Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

JANUARY 2024

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 ~$150M

Runway expected till 1Q-2025

A Management Team with Proven Drug Development and Operational Capabilities

Carlos Buesa
PhD
CEO

ORYZON

inveready

Douglas Faller
MD, PhD
Global CMO

Takeda

HARVARD MEDICAL SCHOOL

BRIGHAM AND WOMEN'S HOSPITAL

Boston Children's Hospital
Until every child is well

Dana-Farber Cancer Institute

Michael Ropacki
PhD
CMO for CNS

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

UCLA David Geffen School of Medicine

BROWN UNIVERSITY

THE WARREN ALPERT Medical School

LOMA LINDA UNIVERSITY School of Medicine

Ana Limon
PhD
SVP Clinical Dev & Medical Affairs

AMGEN

MILLENNIUM PHARMACEUTICALS, INC

Takeda

decīphera

Jordi Xaus
PhD
CSO

Genentech
A member of the Roche Group

PULEVA

PALAU PHARMA

Sonia Gutierrez
MS
Chief of Clinical Operations

Pharmacia & Upjohn

sanofi

Lundbeck

REGENERON

Enric Rello
JD; PhD
CFO-COO

SANDOZ
a Novartis company

Harvard Business School

Universitat Abat Oliba CEU

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

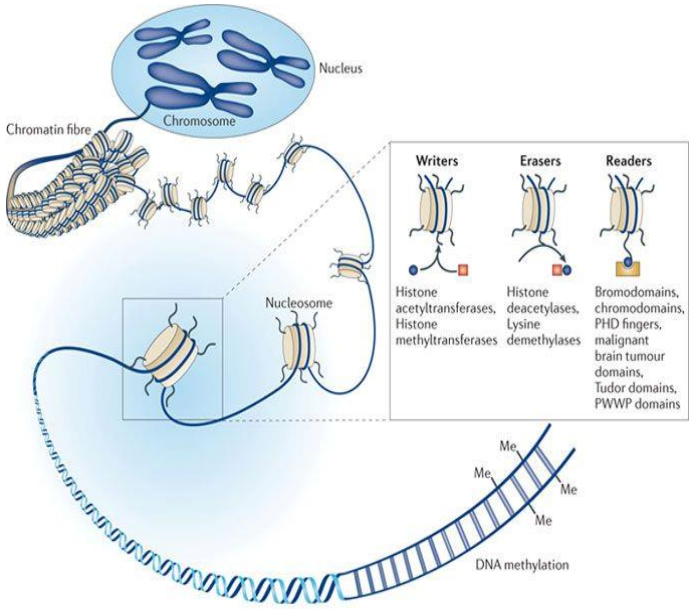

Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* **Volume 11** (2012)

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, and another in SCZ ongoing**

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

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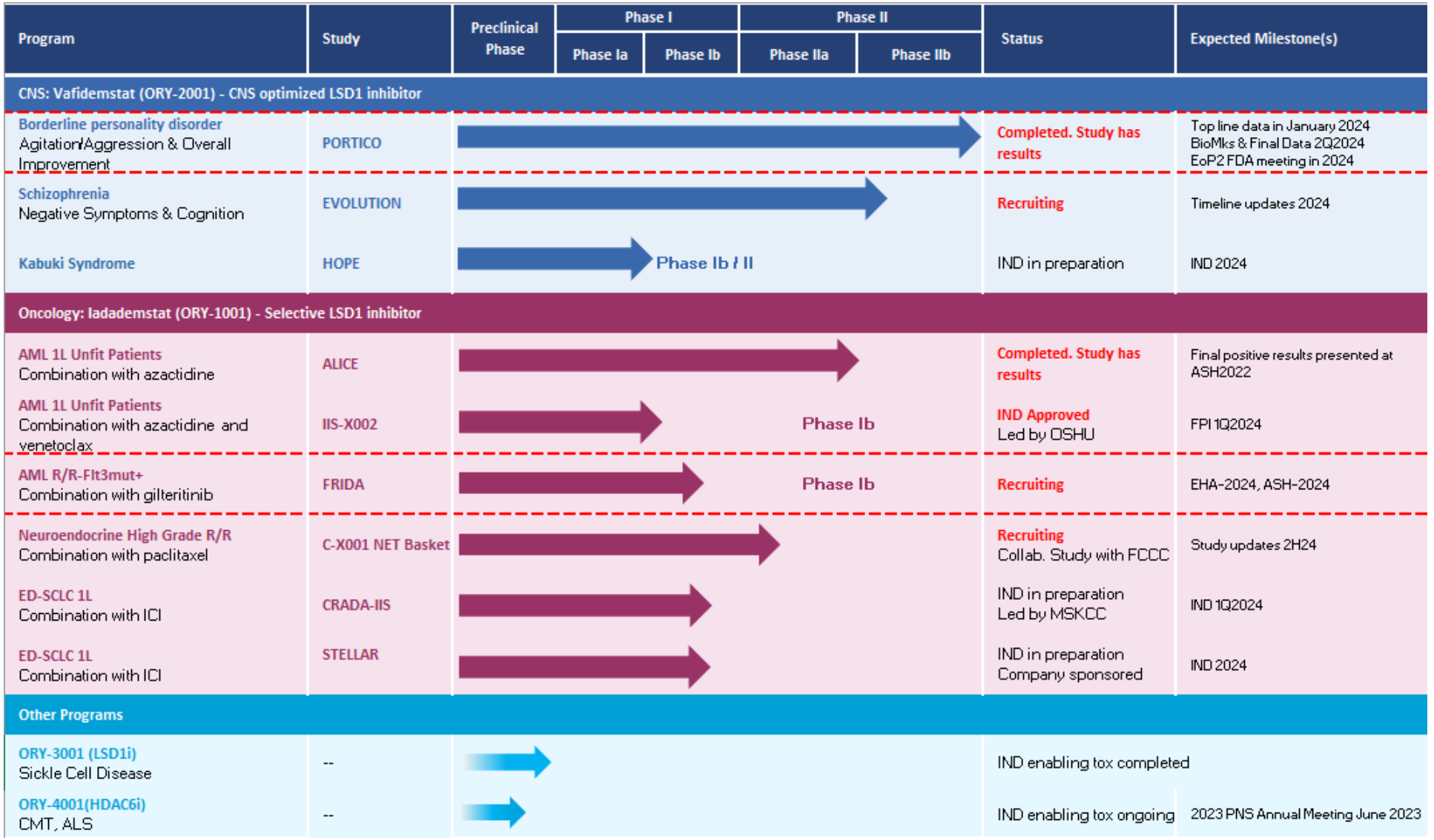
Multiple Shots on goal & main investment thesis in the short-mid term

TWO MAIN CATALYSTS IN 2024:

- **PORTICO IN BPD**
- **FRIDA IN AML**



Note: Other 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; CMT: Charcot-Marie-Tooth disease
FCCC: Fox Chase Cancer Center; MSKCC Memorial Sloan Kettering Cancer Center; OSHU Oregon Health & Science University

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 **modulates** the response to environmental stress and improves **aggressivity and sociability**

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
  - Signals of reduction in aggression in pilot Phase IIa studies in AD, ASD, ADHD & BPD, and in PORTICO PhIIb trial in BPD
  - Improvements in overall patient functioning, particularly in ADHD & BPD patients (REIMAGINE basket trial) & in PORTICO trial in BPD

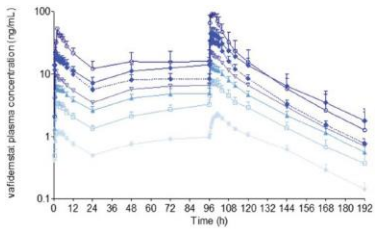
Safe & well tolerated

No differences between placebo and vafidemstat-treated patients

Excellent Brain Penetration

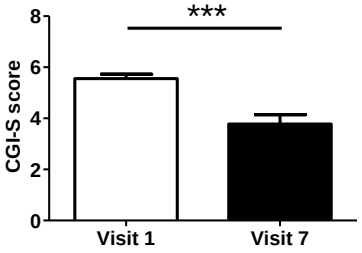
An optimal CSF : plasma ratio of 0.9

Oral, once a day

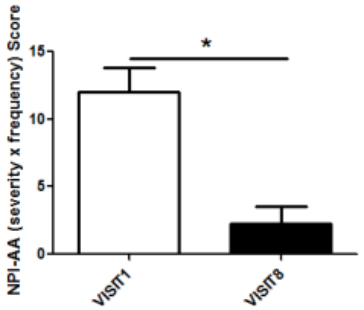


PK data supports once daily dosing in both adult and elder subjects

Reduces aggression



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



Reduces Aggression in Alzheimer's patients after 6 months of treatment

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EVOLUTION, an ongoing PoC schizophrenia study with vafidemstat

EVOLUTION: *An adaptative randomized double blind, placebo-controlled 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
- Vafidemstat as add-on to SoC
- N=100
- **Cognition.** Treatment duration sufficient to assess changes in CIAS: 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.

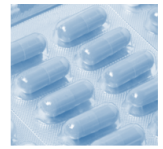
~5 million in US & EU

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:
+ $ 3.5 Billion

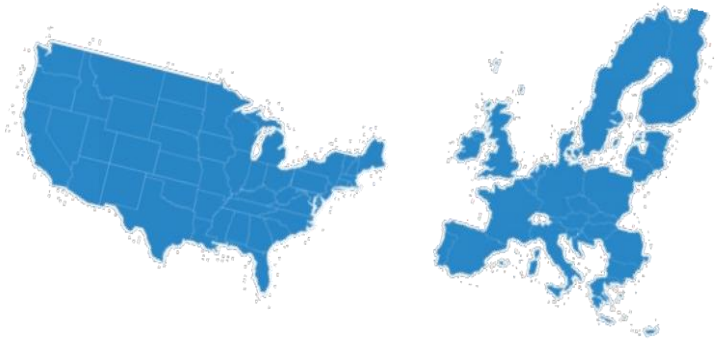
Moderate competition

Vafidemstat achieved nominal statistical significance in an exploratory endpoint of cognition using Brief Assessment of Cognition in Schizophrenia (BACS) (p=0.05) in the PORTICO study

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

A Prevalent & impairing disease

9 million in US & EU



Two main types of symptoms

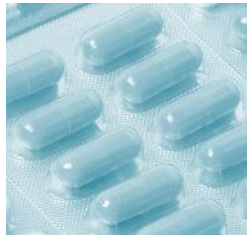
Unstable-extreme interpersonal relationships

+

Aggression & self-aggression

No approved drugs yet

Patients in off-label anti-psychotics



Vafi improves these symptoms in:

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

Vafidemstat commercial opportunity

- **BPD multi-symptom treatment** represents a substantial peak revenue opportunity of **+$3.5B**
- **Aggression.** Positive results, only in BPD, would still represent a meaningful business opportunity with peak sales of **~$1.4B.** Additional market opportunities, e.g. **Aggression in AD,** would increase this figure
- **Schizophrenia negative symptoms** treatment also represents a big commercial opportunity, where global net revenues could reach **~$2.5B at peak**

PORTICO: A Global Phase IIb randomized, placebo-controlled, double blinded trial in BPD

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

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

Placebo
Once daily,
N = 104

14-week trial

Primary Endpoints

Improvement in Clinical Global Impression-Severity by **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 Endpoints (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)**

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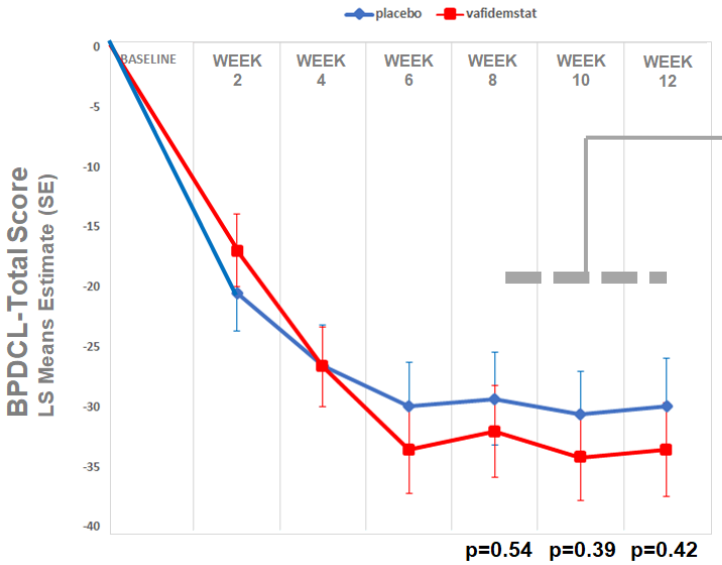
Topline Results

Phase 2b PORTICO study

Efficacy of vafidemstat in
Borderline Personality Disorder

January 7, 2024

No Statistical Significance in the two Primary Endpoints: BPDCL and CGI-S A/A



Topline Results

Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorder

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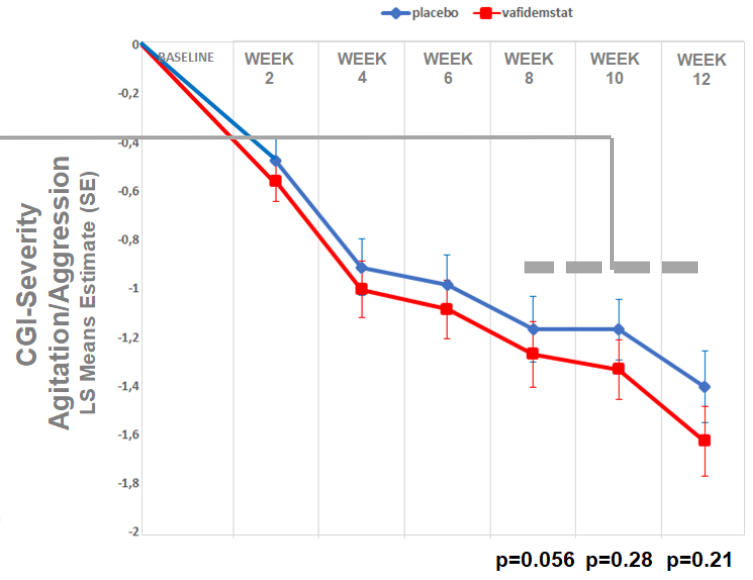
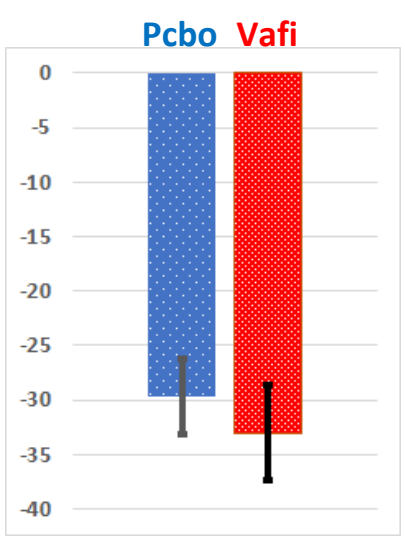


BPDCL-Total Score Across weeks 8-12

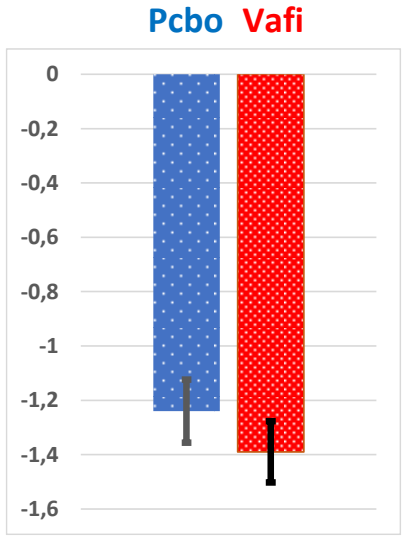
LS Means Estimate (SE)



p=0.412

CGI-Severity A/A Across weeks 8-12

LS Means Estimate (SE)



p=0.254

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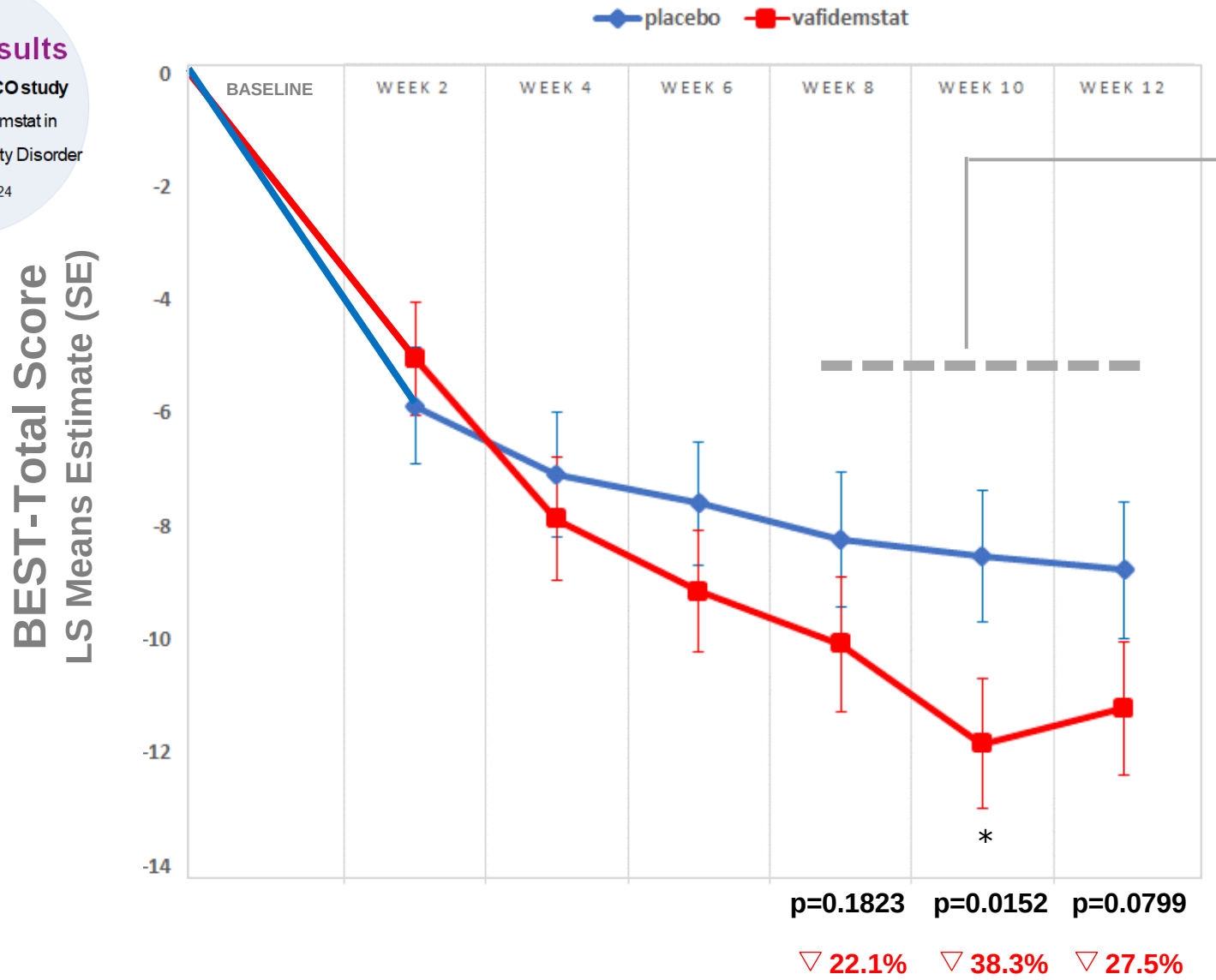
Nominal Statistical Significance in Secondary endpoint: Improvement in BEST across weeks 8-12

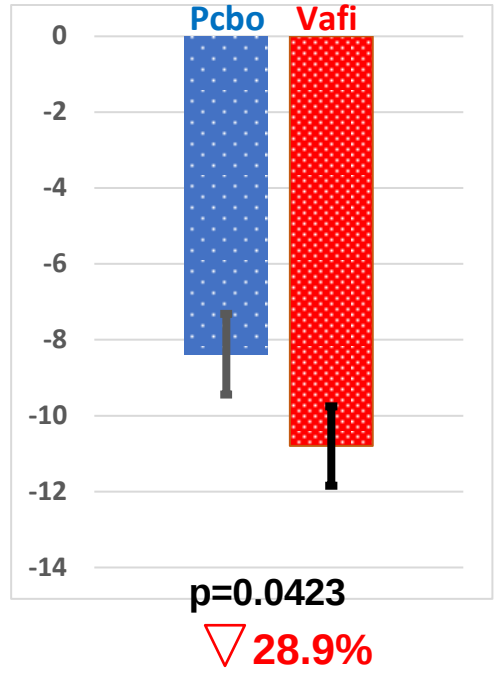
Topline Results

Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorder

January 7, 2024





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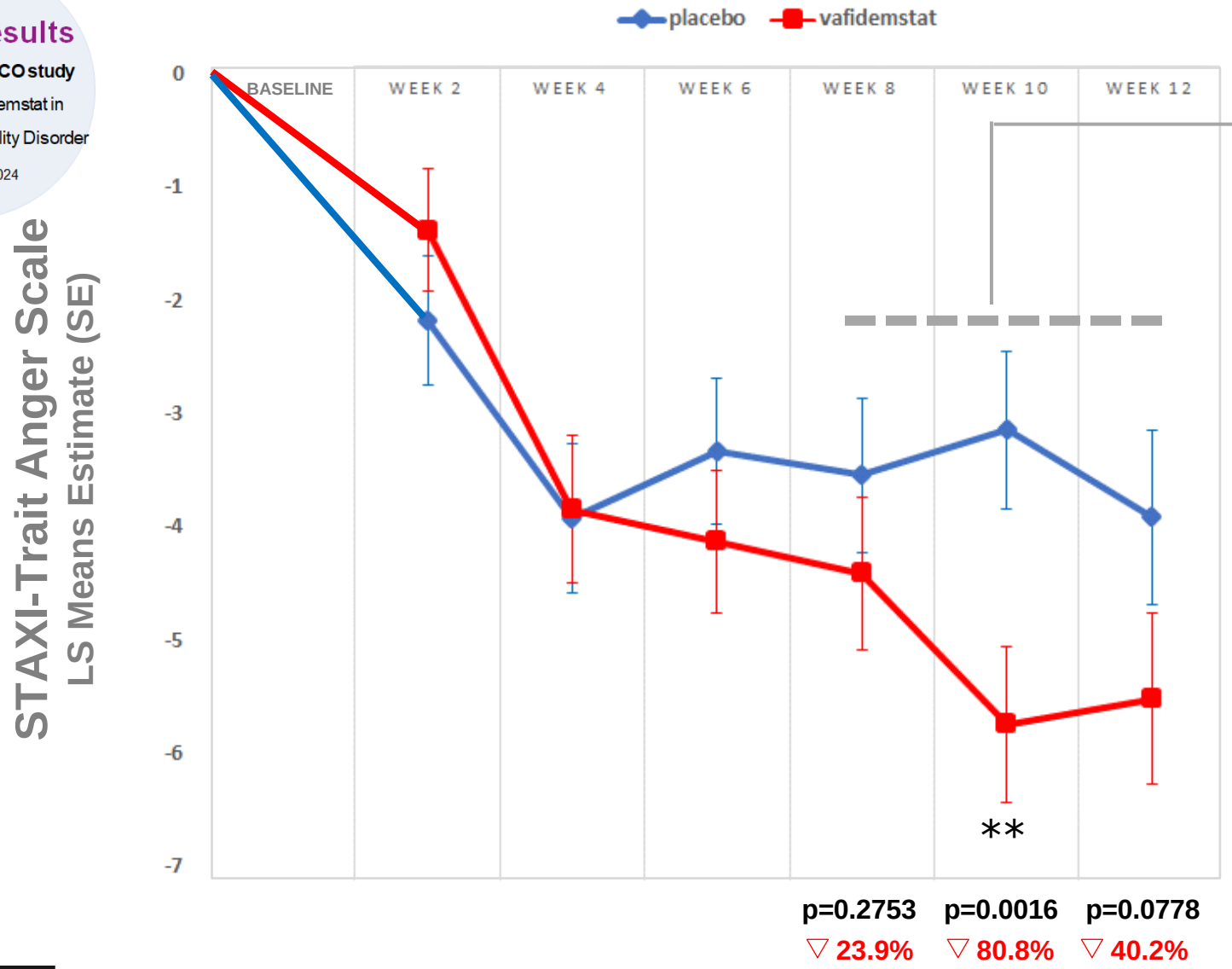
Nominal Statistical Significance in Secondary endpoint: Improvement in STAXI Trait Anger across weeks 8-12

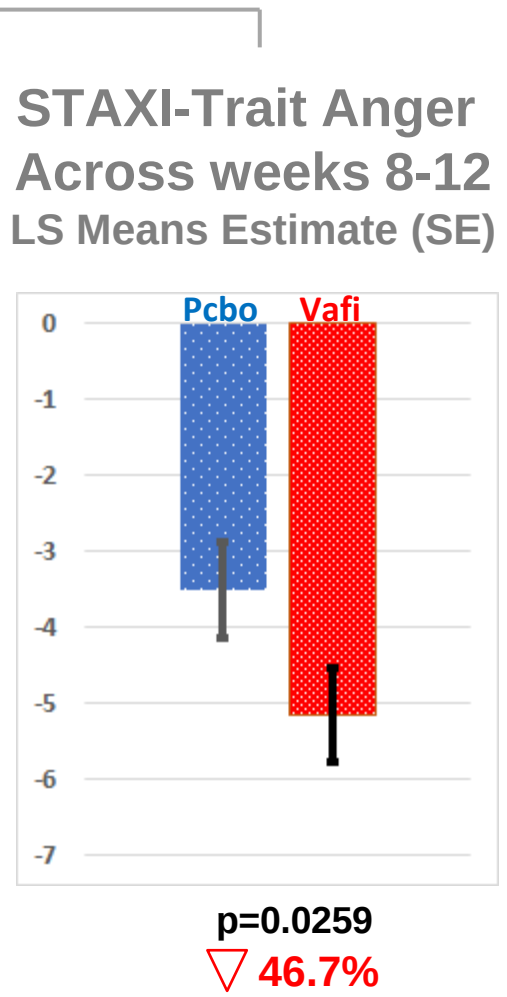
Topline Results

Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorder

January 7, 2024





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PORTICO: All efficacy endpoints consistently favored vafidemstat over placebo

Topline Results

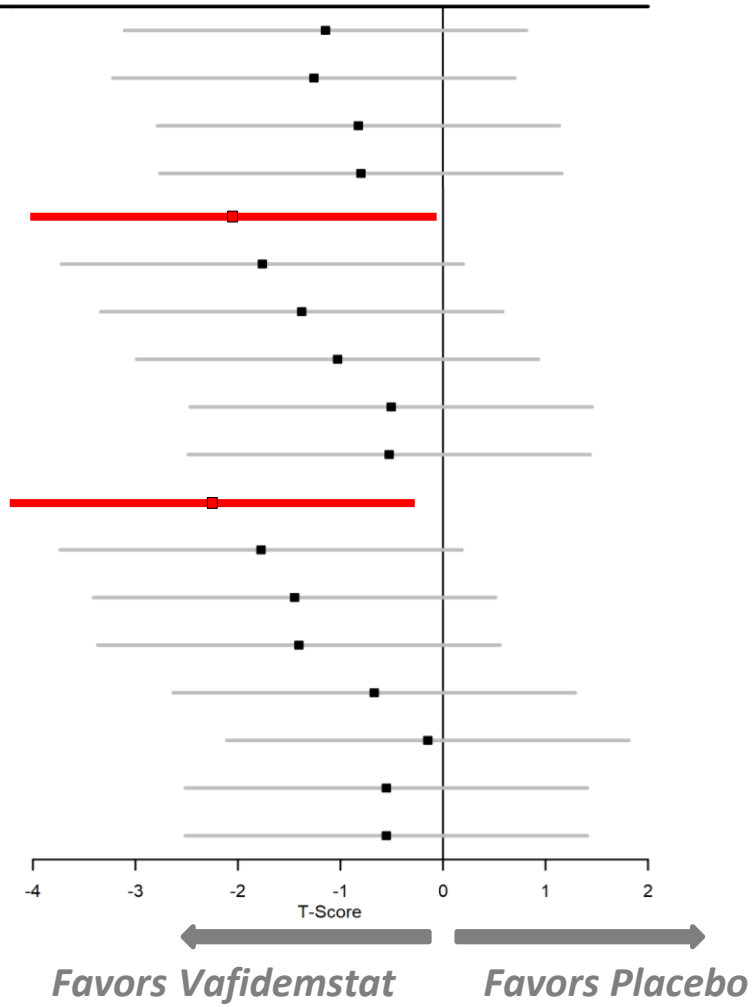
Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorder

January 7, 2024

Full Analysis Set

Parameter	Analysis Type	P-value	Difference	CI	T-Score
CGI02-Severity	Average Mean	0.2541	-0.16	(-0.42,0.11)	-1.14
	Week 12 Mean	0.2103	-0.22	(-0.56,0.12)	-1.26
BPDCL1-Total Score	Average Mean	0.4107	-3.24	(-11.01,4.52)	-0.82
	Week 12 Mean	0.4253	-3.61	(-12.53,5.31)	-0.80
BEST01-Total Score	Average Mean	**0.0423**	-2.43	(-4.77,-0.09)	**-2.05**
	Week 12 Mean	**0.0799**	-2.35	(-4.98,0.28)	**-1.76**
BD201-Total Score	Average Mean	0.1699	-2.11	(-5.14,0.91)	-1.38
	Week 12 Mean	0.3054	-1.71	(-5.00,1.58)	-1.03
STAXI1-State Anger Scale Raw Score	Average Mean	0.6143	-0.49	(-2.38,1.41)	-0.50
	Week 12 Mean	0.6004	-0.57	(-2.69,1.56)	-0.52
STAXI1-Trait Anger Scale Raw Score	Average Mean	**0.0259**	-1.64	(-3.09,-0.20)	**-2.25**
	Week 12 Mean	**0.0778**	-1.56	(-3.30,0.18)	**-1.77**
STAXI1-AX Index Raw Score	Average Mean	0.1495	-2.22	(-5.25,0.81)	-1.45
	Week 12 Mean	0.1616	-2.41	(-5.78,0.97)	-1.41
STAI01-S-Anxiety Raw Score	Average Mean	0.5035	-0.96	(-3.77,1.86)	-0.67
	Week 12 Mean	0.8825	-0.25	(-3.65,3.14)	-0.15
STAI02-T-Anxiety Raw Score	Average Mean	0.5813	-0.67	(-3.05,1.72)	-0.55
	Week 12 Mean	0.5813	-0.67	(-3.05,1.72)	-0.55



**P-values are uncorrected for multiplicity*

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Global statistical test (GST) consistent with a global treatment effect favoring vafidemstat

Topline Results
Phase 2b PORTICO study
Efficacy of vafidemstat in
Borderline Personality Disorder
January 7, 2024

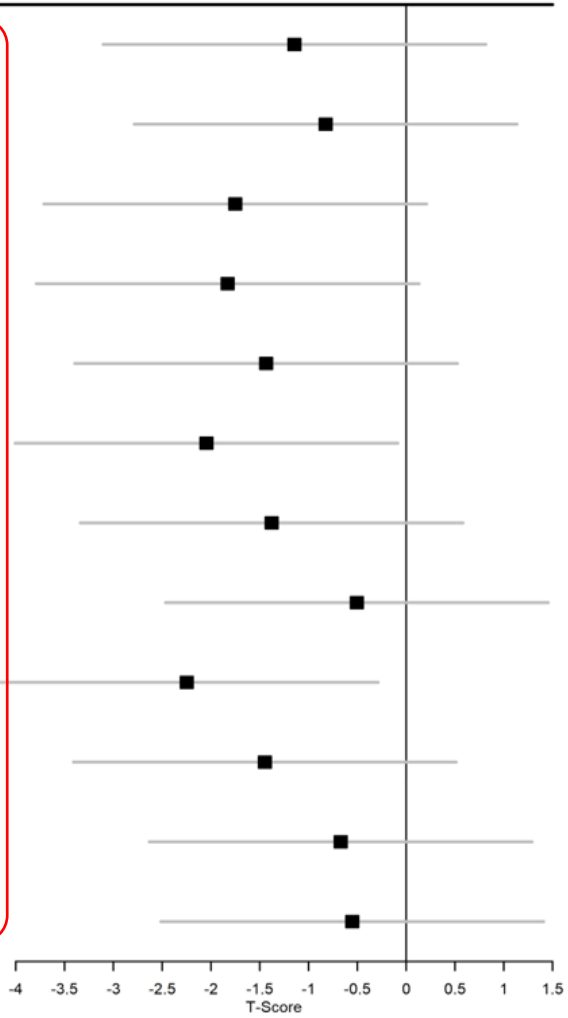
BPD is a multisymptomatic disease with psychiatric, behavioral, and functional outcomes.

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.

When a treatment improves all target outcomes, the GST often has a higher power than tests of single outcomes or other multiple-test procedures. As such, GST incorporates the impact of consistent directional change across multiple key target outcomes, even when individual outcomes may not show statistically significant improvement on their own.

Full Analysis Set

Parameter	P-value	Difference	CI	T-Score	GST P-value
CGI02-Severity	0.2541	-0.16	(-0.42,0.11)	-1.14	
BPDCL1-Total Score	0.4107	-3.24	(-11.01,4.52)	-0.82	0.2476
BEST01-A_Thoughts and Feelings Score	0.0817	-1.31	(-2.79,0.17)	-1.75	0.1419
BEST01-B_Behaviors Negative Score	0.0692	-0.56	(-1.17,0.04)	-1.83	0.0920
BEST01-C_Behaviors Positive Score*	0.1531	-0.47	(0.17,-1.11)	-1.43	0.0694
BEST01-Total Score	0.0423	-2.43	(-4.77,-0.09)	-2.05	
BD201-Total Score	0.1699	-2.11	(-5.14,0.91)	-1.38	0.0689
STAXI1-State Anger Scale Raw Score	0.6143	-0.49	(-2.38,1.41)	-0.50	0.0845
STAXI1-Trait Anger Scale Raw Score	0.0259	-1.64	(-3.09,-0.20)	-2.25	0.0573
STAXI1-AX Index Raw Score	0.1495	-2.22	(-5.25,0.81)	-1.45	0.0564
STAI01-S-Anxiety Raw Score	0.5035	-0.96	(-3.77,1.86)	-0.67	0.0664
STAI02-T-Anxiety Raw Score	0.5813	-0.67	(-3.05,1.72)	-0.55	0.0819



GST p-value shows a strong trend. Particularly when considering specifically global improvement in the disease and in agitation/aggression

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PORTICO: Final Summary of TLD as of January 7th, 2023

- Primary endpoints not met. Two important pre-specified secondary endpoints reached nominal statistical significance:
  - **Overall improvement in BPD disease severity,** measured by BEST across weeks 8-12 (p=0.042). Clinically meaningful reduction compared to placebo
  - **Improvement in Agitation/Aggression** measured by STAXI-2 across weeks 8-12 (p=0.026). Clinically meaningful reduction compared to placebo
- Reduction in overall BPD disease severity and agitation/aggression consistent with Phase IIa REIMAGINE trial results, albeit measured by different scales (BEST versus BPDCL; STAXI-2 versus CGI-S A/A).
- Results across ALL primary and secondary efficacy endpoints favored vafidemstat over placebo.
- Global Statistical Test (GST-p values) consistent with a global treatment effect favoring vafidemstat.
- Vafidemstat was safe and well tolerated.
- No deaths/suicides, and suicidal ideation was low (one case each in the placebo and vafi treated groups; 0.9% overall).
- This is the first time, to the best of our knowledge, that a large, randomized Phase II BPD trial had two statistically significant secondary endpoints reflecting improvements in agitation/aggression as well as in overall BPD disease severity.

PORTICO's efficacy and safety results pave the way to define further clinical development and Oryzon intends to request an End-of-Phase II meeting with the FDA to discuss plans for a registrational BPD Phase III trial

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

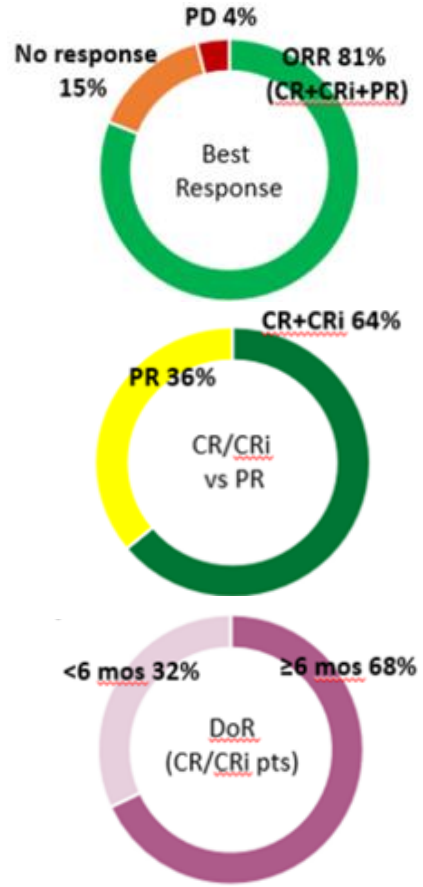
Mechanism of Action

- 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



ORYZON

IIS-X002 Program continues to explore iadademstat potential in 1L AML

- **Investigator Initiated trial**
- IND approved Q4 2023
- Expected FPI by Q1 2024:
  - **A Phase Ib Dose Finding of iadademstat combined with venetoclax and azacitidine in AML 1L Unfit patients**
  - **N= 21 patients**

Led by

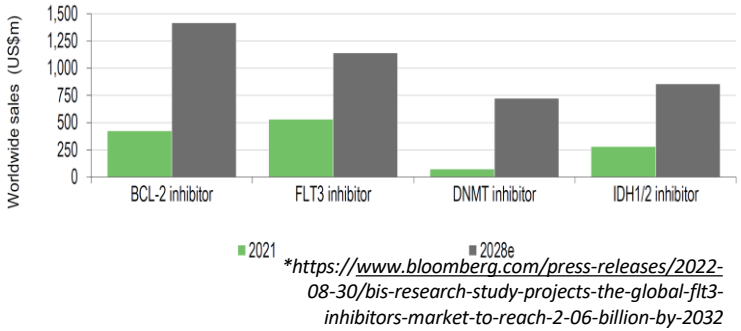
Dr. Curtis Lachowiecz

OREGON HEALTH & SCIENCE UNIVERSITY

FLT3mut+ R/R AML, an interesting market opportunity and a clinical development strategy

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%**)
- **Global FLT3 inhibitors market expected to reach $2.06 Billion by 2032***



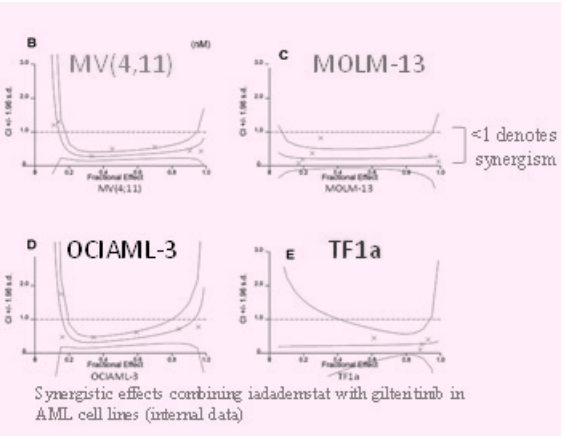
*https://www.bloomberg.com/press-releases/2022-08-30/bis-research-study-projects-the-global-flt3-inhibitors-market-to-reach-2-06-billion-by-2032

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

(Source Edison Research 2023 & Evaluate Pharma)

FRIDA: A Phase Ib in FLT3 mut+ R/R AML patients

- Combining iadademstat and gilteritinib (Xospata®)
- These patients are now treated with gilteritinib, yet there is a high medical need **(mEFS 2.8 months & CR+CRi 34%)**
- **Iadademstat and gilteritinib show a strong synergism**, providing a strong preclinical rationale for enhanced clinical benefit
- Led by the Mass General Hospital. 15 US sites



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

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

ORYZON

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

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

FINAL ANALYSIS selected endpoints:

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

ORYZON

FRIDA follows FDA's Project Optimus: requiring identification of the lowest possible effective dose

- 12 patients recruited (90% of patients were refractory to the previous treatment)
- 6 patients treated in First Cohort. Starting Dose 100ug. Safe and with strong antileukemic activity
- 6 Patients in Second Cohort accrued and ongoing
- Expansion and/or starting Third Cohort under consideration
- FRIDA Preliminary Data promising compared to gilteritinib alone in historical data (*Internal Company assessment*)
- Preliminary data expected to be presented at EHA-2024 (June 13-16 Madrid, Spain)

Neuroendocrine Program:

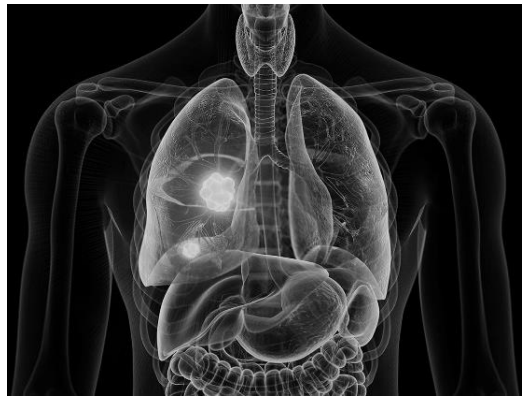
STELLAR and NET trials

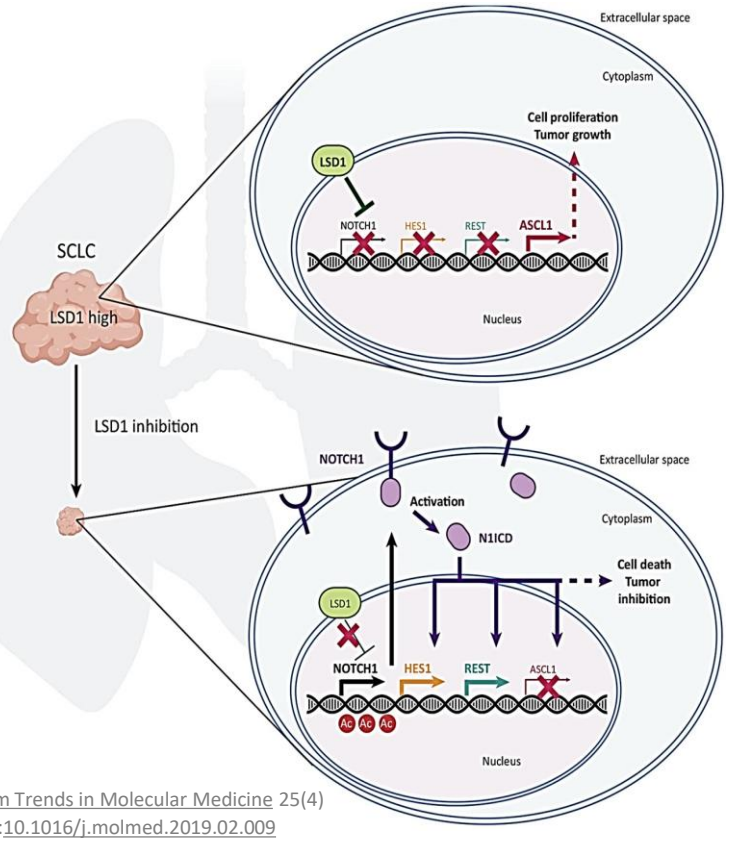
Iadademstat: potentially first and best-in-class LSD1 inhibitor in SCLC and other Neuroendocrine tumors

Mechanism of Action

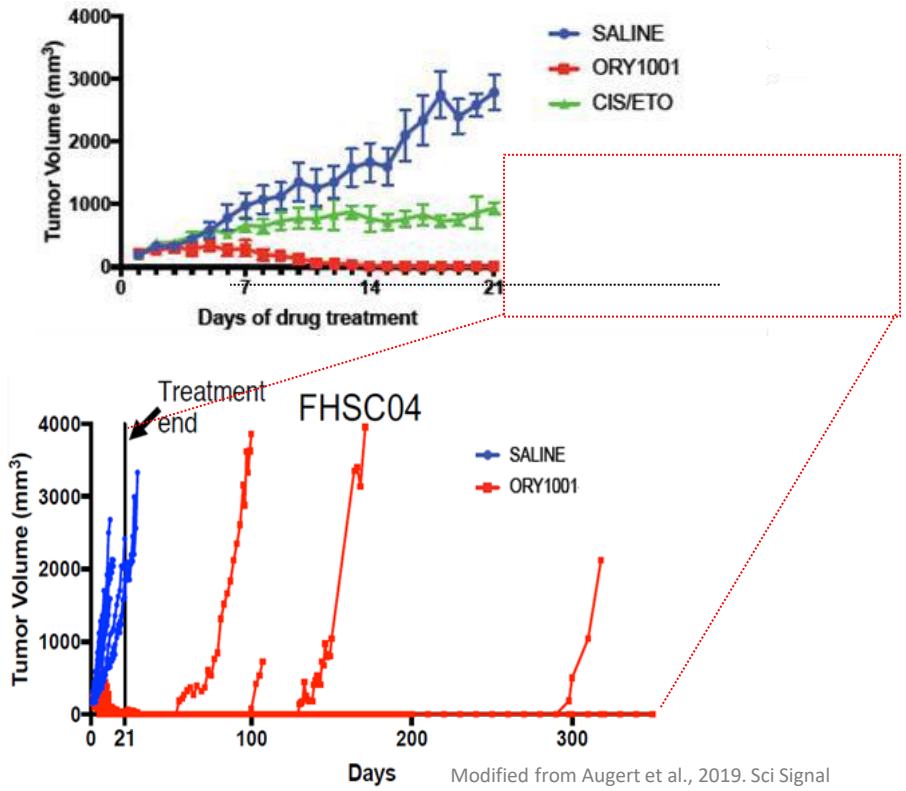
- LSD1 is required for survival & proliferation of **neuroendocrine/SCLC tumor cells**
- Iadademstat **induces Notch**, a well characterized tumor suppressor in SCLC **and represses ASCL1**
- **Iadademstat blocks LSD1's actions and promotes neuroendocrine/SCLC tumor differentiation and death**
- **Iadademstat 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





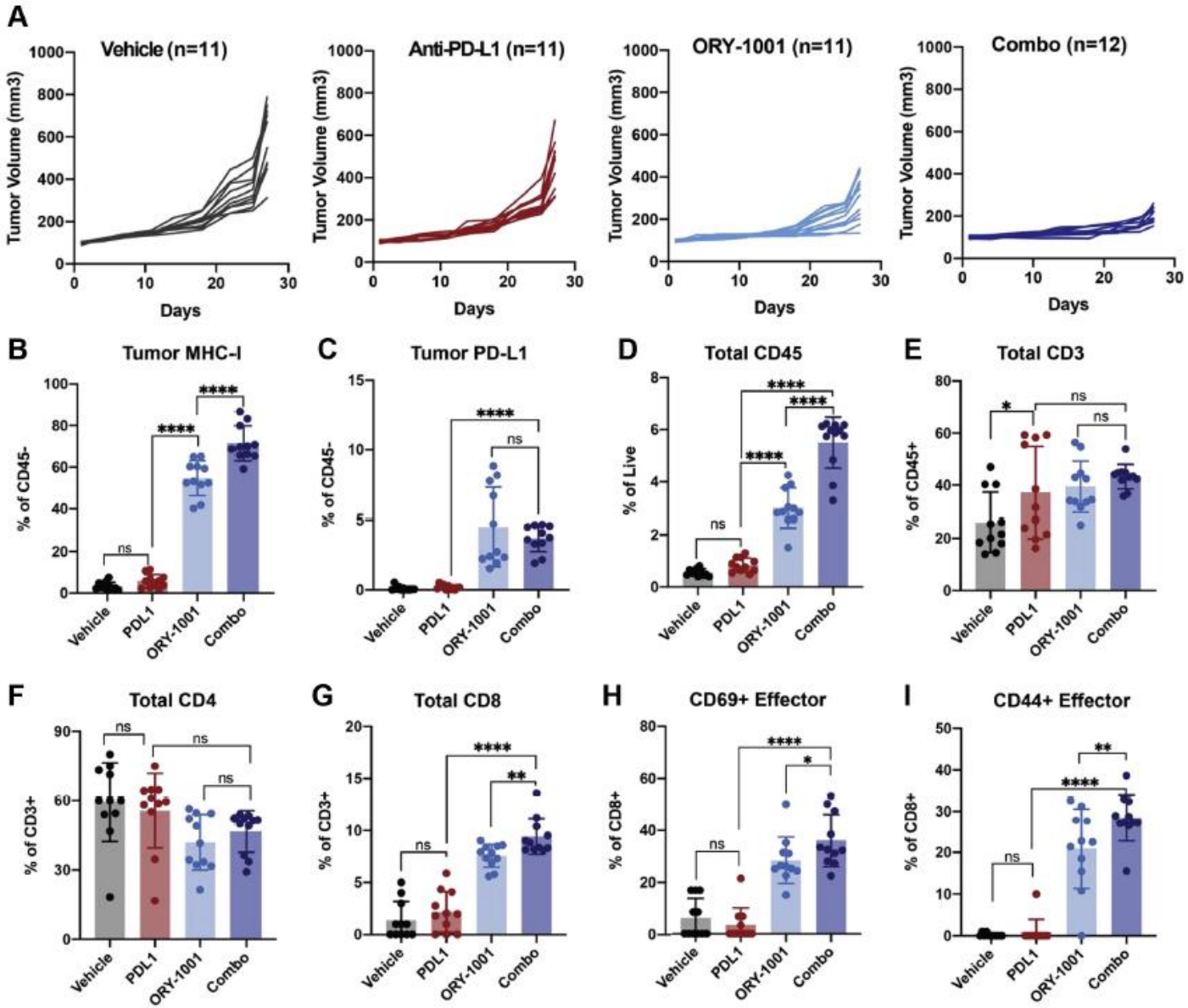
From Trends in Molecular Medicine 25(4)
DOI:10.1016/j.molmed.2019.02.009



Modified from Augert et al., 2019. Sci Signal

ORYZON

Iadademstat and anti-PD-L1 combination inhibits SCLC progression

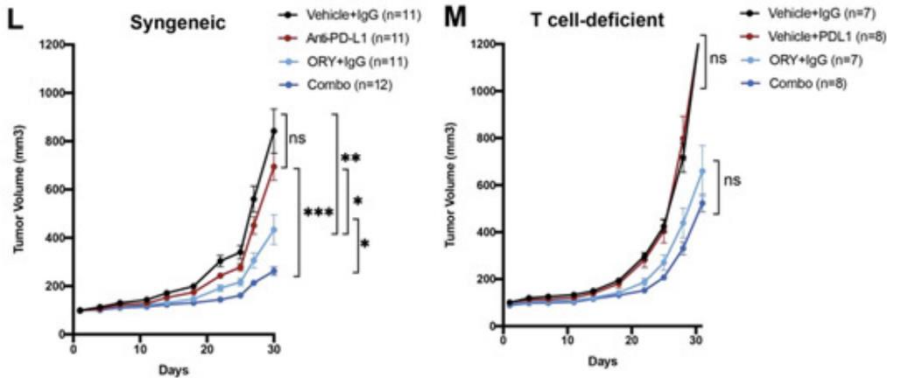


> J Thorac Oncol. 2022 Jun 9;S1556-0864(22)00273-8. doi: 10.1016/j.jtho.2022.05.014. Online ahead of print.

Targeting Lysine-Specific Demethylase 1 Rescues Major Histocompatibility Complex Class I Antigen Presentation and Overcomes Programmed Death-Ligand 1 Blockade Resistance in SCLC

Evelyn M Nguyen [1], Hirokazu Taniguchi [2], Joseph M Chan [2], Yingqian A Zhan [3], Xiaoping Chen [4], Juan Qiu [4], Elisa de Stanchina [4], Viola Allaj [2], Nisargbhai S Shah [2], Fathema Uddin [2], Parvathy Manoj [2], Michael Liu [2], Sheng F Cai [5], Ross Levine [6], Álvaro Quintanal-Villalonga [2], Triparna Sen [2], Andrew Chow [2], Charles M Rudin [7]

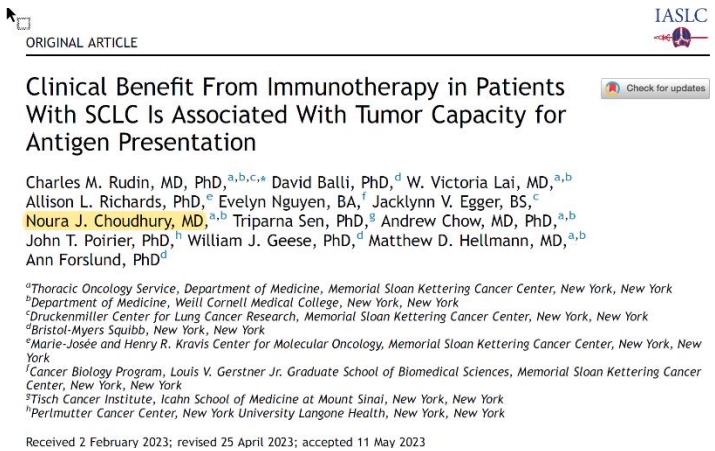
7 Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York; Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, New York; Graduate Program in Pharmacology, Weill Cornell Medical College, New York, New York. Electronic address: rudinc@mskcc.org.



Nguyen et al 2022

NEXT-CTEP-NCI Program

- **CRADA agreement**
- IND ready for submission
- FPI expected by Q1 2024:
  - **A Phase 1 Dose Finding and Phase II Randomized Trial of Iadademstat Combined with Immune Checkpoint Inhibition Maintenance After Initial Chemoimmunotherapy in Patients with Extensive-Stage Small Cell Lung Cancer**



ORIGINAL ARTICLE

IASLC

Clinical Benefit From Immunotherapy in Patients With SCLC Is Associated With Tumor Capacity for Antigen Presentation

Check for updates

Charles M. Rudin, MD, PhD,[a,b,c,*] David Balli, PhD,[d] W. Victoria Lai, MD,[a,b] Allison L. Richards, PhD,[e] Evelyn Nguyen, BA,[f] Jacklynn V. Egger, BS,[c] Noura J. Choudhury, MD,[a,b] Triparna Sen, PhD,[g] Andrew Chow, MD, PhD,[a,b] John T. Poirier, PhD,[h] William J. Geese, PhD,[d] Matthew D. Hellmann, MD,[a,b] Ann Forslund, PhD[d]

[a]Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
[b]Department of Medicine, Weill Cornell Medical College, New York, New York
[c]Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, New York
[d]Bristol-Myers Squibb, New York, New York
[e]Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, New York
[f]Cancer Biology Program, Louis V. Gerstner Jr. Graduate School of Biomedical Sciences, Memorial Sloan Kettering Cancer Center, New York, New York
[g]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York
[h]Perlmutter Cancer Center, New York University Langone Health, New York, New York

Received 2 February 2023; revised 25 April 2023; accepted 11 May 2023

Led by

Dr. Noura Choudhury

Memorial Sloan Kettering Cancer Center

NIH NATIONAL CANCER INSTITUTE
DCTD Division of Cancer Treatment & Diagnosis

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, currently accruing in US sites

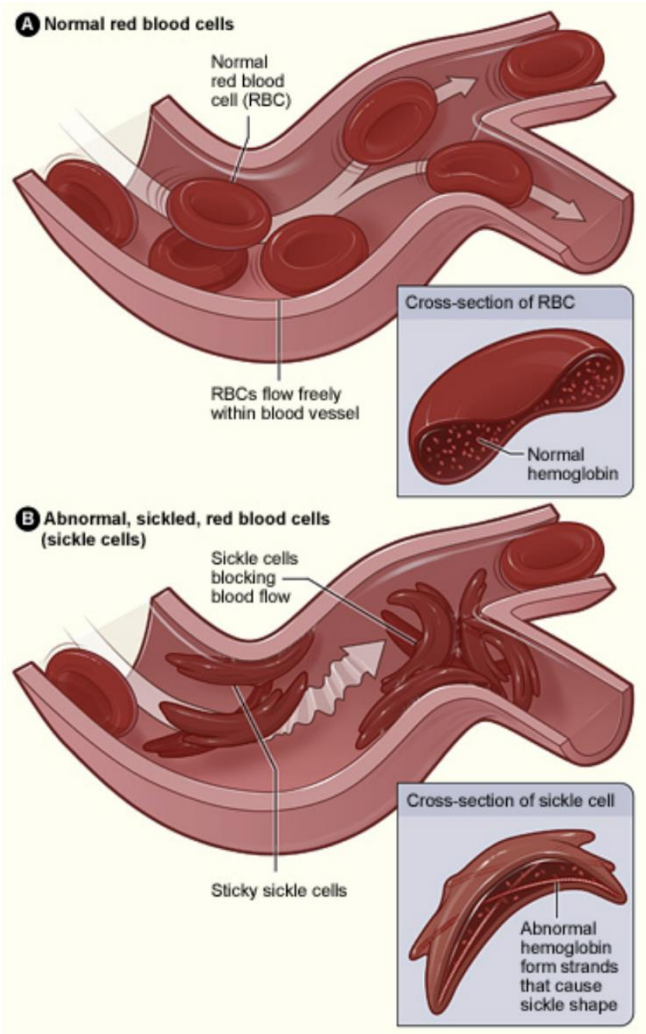
PI: Dr. Namrata Vijayvergia
Assistant Chief, Gastrointestinal Medical Oncology
Associate Professor, Department of Hematology/Oncology
Medical Director, Medical Oncology

ORYZON

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.

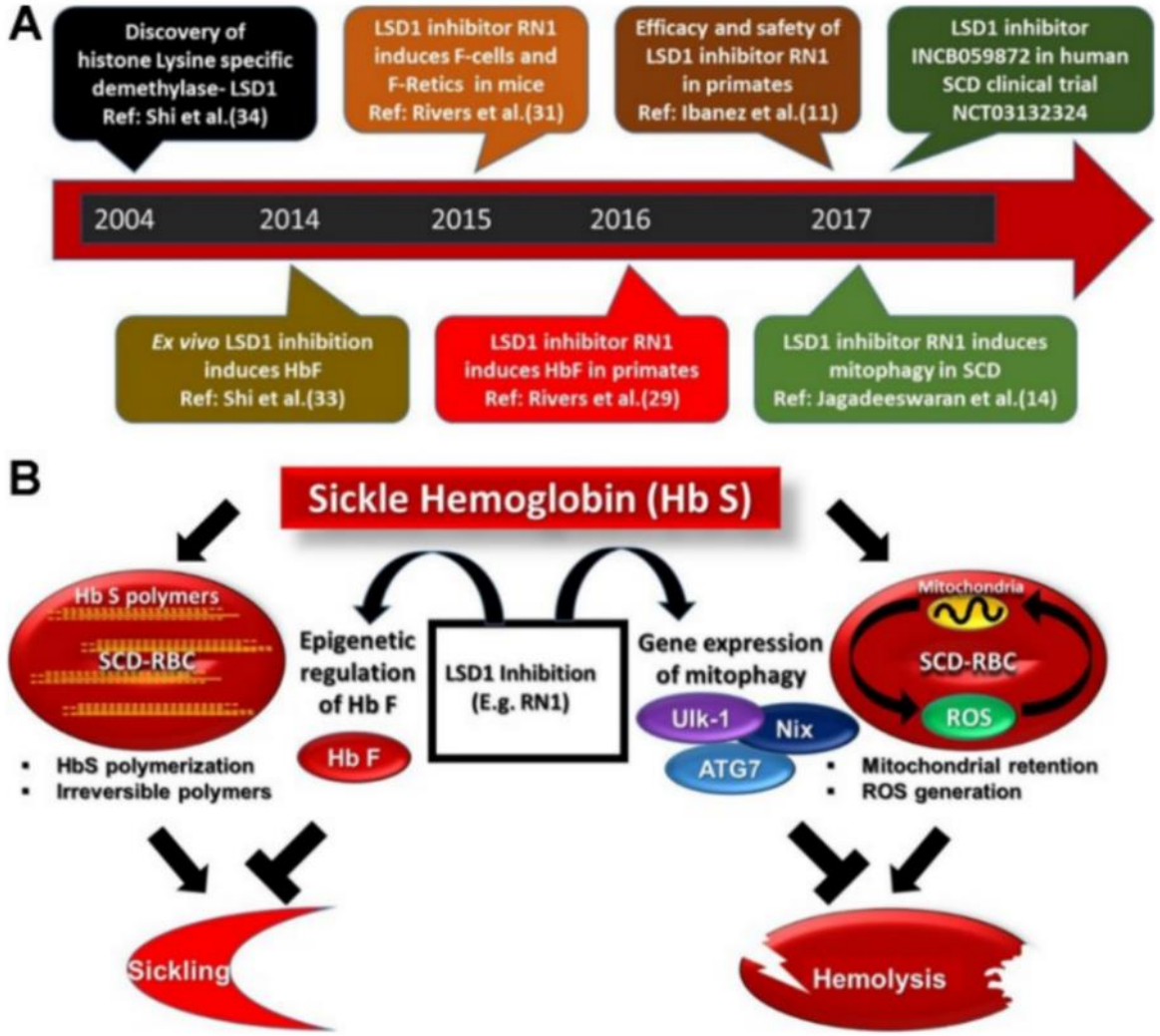
The sickling process occurs under deoxygenated conditions in which hemoglobin S polymerizes, forming aggregates called tactoids that give the resulting product a rigid structure.

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

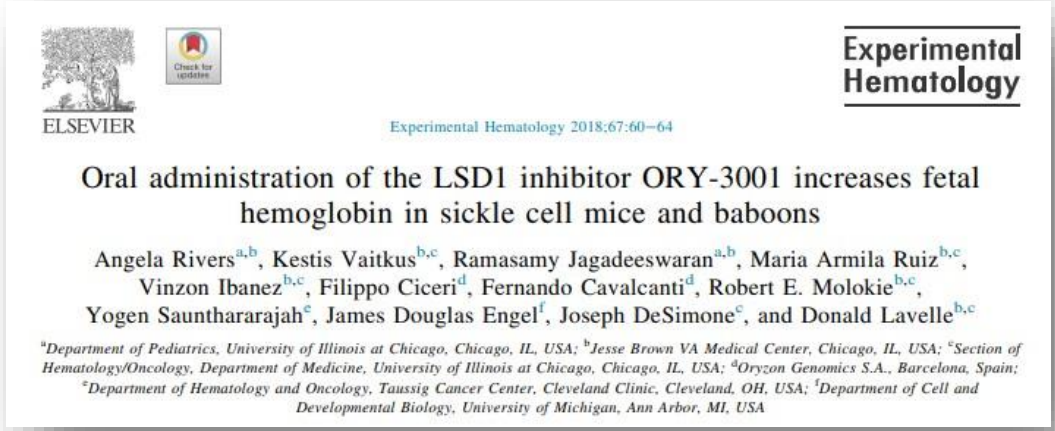
- ORY-3001 is a highly potent and selective oral LSD1 inhibitor with a very good pharmacology
- It has completed the IND enabling toxicology
- Its action over SCD is based on two distinct mechanisms:
  - one addresses sickle hemoglobin (HbS) polymerization-mediated sickling, and
  - the other addresses 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

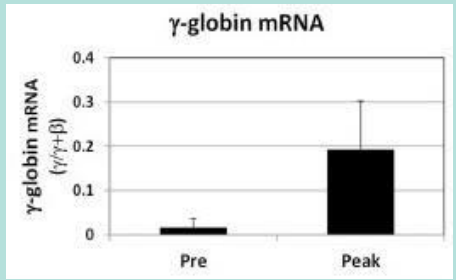
Angela Rivers[a,b], Kestis Vaitkus[b,c], Ramasamy Jagadeeswaran[a,b], Maria Armila Ruiz[b,c], Vinzon Ibanez[b,c], Filippo Ciceri[d], Fernando Cavalcanti[d], Robert E. Molokie[b,c], Yogen Saunthararajah[e], James Douglas Engel[f], Joseph DeSimone[c], and Donald Lavelle[b,c]

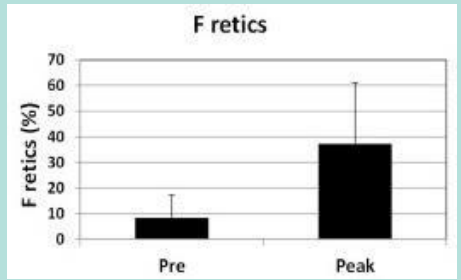
[a]Department of Pediatrics, University of Illinois at Chicago, Chicago, IL, USA; [b]Jesse Brown VA Medical Center, Chicago, IL, USA; [c]Section of Hematology/Oncology, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA; [d]Oryzon Genomics S.A., Barcelona, Spain; [e]Department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

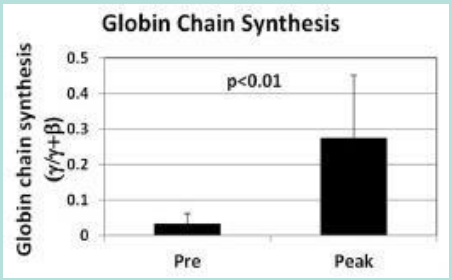
- **LSD1 occupancy confirmed** by target engagement analysis and platelet reduction

In these models, ORY-3001 increased:

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



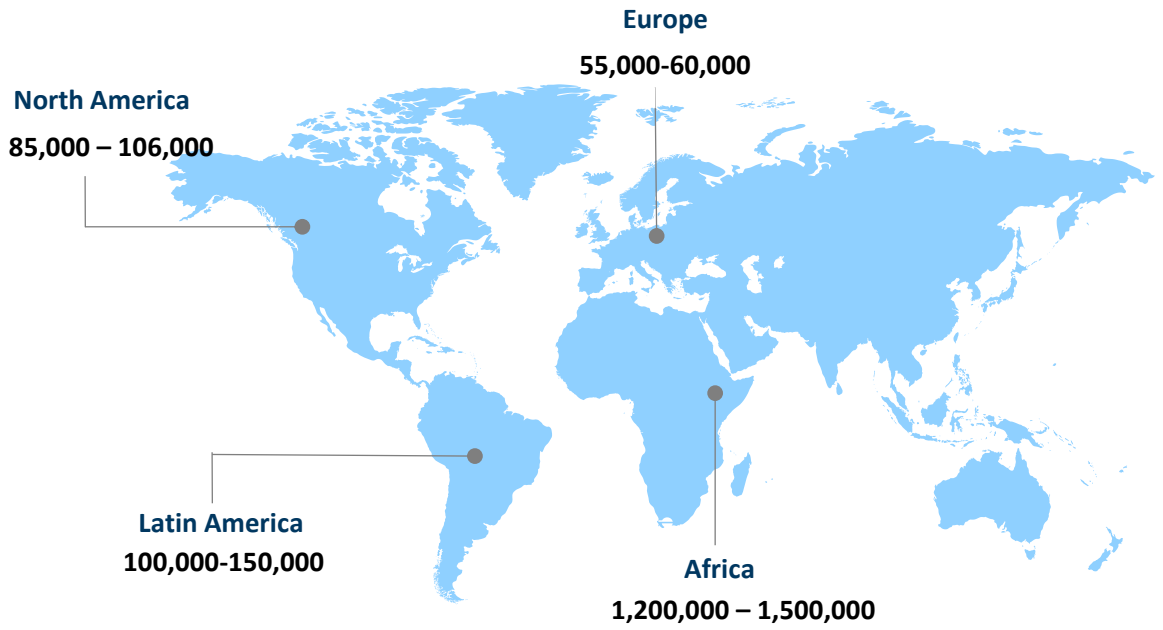




Sickle cell disease prevalence

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



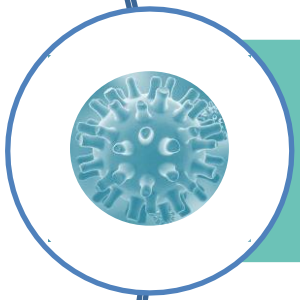
Number of Sickle Cell Births Per Year	
Country	**No. of SCD Birth/Year**
U.S.	3,000
India	5,200
U.K.	270
Nigeria	91,011
Tanzania	11,877
Angola	9,017
Uganda	10,877
Ghana	5,815
Niger	5,310
Zambia	6,039
Cameroon	7,712
Global	305,773

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

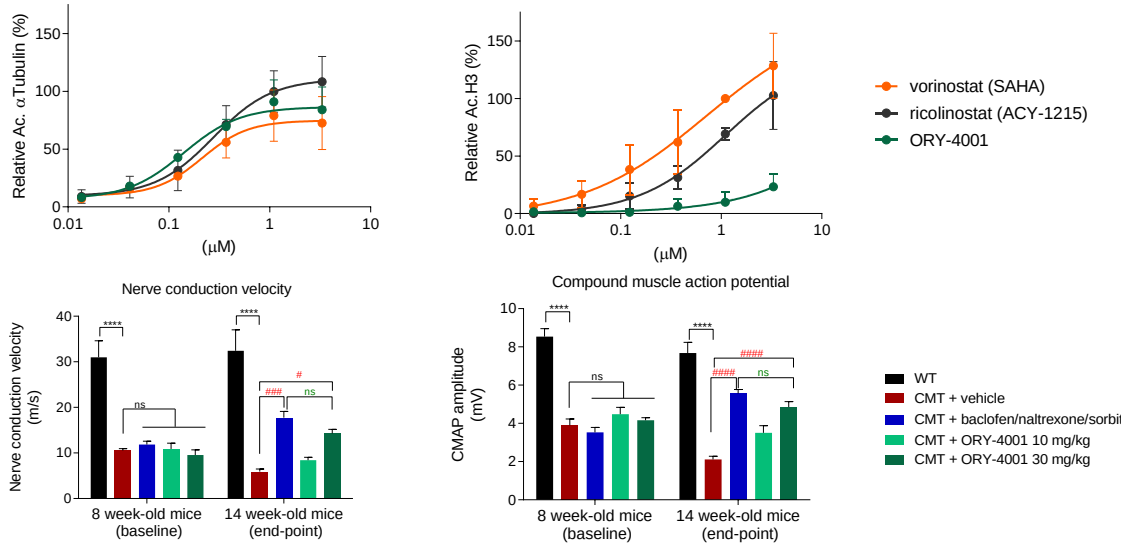
HDAC-6 has been suggested as a therapeutic target in Charcot-Marie-Tooth (CMT), ALS, and other CNS diseases

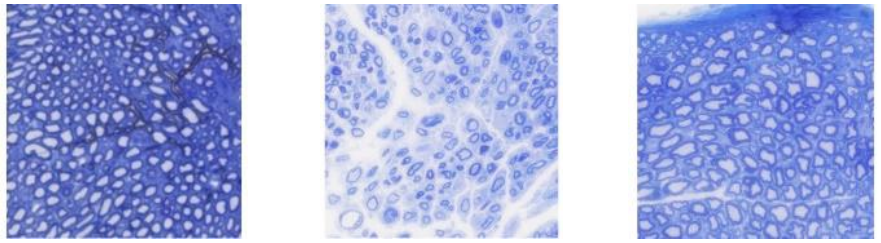
ORY-4001 is a highly potent and selective HDAC6 inhibitor with good pharmacology

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

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

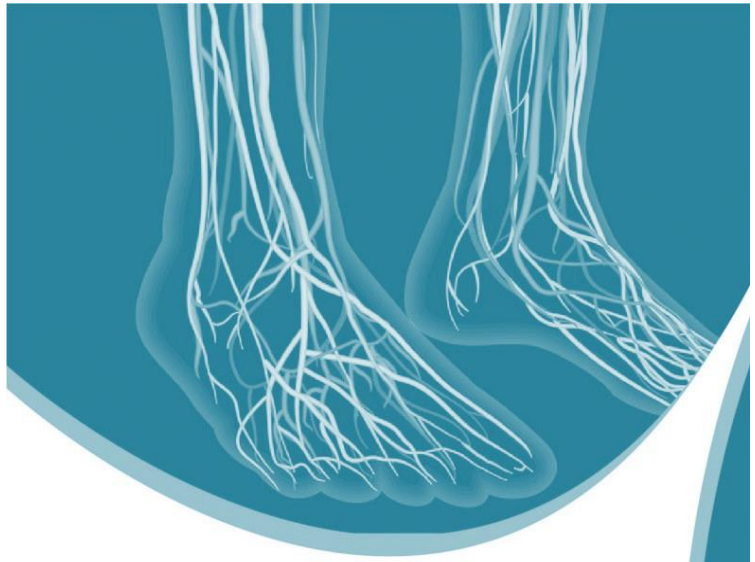
The age-specific cases in EU-5

41-60 years – Most affected

0-18 years – Least affected

The diagnosed prevalent population

EU-5	116,794
United States	95,221
Germany	32,291
Japan	13,691



Market Size 2021
US$ 793.9 MILLION

Value Projection 2028
US$ 3,459.1 MILLION

ORYZON


VAFIDEMSTAT
Personalized medicine in CNS
Pioneering
personalized medicine
in epigenetics

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

COMPASS Pathologies: H3K4-met related indications

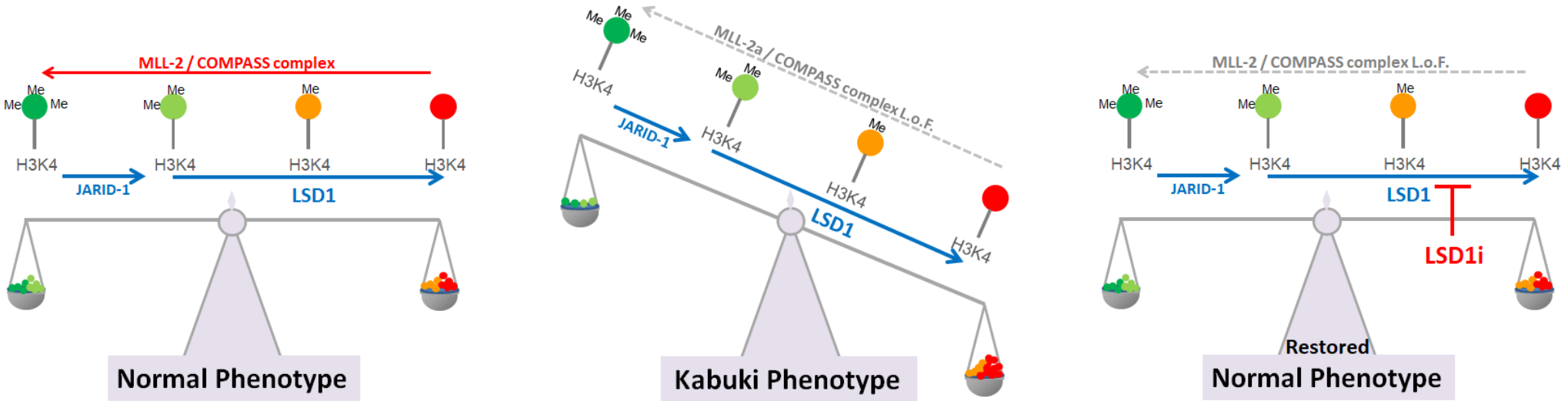
- **KMT2D (MLL2) – Kabuki Syndrome**
- **KMT2F (SetD1a) - Schizophrenia susceptibility**
- KMT2A - Wiedemann–Steiner syndrome
- KMT2B - Dystonia 28, Childhood-Onset
- KMT2C - Kleefstra syndrome –Autism spectrum disorders
- KMT2G (SetD1b) - Syndromic intellectual disability

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

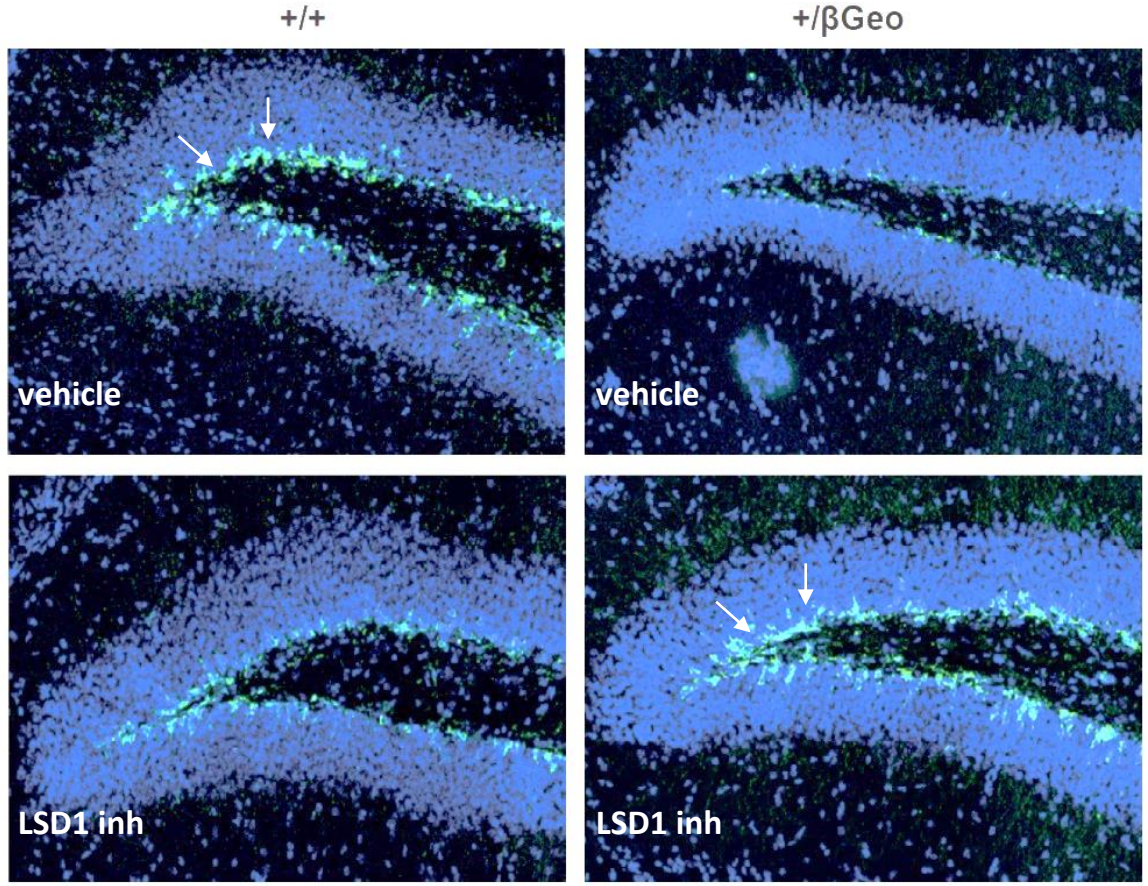
- Kabuki syndrome is a congenital disorder characterized by intellectual disability, growth retardation, dysmorphic facial features and immune defects
- **Mutations of *MLL2 (KMT2D)* cause Kabuki syndrome in >70% of cases** (known as KS type I)
- *MLL2* is a Histone Methyl transferase. Unbalance methylation 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

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 the 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

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 2024

Multiple inflection points

- **Final Read Out in BPD PORTICO 2Q24**
- **EoP2 FDA Meeting to discuss PORTICO**
- **2L AML FRIDA and NET trials preliminary readouts in 2024**
- **SCLC trial in combination w ICIs to start accruing in Q12024**
- **SCZ trial EVOLUTION enrolling**
- Kabuki Syndrome Phase I/II trial IND e1H2024

Pioneering personalized medicine in epigenetics