ORYZON

Pioneering personalized medicine in epigenetics

Corporate Presentation
January 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

Developing highly potent and selective drugs against LSD1

2 Programs with well-defined registrational pathways:

- iadademstat in Oncology (PhII)
- vafidemstat in CNS (PhIII-ready)

Listed in Europe (Madrid)

- Highly liquid company
- €121M raised in equity(1) since listing in 2015
- €33.5M raised in equity(1) since 2022

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(1) including convertible notes

Oryzon investment thesis

A unique dual EPIGENETIC approach

A molecule in psychiatry (BPD-Phase III-ready, SCZ-Phase II)

Area of great interest for Pharma (M&A and licensing)

Following End-of-Phase II meeting with FDA, preparing a **Phase III trial** in BPD

Options to expand to precision medicine in rare CNS disorders

A Phase II molecule with promising clinical data in AML and SCLC

Endorsed by the NCI-NIH CRADA Agreement

2 ongoing trials in AML and SCLC that may set up the basis for accelerated approval

Additional ongoing trials in hemato-oncology

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

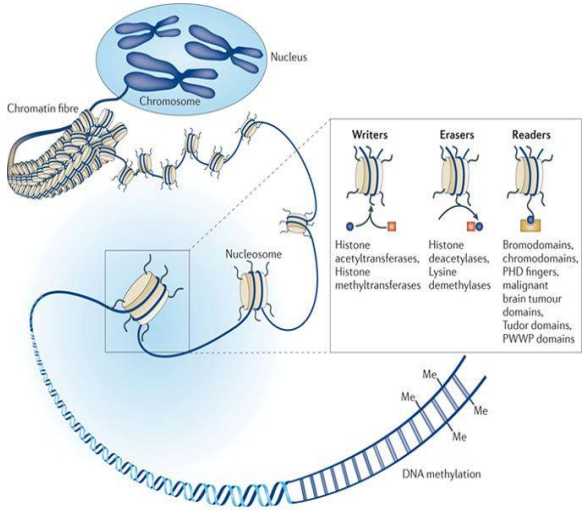


Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* **Volume 11** (2012)

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. Trials ongoing in AML and SCLC/NET

- 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; NETs: neuroendocrine tumors; SCZ: Schizophrenia; BPD: Borderline Personality Disorder

Multiple Shots on goal & main investment thesis in the short-mid term

Two main catalysts in 2025: PORTICO-2 in BPD Phase III protocol approval and FRIDA in AML

Program	Study	Preclinical Phase	Phase I		Phase II		Status	Expected Milestone(s)
			Phase Ia	Phase Ib	Phase IIa	Phase IIb		
CNS: Vafidemstat (ORY-2001) – CNS optimized LSD1 inhibitor								
Borderline personality disorder Agitation / Aggression & Overall Improvement	PORTICO						**Completed.** Study has results	Final Data 3Q24 ECNP-2024 EoP2 FDA meeting 3Q24 Ph III protocol submission 1H25 ★
Schizophrenia Negative Symptoms	EVOLUTION						**Recruiting**	Timeline updates in 2025
Kabuki Syndrome	HOPE			Phase Ib/II			**IND in evaluation**	IND in 2025 (subject to additional resources)
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	1st cohort dosed
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 EHA-2025 ★
MDS Combination with azacitidine	IIS-X005			Phase I			**Recruiting** Sponsor: MCW	1st patient dosed
Neuroendocrine High Grade R/R Combination with paclitaxel	C-X001 NET Basket						**Recruiting** Collab Study with FCCC	Study Updates 1H25
ED-SCLC 1L Combination with ICI	STELLAR-0 (CRADA-SCLC)				Phase I/II		**IND Approved** Sponsor: NCI, Led by MSKCC	FPI 1Q25
ED-SCLC 1L Combination with ICI	STELLAR					Phase II pivotal	**In preparation**(*) Company sponsored	IND 2025
Other Programs								
ORY-3001 (LSD1i) Sickle Cell Disease							IND enabling tox completed	
ORY-4001 (HDAC6i) CMT, ALS							IND enabling tox ongoing	

ALS: amyotrophic lateral sclerosis; AML: acute myeloid leukemia; CMT: Charcot-Marie-Tooth disease; CRADA: Cooperative Research and Development Agreement; FCCC: Fox Chase Cancer Center; ICI: immune checkpoint inhibitor; IIS: investigator-initiated study; MCW: Medical College of Wisconsin; MDS: myelodysplastic syndrome; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; NETs: neuroendocrine tumors; OHSU: Oregon Health & Science University; SCLC: small cell lung cancer; UPMC: University of Pittsburgh Medical Center

Notes: Study names indicated for IIS or CRADA trials correspond to Oryzon's internal names for these trials. (*) STELLAR trial to be informed by the data to be obtained in the STELLAR-0 trial.

ORYZON, the only company developing epigenetic drugs in CNS

VAFIDEMSTAT

A Phase III-ready LSD1 inhibitor for CNS diseases

Oryzon Product Portfolio in CNS

VAFIDEMSTAT	Study	Preclinical	Phase I	Phase II	Phase III	FILED
Vafidemstat (ORY-2001) - the only CNS optimized LSD1 inhibitor						
Borderline personality disorder Agitation/Aggression & Overall Improvement	PORTICO					
Schizophrenia Negative Symptoms	EVOLUTION					

- Final Data of PORTICO in BPD released at the European College of Neuropharmacology (ECNP) Sept 23rd 2024.
- Positive Outcome Minutes from FDA end-of-Phase 2 meeting received in Sept
- FDA IND approval for Phase III in BPD expected 1H25

Vafidemstat is safe and well tolerated drug

A very robust safety package. +430 treated subjects

Brain Penetrant

An optimal
CSF: plasma
ratio of 0.9

Safe, No DDIs

Comparable SARs between
placebo and vafidemstat arms
in 6 Phase II trials:
1.0% vafidemstat vs 1.0% placebo

No side effects

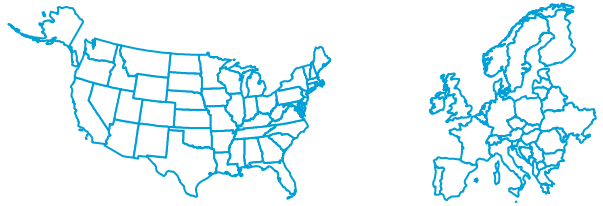
No weight gain

No sedation / somnolence

No sexual dysfunction

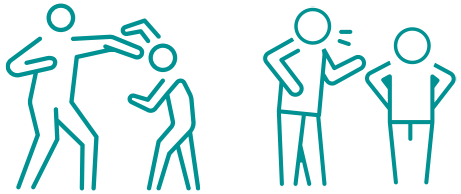
No extrapyramidal signs

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



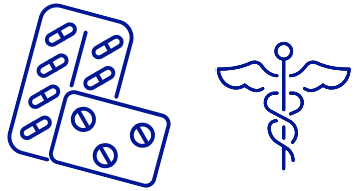
Prevalent & impairing disease

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=210
Randomized
1:1

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

Placebo
Once daily, N=104

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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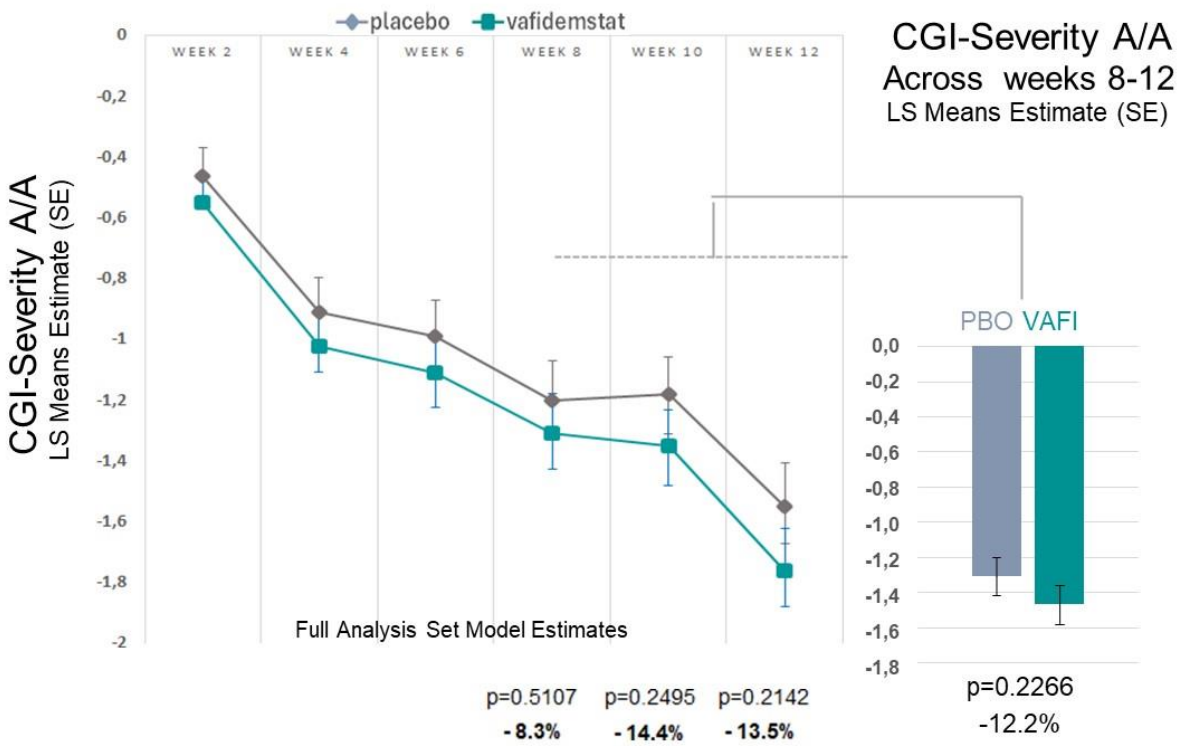
FINAL ANALYSIS

Phase IIb PORTICO study
Efficacy of vafidemstat in Borderline Personality Disorder

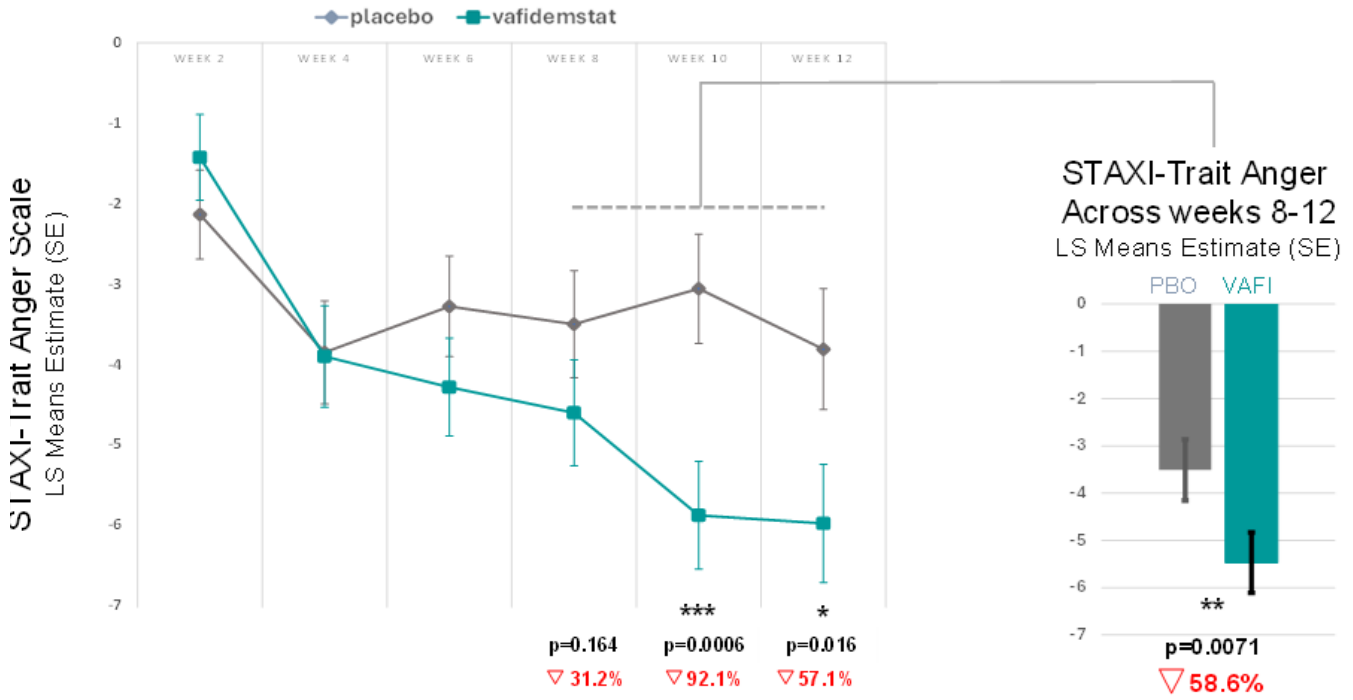
ECNP-2024

Treatment improves aggression over placebo (Secondary endpoint)

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



Secondary endpoint
STAXI-2 (Patient rated)



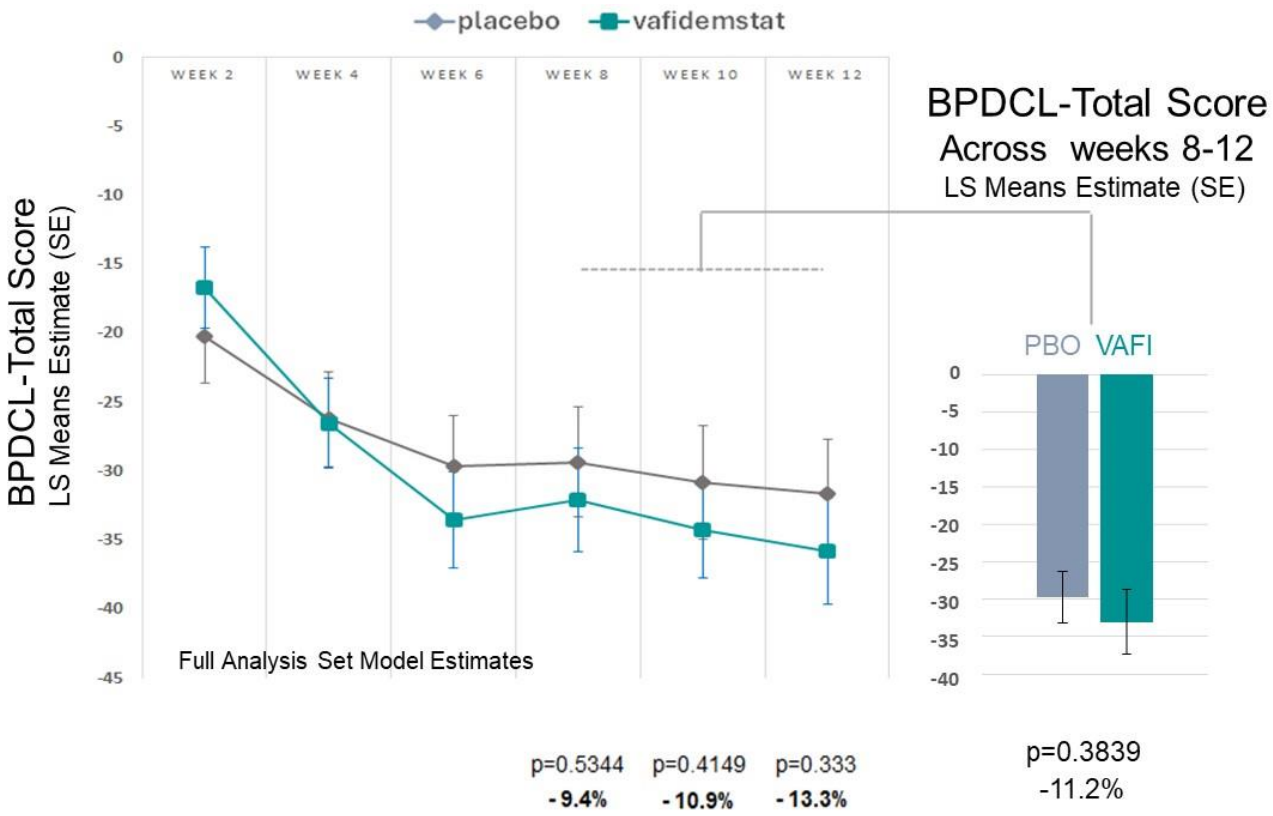
FINAL ANALYSIS

Phase IIb PORTICO study
Efficacy of vafidemstat in Borderline Personality Disorder

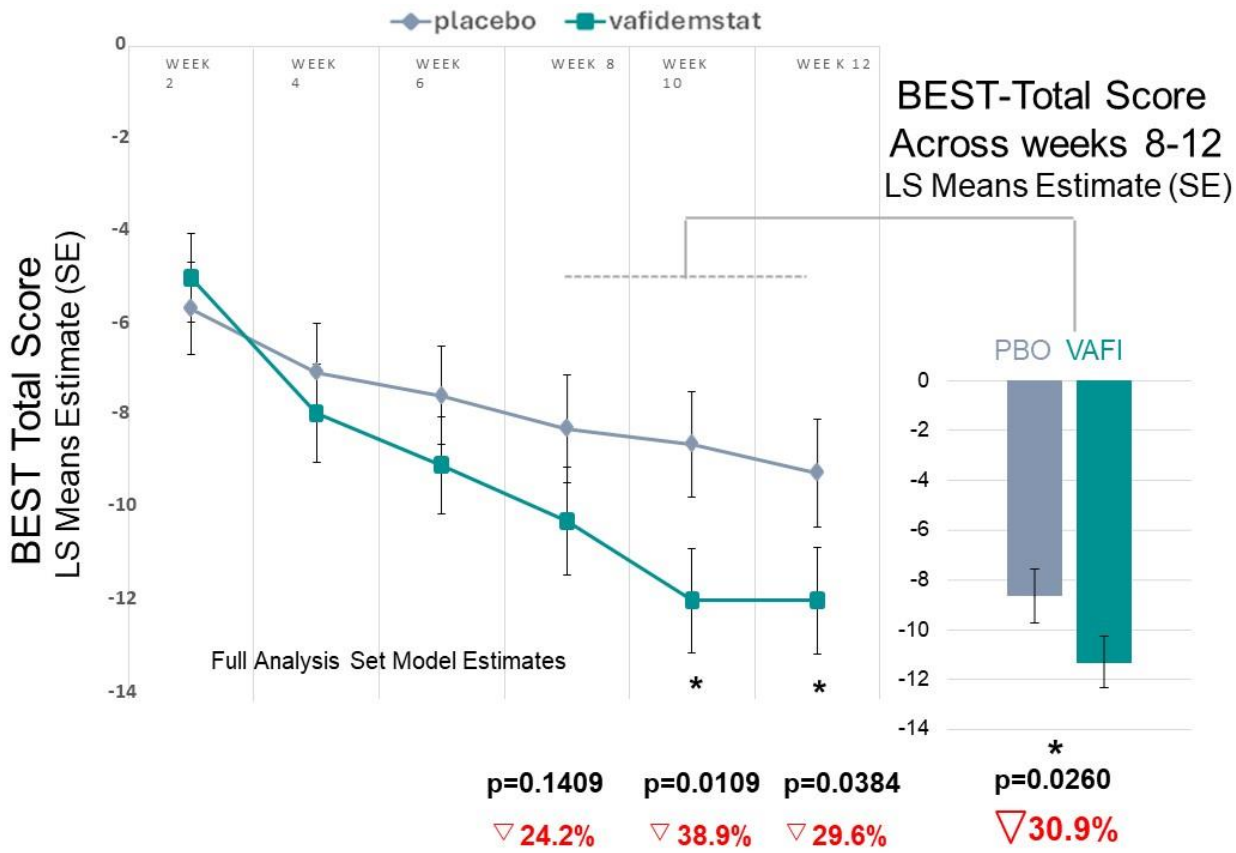
ECNP-2024

Treatment improves overall severity over placebo (Secondary endpoint)

Primary endpoint
BPDCL (Patient rated)



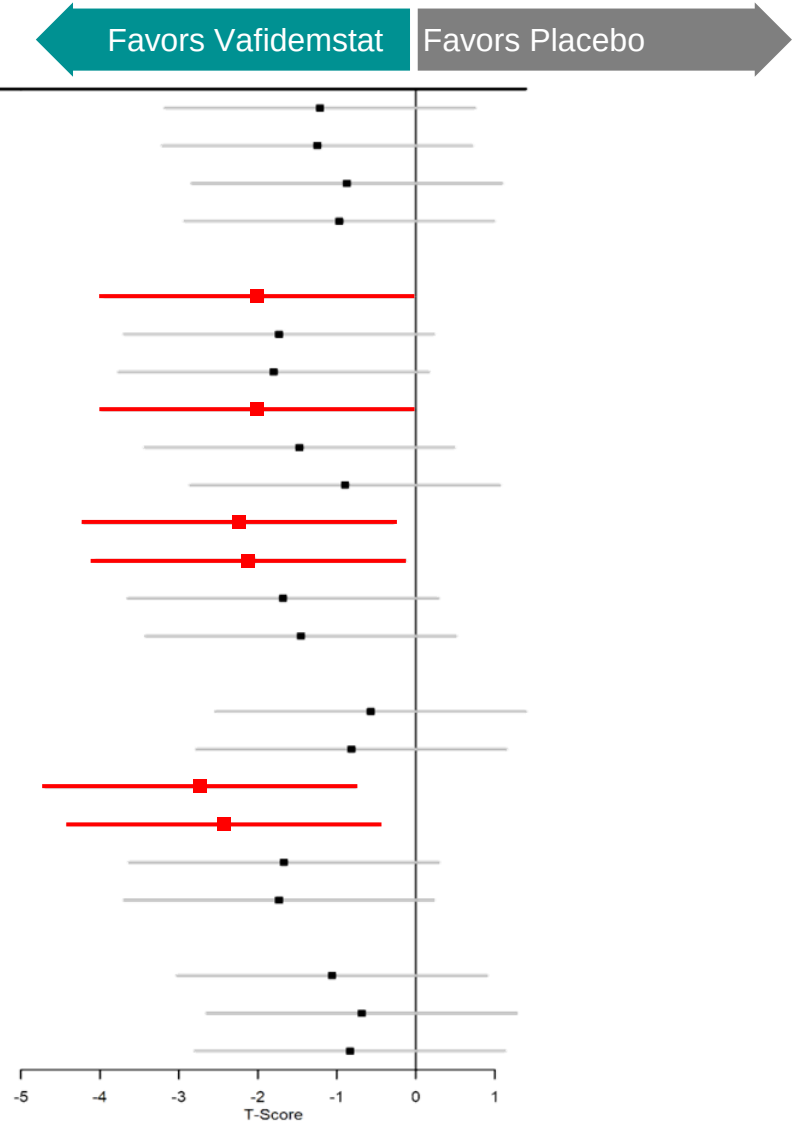
Secondary endpoint
BEST (Patient rated)



All primary and secondary efficacy endpoints consistently favored vafidemstat over placebo

Full Analysis Set

Parameter	Analysis Type	Cohen's D	P-value	Difference	CI	T-Score
CGI - Severity	Average Mean	-0.1672	0.2266	-0.16	(-0.42,0.10)	-1.21
	Week 12 Mean	-0.1718	0.2142	-0.21	(-0.54,0.12)	-1.25
BPDCL - Total Score	Average Mean	-0.1202	0.3839	-3.44	(-11.22,4.34)	-0.87
	Week 12 Mean	-0.1336	0.3333	-4.21	(-12.78,4.36)	-0.97
BEST						
Thoughts and Feelings Score	Average Mean	-0.2733	0.0488	-1.50	(-2.98,-0.01)	-1.98
	Week 12 Mean	-0.2386	0.0851	-1.44	(-3.09,0.20)	-1.73
Behaviors Negative Score	Average Mean	-0.2479	0.0736	-0.55	(-1.16,0.05)	-1.80
	Week 12 Mean	-0.2768	0.0462	-0.66	(-1.31,-0.01)	-2.01
Behaviors Positive Score*	Average Mean	-0.2030	0.1424	-0.50	(0.17,-1.16)	-1.47
	Week 12 Mean	-0.1234	0.3715	-0.37	(0.45,-1.19)	-0.90
Total Score	Average Mean	-0.3093	0.0260	-2.67	(-5.02,-0.32)	-2.25
	Week 12 Mean	-0.2875	0.0384	-2.71	(-5.27,-0.15)	-2.09
BDI - Total Score	Average Mean	-0.2316	0.0944	-2.61	(-5.68,0.45)	-1.68
	Week 12 Mean	-0.2005	0.1473	-2.45	(-5.78,0.87)	-1.46
STAXI						
State Anger Scale Raw Score	Average Mean	-0.0787	0.5684	-0.57	(-2.53,1.39)	-0.57
	Week 12 Mean	-0.1124	0.4157	-0.84	(-2.88,1.20)	-0.82
Trait Anger Scale Raw Score	Average Mean	-0.3755	0.0071	-2.02	(-3.49,-0.56)	-2.73
	Week 12 Mean	-0.3359	0.0158	-2.17	(-3.92,-0.41)	-2.44
Anger Expression Index Raw Score	Average Mean	-0.2300	0.0966	-2.62	(-5.72,0.48)	-1.67
	Week 12 Mean	-0.2385	0.0851	-3.05	(-6.53,0.43)	-1.73
STAI						
State Anxiety Raw Score	Average Mean	-0.1461	0.2901	-1.54	(-4.41,1.33)	-1.06
	Week 12 Mean	-0.0943	0.4942	-1.20	(-4.64,2.25)	-0.69
Trait Anxiety Raw Score**	Week 12 Mean	-0.1148	0.4057	-1.05	(-3.54,1.44)	-0.83



* P-values are uncorrected for multiplicity

Global statistical test (GST) is statistically significant and consistent with a global treatment effect favoring vafidemstat

BPD is a multisymptomatic disease with psychiatric, behavioral, and functional outcomes. GST is designed to address whether a treatment is efficacious across different aspects of a condition. GST efficiently summarizes a treatment's merit when the medical question is complex.

The final analysis confirmed now a global treatment effect favoring vafidemstat by GST, with the GST p-value showing a statistical significance, particularly when considering global improvement in the severity of the disease and in agitation/aggression (p = 0.0362).

Full Analysis Set

Parameter	Cohen's D	GST P-value	Difference	CI	T-Score	P-value
CGI - Severity	-0.1672		-0.16	(-0.42,0.10)	-1.21	0.2266
BPDCL - Total Score	-0.1202	0.2134	-3.44	(-11.22,4.34)	-0.87	0.3839
BEST - Total Score	-0.3093	0.0811	-2.67	(-5.02,-0.32)	-2.25	0.0260
BDI - Total Score	-0.2316	0.0661	-2.61	(-5.68,0.45)	-1.68	0.0944
STAXI						
State Anger Scale Raw Score	-0.0787	0.0853	-0.57	(-2.53,1.39)	-0.57	0.5684
Trait Anger Scale Raw Score	-0.3755	0.0397	-2.02	(-3.49,-0.56)	-2.73	0.0071
Anger Expression Index Raw Score	-0.2300	0.0362	-2.62	(-5.72,0.48)	-1.67	0.0966
STAI						
State Anxiety Raw Score	-0.1461	0.0403	-1.54	(-4.41,1.33)	-1.06	0.2901
Trait Anxiety Raw Score**	-0.1148	0.0503	-1.05	(-3.54,1.44)	-0.83	0.4057

PORTICO safety: 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

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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*

FDA End-of-Phase II Meeting official minutes: summary

- FDA's feedback supports the initiation of the Phase III trial
- Agitation-Aggression in BPD acknowledged as a possible therapeutic indication
- FDA agrees that Oryzon may pursue a Phase III study using STAXI-2 Trait anger as a primary efficacy endpoint measure
- Secondary endpoints will include patient-rated and clinician-rated scales to assess agitation/aggression and overall BPD improvement
- The estimated total sample size for the PORTICO-2 Phase III study is 350 patients (randomized 1:1 vafidemstat or control), with a trial duration of 18 weeks in total
- Subject to FDA's review of the final data, the PORTICO-2 Phase III study has the potential to be one of the two registrational trials required by the FDA

See complete info at:
https://www.oryzon.com/en/news-events/news/oryzon-receives-minutes-end-phase-ii-meeting-fda-portico-2-phase-iii-vafidemstat

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

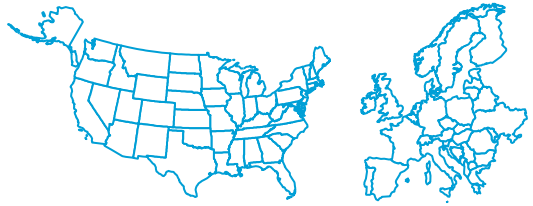
Strong market interest & huge M&A activity

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

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

Market Value in 2021

US$ ~8 billion

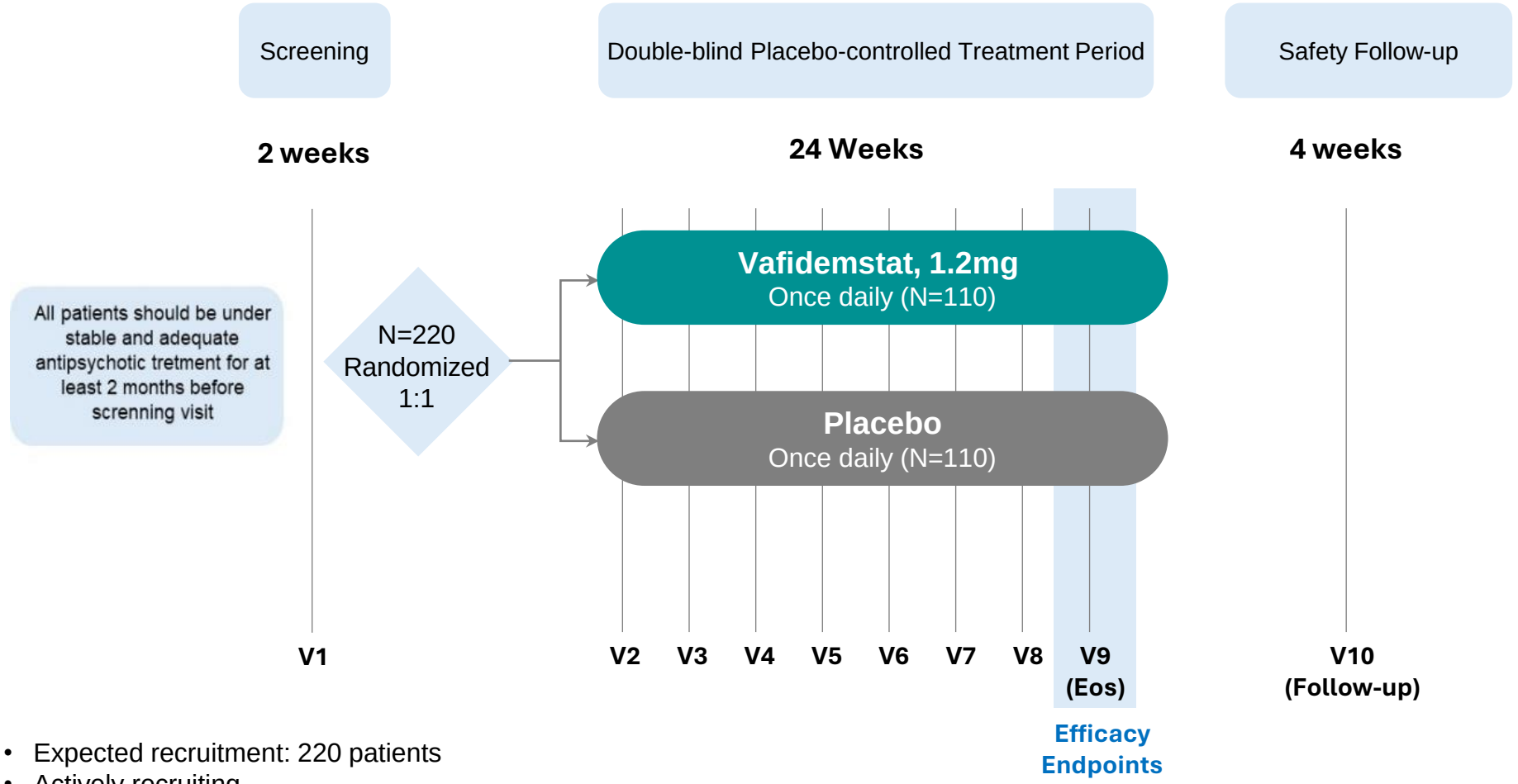
Highest Revenue Drug Category long-acting injectable (LAI) antipsychotics

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

Moderate competition

EVOLUTION: Study design

- Trial in Adult SCZ general population



Final Analysis

Primary endpoint: Improvement in Negative Symptoms

Secondary endpoints – Efficacy
Improvements in:

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

Secondary endpoints - Safety

- To evaluate vafidemstat safety in adult schizophrenia patients

- Expected recruitment: 220 patients
- Actively recruiting
- Spanish government funded
- To be converted into a global trial when new funds are secured

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IADADEMSTAT

A Phase II LSD1 inhibitor for oncological diseases

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

- A unique asset to address specific cancers (rare or orphan designations)
- Focusing on clinical execution in hemato-oncology and solid tumors with a registrational plan
- Reinforcing institutional collaborations
- Exploring additional indications in collaborative settings (NIH-NCI and IIS)
- Setting an optimal long-term corporate strategy

ODD AML ODD SCLC	ODD AML
CRADA Agreement ORYZON-NCI	Excellence Program EU Commission

IIS: investigator-initiated study

LSD1i in clinical development

- **In AML**
  - Leukemic Stem Cells are forced to differentiate by LSD1i
  - LSD1i synergizes with other agents in AML as azacitidine, gilteritinib, and venetoclax amongst others
  - Clinical evidence of benefits in diverse AML 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 Thrombocytemia** → Preliminary clinical evidence of benefits
- **In Sickle Cell Disease** → Strong preclinical evidence of benefits

Multiple Shots on goal in Oncology & leverage on CRADA-NCI agreement

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	1st cohort dosed	
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 EHA-2025	★
MDS Combination with azacitidine	**IIS-X005**			**Phase I**			**Recruiting** Sponsor: MCW	1st patient dosed	
Neuroendocrine High Grade R/R Combination with paclitaxel	**C-X001 NET Basket**						**Recruiting** Collab Study with FCCC	Study Updates 1H25	
ED-SCLC 1L Combination with ICI	**STELLAR-0 (CRADA-SCLC)**			**Phase I / II**			**IND Approved** Sponsor: NCI, Led by MSKCC	FPI 1Q25	★
ED-SCLC 1L Combination with ICI	**STELLAR**				**Phase II pivotal**		**In preparation**(*) Company sponsored	IND 2025	

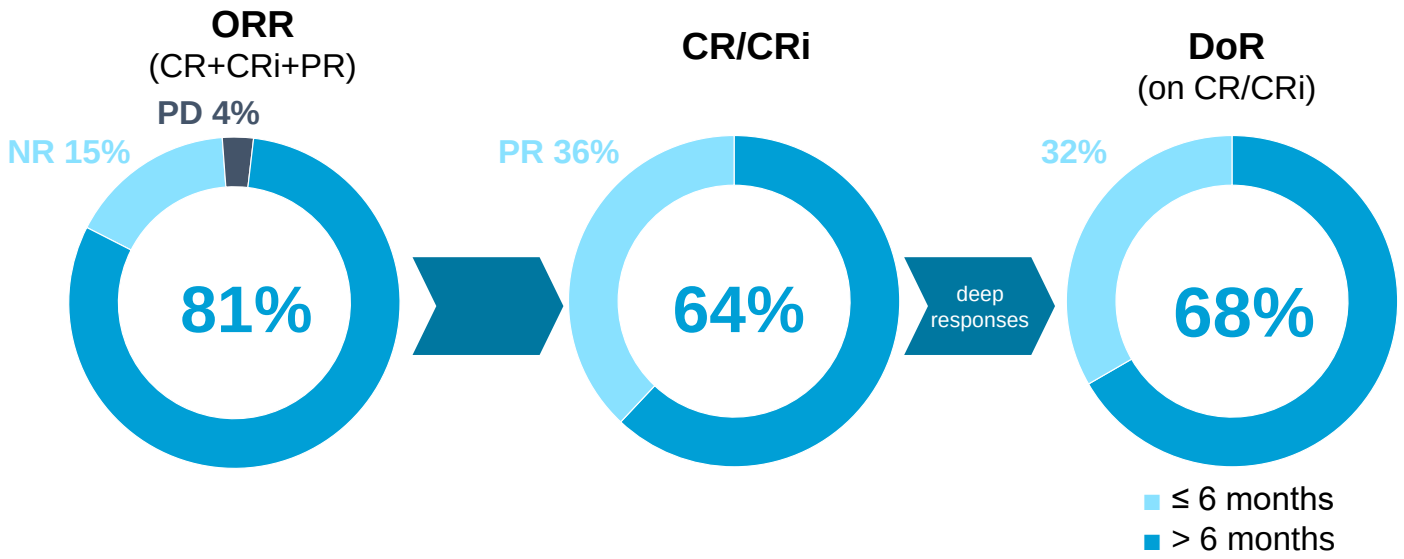
AML: acute myeloid leukemia; CRADA: Cooperative Research and Development Agreement; FCCC: Fox Chase Cancer Center; ICI: immune checkpoint inhibitor; IIS: investigator-initiated study; MCW: Medical College of Wisconsin; MDS: myelodysplastic syndrome; MSKCC: Memorial Sloan Kettering Cancer Center; NCI: National Cancer Institute; NETs: neuroendocrine tumors; OHSU: Oregon Health & Science University; SCLC: small cell lung cancer; UPMC: University of Pittsburgh Medical Center

(*) STELLAR trial to be informed by the data to be obtained in the CRADA-SCLC trial.

AML Program

Iadademstat Combination with Azacitidine is a Safe and Effective Treatment in First Line Acute Myeloid Leukemia. Final Results of the ALICE Trial.

Rapid, deep, and durable responses



Selected as one of the 25 most relevant AML Comms in ASH2022

Summary of Responses		
n = 27	**n**	**%**
CR	9	**33%**
CRi	5	**19%**
PR	8	**30%**
NR	4	**15%**
PD	1	**4%**
CR/CRi	14	**52%**
ORR (CR/CRi/PR)	22	**81%**
TTR	n=22 Median [95% CI]	**2.1 mos** [1.1,2.6]
DoR	n=22 Median [95% CI]	**8.8 mos** [1.8,17.4]

CR/CRi pts		
n=14	**n**	**%**
MRD neg	10 out of 11 evaluable	**91%**
Achieved TI (RBC & Plt)	10	**71%** 10/14

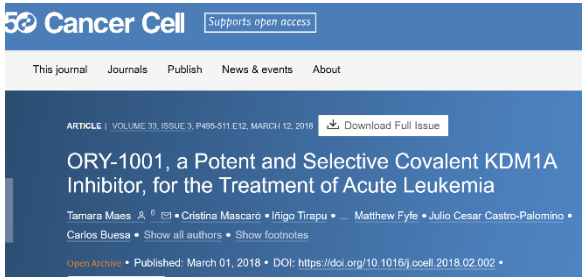
CR: Complete Remission; CRi: Complete Remission with incomplete hematologic recovery; PR: Partial Response; NR: No response; PD: Progressive Disease; ORR: Overall Response Rate; MRD: Measurable Residual Disease; TTR: Time To Response; DoR: Duration of Response; TI: Transfusion Independence; RBC: Red blood cells; Plt: Platelets

ORYZON

ALICE results published in Lancet Haematology in May 2024

One of the most influential scientific journals in the field of oncology

This notable publication is a continuation of Oryzon's previous pioneering research featured in the **Journal of Clinical Oncology** (First-in-Human study in AML with iadademstat) and **Cancer Cell** (Characterization of iadademstat as a potent and selective LSD1 inhibitor), cementing the company's position at the forefront of epigenetics in oncology and LSD1 innovation



Two new trials continue to explore iadademstat's potential in 1L AML

A Phase Ib Investigation of the LSD1 Inhibitor Iadademstat (ORY-1001) in Combination With Azacitidine and Venetoclax in Newly Diagnosed AML

ClinicalTrials.gov ID: NCT06357182

- Sponsor: OHSU Knight Cancer Institute
- Principal Investigator: Dr. Curtis Lachowiecz
- Collaborators:
  - Oregon Health and Science University
  - Oryzon Genomics
- **Ongoing; 1st cohort recruited, 2nd cohort recruiting**
- N=24 patients
- Oryzon to provide drug

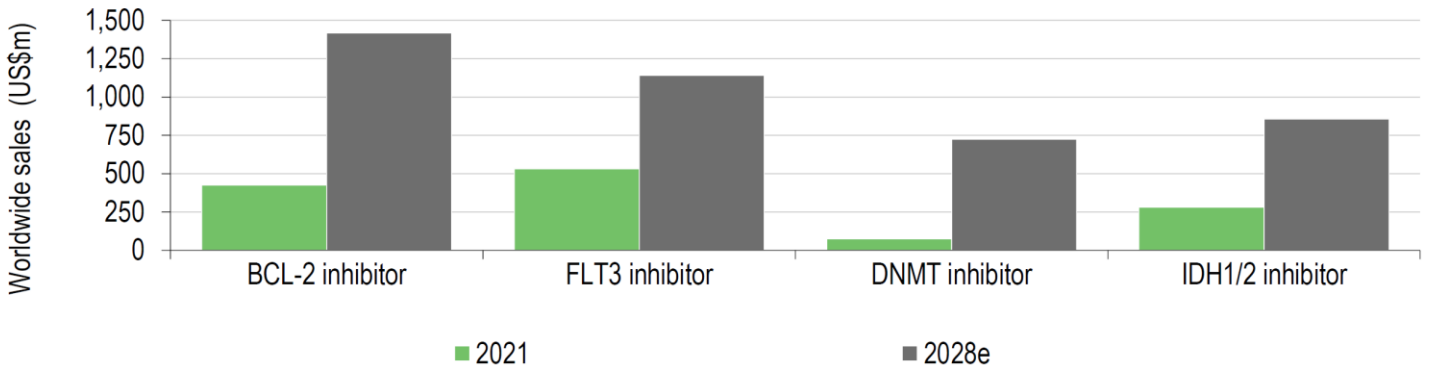
A Phase I Trial of Iadademstat in Combination With Venetoclax and Azacitidine in Patients With Treatment Naive AML

ClinicalTrials.gov ID: NCT06514261

- Sponsor: National Cancer Institute (NCI)
- Principal Investigator: Natalie Galanina (University of Pittsburgh Cancer Institute)
- **Ongoing; 1st patient dosed**
- N=45 patients
- Oryzon to provide drug

FLT3mut+ R/R AML, the best and shortest market opportunity for iadademstat

- 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%)**
- **Very strong preclinical synergism between gilteritinib and iadademstat**
- **Global FLT3 inhibitors market expected 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

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

	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

Pharmacologically active dose/s

Expansion

Up to ~ 14 pts/dose cohort

Dose C1:
Iadademstat + Gilteritinib

Dose C2:
Iadademstat + Gilteritinib

Bayesian Monitoring

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)*

Final Analysis (Selected endpoints)

Primary	Secondary	Exploratory
• Safety • RP2D	• Efficacy: CR/CRh, OS, EFS,ORR, DoR • Transfusion rates	• MRD • Gene mutation status • Biomarkers

ORYZON

FRIDA: Initial observations at EHA-2024

Fast time to responses & Encouraging antileukemic activity

- Actively recruiting
- Encouraging antileukemic activity observed, with 9 out of 13 patients (ORR 69%) **achieving bone marrow (BM) blast clearance in the first cycle.**
- TTR faster than Giltertinib. Most responses are already seen by the end of the first cycle, with a **median time to CR/CRh/CRi of 35 days**
- 43% achieved complete remission (CR), complete remission with partial hematological recovery (CRh) or complete remission with incomplete blood count recovery (CRi) in DL-1
- All but 2 patients were refractory to prior standard regimens including venetoclax,7+3 and midostaurin.
- Two patients (one in the starting cohort and one in DL-1 cohort) have undergone hematopoietic stem cell transplantation.
- Recruitment continues to identify the lowest possible effective dose in accordance with FDA's Optimus guidance

Best responses	Starting dose (n=6)	DL-1 (n=7)
CR	-	1 (1 HSCT)
CRh	-	1
CRi	2	1
MLFS	3 (1 HSCT)	1
NR	1	3
ORR	5 out of 6 83%	4 out of 7 57%
% CR/CRh/CRi	33%	43%

Neuroendocrine Program

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

Mechanism of Action

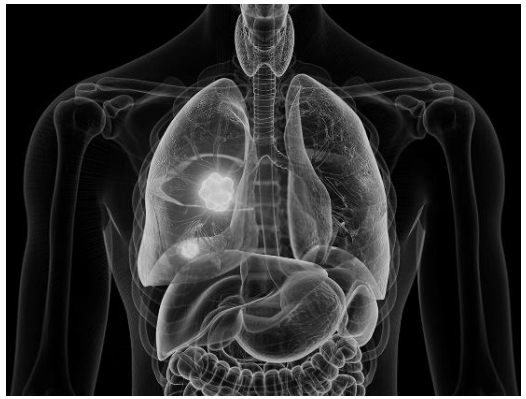
LSD1 is required for survival & proliferation of **neuroendocrine/SCLC tumor cells**

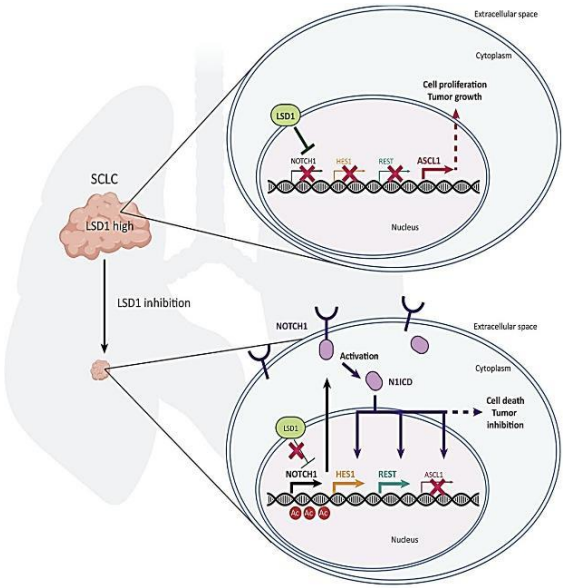
Iadademstat **induces Notch**, a well characterized tumor suppressor in SCLC **and represses ASCL1**

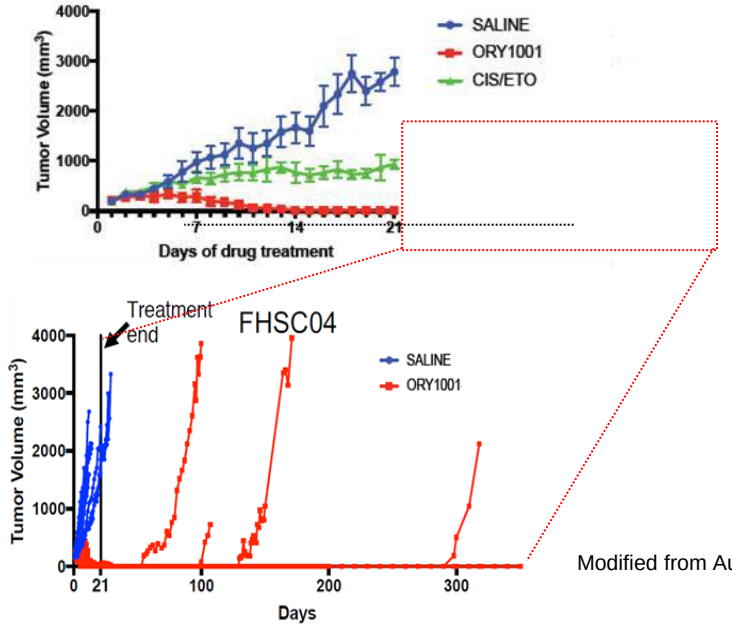
Iadademstat blocks LSD1's actions and promotes neuroendocrine/SCLC tumor differentiation and death

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



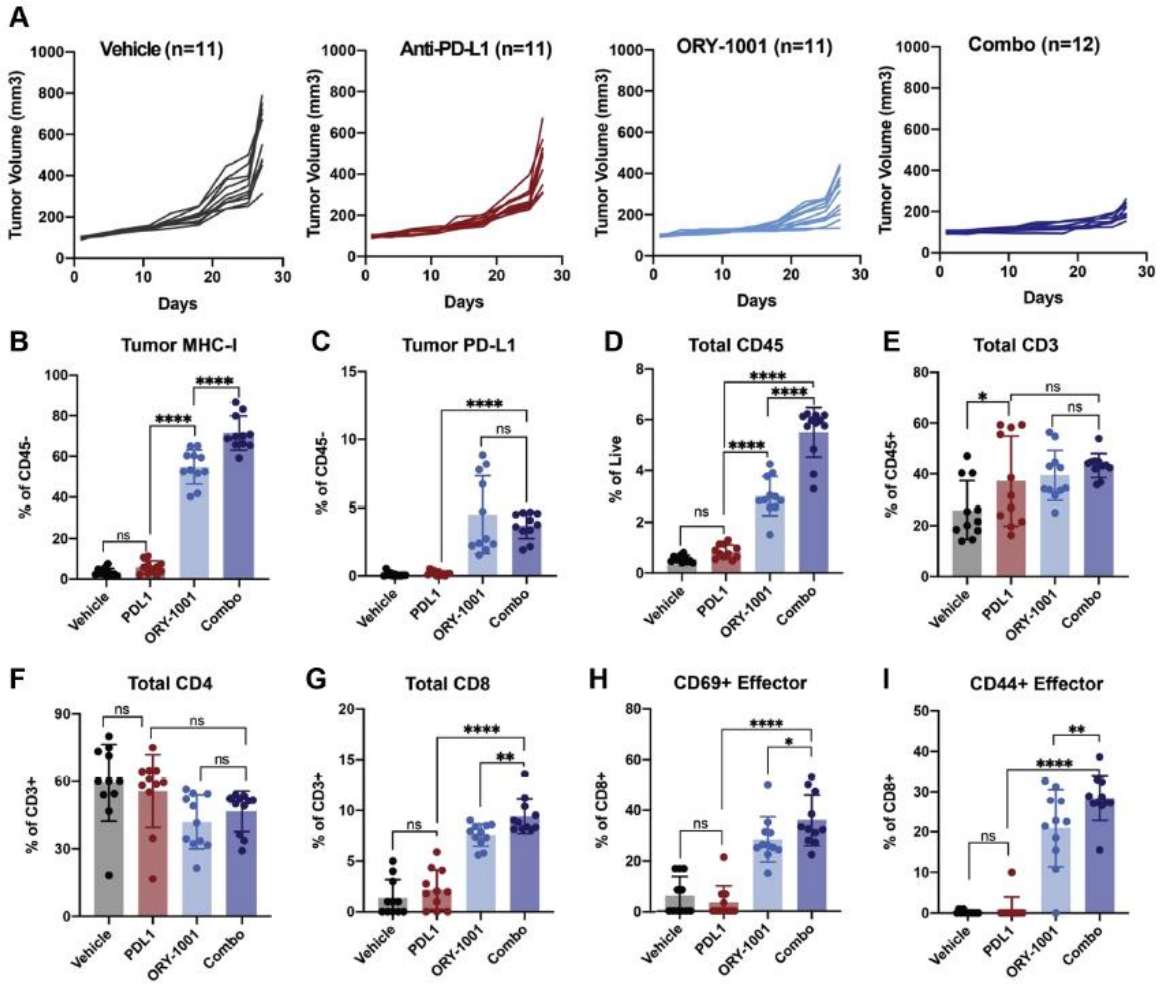


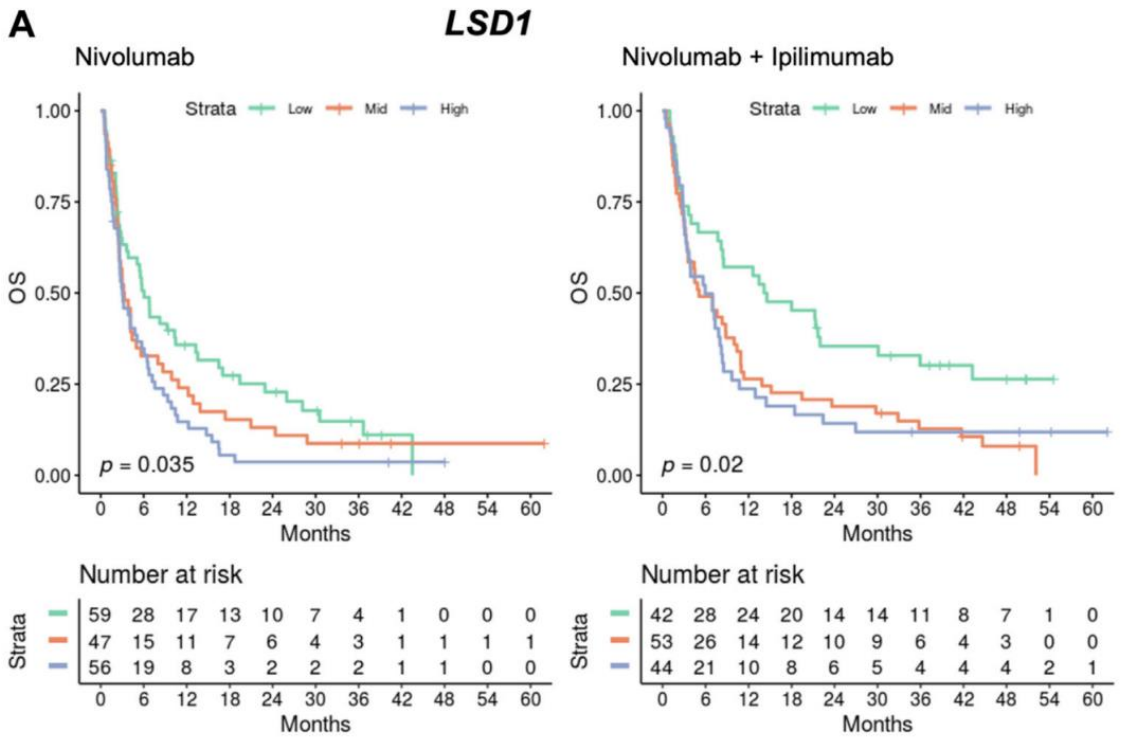


Modified from Augert et al., 2019. Sci Signal

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

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

ORYZON

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

NEXT-CTEP-NCI Program – CRADA: new 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
IND approved
Expected start 1Q25

- MSKCC
- JHU Sidney Kimmel Comprehensive Cancer Center at the John Hopkins
- Dana Farber at Harvard Cancer Center
- Ohio State Univ Cancer Center
- MD Anderson
- City of Hope Cancer Center
- UPMC Hilman Cancer Center (University of Pittsburgh)
- Univ. Health Network Princess Margaret Cancer Center Toronto
- Yale University
- National Cancer Institute

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

ORYZON

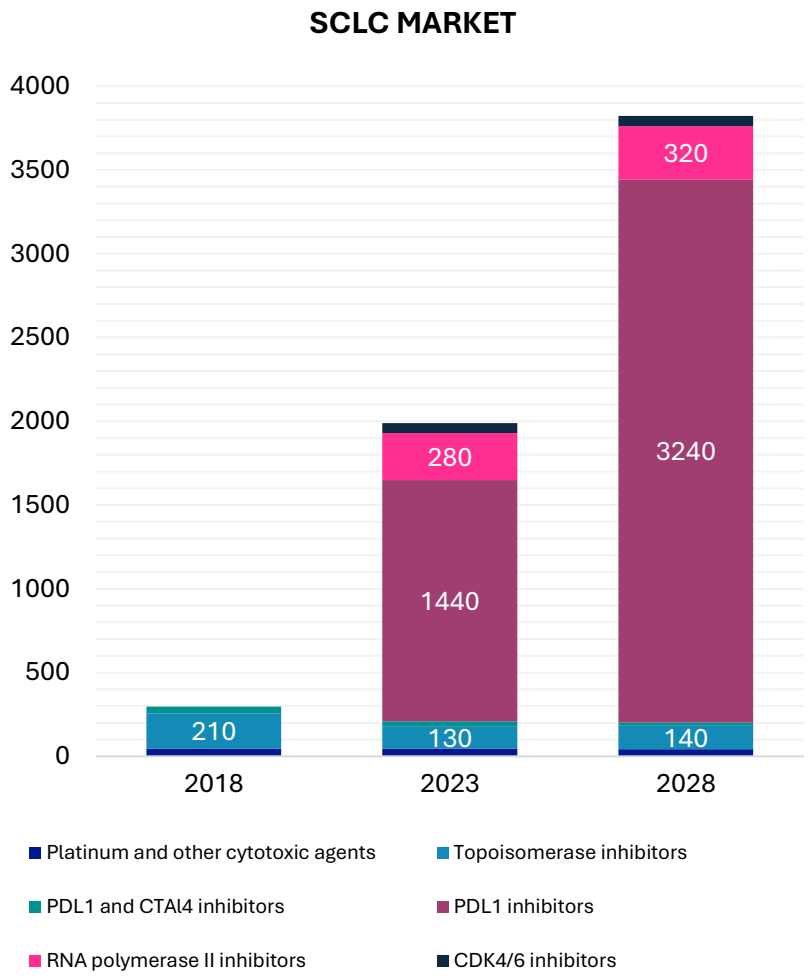
ED-SCLC, an interesting market opportunity

Best route to Market: Combo with ICI, 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



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

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

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

FOX CHASE CANCER CENTER
TEMPLE HEALTH

- 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
- Recruiting

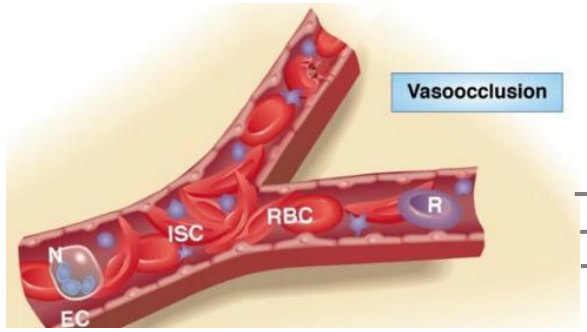
ORY-3001

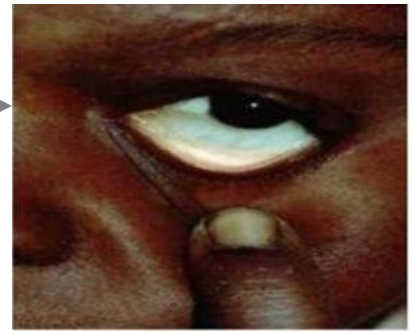
A refined LSD1 inhibitor for hematological disorders

Sickle cell disease (SCD)

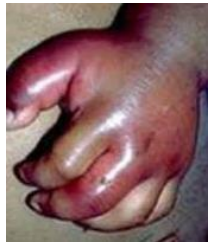
Patients suffer anemia, pain, progressive organ damage, early mortality

SCD is an inherited autosomal recessive disorder resulting in mutation of the hemoglobin (Hb) structure in red blood cells. 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

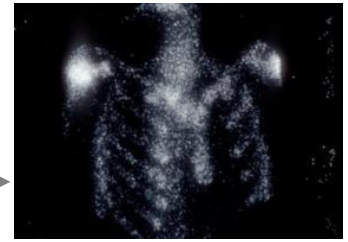




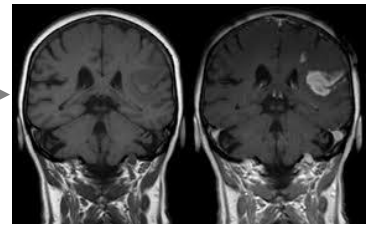
Anemia



Dactylitis



Bone infarcts

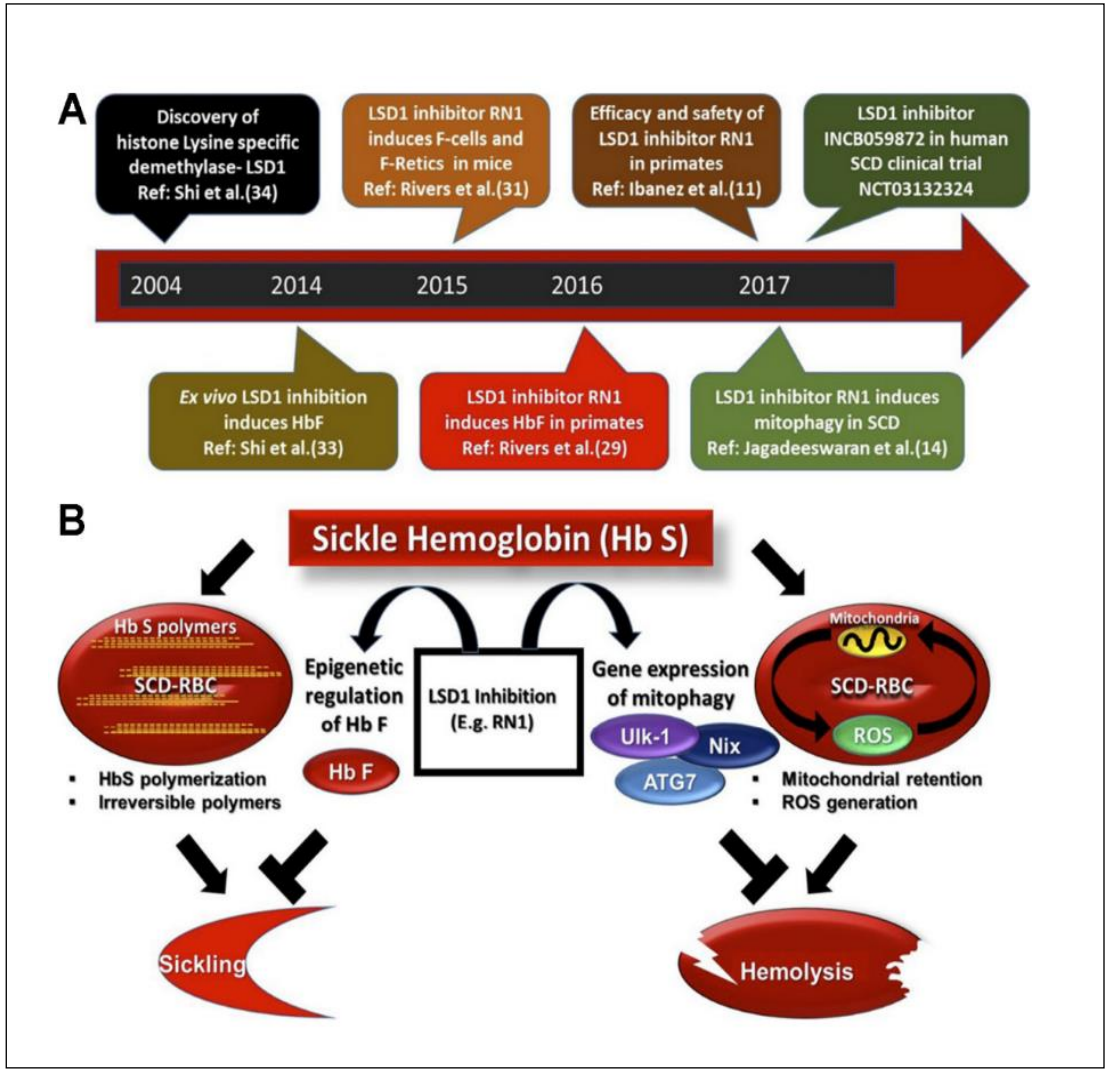


Stroke

ORY-3001 is a therapeutic option for SCD

- 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 et al. . 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

LSD1 occupancy confirmed by target engagement analysis and platelet reduction

ELSEVIER

Experimental Hematology

Experimental Hematology 2018;67:60–64

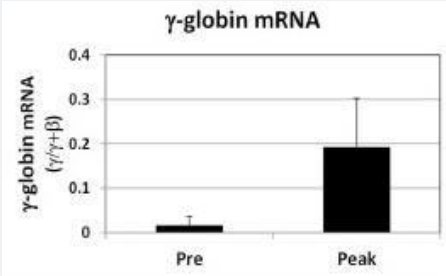
Oral administration of the LSD1 inhibitor ORY-3001 increases fetal hemoglobin in sickle cell mice and baboons

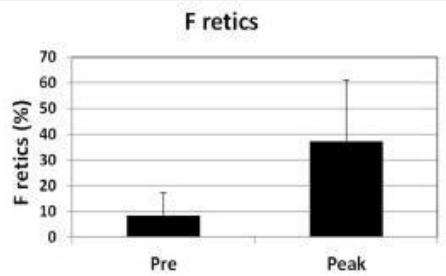
Angela Rivers[a,b], Kestis Vaitkus[b,c], Ramasamy Jagadeeswaran[a,b], Maria Armila Ruiz[b,c], Vinzon Ibanez[b,c], Filippo Ciceri[d], Fernando Cavalcanti[d], Robert E. Molokie[b,c], Yogen Saunthararajah[e], James Douglas Engel[f], Joseph DeSimone[c], and Donald Lavelle[b,c]

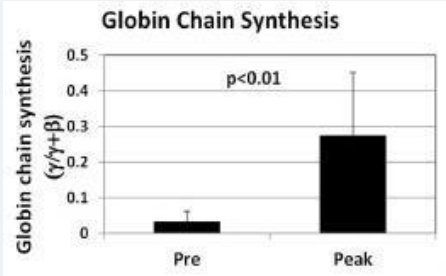
[a]*Department of Pediatrics, University of Illinois at Chicago, Chicago, IL, USA;* [b]*Jesse Brown VA Medical Center, Chicago, IL, USA;* [c]*Section of Hematology/Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA;* [d]*Oryzon Genomics S.A., Barcelona, Spain;* [e]*Department 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*

In these models, ORY-3001 increased:

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



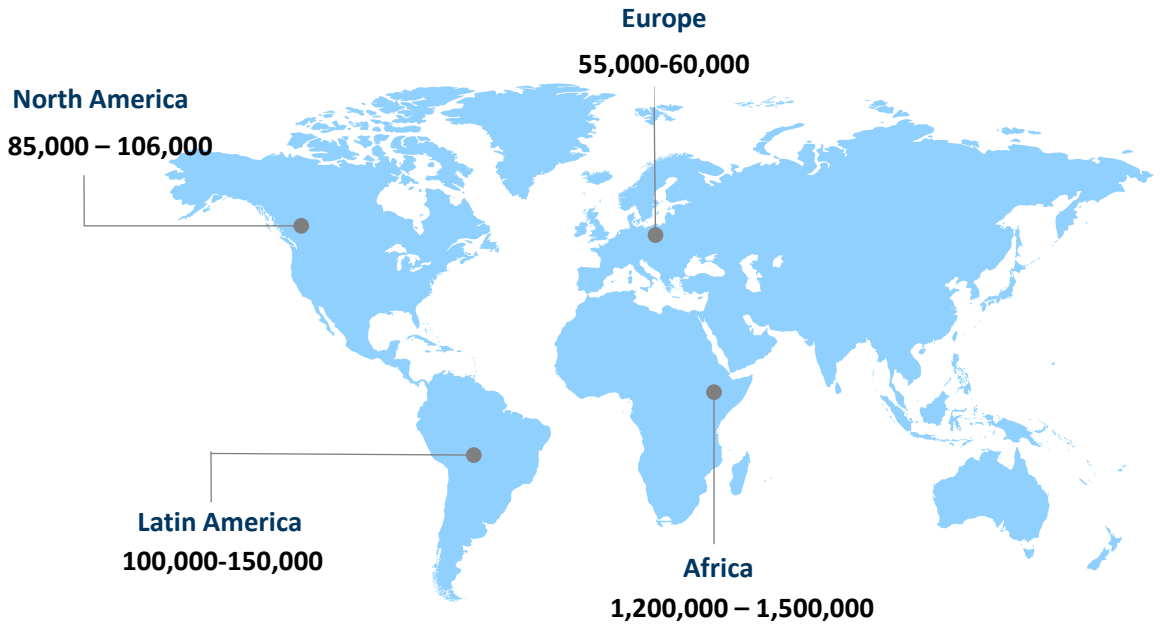




Sickle cell disease prevalence

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

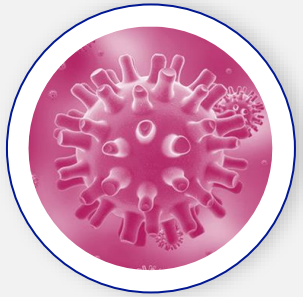
ORYZON

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

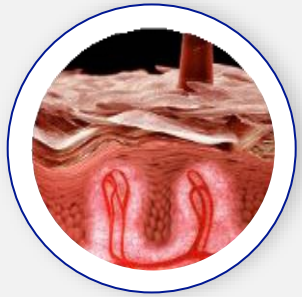
Non-malignant hematological diseases

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

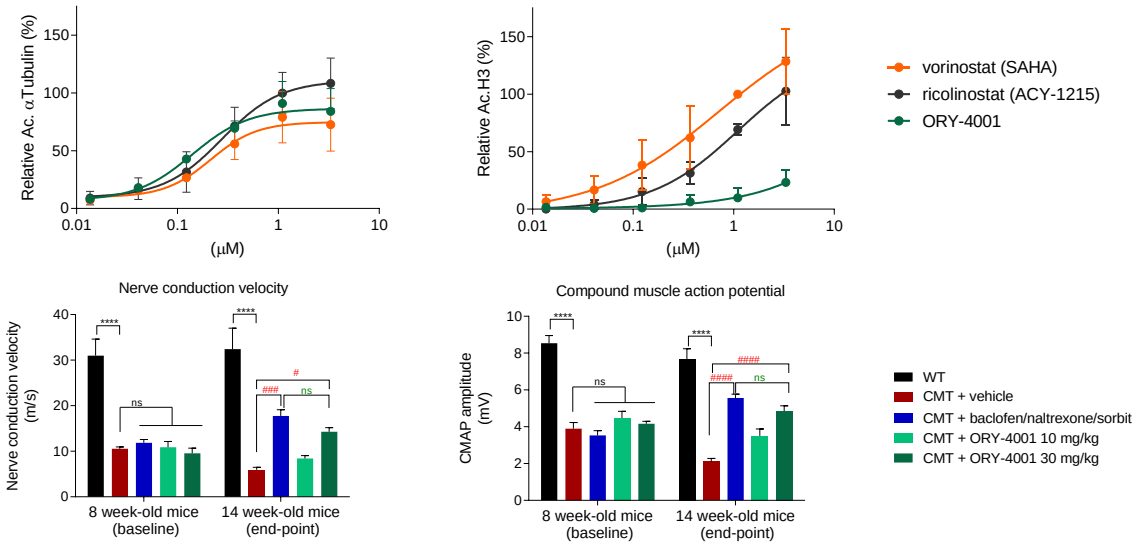
ORY-4001 is a highly potent and selective HDAC6 inhibitor

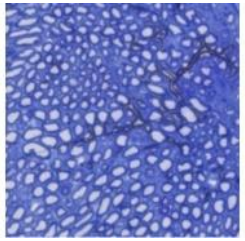
HDAC-6 has been suggested as a therapeutic target in Charcot-Marie-Tooth (CMT), ALS, and other CNS diseases

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





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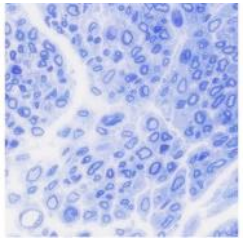
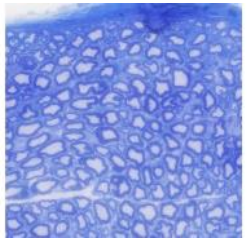


CMT1A + vehicle



CMT1A + ORY-4001 30 mg/kg

First in Man readiness is expected by 2025

ORYZON

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

Charcot-Marie-Tooth disease

A medical need and a market opportunity

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)

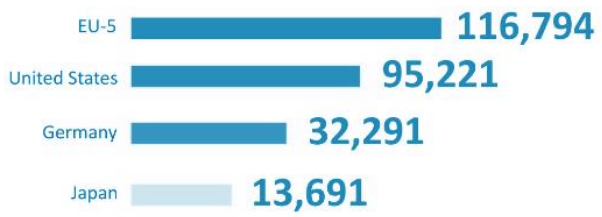
263,835
The total prevalent population in 7MM

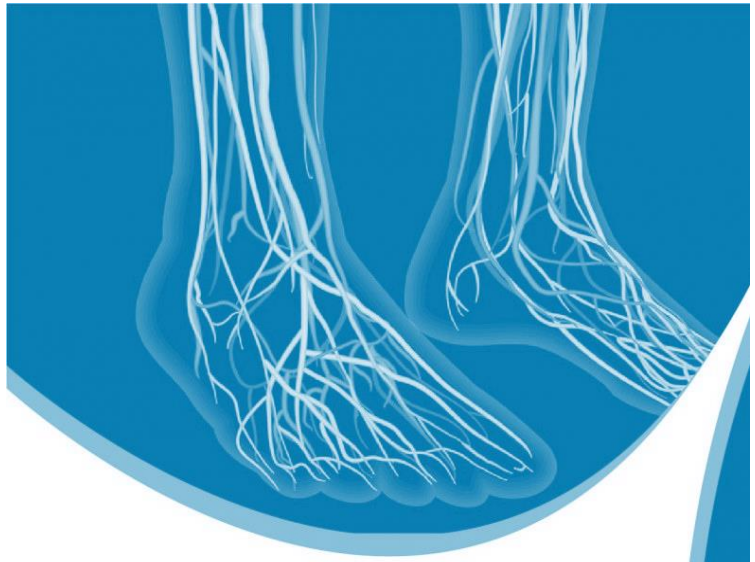
The age-specific cases in EU-5

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

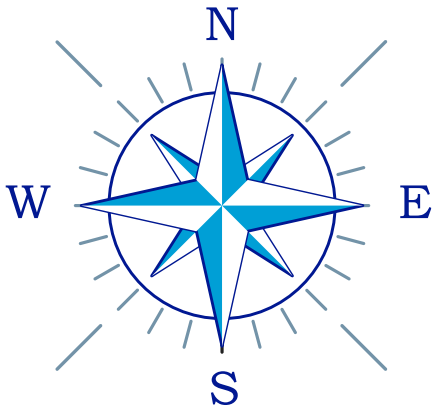
ORYZON

VAFIDEMSTAT
Personalized medicine in CNS

LSD1i, a precision medicine therapeutic option in CNS to rescue deficits caused by mutations in key genes

COMPASS Pathologies: H3K4-met related indications

- **KMT2D (MLL2) – Kabuki Syndrome**
- **KMT2F (SetD1a) - Schizophrenia susceptibility**
- KMT2A - Wiedemann–Steiner syndrome
- KMT2B - Dystonia 28, Childhood-Onset
- KMT2C - Kleefstra syndrome –Autism spectrum disorders
- KMT2G (SetD1b) - Syndromic intellectual disability

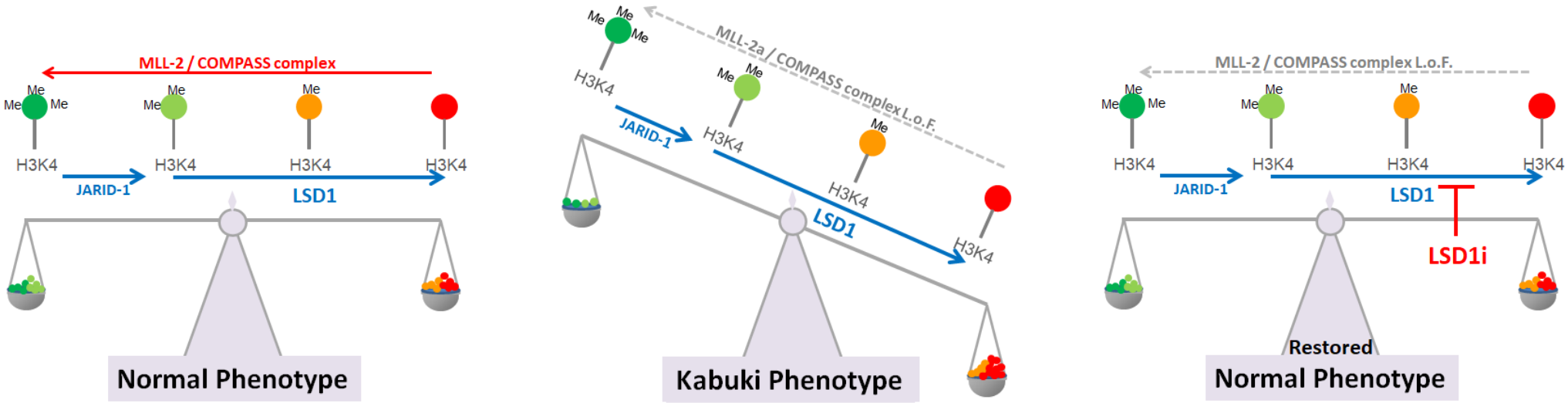


Other genetically driven indications

- MeCp2 (Methyl-CpG-binding protein) – Rett syndrome
- EHMT1 (H3K9 - Histone methyltransferases) Kleefstra syndrome
- **Shank3 - Autism spectrum disorders**
- Gtf2i - Williams-Beuren syndrome - 7q.23 microduplication including ASD

Methylation is involved in Kabuki Syndrome and LSD1 inhibition rescues phenotypes in a genetic model

- Kabuki syndrome is a congenital disorder characterized by intellectual disability, growth retardation, dysmorphic facial features and immune defects
- **Mutations of *MLL2 (KMT2D)* cause Kabuki syndrome in >70% of cases** (known as KS type I)
- *MLL2* is a Histone Methyl transferase. Unbalance methylation in the brain triggers the CNS component of the disease
- **To rebalance the methylation equilibrium could be a therapeutic strategy**

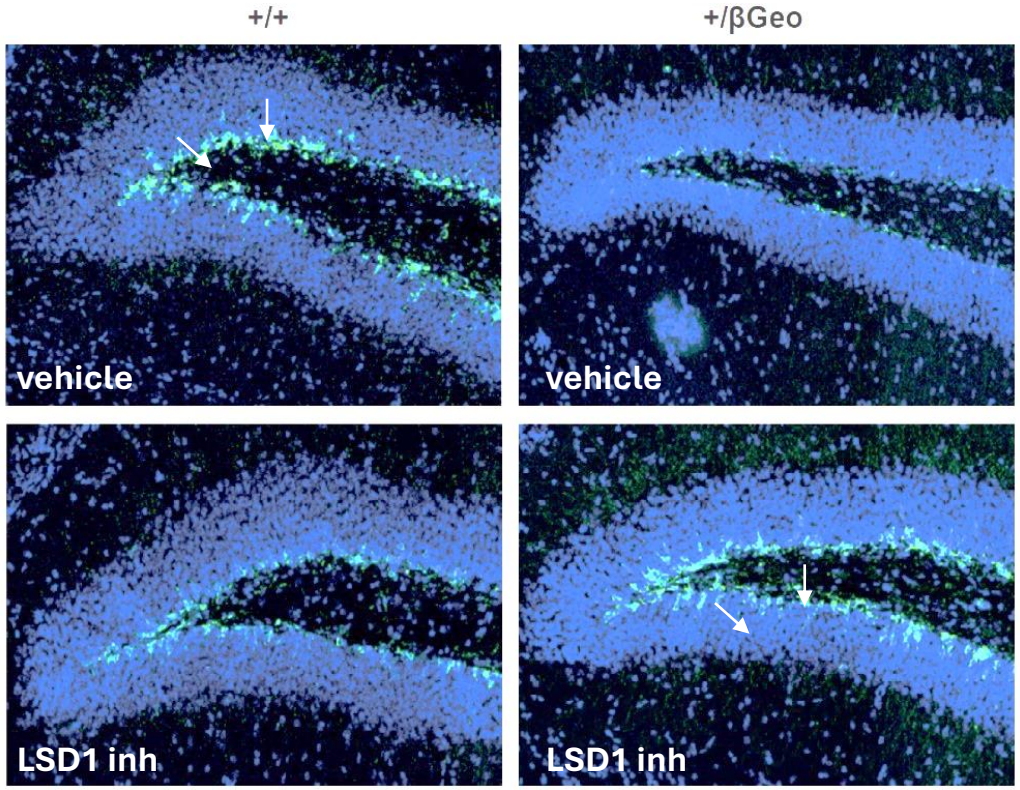


Methylation is involved in Kabuki Syndrome and LSD1 inhibition rescues phenotypes in a genetic model

Effects of LSD1i in the phenotype of a KO Kabuki mice*

- LSD1i restores methylation balance in the hippocampus
- LSD1i rescues adult neurogenesis
- LSD1i restores normal neuronal morphology
- LSD1i rescues global gene expression changes
- LSD1i rescues the visuospatial learning and memory defects
- LSD1i rescues immune defects (splenomegaly)

LSD1i rescues neurogenesis defects in hippocampus of Kmt2d$^{+/bGeo}$ mice



Modified from Zhang et al, Molecular Therapy: Methods & Clinical Development ,Vol. 20 , 779-791 (March 2021)

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

- 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**

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

JOHNS HOPKINS UNIVERSITY

Kennedy Krieger Institute

- Phase Ib objectives: evaluate safety/tolerability, and determine the RP2D
- Phase II objective: evaluate the efficacy of vafidemstat at the RP2D in KS Type 1 patients
- IND 2025 (subject to additional resources)
- **HOPE may set the basis for an expedited development if a significant clinical benefit in the population is demonstrated over placebo**

Pioneering personalized medicine in epigenetics