#630: TOPLINE ETHERAL PHASE II TRIAL DATA

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OBJECTIVES:

ETHERAL is a randomized, double-blind, parallel-group, placebo-controlled, 12-month phase II trial to evaluate safety and tolerability of two doses of vafidemstat (0.6 mg & 1.2 mg) in a mild-to-moderate Alzheimer's disease (AD) population. Interim 6-month analyses from ETHERAL-EU, presented at AAT-AD/PD-2020, confirmed vafidemstat was safe and well-tolerated. Topline 12-month results from ETHERAL-EU and ETHERAL-US, including safety, efficacy and biomarker data are presented in this poster.

METHODS:

ETHERAL-EU and ETHERAL-US trials were conducted under essentially identical protocols, including a 6-month double-blind placebo-controlled treatment period followed by a double-blind non-placebo controlled 6-month extension period, where placebo subjects were randomized to vafidemstat 0.6 or 1.2 mg. Subjects previously treated with vafidemstat maintained their original dosing (Fig. 1).

	Gender N (%)	Age avg (min-max)	Race N (%)	AD severity N (%)
ETHERAL-EU N=116	Male 50 (43%) Female 66 (57%)	73.5 (50 - 85)	Caucasian 111 (96%) Other 5 (4%)	Mild 60 (52%) Moderate 56 (48%)
ETHERAL-US N=24	Male 8 (33%) Female 16 (67%)	78 (53 - 85)	Caucasian 18 (75%) Other 6 (25%)	Mild 13 (54%) Moderate 11 (46%)
Both cohorts N=140	Male 58 (41%) Female 82 (59%)	75.75 (50 - 85)	Caucasian 129 (92%) Other 11 (8%)	Mild 73 (52%) Moderate 67 (48%)

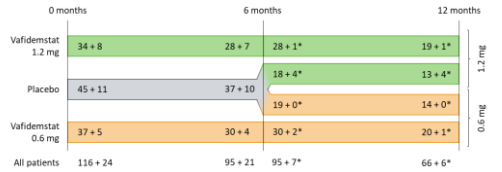

Fig. 1: *Demographics and subject randomization for ETHERAL (ETHERAL-EU + US studies). * ETHERAL-US was terminated prematurely due to COVID-19 pandemic*

HIGHLIGHTS:

- Primary endpoint met: Vafidemstat treatment for 12 months was safe and well tolerated in AD patients
- Vafidemstat reduced CSF levels of the well-described inflammatory biomarker YKL-40
- CSF levels of NFL, a neuronal damage marker, showed also a trend in reduction with treatment
- Preliminary analysis shows no effect of vafidemstat treatment on clinical scales compared to placebo

RESULTS:

116 recruited subjects were randomized into ETHERAL-EU and 24 subjects in ETHERAL-US, for a combined N = 140. ETHERAL baseline demographics and subject randomization are presented in Fig.1.

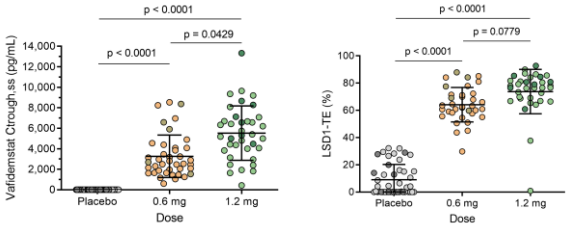

Fig. 2: *Drug exposure and LSD1 occupancy at day 26, compiled data (light color for ETHERAL-EU and dark color for ETHERAL-US).*

Vafidemstat was safe and well tolerated, with only 2 drug-related SAEs reported in the placebo and 2 in the treatment arms. No clinically relevant differences were observed on the number of drop-outs, AEs or SAEs between study arms (Table 1).

Table 1: *Distribution of AEs and SAEs*

ETHERAL-EU and US trial AEs (N=140) Number of patients (%) event count	Placebo-controlled period			Non placebo-controlled period	
	Placebo (N=56)	Vafidemstat 0.6 mg (N=42)	Vafidemstat 1.2 mg (N=42)	Vafidemstat 0.6 mg (N=51)	Vafidemstat 1.2 mg (N=51)
Dropout patients	9 (16%)	8 (19%)	7 (17%)	15 (29%)	15 (29%)
Total AEs	40 (71%) 140	39 (93%) 146	37 (88%) 168	35 (69%) 95	44 (86%) 139
Drug-related AEs	17 (30%) 30	16 (43%) 34	17 (50%) 38	11 (22%) 15	14 (27%) 23
Total SAEs	4 (9%) 4	3 (8%) 3	4 (12%) 8	4 (8%) 5	3 (6%) 4
Drug-related SAEs	1 (2%) 2	-	1 (3%) 1	1 (2%) 1	-

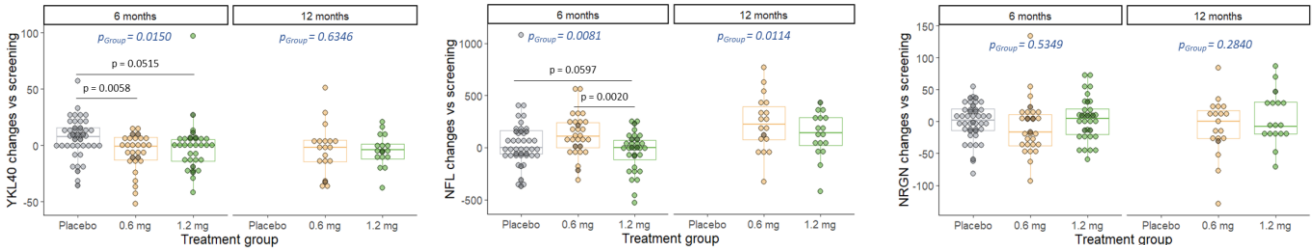

Fig. 3: *Differences for CSF biomarkers and ADAS-Cog14 data (Placebo in grey, 0.6 mg in orange and 1.2 mg in green and, light color for ETHERAL-EU and dark color for ETHERAL-US). ANCOVA analysis comparing the three arms during the initial 6-month period (placebo-controlled period). Additionally, a mixed model repeated measures (MMRM) comparison between both vafidemstat doses through the 12-month period is presented to evaluate non-placebo controlled vafidemstat dose differences. ANCOVA/MMRM significance of global group comparisons are shown in blue, while individual differences between groups are represented in black (only significant differences or with a clear trend are showed).*

Treatment exposure between both vafidemstat doses (0.6 and 1.2 mg) was proportional and both doses achieved high LSD1 target engagement (Fig. 2). No statistically significant differences between study arms were observed during the placebo-controlled 6-month period on the ADAS-Cog14 (Fig. 3), MMSE or CMAI scores in any of the trials. Complete analysis of the data, as well as other endpoints such as the CogState Brief Battery or volumetric MRI are still ongoing.

Nevertheless, ETHERAL has provided human pharmacological evidence of vafidemstat's effects in the CNS. As seen in Fig. 3, vafidemstat significantly reduced overall protein levels of proinflammatory YKL40 in CSF during the 6-month placebo-controlled period. These reductions in YKL40 CSF levels were maintained after 12-month treatment (Fig. 3).

The impact of vafidemstat is further supported by a clear trend in reducing CSF levels of the neurofilament light chain (NFL), a marker of neuronal damage, in the high dose group. There were no significant differences in CSF-measured neurogranin globally or between groups at 6- or 12-months (Fig. 3).

CONCLUSION:

ETHERAL is the first epigenetic Phase II trial in AD. 12-month treatment data supports that vafidemstat was safe and well-tolerated in a mild-to-moderate late onset AD. CSF levels of inflammation (YKL40) and neuronal damage (NFL) biomarkers were reduced by the treatment.

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