04- Vafidemstat, a new approach to treat aggression in central nervous systems disorders: clinical study REIMAGINE.

Report in a cohort of Borderline Personality patients.


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

Background

Basket trials are often used in oncology as open-label adaptive designs to prove concept and target best responders, yet they are less common in CNS trials. Vafidemstat (DRY-001) is a small, brain penetrant molecule that modifies transcription in the brain through epigenetic effects. In different preclinical models this drug has shown to produce neuroprotection, improve cognition and sociability, as well as reduce neuroinflammation and aggression. REIMAGINE is a first clinical study assessing the impact of Vafidemstat on human neurological disease using this methodology.

Objectives

To explore Vafidemstat effect on treating aggression in patients with Alzheimer’s disease (AD), Lewy Body Dementia (LBD), autist spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD).

Methods

Six patients (age 18-85) per disorder will receive Vafidemstat for eight weeks in a phase IIa open-label study (REIMAGINE) (Fig. 1). Entry is 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.

Results:

This is the first presentation of REIMAGINE data from the Borderline personality disorder (BPD) cohort. The essential features of a personality disorder are impairments in personality (self and interpersonal) functioning and the presence of pathological personality traits. Patients with BPD typically experience emotional instability, impulsivity, irrational beliefs and distorted perception, as well as intense but unstable relationships with others. Treatment with Vafidemstat in these patients was safe and well tolerated without significant adverse events (Fig. 2). Pharmacokinetic and target engagement results are in line with previous Phase I data (not shown). An improvement in CGI Severity (CGI-S) and CGI-Improvement (CGI-I) scales was achieved after 2 months treatment with Vafidemstat (Fig. 3A). The 4-item agitation/aggression NPI subscale score and the total NPI score evidenced a significant reduction after 2 months of treatment (Fig. 3B). The total BPD checklist (BPDCL), a combination of the aggression-related scores and the combination of the remaining scores (i.e. BPDCL are not related with aggression) all showed a statistically significant reduction (Fig. 3C).

Conclusions

This is the first readout of the REIMAGINE trial in a psychiatric population and Vafidemstat produced significant improvements across several commonly used scales that measure agitation and aggression. In addition, the significant improvements in the overall BPDCL Total Score and the sub-items analyses suggest that Vafidemstat has a broader pharmacologic effect beyond agitation and aggression. This FiM neurological effect in BPD patients is the first proof of concept for Vafidemstat in human patients. Oryzon will continue to explore additional CNS conditions to provide further insight into the role of this epigenetic drug in important psychiatric diseases.

Acknowledgements:

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