Vafidemstat: An epigenetic drug with emerging therapeutic potential, composite data from three psychiatric disorders from the REIMAGINE trial

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Background and objectives

Epigenetic dysregulation has been associated with neuropsychiatric diseases such as schizophrenia, major depressive disorder, autism spectrum disorder, attention deficit and hyperactivity disorder and others. Vafidemstat is a highly brain-penetrant small molecule that covalently inhibits LSD1 and modifies gene transcription in the brain. In rodents, vafidemstat produces strong anti-neuroinflammatory action and upregulation of genes involved in synaptic plasticity, as well as producing a variety of phenotypic outcomes, including reduction of aggression and social avoidance, and increase of sociability. In animals, vafidemstat also corrects the abnormal response to stress of immediate early genes, such as c-Fos, in the prefrontal cortex. REIMAGINE is a CNS-basket trial testing whether vafidemstat can positively impact aggression across multiple psychiatric disorders: attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD) and borderline personality disorder (BPD).

Trial Design

REIMAGINE is a Phase IIa open-label trial evaluating the safety, tolerability and efficacy of vafidemstat in the treatment of aggression in adult ASD, ADHD and BPD patients. Inclusion was 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 visit. Thirty subjects have been enrolled and treated with 1.2 mg of vafidemstat for eight weeks (Fig 1). Aggression was assessed using the Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I) and the Neuropsychiatric Inventory (NPI) 4-item agitation-aggression (NPI-A/A) scales. Overall patient functioning was assessed using Total NPI, plus disease-specific scales (ADHD-Rating Scale (ADHD-RS) and BPD Checklist (BPDCL)).

Results and Discussion

Thirty patients were recruited across the three psychiatric indications (Fig 2). All patients included in the safety evaluation (n=30). Twenty-two patients finalized the 8 weeks treatment period, one is still in progress and there were 7 drop-outs. Among the 7 drop-outs, 2 patients completed a treatment period of at least 6 weeks and were included in the analysis for efficacy. The patient set evaluated for efficacy (n=24) includes 10 ADHD, 8 BPD and 6 ASD subjects.

Treatment with vafidemstat was safe and well tolerated without clinically relevant adverse events (Fig 2). Significant reductions in CGI-I, CGI-S, NPI A/A and Total NPI after vafidemstat treatment were observed both in the aggregated data for all subjects (Fig 3A) and in all three individual cohorts (Fig 4). Moreover, vafidemstat treatment was also able to significantly improve the patient scoring in the disease-specific scales: BPDCL for BPD patients and ADHD-RS for ADHD subjects (Fig 3B). No validated treatment-sensitive scale for ASD subjects is currently available. A significant reduction of Suicidal ideation (C-SSRS scale) was observed (p=0.0033, only assessed for efficacy in BPD).

Highlights

- **The study has enrolled 30 patients across ADHD, ASD and BPD**
- **Vafidemstat was safe and well-tolerated in all tested populations**
- **Vafidemstat reduced aggression and improved other functional features on the three investigated psychiatric disorders**
- **REIMAGINE supports vafidemstat as an emerging therapeutic option to treat aggression**

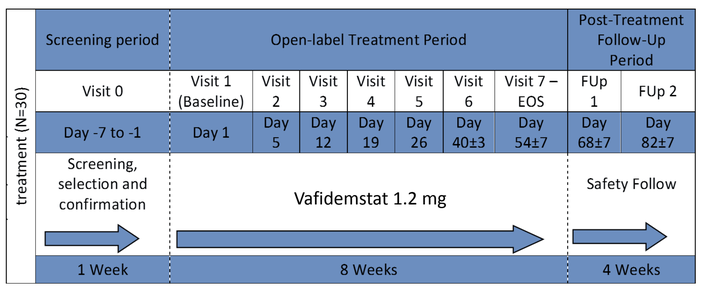

Figure 1. REIMAGINE study design (EudraCT No. 2018-002140-88). REIMAGINE is a Phase IIa open-label study, 1-arm, 8-week treatment period followed by a 4-week follow-up period. The study has been performed at Hospital Vall d'Hebron in Barcelona, Spain.

Demographic data		
nº of patients		30
Sex	Male	14 (46.66 %)
	Female	16 (53.33 %)
Age	Median	33.53
	(Min /Max)	(19 /64)
Race	Caucasian	26 (86.66 %)
	Latin	4 (13.33 %)
Weight	Median(kg)	76.0
	(Min /Max)	(52.7/150.5)
Height	Median (cm)	170
	(Min /Max)	(152/193)
BMI	Median	26,08
	(Min / Max)	(18.59/49.14)
Diagnose	ADHD	11 (36.7%)
	BPD	12 (40.0 %)
	ASD	7 (23.3 %)

Study-drug related TEAEs (ADRs) by SOC and PT (n=30)	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**1 (3.03 %) 1**
Thrombocytopenia	1 (3.03) 1
Gastrointestinal disorders	**3 (9.09%) 3**
Constipation	1 (3.03) 1
Abdominal Pain	1 (3.03) 1
Dry mouth	1 (3.03) 1
General disorders and administration site conditions	**2 (6.06%) 3**
Discomfort	1 (3.03) 2
Thirst	1 (3.03) 1
Infections and infestations	**1 (3.03%) 1**
Oral herpes	1 (3.03) 1
Nervous system disorders	**7 (21.21%) 20**
Headache	6 (18.18) 19
Sensory disturbance	1 (3.03) 1
Psychiatric disorders	**4 (12.12%) 5**
Abnormal behaviour	1 (3.03) 1
Anxiety	3 (9.09) 4

Figure 2. Demographics and Safety. *Left panel.* Baseline demographics of all patients (n=30). *Right panel. Safety data.* AEs reported here correspond only to those with a potential causality (certainly, probably/likely and possibly related) to vafidemstat treatment for all patients (n=30) (TEAE, Treatment emergent adverse event; ADR, Adverse drug reaction; SOC, System organ class; PT, Preferred term).

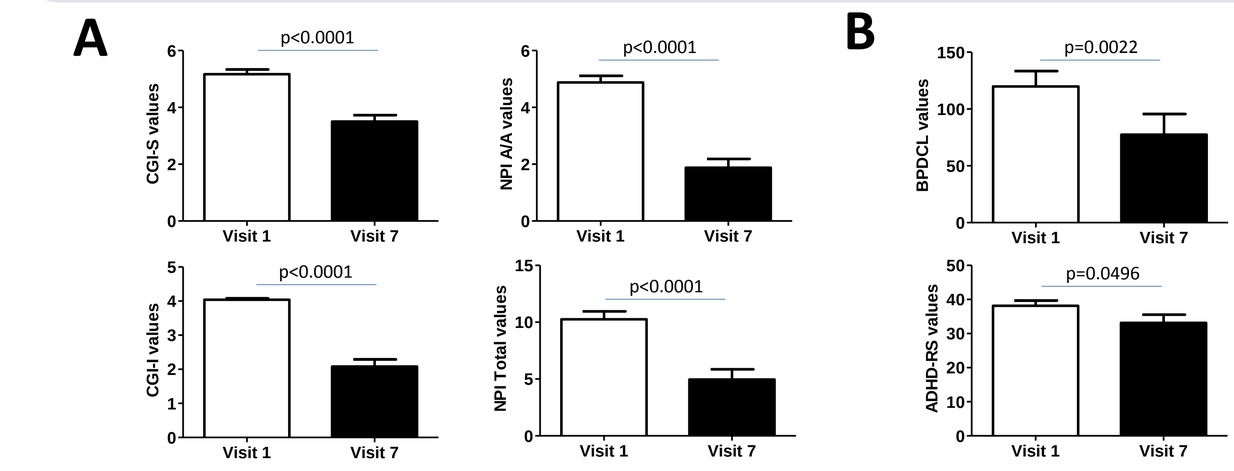

Figure 3. Efficacy. A) Aggregated data for all subjects; n= 24 (22 subjects that finalized the 8 week treatment period plus 2 drop-outs with at least 6 weeks of treatment). CGI values reflect physician ratings of participants' severity (CGI-S) and improvement (CGI-I) in aggressive behaviour. NPI Scores: 4-Item Agitation/Aggression NPI Subscale (NPI-A/A) (i.e. agitation/aggression, disinhibition, irritability and aberrant motor disturbance) and Total NPI (12-items). B) Data from disease-specific scales: BDPCL Total score (n=8) and ADHD-RS score (n=8, since two patients did not perform the last evaluation).
In all panels, paired one-tail t-test analysis was used to compare Visit 1 (Baseline) with Visit 7 (end of treatment) (after 8 weeks of treatment, 2 subjects only 6 weeks). Data is represented by mean ± SEM.

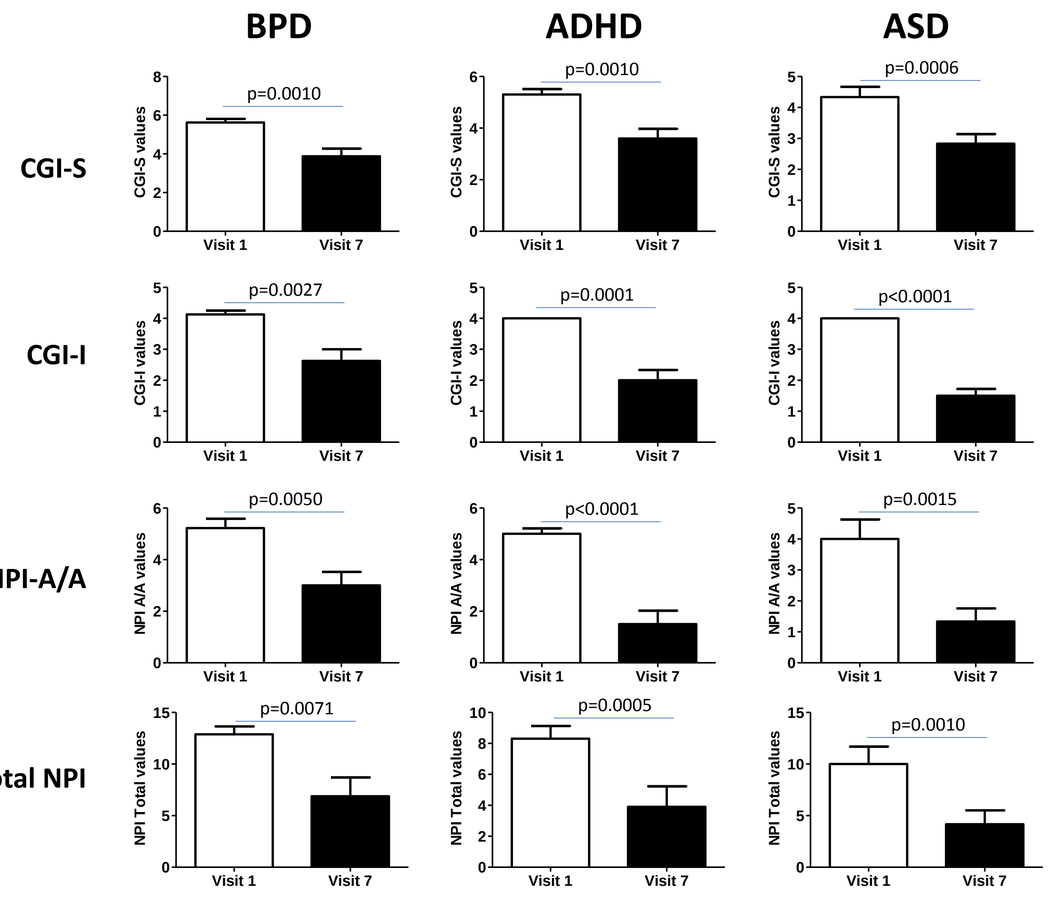

Figure 4. Efficacy per cohort. CGI-S, CGI-I, NPI-A/A and Total NPI values per indication (BPD, ADHD, ASD) at baseline (Visit 1) compared with values at Visit 7 (end of treatment) (after 8 weeks of treatment, two subjects only 6 weeks). Data is represented by mean ± SEM. Statistical analysis done as in Fig 3. Sample size: ADHD n=10, BPD n=8, ASD n=6.

Conclusions

Vafidemstat is a novel aggression treatment, which importantly does not involve sedation, weight gain or other unpleasant effects. Vafidemstat produced significant improvements across commonly used scales that measure overall functioning, aggression and core features of three distinct psychiatric conditions. The robust neurological effect across ADHD, ASD and BPD and across different scales serves as proof of concept for vafidemstat in human patients, providing evidence that epigenetic dysregulation may be a common underlying cause of these psychiatric diseases. Overall, REIMAGINE supports vafidemstat as an emerging therapeutic option to treat aggression, as well as non-aggression features of these psychiatric diseases with high unmet medical need where current treatments do not exist or have unfavorable side effects.

CONFLICT OF INTERESTS: *R Bullock, S Gutierrez, J Xaus and M Ropacki are employees of ORYZON GENOMICS S.A. Carlos Buesa is Chief Executive Officer and shareholder of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A.*