

Pioneering Personalized Medicine in

EPIGENETICS

CORPORATE PRESENTATION
July 2020

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Risk Factors

In addition to the existing registration document (documento de registro) filed with the Spanish National Securities Market Commission (Comisión Nacional del Mercado de Valores) (the "CNMV") on 23 July 2019, please see an additional risk factor below

Risk Related to Public Health Emergency or Pandemic

A strain of SARS-CoV-2 coronavirus, which causes the disease known as COVID-19, originated in China, has progressively spread to other countries around the world since the end of 2019. In March 2020 the World Health Organization declared COVID-19 a global pandemic.

Given the fast spread of the coronavirus globally, many states are taking unprecedented decisions such as closing their borders to international travelers and placing restrictions on the movement of their citizens in order to contain the pandemic.

Risks related to public health emergencies or pandemics have revealed a potential risk to ORYZON clinical trials. In this sense, ORYZON currently has two drugs in clinical phases, VAFIDEMSTAT and IADADEMSTAT, in which several clinical trials are being conducted.

The protection of the patients' health participating in clinical trials, their families and the health personnel involved, may result in a loss of data relating to visits and/or evaluations not being carried out.

Likewise, in the event of health emergencies or pandemics, situations of confinement of the population may occur in certain geographical areas, leading to delays, cancellations and early termination of clinical trials.

In addition, the impact, effects and duration of the effects of health emergencies or pandemics are highly uncertain and could affect the financial markets, limiting the Company's financing capacity and adversely affecting the equity, financial position and results of ORYZON.

The impact of the risk related to health emergencies or pandemics materializing could increase the probability of failure to enter into license agreements and, consequently, reduce the income those could generate, as illustrated by the risk of loss associated with failure to enter into license agreements.

Company Highlights

- A clinical stage biopharmaceutical company developing innovative therapies in the field of Epigenetics
- ✓ Two molecules that have already shown positive data in humans
- 2 Phase IIa trials in oncology; 4 Phase IIa trials in CNS and 1 Phase II trial in Covid-19
- Large IP portfolio with technology fully developed in-house
- A publicly traded company on the Spanish Stock Exchange (MADX: ORY)
- ✓ Integrated in the IBEX Small Cap Index¹
- Raised an aggregate of approximately €105M (in 2015-2020)
- Cash runway expected until 1Q2023
- One of the most liquid companies in the MicroCap group on the Spanish Stock Exchange
 - 53.1 M shares outstanding. Fully diluted
 - √ ≈500,000 daily volume (Avg Traded Volume in 2020³)
 - ✓ More than 43M shares negotiated in 2020 / ≈4.6 months for share full turnover⁴





ORYZON GENOMICS SA BALANCE SHEET DATA (UNAUDITED) (Amounts in thousands US \$\frac{9}{c}\$

| | March 31st, 2020 | March 31st, 2019 |
|----------------------------|---------------------|---------------------|
| Cash and cash equivalents | 32,121 | 32,551 |
| Marketable securities | 155 | 159 |
| Total Assets | 84,301 | 73,158 |
| Deferred revenue | 0 | 0 |
| Total Stockholders' equity | 65,709 | 49,240 |

- https://www.bolsamadrid.es/docs/SBolsas/InformesSB/FS-
- Spanish GAAPs: €29,5M see https://www.oryzon.com/es/noticias-eventos/noticias/oryzon-anuncia-sus-resultados-y-avances-en-el-primer trimestre-de-2020
 - https://finance.yahoo.com/quote/ORY.MC?p=ORY.MC (as per 19.05.2020) http://www.infobolsa.es/cotizacion/oryzon?noAds=1 (as per 19.05.2020)

Epigenetic Modifications: New Targets for Drug Development

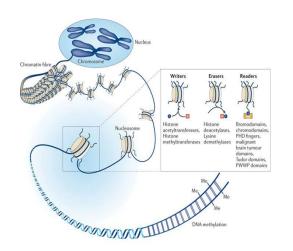
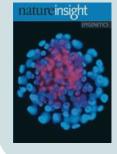


Figure from Arrowsmith et al. *Nature Reviews Drug Discovery* **volume** 11 (2012)

- Heritable DNA modifications that do not alter the actual DNA sequence but change gene activity and expression
 - Histone modifications
 - DNA methylation
 - microRNA, etc
- Histone modifying enzymes are "writers" or "erasers" - adding or removing epigenetic marks from histone tails
- Epigenetic dysfunctions are associated with aberrant gene expression and disease
- Epigenetic drugs can restore these transcriptional imbalances

An exciting area of world class science





Lysine specific histone demethylase 1 (LSD1): an epigenetic "eraser" that removes methyl groups from histones





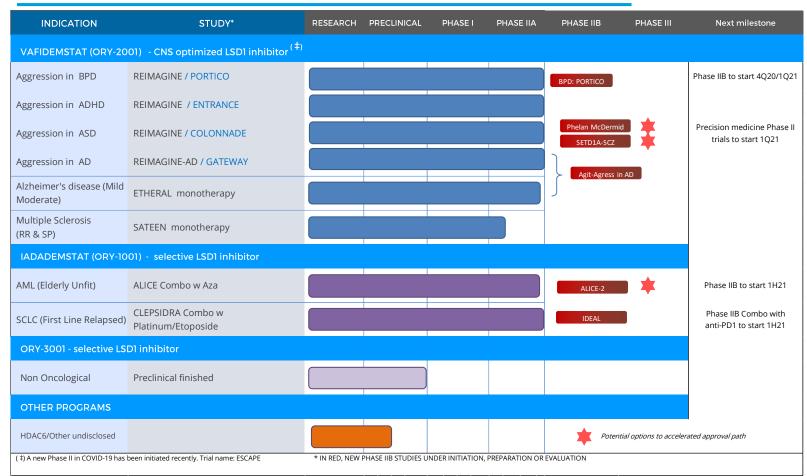
LSD1 expression and activity can play a role in blocking and promoting gene expression



LSD1 plays an important role in cancer, CNS, inflammatory and viral diseases



Oryzon is pioneering epigenetics in CNS and is active in oncology





VAFIDEMSTAT a Phase II Clinical Stage Compound with a broad developability in CNS diseases

Vafidemstat (ORY-2001): a "Neuron-fixer" ready for Phase IIb

Preclinical characterization

- Vafidemstat is a small molecule LSD1 inhibitor optimized for CNS. Highly potent: low nM activity.
- Excellent pharmacology. High oral bioavailability
- Positive results in 7 different animal models and in invitro models
- Epigenetic MoA that modulates neuroinflammation and expression of key plasticity neuronal genes



Clinical characterization

- Safe and well tolerated so far in Phase I and various Phase II studies⁽¹⁻³⁾
 - Vafidemstat has already been administered to around 250 volunteers and patients
 - Phase IIs (MS, AD, ADHD, BPD and ASD patients) with no safety signals to date
 - Longest exposure to date: 18 months
- High BBB penetrance (CSF levels)
- Indirect human brain target engagement established
- Pharmacologically active in humans

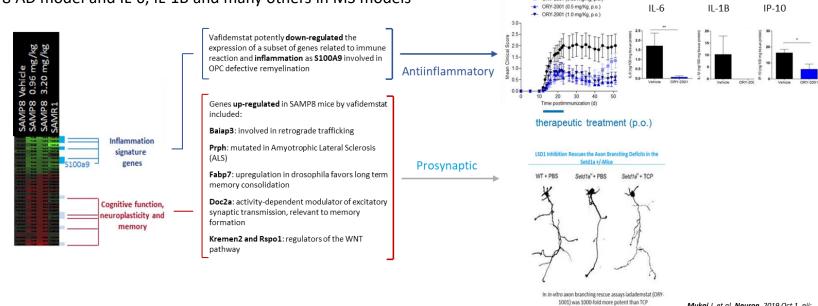
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0233468

MoA: an upstream epigenetic mechanism producing a dual activity, anti-inflammatory and prosynaptic

LSD1 localizes *in-vivo* to enhancers and promoters of confirmed CNS disease risk genes LSD1 binds to TFs that control IEG expression and stress in the PFC-amygdala axis, including SRF

Vafidemstat up-regulates genes associated with Neuroplasticity & Cognition

Vafidemstat **reduces** the expression of **inflammatory** genes as S100A9 and others in SAMP8 AD model and IL-6, IL-1B and many others in MS models



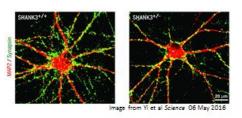
LSD1 inhibition rescues different phenotypes in genetic models of ASD and Schizophrenia

nature neuroscience

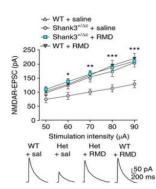
Article | Published: 12 March 2018

Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition

Luye Qin, Kaijie Ma, Zi-Jun Wang, Zihua Hu, Emmanuel Matas, Jing Wei & Zhen Yan



Mutation of SHANK3 gene is causally linked to ASD. HDAC & LSD1 inhib rescue the mice phenotype Qinetal Nat Neurosci. 2018. & Zhen Yan Oral Comm SF-2019





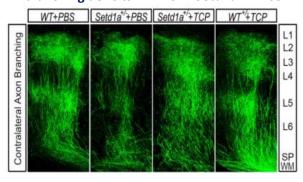
Neuron ARTICLE | CALIFE NOW Recapitulation and Reversal of Schizophrenia-Related Phenotypes in Setd1a-Deficient Mice Jun Middai ^{7, 8} - Enrico Cannavó ⁷ - Gregg W. Crabtree * ... Atsushi Tákasta · Bin Xu · Joseph A. Gogos A. ¹⁰ © · Show all authors · Show hostnotes Published: October 09, 2019 · DOI: https://doi.org/10.1016/j.neuron.2019.09.014

H3K4

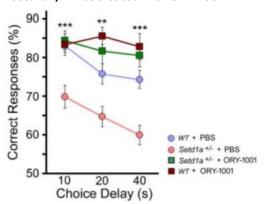
LSD1

H3K4

LSD1 inhibition rescues the contralateral axon branching deficits in-vivo in Setd1a +/-mice

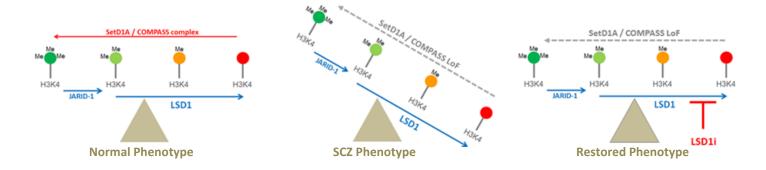


Rescue of WM performance in Setd1a+/- mice treated with ORY-1001



LSD1 inhibition paves the way for personalized medicine in psychiatry

- SETD1A is a key schizophrenia (SCZ) susceptibility gene¹. Mutations in SETD1A increase the risk of SCZ by 35 times, as well as a number of other neurological disorders. SETD1A is part of the Set1/COMPASS complex, mediates mono-, di-, and tri-methylation of the lysine 4 on the histone H3 protein
- In addition to SETD1A, mutations in other subunits of Set1/COMPASS complex have been reported in SCZ and other neurodevelopmental disorders
- Mutant mice carrying a heterozygous loss-of-function mutation of the orthologous gene exhibit alterations in axonal branching and cortical synaptic dynamics, accompanied by specific deficits in working memory that recapitulate SCZ-related alterations
- SCZ patients carrying these mutations identified
- Increased interest by FDA and other regulators to explore a personalized medicine approach in these hard to treat populations



Vafidemstat reduces agitation and aggression: REIMAGINE and REIMAGINE-AD Phase IIa trials

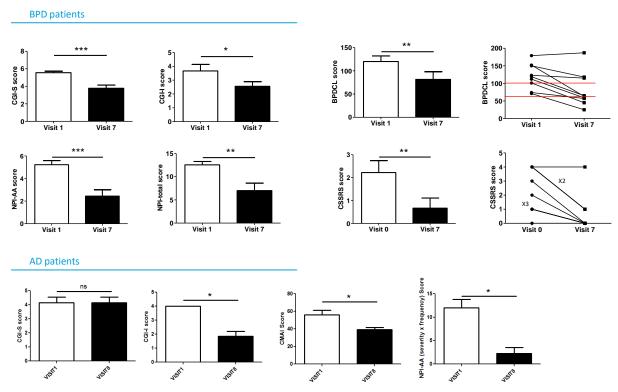
Open label trials: **REIMAGINE** (30 patients, PPAS: n=23 : 9 BPD, 6 ASD, 8 ADHD). **REIMAGINE-AD** (12 moderate/severe AD patients, PPAS: n=7) Primary endpoint: Safety& Tolerability. Secondary endpoints: Reduction of aggression as measured by validated scale / Other significant measures

REIMAGINE basket trial

Vafidemstat reduces agitation-aggression and improves overall status in BPD patients and also in ADHD and ASD patients after 2 months of treatment

REIMAGINE-AD trial

Vafidemstat reduces agitation-aggression in moderate and severe AD patients after 6 months of treatment



Next steps: The company recognizes a significant development potential for vafidemstat in psychiatric indications

- ❖ A personalized medicine Phase II trial in SetD1a mutant schizophrenic patients under study in collaboration with a Top US Institution
- ❖ A personalized medicine Phase II trial in Shank3 mutant Phelan McDermid (ASD) patients under study in collaboration with one of the most important Hospitals in Spain

OPTIONS TO ACCELERATED
APPROVAL IN GENETICALLY DEFINED
SUBPOPULATIONS OF SCZ AND ASD
(45.000-60.000 patients in US^{1,2,3})

Precision Medicine Approach

PORTICO: a Phase IIb in BPD Under Preparation

- Double blind, randomized, placebo-controlled, 16-week treatment period
- Spain, US and Europe TBD
- N=100
- Expected FPI: TBD (4Q20-1Q21 examining Covid-19 impact)
- Expected LPO: TBD
- ❖ Additional Phase IIb in agitated-aggressive CNS patients under consideration

Canonical Clinical Development

PORTICO, a Phase IIb trial with vafidemstat in all-in BPD patients to treat agitation-aggression (80.000-100.000 patients in US^{4,5})

- https://www.cdc.gov/ncbddd/autism/data.html
- <u>htt</u>
 - Takata et al.. Neuron 82, 773–780, May 21, 2014
 - Samuels J, et al. Br J Psychiatry. 2002;180:536–542
- Company real-life assumptions stimates



IADADEMSTAT a Phase II Clinical Stage Compound with a broad developability in oncology

LSD1 and cancer

- LSD1 is involved in different cancers and in cancer stemness
- High levels of LSD1 often correlate with more aggressive forms of cancer and/or bad prognosis
- ladademstat is a small molecule that selectively inhibits LSD1. Positive preclinical in-vivo results in different xenograft models. Best in class.
 Full characterization published in top-ranked journal





ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia

Tamara Maes. ^{1,6} Cristina Mascaró, Ínligo Triapu, Angels Estiarte, Filippo Ciordi, Serena Lunardi, Nathalie Guibourt,

Alvaro Perdonse, Michele MP, Lufino, ¹Tm C.P. Somervalie, ²O and H. Wiseman, ²Changir Duy, ² Ari Melnick, ^{2,4} Christophe Willekens, ² Alberto Ortega, ³Marc Martinell, ³Nuria Valls, ³Guido Kurz, ³Matthew Fyfe, ³Usilio Cesar Castro-Palomino, ³ and Garios Buses³

¹Oryzon Genomics, S.A. Carrer Sant Ferran 74, 08940 Cornellà de Llobregat, Spain

*Leukaemia Biology Laboratory, Cancer Research UK Manchester Institute, The University of Manchester, Manchester M20 4BX, UK
*Department of Medicine, Division of Hematology & Medical Oncology, Welli Cornell Medicine, New York, 10065 NY, USA

⁴Department of Pharmacology, Weill Cornell Medicine, New York, 10065 NY, USA

Drug Development Department (DITEP) and Hematology Department, Gustave Roussy, Université Paris-Saclay, 94805 Villejuif, France Lead Contact

*Correspondence; tmaes@oryzon.com

https://doi.org/10.1016/j.ccell.2018.02.002

POTENTIAL ONCOLOGICAL INDICATIONS:

Solid Tumors



Small Cell Lung Cancer Prostate cancer Colorectal cancer Bladder cancer Some breast cancers Merkel Cell Carcinoma

HemONC



MDS Myelofibrosis Non Hodgkin Lymphoma

AML

Brain/rare Tumors



Medulloblastoma Glioblastoma

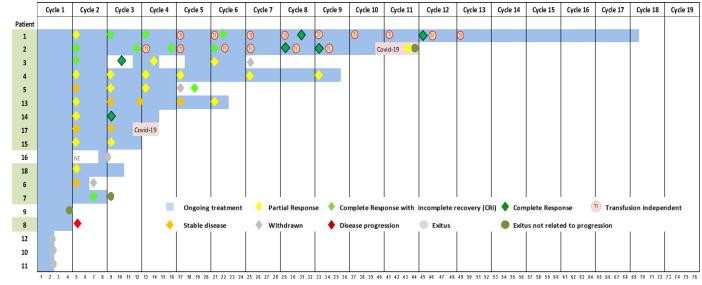
MoA well-characterized in SCLC, AML and Medulloblastoma

ALICE: An AML trial with LSD1i in Combination with azacitidine in the Elderly

A Phase IIa study to evaluate the safety, tolerability, dose finding and efficacy of iadademstat (ORY-1001) in combination with azacitidine in older patients with AML in first line therapy

- Single arm & open label. Up to 36 patients to be enrolled. **Primary endpoint**: Safety and tolerability of the combo with hypomethylating agent Azacitidine. **Secondary endpoints**: Responses; time to responses; duration of response; and overall survival. Data for first 6 and 12 and 18 enrolled patients reported at **EHA-2019**, **ASH-2019** & **EHA-2020**
- Robust signals of clinical efficacy, with ORR of 77%, of which 60% are CR/CRi
- Fast clinical responses, with mean time to response of 37 days
- Longest remission to date 488 days, still ongoing
- ladademstat and azacitidine combination shows a good safety profile
- Following an interruption of two months due to the Covid-19 pandemic, recruitment has now resumed at the expected rate

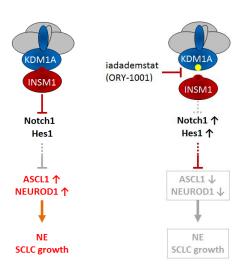
ORYZON latest Phase II iadademstat efficacy data in AML at EHA-2020



ladademstat a therapeutic approach for SCLC with a well defined MoA

- LSD1 is a well characterized target in SCLC
- LSD1 inhibitors are effective in several invitro and in-vivo models of SCLC
- Characterized MoA
- ladademstat produces complete and durable tumor regression in different chemoresistant PDX models
- ladademstat is efficacious in combos with platinum/etoposide and other agents
- Identified and patented biomarkers that differentiate tumors by their sensitiveness to LSD1i
- Phase II trial ongoing in second line SCLC patients using these biomarkers to stratify patients and identify super-responders

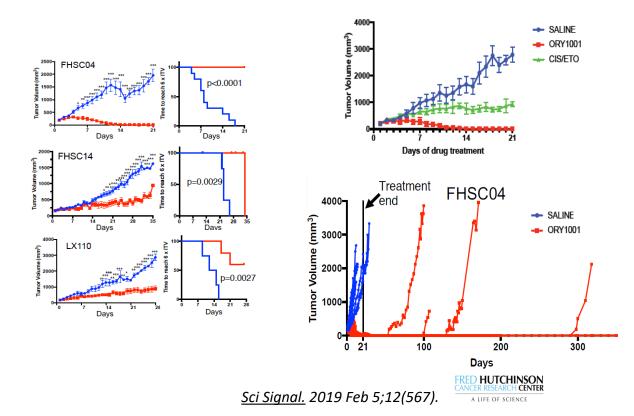




ladademstat is efficacious in monotherapy in some PDX-SCLC xenografts

Response to iadademstat in PDX models of SCLC is remarkably strong and durable in some cases

- FHSC04 model: derived from a SCLC patient who relapsed after first line therapy
- 6/10 FHSC04 mice treated with iadademstat did not show relapse after 300 days
- Biomarkers for LSD1
 responsiveness identified
 and used to stratify
 patients in CLEPSIDRA



ladademstat: SCLC - Phase II CLEPSIDRA - preliminary efficacy signals

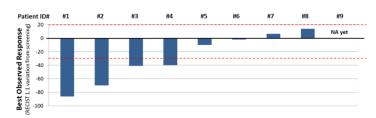
CLEPSIDRA: A Phase IIa study to assess the safety and efficacy of iadademstat (ORY-1001) in combination with CbEt chemotherapy in 2L-ED SCLC patients who are positive to candidate predictive biomarkers

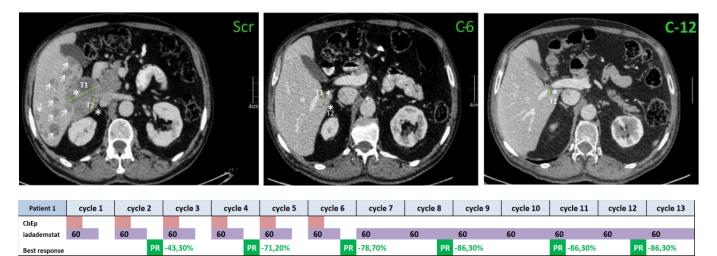
Preliminary Results





- ❖ 75% clinical benefit rate (6/8 eval.): 50% OR: 4 PRs and 2 long-term SD
- Current level of observed responses suggests that patient selection by Biomarkers may be effective to increase ratio of ORs



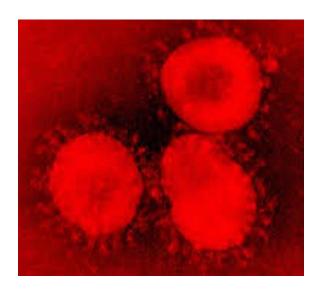


- Main toxicity observed in the combination with carboplatin-etoposide is hematological
- ladademstat alone is safe and shows no hematological, general or neuronal toxicity in ED-SCLC patients, suggesting potential for monotherapy and other combos
- ladademstat alone sustains further therapeutic benefit

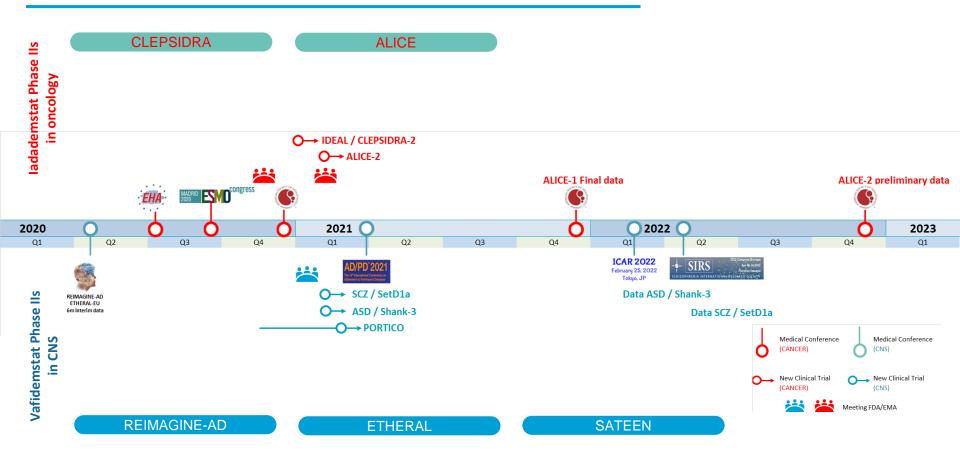
Covid-19 trial: ESCAPE - vafidemstat to prevent ARDS. Summary

ESCAPE: a Phase II study in adult severe COVID-19 patients to prevent ARDS

- Multicenter, open label, two arms randomized vafidemstat in combination with best supportive care
- Two arms, N=20 each
- Primary endpoint: efficacy of vafidemstat, in combination with standard of care to prevent Acute Respiratory Distress Syndrome (ARDS) in adult severely ill patients with CoVID-19
 - Reduction in the incidence of patients (%) requiring mechanical ventilation and referral to ICU from day 1 to day 14
 - Decrease in global mortality and mortality associated to CoVID-19 pneumonia within the period from Day 1 to Day 14
- Secondary endpoints
 - Reduction of Systemic and pulmonary inflammatory biomarkers associated to CoVID-19 pneumonia: IL-6, IL1-beta, D-dimer-D, PCR, LDH, Ferritin, Total Lymphocytes
 - Others
- Recruiting (FPI in April)



Anticipating a rich flow of clinical catalysts (non-comprehensive selection)



ORYZON – a unique investment opportunity in an epigenetic platform

- A differentiated proposition in EPIGENETICS drugs in CNS and ONCOLOGY around one of the most interesting targets in the field: LSD1
- 2 molecules in Phase II with promising clinical signals of efficacy in patients
- Pioneers in CNS epigenetics
 - ❖ Vafidemstat shows efficacy in agitation in psychiatric disorders (BPD, ADHD, ASD) and in AD
 - Phase IIb in Borderline personality disorder in preparation. Additional trials in agitation in AD, ADHD or ASD under evaluation
 - Trials in genetically-defined patient subpopulations in SCZ and ASD under study > Options to get accelerated approval
- Most advanced LSD1i (iadademstat) in Oncology
 - Positive preliminary efficacy results reported in the ongoing Phase II trials in AML and SCLC
 - SCLC trial is a biomarker-guided study to stratify responsive patients
 - Options to get accelerated approval
- Rich pipeline of clinical news expected in the next quarters. Clinical operations in US started and under expansion
- A cash efficient company with a seasoned international management team
- ≈€150M market cap. One of the most liquid¹ stocks in the microcap group on the Spanish Stock Exchange with a potential dual listing on Nasdaq in the future
- Steady **presence in the US market in the last 4 years**. Four successful PIPEs executed in 2017-20 led by US investment Banks and with participation of US-EU-Israeli investors

An experienced and committed Management Team

CFO



CARLOS BUESA: CEO & President, Spain/US

PhD in Biochemistry and Molecular Biology. Founder and CEO since inception. Advanced programs on finance, business development, negotiation skills and human resources. He is also PADE at the IESE Business School. He is Board Member of the VC Fund Inveready

CSO



TAMARA MAES: CSO & VicePresident, Spain

PhD in Biotechnology . Founder and Chief Scientific Officer since inception, Responsible for the creation of the whole pipeline of the company and the biological target validation programs. She is SAB member on several public institutions as CSIC and private companies, Since 2016 Scientific Advisor of the ADDF

 VP Clinical Development



 Medical Director



Clin Ops Director



Director





BDO



 VP of Clinica Portfolio



MICHAEL T. ROPACKI: US

VP of Clinical Development

PhD in Clinical Neuropsychology . Dr. Ropacki has held roles of increasing responsibility for + 10v at Johnson & Johnson, his last as Director of Clinical Development. Neuroscience, Research and Development, for Janssen R&D serving as the Clinical Lead responsible for developing and leading the Cognitive Health in Aging Registry. Prior to that role he served as Global Medical Affairs Leader, Head of Late-Stage Development at Janssen AD Immunotherapy, LLC.

ROGER BULLOCK: UK /PT/Spain

Chief Medical Officer

Graduated in Physiological Sciences at Keble College in Oxford University and got his MB.BS at London University

Extensive experience as clinical researcher, having participated in more than 70 clinical trials in Alzheimer's disease and other CNS conditions

30-year research career, more than 100 peer-reviewed publications and book chapters

He has worked as a consultant for companies active in the CNS space, including Lilly and Merck

SONIA GUTIERREZ: Spain

Chief of Clinical Operations

BSc. Pharm. & MSc. & PDD in IESE Business School. More than 20 years of experience in the clinical research and operations area at different International Pharma & Biotech companies. CNS: +13y in Lundbeck involved in + 40 Clinical Trials in CNS.

Experience in oncology and other indications in Regeneron and other companies.

Chief IP Officer

B.Sc. in Organic Chemistry from the University of Barcelona

Qualified European Patent Attorney

She has +20vs experience in pharmaceutical IP

Since 2011 Chief IP Officer at Oryzon

NEUS VIRGILI: Spain

ENRIC RELLO: Spain Chief Financial Officer

J.D.; PhD in Economics & Business Administration.

PLD - Program for Leadership Development, Harvard Business School.

BSc & MSc in Business Administrations & Laws,

HBS Finance Excell, Prog. Harvard Business School.

From 1997 untill 2007 CFO of SANDOZ (NOVARTIS), Spanish Arm.

CFO at Oryzon since 2011

EMILI TORRELL: Spain

Chief BD Officer

B.Sc. in Sciences, Autonomous University of Barcelona

MBA at ESADE and PDG at **IESE Business School**

In the business development area from 1990 in the most relevant Spanish companies Prodesfarma, Almirall and Laboratorios Esteve

From 2007 BD Director at Oryzon

JORDI XAUS: Spain

VP of Clinical Portfolio & Innovation

PhD in Immunology

Former CSO at Palau Pharma

Head of Immunology at Puleva Biotech

Researcher at Genentech

Exec Master in Ops and Innovation by ESADE

- An experienced and respected managerial team in the Biopharmaceutical industry
- Team members have a track record in product discovery & in advancing successfully through product development phases
- Demonstrated ability to close world class deals and to lead and participate in international consortia

ORYZON

Pioneering Personalized Medicine in **EPIGENETICS**

