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Xanamem® CNS Activity in Alzheimer's disease

Utility of plasma p-Tau181 as a predictor of progression and Xanamem clinical effect in mild Alzheimer's disease: XanADu Phase 2a biomarker trial

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Dana C Hilt MD Disclosures

D C Hilt MD is employed by Actinogen as Chief Medical Officer.

D C Hilt MD is presently a consultant to the following entities: Frequency Therapeutics, Alacrita, Recognify Therapeutics, Lysosomal Therapeutics, Bial BioTech, and Cognition Therapeutics.

Served as a referee/panel member on numerous NIH and EU grant review panels.

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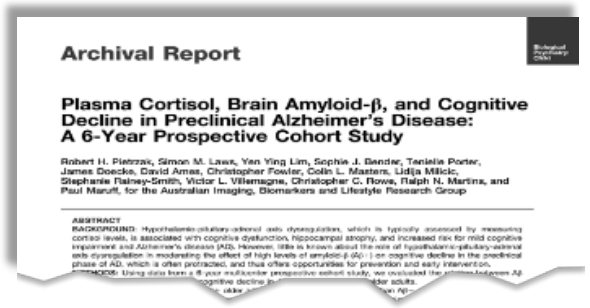
Elevated cortisol may contribute to CNS dysfunction

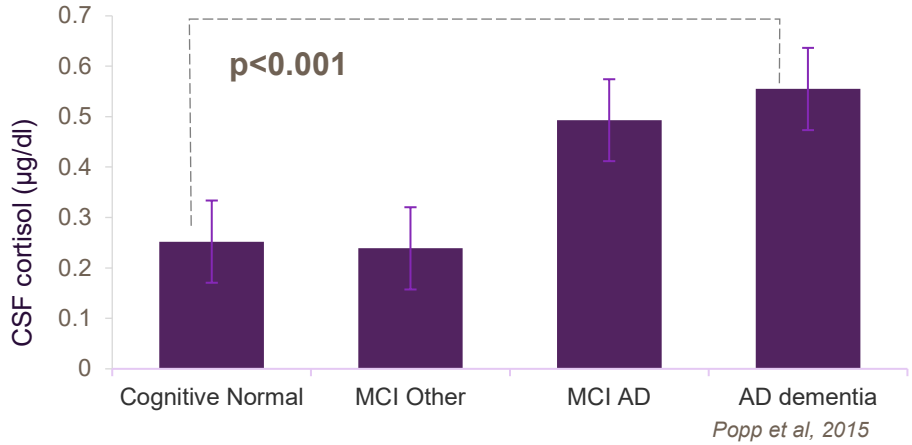
- Multiple studies support the association between elevated cortisol and Alzheimer's disease (AD) development and progression[1-5]
- Cognitive impairment in patients with neuroendocrine dysfunction[6-9]
- Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017)[5]
  - Higher plasma cortisol leads to a much greater risk of developing AD
  - Accelerated effect of Aβ+ on decline in global cognition, episodic memory, and attention
- Individuals with the APOE-ε4 allele have higher CSF cortisol[8]
- Higher CSF cortisol levels in AD patients are associated with more rapid clinical worsening and cognitive impairment[10,11]
- High cortisol and low folate predict probable AD after age 75[12]


Archival Report

Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

MEAN CSF CORTISOL LEVELS



Popp et al, 2015

[1] Geerlings et al., 2015, Neurology 85: 1-8; [2] Lehallier et al., 2016, JAMA Neurology 73(2), 203-212; [3] Popp et al., 2015, Neurobiol. Aging 36:601–607; [4] Ennis et al., 2017, Neurology 88(4):371-378; [5] Pietrzak et al., 2017, Biol Psychiatry: Cognitive Neuroscience and Neuroimagery, 2:45-52; [6] Lupien et al., 2009, Nat Rev Neurosci 10:434–445; [7] Starkman et al., 1999, Biol Psychiatry 46: 1595–1602; [8] Lupien et al., 1998, Nat Neurosci 1:69–73; [9] MacLullich et al., 2005, Psychoneuroendocrinology 30:505–515; ; [10] Cernansky et al., 2006, Am J Psychiatry 163:2164-2169; [11] Kornhuber & Jensen, 2015, Neurobiol Aging 36:601-607; [12] Hinterberger et al., J Am Ger Soc 2013 61(4):648-651;

Xanamem: Oral, low dose, once-a-day treatment with a unique (mainly) non-amyloid/tau mechanism

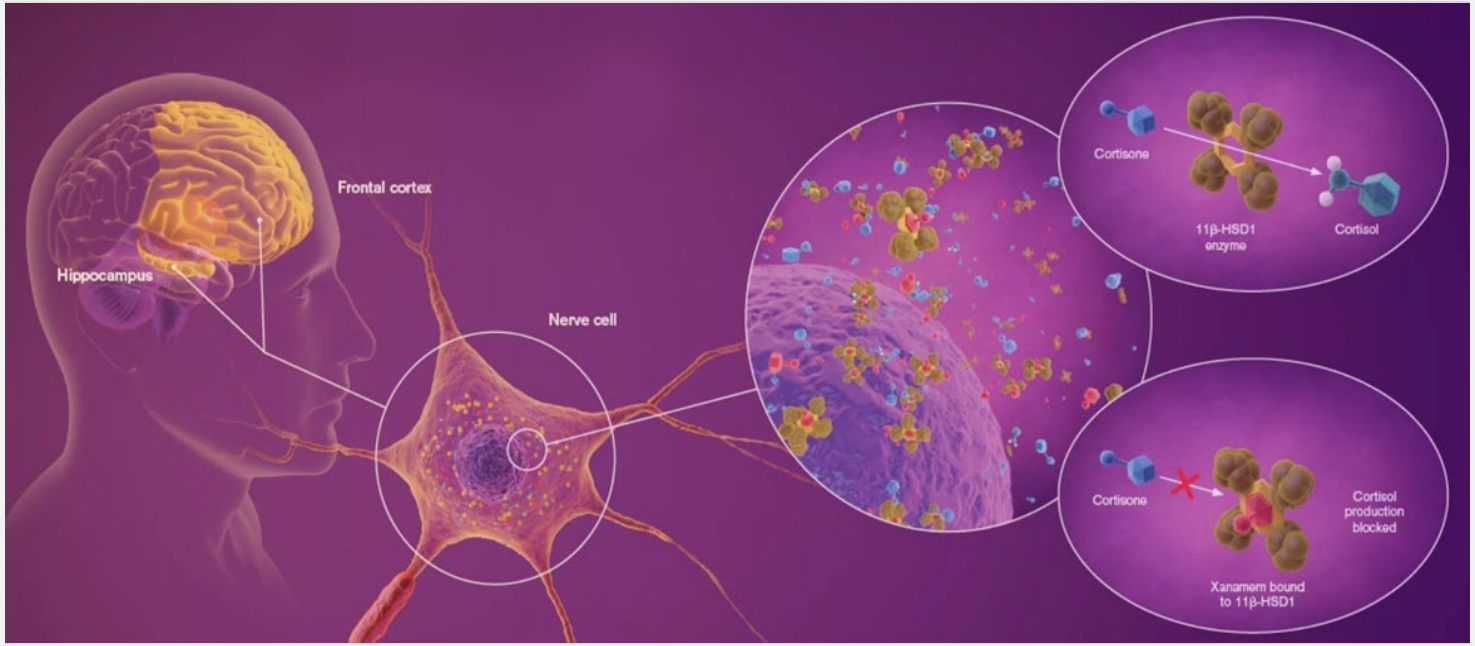
Only known brain penetrant 11β-HSD1 small molecule enzyme inhibitor

Reduces cortisol in brain - modulating signalling pathways and potentially underlying disease processes[1,2]

11β-HSD1 is preferentially expressed in brain and liver but minimally expressed in endocrine tissues

Xanamem may have potential to be:

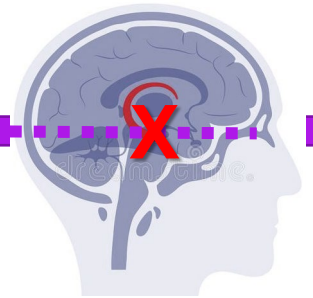
- Enhance cognition
- Slow progression or produce durable delay in symptoms progression in AD
- Anti-depressant/procognitive in depression with cognitive impairment



1. Xanamem® is a CNS (Central Nervous System) penetrant small molecule based on human PET scan evidence and cerebrospinal fluid (CSF) measurements
2. Sooy et al. 2015 showing effects on amyloid plaque reduction in an aged mouse model after 28 days associated with increases in insulin degrading enzyme; Popoli et al. 2011 microglial cell modulation in rats, effects on glutamate, cannabinoid and other signalling pathways

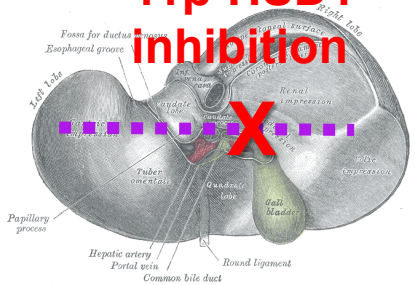
11β-HSD1 inhibition and attenuated cognitive decline

Potential mechanisms of action to reduce or halt cognitive decline

cortisone (inert) →  → Lowers brain cortisol → [reduced GR/MR activation]

Less negative feedback

- Increases pituitary ACTH within normal range (biomarker)
- No reduction of plasma cortisol at doses ≤10 mg

cortisone (inert) → **11β-HSD1 inhibition**  → Lowers liver & fat cortisol → [improved Insulin sensitivity]

- Increased synaptic plasticity
- Greater dendritic complexity
- Larger hippocampal volume

+

- Reduced amyloid synthesis
- Increased amyloid catabolism
- Reduced tau phosphorylation
- Less excitotoxicity - glutamate
- Altered neuroinflammation

+

- Improved glucose handling
- Reduced vascular pathology

Better working & episodic memory

Reduced neurodegeneration

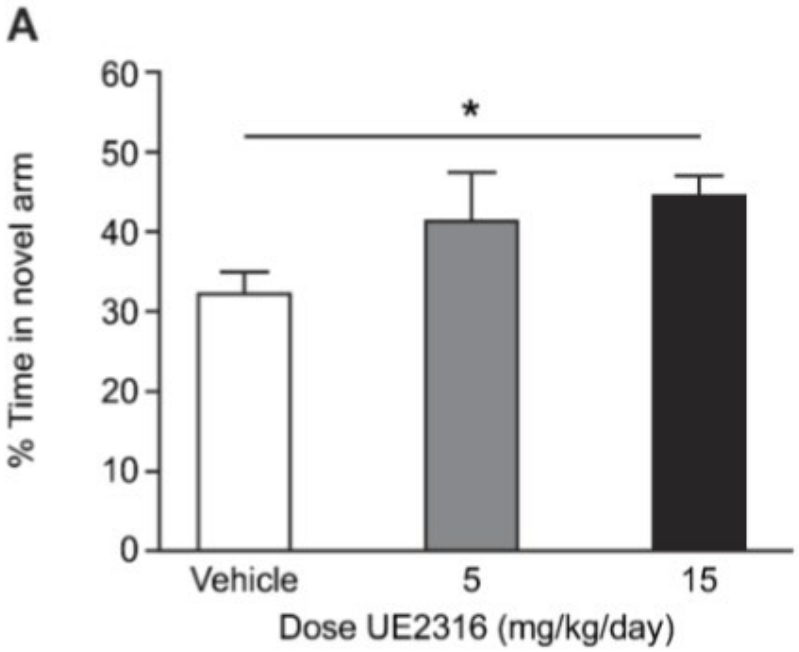
Potential metabolic benefits

Xanamem Preclinical Pharmacology

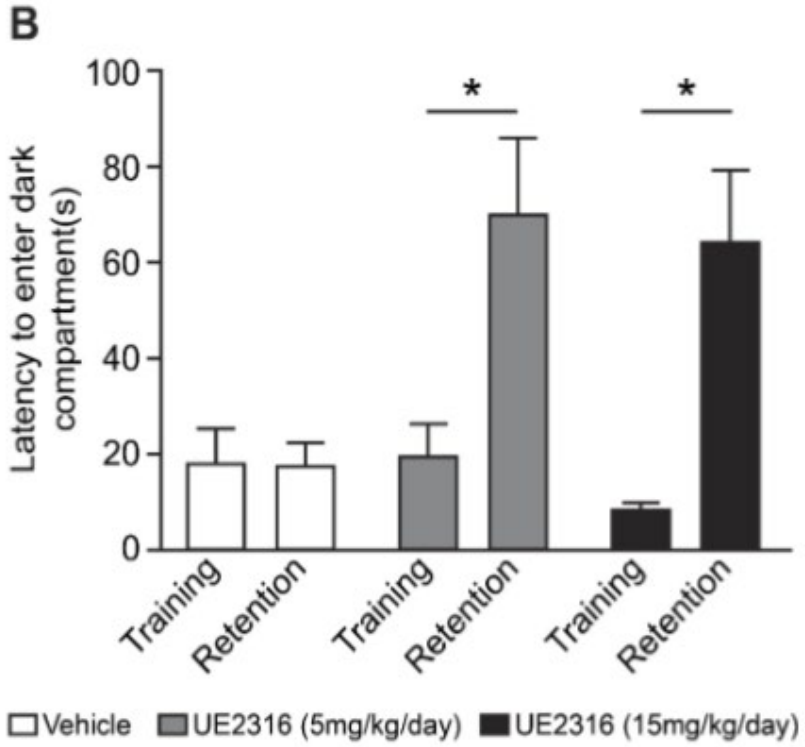
Inhibition of 11β-HSD1 enhances cognition in aged wild-type mice

Significant improvement in cognition after only 28 days treatment, continuing out to 41 weeks

Passive Avoidance: 10mg/kg s.c.



Passive Avoidance: oral dosing 30mg/kg



In human amyloid precursor protein-transgenic (Tg2576) mice, an established AD model, UE2316, a closely related Xanamem analogue, delivered for 29 days subcutaneously at 10mg/kg/day
(A) or for 41 weeks orally in food at ~30mg/kg/day
(B) to 14-month old Tg2576 mice. Increased latency to enter the dark compartment 6 hours after shock observed to a greater extent in Tg2576 mice than in WT mice. * * $\rho < 0.01$.
Sooy et al., 2015, Endocrinology 156(12):4592-4603
Preclinical rodent pharmacology studies conducted with closely related analogues as UE2343 does not bind to rodent 11β-HSD1 enzyme

Clinical data

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Two separate normal volunteer studies have shown procognitive effects of Xanamem: Attention, working memory, and executive function

Re-analysis of the Phase 2 XanADu AD study shows procognitive and potentially clinical benefit in high pTau subgroup

These data taken together support further studies of Xanamem as a procognitive and potential disease-course altering drug

Two large Phase 2 studies will be conducted

- **Depression with cognitive impairment (XanaCIDD)**
- **Mild/moderate AD with elevated pTau (XanaMIA)**

Evidence of Xanamem activity on cognition from multiple sources

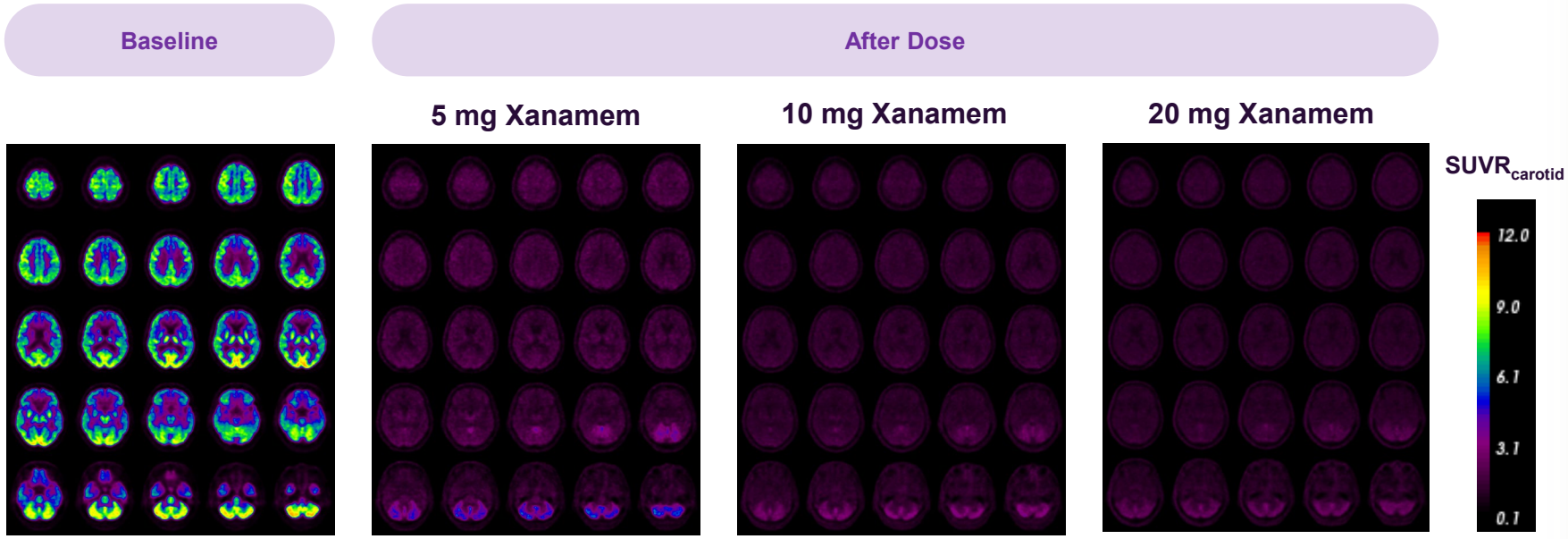
- ✓ **In animals**
  - ✓ **Protection against cognitive decline in animal model of AD using a Xanamem analogue independent of amyloid plaque[1]**
- ✓ **In humans**
  - ✓ **Consistent target engagement measured by PET[2] (significant/optimal target occupancy at 5/10 mg) & minimal ACTH response**
  - ✓ **XanaHES trial in cognitively normal older volunteers – Positive effects on CogState attention & working memory[3]**
  - ✓ **XanaMIA trial in cognitively normal older volunteers – Positive effects on CogState attention & working memory[4]**
  - ✓ **Re-analysis of Phase 2 AD XanADu data shows activity in patients with mild AD with elevated pTau181[2]**

Human and animal data support Xanamem activity at doses of 5 to 10 mg daily

1. Sooy et al. 2015 2. Publication pending 3. Actinogen data on file 4. Presented at CTAD 2022: https://wcsecure.weblink.com.au/pdf/ACW/02608009.pdf

PET data shows full target engagement in the brain in the dose range of 5-30 mg (5-20 mg shown)

Previous molecules to this target have not achieved adequate brain concentrations as they were poorly CNS penetrant



PET data demonstrates that Xanamem extensively binds to the 11β-HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.

This is consistent with full hormonal pharmacodynamic activity seen with 10 mg in clinical trials. 5 and 10 mg show excellent clinical tolerability and safety and minimal systemic endocrine effects.

Note: Study population consisted of ~50% healthy older subjects who were cognitively normal and ~50% with Alzheimer's disease. Subjects dosed for seven days.
Baseline: Mean of baseline scans of patients in that dose group; After dose: Mean of post-dosing (7 days) scans in that dose group.

Xanamem in normal volunteers: Attention domains improved in XanaHES* by Week 4

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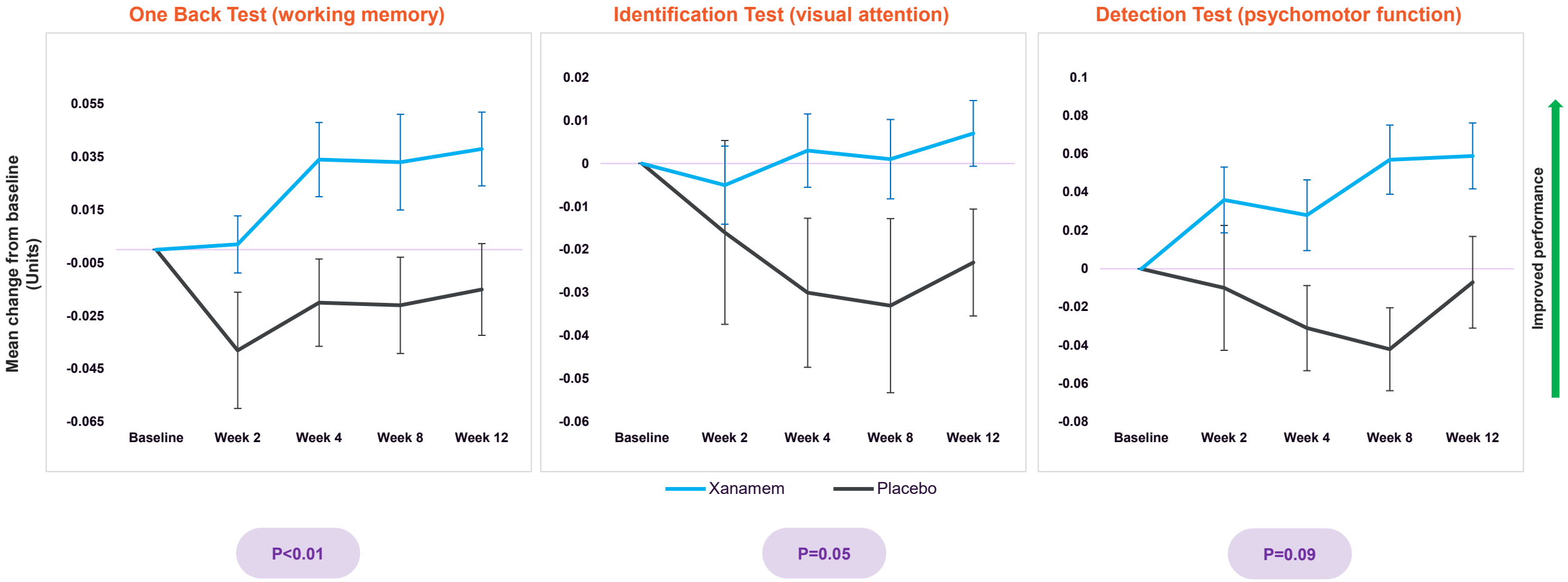


P<0.01

P=0.05

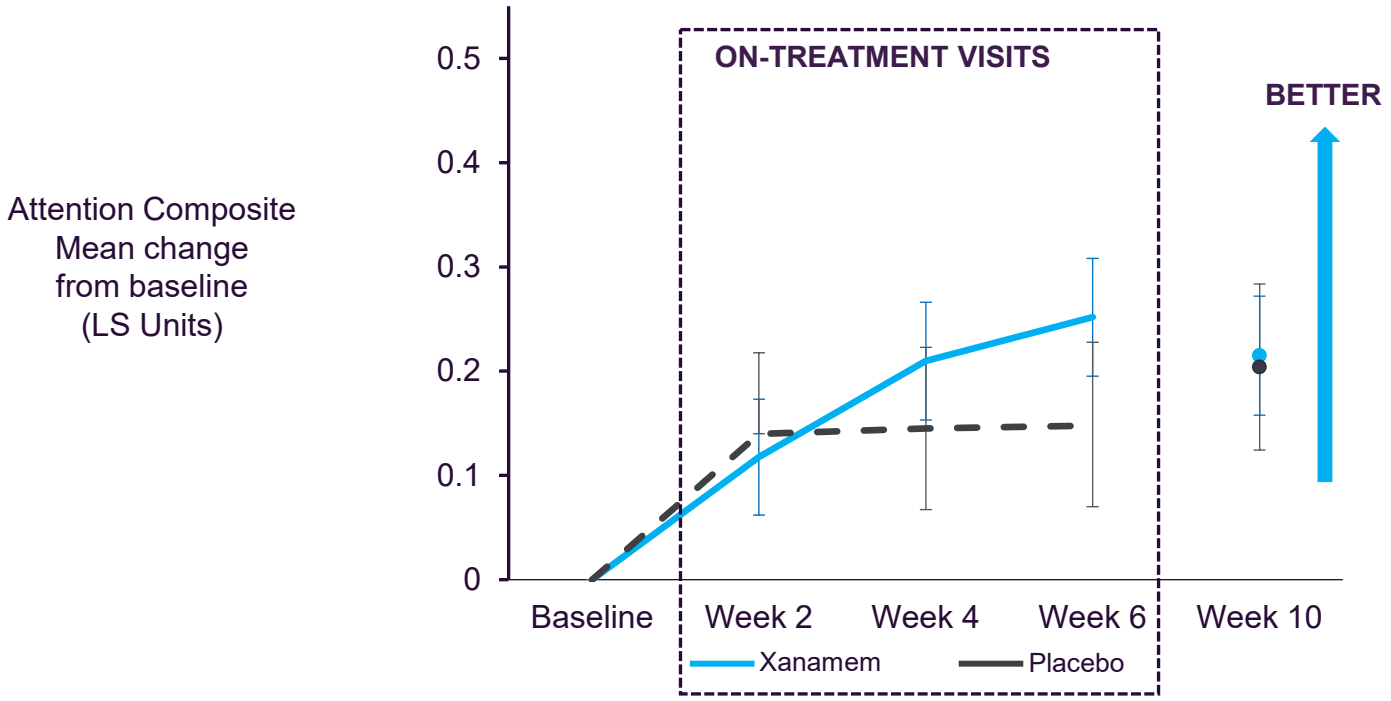
P=0.09

* n = 30 Xanamem 20mg vs n = 12 Placebo (Actinogen data on file)

Xanamem confirms improved attention/working memory by 4-6 weeks at lower doses in second trial

Computerized Cogstate test battery positive results in cognitively normal older people

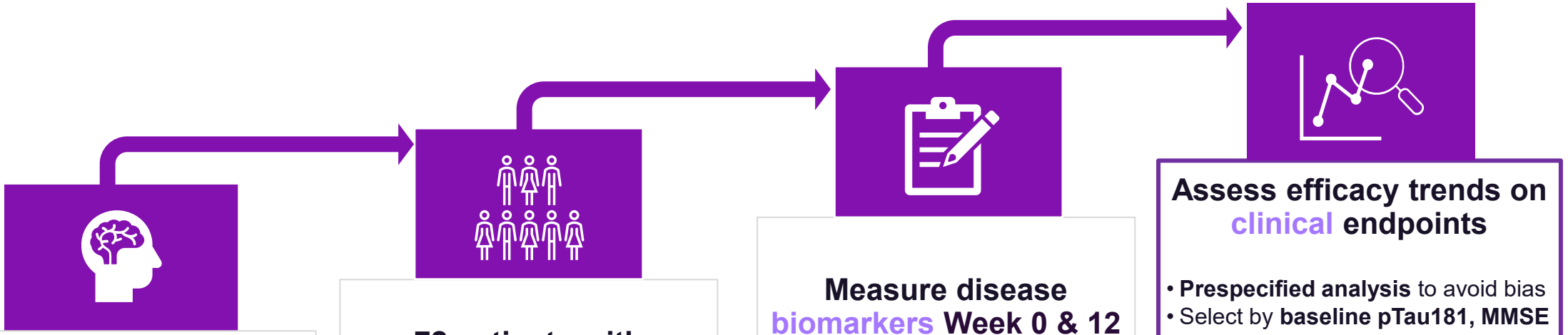
XanaMIA Phase 1b trial (n=107, Xanamem 10 mg & 5 mg)



Procognitive effects of Xanamem confirmed in second randomized trial

2022: Phase 2a AD blood biomarker study design and methods

Uses a pre-specified protocol and analysis plan to avoid bias



Phase 2a trial (XanADu)

- **185 people with mild AD** (MMSE 20-26)
- Clinical diagnosis: no amyloid imaging or biomarkers
- Placebo-controlled
- 12 weeks
- 10 mg Xanamem vs. placebo
- Primary analysis (ADAS-Cog) neg

72 patients with stored blood samples

- Available plasma stored at -80°C
- Evaluated by expert biomarker laboratory blinded to treatment assignment

Measure disease biomarkers Week 0 & 12

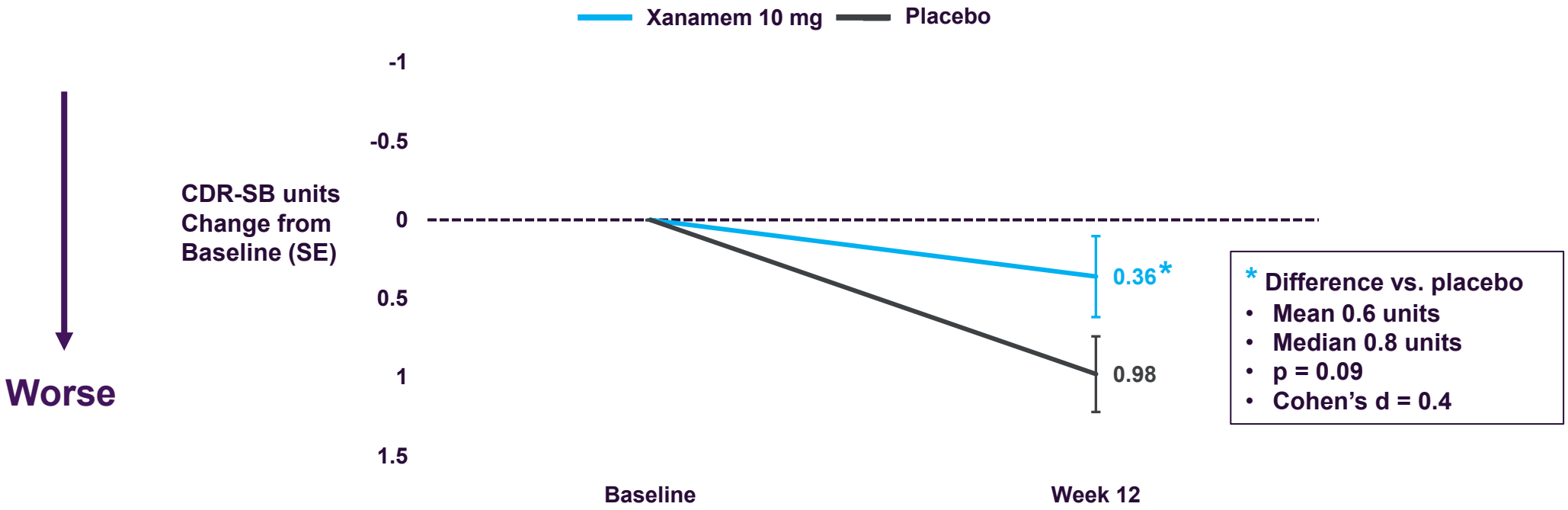
- **pTau181**
- **Amyloid 42/40 ratio**
- **GFAP**

Assess efficacy trends on clinical endpoints

- **Prespecified analysis** to avoid bias
- Select by **baseline pTau181, MMSE and amyloid ratio levels to reassess** efficacy
- Focus on **endpoints most sensitive to change** in a MCI/mild AD population (**CDR-SB)**
- Cohen's d to measure clinical effect size with no correction of p values for multiple comparisons

Xanamem prevents clinical decline in p-Tau181 elevated AD patients

In trial participants with p-Tau181 > 6.74 pg/mL, Xanamem demonstrates disease stabilization on CDR-SB



Xanamem largely prevented clinical progression over 12 weeks

Xanamem doubled rate of disease stabilization on CDR-SB in mild/moderate AD

Response analysis in pTau181-positive[1] XanADu patients (patients more likely to progress)

Twice as many patients in the Xanamem group had stable or improved disease compared with placebo[2]

56% of patients treated with Xanamem were stable or improved vs. 28% in placebo

Xanamem treatment effect size vs. placebo of 0.6 – 0.8 SD units over 12 weeks

Xanamem 10 mg protected the majority of patients in the study from progression

1. Pre-specified level of pTau181 above the median in plasma at baseline
2. Where CDR-SB decreased or was unchanged - Xanamem 9 of 16 (56%) vs. Placebo 5 of 18 (28%)

Effect on CDR-SB in other three pre-specified groups

Groups defined by biomarker median value, MMSE by 20-23 vs. 24-26

	N	CDR-SB				
Group		**Desired change**	**Xanamem**	**Placebo**	**Cohen's d**	**p value**
pTau >10.2 pg/mL[1] (mean)	**9**	**Down**	**0.1**	**0.8**	**0.6**	**0.33**
Aβ42/40 ratio < 0.19 (mean)	29	Down	0.5	0.4	0.1	0.91
MMSE 20-23	46	Down	0.5	0.5	0.0	0.82

Clinically significant effect size of CDR-SB 0.7 units in very high pTau group, with no apparent utility of low amyloid ratio or lower MMSE

1. Published cutoff of 10.2 pg/mL[2] cutoff by Cullen et al. 2022 for progression to clinical AD. 6.74 pg/mL represents the median value of the dataset

High pTau group: NTB and other endpoints

NTB: a composite for executive function consisting of Controlled Oral Word Association (COWAT) and Category Fluency Test (CFT)

- **Improved NTB: Xanamem +0.5 vs. Placebo -2.3, Cohen's d = 0.3**
- **No effects on ADAS-Cog14, ADCOMS, MMSE, RAVLT, NPI (Cohen's d < 0.2)**

Clinically significant effect size on NTB further explored in analysis of composite characteristics

Exploring the high pTau group: baseline characteristics

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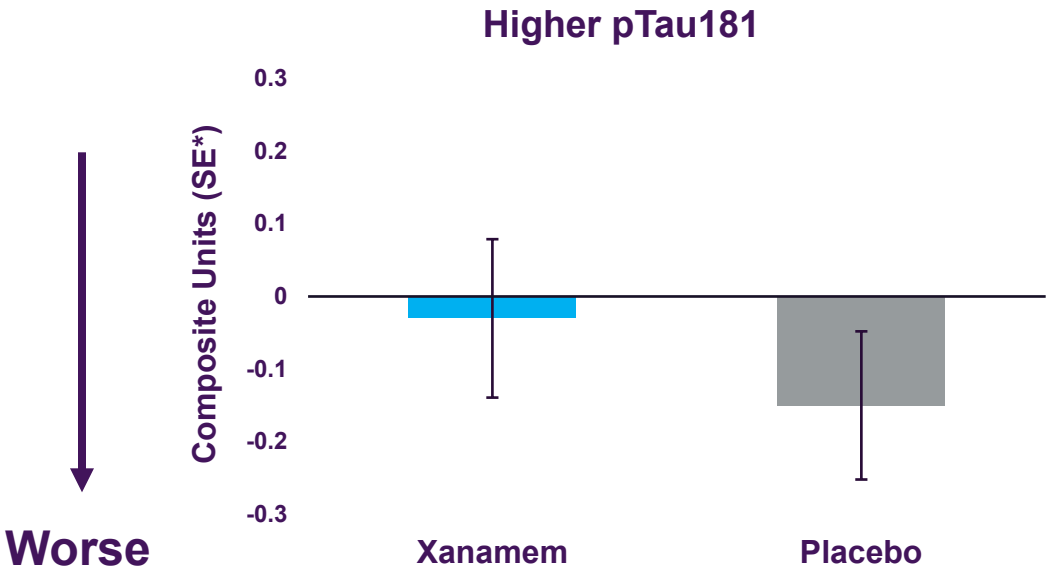
	Xanamem (n=16)	Placebo (n=18)
Age (mean, SD)	71 (8)	71 (8)
% female	50%	56%
% donepezil therapy[1]	44%	61%
ADASCog14 (mean, SD)	34 (5)	32 (8)
ADCOMS (mean, SD)	0.56 (0.13)	0.52 (0.19)
MMSE (mean, SD)	22 (3)	23 (2)
CDR-SB (mean, SD)	4.1 (1.2)	3.6 (1.6)
pTau pg/mL (mean, SD)	9.3 (2.6)	11.9 (11.6)
pTau pg/ml (median)	8.6	8.8
Aβ42/40 ratio (mean, SD)	0.19 (0.03)	0.19 (0.03)
GFAP pg/mL (mean, SD)	132 (77)	136 (95)

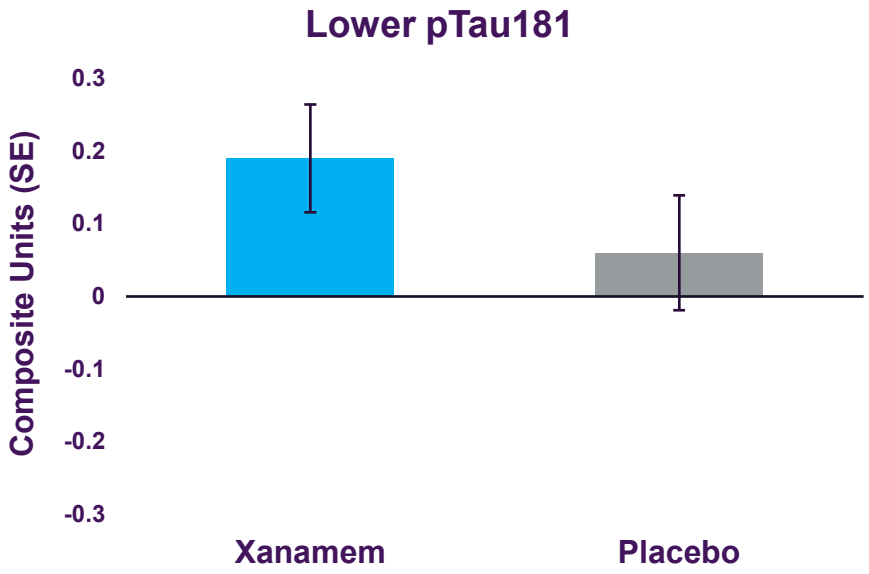
Groups were generally well balanced in key characteristics
Beneficial effects not likely due to group imbalance

1. Including other AChE inhibitiors and/or memantine

Exploratory analyses: Change from baseline in cognition composite

Trends in change of composite of word recall & recognition, CFT & COWAT (p=NS)





Preserved cognition

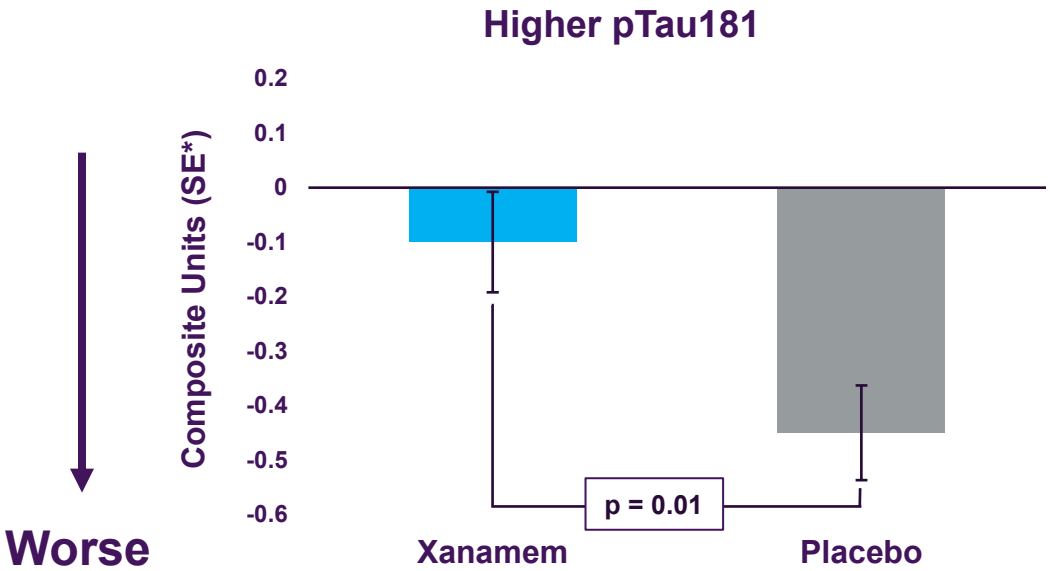
Cognitive enhancement

Consistent with Xanamem activity as a cognitive enhancer & disease-modifier

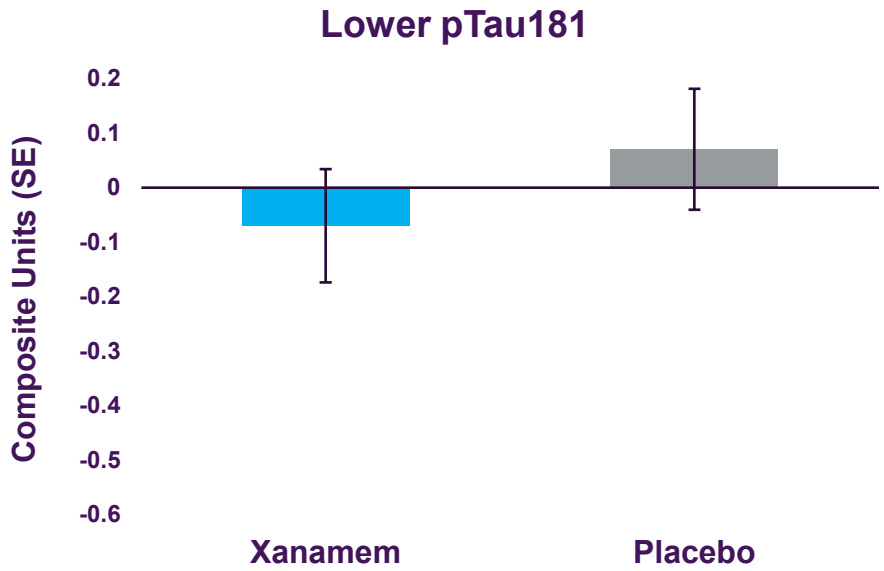
* Standard Error of the mean

Exploratory: Change from baseline in cognitive-functional composite (with CDR-SB)

Trends in change of composite of CDR-SB, word recall & recognition, CFT, COWAT



Preserved cognition & function



No effect

Consistent with Xanamem activity as a cognitive & functional preserver

* Standard Error of the mean

Safety data phase 2a AD patients

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10mg daily over 12 weeks - clinically diagnosed, mild AD

✓ No treatment-related SAEs in program to date (n=301)

TEAE term ACW0002*	Xanamem (n=91)	Placebo (n=94)	Total (n=185)
Headache	5 (5.5%)	2 (2.1%)	7 (3.8%)
Dizziness	4 (4.4%)	3 (3.2%)	7 (3.8%)
Diarrhoea	1 (1.1%)	4 (4.3%)	5 (2.7%)
Fatigue	3 (3.3%)	1 (1.1%)	4 (2.2%)
Nerve conduction abnormal	1 (1.1%)	3 (3.2%)	4 (2.2%)
Somnolence	1 (1.1%)	3 (3.2%)	4 (2.2%)
Decreased appetite	2 (2.2%)	0 (0.0%)	2 (1.1%)

* TEAEs reported by more than one patient in any group in the largest clinical study to date

The new analyses indicate further study of Xanamem in AD is indicated

- ✓ **Analysis suggests clinical activity of Xanamem in mild AD patients with more rapidly progressing disease**
- ✓ **Large clinical effect size, (p=0.09 in modest sample size) will need to be confirmed in larger studies**
- ✓ **Indicates potential utility of elevated blood pTau 181 levels to select suitable patients that are likely to progress for next larger and longer Phase 2b trial**
- ✓ ***Phase 2b XanaMIA study will enroll mild/moderate AD patients with elevated pTau 181 and measure Cognition Composite, CDR-SB, Amsterdam IADL and other endpoints***

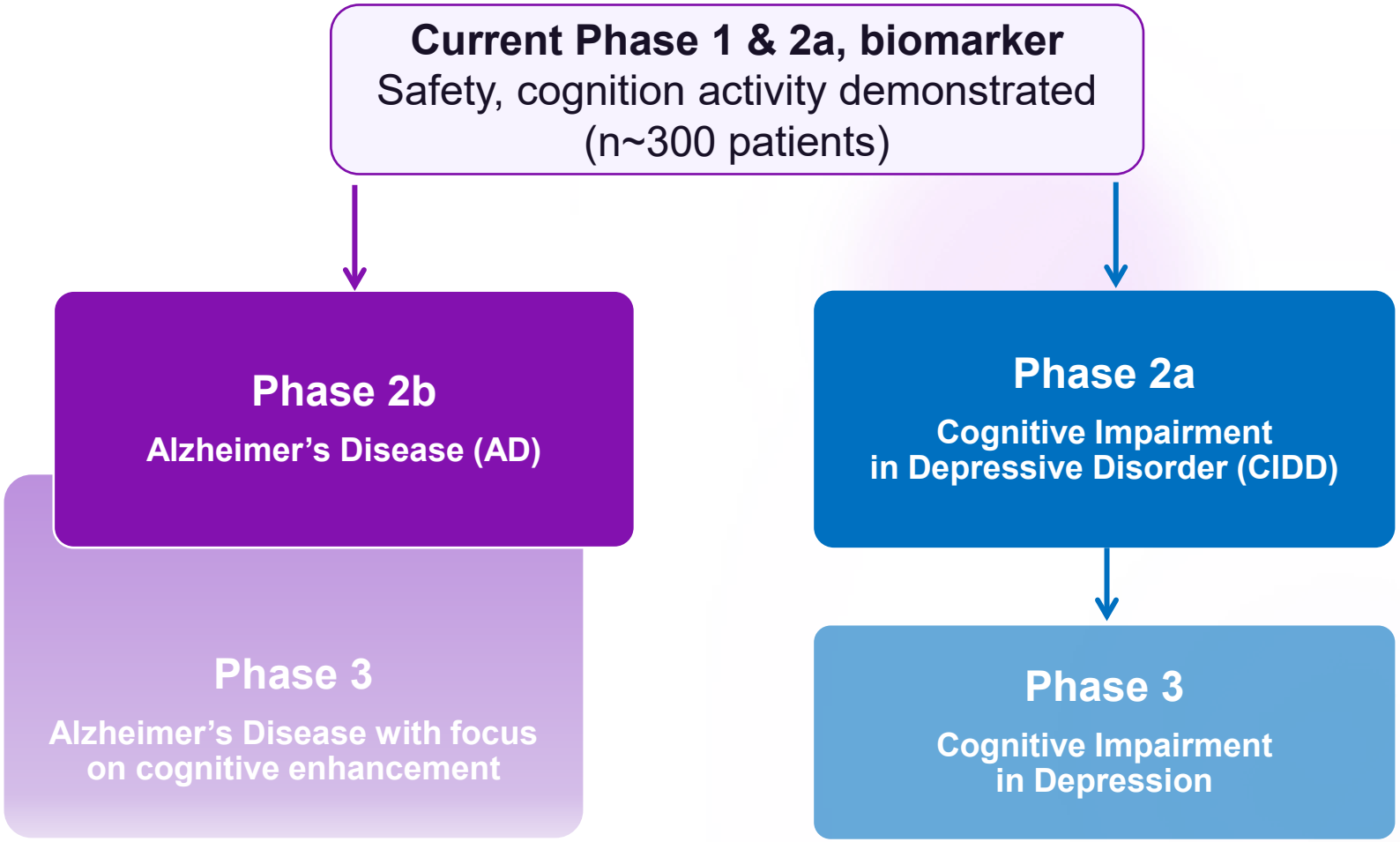
Confirms the procognitive & positive clinical effects of Xanamem at 10 mg daily

Xanamem moving to POC Phase 2 studies: AD and Cognitive Impairment in Depression

Biomarker data validate planned Phase 2b protocol in Mild Cognitive Impairment / mild AD with positive blood pTau

Xanamem Phase 2 & 3 program

Building on three independent Phase 1 and 2 studies showing safety and procognitive activity



The XanaMIA Phase 2b Trial

A double-blind, randomized, 6-month, 3-arm clinical trial to assess safety, tolerability, and efficacy of Xanamem 5 mg and 10 mg daily in patients with MCI and Mild AD