ADVANCES IN ALZHEIMER'S AND PARKINSON'S THERAPIES AN AAT-AD/PD™ FOCUS MEETING

2 - 5 APRIL 2020 | VIENNA, AUSTRIA

SYMPOSIUM 37 - TREATING AD: ALTERNATIVES TO IMMUNOTHERAPY II

VAFIDEMSTAT IN ALZHEIMER'S DISEASE: INITIAL 6-MONTH ETHERAL DATA

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ORYZON

Conflict of Interest

Due to the exceptional situation related to COVID-19 lock-down, this presentation will be led by Dr. Michael Ropacki

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- President of Strategic Global Research & Development (SGR&D)

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Solid Evidence of an Epigenetics Axis in CNS Diseases

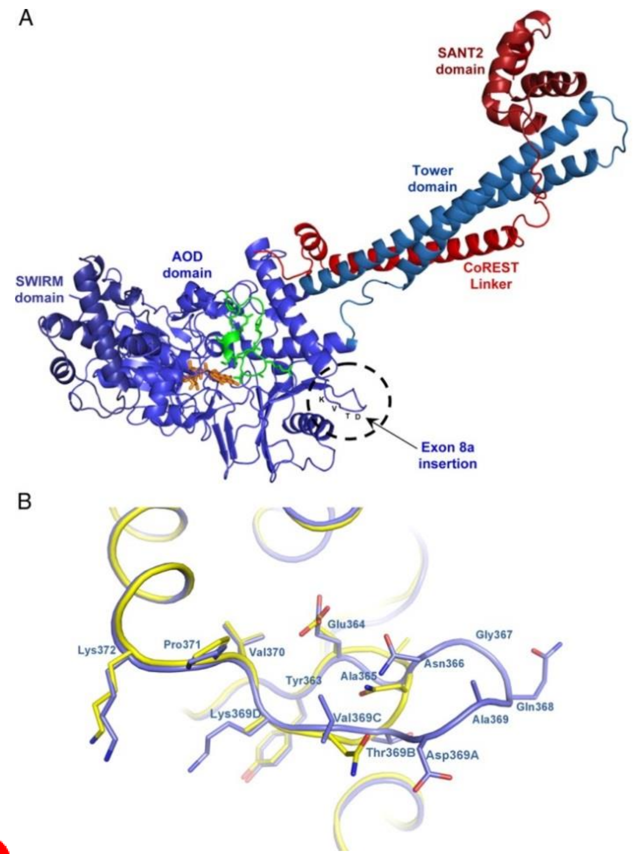
- **EPIGENETICS:** Epigenetic mechanisms modify chromosome functioning, chromatin 3D conformation and control gene expression

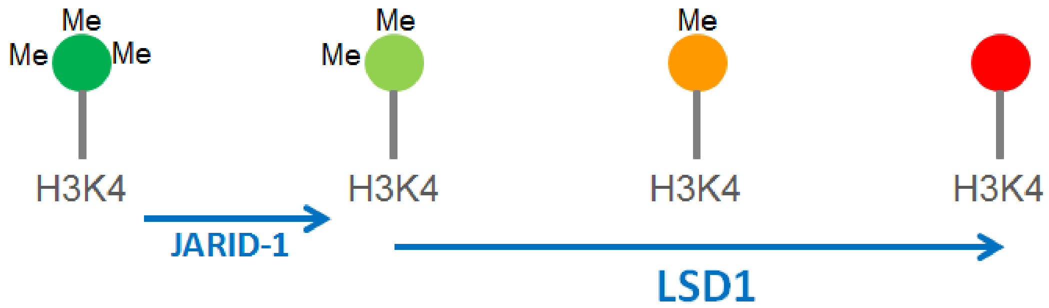
- Many features of psychiatric and neurological diseases are consistent with an epigenetic dysregulation, such as:
  - Discordance in monozygotic twins
  - Late age of onset
  - Parent-of-origin
  - Gender effects
  - Fluctuating disease course

Psychiatric disorders		Neurodegenerative disorders	
Observation	Species/ Sample / Gene	Observation	Species/ Sample / Gene
Major Depression HDAC inhibition appears to play a role in major depression. SAHA partially rescues the depressive-like behavior of Crtc1–/– mice. Meylan et al., 2016	Crtc1	**Alzheimer's disease** APP promoter hypomethylation in patients (Miller, 2003)	Human brains
Depression Histone methylation is also implicated in depression. Peña and Nestler 2018	BDNF and others	**Alzheimer's disease** Hypomethylation of promoters of ribosomal genes with aging (Decottignies and d'Adda di Fagagna, 2011)	Human lymphocytes
Schizophrenia. Altered promoter methylation of dopamine receptor genes , serotonin receptors and serotonin transporter genes were reported in SCZ patients. Swathy & Banerjee 2017	DRD4, DRD5 and DRD2/HTR1A and HTR2A /5-HTT	**Alzheimer's disease** Decrements in DNA methylation (Al-Mahdawi, et. al., 2014)	Human prefrontal cortex
Schizophrenia. Haploinsufficiency of a histone methyltransferase reported to be linked to human SCZ. Inhibition of LSD1 restores PFC connectivity and working memory in SCZ mice. Mukai et al., 2019	SETD1A / **LSD1**	**Alzheimer's disease** Differences in DNA methylation in a twin pair discordant (Al-Mahdawi, et. al., 2014)	Human temporal neocortex
Autistic Spectrum Disorder. Haploinsufficiency of the SHANK3 gene is causally linked to autism spectrum disorder. HDAC and LSD1 inhibition restore the Shank3 phenotype. Qin et al 2018. Zhen Yan SFN-2019	SHANK3 / **LSD1**	**Parkinson Disease** Reduced SNCA methylation in substantia nigra of PD patients	SNCA
Autistic Spectrum Disorder. Increased GTF2I dosage represses key genes involved in intellectual disability, autism and neuronal function by associating with lysine demethylase 1 (LSD1), a key chromatin modifier, and found that LSD1 inhibition rescues GTF2I-dependent alterations	GTF2I / **LSD1**	**Parkinson Disease** SNCA gene silencing mediated by histone methylation (Nalls et. Al., 2014)	SNCA
Bipolar Disorder: Monozygotic twins discordant for DNA meyhylation of suspected key genes highly expressed in the pituitary gland and the substantia nigra	Humans: PPIEL gene / SLC6A4 gene / KCNQ3 gene	**Parkinson Disease** HDAC inhibitors are neuroprotective against α-synuclein mediated neurotoxicity in PD animal models (IPDGC, 2011)	LRRK2

LSD1, an Epigenetic Chromatin Remodeling Enzyme With a Strong Role in CNS

- Lysine specific histone demethylase 1 (LSD1), aka KDM1A, removes methyl marks at mono- and dimethyl-H3K4 (histone H3 lysine 4) and H3K9 (histone H3 lysine 9). Also has scaffolding role in various TFs Complexes
- LSD1 plays a very important role in the development and function of the CNS, regulating neural stem cell proliferation and neuronal development
- LSD1/CoREST (as part of a complex) mediates the repression of neuronal-specific genes and its disassembly is needed for differentiation into mature neurons
- RNA-Seq and scRNA-Seq analysis identifies **LSD1 as the most abundant Histone demethylase in the frontal cortex**
- LSD1 binds in vivo in genomic regions that overlap with those of different confirmed CNS risk genes
    - LSD1 inhibition rescues different phenotypes in genetic models of schizophrenia and autism





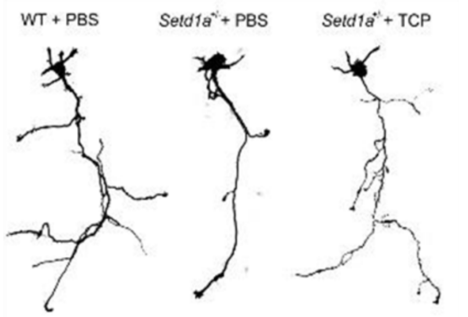
Vafidemstat – a Phase II Compound with Broad CNS Potential

- Vafidemstat is a **small molecule** LSD1 inhibitor optimized for CNS
- **Excellent Pharmacology**. High **oral** bioavailability. Highly **Brain Penetrant**
- **Positive** results in **7 different animal models** and in i*n-vitro* models
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Aggression / Agitation
  - Others
- Epigenetic **MoA** that modulates **neuroinflammation** and expression of key **plasticity neuronal genes**
- Biomarkers identified
- **Good Safety in humans in Phase I and II trials with +250 participants** so far
- **BBB penetrance** and (indirect) human brain target engagement established
- Pharmacologically active in humans

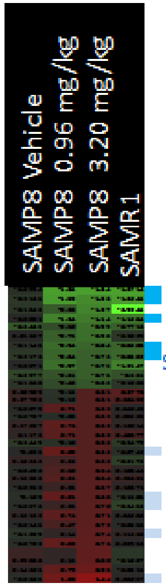
An Upstream Epigenetic Mechanism with Dual Activity: Antinflammatory and Prosynaptic

- Vafidemstat **up-regulates** genes associated with **Neuroplasticity & Cognition**
- Vafidemstat **reduces** the expression of **inflammatory** genes including S100A9 and many others

LSD1 Inhibition Rescues the Axon Branching Deficits in the Setd1a +/-Mice



In *in-vitro* axon branching rescue assays iadademstat (ORY-1001) was 1000-fold more potent than TCP



Inflammation signature genes

Cognitive function, neuroplasticity and memory

Vafidemstat potently **down-regulated** the expression of a subset of genes related to immune reaction and **inflammation as S100A9** involved in OPC defective remyelination

Genes **up-regulated** in SAMP8 mice by vafidemstat included

Baiap3: involved in retrograde trafficking

Prph: mutated in Amyotrophic Lateral Sclerosis (ALS),

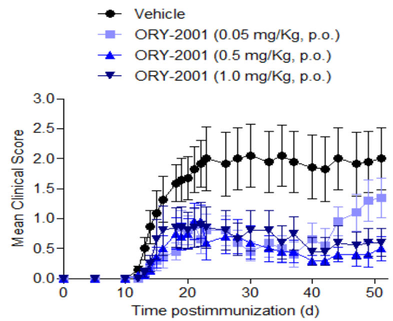
Fabp7: upregulation in drosophila favors long term memory consolidation

Doc2a: activity-dependent modulator of excitatory synaptic transmission, relevant to memory formation

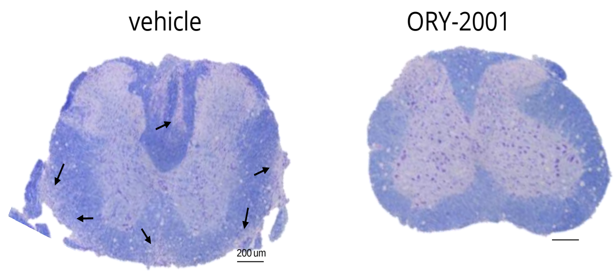
Kremen2 and **Rspo1**, regulators of the WNT pathway

Prosynaptic

Anti-inflammatory



therapeutic treatment (p.o.)



Vafidemstat is also known as ORY-2001

Current human safety data

Vafidemstat has proven to be **safe and well tolerated** in several Phase I and Phase II clinical trials – over 250 volunteers & patients to-date

- **Phase I:** +100 healthy volunteers **Phase I (SAD+MAD) study →** No hematological impact at the planned doses
- **Multiple Phase II trials (i.e., AD, ADHD, ASD, BPD and MS) with no safety signals to date***
  - Approximately **250 subjects** dosed with vafidemstat, and of them:
    - ~ 180 subjects treated for more than 1 week with a dose higher than 0.5 mg
    - ~ 150 subjects treated for more than 2 months with a dose equal or higher than 0.6 mg (~ 80 treated at 1.2 mg)
    - ~ 85 treated for more than 6 months with a dose equal or higher than 0.6 mg (~ 50 treated at 1.2 mg)
    - ~ 40 treated for more than 12 months with a dose equal or higher than 0.6 mg (~ 20 treated at 1.2 mg)
    - 1 with more than 18 months at 1.2 mg

** Includes safety data of REIMAGINE-AD and ETHERAL to be further disclosed in this presentation*

Vafidemstat Efficacy in AD patients

REIMAGINE-AD – Efficacy in AD agitation and aggression

- A single center, open-label, 1-arm, **24-week study** to evaluate the efficacy, safety and tolerability of vafidemstat in agitation and aggression in Alzheimer's Disease
- Primary Objective: **Investigate the efficacy of vafidemstat in treating AD agitation and aggression**
- Secondary Objectives:
  - Evaluate the safety and tolerability of vafidemstat in an AD population
  - Investigate other changes on behavior, cognition and caregiver burden
- N = 12 patients

Screening Period	**Open-label Treatment period**											**Post-Treatment Follow-Up Period**
Visit 0	Visit 1 (Baseline)	Phone contact 1	Visit 2	Phone contact 2	Visit 3	Phone contact 3	Visit 4	Visit 5/EOS	Visit 6/EOS	Visit 7/EOS	Visit 8/EOS	FUp
Day-7 ot -1	Day 1±1	Day 5±2	Day 14±2	Day 19±2	Day 28±2	Day 42±2	Day 56±7	Day 84±7	Day 112±7	Day 140±7	Day 168±7	Day 196±7
Screening, Selection and confirmation	**Vafidemstat 1.2mg**											**Safety Follow**
1 Week	**24 Weeks**											**4 Weeks**

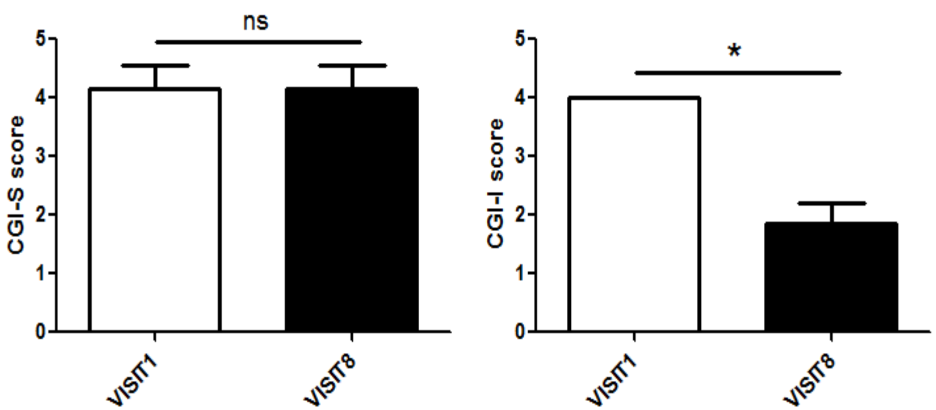
Please refer to R Bullock et al, VAFIDEMSTAT SAFETY AND EFFICACY IN ALZHEIMER-RELATED AGITATION & AGGRESSION: PHASE II REIMAGINE-AD 6-MONTH DATA (poster #668 AAT-ADPD2020) for additional information on the REIMAGINE-AD trial

Vafidemstat Efficacy: Reduction of AD Agitation and Aggression (REIMAGINE-AD)

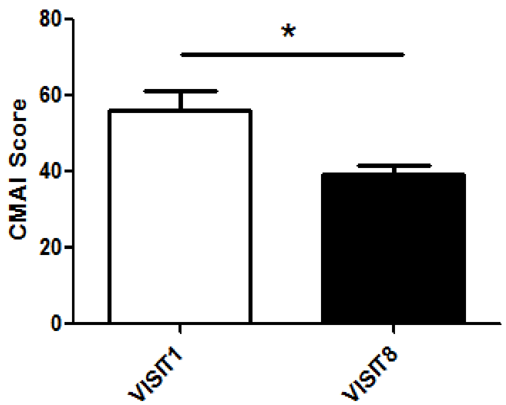
Agitation & aggression significantly decreased in moderate and severe AD patients after 6 months

- Statistical improvements observed across different Agitation/Aggression scales after 6 months of treatment:
  - CGI-I
  - CMAI
  - NPI-A/A
- Reduction in Agitation & aggression took longer in moderate to severe AD patients than previously observed in psychiatric indications (REIMAGINE trial)

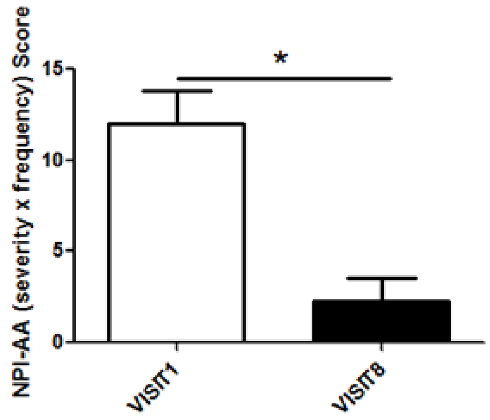
CGI



CMAI



NPI-A/A



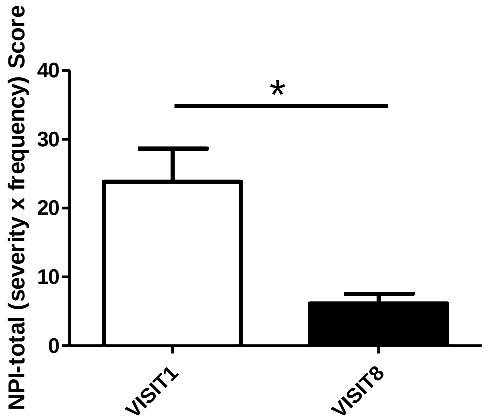
*One-tail paired Wilcoxon signed-rank test (*p<0.05)*

Vafidemstat Efficacy: Reduction of AD Agitation and Aggression (REIMAGINE-AD)

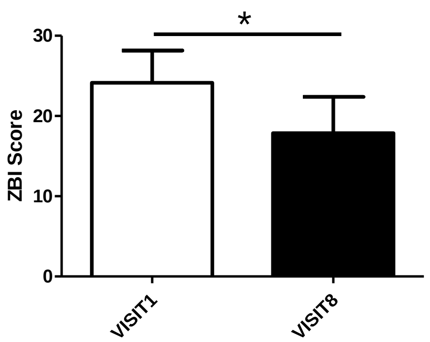
Total NPI also significantly decreased in moderate and severe AD patients after 6 months

- Total NPI was improved after 6 months of treatment
- The beneficial impact on AD patient behavior translated into reduced caregiver burden
- This was reflected in the NPI Emotional Distress scores, as well as the ZBI

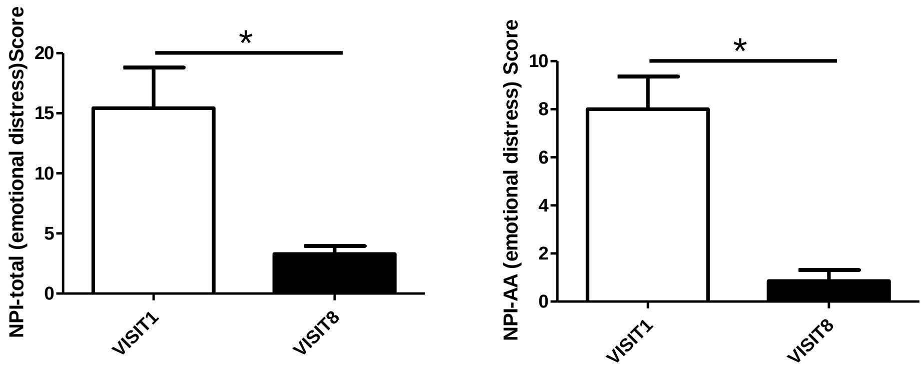
Total NPI



ZBI



NPI emotional distress

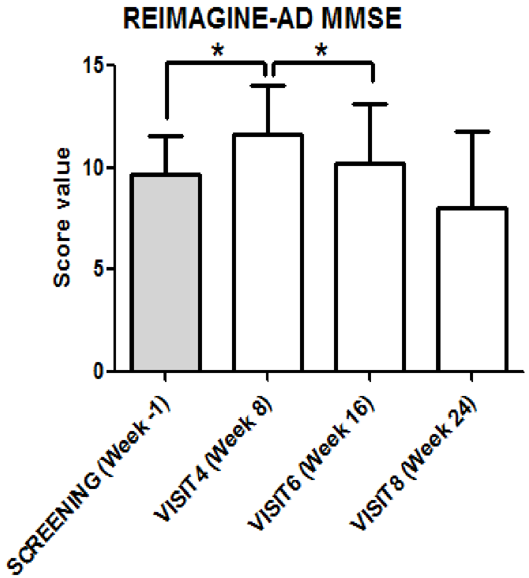


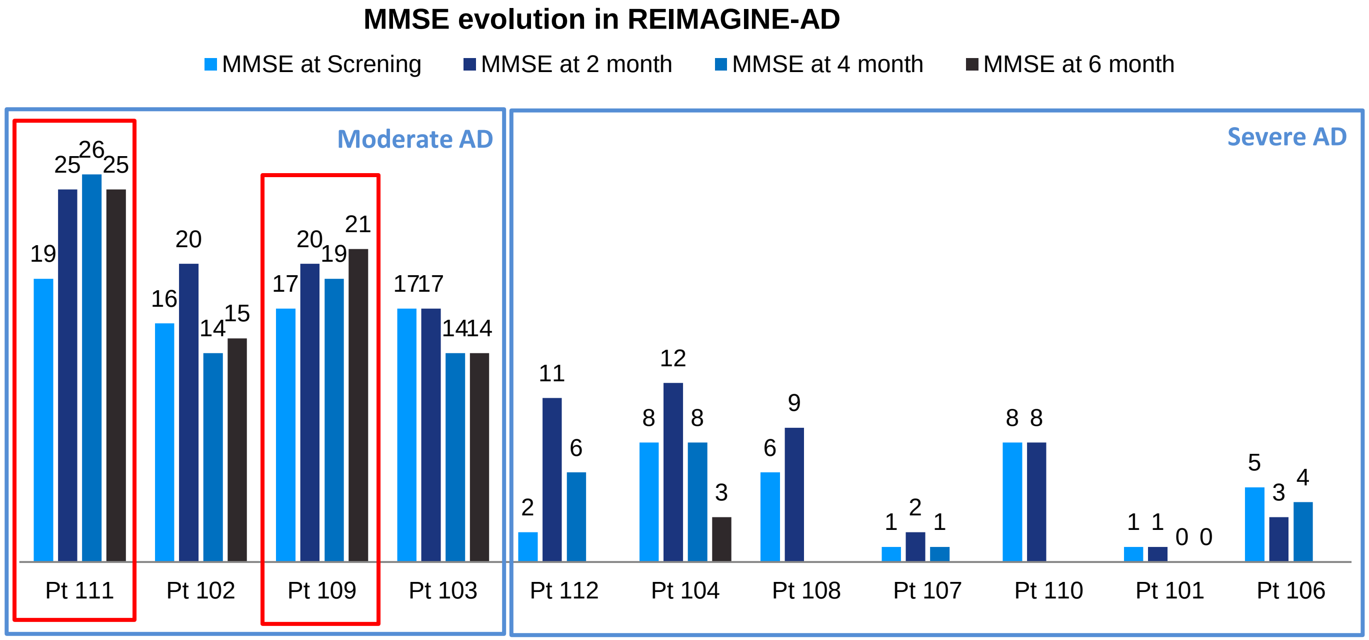
*One-tail paired Wilcoxon signed-rank test (*p<0.05)*

Vafidemstat Efficacy: Reduction of AD Agitation and Aggression (REIMAGINE-AD)

Transient observations in cognition

- A statistical improvement in MMSE was detected in severe and moderate AD patients by month 2, but it did not persist in the following months
- Two patients (Pt111 and Pt109), however, showed consistent MMSE improvement after 4 and 6 months (red boxes)
- Pt111 and Pt109 treatment has been extended to 12 months





*One-tail paired Student t test (*p<0.05; ns, not significant)*

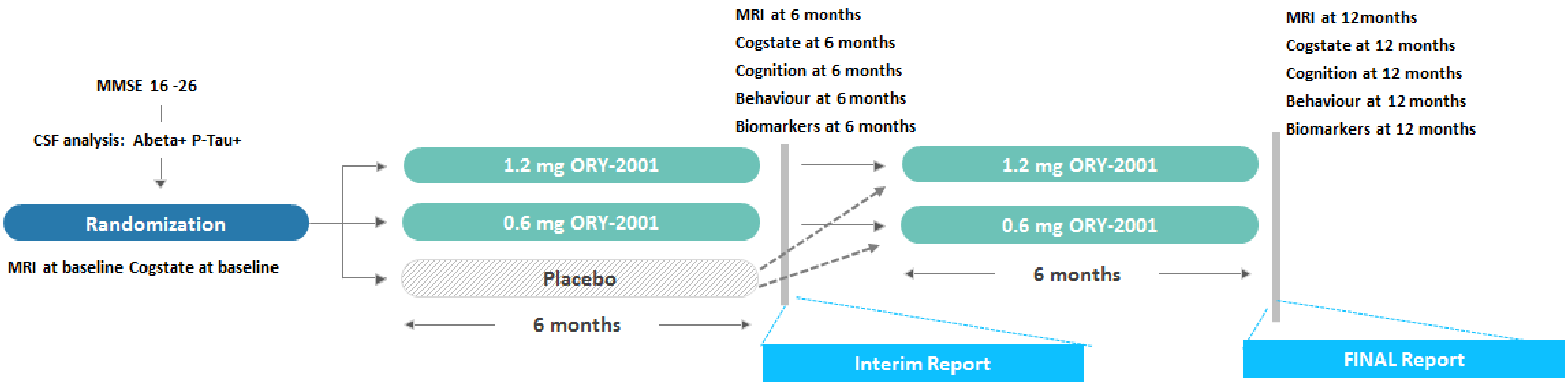
ETHERAL – Epigenetic THERapy in ALzheimer's Disease

Trial design: Double blind placebo controlled Phase IIa safety study to provide data to inform future Phase II/III studies

- **150 Mild to Moderate AD** patients (6+6 months)
  - **Primary Objective: → Safety & Tolerability**
  - **Secondary Objectives:**
    - Cognition/Agitation/Apathy/Depression/QoL /Volumetric MRI
  - **Biomarker guided study** (with 8 CSF Biomarkers)
    - Inflammation
    - Synaptic integrity
    - Others

- 17 sites; 117 patients
- Spain, France & UK
- **Recruitment finalized**

- Twin study in US: around 25 patients
- FPI recruited in May
- Recruitment ongoing



All data presented here is a preliminary analysis of the 6 month EU double blind cohort data

ETHERAL: Key Inclusion & Exclusion Criteria

Inclusion criteria

- Men and women **50-85 years of age**
- Probable AD **diagnosed according** to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association **(NINCDS-ADRDA) criteria**
- MMSE score at Screening and Baseline Visits of at least 16 and not greater than 26
- **Evidence of the AD pathophysiological process** indicated by decreased levels of amyloid AB and increased levels of total-Tau (t-Tau) protein or phosphorylated-Tau (p-Tau) protein in CSF
- Stable treatment with an acetylcholinesterase inhibitor and/or memantine before and during the trial or AD treatment naïve subjects that were required to remain off AD therapies throughout the trial
- Signed informed consent by patient (or legal representative, if applicable)

Exclusion criteria

- Hospitalisation or change of concomitant medication 1 month prior to Screening visit or during Screening Period
- Clinical, laboratory or neuroimaging findings consistent with: a) Other primary degenerative dementias, b) Other neurodegenerative diseases, c) Cerebrovascular disease, or d) Other central nervous system diseases
- A current DSM-5 diagnosis of major depression, schizophrenia or bipolar disorder
- Clinically significant, advanced or unstable disease that may interfere with evaluation or disability that may prevent the patients from completing all study requirements (for instance, blindness, deafness, severe language difficulty)
- Chronic drug intake of acenocoumarol, warfarin or digitoxin; antidepressants other than SSRIs or SSNRIs, neuroleptics or sedatives; memantine; systemic anticholinergics; nootropics; centrally active anti-hypertensive drugs; corticosteroids or immunosuppressant; antipsychotics; MAO inhibitors; or any medication acting directly on central nervous system that investigator consider relevant to the study. Treatment with anti-amyloid beta or anti-Tau protein monoclonal antibodies.
- Suicide attempt within the last year or significant risk of suicide

ETHERAL: Demographics

- No differences of distribution between groups were observed in any of the demographic variables
- No differences of distribution between groups were observed with regard to the time from diagnosis or disease stage (mild/moderate) at baseline

	0.6 mg	1.2 mg	PLACEBO	Total
Number of patients (% of Total)	38 (32%)	34 (29%)	45 (38%)	117 (100%)
Male (% in treatment arm)	13 (34%)	16 (47%)	21 (47%)	50 (43%)
Female (% in treatment arm)	25 (66%)	18 (53%)	24 (53%)	67 (57%)
Caucasian (% in treatment arm)	35 (92%)	33 (97%)	44 (98%)	112 (96%)
Asian (% in treatment arm)	1 (3%)	0	0	1 (1%)
Black (% in treatment arm)	1 (3%)	0	0	1 (1%)
Other (% in treatment arm)	1 (3%)	1 (3%)	1 (2%)	3 (3%)
Some school/blanck (% in treatment arm)	15 (39%)	14 (41%)	13 (29%)	42 (36%)
High School (% in treatment arm)	14 (37%)	8 (24%)	16 (36%)	38 (32%)
College (% in treatment arm)	6 (16%)	3 (9%)	8 (18%)	17 (15%)
University (% in treatment arm)	3 (8%)	9 (26%)	8 (18%)	20 (17%)
Age (mean±SD)	72.5±8.0	72.3±8.2	73.7±6.1	72.9±7.4
Weight (mean±SD)	67.2±10.2	67.4±11.9	69.3±14.1	68.1±12.2
Height (mean±SD)	162.8±8.8	163.5±11.5	165±9.9	163.9±10.0
BMI (mean±SD)	25.4±3.6	25.1±3.2	25.3±3.6	25.3±3.5

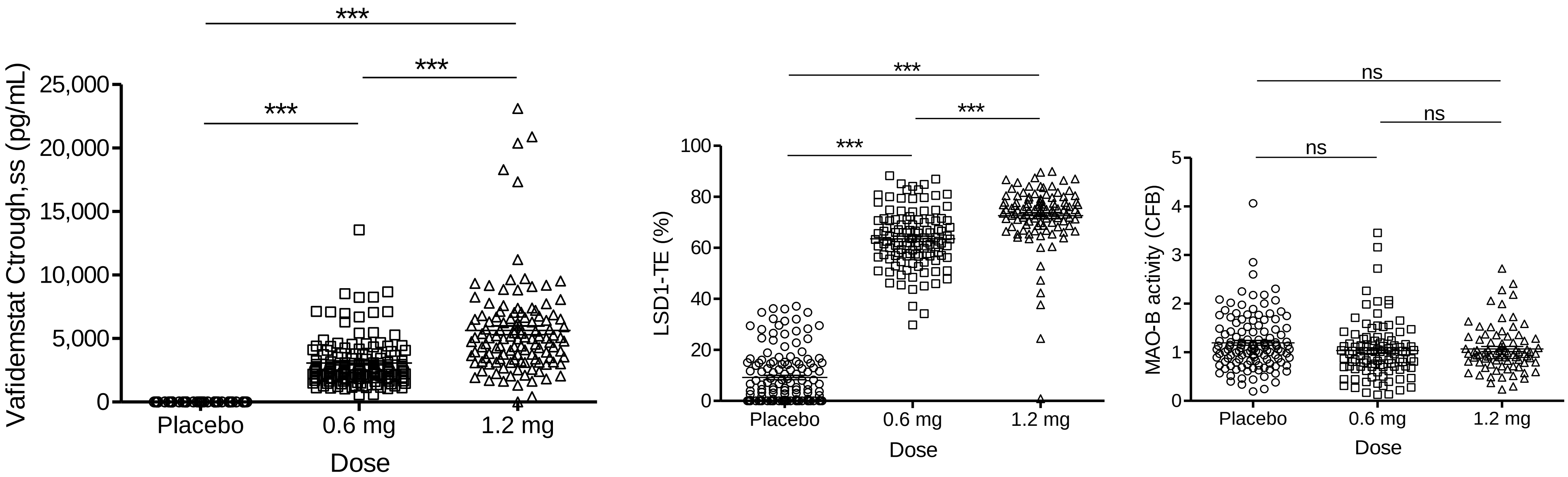
		FAS population (N=115)			
		0.6 mg (N=38)	1.2 mg (N=33)	Placebo (N=44)	Total (N=115)
Time from diagnosis (years)	n	38	33	44	115
	N. missing	0	0	0	0
	95% CI Mean	(1.83, 2.77)	(1.72, 4.03)	(2.06, 3.18)	(2.18, 3.00)
	Mean (SD)	2.30 (1.42)	2.88 (3.26)	2.62 (1.85)	2.59 (2.23)
	Median	2.17	1.82	1.93	1.97
	(Q1, Q3)	(1.03, 3.40)	(1.07, 2.59)	(1.28, 3.48)	(1.14, 3.40)
	(Min, Max)	(0.00, 5.85)	(0.21, 15.65)	(0.62, 7.99)	(0.00, 15.65)
	P-value Kruskal Wallis test				0,7544
Symptomatic stage of the disease at study start	Mild	22 (57.89%)	18 (54.55%)	23 (52.27%)	63 (54.78%)
	Moderate	16 (42.11%)	15 (45.45%)	21 (47.73%)	52 (45.22%)
	P-value Fisher test				0,8662

Fisher test (gender, education, stage of the disease); Kruskal Wallis test (age, weight, time from diagnose) or ANOVA test (Height, BMI).

ETHERAL: PK/PD Results

Vafidemstat acts as a selective LSD1 inhibitor in humans

- Pharmacokinetic results correlate with previous observations (Phase I data)
- No MAO-B inhibition detected in the PBMCs of AD patients, as expected from Phase I data
- Vafidemstat acts as a selective LSD1 inhibitor in humans at the therapeutic doses tested



*One-tail Student t test (***, p<0.001; ns, not significant)*
LSD1-TE: LSD1 Target Engagement

ETHERAL: Safety – Drop Outs & TEAEs

TEAEs and drop-outs are randomly distributed between study arms

		0.6 mg (N=38)	1.2 mg (N=34)	Placebo (N=45)	Total (N=117)
Drop-outs	**Mild**	1 (2.63%)	3 (8.82%)	1 (2.22%)	5 (4.27%)
	Moderate	6 (15.79%)	2 (5.88%)	6 (13.33%)	14 (11.97%)
	Total	7 (18.42%)	5 (14.71%)	7 (15.56%)	19 (16.24%)
	P-value Fisher test				**0.220**

		0.6 mg (N=38)	1.2 mg (N=34)	Placebo (N=45)	Total (N=117)
Patients with any TEAEs	Yes	37 (97.37%)	32 (94.12%)	37 (82.22%)	106 (90.60%)
	Overall number of TEAEs	138	155	131	424
	P-value Fisher test				**0.0633**
Patients with any serious TEAEs	Yes	3 (7.89%)	4 (11.76%)	4 (8.89%)	11 (9.40%)
	Overall number of TEAEs	3	9	4	16
	P-value Fisher test				**0.8531**
Patients with any related TEAEs (*)	Yes	17 (44.74%)	18 (52.94%)	16 (35.56%)	51 (43.59%)
	Overall number of TEAEs	32	41	30	103
	P-value Fisher test				**0.3080**
Patients with any serious TEAEs related to study drug (*)	Yes	0 (0.00%)	1 (2.94%)	1 (2.22%)	2 (1.71%)
	Overall number of TEAEs		1	1	2
	P-value Fisher test				**0.7480**
Patients with any severe TEAEs	Yes	2 (5.26%)	1 (2.94%)	4 (8.89%)	7 (5.98%)
	Overall number of TEAEs	2	3	5	10
	P-value Fisher test				**0.6266**

** Study drug relation Definite, Probable or Possible*

ETHERAL: Safety – Adverse Events

Vafidemstat treatment for 6 months was safe and well tolerated

- No differences were observed between study arms in the number of patients showing any AEs

	0,6 MG (n=38; 32%)	1,2 MG (n=34; 29%)	PLACEBO (n=45; 38%)	TOTAL (n=117; 100%)
Total patients with AEs (% of Total)	**38 (35.7)**	**32 (28.6)**	**40 (35.7)**	**112 (100)**
mild (% of Total/% in arm)	37 (34.3/97.4)	31 (28.7/96.9)	40 (37.0/100)	108 (100/96.4)
moderate (% of Total/% in arm)	19 (34.5/47.5)	18 (32.7/56.3)	18 (32.7/45.0)	55 (100/49.1)
severe (% of Total/% in arm)	1 (25,0/2,5)	0	3 (75,0/7,5)	4 (100/3,6)
Patients with AEs non-related to drug (% of Total/% in arm)	**37** (35.2/100)	**30** (28.6/93.8)	**38** (36.2/95.0)	**105** (100/93.8)
Blood & Lymphatic system disorders (% of Total/% in arm)	3 (27.3/8.1)	4 (36.4/13.3)	4 (36.4/10.5)	11 (100/10.5)
Laboratory Findings (ALL) (% of Total/% in arm)	14 (43.8/37.8)	13 (40,6/43.3)	5 (15,6/13.2)	32 (100/30.5)
Laboratory Findings (CBC) (% of Total/% in arm)	4 (80.0/10.8)	1 (20.0/3.3)	0	5 (100/4.8)
Psychiatric (% of Total/% in arm)	8 (24.2/21.6)	13 (39.4/43.3)	12 (36.4/31.6)	33 (100/31.4)
Patients with AEs drug related* (% of Total/% in arm)	**24** (34.3/63.2)	**21** (30,0/65,6)	**25** (35,7/62,5)	**70** (100/62,5)
mild (% of Total/% in arm)	15 (30.6/62.5)	17 (34.7/81.0)	17 (34.7/68.0)	49 (100/70.0)
moderate (% of Total/% in arm)	9 (45.0/37.5)	4 (20./19.0)	7 (35.0/28.0)	20 (100/28.6)
severe (% of Total/% in arm)	0	0	1 (100/4.0)	1 (100/1.4)
Blood & Lymphatic system disorders (% of Total/% in arm)	2 (22.2/8.3)	6 (66.7/28.6)	1 (11.1/4.0)	9 (100/12.9)
Cardiac disorders (% of Total/% in arm)	2 (25.0/8.3)	4 (50.0/19.0)	2 (25.0/8.0)	8 (100/11.4)
Gastrointestinal (% of Total/% in arm)	3 (33.3/12.5)	3 (33.3/14.3)	3 (33.3/12.0)	9 (100/12.9)
General & Administration (% of Total/% in arm)	4 (80.0/16.7)	1 (20.0/4.8)	0	5 (100/7.1)
Injury/poisoning (% of Total/% in arm)	5 (41.7/20.8)	4 (33.3/19.0)	3 (25.0/12.0)	12 (100/17.1)
Laboratory Findings (ALL) (% of Total/% in arm)	2 (11.1/8.3)	9 (50.0/42.9)	7 (38.9/28.0)	18 (100/25.7)
Laboratory Findings (CBC) (% of Total/% in arm)	0	4 (57.1/19.0)	3 (42.9/12.0)	7 (100/10.0)
Musculoeskeletical (% of Total/% in arm)	2 (66.7/8.3)	0	1 (33.3/4.0)	3 (100/4.3)
Nervous system (% of Total/% in arm)	3 (25.0/12.5)	2 (16.7/9.5)	7 (58.3/28.0)	12 (100/17.1)
Psychiatric (% of Total/% in arm)	6 (75.0/25.0)	0	2 (25.0/8.0)	8 (100/11.4)
Renal & urinary (% of Total/% in arm)	1 (25.0/4.2)	1 (25.0/4.8)	2 (50.0/8.0)	4 (100/5.7)
Skin & subcutaneous (% of Total/% in arm)	1 (20.0/4.2)	2 (40.0/9.5)	2 (40.0/8.0)	5 (100/7.1)
Vascular disorder (% of Total/% in arm)	2 (100/8.3)	0	0	2 (100/2.9)

Table only shows AEs categories with at least a 5% incidence in any of the study arms

** Study drug relation Definite, Probable or Possible*

ETHERAL: Safety – Vital Signs, Labs & ECG

No safety signals nor clinically relevant hematological impact observed after 6 months of treatment

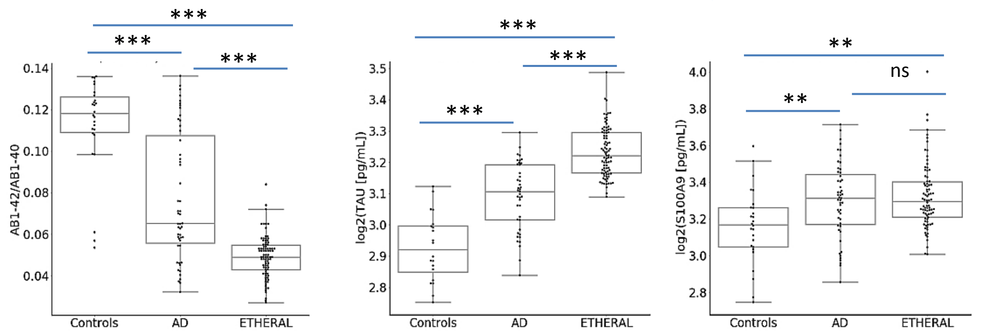
- No differences observed between study arms in any of the vital signs, ECG variable or laboratory safety evaluations
- No differences observed between groups in change over-time on any lab findings
- No clinically relevant hematological impact observed after 6-months of treatment.
- More specifically, in terms of **Hematology**:
  - **No clinically relevant differences between study arms** in blood cell populations including platelets or neutrophils, although in the high dose group a lab finding on reduction of absolute platelet count in the last visit has been observed
  - Individual cases of platelet or neutrophil reductions higher than 50% from baseline or achieving less than 100,000 platelets o 1.000 neutrophils per blood microliter were seen in this fragile population, which **distributed similarly between placebo and treated arms**.
    - Platelets: 3.8% of patients at the 1.2 mg high dose vs 2.1% in PBO arm
    - Neutrophils: 5% of patients dosed with the 1.2 mg high dose vs 8.5 % in the PBO arm

ETHERAL: CSF Biomarkers – Abeta, t-Tau, p-Tau & S100A9

Vafidemstat MoA does not relate to Abeta or Tau CSF biomarkers

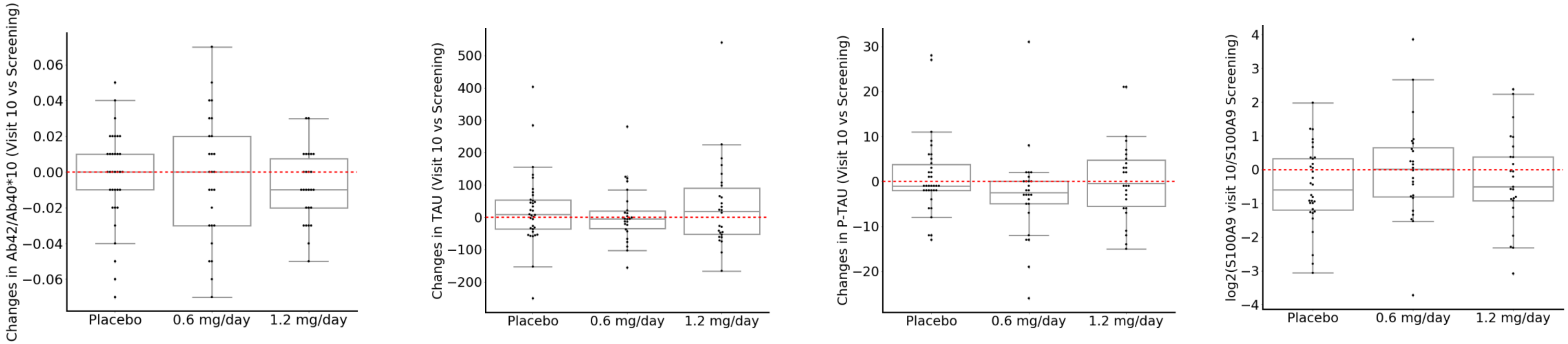
- A low Abeta ratio while higher levels of t-Tau, p-Tau are NIA-AA criteria for AD
- ETHERAL population aligns with NIA-AA criteria for AD diagnosis based on baseline CSF biomarker data (top graphs)
- No differences observed in the baseline distribution between treatment groups of the CSF AD diagnose biomarkers
- No differences on biomarker change after 6 months of treatment observed in any of the CSF biomarkers (bottom graphs)

Abeta ratio | **Total Tau (t-Tau)** | **S100A9**



*One-way ANOVA with post-hoc multiple comparisons Tukey test (**, p<0.01; ***, p<0.001) Control and AD correspond to healthy and AD CSF biobank samples*

Abeta ratio | **Total Tau (t-Tau)** | **Phosphorylated-Tau (p-Tau)** | **S100A9**



One-way ANOVA with post-hoc multiple comparisons Tukey test

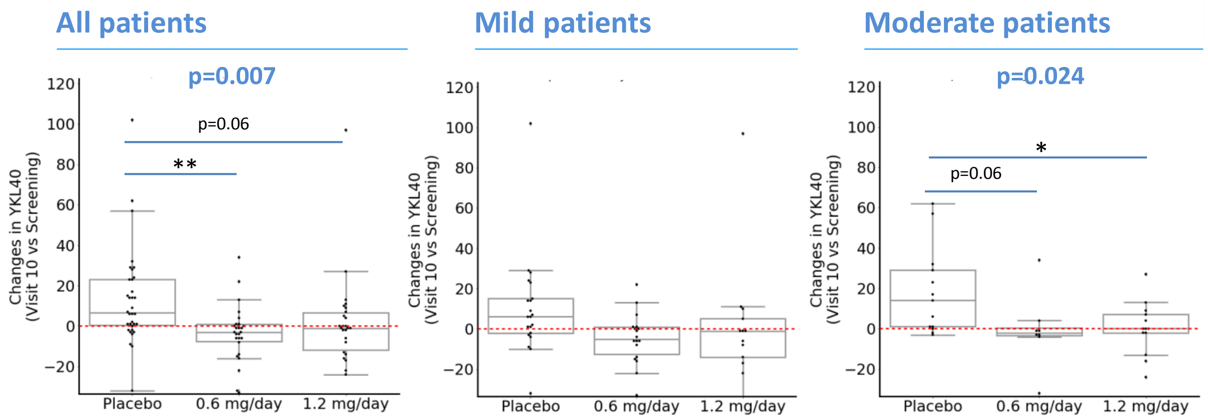
ETHERAL: CSF Biomarkers – YKL40

Vafidemstat treatment reduces the levels of the inflammatory CSF marker YKL40

- YKL40, a secreted inflammatory chitinase, has been described to be found in higher levels in AD patients
- No differences were observed in the distribution between treatment groups of YKL40 at baseline (data not shown)
- After 6 month of treatment, a treatment effect on the CSF levels of the inflammatory YKL-40 biomarker was observed (Table), which appears mainly driven by the effect in moderate patients (bottom graphs)

	Fixed effect	Treatment	P	Estimate	Standard Error	P	Lower	Upper
MMRM model - Type 3 Tests of Fixed Effects	Treatment		**0.0104**					
	Age at baseline		**0.6277**					
	MMSE stratification level		**0.4080**					
MMRM model - Least Squares Means	Treatment	0.6 mg		-3.0409	4.3884	**0.4903**	-11.7725	5.6906
		1.2 mg		0.2324	4.3309	**0.9573**	-8.3847	8.8494
		Placebo		13.3881	3.7589	**0.0006**	5.9090	20.8672
	MMSE stratification level	MMSE 16-19		5.6183	3.8254	**0.1458**	-1.9930	13.2296
		MMSE 20-26		1.4347	3.1162	**0.6465**	-4.7656	7.6350

Mixed-model repeated-measures: Higher Biomarker values indicates inflammation. Negative variation (V10-V1) means potential inflammatory improvement



Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population) (ANOVA p value in blue, not showed when not significant) with Post-hoc multiple comparisons Tukey test (, p<0.05; **, p<0.01)*

ETHERAL: CSF Biomarkers - Neurogranin

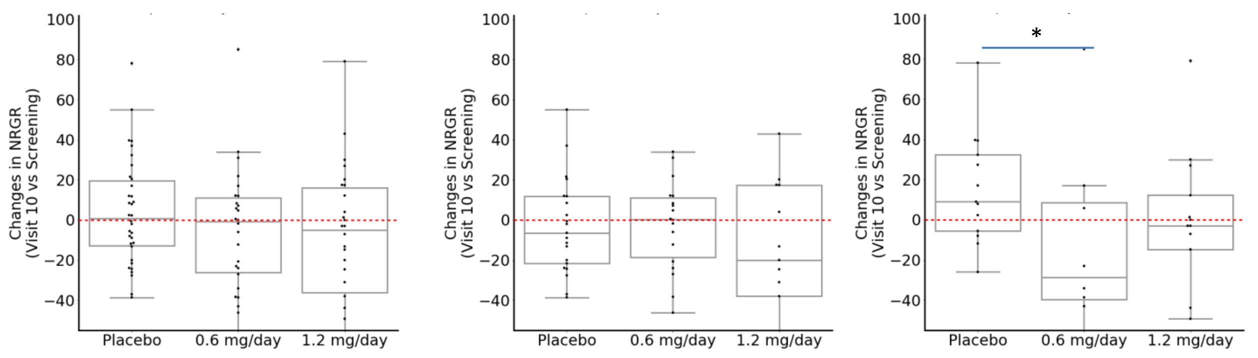
Vafidemstat treatment has a mild impact on the levels of the synaptic marker Neurogranin

- Neurogranin is a calmodulin-binding protein expressed primarily in the brain and considered a synaptic damage marker in neurodegenerative disorders
- Although no statistically differences were observed between groups, a trend to reduce CSF neurogranin levels was observed in vafidemstat treatment arms, achieving statistically significance in the low dose arm in moderate patients

	Fixed effect	Treatment	P	Estimate	Standard Error	P	Lower	Upper
MMRM model - Type 3 Tests of Fixed Effects	Treatment		**0.3644**					
	Age at baseline		**0.6230**					
	MMSE stratification level		**0.3651**					
MMRM model - Least Squares Means	Treatment	0.6 mg		-3.4979	6.3382	**0.5826**	-16.1088	9.1131
		1.2 mg		-9.3889	6.2416	**0.1364**	-21.8076	3.0298
		Placebo		2.4101	5.3978	**0.6564**	-8.3298	13.1500
	MMSE stratification level	MMSE 16-19		-0.2582	5.4533	**0.9624**	-11.1086	10.5922
		MMSE 20-26		-6.7262	4.4486	**0.1344**	-15.5775	2.1251

Mixed-model repeated-measures: Higher Biomarker values indicates synaptic damage. Negative variation (V10-V1) means potential neuronal improvement

All patients **Mild patients** **Moderate patients**



Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population) with Post-hoc multiple comparisons Tukey test (, p<0.05)*

ETHERAL: CSF Biomarkers - NFL

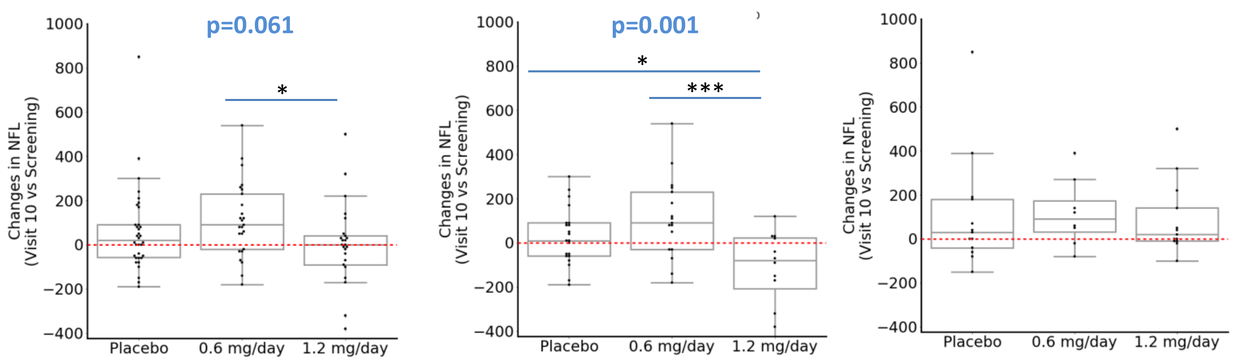
High dose vafidemstat treatment reduces the increase of NFL levels in CSF

- Plasma neurofilament light chain (NFL) has been proposed as a blood-based biomarker for neurodegeneration in AD
- CSF NFL levels increased through study visits in the 3 arms suggesting disease progression in all arms and subpopulations (Table)
- In mild patients, vafidemstat treatment at 1.2 mg was able to reduce the increase of NFL

	Fixed effect	Treatment	P	Estimate	Standard Error	P	Lower	Upper
MMRM model - Type 3 Tests of Fixed Effects	Treatment		**0.1542**					
	Age at baseline		**0.9657**					
	MMSE stratification level		**0.4605**					
MMRM model - Least Squares Means	Treatment	0.6 mg		5.2778	0.2940	**<.0001**	4.6852	5.8704
		1.2 mg		4.4370	0.3823	**<.0001**	3.6666	5.2075
		Placebo		4.6294	0.2911	**<.0001**	4.0427	5.2161
	MMSE stratification level	MMSE 16-19		4.9209	0.2789	**<.0001**	4.3588	5.4829
		MMSE 20-26		4.6420	0.2400	**<.0001**	4.1583	5.1256

Mixed-model repeated-measures: Higher Biomarker values indicates neurodegeneration. Negative variation (V10-V1) means potential improvement

All patients | **Mild patients** | **Moderate patients**

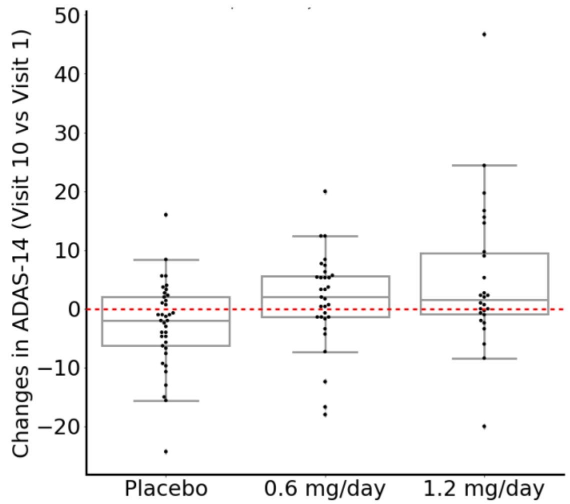


Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population (ANOVA p value in blue, not showed when not significant) with Post-hoc multiple comparisons Tukey test (, p<0.05; ***, p<0.001)*

ETHERAL: Preliminary Cognitive Efficacy- ADASCog14

6 month Interim analysis did not show cognitive improvement after vafidemstat treatment

- No statistically significant differences were expected or observed at 6 months in the ADAS-Cog14 between treatment arms
- No significant progression was seen through visits (change over time) in any of the treatment arms
- An unexpected Placebo behavior was observed and will require further analysis



	Fixed effect	Treatment	P	Estimate	Standard Error	P	Lower	Upper
MMRM model - Type 3 Tests of Fixed Effects	Treatment		**0.5844**					
	Age at baseline		**0.7276**					
	MMSE stratification level		**0.0565**					
	Visit		**0.5556**					
	Treatment-by-visit interaction		**0.1265**					
MMRM model - Least Squares Means	Treatment	0.6 mg		1.4637	1.1623	**0.2112**	-0.8456	3.7730
		1.2 mg		1.5945	1.1660	**0.1748**	-0.7209	3.9100
		Placebo		0.1494	1.0273	**0.8847**	-1.8922	2.1910
	MMSE stratification level	MMSE 16-19		2.3356	1.0025	**0.0220**	0.3443	4.3270
		MMSE 20-26		-0.1972	0.8299	**0.8127**	-1.8460	1.4516

Mixed-model repeated-measures: Higher ADASCog14 values indicates poor cognition. Positive variation (V10-V1) means therefore potential worse cognition

ETHERAL - Key Findings Summary

- ETHERAL-EU at 6 month has met the Primary Safety Endpoint
  - *Vafidemstat was safe and well-tolerated in a mild-to-moderate AD population*
- ETHERAL has produced interesting biomarker data that require further exploration
  - *Significant reduction in the CSF levels of YKL40 (an anti-inflammatory biomarker)*
  - *Improvements in the levels of neurogranin (a synaptic damage biomarker) and NFL*
    - *First in human data supporting decreased inflammatory biomarkers with vafidemstat treatment*
  - *No improvement in other biomarkers like Abeta, t-Tau, p-Tau or S100A9 detected*
- ETHERAL is not powered for efficacy analyses
  - *No differences observed between groups on the ADAS-Cog14*
  - *Additional analyses of the other efficacy endpoints is currently underway*
- ETHERAL study is still ongoing and patients are to be treated up to 12 months
  - *Current analysis of all data should be considered preliminary*
  - *Final 12 month data release for the EU study expected by Q2 2021*

Vafidemstat: Additional Take Home Messages

- Solid published evidence supports the role of epigenetics across several CNS disorders
- Key emerging role of LSD1 as a therapeutic target of interest in both psychiatric and neurodegenerative disorders
- Vafidemstat is a CNS optimized LSD1 inhibitor with a high brain penetrant potential
- Vafidemstat has a dual MoA with presynaptic and anti-inflammatory activities
- Several clinical trials confirmed vafidemstat's safety and tolerability in humans
- Phase IIa trials have demonstrated vafidemstat's safety, tolerability and efficacy in reducing agitation and aggression
  - *REIMAGINE: Significant improvement in agitation and aggression across three different psychiatric disorders (ASD, BPD and ADHD) after two months of treatment*
  - *REIMAGINE-AD: Vafidemstat produced significant improvement in agitation and aggression, as well as reducing caregiver burden after six months of treatment*