Sporadic Alzheimer’s disease (AD) has unknown etiology and a challenging heterogeneous pathology presentation. Epigenetic plays a role in CNS disorders. A Histone demethylase, LSD1, is important in the development and functioning of CNS. LSD1 has been reported as the most abundant histone demethylase in the Prefrontal Cortex but is also expressed in other organs and is a key regulator of hematopoiesis. Oryzon is developing vafidemstat, a dual LSD1/MAC3B inhibitor, whose epigenetic upstream MoA restores transcriptional imbalances, for the treatment of several CNS diseases. Oryzon is running a Phase 1 studies safety and efficacy study on to assess safety and efficacy of vafidemstat in moderate AD patients. Preclinical work has shown that vafidemstat has significant effects in many areas relevant to AD phenotype, restoring memory, decreasing neuro-inflammation, eliminating aggressiveness and restoring sociability. Recently, in ADHD and Borderline Personality Disorder patients, we have reported improvements in aggression/agitation, as well as other core features of these diseases. In these patient populations, 8 weeks of vafidemstat treatment were safe and did not produce hematological impact. One of the main goals for vafidemstat AD clinical development is to establish safety with long-term administration, while demonstrating that it does not have a deleterious impact on patients at therapeutically relevant doses in an elderly AD population.

**Methods**

ETHERAL is a Phase IIa study in mild-to-moderate AD to determine vafidemstat safety profile, as well as explore symptomatic and potential disease modifying benefits of treatment in approximately 125 subjects in the EU and 30 in the US. The trial is a double-blind, multinational-multicentric, randomized, parallel-group study with a 24-week placebo-controlled period, then a 24-week extension where placebo patients are randomized to vafidemstat therapy (See Figure 1). In an adaptive design, the first 40 patients used a randomization of 1:2:2 to maximize exposure to vafidemstat and safety measures, the rest of the patients are being randomized to vafidemstat therapy and placebo subjects for 6-month analyses. ETHERAL is measuring relevant markers in the CSF both for recruitment (AB 42/40 ratio, Tau and p-tau) and pharmacodynamic purposes (XYL- 46, neuraminidase) via a coding system to maintain the blind to investigators and sponsors. Collected CoAs include the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Cohen-Mansfield Agitation Inventory (CMAI), Apathy Evaluation Scale (AES-C), Cornell Scale for Depression in Dementias (CSD) and the EuroQOL-5 dimensions questionnaire (EQ-SD). Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-cog), Alzheimer’s Disease Assessment Scale-Non-Cognitive (ADAS-noc), Mini-mental State Examination (MMSE), Computerized Cognitive Test Battery (Cognate) are also assessed. Finally, volumetric MRI is being performed at 0, 6 and 12 months.

**Highlights**

ETHERAL has recruited to-date 104 out of the 125 European subjects

- Vafidemstat shows a good safety profile and tolerability in this aged frail population

- No signs of hematological clinical impact (thrombocytopenia or neutropenia)

- Trial to produce useful novel biomarker data

- Efficacy data will be informative for future clinical development as a disease modifying and/or symptomatic therapy

**Results and Discussion**

By mid-June, ETHERAL achieved the 75% of the intended sample size (N = 104), and current recruitment suggests the EU LPI may be achieved by end of July 2019 (ETHERAL is expected to recruit all 125 elderly enrolment is ongoing). Vafidemstat treatment appears to be safe and is being well tolerated so far. four SAEs were reported in three subjects, all suspected to be unlikely related to the treatment. All AEs with a potential causality to the drug by the Principal Investigators are detailed in Figure 2 below. Platelet, neutrophils decreases, increasing neuro-inflammation, eliminating aggressiveness and restoring sociability. Recently, in ADHD and Borderline Personality Disorder patients, we have reported improvements in aggression/agitation, as well as other core features of these diseases. In these patient populations, 8 weeks of vafidemstat treatment were safe and did not produce hematological impact. One of the main goals for vafidemstat AD clinical development is to establish safety with long-term administration, while demonstrating that it does not have a deleterious impact on patients at therapeutically relevant doses in an elderly AD population.

**Conclusion**

ETHERAL is an ongoing Phase IIa trial designed to demonstrate the safety of vafidemstat in an elderly AD population. With 87.5% (91/104) patients being treated for more than 28 days, there are no clinically relevant hematological safety signals that have arisen, in keeping with the previous vafidemstat safety data from other patient populations. In addition, 36 patients have already passed the 6-month threshold, and no significant safety issues have been reported. Data collected to date supports that vafidemstat treatment is safe and well-tolerated by AD patients. Overall, ETHERAL safety data is encouraging, and useful biomarker and efficacy data is forthcoming that will be useful to inform future vafidemstat clinical development as an AD disease modifying and/or symptomatic therapy.

**Figure 1. ETHERAL study scheme.** Full: follow-up; V: visit; R: randomisation; 3:2:1 for the first 40 patients and 1:1:2 for the following 85 patients. *Patients should be under treatment with the same ACER (oral donepezil, oral or transdermal patch rivastigmine, or oral galantamine) for at least 6 months prior to the Screening Visit and on a stable dose for at least 4 months prior to the Screening Visit and throughout the Screening Period.

**Figure 2. Recruitment status, demographics and safety.** Baseline demographics of 104 recruited subjects by mid-June is provided as it is also the current distribution number of patients per completed visit. AEs observed so far and referred as SOC Terms correspond only to those with a potential causality (certainly, probably/likely and possibly related) with vafidemstat treatment. No overall clinically significant hematological effect is observed on platelets, neutrophils or any other laboratory parameters.

**Figure 3. Biomarkers and PKPD parameters.** Plasma vafidemstat levels are shown in Table 1 (Chloroh) and LSD1 Target Engagement (TE) in blood PMBCs were determined at pre-dose on days 1, 5, 12, 19 and 26 of treatment. Data below LOD (LOD not shown) correspond to blind data of the available samples as per mid-June 2019. Almost all patients were included with previous Phase 1 and demonstrate that steady state values in both parameters are achieved already at day 5. CSF biomarkers: Aβ 42/40 ratio (±10). Total Tau and S100A4 protein levels were assayed at baseline and compared with <90% samples from healthy (50) and mild and moderate AD subjects. These data suggest to characterise the ETHERAL patient population.

**Figure 4. Functional Scores evolution.** Clinical outcome assessments include cognition, behavior, function and quality of life scales, such as Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-cog), Mini-mental State Examination (MMSE), Cohen-Mansfield Agitation Inventory (CMAI) or Apathy Evaluation Scale (AES-C). Volumetric MRI is also being performed. Change from Baseline in principal health assessments, the individual differences as Change from Baseline (CFB) in absolute value observed for MMSE, CMAI, AES-C, are shown at follow-up. CFB scores and the absolute value of MMSE, CMAI, AES-C show a mild to moderate trend in blinded patients after 24 weeks of treatment.