**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 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).

**Results:** REIMAGINE ADHD 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-Score (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.

**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.

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