Safety Evaluation of Vafidemstat on Mild to Moderate Alzheimer's Subjects

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Background

Sporadic Alzheimer's disease (AD) has unknown etiology and a challenging heterogeneous pathology presentation. Epigenetics play 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/MAO-B inhibitor, whose epigenetic upstream MoA restores transcriptional imbalances, for the treatment of several CNS diseases. ETHERAL is a Phase IIa safety and efficacy study on mild-moderate AD patients. Preclinical work has shown that vafidemstat has significant effects in many areas relevant to the 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 hematology 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 block (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 2:1:1 to balance the active therapy and placebo subjects for 6-month analyses. ETHERAL is measuring relevant markers in the CSF both for recruitment (Aβ 42/40 ratio, Tau and p-Tau) and pharmacodynamic purposes (YKL-40, neurogranin, and neurofilament light chain) at baseline, 6 and 12 months. 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 Dementia (CSDD) and the EuroQOL five dimensions questionnaire (EQ-5D). Alzheimer´s Disease Assessment Scale-Cognitive (ADAS-cog), Mini-mental State Examination (MMSE) and Computerized Cognitive Test Battery (Cogstate) are also assessed. Finally, volumetric MRI is being performed at 0, 6 and 12 months.

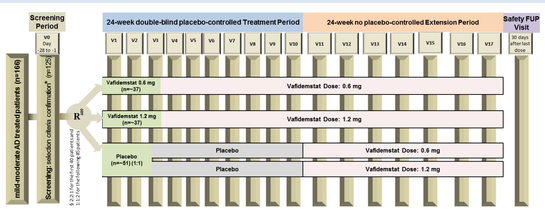


Figure 1. ETHERAL study scheme. FUP, follow-up; V, visit; R, randomisation: § 2:2:1 for the first 40 patients and 1:1:2 for the following 85 patients. * Patients should be under daily treatment with the same AChEI (oral donepezil, oral or transdermal patch rivastigmine, or oral galantamine) for at least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

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 AD therapy

Results and Discussion

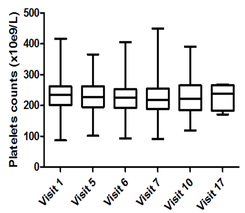
By mid-June, ETHERAL achieved the 75% of the intended sample size (N = 104), and current recruitment suggests the EU LPI may be achieved by end of July 2019 (ETHERAL-US received an IND early 2019, enrollment is ongoing). Vafidemstat treatment appears to be safe and is being well tolerated so far: four 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 and other hematological parameters do not show clinically relevant variations due to vafidemstat treatment (Fig. 2) despite almost 90% of the recruited patients have been treated for more than 1 month, sufficient time to demonstrate hematological impact related to LSD1 inhibition (Fig. 3). No abnormal and clinically significant liver enzymes levels or other laboratory findings have been reported-to-date. Pharmacokinetics and Target engagement (TE) was established in the first 77 out of 104 subjects analyzed to-date, accomplishable via a coding system to maintain the blind to investigators and sponsor. Preliminary PK and LSD1 TE data (Fig. 3) are in accordance with previous Phase I results and show sufficient LSD1 TE to achieve efficacy based on preclinical models.

As the overall ETHERAL is blinded and recruitment is ongoing, it is way too early at this time point to extract any conclusion related to efficacy, but an initial blind analysis by individual patients (on the first 33 patients completing the first 24-weeks of therapy) shows that while some patients clearly progress, others maintain baseline values or even improve, as observed for example in MMSE or CMAI values (Fig. 4). According to the randomization criteria of these initial subjects (1:2:2) these should be approximately 7:14:14 (PBO:Low dose:High dose). Similarly, variations on the S100A9 CSF levels observed in these patients show a comparable profile after 24 weeks of treatment; in this regard, only 6 patients showed a clear increase on S100A9 levels while the others are stable or show a significant decrease. This observation might be compatible with the preclinical data that shows that vafidemstat decreases S100A9 levels in the CNS. If confirmed at the end of the study, this observation could pave the way to consider S100A9 a surrogate pharmacological biomarker for vafidemstat.

Demographic data		
nº of patients		104
Alzheimer Diagnosis	Mild Moderate	51 (49 %) 53 (51%)
Sex	Male Female	43 (41.35 %) 61 (58.65 %)
Age	Median (Min , Max)	73,00 (50/85)
Race	Black Caucasian Other	1 (0.96%) 101 (97.12%) 2 (1.92%)
Weight(Kg)	Median (Min , Max)	68.79 (46.8 / 104.6)
Height (cm)	Median (Min , Max)	164 (150/185)
BMI	Median (Min , Max)	25.6 (20.8/30.6)

	Month of vafidemstat treatment					
Visit	0	1	2	3	6	12
1	104					
5		91				
6			77			
7				65		
10					36	
17						5

Study-drug related TEAEs (ADRs) by SOC and PT (n= 104)	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**4 (3.84 %) 5**
Neutropenia	2 (1.92%) 2
Monocytosis	1 (0.96%) 1
Thrombocytopenia	1 (0.96%) 1
Leukopenia	1 (0.96%) 1
Cardiac Disorder	**6 (5.77 %) 6**
Ear and labyrinth disorders	**1 (0.96%) 1**
Gastrointestinal disorders	**4 (4.80 %) 4**
General disorders and administration site conditions	**2 (1.92%) 2**
Infections and infestations	**1 (0.96%) 1**
Investigations	**11 (13.46 %) 14**
Neutrophil count decreased	2 (1.92%) 2
Monocyte count increased	1 (0.96%) 1
Muscle enzyme increased	1 (0.96%) 1
Electrocardiogram QT prolonged	1 (0.96%) 1
Electrocardiogram PR prolongation	1 (0.96%) 1
Gamma-glutamyltransferase increased	1 (0.96%) 1
Hepatic enzyme abnormal	1 (0.96%) 1
Weight decreased	2 (1.92%) 2
Blood creatine phosphokinase increased	2 (1.92%) 2
Haematology test abnormal	1 (0.96%) 1
Electrocardiogram T wave inversion	1 (0.96%) 1
Metabolism and nutrition disorders	**1 (0.96%) 1**
Musculoskeletal and connective tissue disorders	**1 (0.96%) 1**
Nervous system disorders	**6 (5.77 %) 6**
Psychiatric disorders	**4 (3.84%) 5**
Renal and urinary disorders	**2 (1.92%) 2**
Skin and subcutaneous tissue disorders	**3 (2.88%) 3**
Vascular disorders	**1 (0.96 %) 1**



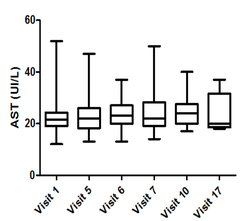


Figure 2. Recruitment status, demographics and safety. Baseline demographics of 104 recruited subjects by mid-June is provided as it is also the current distribution number of patients per completed visit. AEs observed so far and referred as SOC Terms correspond only to those with a potential causality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

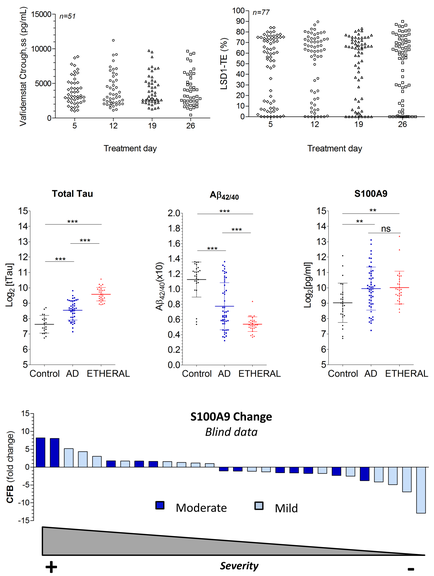


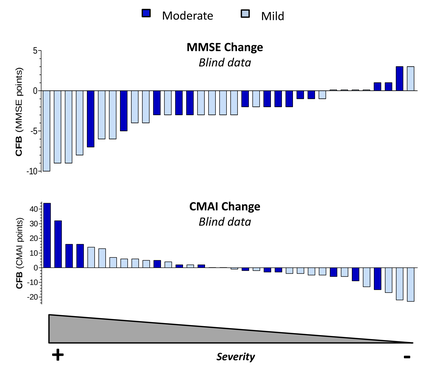
Figure 3. Biomarkers and PKPD parameters. Plasma vafidemstat's PK (Cthrough) and LSD1 Target Engagement (TE) in blood PBMCs were determined at pre-dose on days 5, 12, 19 and 26 of treatment. Data below LOQ not shown. Data correspond to blind data of the available samples as per mid-June cut-off. Observed values are in line with previous Phase I and demonstrate that steady state values in both parameters are achieved already at day 5.

CSF biomarkers Aβ 42/40 ratio (x10), Total Tau and S100A9 protein levels were assayed at baseline and compared with 90 biobank samples from healthy (30) and mild and moderate AD subjects (60) to better characterize the ETHERAL patient population.

Moreover, blind individual patient S100A9 Change from Baseline (CFB) is shown as fold induction after 24 weeks treatment.

In all cases, S100A9 CSF protein levels were measured as S100A8/A9 heterodimer.

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), Mini-mental State Examination (MMSE), Cohen-Mansfield Agitation Inventory (CMAI) or Apathy Evaluation Scale (AES-C). Volumetric MRI is also being performed. Figure shows as example the individual differences as Change from Baseline (CFB) in absolute value observed on MMSE and CMAI of blinded patients after 24 weeks of treatment.



Conclusions

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 1 month, no clinically relevant hematological safety signals 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.

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