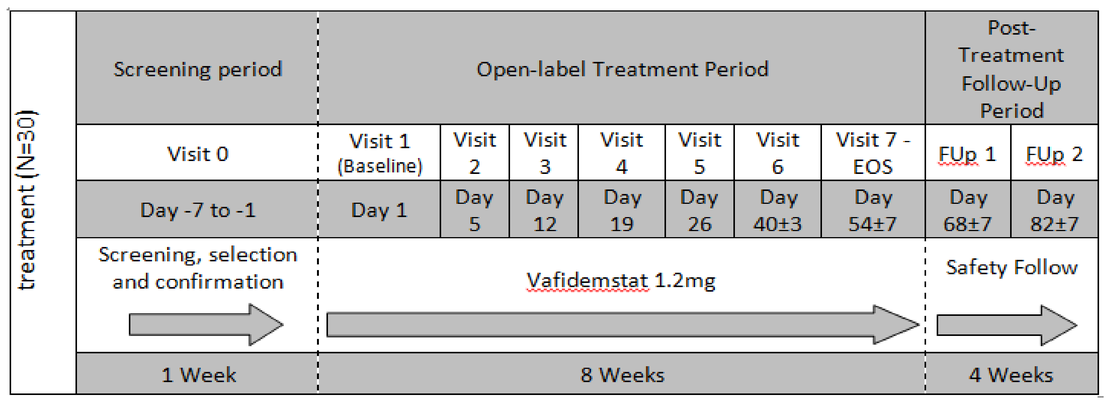
005 - Vafidemstat is safe and effective in treating adult ADHD patients: Phase II REIMAGINE clinical trial

R. Bullock*, S. Gutierrez*, JA Ramos Quiroga**, M. Valverde**, C. Buesa*, T. Maes*

*Oryzon Genomics S.A., Cornellà de Llobregat, Barcelona (Spain); **Hospital Universitari Vall d'Hebron. CIBERSAM, Barcelona

Objectives: Basket trials are frequently used in oncology to prove concept and target optimal responders. They are relatively uncommon in psychiatric disorders. Vafidemstat (ORY-2001) is a small, brain penetrant molecule that modifies transcription in the brain through modulation of the lysine-specific demethylase LSD1. Preclinical studies in animal models with vafidemstat showed memory restoration and correction of behavior alterations in the resident intruder and three chamber tests in SAMP8 mice and in the rat isolation rearing model. In the Alzheimer's SAMP8 mice model, vafidemstat reverts strong aggressive behavior and among other effects, corrects the abnormal response to stress of immediate early genes in the prefrontal cortex. If aggression was considered a phenotype, then a CNS-basket design would be helpful to test its management with a single compound across multiple disorders.

Design and Methods: REIMAGINE is a Phase IIa open-label study including three psychiatric patient cohorts: Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and Borderline Personality Disorder (BPD). The aims of this study are to evaluate the safety and tolerability of vafidemstat treatment and to assess its efficacy on the treatment of aggression. Six patients (aged 18-85 and on stable existing medication) per cohort will be given vafidemstat for eight weeks. Inclusion is based on significant or persistent agitation or aggression that was disruptive to the patient's daily living or put the patient in danger for at least 3 days per week for at least 4 weeks prior to screening visit (**Fig. 1**).



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).

Figure 1. REIMAGINE study design (EudraCT # 2018-002140-88). 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.

Results: REIMAGINE BPD cohort data were previously presented at EPA 2019. Here we present data from the ADHD cohort, as well as aggregated data for the ADHD and BPD cohorts (**Fig. 2**). ADHD is characterized by a persistent pattern of difficulty paying attention, hyperactivity and impulsiveness. Treatment with vafidemstat in these patients **(Fig. 2A)** was safe and well tolerated without significant adverse events (data not shown). A significant improvement in CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) scales was achieved after 2 months treatment with vafidemstat both in the ADHD cohort **(Fig. 2B1)** and aggregated cohorts **(Fig. 2B2).** Similarly, the 4-item agitation/aggression NPI (NPI A/A) subscale score and the total NPI score evidenced a significant reduction after 2 months of treatment in the ADHD (**Fig. 2C1** and **2D1**) and aggregated cohorts (**Fig. 2C2** and **2D2**). A statistically significant reduction in the ADHD-RS score after 2 months of treatment with vafidemstat was also observed (**Fig. 2E**). Pharmacokinetic and target engagement results (**Fig. 2F** and **2G**) were in line with previous Phase I data and support the treatment compliance in these psychiatric populations.

A

Demographic data ADHD patients		
nº of patients		6
Sex	Male	5 (83,33%)
	Female	1 (16,66%)
Age	Median	36,00
	(Min , Max)	(19/53)
Race	Caucasian	4 (66,66%)
Weight	Median	73,17
	(Min , Max)	(62,0/101,0)
Height	Median	169,50
	(Min , Max)	(160/177)
BMI	Median	25,49
	(Min , Max)	(19,15/36,07)

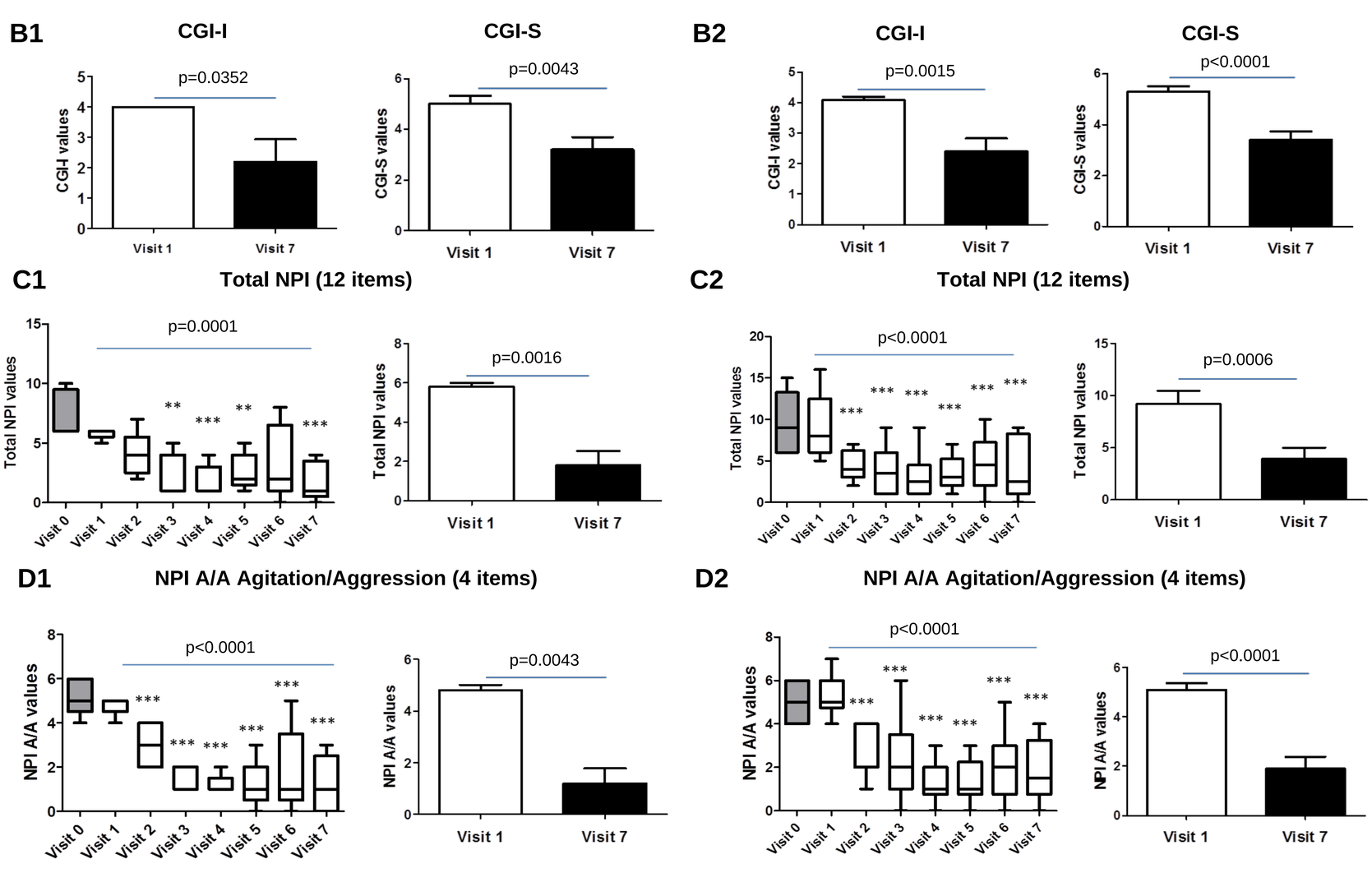


Figure 2. A. Baseline demographics of ADHD cohort (N=6) (one drop-out). **B.** CGI values reflect physician ratings of participants' severity and improvement in aggression (CGI-S and CGI-I, respectively); **B1** – ADHD cohort, **B2 -** aggregated ADHD and BPD cohorts. **C.** Total NPI score; **C1** – ADHD cohort, **C2 -** aggregated ADHD and BPD cohorts. **D.** 4-Item Agitation/Agression NPI (NPI A/A) Subscale (i.e. agitation/aggression, disinhibition, irritability and aberrant motor disturbance); **D1** – ADHD cohort, **D2 -** aggregated ADHD and BPD cohorts. **E.** ADHD-RS score. **F.** Plasma vafidemstat trough concentrations (Ctrough) from aggregated cohorts, determined using a LC-MS/MS validated method on days 5 and 26 of treatment. Steady state (ss) was reached from the first week of treatment. **G.** LSD1 Target Engagement (TE), determined in PBMCs using a proprietary chemiluminescent ELISA-based relative quantitative method at pre-dose of days 5 and 26 of treatment. Maximum LSD1-TE is observed from the first week and kept sustained throughout treatment. 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 ; p<0.001 from Visit 1) while paired one-tail t-test analysis was used to compare V1 with V7 values (mean ± SEM).

Conclusions: Vafidemstat is a novel approach for treatment of aggression, which importantly does not involve sedation or weight gain. This is the second readout of the REIMAGINE trial, specifically in ADHD. Vafidemstat produced significant improvements across commonly used scales that measure agitation and aggression. In addition, significant improvements in the ADHD-RS score suggest that vafidemstat has a broader psychiatric effect in ADHD beyond agitation and aggression. When aggregated with the previously reported BPD data, the scores continue to be consistently significantly improved in the NPI A/A subscale (66% of improvement) and in the Total NPI scale (50% of improvement), n = 11. This consistent neurological effect in BPD and now in ADHD patients is the first proof of concept for vafidemstat in human patients and shows therapeutic activity across different indications, suggesting that epigenetic dysregulation may be a treatable underlying cause of these psychiatric diseases. Overall, the REIMAGINE basket trial illustrated vafidemstat's role in treating aggression, as well as non-aggression features of psychiatric disease with high unmet medical need where current treatments either do not exist or have unfavourable side effect profiles.

Acknowledgements: We thank the investigators' team and all clinical trial participants, and most importantly, the patients participating in the study.

CONFLICT OF INTERESTS: *Roger Bullock and Sonia Gutierrez are employees of ORYZON GENOMICS S.A. Carlos Buesa and Tamara Maes are executive directors and shareholders of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A.*