Vafidemstat (ORY-2001) is a highly brain penetrant LSD1 inhibitor designed for CNS indications with good selectivity, ADME and PK properties. Vafidemstat restores memory in SAMP8 Alzheimer’s (AD) and in R6/1 Huntington (HD) disease mice models. Others have also shown that LSD1 inhibition restores working memory in schizophrenia (SZ) and psychosis mice models. Vafidemstat also reduces significantly aggression and enhances sociability in rodent models. Vafidemstat’s hypothesized impact on the CNS is mediated by overexpression of genes associated with neuronal plasticity and reduction of genes associated with neuro-inflammation, which is supported by preclinical studies to-date. In addition, supporting evidence in humans was reported in REIMAGINE, a single arm, open label Phase IIa trial conducted in ADHD, ASD and Borderline Personality Disorder patients, where a two month treatment with vafidemstat was efficacious in reducing agitation-aggression and improving the general status of study patients. In general, the prevalence of agitation-aggressive behavior increases as AD severity increases, reducing quality of life of patients and caregivers. This behavior is also the main reason for institutionalization. Current treatment options for agitation-aggressive AD patients include off-label antipsychotics; however, these drugs are associated to a higher risk of serious adverse effects. Therefore, new clinical options are needed to improve the management of behavioral disorders in AD patients. Vafidemstat has been shown to be safe in previous clinical trials.

Methods

REIMAGINE-AD (EudraCT Number: 2019-001436-54) is a single center, open-label, 1-arm study to evaluate the efficacy, safety and tolerability of vafidemstat in aggression in adult population with moderate-to-severe AD. Initially, the study was designed as a 13-week treatment study, but due to initial observations made by the PIs, it was decided to extend the treatment period up to 24 weeks. The Primary Objective is to investigate the efficacy of vafidemstat in aggression in AD population, while secondary objectives include the evaluation of the safety and tolerability of vafidemstat in AD population and to investigate other changes on behavior, cognition and caregiver burden. The scales used to measure agitation-aggression included the Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory (NPI) (4-item) Agitation/Aggression subscale (NPI A/A subscale), as well as the Clinical Global Impression (CGI) focused on agitation and aggression. Other measures included measures of global patient well-being (NPI), cognition (MMSE) and caregiver burden (Zarit Caregiver Burden Interview, ZBI).

Results

A total of 12 patients were enrolled (Table 1). One patient withdrew consent during the first two months of treatment. After two months, subjects were offered to continue in the study and 9 and 7 patients completed the 4 and 6 months study visits, respectively. The study population included 58% females and 42% males. Median age was 75 years. Seven (58%) patients had severe AD and four (42%) patients moderate AD (median MMSE values of 5 and 17, respectively). Safety data support the safety and tolerability of long-term vafidemstat treatment in this patient population, which is aligned with the safety data obtained in the parallel running randomized, double-blind placebo controlled AD disease trial (ETHERAL trial). AEs observed in REIMAGINE-AD are presented in Table 2. Only mild thromboctopenia and neutropenia was observed in one patient who withdrew consent during the first two months of treatment. As regards efficacy outcomes, treatment with vafidemstat produced the following statistically significant findings when comparing patients treated for 6 months (Visit 8) with respect to baseline (Visit 1): • Regarding agitation-aggression measurements, improvement in CGI-I as well as a reduction in the CMAI scale, and in the NPI Agitation/Aggression subscale (Fig 1A). • A global improvement on the caregiver burden as measured by ZBI and both of the NPI related emotional distress scores (Fig 1B). • A global improvement on the total NPI (Fig 1C).

Vafidemstat appears safe and well tolerated in this elderly moderate-to-severe AD population. These findings are aligned with preliminary safety data from ETHERAL and in the three REIMAGINE psychiatric patient populations. Findings support that vafidemstat controlled agitation and aggression symptoms of AD patients, as well as improved caregiver burden after 6 months of treatment. Interesting anecdotal findings in the moderate subjects included a concomitant increase in memory performance in the ETHERAL in 2 out of 4 subjects in 6 months. These data are preliminary but support further clinical investigations in this difficult to treat disease with limited treatment options.