Pioneering personalized medicine in epigenetics

ORYZON

CORPORATE PRESENTATION

September 2022

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 **LSD1 inhibitors with best-in-class characteristics**

2 Programs with well-defined registrational pathways: **Iadademstat in Oncology and Vafidemstat in CNS**

Listed in Europe (Madrid)
MK Cap ~$150M

Runway expected till mid 2024

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

CNS: vafidemstat (ORY-2001) - CNS optimized LSD1 inhibitor

Indication	Borderline Personality Disorder	Schizophrenia Negative Symptoms & Cognition	Kabuki Syndrome	SetD1A Compass related SCZ	Aggression in AD
Study	PORTICO	EVOLUTION	HOPE	New Study	New Study *Continuation of REIMAGINE-AD*
Phase	**Phase IIb**	**Phase IIb**	**Phase Ib/II**	Phase Ib/II	
Status	Recruiting	Recruiting	IND in preparation	Under study	Under study
Anticipated Milestones	Interim analysis 1Q23	Study updates 2023	IND 2H22/FPI 1Q23		

Oncology: iadademstat (ORY-1001) - Selective LSD1 inhibitor

Indication	AML 1L Elderly/Unfit	AML R/R-Flt3mut+	ED-SCLC 1L	NETs R/R
Study	ALICE *(Combo w azacitidine)*	FRIDA *(Combo w gilteritinib)*	STELLAR *(Combo w ICI)*	NET Basket *(Combo w other agents)*
Phase	**Phase IIa**	**Phase Ib**	**Phase Ib/II**	**Phase Ib/II**
Status	Ongoing – fully enrolled	IND approved	IND in preparation	IND in preparation (Collaborative Study)
Anticipated Milestones	2H22 ASH Final Data	FPI 2H22	IND 2H22	IND 2H22/FPI 2H22

Note: Finalized clinical trials for iadademstat and vafidemstat are not shown. See www.oryzon.com for more details

ORYZON has an ambitious epigenetic program in Oncology

IADADEMSTAT
A Phase II LSD1 inhibitor in Oncology

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

- A unique asset to address specific cancers
- Focusing on clinical execution in hemato-oncology and solid tumors with a registrational plan
- Reinforcing institutional collaborations
- Exploring niche indications in collaborative settings
- Setting an optimal long-term corporate strategy

FDA

ODD granted

AML
SCLC

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

AML

NIH NATIONAL CANCER INSTITUTE Technology Transfer Center

CRADA Agreement ORYZON-NCI

SEAL OF EXCELLENCE
European Commission

Excellence Program EU Commission

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

The asset

- The most potent (nM) oral inhibitor of the lysine histone demethylase LSD1 in clinical development
- +100 pts treated with iadademstat in 4 Phase I/II oncology trials – safety profile well established

ACS Pharmacology & Translational Science
pubs.acs.org/ptsci
Article

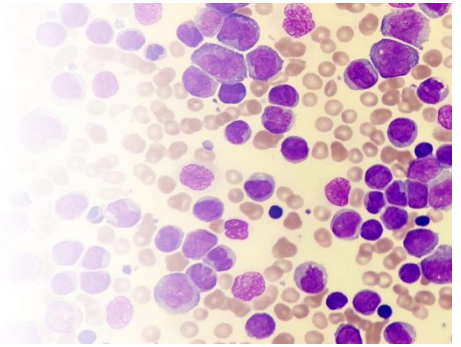
Comprehensive *in Vitro* Characterization of the LSD1 Small Molecule Inhibitor Class in Oncology

Published as part of the ACS Pharmacology & Translational Science special issue "Epigenetics 2022".

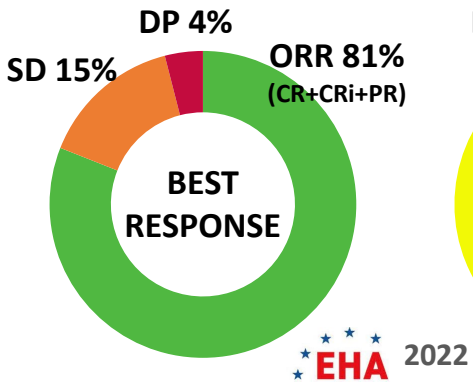
Natalia Sacilotto,[⊥] Paola Dessanti,[⊥] Michele M. P. Lufino, Alberto Ortega, Alejandra Rodríguez-Gimeno, Jordi Salas, Tamara Maes, Carlos Buesa, Cristina Mascaró,[*] and Robert Soliva[*]

Mechanism of Action

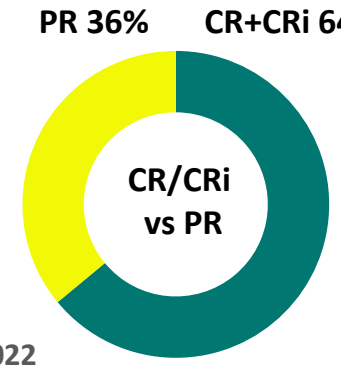
- LSD1 is required for leukemic stem cell survival and blocking leukemic cell differentiation
- Iadademstat prevents leukemic stem cell survival and promotes rapid differentiation/death of leukemia cells

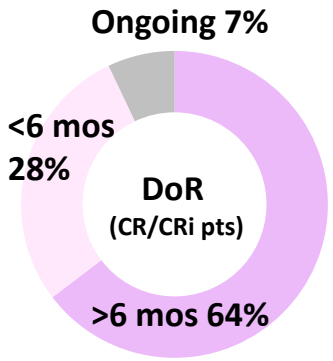


Key Clinical Data in ALICE as PoC



EHA 2022





ALICE, an AML Phase II trial with LSD1i in combination with azacitidine in unfit patients

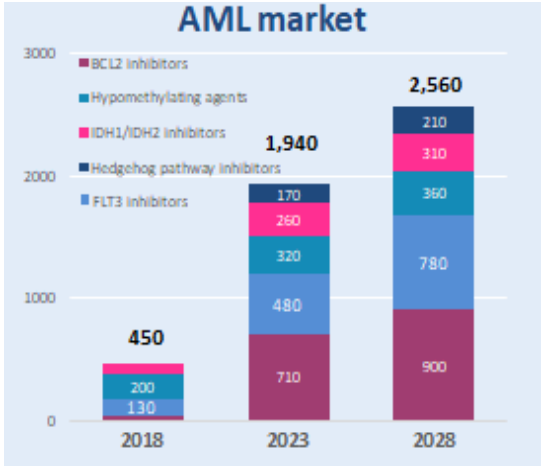
- Multicenter, single arm & open label study
- 36 patients enrolled (LPI 10/2021)
- **Primary endpoint:** Dose finding, safety and tolerability of combo therapy
- **Secondary endpoints:** Response; time to response; duration of response; overall survival

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

Best route to Market

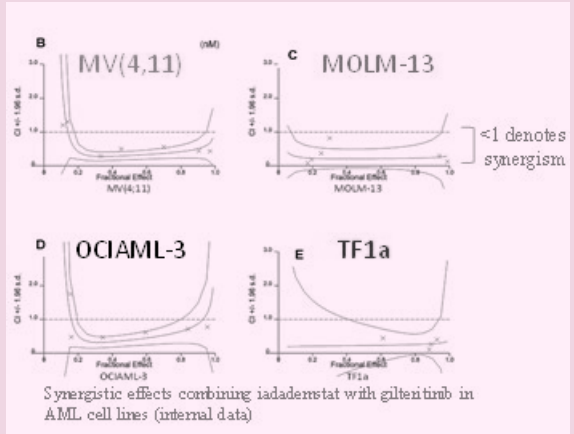
- In a competitive market, R/R AML is an underserved population: **Majority of AML patients relapse after 1L treatment and require further treatment**
- FLT3 is the most common mutation in AML (**30-40%**) and is currently modestly served with existing drugs
- These patients are now treated with **gilteritinib,** yet there is a **high medical need (mEFS 2.8 months & CR+CRi 34%)**

R/R-AML a Market opportunity



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
  - IND approved March 2022 / FPI 2H2022
  - 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)

IND Approved

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 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**

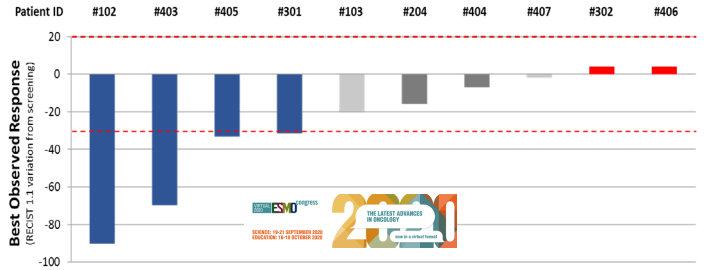
Key Clinical Data

- **Safety demonstrated as a single agent** (R/R ED-SCLC)
- **CLEPSIDRA trial**: iadademstat in combination with SoC chemotherapy in R/R Pt-sensitive ED-SCLC showed preliminary efficacy but challenging to manage overlapping thrombocytopenia, however as monotherapy was well tolerated
  - **ORR 40%:** (4 PR/10 evaluable patients); 2 additional long-term SD (CBR 60%)
  - DoR 4.5 months
  - 1 patient received **15 cycles iadademstat in monotherapy maintenance** and tumor response continued to improve (up to 90% tumor reduction)
  - No lung, hepatic, renal, or cardiac toxicity. **No hematotoxicity as a single agent (0 out 6 patients)**

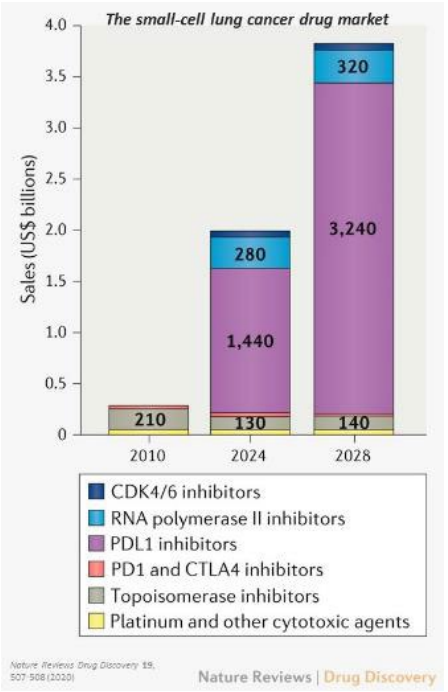
Route to Market

- SCLC is approx. 15% of lung cancer (around 28,000 pts in the US in 2021, similar in EU5 and close to 100,000 in China)
- 1L SCLC has a global market potential of **~$3.5Billion by 2027, expanding at a CAGR of 19.4% over the forecast period**
- An underserved population: **Recently approved ICIs provide only modest benefit**

A Proof of Concept (CLEPSIDRA)



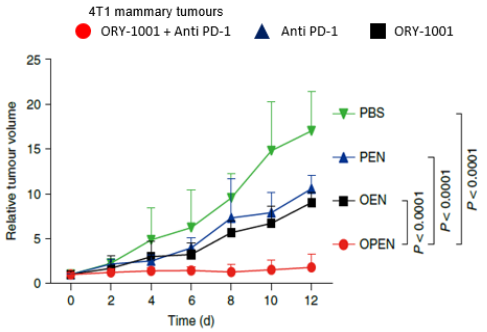
A Market opportunity



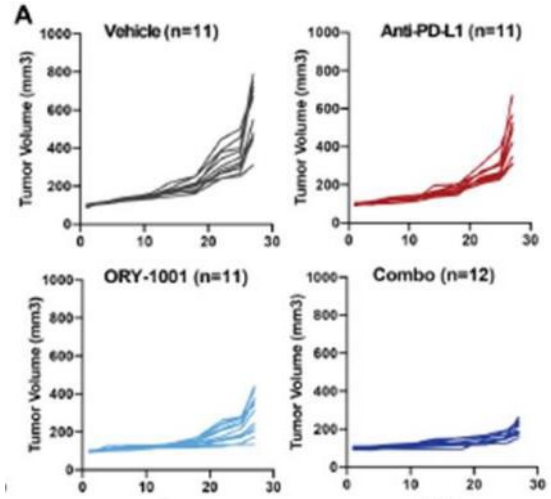
A future Phase Ib/II trial in 1L ED-SCLC with potential for accelerated development

A strong rationale with ICIs

- **Iadademstat and ICIs show a strong synergism**, suggesting potential clinical benefit
- LSD1i enhances the immunological response by overexpressing MHC-1 class genes and deferring lymphocyte exhaustion



Zhai et al., Nat Nanotechnol 2021



Nguyen et al., J Thorac Oncol. 2022 Aug;17(8):1014-1031.

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 2H2022

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

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

A Phase Ib/II study of iadademstat in combination with synergistic agents in platinum R/R SCLC and extrapulmonary high grade neuroendocrine carcinomas

- **Label expansion opportunity**
- **High unmet medical need: Treatment of platinum relapsed (<6 mos)**
- **Low hanging fruit: R/R NETs have dismal outcomes** ranging from ORR 5% (extrapulmonary) to ~20-30% in SCLC; and PFS 3 to 4 months respectively
- **Strong rationale** for combination of iadademstat with synergistic platelet-sparing agents in several tumors
- IND 2H2022
- FPI 2H2022

ORYZON, the only company developing epigenetic drugs in CNS

VAFIDEMSTAT
A Phase II LSD1 inhibitor for CNS diseases

CNS disorders: a field evolving towards Precision Medicine

LSD1 is key for the function of the CNS and is involved in multifactorial CNS disorders and monogenic syndromes

Large multifactorial indications

- Largely unknown pathogenesis
- Still diagnosed by predominant symptoms
- Confounding comorbidities
- May include genetically defined subpopulations
- Large market opportunities

Small/rare monogenic indications

- Molecular diagnosis
- Allows smart drug design based on MoA
- Fast Market Approval conceivable
- Small markets but premium price
- May expand label to similar indications

Vafidemstat may be developed in both types of indications based on different formulations and commercial channels

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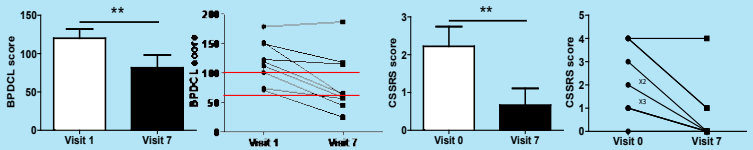
Vafidemstat: an LSD1 inhibitor to treat large multifactorial CNS indications including borderline personality disorder (BPD) and schizophrenia (SCZ)

Mechanism of Action

- A potent (nM) oral inhibitor of LSD1 with **high BBB penetration**
- **LSD1i induces** the **neuronal plasticity & downregulates neuroinflammation**
- LSD1i **modulates** the response to environmental stress and improves **aggressivity and sociability**

Key Clinical Data

- **+300 subjects treated** with vafidemstat
- **Safety and effectiveness demonstrated as a single agent**
- **REIMAGINE trial** (basket trial in BPD, ASD and ADHD). Data showed:
  - **Reduction in aggression**
  - **Improvements** in **overall patient functioning**, particularly in BPD patients



28th European Congress of Psychiatry, EPA 2020

Overall improvement in BPDCL scale to diagnosis threshold level Supporting general treatment of the disease

Route to Market

- Clinical development program is focused on two CNS indications: **BPD** (PORTICO Phase IIb study) and **SCZ** (EVOLUTION Phase IIb study), both actively recruiting
- BPD alone has a global market potential of **~$3Billion by 2027**

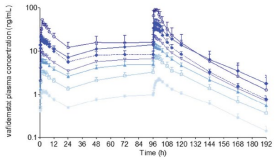
Safe

No differences between placebo and vafidemstat-treated patients

Brain Penetrant

An optimal CSF : plasma ratio of 0.9

Oral, once a day



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

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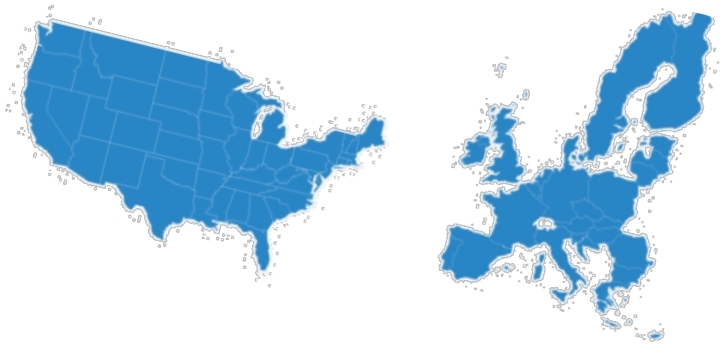
Borderline personality disorder: a snapshot

A Prevalent & impairing disease

9 million in US & EU



Two main types of symptoms

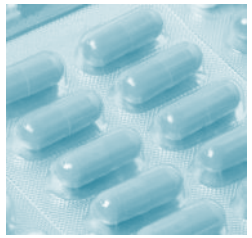
Unstable-extreme interpersonal relationships

+

Aggression & self-aggression

No approved drugs yet

Patients in off-label anti-psychotics



Vafi improves these symptoms in PC models

Expected Market Value in 2027

US$ ~3 billion

Highest Revenue Drug Category: Anti-psychotics followed by anti-depressants

Aggregated sells: ~ 1 Billion

Very low competition

0 Phase III trials

2 Phase II trials

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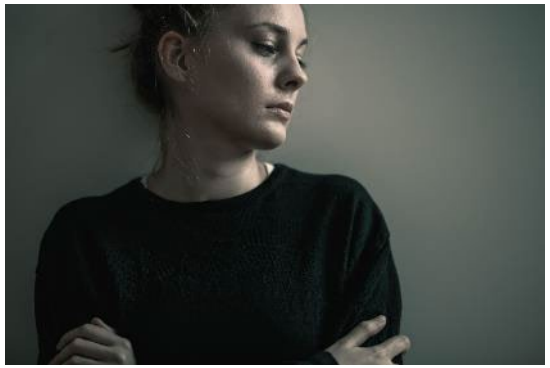
Ongoing Study: a Phase IIb in Borderline Personality Disorder

PORTICO:

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



- **High unmet need**: no drugs specifically approved for BPD. 1.4 million patients in US are being treated with off-label anti-psychotics
- **PORTICO** plans to enroll initially 156 patients (to be reassessed in the interim analysis)
- Two primary independent endpoints:
  - Overall clinical BPD improvement, and
  - Improvement in aggression
- Actively enrolling in EU and US

An interim analysis (90 patients) is anticipated by 1Q23. Assuming current accrual expects:

Final read out 4Q 2023

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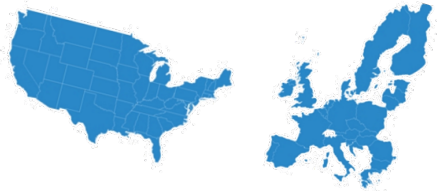
EVOLUTION an ongoing PoC Schizophrenia study with vafidemstat

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

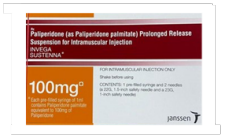
US$ ~8 billion

Three main types of symptoms

Positive or Negative
+
Cognitive Impairment

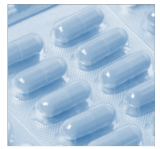
Highest Revenue Drug Category: long-acting injectable (LAI) antipsychotics

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

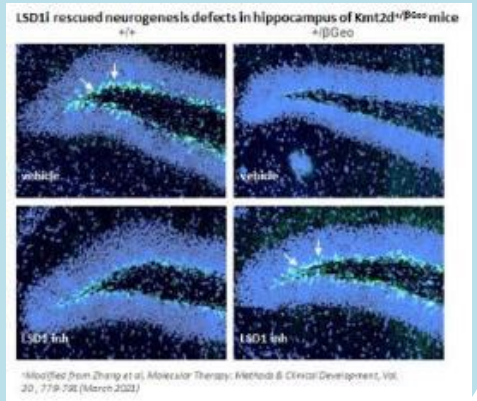
Vafidemstat: an LSD1 inhibitor targeting genetically defined neurodevelopmental syndromes, e.g., Kabuki

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

- **+300 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 Q42022 /FPI Q12023
- **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**

Vafidemstat has a growing avenue for personalized therapy in CNS

COMPASS-related Pathologies

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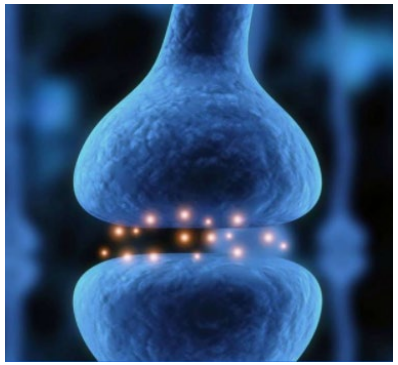

Glutamatergic pathway-related Pathologies

- **Shank3 : Shankopaties – PMS / ASD**
- NMDA-R hypofunction SCZ

Other yet unknown genetic relationships

- Rett Syndrome
- ASD syndromes
- Other schizophrenia subpopulations

Beyond monogenic syndromes, LSD1 is also involved in the direct or indirect regulation of genes or regulators of specific pathways involved in CNS diseases, e.g. miR137, whose targets are genes involved in schizophrenia and Huntington's disease, opening the door for targeting subpopulations of large CNS indications

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 400+ subjects dosed

Value Creation in 2022-23

Multiple inflection points

- Final data for 1L AML PoC ALICE
- 2L AML and NET trials preliminary readouts in 2023
- Read-out Phase II in BPD
- Kabuki Syndrome Phase I/II trial start in 2023
- 1L ED-SCLC with potential to support accelerated development to start in 2023

Pioneering personalized medicine in epigenetics