Pharma)

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

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

- **Iadademstat and gilteritinib show a strong synergism**, providing a strong preclinical rationale for enhanced clinical benefit
  - Primary objectives: evaluate safety/tolerability, and determine the RP2D of the combination
  - Secondary objective: evaluate efficacy of the combination (CR rate, DoR, MRD)
  - Up to 50 patients
  - Study conducted in the US. **Recruiting**
  - Agreement with FDA to discuss next steps for pivotal trial development after this Phase Ib



Synergistic effects combining iadademstat with gilteritinib in AML cell lines (internal data)

Study presented at

2023 ASCO ANNUAL MEETING

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

***PI*: Dr. Amir Fathi,** *Leukemia Lead & Program Director, Center for Leukemia at Massachusetts General Hospital and Dana Farber Cancer Center (Harvard Medical School)*

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Neuroendocrine Program:

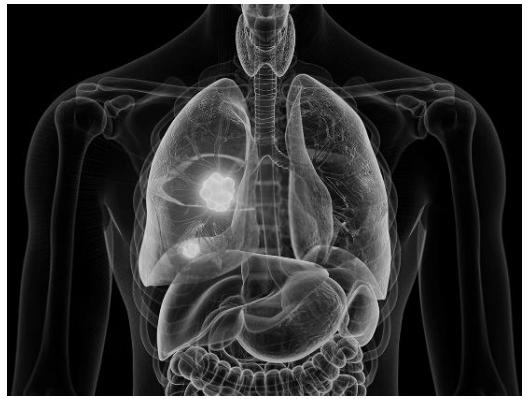
STELLAR and NET trials

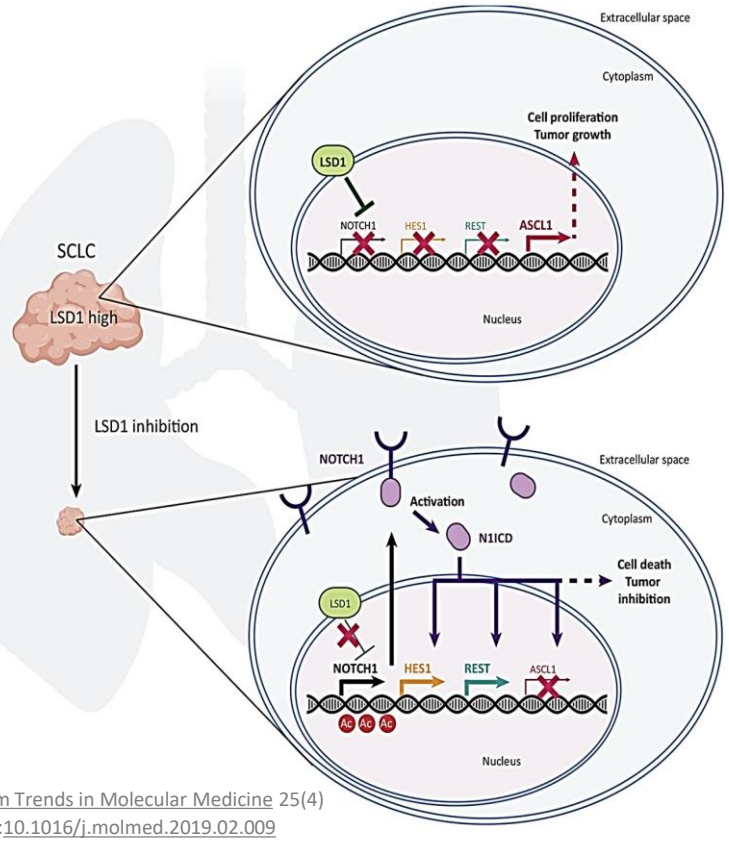
Iadademstat: potentially first and best-in-class LSD1 inhibitor in SCLC and other Neuroendocrine tumors

Mechanism of Action

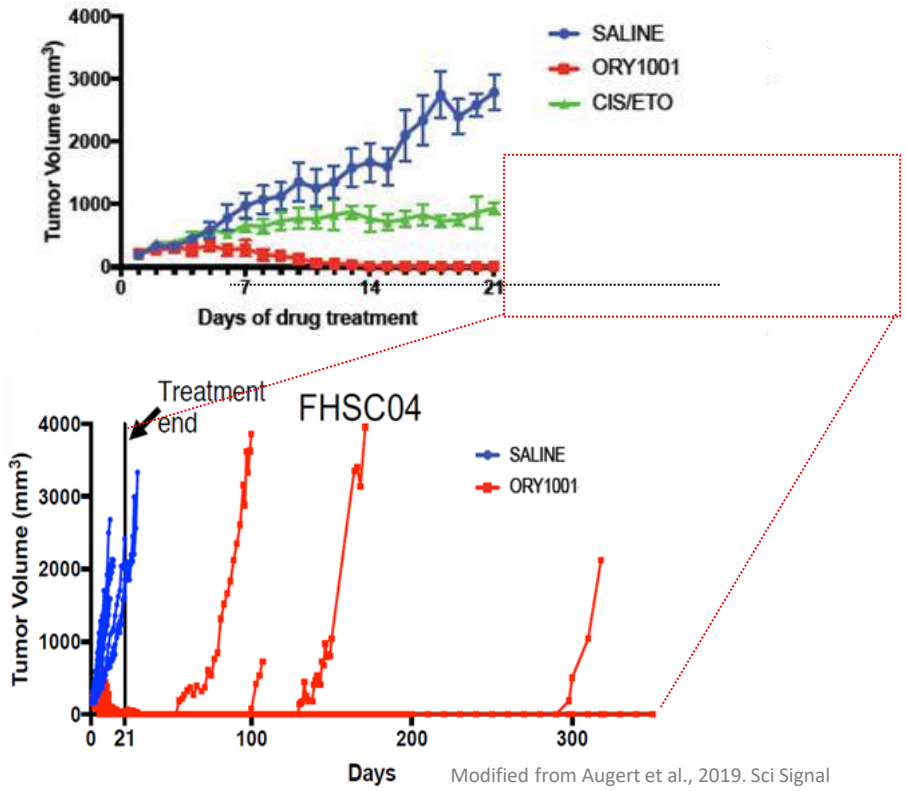
- LSD1 is required for survival & proliferation of **neuroendocrine/SCLC tumor cells**
- Iadademstat **induces Notch**, a well characterized tumor suppressor in SCLC **and represses ASCL1**
- **Iadademstat blocks LSD1's actions and promotes neuroendocrine/SCLC tumor differentiation and death**
- **Iadademstat synergizes with ICIs and boosts the host immune system by increasing T cell infiltration and preventing T-cell exhaustion**

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





From Trends in Molecular Medicine 25(4)
DOI:10.1016/j.molmed.2019.02.009



Modified from Augert et al., 2019. Sci Signal

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Neuroendocrine Tumors: a Collaborative PoC basket trial in NETs with iadademstat

FOX CHASE CANCER CENTER
TEMPLE HEALTH

NET:
A Phase II study of iadademstat in combination with paclitaxel in platinum-R/R SCLC and extrapulmonary high grade neuroendocrine carcinomas

- High unmet medical need: NETs have dismal outcomes ranging from ORR 5% (extrapulmonary) to ~20-30% in second line SCLC; with mPFS 3 to 4 months, respectively
- Strong rationale for combination: preclinical data showing synergy between iadademstat and paclitaxel
- Sponsor: Fox Chase Cancer Center
- FPI Jan23, **recruiting**

PI: Dr. Namrata Vijayvergia
Assistant Chief, Gastrointestinal Medical Oncology
Associate Professor, Department of Hematology/Oncology
Medical Director, Medical Oncology

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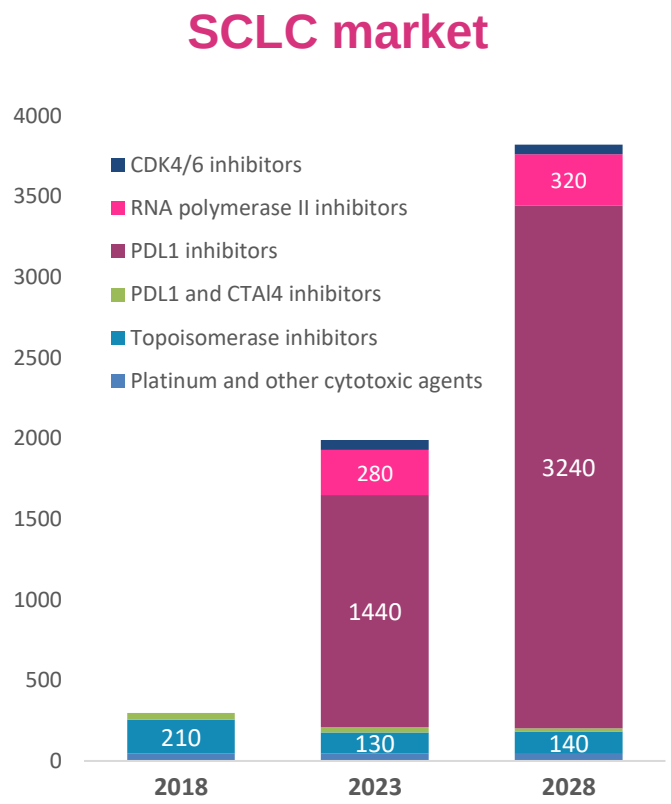
ED-SCLC, an interesting market opportunity

Best route to Market:

Combo with IO, 1L ED-SCLC in maintenance

- **Tolerability profile of both drugs suggesting high compatibility**
- The **global market for small-cell lung cancer drugs** expected to reach **+$3.4 billion by 2027,** expanding at a CAGR of 19.4% over the forecast period, driven by the approval and uptake of premium-priced targeted therapies
- **Iadademstat peak sales are estimated to be +$1.5 billion in 1L maintenance therapy**



A future Phase Ib/II trial in 1L ED-SCLC with potential for accelerated development

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

- **High unmet medical need** + relative low bar for improving efficacy due to the modest efficacy improvements (**2 months OS increment with recent approval of ICI in combo with chemotherapy**) shown in the IMPower-133, CASPIAN and Keynote-604 trials in 1L SCLC
  - Phase Ib objectives: evaluate safety/tolerability, and determine the RP2D and MTD of iadademstat in combination with ICI
  - Phase II objective: evaluate efficacy of the combination of iadademstat and ICI vs ICI alone in maintenance after SoC chemotherapy measured as PFS
  - IND 2024

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PI: Dr. Hossein Borghaei, Chief, Division of Thoracic Medical Oncology Professor, Department of Hematology/Oncology Co-Director, Immune Monitoring Facility at FCCC

STELLAR could potentially support an accelerated approval if a significant clinical benefit in the population is demonstrated over the efficacy of SoC treatment

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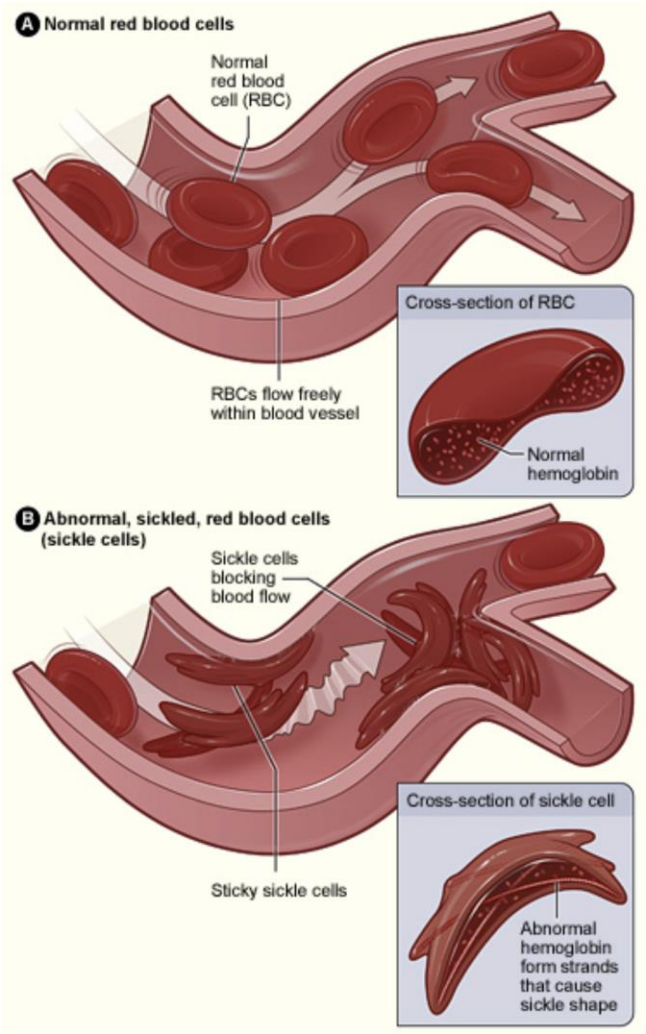
ORY-3001

A refined LSD1 inhibitor for hematological disorders

Sickle cell disease



Source: wikipedia

Sickle cell anemia is an inherited autosomal recessive disorder resulting in qualitative mutation of the hemoglobin structure in red blood cells (RBCs).

The mutation of normal hemoglobin A (α2ß2) to hemoglobin S (α2ß26 Val) is caused by the amino acid substitution of valine (GTG) for glutamic acid (GAG) on the sixth position of the ß chain.

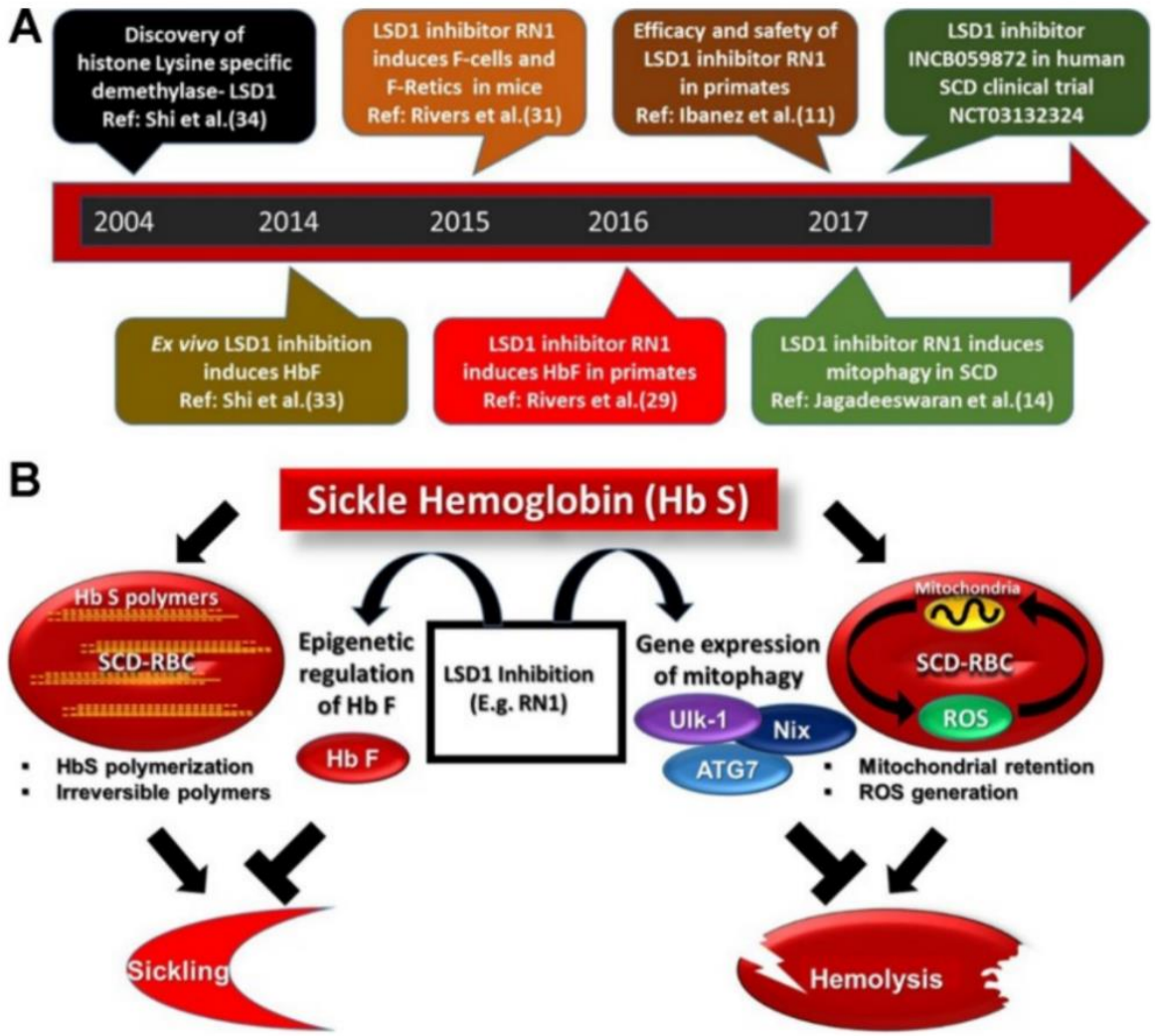
The sickling process occurs under deoxygenated conditions in which hemoglobin S polymerizes, forming aggregates called tactoids that give the resulting product a rigid structure.

As a consequence, patients suffer from:

- Anemia. Sickle cells break apart easily and die
- Episodes of acute pain. Periodic episodes of extreme pain, called pain crises, are a major symptom of sickle cell anemia
- Swelling of hands and feet
- Frequent infections
- Delayed growth or puberty

ORY-3001 inhibition in Sickle Cell Disease

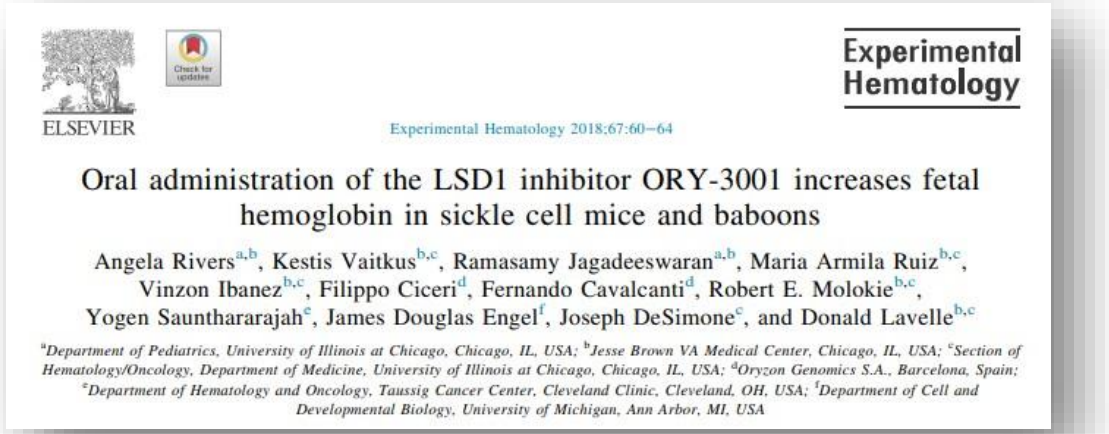
- ORY-3001 is a highly potent and selective oral LSD1 inhibitor with a very good pharmacology
- It has completed the IND enabling toxicology
- Its action over SCD is based on two distinct mechanisms:
  - one addresses sickle hemoglobin (HbS) polymerization-mediated sickling, and
  - the other addresses RBC reactive oxygen species (ROS) generation-induced hemolysis. HbF, fetal hemoglobin; Retics, reticulocytes



Rivers A, Jagadeeswaran R, Lavelle D. Potential role of LSD1 inhibitors in the treatment of sickle cell disease: a review of preclinical animal model data. Am J Physiol Regul Integr Comp Physiol. 2018 Oct 1;315(4):R840-R847. doi: 10.1152/ajpregu.00440.2017. Epub 2018 Aug 1. PMID: 30067082; PMCID: PMC6734057.

ORY-3001 Efficacy in SCD models

- **PoC** demonstrated in:
  - **SCD Townes mouse** model
  - **SCD non-anemic baboon model**
  - **SCD anemic-bled baboons**



ELSEVIER

Experimental Hematology

Experimental Hematology 2018;67:60–64

Oral administration of the LSD1 inhibitor ORY-3001 increases fetal hemoglobin in sickle cell mice and baboons

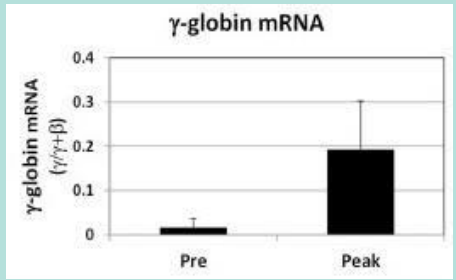
Angela Rivers[a,b], Kestis Vaitkus[b,c], Ramasamy Jagadeeswaran[a,b], Maria Armila Ruiz[b,c], Vinzon Ibanez[b,c], Filippo Ciceri[d], Fernando Cavalcanti[d], Robert E. Molokie[b,c], Yogen Saunthararajah[e], James Douglas Engel[f], Joseph DeSimone[c], and Donald Lavelle[b,c]

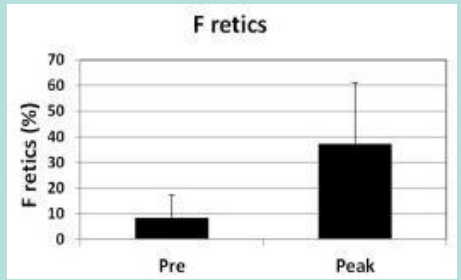
[a]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL, USA; [b]Jesse Brown VA Medical Center, Chicago, IL, USA; [c]Section of Hematology/Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA; [d]Oryzon Genomics S.A., Barcelona, Spain; [e]Department of Hematology and Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, USA; [f]Department of Cell and Developmental Biology, University of Michigan, Ann Arbor, MI, USA

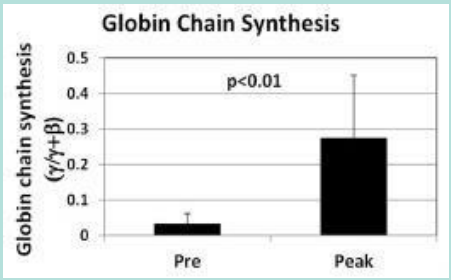
- **LSD1 occupancy confirmed** by target engagement analysis and platelet reduction

In these models, ORY-3001 increased:

- Expression of **γ-globin mRNA**
- **Fetal reticulocytes** (F retics)
- **γ–globin chain synthesis** or fetal hemoglobin (**HbF**)



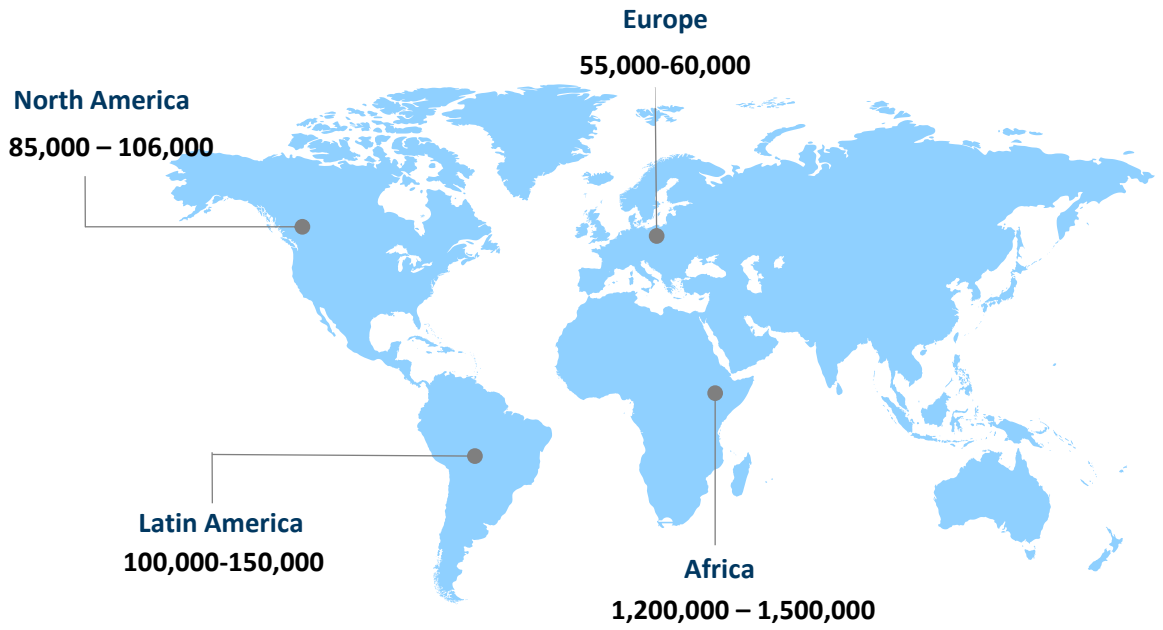




Sickle cell disease prevalence

Around 20-25 million people are living with SCD across the globe and the number is anticipated to increase by 30% by 2050. Approximately, SCD accounts for 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



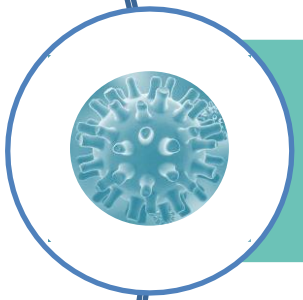
Number of Sickle Cell Births Per Year	
Country	**No. of SCD Birth/Year**
U.S.	3,000
India	5,200
U.K.	270
Nigeria	91,011
Tanzania	11,877
Angola	9,017
Uganda	10,877
Ghana	5,815
Niger	5,310
Zambia	6,039
Cameroon	7,712
Global	305,773

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

ORY-3001 is available for partnering in non-oncological indications

Non-malignant hematological diseases

Sickle Cell disease, Polycythemia vera, etc…



Viral Infections

Viral infections caused by a variety of viruses

Immune-mediated disease: Psoriasis

Inhibits CCL2 release in cultured keratinocytes

ORY-4001

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

ORY-4001 is a highly potent and selective HDAC6 inhibitor

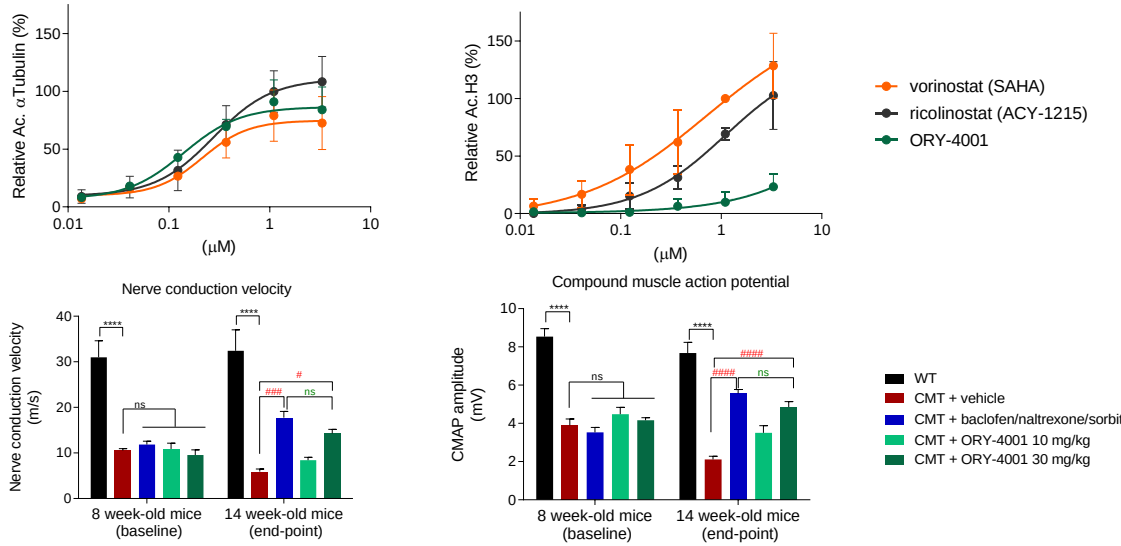
HDAC-6 has been suggested as a therapeutic target in Charcot-Marie-Tooth (CMT), ALS, and other CNS diseases

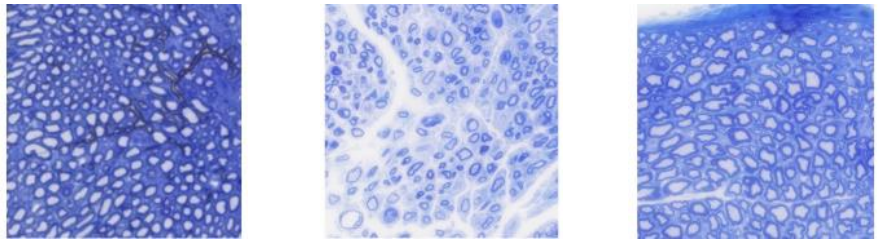
ORY-4001 is a highly potent and selective HDAC6 inhibitor with good pharmacology

ORY-4001 increases nerve conduction velocity and CMAP in a CMT1A mice model

ORY-4001 increases axonal number and myelination in a CMT1A mice model

First in Man readiness is expected by end of 2024





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

ORYZON

CMT: a medical need and a market opportunity

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease is a group of inherited disorders that cause nerve damage. This damage is mostly in the arms and legs (peripheral nerves).

Facts

- It is an inherited, genetic condition
- Males are more affected by this disease
- The most common type of CMT is CMT1

Diagnosis

- Physical exam
- Nerve conduction studies
- Electromyography (EMG)
- Nerve biopsy
- Genetic testing

Types

- CMT1A
- CMT1B
- CMT1D

Epidemiology Insights (2020)

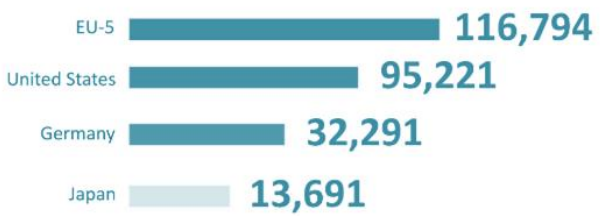
263,835
The total prevalent population in 7MM

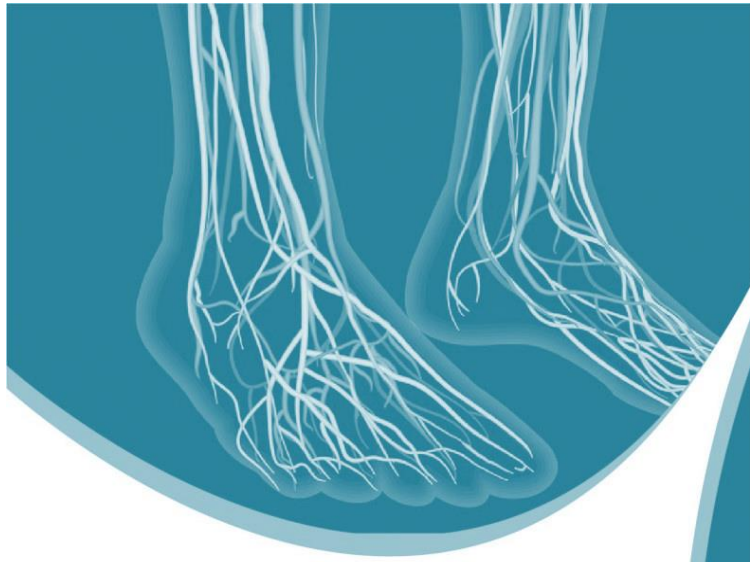
The age-specific cases in EU-5

41-60 years – Most affected

0-18 years – Least affected

The diagnosed prevalent population





Market Size 2021
US$ 793.9 MILLION

Value Projection 2028
US$ 3,459.1 MILLION

ORYZON

ORYZON

A unique dual EPIGENETIC proposition in CNS and ONCOLOGY

- A validated approach with multiple shots on goal
- One and only epigenetic company in CNS
- 2 Phase II programs
- Differentiated pipeline of first- and potentially best-in-class LSD1 therapies
- Derisked: Safety proven in +500 subjects dosed

Value Creation in 2023

Multiple inflection points

- **Top Line Read Out in BPD PORTICO 1Q24**
- **2L AML FRIDA and NET trials preliminary readouts in 2024**
- Kabuki Syndrome Phase I/II trial IND 2024
- 1L ED-SCLC with potential to support accelerated development to start in 2024

Pioneering personalized medicine in epigenetics