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Controlling cortisol in CNS[1] disease – Xanamem;® a selective 11β-HSD1 inhibitor as a potential new therapeutic for neuropsychiatric diseases.

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CMO, Actinogen Medical Limited

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1 CNS: Central Nervous System

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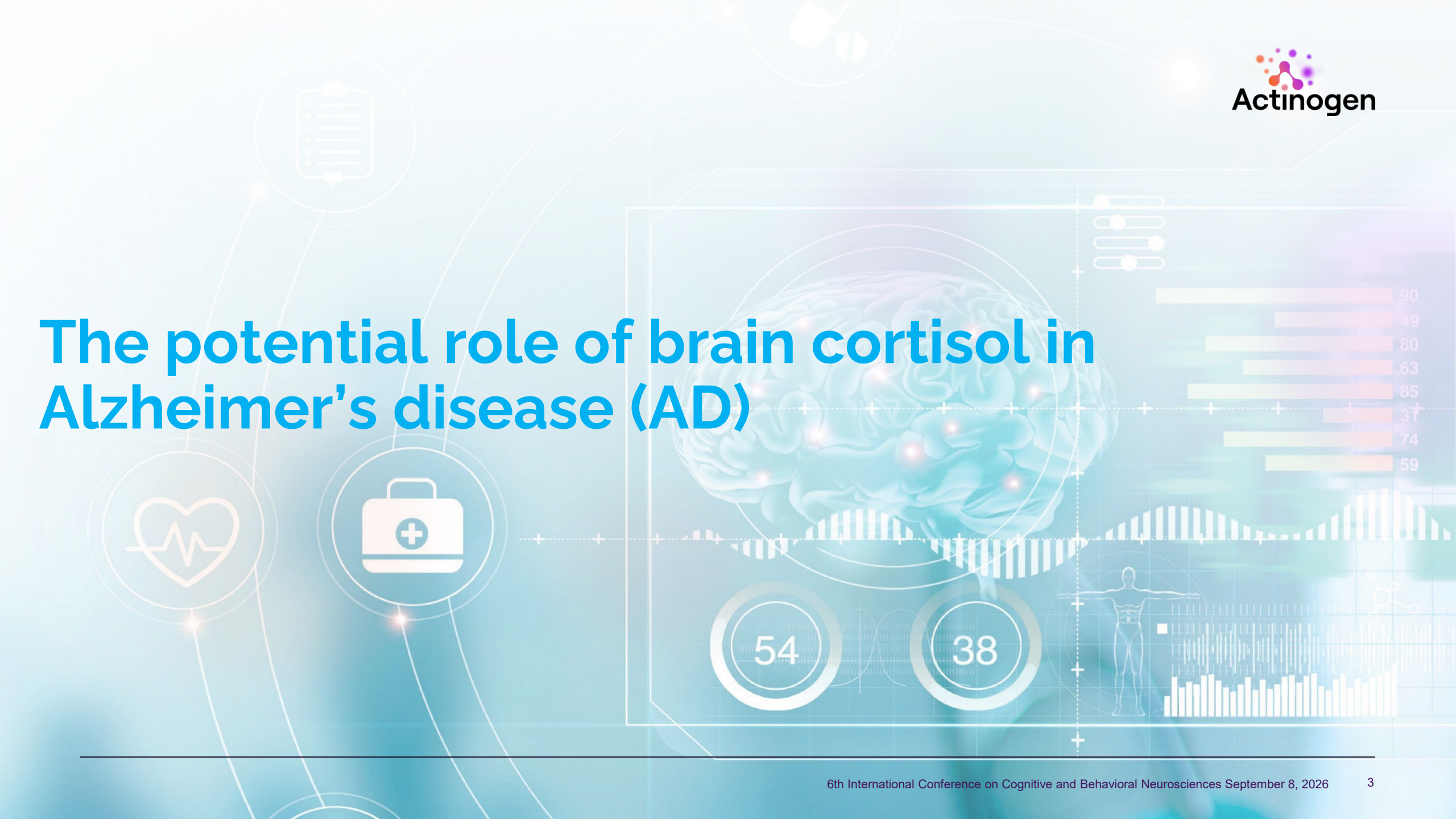
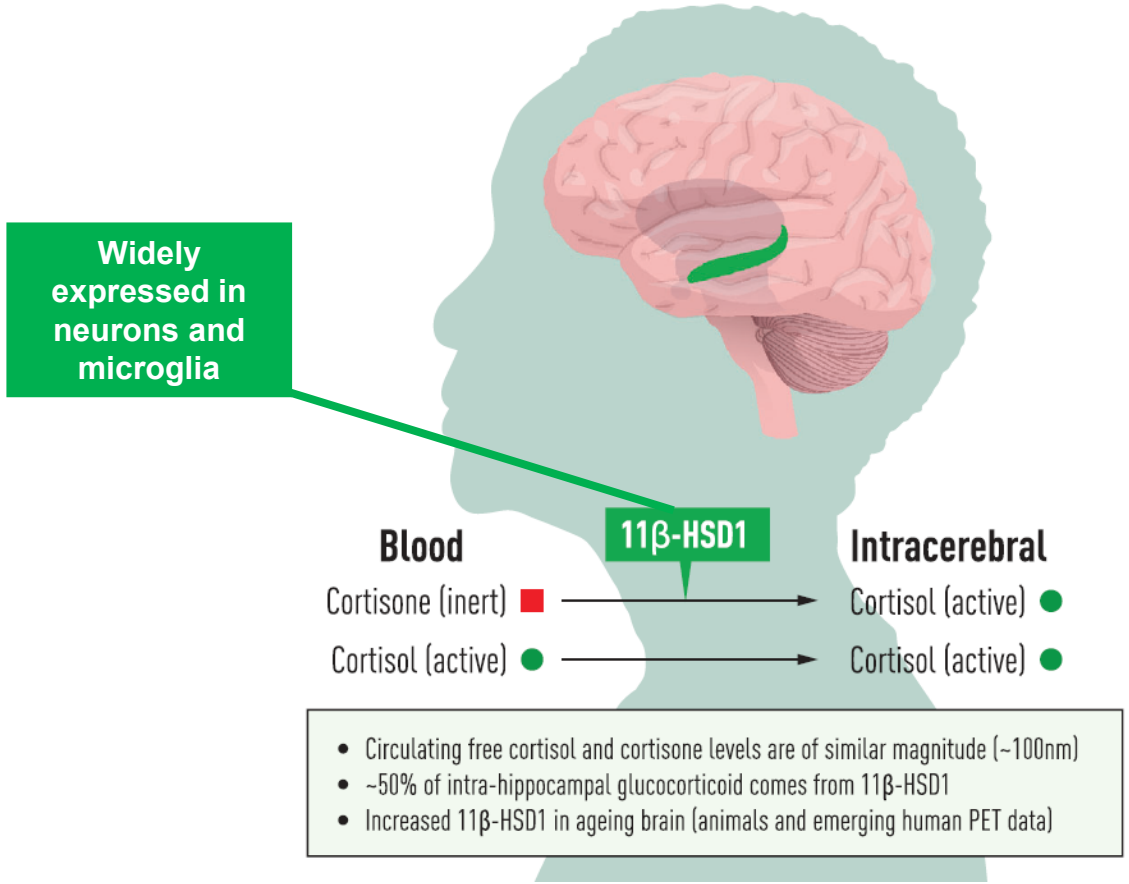
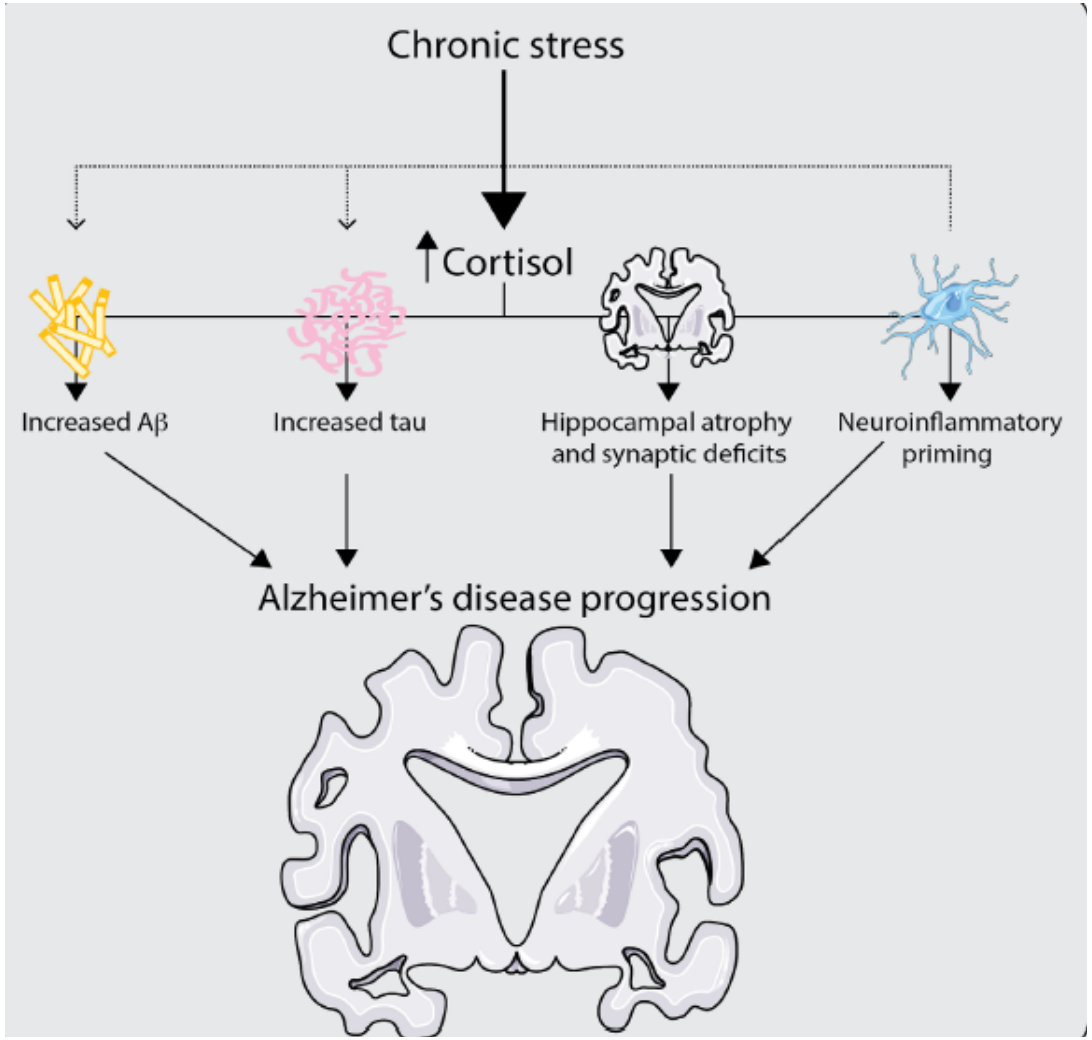
The potential role of brain cortisol in Alzheimer's disease (AD)



Cortisol and the Alzheimer's brain

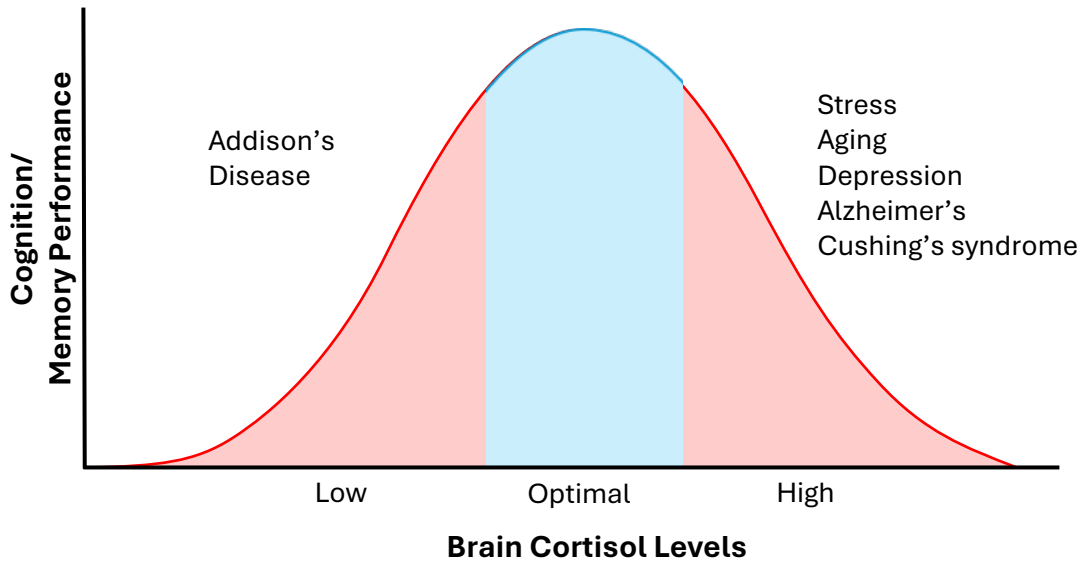
"Stress" and/or genetic factors may drive multiple AD mechanisms via cortisol





Impact of cortisol on cognition

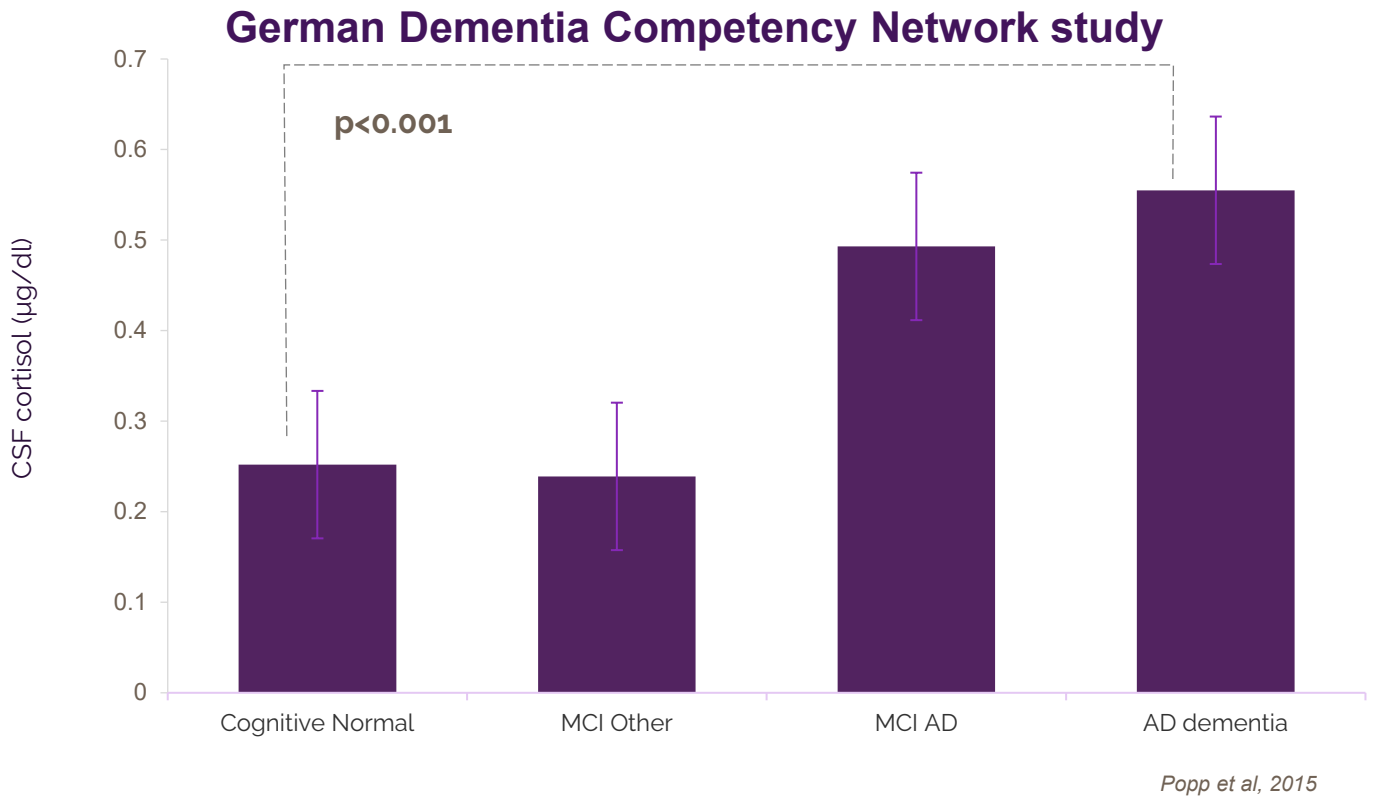
Abnormal brain cortisol levels alter cognition



Optimal cognition requires 'normal' brain cell cortisol levels - largely driven by local 11β-HSD1 activity

Elevated human brain cortisol levels linked to AD

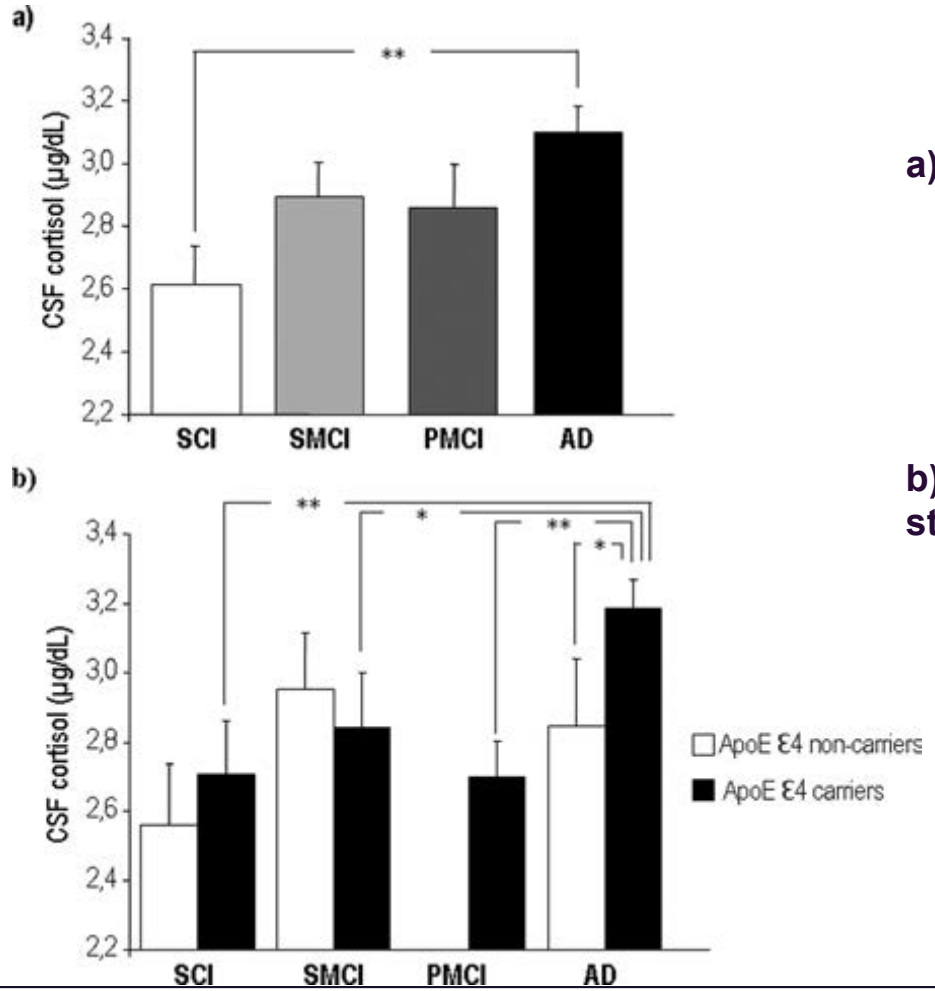
Brain fluid cortisol measurements best reflect the tissue cortisol environment



Popp et al., 2015, Neurobiol. Aging 36:601–607
CSF: Cerebrospinal fluid

Major AD genetic risk factor of ApoE4 associated with elevated brain cortisol levels

~67% of patients in AD trials have one or two copies of the ApoE4 gene



a) CSF cortisol level by disease classification (SCI: subjective cognitive impairment; SMCI stable mild cognitive impairment: progressive mild cognitive impairment; AD Alzheimer's disease

b) As above by known ApoE4 genetic status (0 vs. 1-2 copies)

Gil-Bea et al. 2010

Cortisol excess is toxic to the brain

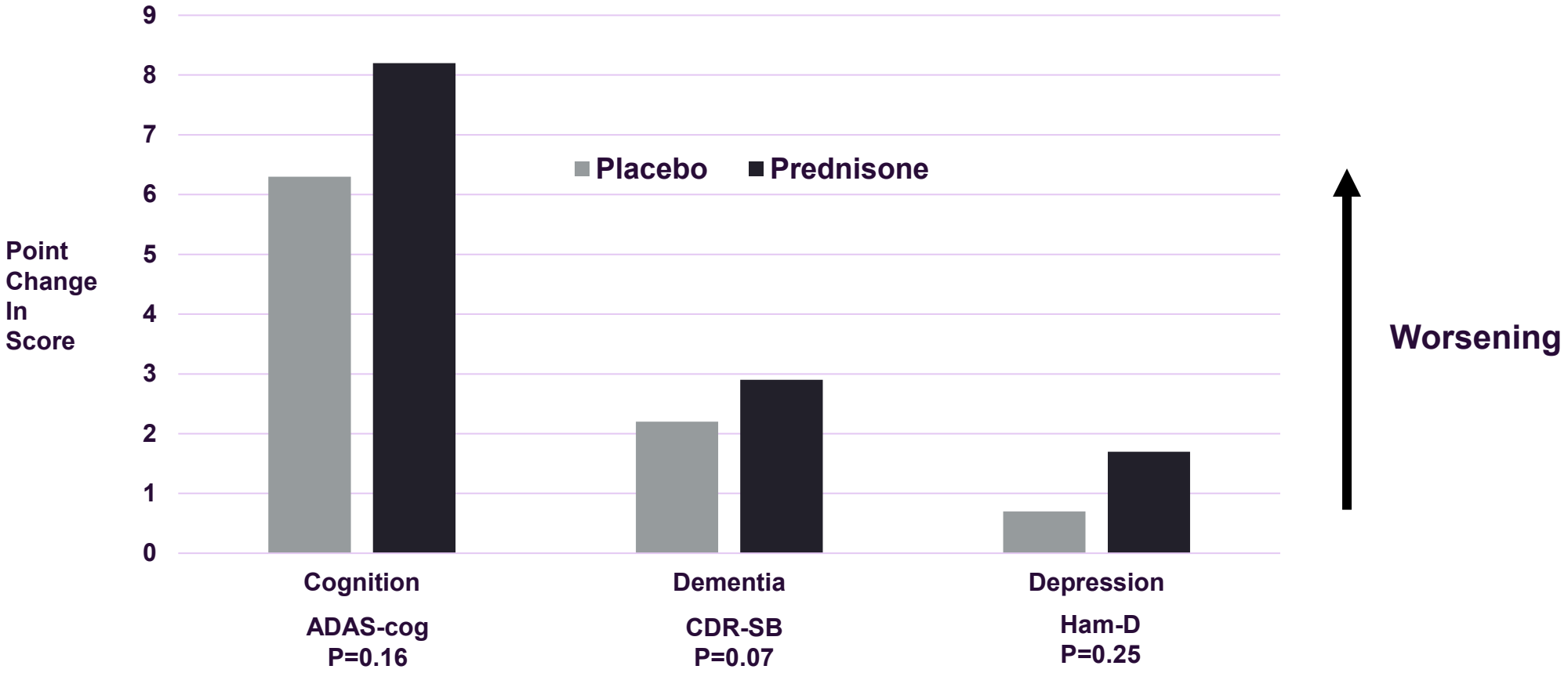
Literature from clinical use as a therapeutic and excess cortisol in Cushing's syndrome

Symptom or sign of brain toxicity
Trends to worsening Alzheimer's disease
Shrinkage to hippocampus
General brain shrinkage
Memory impairment
Executive function impairment
Difficulty learning
Poor concentration
Anxiety
Depression

Data reported for Cushing's syndrome of endogenous excess cortisol and/or therapeutic corticosteroids
Dekkers et al. 2022; Liu et al. 2022; De Alcubierre et al. 2023; Katragadda et al. 2025

Therapeutic cortisol worsened AD over 12 months

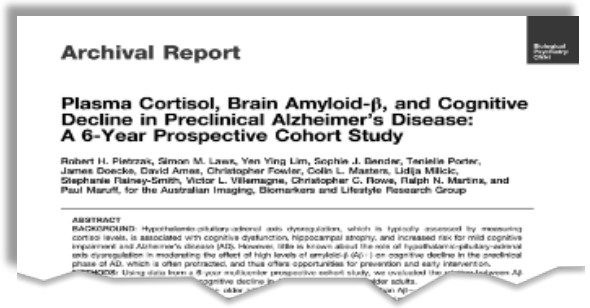
Historical trial of 10mg prednisone in patients with mild to moderate disease (n=138)



Aisen et al. Neurology 54:Feb 2000; dropouts were more common in the prednisolone group

Summary: Cortisol: guilty by association

- Multiple studies support the association between cortisol and 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
  - Cortisol accelerates toxic effects 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 Alzheimer's disease after age 75[12]

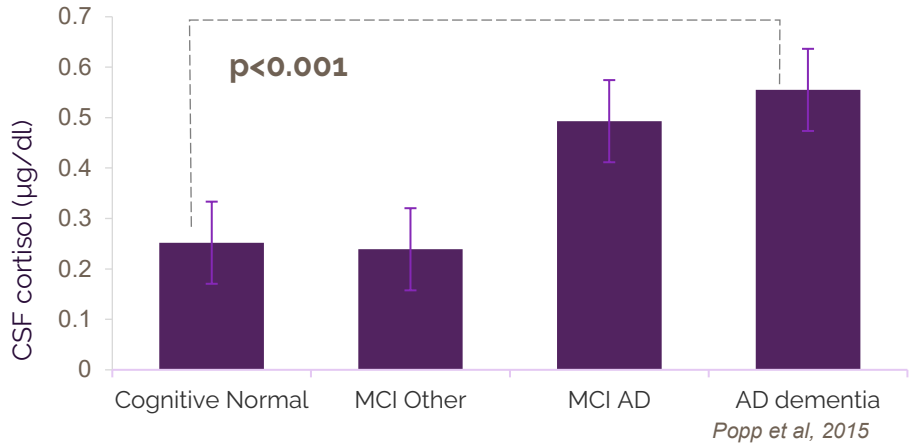

Archival Report

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

aibl

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

MEAN CSF CORTISOL LEVELS



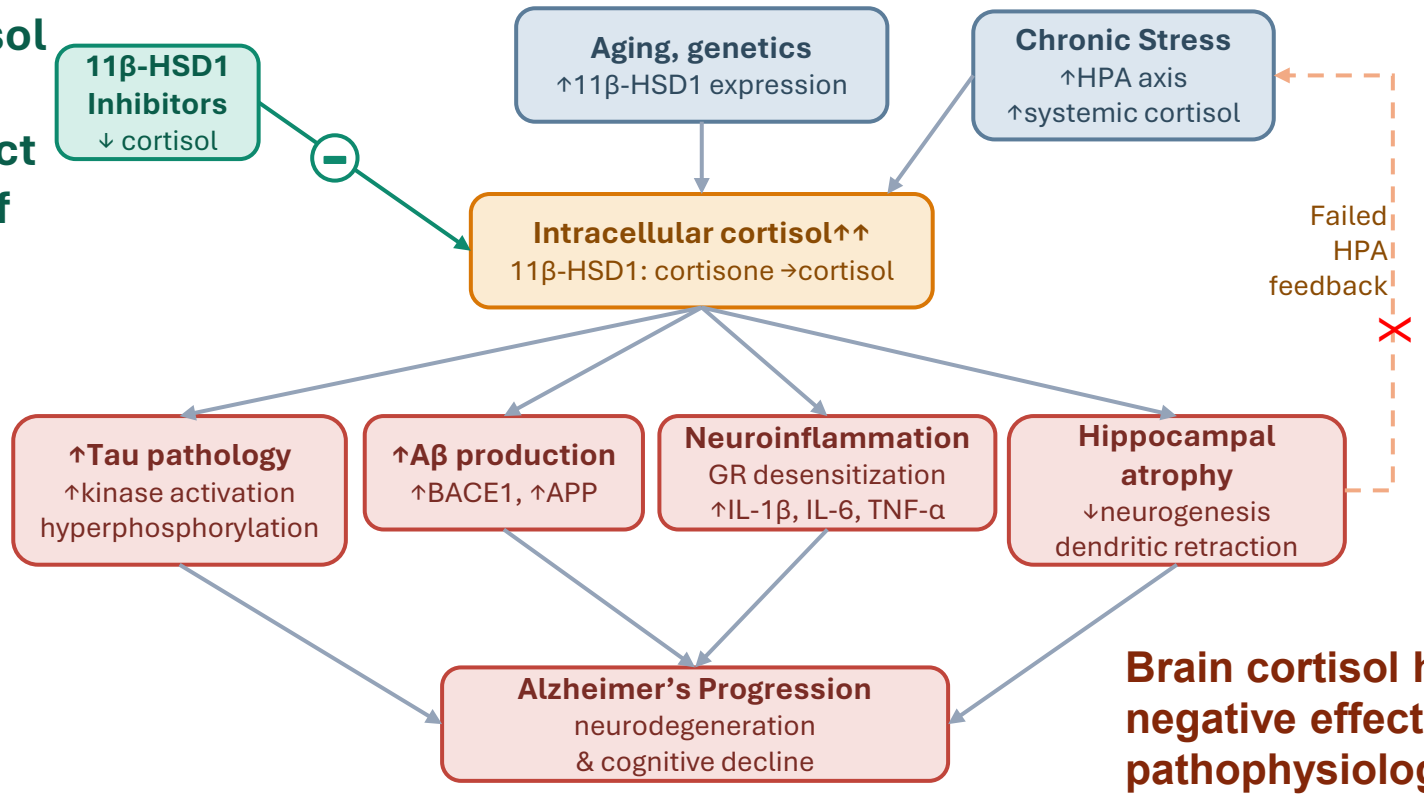
Popp et al, 2015

[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;

Potential benefits of 11β-HSD1 inhibition affect multiple disease pathways

11β-HSD1 inhibitors limit tissue synthesis of cortisol

Xanamem may counteract the deleterious effects of elevated brain cortisol

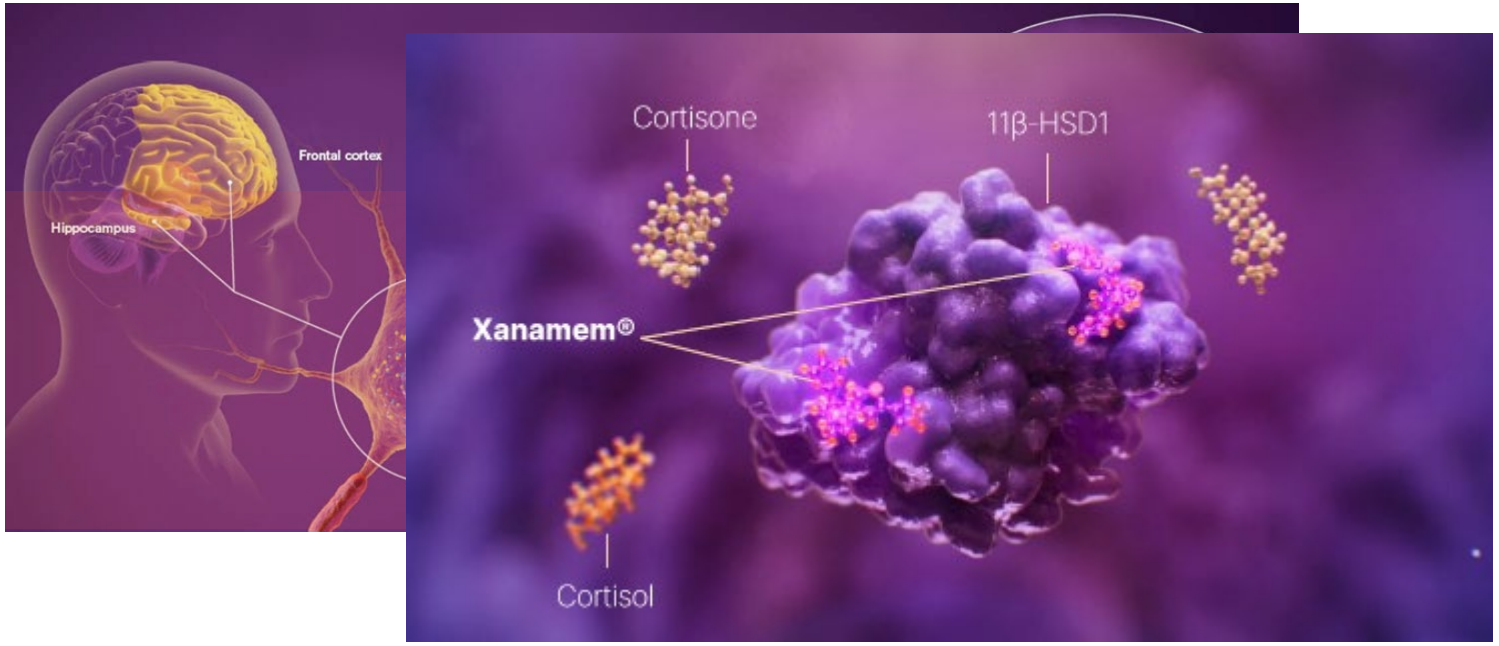


Brain cortisol has multiple negative effects in AD pathophysiology

Once-daily oral treatment with a unique mechanism

Xanamem is a selective cortisol synthesis inhibitor (11β-HSD1 enzyme)

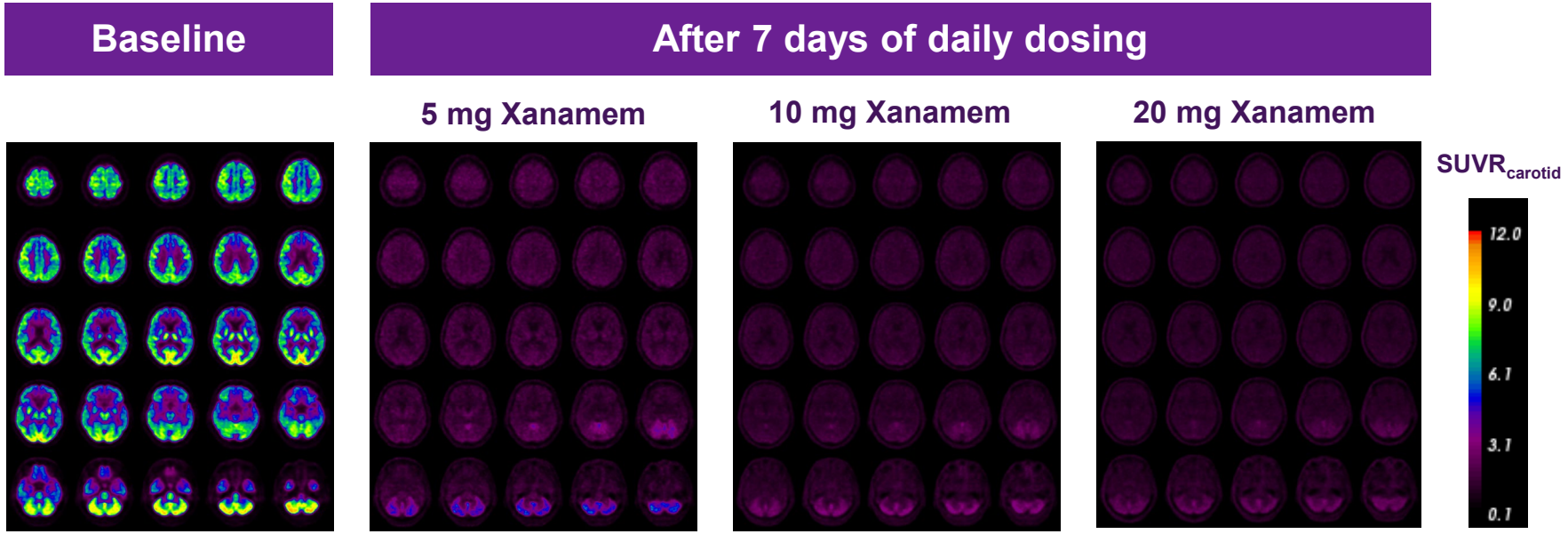
- Good safety profile in ~400 treated
- Brain-penetrant at low doses (5-10mg)
- Potentially disease-modifying in AD
- Anti-depressant activity in phase 2
- Low drug interaction potential ideal for combination therapy



Mouse experimental studies, brain cortisol levels & human clinical trials validate cortisol as a target for the treatment of AD

Xanamem achieves high brain target occupancy

Distribution of cortisol synthesis enzyme 11β-HSD1 shown in left panel



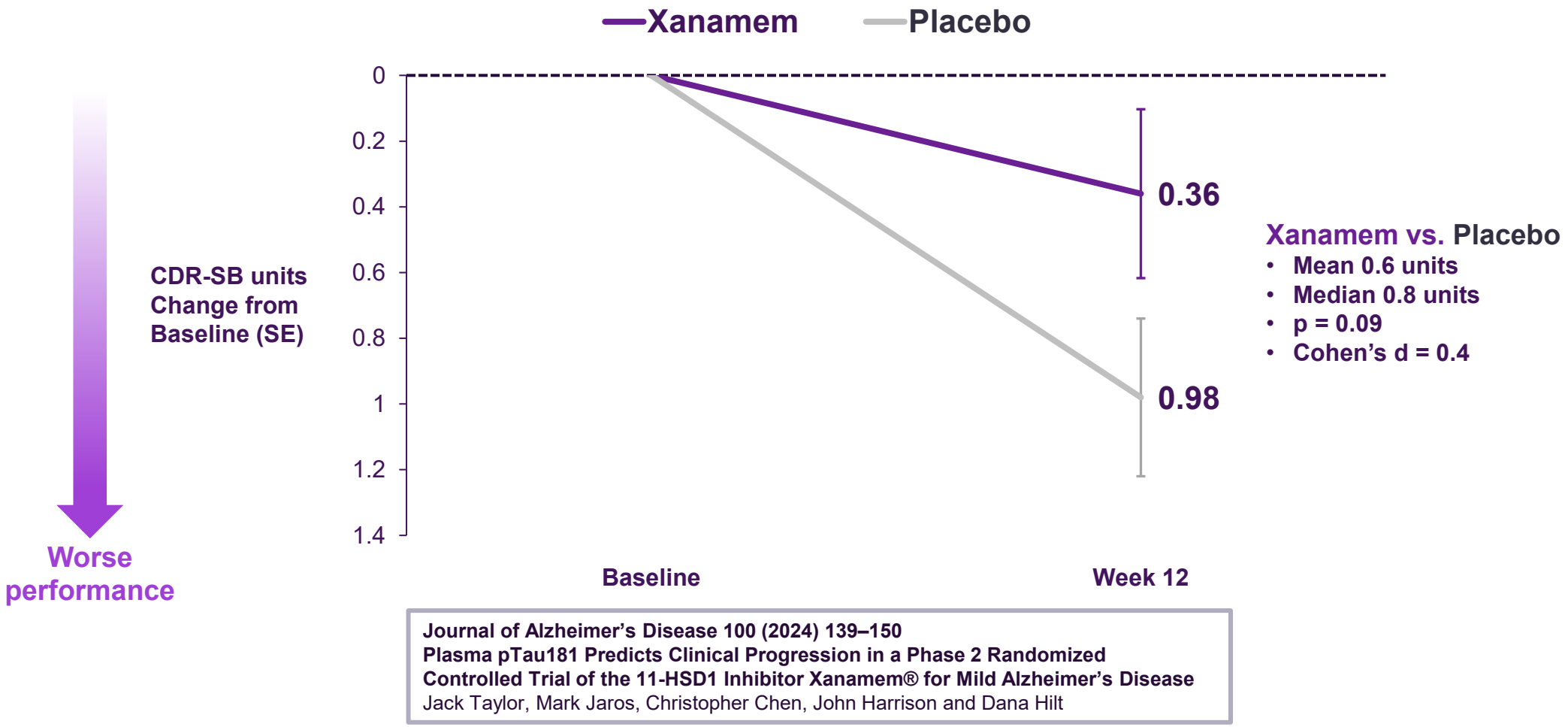
Reduction in tracer signal (loss of color) indicates high 11β-HSD1 occupancy

Strong target occupancy observed across evaluated clinical doses

Journal of Alzheimer's Disease 97 (2024) 1463–1475
Brain 11-Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamem™ Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals
Victor L. Villemagne, Vincent Dor, Lee Chong, Michael Kassiou, Rachel Mulligan, Azadeh Feizpour, Jack Taylor, Miriam Roesner, Tamara Miller and Christopher C. Rowe

Large Xanamem benefit[1] in high pTau181[2] patients (1)

Phase 2a biomarker study: major slowing of CDR-SB decline over 12 weeks (n=34)



Xanamem vs. Placebo

- **Mean 0.6 units**
- **Median 0.8 units**
- **p = 0.09**
- **Cohen's d = 0.4**

Journal of Alzheimer's Disease 100 (2024) 139–150
Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11-HSD1 Inhibitor Xanamem® for Mild Alzheimer's Disease
Jack Taylor, Mark Jaros, Christopher Chen, John Harrison and Dana Hilt

1. Using a linear extrapolation to 18 months 5-6x better than anti-amyloid antibody therapy
2. Pre-specified in SAP as above the median

Large Xanamem benefit in high pTau181 patients (2)

Twice as many patients in the Xanamem group had stable or improved disease compared with placebo[1]

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

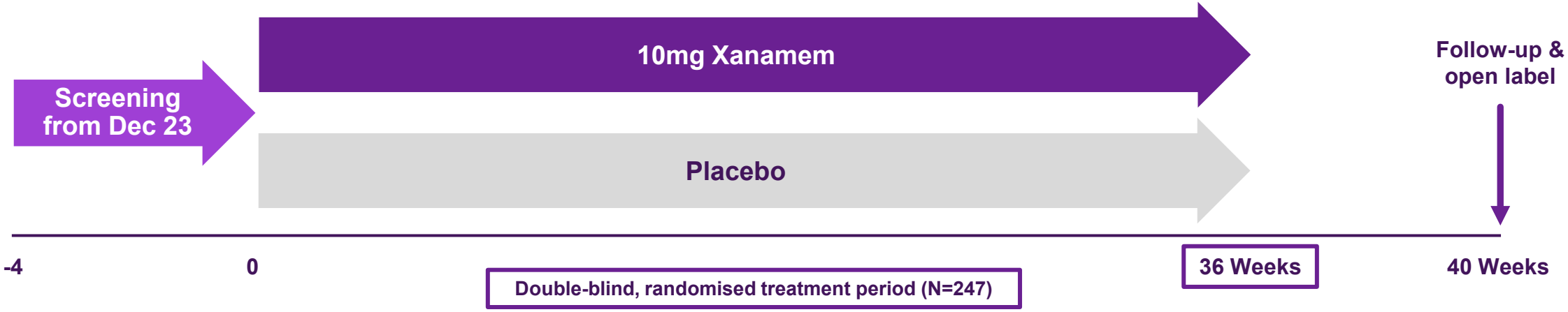
Large effect size vs. placebo of 0.6 – 0.8 units over 12 weeks

Xanamem 10 mg protected the majority of AD patients from progression

1. Where CDR-SB decreased or was unchanged - Xanamem 9 of 16 (56%) vs. Placebo 5 of 18 (28%)

XanaMIA phase 2b/3 trial in Alzheimer's disease

Final study results November 2026



Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
• Blood pTau biomarker positive • (pTau181 >1.6 pg/ml) • Mild-moderate Alzheimer's by NIA-AA clinical criteria	• **CDR-SB (functional and cognitive measure) @36 weeks**	• Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field) • Amsterdam Activity of Daily Living (functional measure)	• Enrolment at 15 Australian & 20 US sites • *2 yr open-label extensions phase open and enrolling

NIA-AA=National Institute of Aging - Alzheimer's Association; **CDR-SB** Clinical Dementia Rating Scale – Sum of Boxes

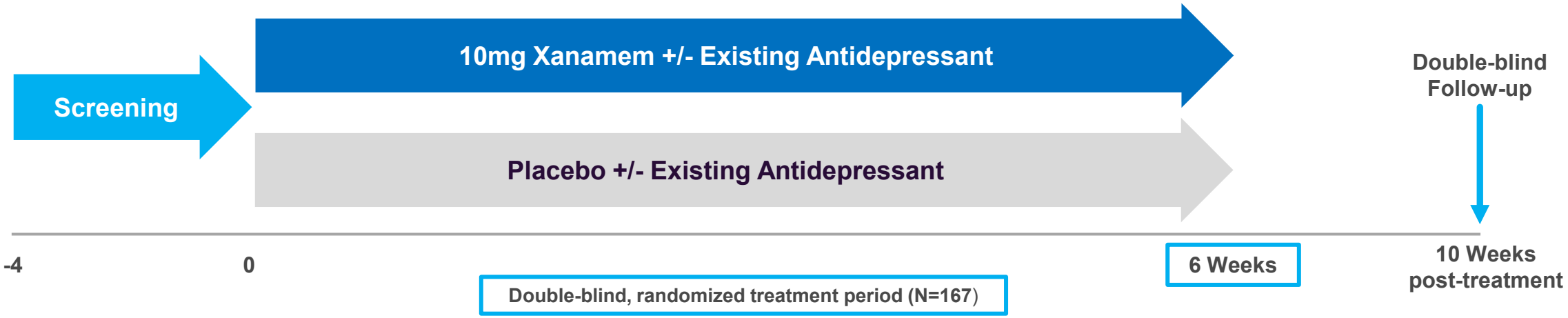
Xanamem for the treatment of Major Depressive Disorder (MDD)

Phase 2 study of difficult-to-treat MDD patients with:

1. Significant residual depression (HamD ≥ 17)
2. Measurable cognitive deficit (≥0.5 SD deficit on a coding test vs. normal)

XanaCIDD trial design and methods – completed CY2024

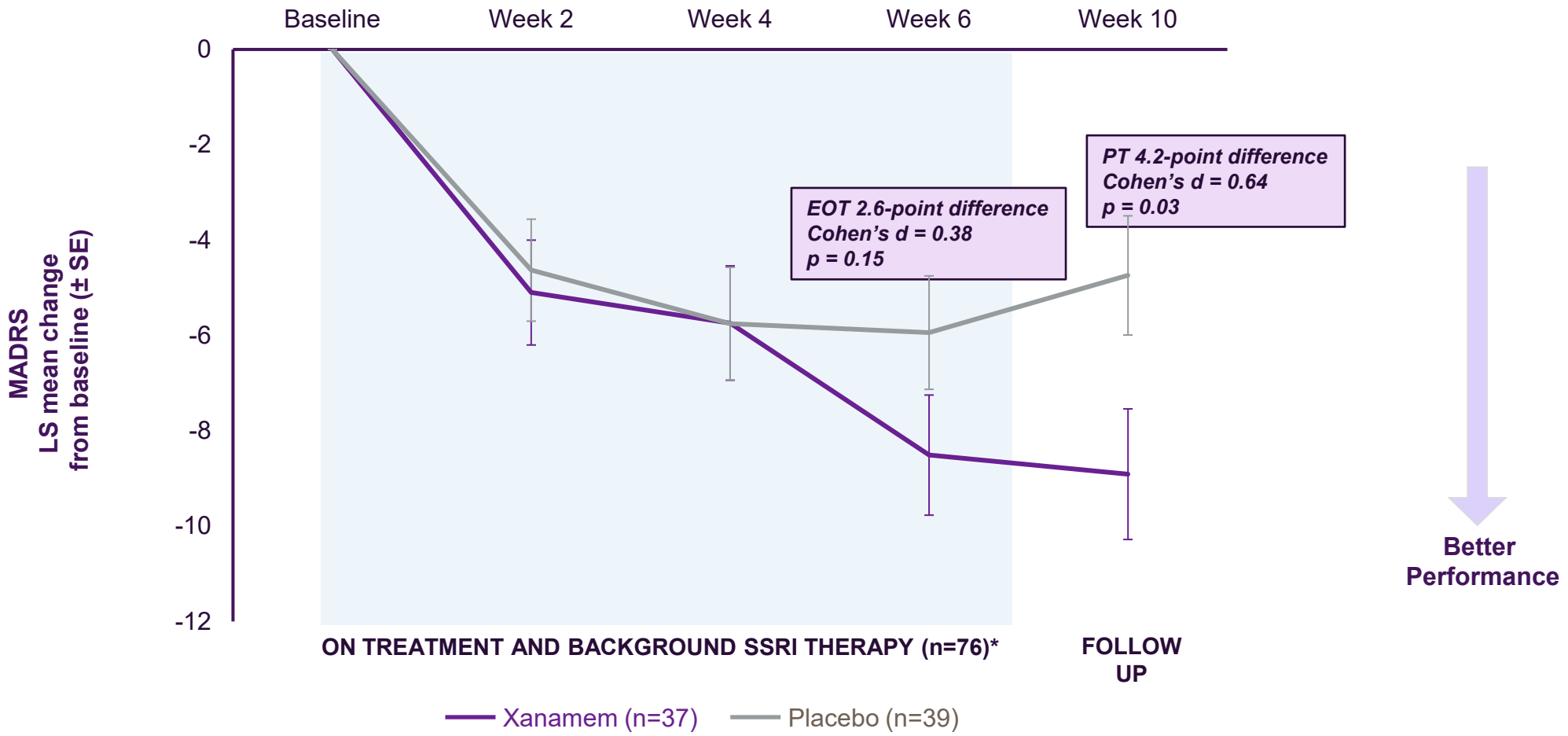
Phase 2, double-blind, proof-of-concept controlled trial to assess safety and efficacy
Enrolled MDD patients that have both depression and measurable cognitive deficit



Primary Endpoint	Key Secondary Endpoints
• **Cogstate Cognitive Test Battery Attention Composite** (attention and working memory)	• Montgomery-Åsberg Depression Rating Scale (**MADRS**) • Patient Global Impression-Severity **(PGI-S)** • Other MDD and cognitive measures

Durable antidepressant activity in phase 2 MDD trial

Separation from placebo overall and on background SSRI therapy*

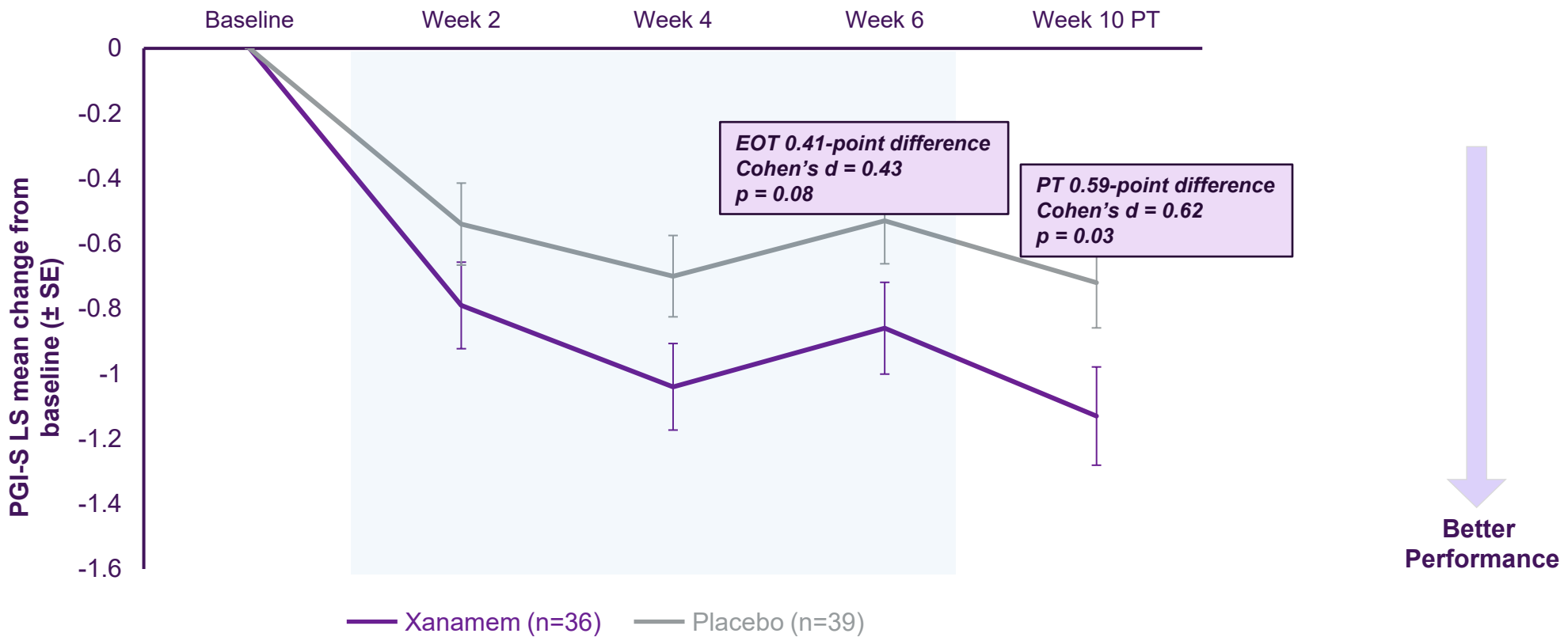


Abbreviations: SSRI, selective serotonin reuptake inhibitor.

*Data from planned phase 3 population with background SSRI therapy shown; Taylor et. al. Brit J Psychiatry 1–8. doi: 10.1192/bjp.2026.10689

Self-reported benefit in patients taking SSRI (n=75)*

Measured by Patient Global Impression – Severity score (PGI-S)



*Data from planned phase 3 population with background SSRI therapy shown; Taylor et. al. Brit J Psychiatry 1–8. doi: 10.1192/bjp.2026.10689

Phase 2a MDD summary

- ✓ ***Clinical benefit observed on both MADRS and PGI-S:***
  - ❖ ***Clinically significant benefits commencing at the end of 6 weeks therapy maintained/increased after 4 weeks of blinded, off-treatment follow up***
- ✓ ***Improvements observed in cognition in both treatment groups with no treatment benefit***
- ✓ ***Contrary to widely held belief, change in depression symptoms and cognition over time did not correlate i.e. in this population, cognitive impairment did not improve alongside depression or vice versa***

Xanamem 10 mg has anti-depressant activity worthy of further investigation

Summary: Xanamem - a potential new therapeutic in neuropsychiatry

An oral, selective and CNS-penetrant 11β-HSD1 inhibitor

- ✓ *Xanamem is a selective 11β-HSD1 inhibitor that inhibits brain cortisol synthesis*
- ✓ *Safe and well tolerated in more than 500 people treated*
- ✓ *Clinical activity observed in two phase 2a trials:*
  - ❖ *Biomarker-confirmed mild/mod Alzheimer's disease (n=34)*
  - ❖ *Difficult-to-treat depression (n=165)*
- ✓ *Phase 2b/3 AD trial topline final results will become available in November 2026*
- ✓ *Potential to expand to treat other neuropsychiatric conditions*

Thank you

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