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04- Vafidemstat, a new approach to treat aggression in central nervous systems disorders: clinical study REIMAGINE.

Report in a cohort of Borderline Personality patients.

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Background

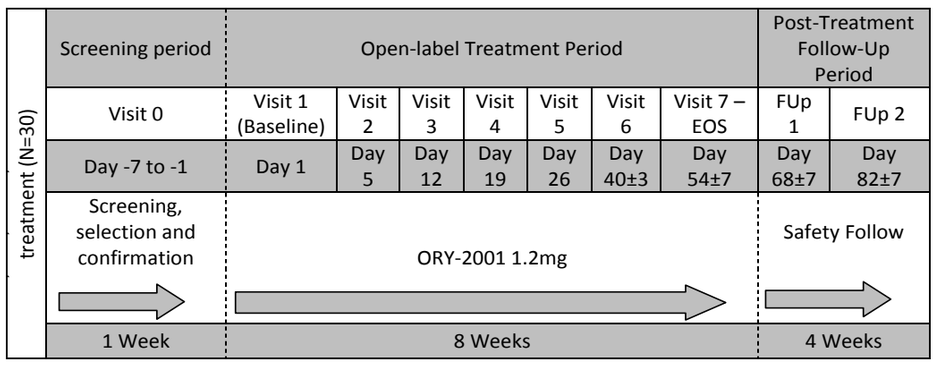
Basket trials are often used in oncology as open-label adaptive designs to prove concept and target best responders, yet they are less common in CNS trials. Vafidemstat (ORY-2001) is a small, brain penetrant molecule that modifies transcription in the brain through epigenetic effects. In different preclinical models this drug has shown to produce neuroprotection, improve cognition and sociability, as well as reduce neuroinflammation and aggression. REIMAGINE is a first clinical study assessing the impact of Vafidemstat on human neurological disease using this methodology.

Objectives

To explore Vafidemstat effect on treating aggression in patients with Alzheimer's disease (AD), Lewy Body Dementia (LBD), autistic spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD).

Methods

Six patients (age 18-85) per disorder will receive Vafidemstat for eight weeks in a phase IIa open-label study (REIMAGINE) **(Fig. 1**). Entry is based on significant or persistent agitation or aggression that was disruptive to patient's daily living or put the patient in harm´s way for at least 3 days per week for at least 4 weeks prior to screening.



Primary Objective: To evaluate the safety and tolerability of Vafidemstat in adults with AD, LBD, ADHD, BPD or ASD.
Secondary Objectives: To investigate the efficacy of Vafidemstat in aggression in adults with AD, LBD, ADHD, BPD or ASD.
Exploratory Objectives: To explore plasma levels of Vafidemstat pre-dose and throughout the study, and to explore the effect of Vafidemstat on the levels of LSD1 target engagement in peripheral blood mononuclear cells (PBMCs).

Demographic data BPD patients		
nº of patients		6
Sex	Male	0 (0%)
	Female	6 (100%)
Age	Median (years)	37,33
	(Min , Max)	(25/46)
Race	Caucasian	6 (100%)
Weight	Median (Kg)	60,72
	(Min , Max)	(52,7/89,8)
Height	Median (cm)	164,37
	(Min , Max)	(162/172)
BMI	Median	22,51
	(Min , Max)	(19,39/33,39)

Figure 1. REIMAGINE study design (EudraCT # 2018-002140-88). ***Top panel***: Study scheme. A phase IIa study unicenter, open-label, 1-arm, 8-week treatment period followed by a 4-week follow-up period. Recruitment stratified to ensure 6 patients per indication. Study performed at Hospital Vall d'Hebron in Barcelona, Spain. ***Bottom panel***. Baseline demographics of BPD cohort (N = 6) (one drop-out)

Results: This is the first presentation of REIMAGINE data from the Borderline personality disorder (BPD) cohort. The essential features of a personality disorder are impairments in personality (self and interpersonal) functioning and the presence of pathological personality traits. Patients with BPD typically experience emotional instability, impulsivity, irrational beliefs and distorted perception, as well as intense but unstable relationships with others. Treatment with Vafidemstat in these patients was safe and well tolerated without significant adverse events **(Fig. 2**). Pharmacokinetic and target engagement results are in line with previous Phase I data (not shown). An improvement in CGI Severity (CGI-S) and CGI-Improvement (CGI-I) scales was achieved after 2 months treatment with Vafidemstat **(Fig. 3A).** The 4-item agitation/aggression NPI subscale score and the total NPI score evidenced a significant reduction after 2 months of treatment (**Fig. 3B**). The total BPD checklist (BPDCL), a combination of the aggression-related scores and the combination of the remaining scores (i.e. BPDCL scores not associated with aggression) all showed a statistically significant reduction **(Fig. 3C).**

Subject ID	System Organ Class	Preferred Term	Seriousness	Severity	Causality
018	Gastrointestinal disorders	constipation	No	Mild	Probably/Likely
005	Infections and infestations	Influenza	No	Moderate	Not related / Unrelated
015	Infections and infestations	Influenza	No	Moderate	Not related / Unrelated
015	Infections and infestations	Bronchitis	No	Moderate	Not related / Unrelated
015	Infections and infestations	Influenza	No	Mild	Not related / Unrelated
015	Infections and infestations	Nasopharyngitis	No	Mild	Not related / Unrelated
018	Infections and infestations	Oral herpes	No	Mild	Possible
012	Investigations	Blood creatine abnormal	No	Mild	Not related / Unrelated
012	Investigations	Blood lactate dehydrogenase abno	No	Mild	Not related / Unrelated
012	Investigations	Amylase abnormal	No	Mild	Not related / Unrelated
018	Nervous system disorders	Headache	No	Mild	Possible
005	Psychiatric disorders	Anxiety	No	Moderate	Possible
005	Psychiatric disorders	Anxiety	No	Mild	Possible
004	Psychiatric disorders	Anxiety	No	Mild	Not related / Unrelated
005	Skin and subcutaneous tissue disorders	Eczema	No	Mild	Unassessable / Unclasifible
005	Vascular disorders	Hypotension	No	Mild	Unlikely

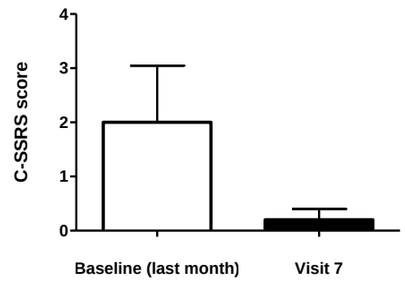


Figure 2. Safety. AES reported and their causality and severity. None of the blood cell counts for any subjects were abnormal during treatment (data not shown). C-SSRS quantification according to Nilsson et al Guide (2013) at V1 and V7 (p=0.086; one-tail paired *t* test) is also shown in the bottom panel (as mean±SEM).

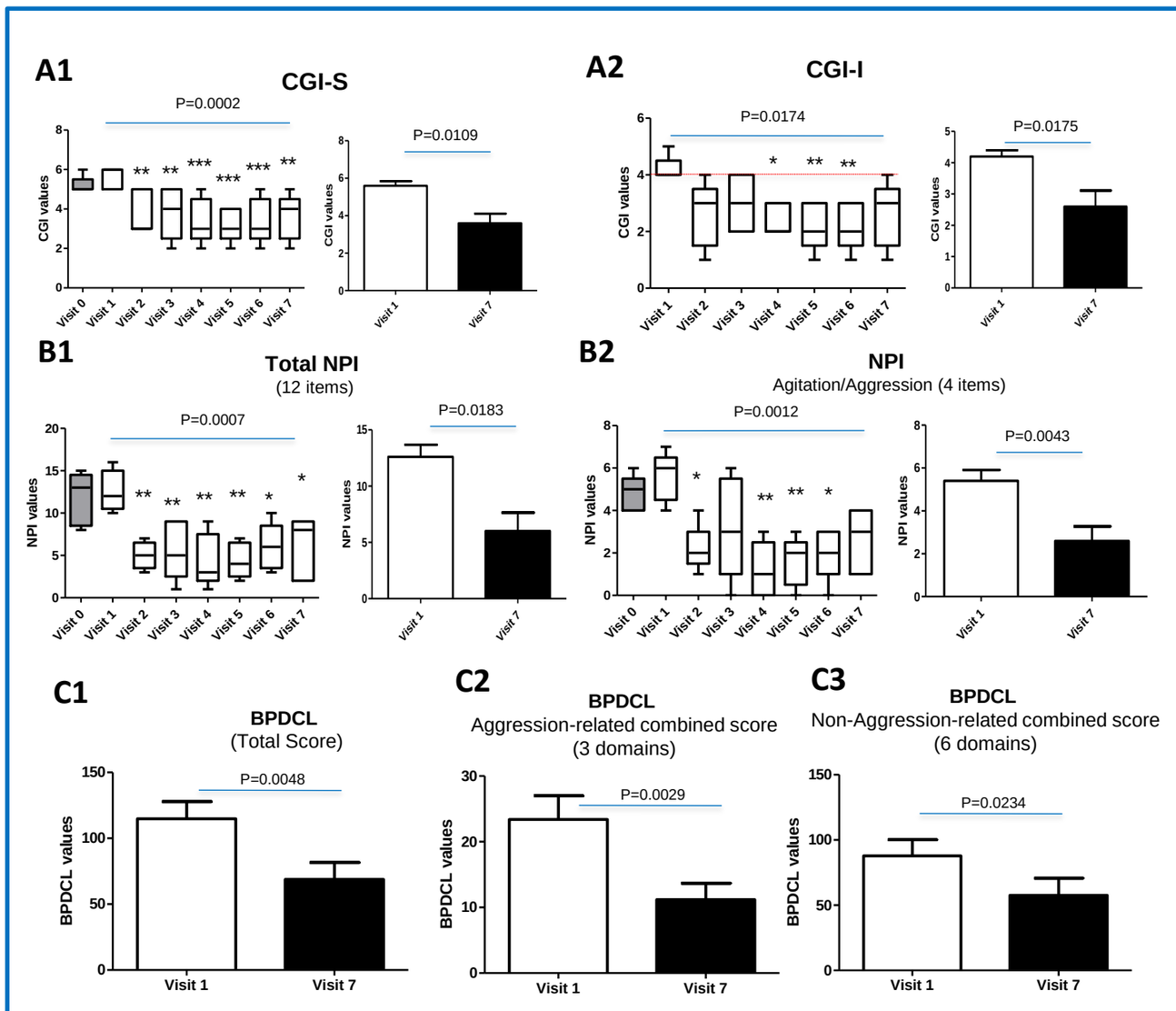


Figure 3. Efficacy. A. CGI values reflect physician ratings of participants' aggression severity (CGI-S) and improvement in aggression (CGI-I). **B.** NPI including B1, Total NPI; B2, 4-Item Agitation/Agression Subscale (i.e., agitation/aggression, disinhibition, irritability and aberrant motor disturbance). **C1.** BDPCL Total Score; **C2**. Aggression-related BPDCL domains combined score (i.e., Anger-control, Impulsivity & (Para)suicide); **C3**. All other BPDCL non-aggression-related domains combined score. Data corresponds to the 5 eligible subjects for analysis. In all panels, Paired one-way ANOVA with Bonferroni's multi comparison post-hoc test was used for complete set on visit comparison (*, **; p<0.05; p<0.01 from Visit 1) while paired one-tail t-test analysis was used to compare V1 with V7 values. In those graph where V1 and V7 values are compared, data is represented by mean±SEM.

Conclusions

This is the first readout of the REIMAGINE trial in a psychiatric population and Vafidemstat produced significant improvements across several commonly used scales that measure agitation and aggression. In addition, the significant improvements in the overall BPDCL Total Score and the sub-item analyses suggest that Vafidemstat has a broader psychiatric effect beyond agitation and aggression. This FiM neurological effect in BPD patients is the first proof of concept for Vafidemstat in human patients. Oryzon will continue to explore additional CNS conditions to provide further insight into the role of this epigenetic drug in important psychiatric diseases.

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