2695. Vafidemstat reduces aggressiveness in three different psychiatric disorders. Final data from the REIMAGINE trial

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Background , Objectives and Methodology.

The influence of epigenetic mechanisms on psychiatric conditions has been proposed, but little molecular and pharmacological evidence is available. Vafidemstat is a brain-penetrant small molecule that inhibits LSD1 and modifies transcription in the brain through epigenetic effects. In preclinical models, vafidemstat reverts aggressive behavior and corrects the abnormal response to stress of immediate early genes in the prefrontal cortex.

REIMAGINE aimed to investigate vafidemstat as a treatment for aggression in autistic spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD).

REIMAGINE is a Phase IIa open-label trial that includes three psychiatric cohorts. 30 subjects (11 ADHD, 7 ASD, 12 BPD) were included based on significant or persistent agitation or aggression that was disruptive to patient's daily living. Patients received 1.2 mg of vafidemstat for eight weeks. Two additional patients were initially included but thereafter substituted due to consent withdrawal at the first week of treatment and not considered for efficacy evaluation (no safety related events were observed in these two subjects).

Demographic data		
N=30		
Sex	Male	14 (46.7%)
	Female	16 (53.3%)
Age	Mean	33.5
	(Min / Max)	(19 / 64)
Race	Caucasian	26 (86.7%)
	Latin	4 (13.3%)
Weight	Mean (Kg)	76.0
	(Min / Max)	(52.7/150.5)
Height	Mean (cm)	170
	(Min /Max)	(152/193)
BMI	Mean	26,08
	(Min / Max)	(18.59/49.14)
Diagnosis	ADHD	11 (36.7%)
	BPD	12 (40.0 %)
	ASD	7 (23.3 %)

Results.

Vafidemstat was safe and well-tolerated. Only no clinically relevant mild events that spontaneously recovered without any intervention or treatment modification were observed. There were no Serious Adverse Events (SAEs) and none of the patients withdrew due to safety related events.

The efficacy of vafidemstat in reducing aggression was assessed using the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) and the 4-item Neuropsychiatric inventory (NPI) agitation-aggression (NPI-A/A) scales, while overall patient functioning was assessed using the Total NPI (12 items) scale in addition to disease-specific scales. After treatment with vafidemstat, significant reductions in the CGI-S, CGI-I, NPI A/A and Total NPI scales were observed both in the aggregated data (all patients), as well as in each of the three disease groups (Panel A). Furthermore, vafidemstat was also able to significantly improve patient scores in the disease-specific scales: BPDCL for BPD patients and ADHD-RS for ADHD subjects (Panel B). Additionally, a significant reduction of suicidal ideation, measured by the C-SSRS scale, was observed in BPD patients, the only cohort where this trait is relevant. Finally, a clear correlation is observed between most of the clinical outcomes used (Panel C) and also with vafidemstat exposure (data not shown). This convergence of signals in scales of different nature and scope support the pharmacological role of vafidemstat in controlling aggression-agitation in different psychiatric conditions.

Study-drug related TEAEs (ADRs) by SOC and PT (N=30)	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**1 (3.33%) 1**
Thrombocytopenia	1 (3.33) 1
Gastrointestinal disorders	**3 (10%) 3**
Constipation	1 (3.33) 1
Abdominal pain	1 (3.33) 1
Dry mouth	1 (3.33) 1
General Disorders & Administration site conditions	**2 (6.67%) 3**
Discomfort	1 (3.33) 2
Thirst	1 (3.33) 1
Infections & Infestations	**1 (3.33%) 1**
Oral herpes	1 (3.33) 1
Nervous system disorders	**7 (23.33%) 20**
Headache	6 (20) 19
Sensory disturbance	1 (3.33) 1
Psychiatric disorders	**4 (13.33%) 5**
Abnormal behaviour	1 (3.33) 1
Insomnia	3 (10) 4

Treatment-emergent adverse events (TEAEs) with potential causal relationship to study drug documented as certain, probable/likely, possible A patient with more than one finding in a specific category was only counted once. Percentages based on total no. of patients (N=30) ADR-Adverse drug reaction; SOC-System Organ Class; PT-Preferred Term

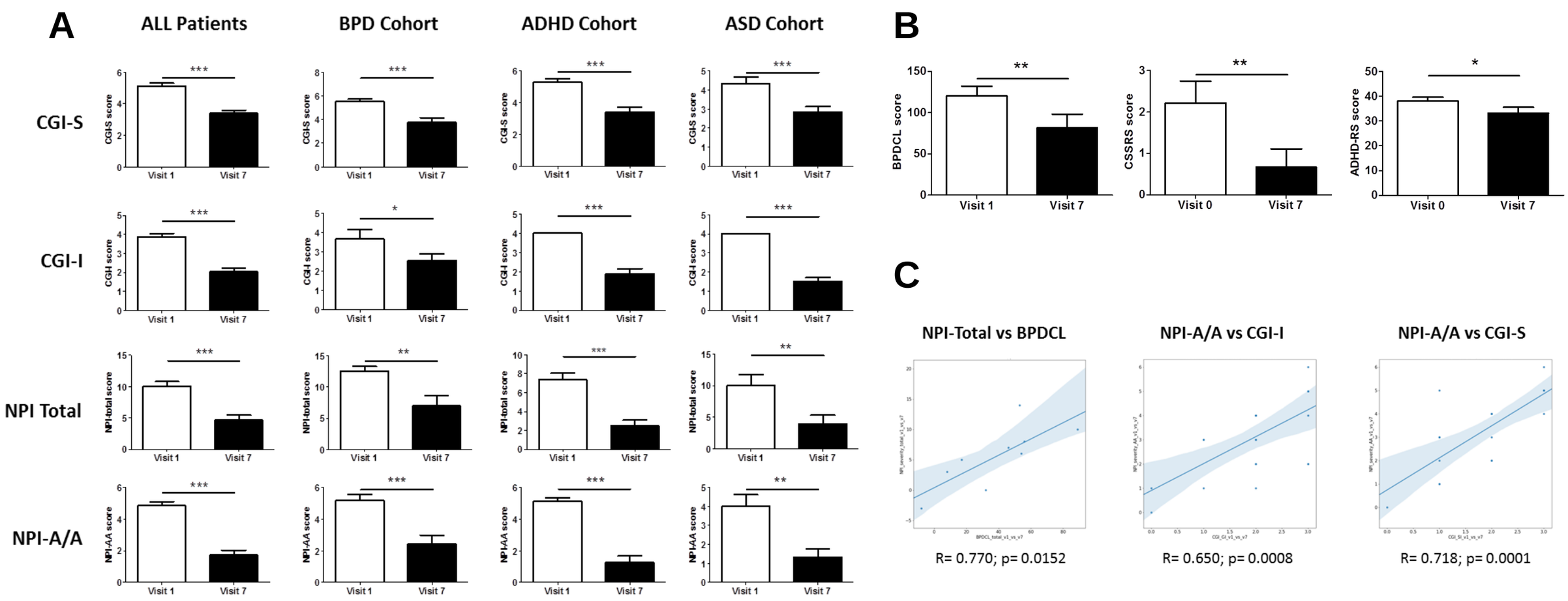

Figure Legend: Study-drug related TEAEs of all included subjects (n=30) is shown in Table. A) and B) Comparison between the values of clinical scores CGI-S, CGI-I, NPI-AA, NPI-total (A) and BPDCL-total and C-SSRS scores in BPD Cohort and ADHD-RS score in ADHD Cohort (B) at the beginning of the study (visit 1) and after 8 weeks of treatment with vafidemstat (visit 7). Each bar represents mean ± SEM. All graphs include p-values for the 1-tail, paired Student's t-test comparing scores at visit 1 and visit 7 (*: p-value<0.05; **: p-value<0.01; ***: p-value<0.001). Similar data is obtained when 1 tail paired Wilcoxon signed-rank is used as non-parametric test on the specific subsets (not shown). NPI scores correspond to the sum of severity values for each NPI item. C) Linear correlation graphs of pairs of clinical scores at visit 1 and visit 7. Pearson R value is reported in the figure together with the related p-value. The 95% confidence interval for the linear regression is shaded in blue. All efficacy data has been evaluated in the Per Protocol Analysis Subset (PAS) corresponding to the patients that completed the 8 weeks treatment (n=23, 9 BPD, 8 ADHD, 6 ASD).

Conclusions

REIMAGINE supports vafidemstat as an emerging therapeutic option to treat aggression-agitation, as well as non-aggression features of psychiatric diseases with high unmet medical need where current treatments do not exist or have unfavorable side effects, including sedation or weight gain. Further randomized placebo controlled clinical trials to confirm vafidemstat potential to treat aggression-agitation in psychiatric disorders are warranted. This is the case of PORTICO, a Phase IIb trial in BPD patients planned to be initiated in the following months.

CONFLICT OF INTERESTS: *RB, SG, MR, JX and CB are employees of Oryzon Genomics, S.A. CB is Chief Executive Officer and shareholder of Oryzon Genomics, S.A. This study was sponsored by Oryzon Genomics, S.A.*