PORTICO, a double-blind, randomized placebo-controlled, adaptive Phase IIb trial with vafidemstat in Borderline Personality Disorder

Michael T. Ropacki
Chief Medical Officer, CNS Clinical Development
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- Full time employee of Oryzon

Background – Borderline Personality Disorder (BPD)

- **Prevalence**: 0.5-5.9% of adults in general population[1, 2] & higher in clinical settings
  - 6% in Primary Care Clinics
  - 10% in Psychiatric Outpatient Clinics
  - 20% in Psychiatric Inpatient Clinics[3, 4]
- **Diagnosis**: DSM-5 (American Psychiatric Association, 2013)
  - According to the DSM-5 BPD manifests as:
  - "a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts"
  - There are 9 criteria or clinical features
  - Diagnosis requires patient to exhibit 5 or more of the nine criteria
- **Age of Onset**: According to DSM-5, symptoms begin in early adulthood
  - Reports that BPD characteristics are identifiable in adolescence[5]
- **Course**: Highly variable

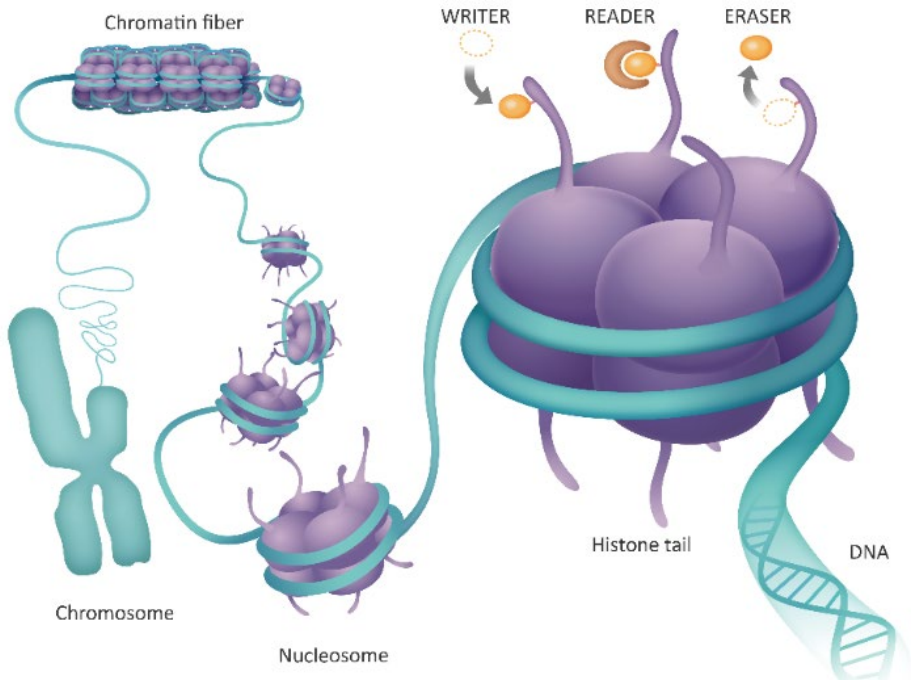
[1]Grant et al 2008; [2]Lenzenweger et al., 2007; [3]Torgersen, 2005; [4]Gunderson et al., 2009 ; [5]Bradley et al., 2005

Background – BPD (Continued)

- **Etiology:** Interaction between biological factors and psychosocial factors (e.g., adverse childhood events) in early stages of human development.
  - **Genetic bases for BPD** – Familial and twin studies with heritability estimated to be 40%
  - **Gene-environment interactions and epigenetic changes** - According to Bulbena-Cabre[1], gene-environment interactions and epigenetic changes better explain the expression of a BPD phenotype versus the presence of a concrete polymorphism.
- **Treatments**: Currently no approved drug therapy for BPD
  - Drugs used off-label have limited efficacy and/or significant side effects (e.g., weight gain, somnolence, EPS).
  - First line treatment is, therefore, psychotherapy (e.g., Dialectical Behavior Therapy)
    - Efficacy is limited and duration of response variable
    - Majority of BPD patients do not have exposure to the resources (i.e., providers and/or financially) for psychotherapy
- **Unmet Need**: The rate of completed suicide in people with BPD has been estimated to be approximately 10%, 50-times higher than in the general population.[2] Taken together, there remains a high-unmet medical need for a safe and effective treatment for this population.

[1]Bulbena-Cabre A., 2018; [2]Oldham, 2006

Epigenetics: LSD1 is a critical player in the functioning of the CNS



LSD1 is mainly expressed in the CNS and plays a critical role in neurogenesis and the regulation of cortical development

After birth, LSD1 contributes to neurite morphogenesis in the mammalian cortex

LSD1 is the most abundant histone demethylase in the PFC

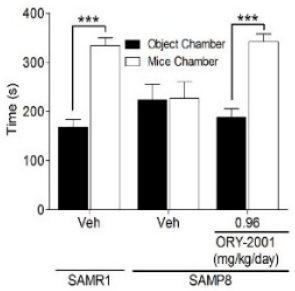
LSD1 localizes in-vivo to enhancers and promoters of confirmed CNS disease risk genes

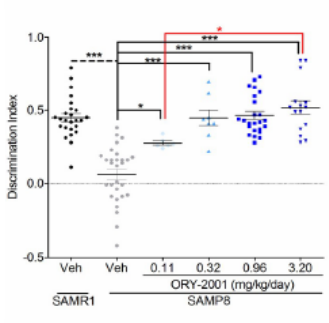
LSD1 is involved in neurodevelopmental diseases and regulation of methylation has emerged as a top pathway significantly correlated with adult psychiatric disorders

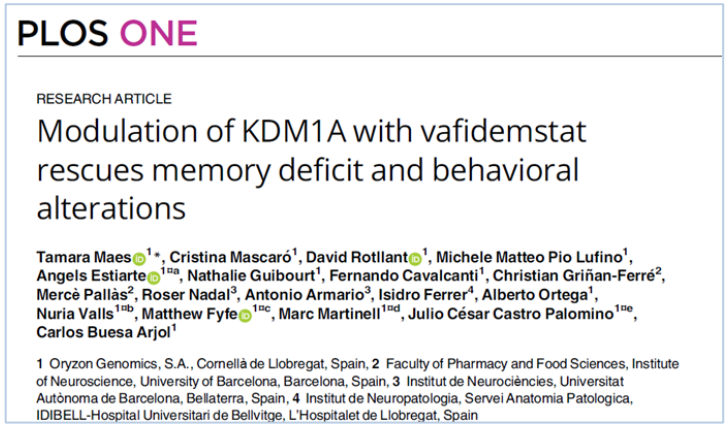
Vafidemstat: Drug Characterization

Preclinical characterization

- Vafidemstat is a highly brain penetrant LSD1i, **optimized for CNS**
- Low nM activity & strong pharmacology
- **Epigenetic MoA** that reduces neuroinflammation and overexpresses key plasticity neuronal genes
- Positive results in 7 different animal model read-outs:
  - Enhances memory
  - Enhances sociability
  - Reduces neuroinflammation
  - Reduces aggression
  - Neuroprotective






PLOS ONE

RESEARCH ARTICLE

Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations

Tamara Maes[1]*, Cristina Mascaró[1], David Rotllant[1], Michele Matteo Pio Lufino[1], Angels Estiarte[1¤a], Nathalie Guibourt[1], Fernando Cavalcanti[1], Christian Griñan-Ferré[2], Mercè Pallàs[2], Roser Nadal[3], Antonio Armario[3], Isidro Ferrer[4], Alberto Ortega[1], Nuria Valls[1¤b], Matthew Fyfe[1¤c], Marc Martinell[1¤d], Julio César Castro Palomino[1¤e], Carlos Buesa Arjol[1]

1 Oryzon Genomics, S.A., Cornellà de Llobregat, Spain, 2 Faculty of Pharmacy and Food Sciences, Institute of Neuroscience, University of Barcelona, Barcelona, Spain, 3 Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain, 4 Institut de Neuropatologia, Servei Anatomia Patologica, IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain

Clinical characterization

- **Safe and well tolerated in Phase I and II studies**
  - + 300 volunteers and patients of different diseases with no safety signals
  - Longest exposure to date: 24 months
- **High BBB penetration in patients (CSF levels)**
- **Clinical efficacy observed in humans**


CNS Drugs
https://doi.org/10.1007/s40263-021-00797-x

ORIGINAL RESEARCH ARTICLE

First-in-Human Randomized Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the KDM1A Inhibitor Vafidemstat

Rosa María Antonijoan[1,2] · Juan Manuel Ferrero-Cafiero[1] · Jimena Coimbra[1] · Montse Puntes[1] · Joan Martínez-Colomer[1] · María Isabel Arévalo[3] · Cristina Mascaró[3] · Cesar Molinero[3] · Carlos Buesa[3] · Tamara Maes[3]

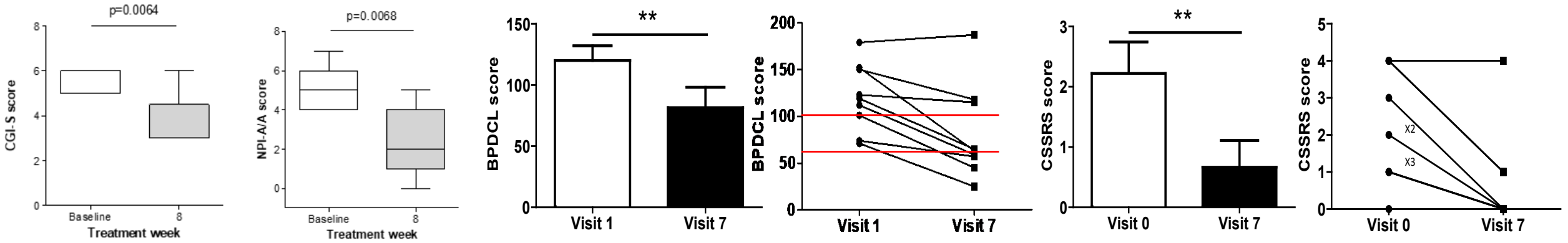
Accepted: 12 February 2021

Vafidemstat: 6 Completed Clinical Trials, safe and well tolerated

- **Phase I**: SAD/MAD in Healthy Volunteers (n=110, 87 treated with vafidemstat))
- **Phase IIa:** (Approximately 300 vafidemstat treated subjects):
  - SATEEN: Randomized, double-blind, placebo-controlled trial in RRMS & SPMS
  - ETHERAL – EU/US: Two randomized, double-blind, placebo-controlled trials in mild-moderate AD
  - REIMAGINE-AD: Open-label PoC trial in AD Agitation/Aggression
  - ESCAPE: Randomized, open-label COVID trial
  - REIMAGINE: Open-label PoC CNS Basket trial in ADHD, ASD & BPD (n=30, 9 with BPD)

Vafidemstat: BPD preliminary findings

- **In BPD, REIMAGINE:** Open-label PoC CNS Basket trial in ADHD, ASD & BPD (n=30, 9 with BPD)
  - Reduced aggression
  - Improved BPD symptoms
  - Reduced suicidal ideation



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

Vafidemstat: Ongoing & Planned Clinical Trials

- **Phase IIb**: Ongoing
  - **Randomized, double-blind, placebo-controlled adaptive trial in BPD**
    - **PORTICO**
  - Randomized, double-blind, placebo-controlled adaptive trial in negative symptoms and cognitive impairment associated with schizophrenia
    - EVOLUTION
- **Phase Ib/II**: IND in preparation
  - Randomized, double, placebo-controlled trial in patients with Kabuki Syndrome

Altogether, there is a great deal of safety data collected in completed and ongoing vafidemstat clinical trials supporting that vafidemstat has been safe and well-tolerated

PORTICO: Overview

- Randomized, double blind, placebo-controlled, adaptive 14-week Phase IIb trial (EUDRA CT# 2020-003469-20, NCT04932291)
- The study is currently active in 4 European countries (Spain, Germany, Serbia, and Bulgaria) and in the US
- Up to 156 participants with BPD will be enrolled and randomized 1:1 to active treatment (1.2 mg) of vafidemstat or placebo
- An interim analysis will be performed after at least 90 subjects complete at least 2/3 of the trial
- Sample size adjustment if there is higher than expected variability in collected data
- Psychotherapy allowed but treated as a concomitant medication

PORTICO – Objectives/Endpoints

- **Two Primary Objectives**:
  - To investigate the efficacy of vafidemstat in the treatment of agitation and aggression in adult BPD patients – CGI-S A/A
  - To investigate the efficacy of vafidemstat in the treatment of adult BPD patients – Borderline Personality Disorder Checklist (BPDCL)
- **Secondary Objectives**:
  - To investigate the effect of vafidemstat in reducing the severity of BPD symptoms in adult patients – Various secondary efficacy endpoints
  - To evaluate the safety of vafidemstat in adult BPD patients – Typical safety endpoints

PORTICO: Preliminary Baseline Characteristics

PORTICO (cut-off 30June2022)		
Demographic data		
Randomized patients		**n=43**
Sex	Male, n (%)	13 (30.23)
	Female, n(%)	30 (69.77)
Age	Mean (SD), yrs	34.3 (10.6)
	Min/Max, yrs	18/57
Race	Caucasian, n (%)	39 (90.70)
	Asian, n (%)	2 (4.65)
	African-American, n (%)	1 (2.33)
	Other (Hispano/Latino), n (%)	1 (2.33)
Weight	Mean (SD), kg	73.52 (14.13)
	Min/Max, kg	46.70/108.27
Height	Mean (SD), cm	168.23 (10.16)
	Min/Max	150.00/192.00
BMI	Mean (SD), kg/m^2	25.92 (3.97)
	Min/Max	18.72/34.01

PORTICO Preliminary blinded safety data: Adverse Events

System Organ Class Preferred Term	Number of Patients (%) Event Count			
	Adverse Events (AEs)	Adverse Reactions (ARs)	Serious Adverse Events (SAEs)	Serious Adverse Reactions (SARs)
Nervous system disorders	**10 (23.3) 31**	**9 (20.9) 22**	**0 (0.0) 0**	**0 (0.0) 0**
Tension headache	7 (16.3) 26	7 (16.3) 18	0 (0.0) 0	0 (0.0) 0
Dizziness	2 (4.7) 2	2 (4.7) 2	0 (0.0) 0	0 (0.0) 0
Cognitive disorder	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Headache	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Hypersomnia	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Infections and infestations	**7 (16.3) 7**	**0 (0.0) 0**	**0 (0.0) 0**	**0 (0.0) 0**
Nasopharyngitis	3 (7.0) 3	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
COVID-19	2 (4.7) 2	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Influenza	2 (4.7) 2	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Investigations	**5 (11.6) 6**	**5 (11.6) 6**	**0 (0.0) 0**	**0 (0.0) 0**
Platelet count decreased	3 (7.0) 3	3 (7.0) 3	0 (0.0) 0	0 (0.0) 0
Blood creatine phosphokinase increased	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Liver function test increased	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Neutrophil count decreased	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Gastrointestinal disorders	**4 (9.3) 5**	**1 (2.3) 2**	**0 (0.0) 0**	**0 (0.0) 0**
Abdominal pain	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Diarrhoea	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Nausea	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Odynophagia	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Teething	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Psychiatric disorders	**4 (9.3) 9**	**0 (0.0) 0**	**0 (0.0) 0**	**0 (0.0) 0**
Intentional self-injury	3 (7.0) 7	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Insomnia	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Panic attack	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Injury, poisoning and procedural complications	**3 (7.0) 5**	**3 (7.0) 5**	**0 (0.0) 0**	**0 (0.0) 0**
Subcutaneous haematoma	3 (7.0) 5	3 (7.0) 5	0 (0.0) 0	0 (0.0) 0
Blood and lymphatic system disorders	**2 (4.7) 2**	**0 (0.0) 0**	**0 (0.0) 0**	**0 (0.0) 0**
Anaemia	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Microcytic anaemia	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Metabolism and nutrition disorders	**2 (4.7) 2**	**1 (2.3) 1**	**0 (0.0) 0**	**0 (0.0) 0**
Decreased appetite	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Increased appetite	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Musculoskeletal and connective tissue disorders	**2 (4.7) 2**	**1 (2.3) 1**	**0 (0.0) 0**	**0 (0.0) 0**
Fibromyalgia	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Pain in extremity	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Respiratory, thoracic and mediastinal disorders	**2 (4.7) 3**	**1 (2.3) 2**	**0 (0.0) 0**	**0 (0.0) 0**
Cough	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Epistaxis	1 (2.3) 2	1 (2.3) 2	0 (0.0) 0	0 (0.0) 0
Reproductive system and breast disorders	**1 (2.3) 1**	**1 (2.3) 1**	**0 (0.0) 0**	**0 (0.0) 0**
Heavy menstrual bleeding	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
Vascular disorders	**1 (2.3) 1**	**1 (2.3) 1**	**0 (0.0) 0**	**0 (0.0) 0**
Hypertension	1 (2.3) 1	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0
TOTAL	**17 (39.5) 74**	**12 (27.9) 41**	**0 (0.0) 0**	**0 (0.0) 0**

Number of patients included 43, Cut-off date June 30th 2022. A patient with more than one finding in the specific category Preferred Term (PT) was only counted once; a patient with more than one finding in the specific category System Organ Class (SOC) was only counted once;; Table is sorted by descending patient count on the SOC and PT level driven by first column "AEs"; Drug related: AEs with causal relationship to medication not documented as unlikely and not related, and not applicable.

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PORTICO – Preliminary blinded safety data: Summary

- Data presented here correspond to the initial randomized 43 patients (Data cut-off 30 June 2022)

- Blinded aggregate safety data shows that there have been 41 adverse reactions, affecting 12 patients
  - ✓ Most of them mild and none reported as severe
  - ✓ None leading to treatment discontinuation or patient withdrawal

- There are no reported serious adverse events

Conclusions

- BPD is a disease with high unmet medical need and no approved drug therapies
- Vafidemstat is an epigenetic drug optimized to target CNS diseases and conditions
- PORTICO was designed to test the efficacy of vafidemstat to treat agitation/aggression as well as overall BPD symptoms
- PORTICO safety data is aligned with aggregated safety data collected from 7 completed vafidemstat clinical trials, supporting that vafidemstat is safe and well-tolerated
- In July 2022, the independent and unblinded Data Monitoring Committee reviewed the presented unblinded safety data and determined that the PORTICO trial should continue

Our gratitude to the patients, caregivers and HCPs participating in the PORTICO study

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• Clinic for Psychiatric Disorders ''Laza Lazarevic''	A. Dutina
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• Emovis	Erik Lauterbach

• University of Chicago Medical Center	Jon Grant
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• The Medical Research Network, LLC	M. R. Liebowitz
• Care Access Research LLC- Reify Health	Philip Bowman

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Thank you for your time and attention!

Questions?

mropacki@oryzon.com

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