alzheimer's association
AAIC 20
ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®
July 27-31, 2020 > Virtual Event

Clinical Manifestations: Update On Pharmacologic And Nonpharmacologic Interventions

Vafidemstat in mild to moderate Alzheimer's disease: The ETHERAL study European cohort interim analysis

Roger Allan Bullock, MD.

alzheimer's association
AAIC 20

POLICIES

Photography is welcome in this presentation.

The information included in this presentation may be shared on other platforms.

Video and audio recording are prohibited.

Disclaimer

This document has been prepared by Oryzon Genomics, S.A. exclusively for use during the presentation. Oryzon Genomics, S.A. does not assume liability for this document if it is used with a purpose other than the above. The information and any opinions or statements made in this document have not been verified by independent third parties; therefore, no express or implied warranty is made as to the impartiality, accuracy, completeness or correctness of the information or the opinions or statements expressed herein. Oryzon Genomics, S.A. does not assume liability of any kind, whether for negligence or any other reason, for any damage or loss arising from any use of this document or its contents. Neither this document nor any part of it constitutes a contract, nor may it be used for incorporation into or construction of any contract or agreement. Information in this document about the price at which securities issued by Oryzon Genomics, S.A. have been bought or sold in the past or about the yield on securities issued by Oryzon Genomics, S.A. cannot be relied upon as a guide to future performance.

This communication contains forward-looking information and statements about Oryzon Genomics, S.A., including financial projections and estimates and their underlying assumptions, statements regarding plans, objectives and expectations with respect to future operations, capital expenditures, synergies, products and services, and statements regarding future performance. Forward-looking statements are statements that are not historical facts and are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates" and similar expressions. Although Oryzon Genomics, S.A. believes that the expectations reflected in such forward-looking statements are reasonable, investors and holders of Oryzon Genomics, S.A. shares are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Oryzon Genomics, S.A., that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the documents sent by Oryzon Genomics, S.A. to the Comisión Nacional del Mercado de Valores, which are accessible to the public. Forward-looking statements are not guarantees of future performance. They have not been reviewed by the auditors of Oryzon Genomics, S.A. You are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date they were made. All subsequent oral or written forward-looking statements attributable to Oryzon Genomics, S.A. or any of its members, directors, officers, employees or any persons acting on its behalf are expressly qualified in their entirety by the cautionary statement above. All forward-looking statements included herein are based on information available to Oryzon Genomics, S.A. on the date hereof. Except as required by applicable law, Oryzon Genomics, S.A. does not undertake any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise. This presentationis not an offer of securities for sale in the United States. The Company's securities may not be offered or sold in the United States absent registration or an exemption from registration. Any public offering of the Company's securities to be made in the United States will be made by means of a prospectus that may be obtained from the Company or the selling security holder, as applicable, that will contain detailed information about the Company and management, as well as financial statements.

Disclosure

Roger Bullock

Chief Medical Officer (CMO)

Dr. Bullock completed his pre-clinical medical training at Keble College, Oxford University, gaining a BA (Hons) in Physiological Sciences in 1978 (converted to MA in 1985). This was followed by clinical medical training at St Bartholomew's Hospital in London where he gained the MB.BS in 1981.

In 1990, he specialized in psychiatry, gained membership of The Royal College of Psychiatry and undertook postgraduate psychiatric training including higher specialist training in geriatric psychiatry which concluded in 1993.

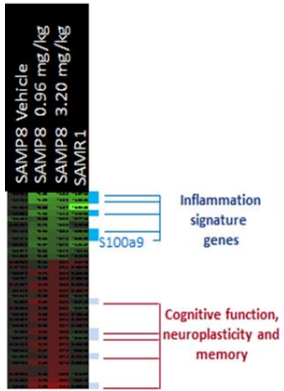
Dr. Bullock is considered a world KOL in the space of neurodegenerative diseases. He has extensive experience as clinical researcher, having participated in more than 70 clinical trials in Alzheimer's disease and other CNS conditions. Over his 30-year research career, he has authored and co-authored more than 100 peer-reviewed publications and book chapters in this domain and presented at numerous conferences. Recently he has been working as a consultant for companies active in the CNS space, including Lilly and Merck.

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

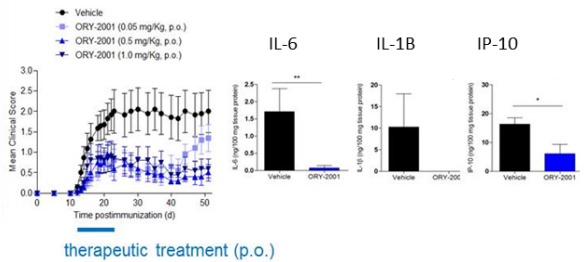
An Upstream Epigenetic Mechanism with Dual Activity: Antinflammatory and Prosynaptic

- Vafidemstat **up-regulates** genes associated with **Neuroplasticity & Cognition**
- Vafidemstat **reduces** the expression of **inflammatory** genes including S100A9 and others in SAMP8 AD model and IL-6, IL-1B and many others in MS models



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

Antiinflammatory



therapeutic treatment (p.o.)

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

Baiap3: involved in retrograde trafficking

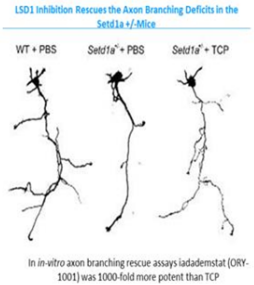
Prph: mutated in Amyotrophic Lateral Sclerosis (ALS)

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



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

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 ETHERAL to be further disclosed in this presentation*

ETHERAL – Epigenetic THERapy in ALzheimer's Disease

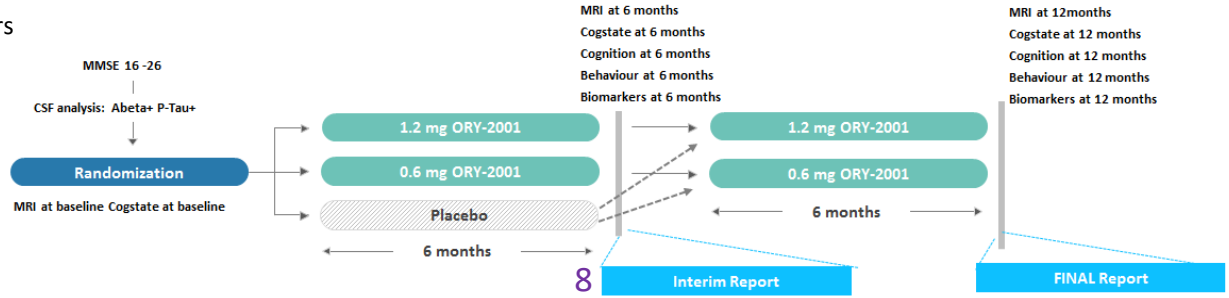
Trial design: Double blind placebo controlled Phase IIa safety study to provide data to inform future Phase II/III studies

- **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: 24 patients
- ✓ FPI recruited in May 2019
- ✓ **Recruitment finalized**

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: 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

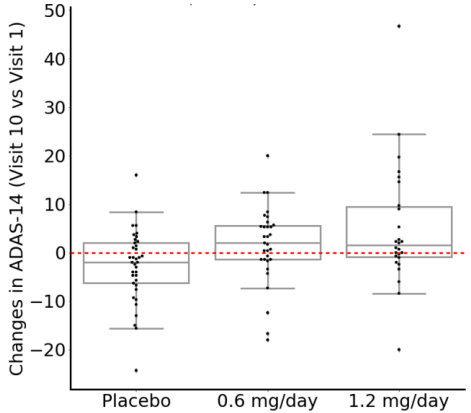
No safety signals nor clinically relevant hematological impact observed after 6 months of treatment

- 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: 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



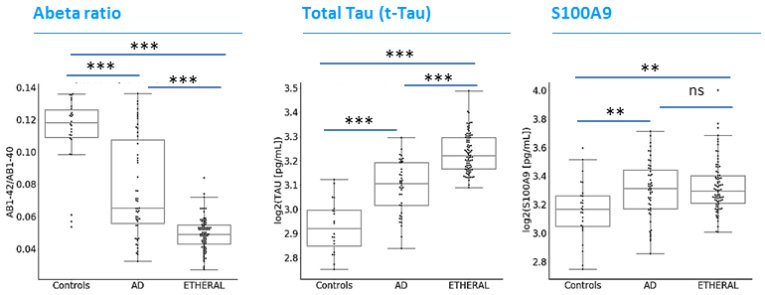
	Fixed effect	Treatment	P	Estimate	Standard Error	P	Lower	Upper
MMRM model - Type 3 Tests of Fixed Effects	Treatment		**0.5844**					
	Age at baseline		**0.7276**					
	MMSE stratification level		**0.0565**					
	Visit		**0.5556**					
	Treatment-by-visit interaction		**0.1265**					
MMRM model - Least 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

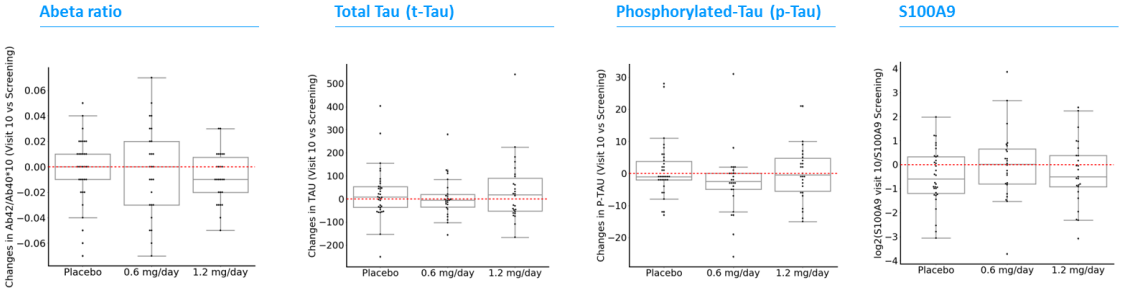
ETHERAL: CSF Biomarkers – Abeta, t-Tau, p-Tau & S100A9

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)



*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



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

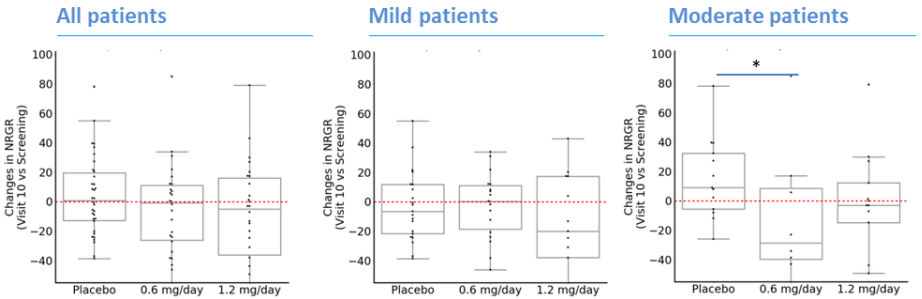
ETHERAL: CSF Biomarkers - Neurogranin

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



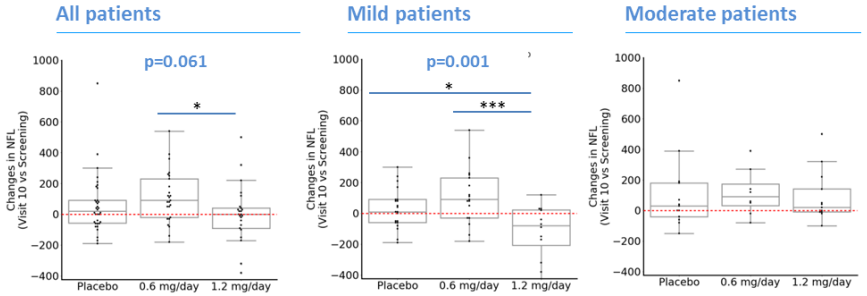
Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population with post-hoc multiple comparisons Tukey test (, p<0.05)*

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

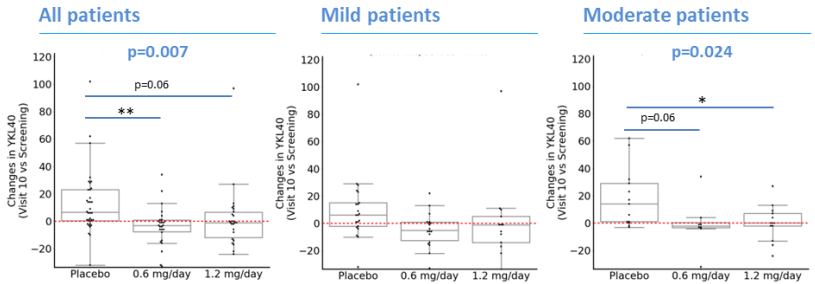
Sub-analysis. One-way ANOVA not corrected by multiplicity in total, mild or moderate population (ANOVA p value in blue, not showed when not significant) with Post-hoc multiple comparisons Tukey test (, p<0.05; ***, p<0.001)*

ETHERAL: 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



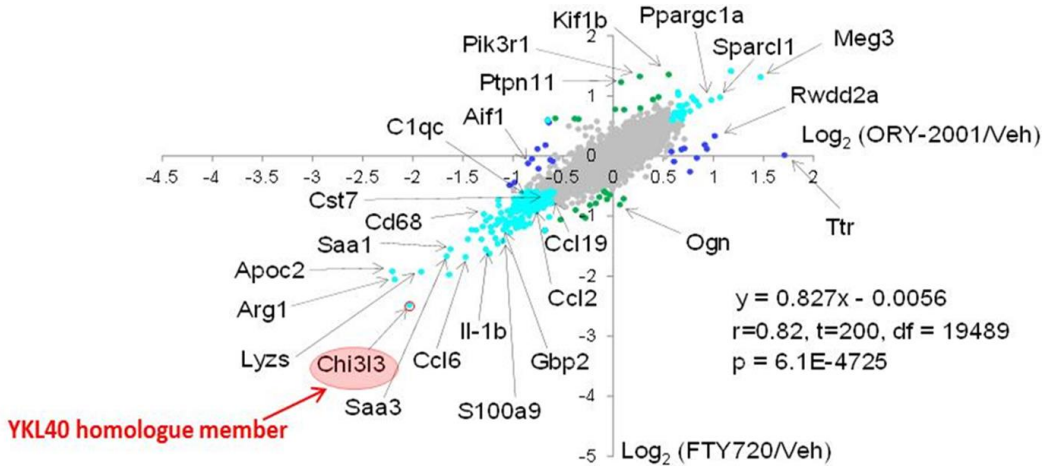
Mixed-model repeated-measures: Higher Biomarker values indicates inflammation. Negative variation (V10-V1) means potential inflammatory improvement

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)*

Vafidemstat and inflammation: Decrease of YKL40 in humans in keeping with previous preclinical data

Vafidemstat treatment reduces the levels of the inflammatory marker YKL40 in brain and spinal chord in the EAE multiple sclerosis model

- Chi3l3, a member of the same family, is strongly induced during the effector phase in the EAE model and was one of the genes most strongly reduced with vafidemstat, especially in the spinal cord. The dose was 0.5 mg/kg of vafidemstat (ORY-2001)



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
  - *No changes detected in biomarkers like Abeta, t-Tau, p-Tau or S100A9*
  - *Improvements in the levels of neurogranin (a synaptic damage biomarker)*
  - *Improvements in NFL*
  - *Significant reduction in the CSF levels of YKL40 (an anti-inflammatory biomarker) in keeping with prior preclinical data*
    - *First in human data supporting decreased inflammatory biomarkers with vafidemstat treatment*
- ETHERAL as initially expected 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*