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Vafidemstat improves aggression scores in Autism: REIMAGINE, third cohort clinical data

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Highlights

- **Vafidemstat was safe and well-tolerated in an ASD population**
- **Vafidemstat produced significant improvements in ASD patients' agitation and aggression levels**

Background

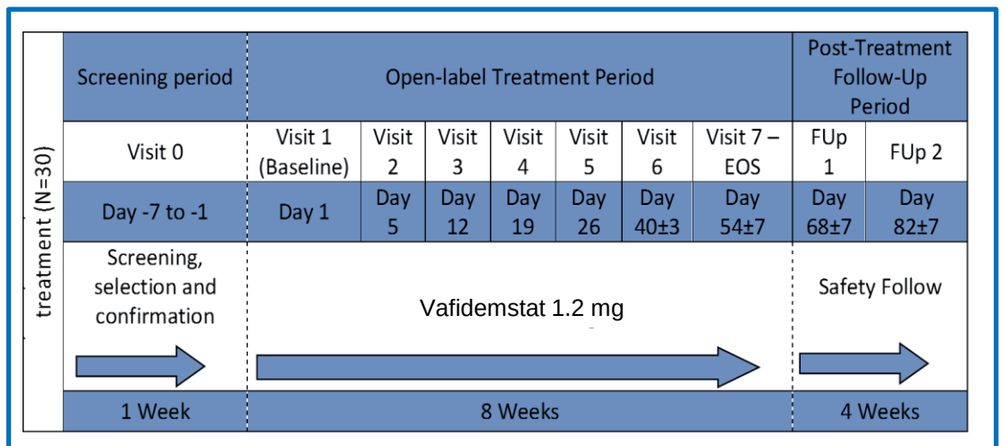
This is the third cohort analyzed in REIMAGINE, a Phase IIa basket trial assessing the effects of vafidemstat, a small, brain penetrant molecule that inhibits histone demethylase LSD1, in aggression as well as other behavioural and psychiatric features in adult population with Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and Borderline Personality Disorder (BPD). In previous reports, we have shown that vafidemstat is safe and well tolerated in BPD and ADHD patients, as well as mild and moderate Alzheimer's patients. Vafidemstat produced significant improvements in aggression and agitation of ADHD and BPD patients, as well as other features of these diseases.

Objectives

REIMAGINE is a Phase IIa open-label study of three psychiatric patient cohorts: ASD, ADHD and BPD (**Fig. 1**). The aims of this study were to evaluate the safety and tolerability of vafidemstat treatment and assess its efficacy on the treatment of aggression.

Methods

Six patients (age 24 to 44) (**Fig. 1**) diagnosed with ASD according to DSM-5 criteria have received vafidemstat for eight weeks. REIMAGINE 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. Aggression was assessed using the Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I), as well as the Neuropsychiatric Inventory (NPI) 4-item agitation aggression (NPI A/A) subscale. The total NPI scale was used to measure global functioning.



Demographic data ASD patients		
nº of patients		6
Sex	Male	5 (83.3 %)
	Female	1(16.6 %)
Age	Median (years)	35.33
	(Min , Max)	(24/44)
Race	Caucasian	6(100%)
Weight	Median (Kg)	95.70
	(Min , Max)	77.5/116.5
Height	Median (cm)	181.08
	(Min , Max)	(174/190)
BMI	Median	29.06
	(Min , Max)	(22.56/37.46)

Figure 1. REIMAGINE study design (EudraCT # 2018-002140-88). ***Top panel***: Study scheme. A Phase IIa unicenter, open-label study, 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 ASD cohort (N = 6) (one drop-out).

Results:

This is the first report of REIMAGINE data from the ASD cohort. Vafidemstat was safe and well-tolerated without significant adverse events **(Fig. 2**). One ASD patient experienced a transitory event related to hematological alteration, although no clinically relevant modification of the hematological and biochemical parameters tested were observed. No sedation was reported. (**Fig. 2**). Pharmacokinetic and target engagement results (**Fig. 3**) are in line with previous data from Phase I and REIMAGINE from the BDP and ADHD cohorts. A significant improvement in CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) scales was achieved after 2 months treatment with vafidemstat **(Fig. 4A).** 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 (**Fig. 4B**). A significant improvement was also observed in the NPI combined score for all other items not related to aggression or agitation.

TEAEs/ADRs by SOC and PT (n=6) ASD patients	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**1 (16.66 %) 1**
Thrombocytopenia	1 (16.66) 1
Gastrointestinal disorders	**1 (16.66 %) 1**
Dry mouth	1 (16.66) 1
General disorders and administration site conditions	**1 (16.66 %) 1**
Thirst	1 (16.66) 1
Nervous system disorders	**1 (16.66 %) 6**
Headache	1 (16.66) 6

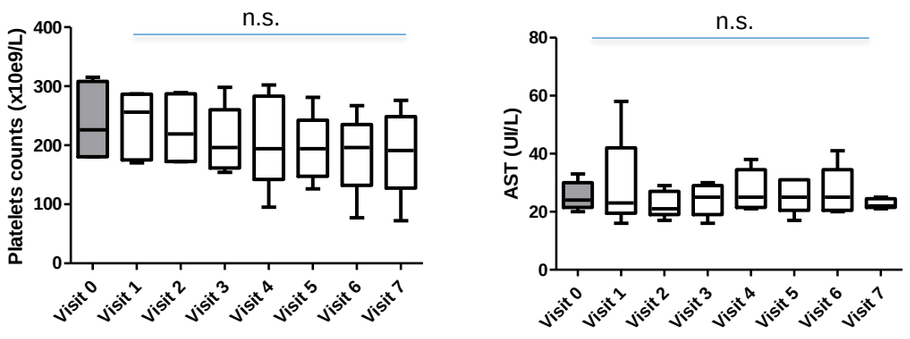


Figure 2. Safety. AEs reported here correspond only to those with a potential causality (certainly, probably/likely and possibly related) to vafidemstat treatment (TEAE, Treatment emergent adverse event; ADR, Adverse drug reaction; SOC, System organ class; PT, Preferred term). No overall clinically significant vafidemstat effect was observed on platelets or any other laboratory parameters (n.s., no significative)

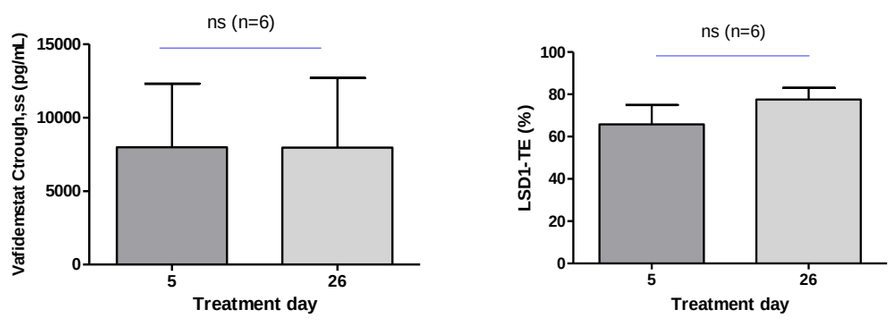


Figure 3. PKPD. Vafidemstat's plasma PK (Ctrough) and LSD1 Target Engagement (TE) in blood PBMCs were determined at pre-dose on days 5 and 26 of treatment. Observed values are in line with previous Phase I and demonstrate that steady state values in both parameters are achieved already at day 5.

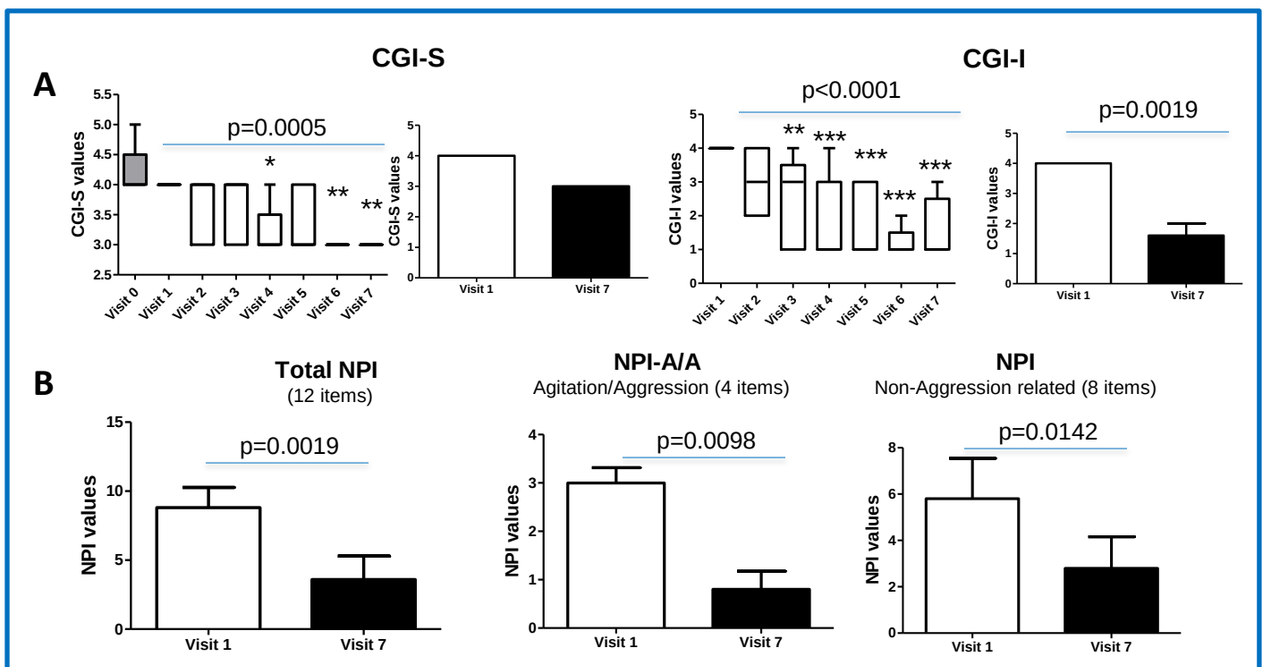


Figure 4. Efficacy. A. CGI values reflect physician ratings of participants' aggression severity (CGI-S) and improvement in aggression (CGI-I). **B.** NPI scores: Total NPI (12 items); 4-Item Agitation/Agression (NPI-A/A) subscale (i.e., agitation/aggression, disinhibition, irritability and aberrant motor disturbance) and NPI non-aggression related items combined score (i.e., 8 items in NPI not included in NPI-A/A).
In all panels, paired one-way ANOVA with Bonferroni's multi comparison post-hoc test was used for complete set by 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 graphs where V1 and V7 values are compared, data is represented by mean±SEM.

Conclusions

There are no currently approved treatments that address the core features of ASD, and approved therapies for irritability associated with ASD have unpleasant side-effect profiles. Vafidemstat is a novel therapy that appears to improve aggression and agitation, as well as overall ASD patient functioning, and importantly does not involve sedation or weight gain. Overall, REIMAGINE data support vafidemstat was safe and well tolerated, as well as effective in treating aggression and agitation, as well as non-aggressive features in three distinct psychiatric diseases, with high-unmet medical needs and where current treatments either do not exist or have unfavourable side effect profiles.

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