

CHRONICALLY ELEVATED CORTISOL AND COGNITIVE IMPAIRMENT: THE THERAPEUTIC POTENTIAL OF XANAMEM™, A POTENT INHIBITOR OF THE 11 β -HSD1 ENZYME

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Disclosures

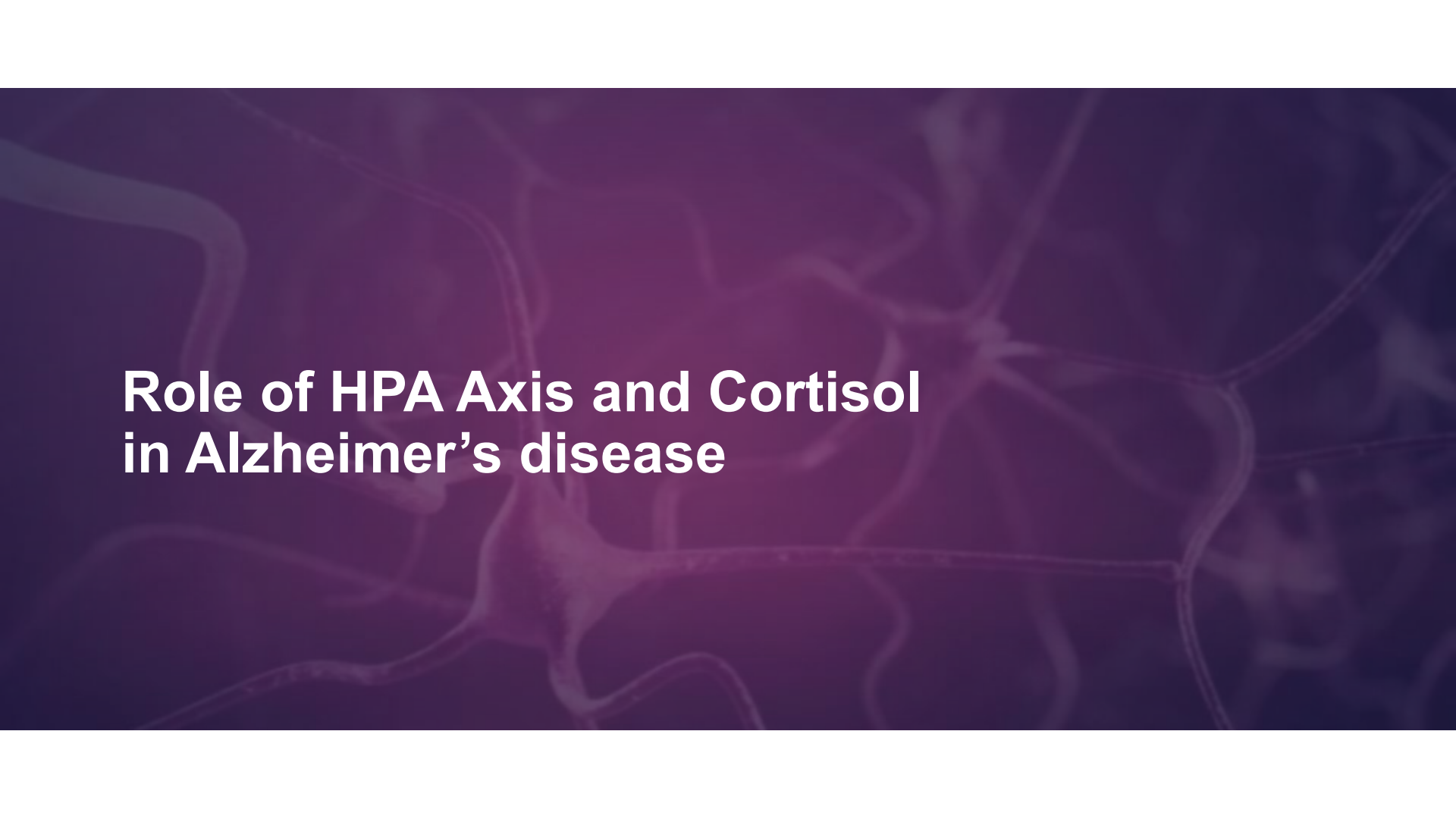
Provided paid consultancy over the last 8 years for:

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Prana Biotechnology, Abbvie, Roche, Eli Lilly, GSK, and Pfizer

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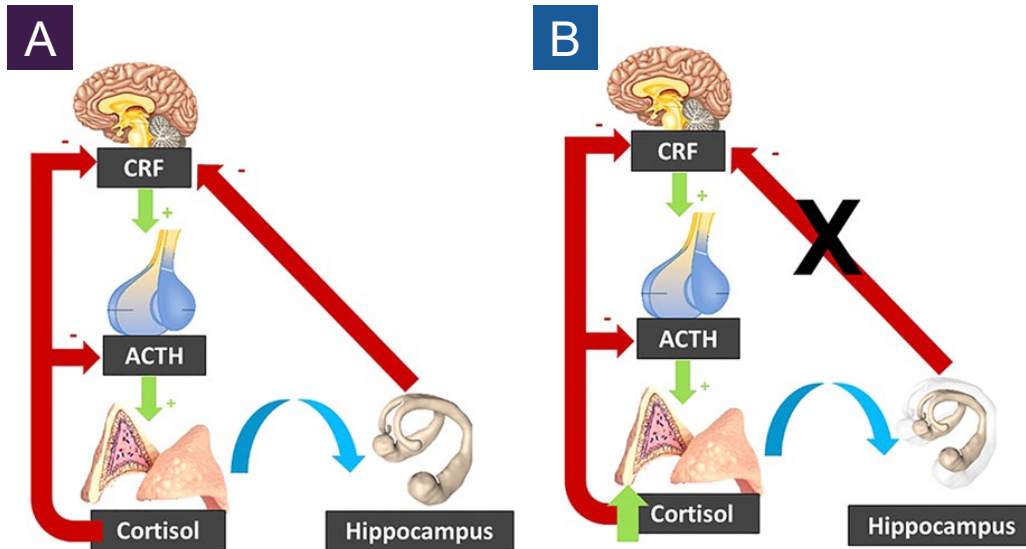
Presentation Overview

1. Role of HPA Axis and Cortisol in Alzheimer's disease
2. Mechanism of action, pre-clinical and clinical work in 11 β -HSD-1 Inhibition
3. Update on results for the XanADu study
4. Update on results for the XanaHES study
5. Update on results for the Target Occupancy studies
6. Plans for next AD study: Xanamem™ in MCI due to Alzheimer's disease
7. Additional therapeutic indications for Xanamem in planning

A microscopic image of neurons, showing cell bodies and branching processes, overlaid with a dark purple gradient. The text is centered on the left side of the image.

Role of HPA Axis and Cortisol in Alzheimer's disease

HPA Axis



A In normal circumstances, the CRF released by the hypothalamus activates ACTH release by the pituitary gland, which stimulates the adrenal glands to secrete cortisol. Cortisol inhibits its own secretion via a negative feedback loop. The hippocampus inhibits the hypothalamo-pituitary-adrenal axis.

B When cortisol is elevated, it can induce hippocampal atrophy, which "lifts the brake" on the hypothalamo-pituitary-adrenal axis. The resulting cortisol increase induces further hippocampal atrophy, resulting in a vicious circle.¹

CRF: corticotropin-releasing factor; ACTH: Adrenocorticotropic hormone

1. Ouanes S and Popp J (2019) High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. *Front. Aging Neurosci.* 11:43. doi: 10.3389/fnagi.2019.00043

Elevated circulating cortisol may contribute to AD pathogenesis^(2,3)

Direct:

1. Increased levels of amyloid precursor protein (APP) and BACE leading to increased A β 42 formation^{2,3,4}
2. Reduced A β 42 degradation via attenuation of insulin degrading enzyme⁵

Indirect:

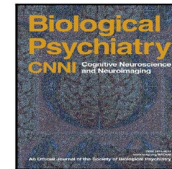
1. Insulin resistance
2. Angiopathic and antiangiogenic actions
3. Increased excitatory (N-methyl-D-aspartate) neurotransmission^{2,3}
4. Increased postsynaptic calcium signaling promoting neurotoxicity, metabolic endangerment of neurons, and deleterious alterations in neuroimmune function⁶
5. Facilitation of β -adrenergic signaling inhibiting the medial prefrontal cortex thus leading to an impairment in frontal functions, in particular in working memory⁷
6. Alteration of long-term potentiation (LTP), potentially worsening long-term memory consolidation⁸
7. Broadly: positive or negative early life experiences may play a key role in cortisol dysregulation⁹

2. Peskind ER, et al. *Neurology*. 2001;56:1094–1098; 3. Cernansky JG et al. *Am J Psychiatry*. 2006;163:2164–2169; 4. Ray B, Gaskins DL, Sajdyk TJ, Spence JP, Fitz SD, Shekhar A, et al. Restraint stress and repeated corticotrophin-releasing factor receptor activation. *Neuroscience*. 2011;184:139–50.; 5. Green KN et al. *J Neurosci*. 2006;26:9047–9056. 6. Wang Y et al. *Endocrinology*. 2011;152:2704–2705; 7. McGaugh, J. L., and Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Curr. Opin. Neurobiol.* 12, 205–210; 8. Lupien, S. J., McEwen, B. S., Gunnar, M. R., and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.* 10, 434–445; 9. Lesuis SL, Maurin H, Borghgraef P, Lucassen PJ, Van Leuven F, Krugers HJ. Positive and negative early life experiences differentially modulate long term survival and amyloid protein levels in a mouse model of Alzheimer's disease. *Oncotarget*. 2016;7(26):39118–35.

Plasma cortisol, brain amyloid- β , and cognitive decline in preclinical Alzheimer's disease: a 6-yr prospective cohort study¹⁰

Methods:

- Cognitively normal older adults (n=416) enrolled in the AIBL study underwent A β neuroimaging at a single timepoint. Fasted cortisol were dichotomized using a median split procedure.
- Five cognitive composites were derived: Episodic Memory, Executive Function, Attention, Language and Global Cognition
- Latent growth curve models were conducted to evaluate the relation between baseline plasma cortisol and A β levels, other risk factors, and cognitive composite scores over the 72-month study period.

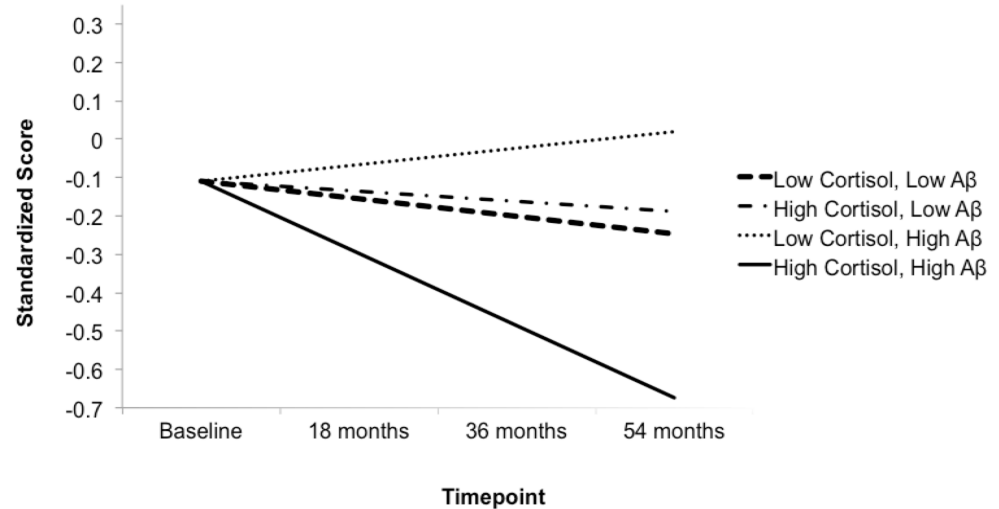


Results

High baseline plasma cortisol levels associated with 2.2 times the risk of $A\beta+$ and associated with greater decline in:

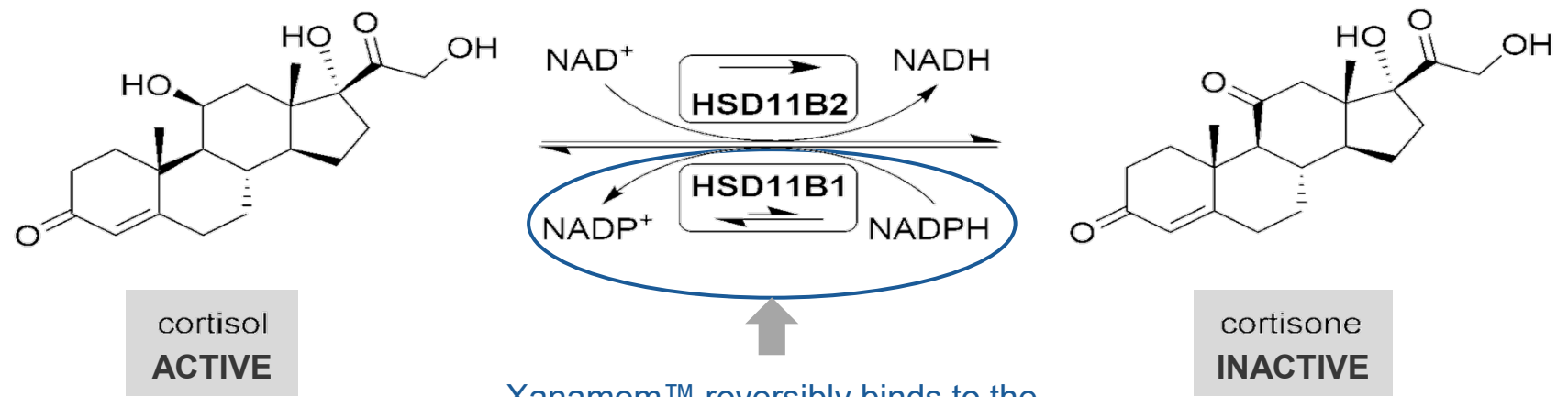
- global cognition (Cohen's $d=0.42$)
- episodic memory (Cohen's $d=0.69$)
- attention (Cohen's $d=0.31$)

*Effects were independent of age, education, premorbid intelligence, *APOE* and *BDNF* genotype, subjective memory complaints, vascular risk factors, and depression and anxiety symptoms.



**Mechanism of action,
pre-clinical and clinical work
in 11 β -HSD1 inhibition**

Function of 11β-HSD1



Xanamem™ reversibly binds to the **11β-HSD1 enzyme**, inhibiting this reaction, preventing the conversion of inactive cortisone into the active cortisol

Pre-Clinical Literature

Cognitive and Disease-Modifying Effects of 11 β -Hydroxysteroid Dehydrogenase Type 1 Inhibition in Male Tg2576 Mice, a Model of Alzheimer's Disease

Karen Sooy, June Noble, Andrew McBride, Margaret Binnie, Joyce L. W. Yau, Jonathan R. Seckl, Brian R. Walker, and Scott P. Webster

University/BHF Centre for Cardiovascular Science (K.S., J.N., A.M., M.B., J.L.W.Y., J.R.S., B.R.W., S.P.W.), Queen's Medical Research Institute, and Centre for Cognitive Aging and Cognitive Epidemiology (J.L.W.Y., J.R.S.), University of Edinburgh, Edinburgh EH16 4TJ, United Kingdom

Chronic exposure to elevated levels of glucocorticoids has been linked to age-related cognitive decline and may play a role in Alzheimer's disease. In the brain, 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) amplifies intracellular glucocorticoid levels. We show that short-term treatment of aged, cognitively impaired C57BL/6 mice with the potent and selective 11 β -HSD1 inhibitor UE2316 improves memory, including after intracerebroventricular drug administration to the central nervous system alone. In the Tg2576 mouse model of Alzheimer's disease, UE2316 treatment of mice aged 14 months for 4 weeks also decreased the number of β -amyloid (A β) plaques in the cerebral cortex, associated with a selective increase in local insulin-degrading enzyme (involved in A β breakdown and known to be glucocorticoid regulated). Chronic treatment of young Tg2576 mice with UE2316 for up to 13 months prevented cognitive decline but did not prevent A β plaque formation. We conclude that reducing glucocorticoid regeneration in the brain improves cognition independently of reduced A β plaque pathology and that 11 β -HSD1 inhibitors have potential as cognitive enhancers in age-associated memory impairment and Alzheimer's dementia. (*Endocrinology* 156: 4592–4603, 2015)

Source: Sooy et al., *Endocrinology* 156: 4592–4603, 2015

Methods:

Short-term Study

- 14-month-old mice: UE2316 10mg/kg/d through SC route (n=20 1:1 active:placebo)

Long-term Study

- 6-7-month-old mice fed UE2316 (n=32) or control diet (n=16) for up to 57 weeks

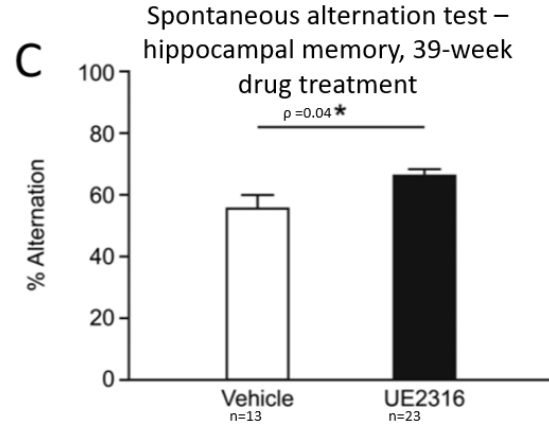
Behavior

- Memory in Passive Avoidance, Y-Maze Testing, Open Field Testing, Spontaneous Alteration and Morris Water Maze

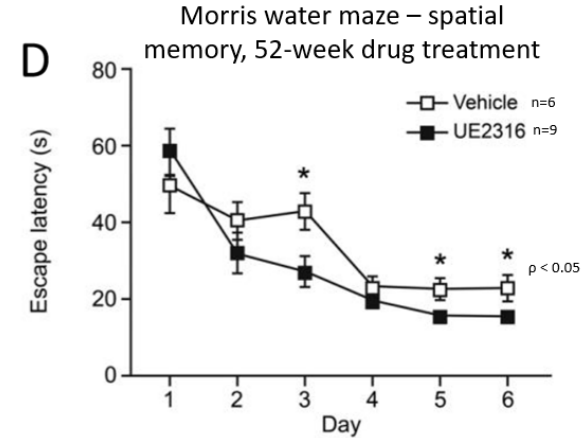
Immunohistochemistry

- Cortical Amyloid Plaque Number and Plaque Area

Inhibition of 11 β -HSD1 enhances cognition in AD-prone mice



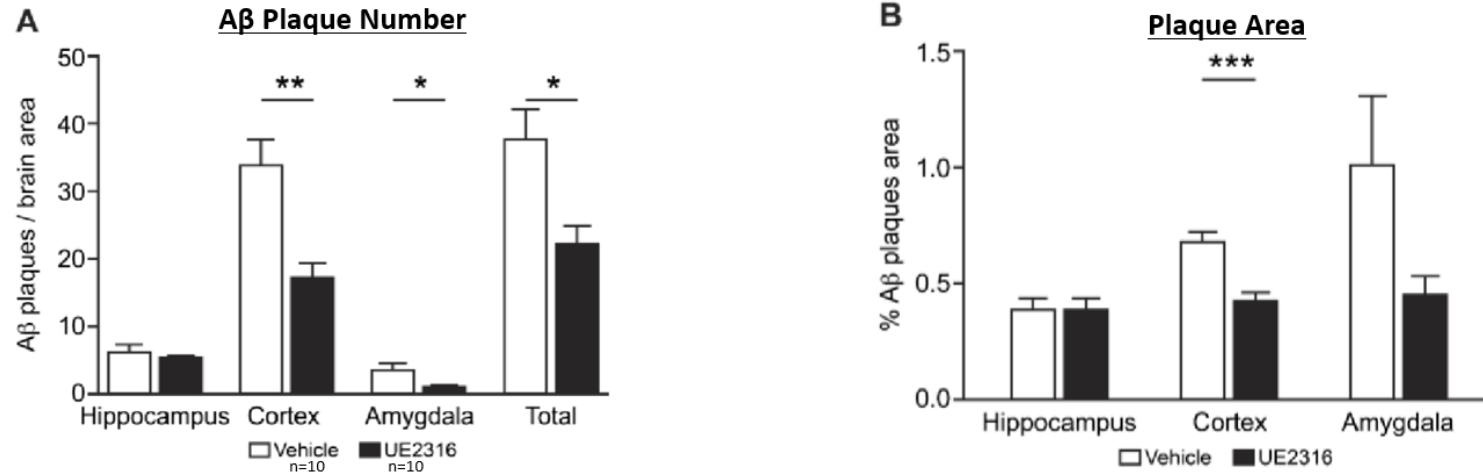
After 39 weeks of treatment, UE2316-treated mice (n=23) exhibited a significant increase in percentage alternation compared with control mice (n=16), $p=0.04$.



After 52 weeks of treatment, UE2316-treated mice (n=9) exhibited significant decreases in latency to find the hidden platform across the testing period compared with the vehicle-treated animals (n=6); *, $p < 0.05$ at days 3, 5, and 6.

Long term inhibition of 11 β -HSD1 maintained cognitive performance with aging in Tg2576 mice

Inhibition of 11 β -HSD1 inhibits AD pathology in AD-prone mice



As shown by 6E10 antibody staining for $A\beta$, treatment with UE2316 for 29 days reduced amyloid plaque levels in the cortex (** $p=0.002$), amygdala (* $p=0.05$) and whole brain ($p=0.01$) compared with vehicle ($n = 10$). Via KS300 imaging software, UE2316 treatment also reduced total plaque area in the cortex and amygdala compared with vehicle, with cortical reduction highly significant (***, $P=0.0001$).

Short term treatment with UE2316 decreased $A\beta$ plaque number and area in the cortex and amygdala in Tg2576 mice

Clinical Literature

11 β -Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics

Thekkepat C. Sandeep*, Joyce L. W. Yau*, Alasdair M. J. MacLulich†, June Noble*, Ian J. Deary‡, Brian R. Walker*, and Jonathan R. Seckl*§

Influence of carbenoxolone on cognitive function in healthy elderly men and patients with type 2 diabetes

In two double-blind, placebo RCT crossover studies, carbenoxolone:

- Improved verbal fluency ($P < 0.01$) after 4 weeks n=10 elderly men (aged 55–75 y)
- Improved verbal memory ($P < 0.01$) after 6 weeks n=12 type 2 diabetics (52–70 y).

Cognitive domain	Neuropsychological measures	Healthy elderly subjects			Patients with type 2 diabetes		
		Placebo with amiloride mean (SD)	Carbenoxolone with amiloride mean (SD)	<i>P</i>	Placebo with amiloride mean (SD)	Carbenoxolone with amiloride mean (SD)	<i>P</i>
Executive function	Verbal fluency	40.6 (12.4)	44.2 (10.6)	0.006	42.2 (8.4)	42.7 (6.4)	0.48
Memory							
Visual	WM visual reproduction	59.2 (18.2)	66.2 (8.4)	0.28	59.9 (13.3)	60.2 (7.9)	0.94
Verbal	WM logical memory	47.0 (19.2)	53.2 (18.1)	0.13	49.7 (13.8)	49.7 (17.7)	0.78
	Rey AVLT	51.5 (10.5)	53.9 (8.5)	0.47	55.2 (8.0)	58.8 (5.2)	0.005
Nonverbal reasoning	RSPM	45.1 (5.9)	46.3 (8.5)	0.45	44.0 (6.6)	45.4 (8.0)	0.17
Processing speed	DSST	50.7 (7.8)	51.9 (8.5)	0.70	50.3 (6.7)	50.6 (5.5)	0.78

WM, Wechsler Memory Scale-revised; AVLT, Rey Auditory Verbal Learning Test; RSPM, Ravens Standard Progressive Matrices; DSST, Digit Symbol Substitution test. Values in bold indicate a significant difference compared with placebo.

Summary of Background

- Strong biological basis for aetiological role of elevated central cortisol in AD pathology
- Epidemiological work associate's elevation of cortisol with AD pathology and clinical progression
- Interventional studies in pre-clinical and clinical models with 11 β -HSD1 shows promise
- Rational target for further clinical trials for symptomatic and potentially disease-modifying treatments for Alzheimer's dementia

Update on results for the XanADu Study



XanADu Phase II clinical trial

Double-blind, randomised, placebo-controlled study to assess the efficacy and safety of Xanamem 10mg in subjects with mild Alzheimer's disease¹



Xanamem treatment course
12 weeks



186 patients with mild
Alzheimer's disease²



10mg daily
Xanamem for 12 weeks (vs. placebo)



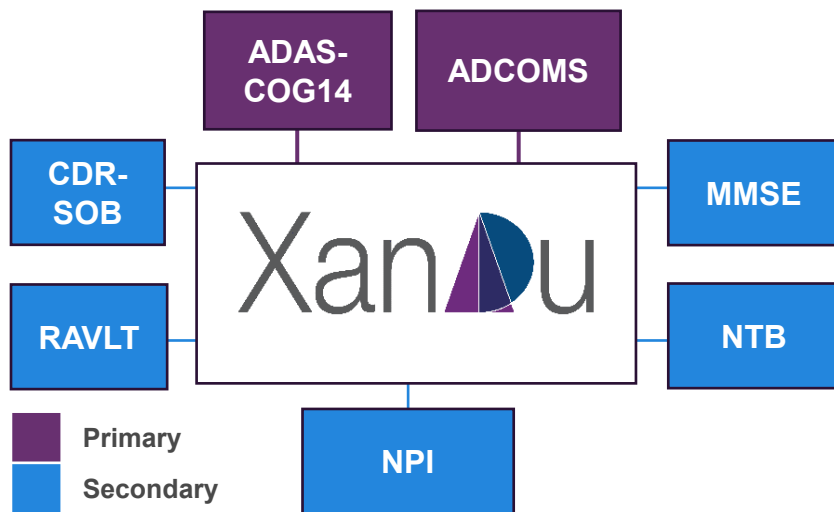
Trial conducted at 25 sites in
AUS, USA and UK

1. Study registered on Clinicaltrials.gov: NCT02727699
2. Fully enrolled 26 November 2018

XanADu endpoints

XanADu's results inform future clinical development

XanADu: primary and secondary efficacy endpoints¹



**Primary and secondary endpoints
were not met with
10mg QD Xanamem
for 12 weeks**

1. ADAS-COG14: Alzheimer's Disease Assessment Scales – Cognitive Subscale Score (version 14); ADCOMS: AD COMposite Scores (composite data derived from ADAS-COG14, CDR-SOB and MMSE); CDR-SOB: Clinical Dementia Rating Scale – Sum of Boxes; RAVLT: Rey Auditory Verbal Learning Test; MMSE: Mini-Mental Status Examination; NTB: Neuropsychological Test Batteries; NPI: Neuropsychiatric Inventory
2. Major efficacy endpoints include: ADAS-COG14, ADCOMS, CDR-SOB, MMSE

XanADu results summary



Significant PD effects

PD BIOMARKER	XANAMEM MEAN CHANGE (Baseline to EOT)	PLACEBO MEAN CHANGE (Baseline to EOT)	p VALUE FOR DIFFERENCE
ACTH	3.0	-1.0	<0.001
ANDROSTENEDIONE	0.22	-0.01	<0.001
DHEAS	42.4	-4.9	<0.001
CORTISONE	11.9	5.8	<0.001



Safety Profile

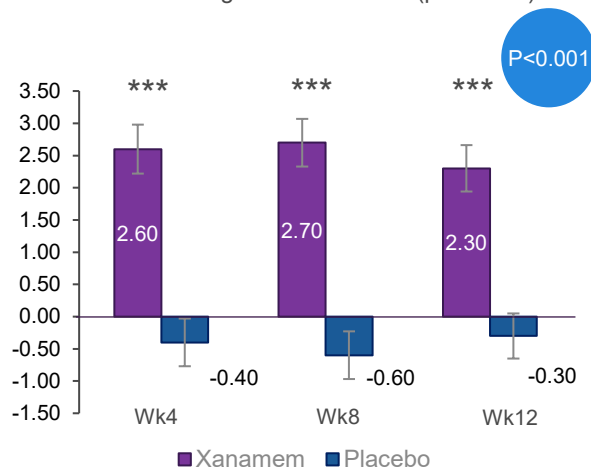
SAFETY RESULTS	XANAMEM	PLACEBO
TOTAL TEAEs	66 (72.5%)	54 (57.4%)
MILD TEAEs	40 (44%)	33 (35.1%)
MODERATE TEAEs	24 (26.4%)	16 (17%)
SEVERE TEAEs	2 (2.2%)	5 (5.3%)
SERIOUS TEAEs	4 (4%)	4 (4%)
AESI	1 (1%)	2 (2%)
WITHDRAWAL DUE TO TEAE	4 (4.4%)	0

XanADu Study – Pharmacodynamic Results

Xanamem 10mg once-daily resulted in early and significant pharmacodynamic modulation of cortisol-related hormones throughout the 12-week study

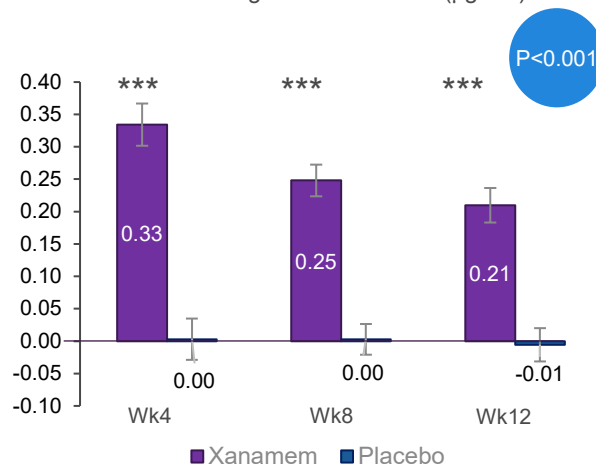
ACTH: 12 weeks treatment

LS Mean Changes from baseline (picomol/L)



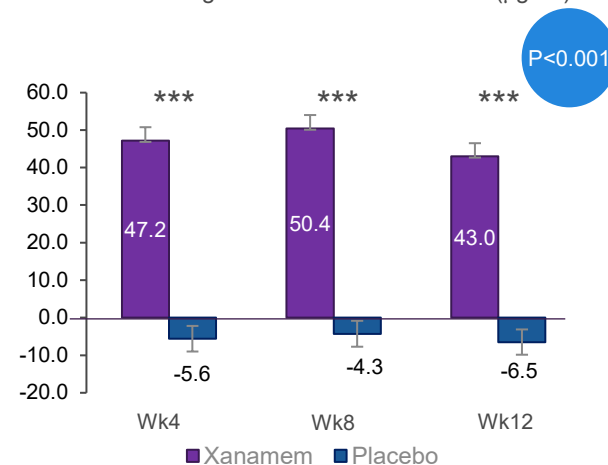
Androstenedione: 12 weeks treatment

LS Mean Changes from baseline (µg/mL)



DHEA-S: 12 weeks treatment

LS Mean Changes from baseline DHEA-S (µg/dL)



No change in testosterone, particularly in women

Results from the XanADu studies demonstrate significant PD effect of Xanamem 10mg in Alzheimer's disease

Source: XanADu results; data are presented as LS (least squares) means ± standard error of the mean (SEM). ***:p<0.001
ACTH: adrenocorticotrophic hormone; DHEA-S: Dehydroepiandrosterone sulfate. LS mean changes in testosterone were not significant.

Update on results for the XanaHES Study



XanaHES Phase I clinical trial

A Phase I, Single Blind, 12-Week, Randomised, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Xanamem 20mg Daily in Healthy Elderly Subjects¹



Xanamem treatment course
12 weeks



42 healthy elderly subjects
(30 Xanamem : 12 Placebo)



20mg daily
Xanamem for 12 weeks (vs. placebo)



Trial conducted at 1 Australian site:
Linear Phase I Unit, Perth

Final Clinical Study Report (CSR) due in April 2020

1. Study registered on Clinicaltrials.gov: NCT03830762

XanaHES (Xanamem in Healthy Elderly Subjects)

Primary objective:	Safety and Tolerability of Xanamem™ compared to placebo
Secondary objective:	Analysis of Pharmacokinetic and Pharmacodynamic data via blood plasma and CSF
Exploratory objective:	Performance in the CogState neuropsychological test battery (NTB) of Xanamem™ compared to placebo
Key subject inclusion criteria includes:	▪ Healthy elderly (>50 years) ▪ No known Alzheimer's or cognitive impairment
Target enrolment of n=42	▪ 5:2 Xanamem 20mg : Placebo ▪ 30:12 subjects completed October 2019

XanaHES (Xanamem in Healthy Elderly Subjects) cont.

- Initial study protocol was to escalate from 20mg to 30mg QD dosing, on a further 42 subjects, once 20mg was deemed safe and well tolerated:
 - However data from the concurrently-run PET Target Occupancy study revealed that escalation to 30mg would not result in higher occupancy than 20mg
 - Hence the decision was made not to escalate to 30mg

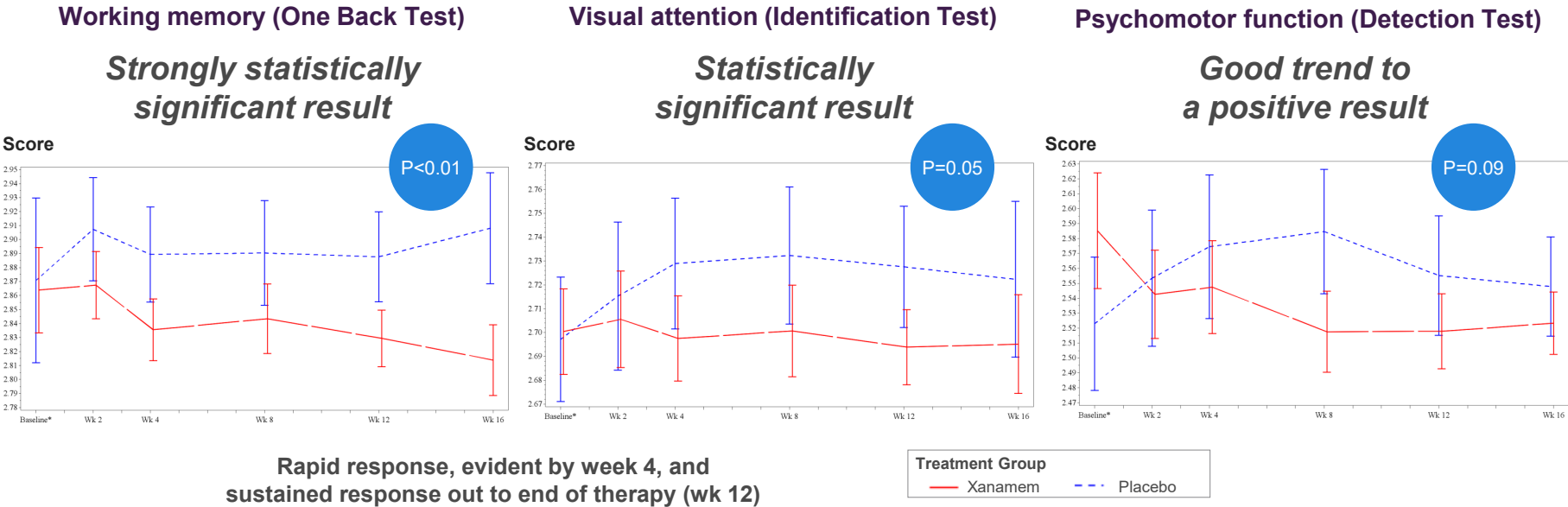
- No SAEs were reported for the 20mg subjects

Data is still being analysed, with the full CSR due mid-April 2020

Cogstate Neuropsychological Test Battery (NTB)

Test	Simple Description	Cognitive Domain	Primary Outcome
Detection (DET)	Has the card turned over?	Simple Reaction Time	Log10 Reaction Time (lms)
Identification (IDN)	Is the card red?	Attention	Log10 Reaction Time (lms)
One Card Learning (OCL)	Have you seen this card before?	Visual Learning	Arcsine Accuracy (arc)
One Back (ONB)	Is this card the same as the previous card?	Working Memory	Log10 Reaction Time (lms)
Continuous Paired Associate Learning (CPAL)	Where is each shape hidden?	Paired Associated Learning	Errors (err)
Continuous Paired Associate Learning – Delayed (CPAL – Delayed)	Where is each shape hidden (after a delay)?	Memory	Errors (err)

XanaHES (Xanamem in Healthy Elderly Subjects) cont.



Efficacy results reflect high quality and consistent data in a small study population

Baseline* Mean of Observed Data

XanaHES (Xanamem in Healthy Elderly Subjects) cont.

XanaHES 20mg Cogstate Cognitive Test Battery: p values and Cohen's d effect size

Cognitive Evaluation (Test)	p value			Treatment Effect Size: Cohen's d			
	All	Male	Female	Week 2	Week 4	Week 8	Week 12
Working Memory (One Back Test)	<0.01*	<0.01*	0.03*	0.64 [#]	0.78 [#]	0.64 [#]	0.83 ^Δ
Visual Attention (Identification Test)	0.05*	0.04*	0.60	0.19	0.67 [#]	0.62 [#]	0.67 [#]
Psychomotor Function (Detection Test)	0.09 [^]	0.94	0.13	0.47	0.65 [#]	1.12 ^Δ	0.76 [#]
Paired Associate Learning (CPAL ¹ Test)	0.21	0.34	0.49	0.87 ^Δ	0.01	0.66 [#]	0.08
Memory (CPAL ¹ – Delayed Test)	0.50	0.55	0.21	0.34	0.23	0.06	0.48
Visual Learning (One Card Learning Test)	0.92	0.41	0.64	0.11	0.12	0.60 [#]	0.19

Notes: * statistical significance achieved; ^ strong trend to statistical significance; # effect size >0.5 (moderate treatment effect); Δ effect size >0.8 (large treatment effect)

1: CPAL – Continuous Paired Associate Learning

A microscopic image of neurons, showing cell bodies and branching processes, overlaid with a dark purple gradient.

Update on results for the Target Occupancy Studies

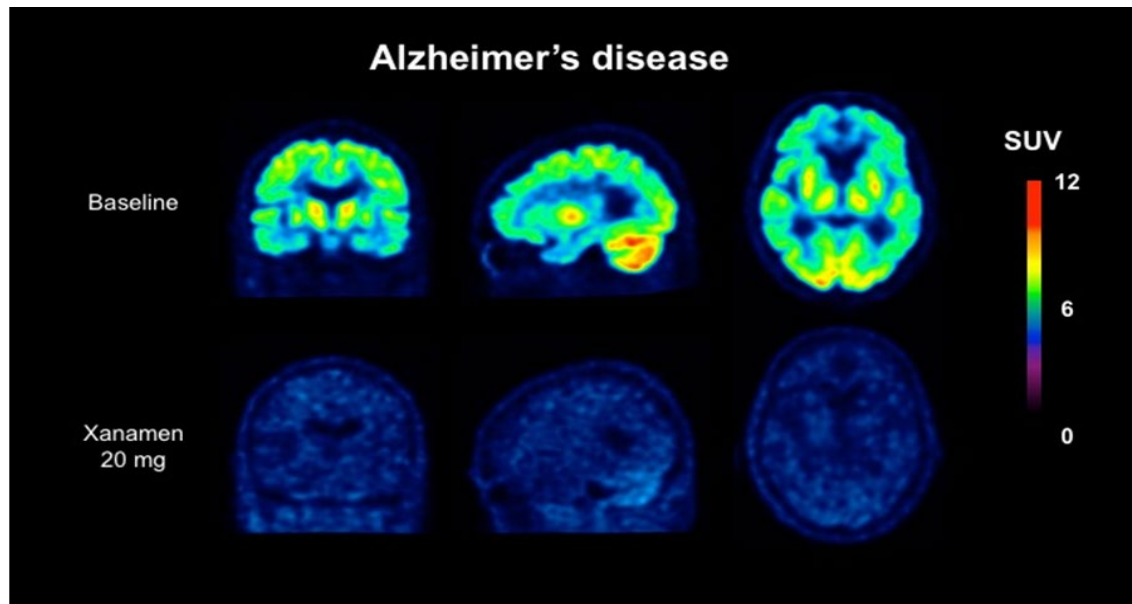
Target Occupancy Study

Target Occupancy Project with 11 β -HSD1-specific PET tracer:

- Pre-Clinical toxicology of the tracer performed
- *in-vitro* autoradiography and human tissue homogenate binding studies performed to quantify K_d, V_{max}, and enzyme activity; results are being collated and will be presented at a later date
- Phase I volunteer study being conducted by Prof Chris Rowe & Prof Victor Villemagne, The Austin Hospital Melbourne
 - 4 HC : 4 MCI/Mild AD in each cohort (5mg, 10mg, 20mg, 30mg)
 - 4 HC in 10mg nocte cohort
 - Total: 20 HC : 16 MCI/Mild AD

Target Occupancy Study: preliminary results

Phase I target occupancy study demonstrates that 5mg to 30mg Xanamem significantly occupies the 11 β -HSD1 enzyme throughout the brain



**50% to 85% occupancy,
dependent upon brain
region, dosage and
study subject¹**

Additional ongoing cohorts at
10mg Xanamem with delayed PET
imaging to demonstrate CNS PK

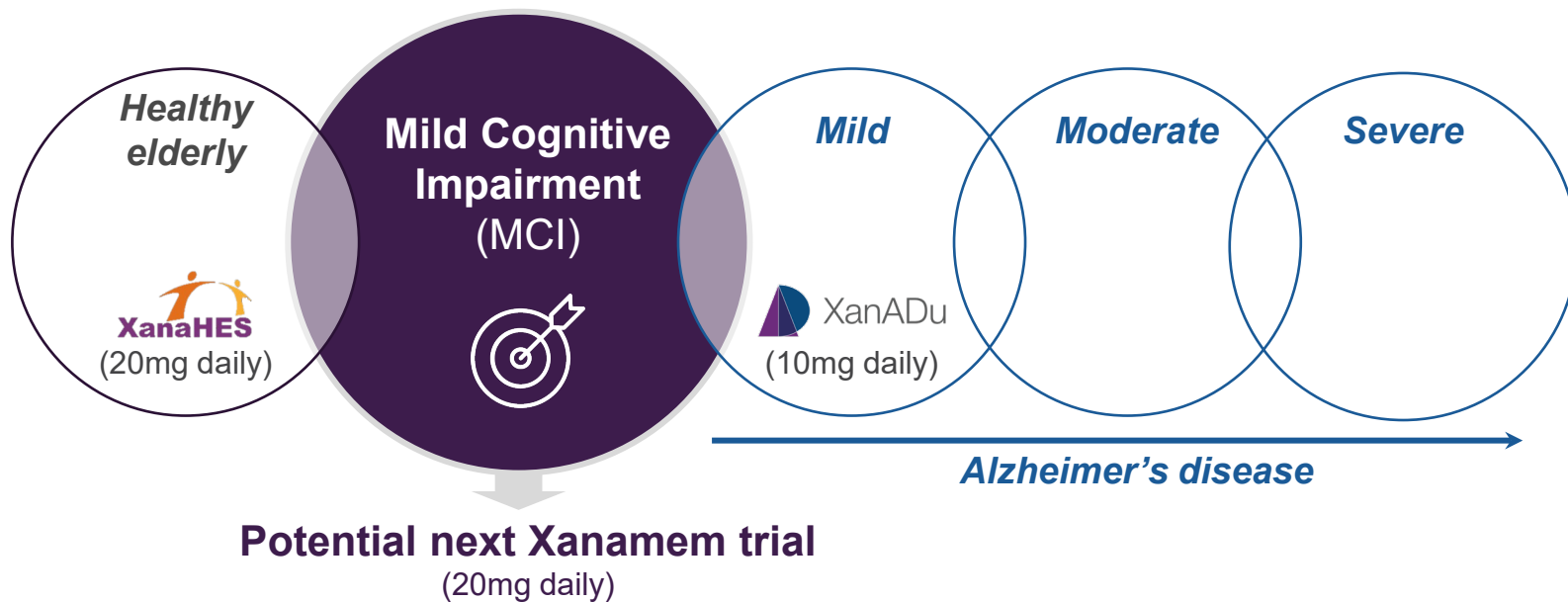
Phase I Target Occupancy supports Xanamem as a potent, orally bioavailable, brain-penetrant 11 β -HSD1 inhibitor

1. Study population consisted of ~50% healthy subjects (cognitively normal) and ~50% with Alzheimer's disease

**Plans for next AD study:
Xanamem in MCI due to
Alzheimer's disease**

MCI in Alzheimer's disease

Actinogen plans to evaluate Xanamem in patients with Mild Cognitive Impairment as part of the next phase of studies, linking the XanaHES results with Alzheimer's disease



Study design under development and will be refined following input from FDA and other regulators

Additional therapeutic indications for Xanamem in planning



Multiple diseases associated with chronically raised cortisol

Phase I and II safety and efficacy data positions Xanomem for trialling in other indications associated with chronically raised cortisol and cognitive impairment.

Actinogen planning to initiate trials in:

- Cognitive impairment associated with Schizophrenia
- Cognitive impairment associated with Type 2 Diabetes

A microscopic image of neurons, showing cell bodies and long, branching processes. The image is overlaid with a semi-transparent purple filter. The word "Summary" is written in white text on the left side.

Summary

The therapeutic potential of Xanamem, a potent inhibitor of the 11β -HSD1 enzyme

- Epidemiological, biological, and current body of evidence associates chronic elevation of cortisol with development and progression of Alzheimer's disease
- The XanaHES safety study confirmed a robust efficacy signal at 20mg QD Xanamem in a healthy elderly population, following a failure to detect a signal at 10mg QD in XanADu
- The target occupancy studies will be complete by end of Q2, 2020
- MCI due to AD planned as the next Alzheimer's study
- Xanamem MoA indicates the potential in numerous additional studies, including schizophrenia and diabetes
- 11β -HSD1 Inhibition, with Xanamem, is a targetable and rational approach to symptomatic therapy and disease modification in Alzheimer's disease, with a range of additional potential therapeutic applications

Special thanks

- **Bill Ketelbey**, CEO & Managing Director Actinogen Medical
- **Tamara Miller**, VP of Drug Development & Strategy Actinogen Medical
- **Chris Rowe** and **Victor Villemagne**, Austin Hospital
- **Linear Clinical Research**
- **Gifford Biosciences**
- **Cogstate**
- **Colin Masters** and **Jeff Cummings** – Xanamem Clinical Advisory Board
- **Jonathan Seckl** and **Scott Webster**, University of Edinburgh
- **Brian Walker**, University of Newcastle

Thank You

- Collaborators
- Investigators
- Research Participants