



ASX ANNOUNCEMENT

Xanamem oral presentation at the 6th International Conference on Cognitive and Behavioral Neurosciences by Actinogen's Chief Medical Officer Dr Dana Hilt

Sydney, 9 September 2026. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce the international presentation by the Company's CMO, Dr Dana Hilt, entitled *Controlling cortisol in CNS¹ disease – Xanamem[®], a selective 11 β -HSD1 inhibitor as a potential new therapeutic for neuropsychiatric diseases*. This academic, oral presentation was given overnight to the 6th International Conference on Cognitive and Behavioral Neurosciences in Paris, France, and is included in this announcement.

Presentation highlights:

- "Stress" and/or genetic factors may drive multiple Alzheimer's disease (AD) mechanisms via cortisol
- Optimal brain function requires "normal" levels of brain cell cortisol which are largely driven by local 11 β -HSD1 enzyme activity
- Elevated brain cortisol levels are associated with AD and its major genetic risk factor, Apoprotein E4
- Inhibition of 11 β -HSD1 in the brain may reduce cortisol's toxic effects on brain cells, inflammation and AD-related proteins
- Xanamem is an oral, brain-penetrant inhibitor of 11 β -HSD1 with a high level of target enzyme engagement in the brain
- Xanamem has shown encouraging clinical activity in two phase 2a trials:
 - a. Ability to slow the progression of AD in biomarker-selected patients over 12 weeks of treatment (n=34)
 - b. Improvement in depression symptoms in a difficult-to-treat population (n=165).
- The first pivotal trial of Xanamem, comparing 36 weeks of treatment to placebo in patients with mild to moderate AD, will report topline, final results in November this year (n=247)
- Xanamem has been safe and well-tolerated in more than 500 people treated.

View this announcement on our InvestorHub: <https://investors.actinogen.com.au/link/rDvJny>

ENDS

Investors

Dr Steven Gourlay
CEO & Managing Director
P: +61 2 8964 7401
E: steven.gourlay@actinogen.com.au

Michael Roberts
Communications
M: +61 423 866 231
E: michael.roberts@actinogen.com.au

Media

George Hazim
Media & Public Affairs Australia
M: +61 417 516 262
E: georgehazim@mediaaffairs.com.au

¹ CNS: Central Nervous System

[®] Xanamem is a registered trademark of Actinogen Medical Limited

Announcement authorised by the Disclosure Committee of Actinogen Medical Limited

About Actinogen Medical

Actinogen Medical (ACW) is an ASX-listed, biotechnology company developing a novel therapy for neurological and neuropsychiatric diseases associated with dysregulated brain cortisol. There is a strong association between cortisol and detrimental changes in the brain, affecting cognitive function, harm to brain cells and long-term cognitive health.

Cognitive function means how a person understands, remembers and thinks clearly. Cognitive functions include memory, attention, reasoning, awareness and decision-making.

Actinogen is currently developing its lead compound, Xanamem, as a promising new therapy for Alzheimer's Disease. It has also conducted a phase 2 trial in patients with cognitive impairment and depression and may study Fragile X Syndrome and other neurological and psychiatric diseases in the future. Reducing cortisol inside brain cells could have a positive impact in these and many other diseases. The cognitive dysfunction, behavioural abnormalities, and neuropsychological burden associated with these conditions is debilitating for patients, and there is a substantial unmet medical need for new and improved treatments.

Clinical Trials

The XanaMIA Phase 2b/3 Alzheimer's disease trial is a double-blind, 36-week treatment, placebo-controlled, parallel group design trial in 247 patients with mild to moderate AD and progressive disease, determined by clinical criteria and confirmed by an elevated level of the pTau181 protein biomarker in blood. Patients receive Xanamem 10 mg or placebo, once daily, and its ability to slow progression of Alzheimer's disease is assessed with a variety of endpoints. The primary endpoint of the trial is the internationally-recognized CDR-SB (Clinical Dementia Rating scale – Sum of Boxes). The trial is being conducted in Australia and the US and is now closed to participant recruitment. It has passed an independent Data Monitoring Committee safety and efficacy futility review and final topline results are expected in November 2026.

The XanaMIA-OLE Alzheimer's disease open-label extension is an open-label phase of up to 25 months treatment where all participants will receive active Xanamem 10 mg once daily. The trial evaluates safety and a limited number of efficacy endpoints such as the CDR-SB. The trial commenced in March 2026 and is open to all former and current participants in the XanaMIA Phase 2b/3 trial.

The XanaCIDD Phase 2a depression trial was a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 167 patients with moderate, treatment-resistant depression and a degree of baseline cognitive impairment. Participants were evenly randomized to receive Xanamem 10 mg once daily or placebo, in most cases in addition to their existing antidepressant therapy, and effects on cognition and depression were assessed. Trial results were reported in August 2024 and showed clinically and statistically significant benefits on depression symptoms with positive effects on the MADRS scale (a validated scale of depression symptom measurement) and the PGI-S (a valid patient reported assessment of depression severity). Cognition improved markedly and to a similar extent in both Xanamem and placebo groups. The peer-reviewed publication relating to this trial can be accessed for free via this link: <https://tinyurl.com/ckm63z63>.

About Xanamem (emestedastat)

Xanamem's novel mechanism is to control elevated levels of cortisol (aka the "stress hormone") in the brain through the inhibition of the cortisol synthesis enzyme, 11 β -HSD1, without affecting production of cortisol by the adrenal glands which is essential for the body's normal functioning. Xanamem is a first-in-class, once-a-day pill designed to deliver high levels of cortisol control in key areas of the brain related to Alzheimer's and other diseases such as the hippocampus and frontal cortex. To view Xanamem's two-minute Mechanism of Action animation, [click here](#).

Chronically elevated cortisol is associated with progression in Alzheimer's Disease and excess cortisol is known to be toxic to brain cells. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials. The recent XanaCIDD trial demonstrated clinically and sometimes statistically significant benefits on depressive symptoms, further validating the cortisol control mechanism for the Xanamem 10 mg oral daily dose.

The Company has studied 11 β -HSD1 inhibition by Xanamem in more than 500 volunteers and patients in eight clinical trials. Xanamem has a promising safety profile and has demonstrated clinical activity in patients with depression, patients

with biomarker-positive Alzheimer's disease and cognitively normal volunteers. High levels of target engagement in the brain with doses as low as 5 mg daily have been demonstrated in a human PET imaging study.

Xanamem is an investigational product and is not approved for use outside of a clinical trial by the FDA or by any global regulatory authority. Xanamem® is a trademark of Actinogen Medical.

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Controlling cortisol in CNS¹ disease – Xanamem;[®] a selective 11 β -HSD1 inhibitor as a potential new therapeutic for neuropsychiatric diseases.

Dana C Hilt MD

CMO, Actinogen Medical Limited

6th International Conference on Cognitive and Behavioral Neurosciences

September 8, 2026

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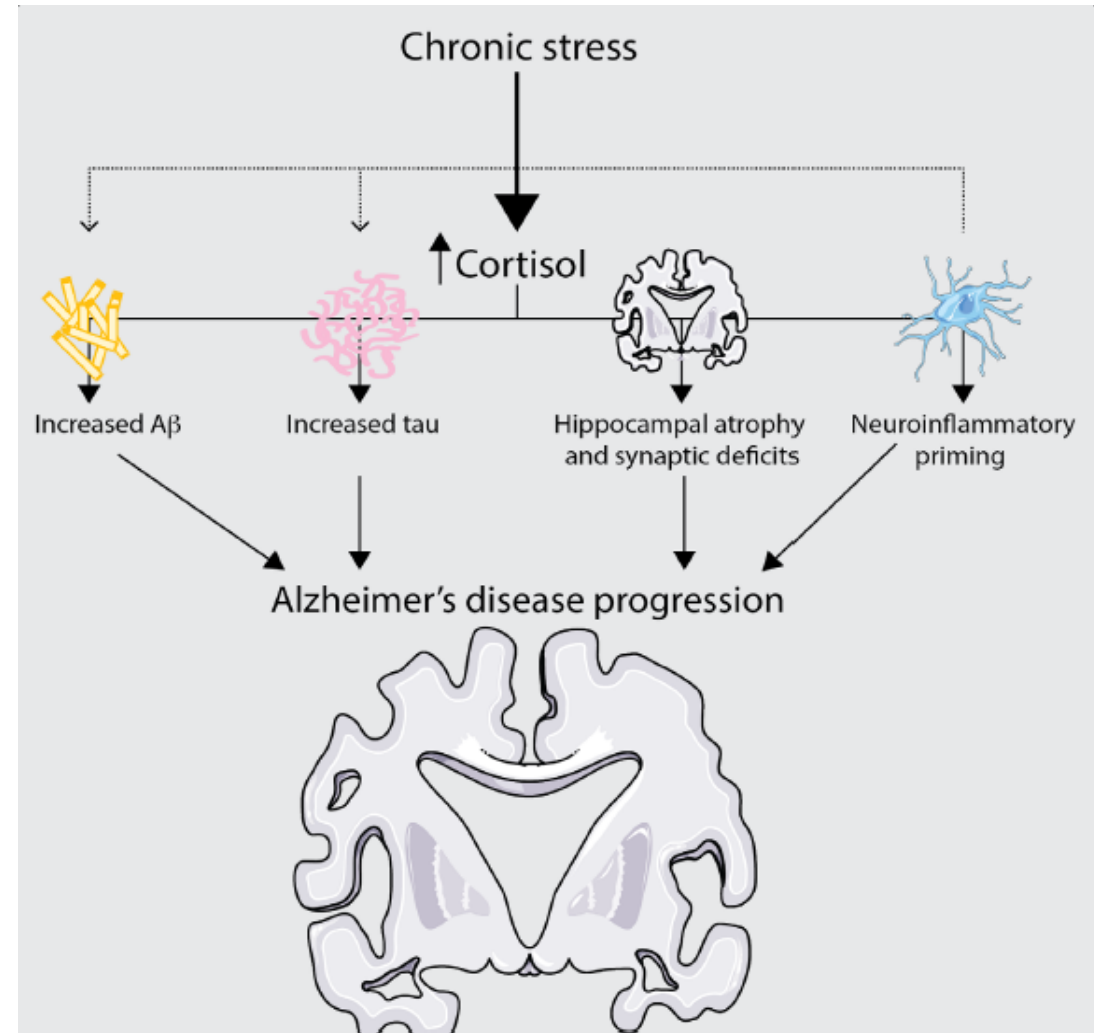
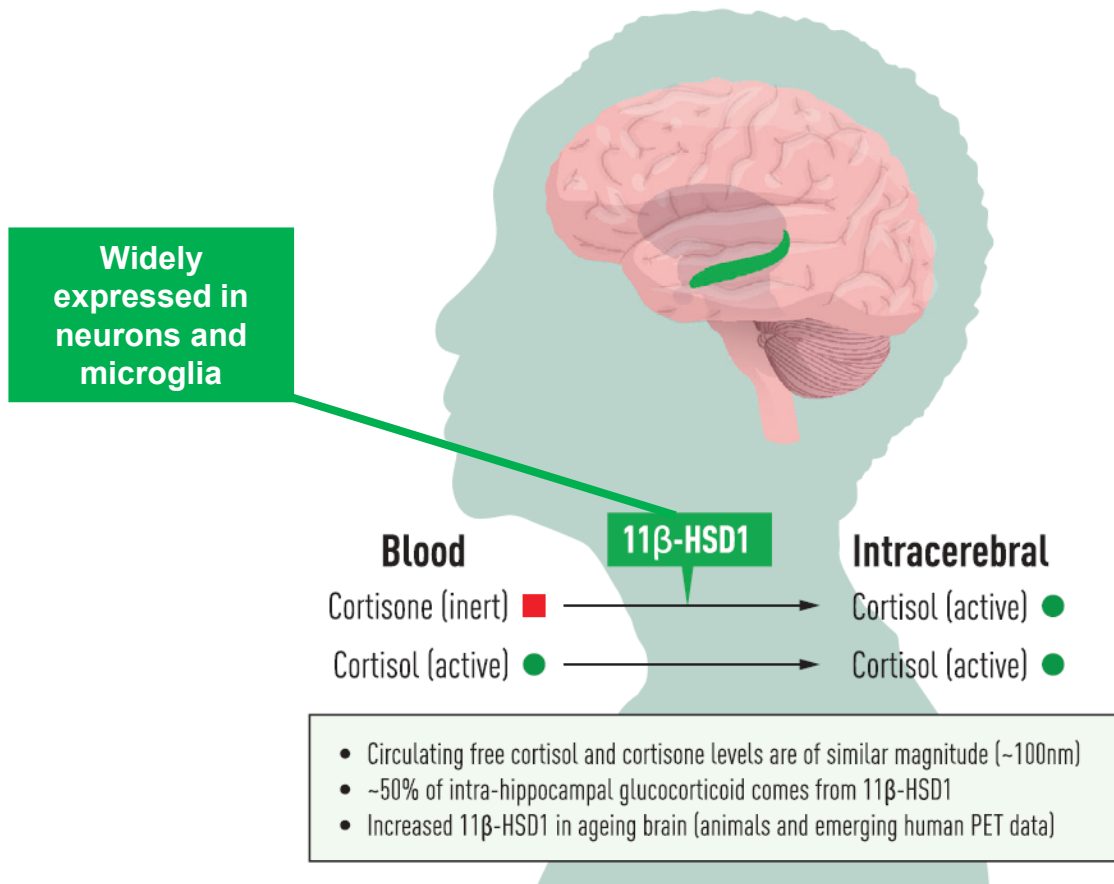
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The potential role of brain cortisol in Alzheimer's disease (AD)

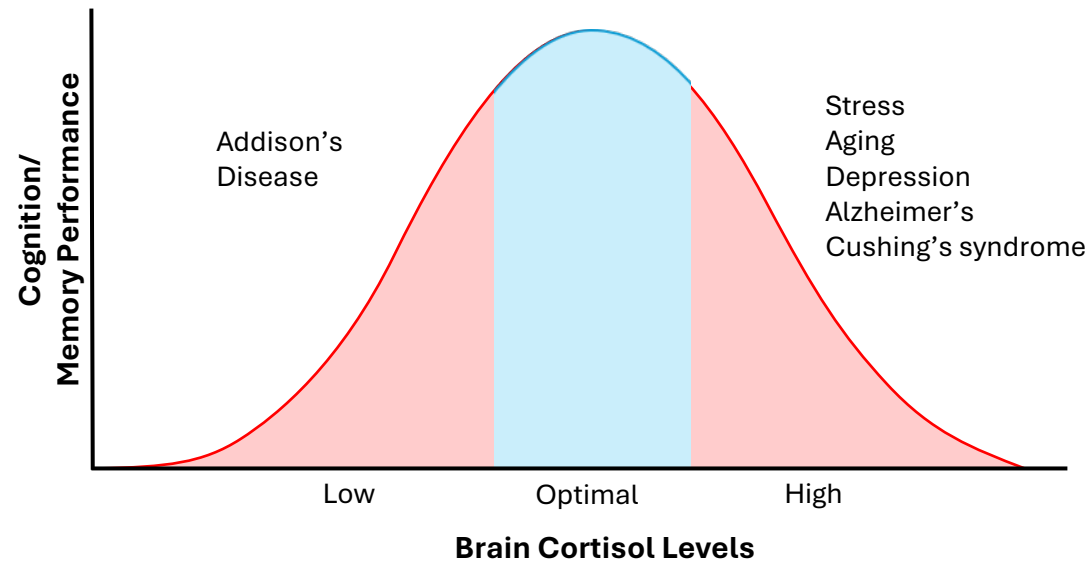
Cortisol and the Alzheimer's brain

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



Impact of cortisol on cognition

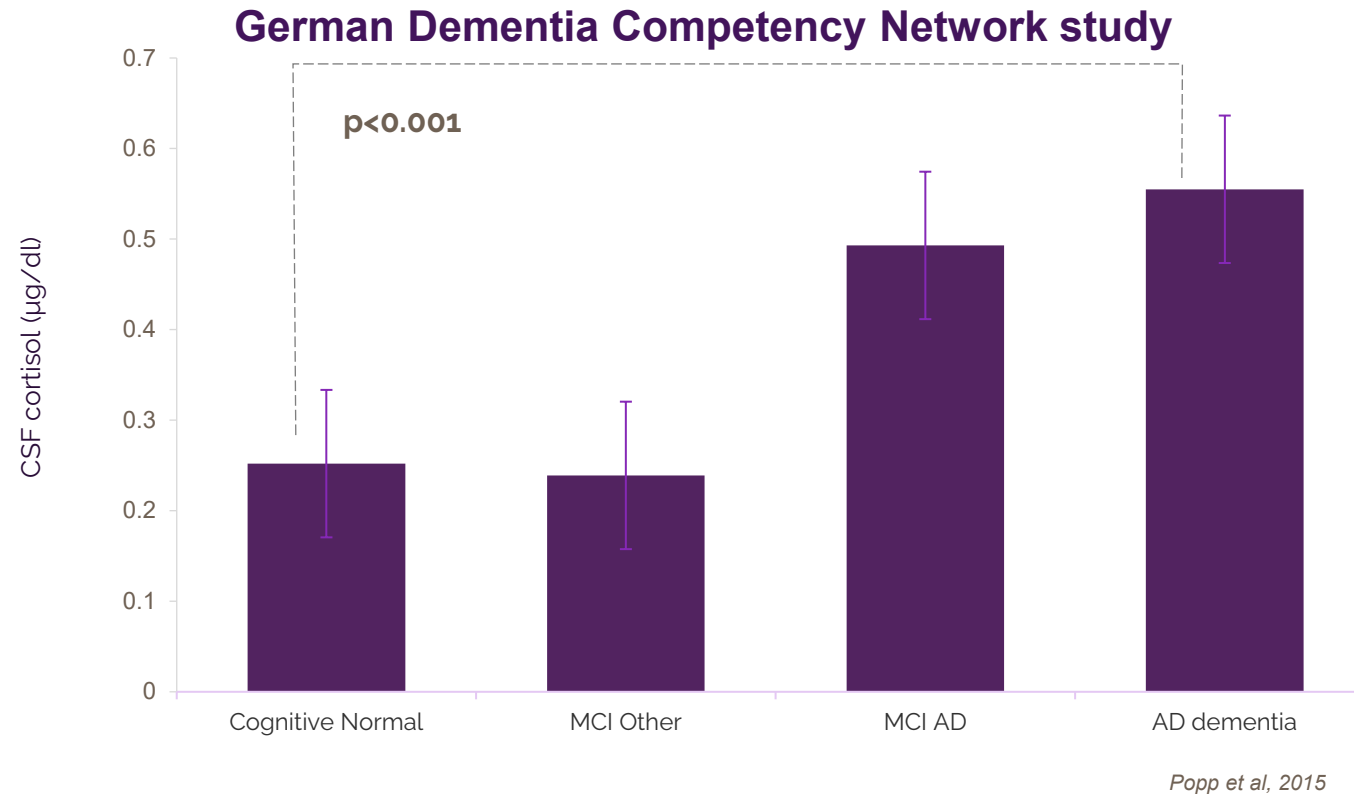
Abnormal brain cortisol levels alter cognition



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

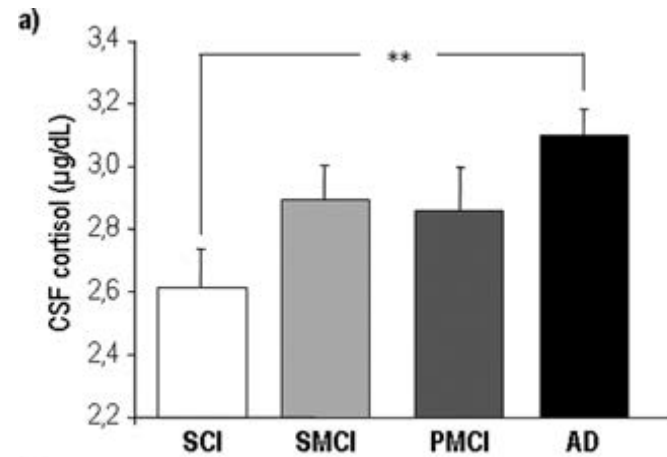
Elevated human brain cortisol levels linked to AD

Brain fluid cortisol measurements best reflect the tissue cortisol environment

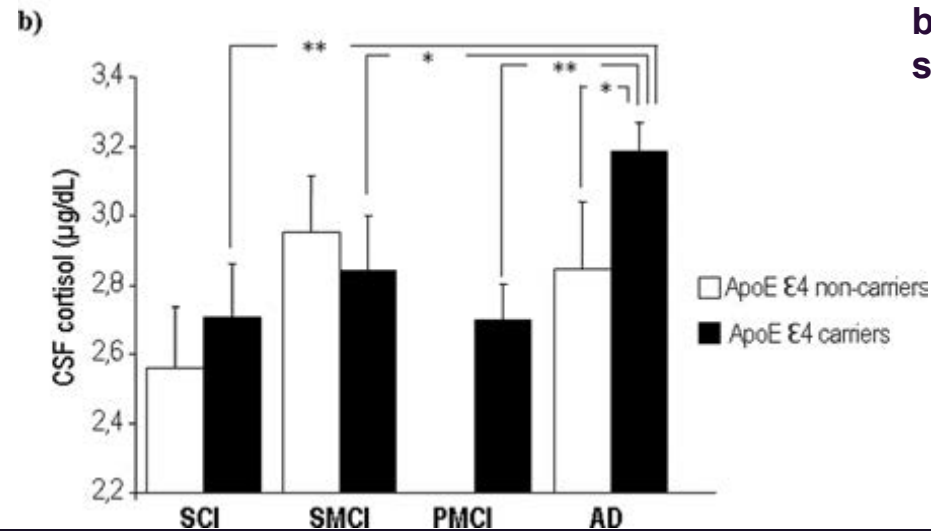


Major AD genetic risk factor of ApoE4 associated with elevated brain cortisol levels

~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; PMCI progressive mild cognitive impairment; AD Alzheimer's disease)



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

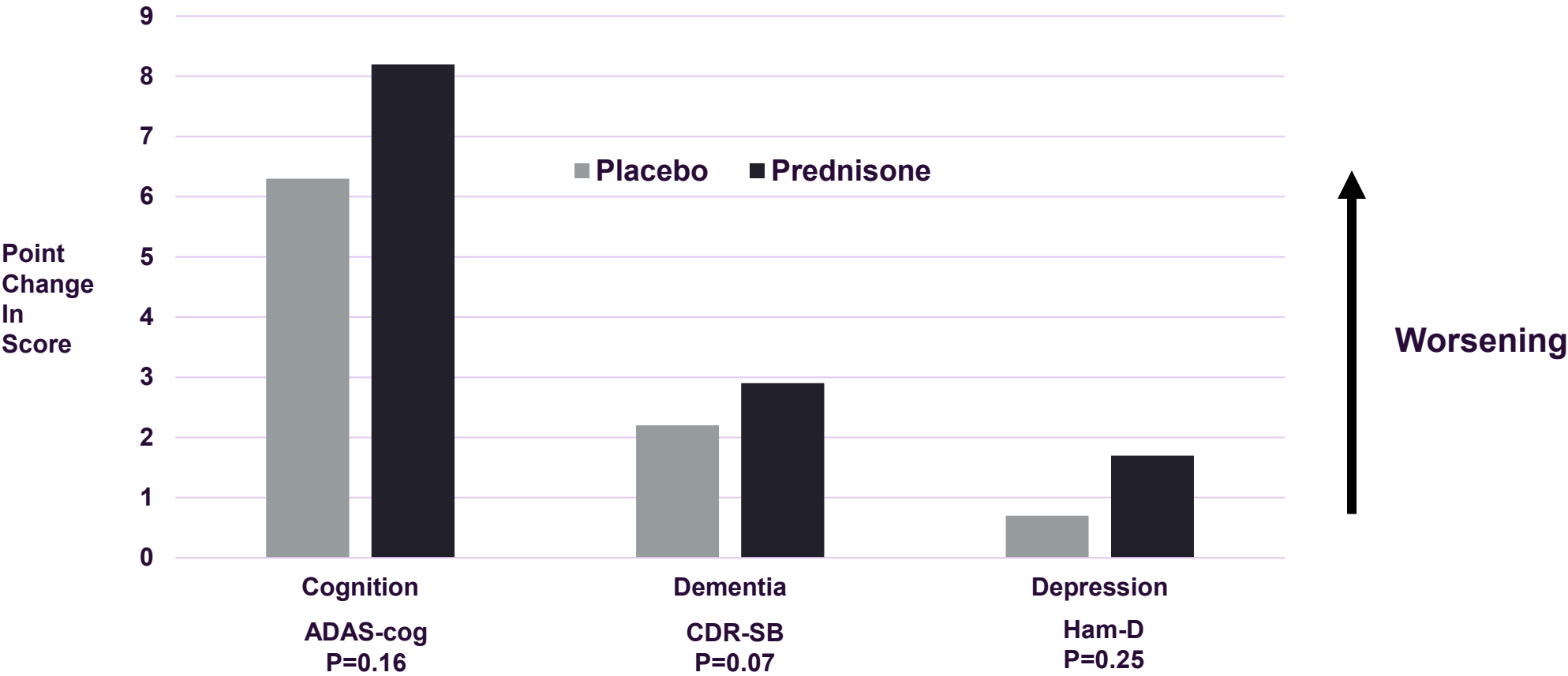
Cortisol excess is toxic to the brain

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

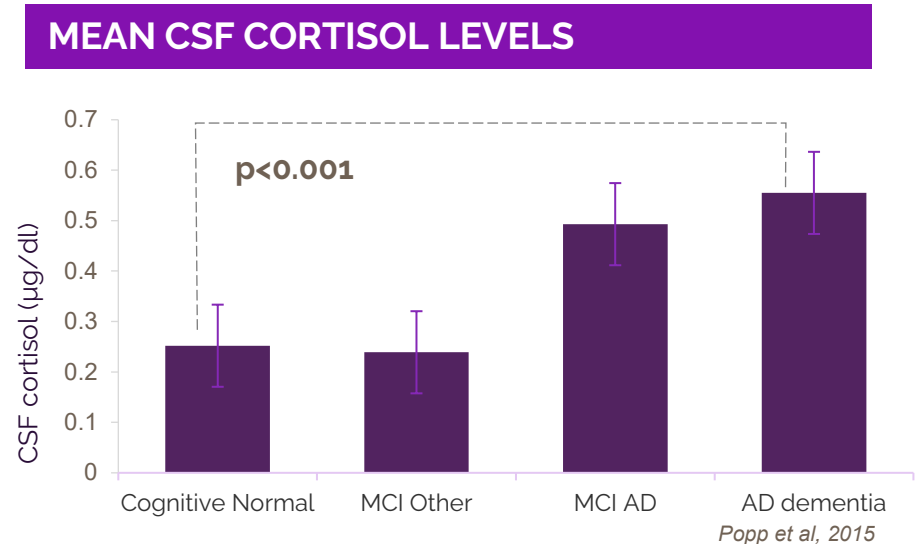
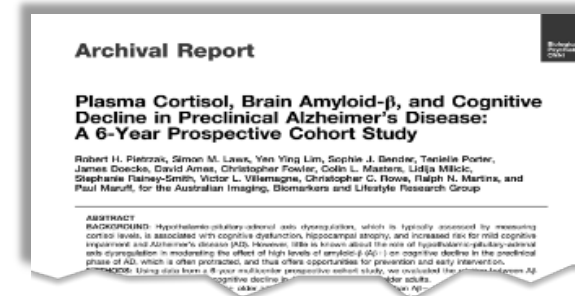
Therapeutic cortisol worsened AD over 12 months

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



Summary: Cortisol: guilty by association

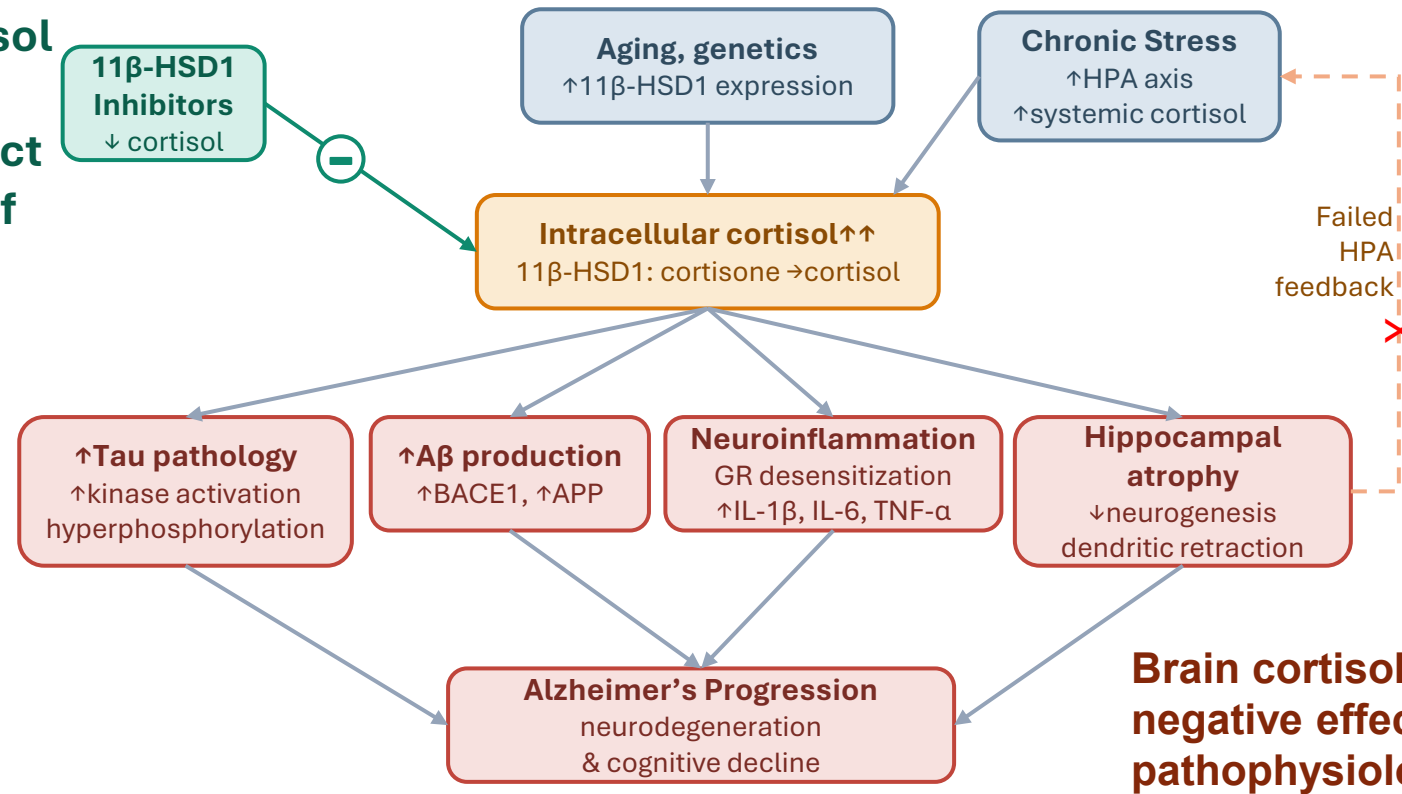
- Multiple studies support the association between cortisol and AD development and progression¹⁻⁵
- Cognitive impairment in patients with neuroendocrine dysfunction⁶⁻⁹
- Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017)⁵
 - Higher plasma cortisol leads to a much greater risk of developing AD
 - Cortisol accelerates toxic effects of A β on decline in global cognition, episodic memory, and attention
- Individuals with the APOE- ϵ 4 allele have higher CSF cortisol⁸
- 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 75¹²



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

11 β -HSD1 inhibitors limit tissue synthesis of cortisol

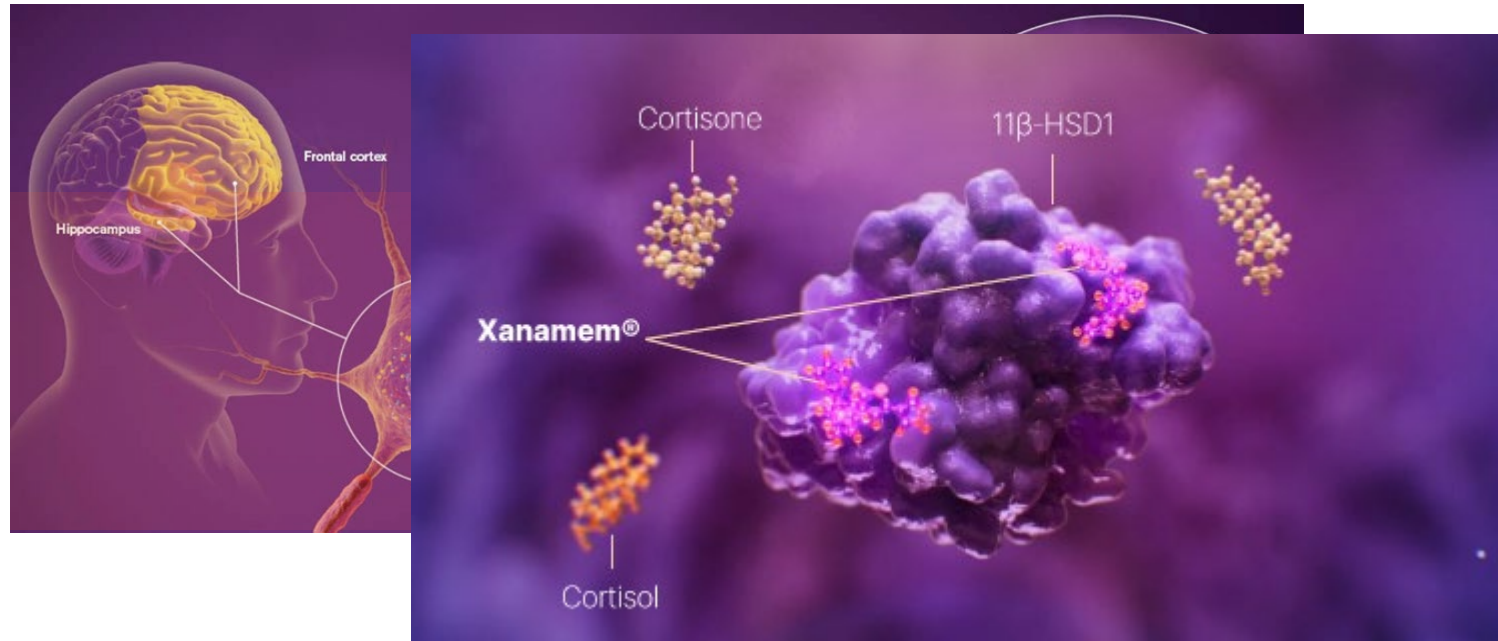
Xanomem may counteract the deleterious effects of elevated brain cortisol



Once-daily oral treatment with a unique mechanism

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

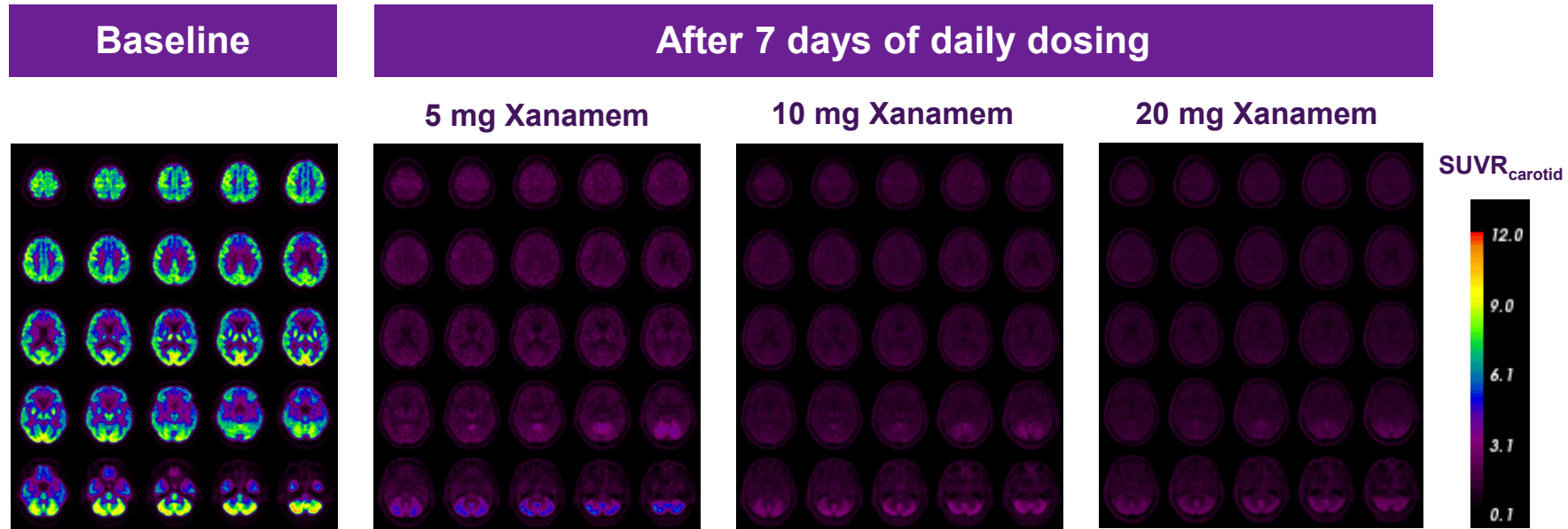
- ✓ Good safety profile in ~400 treated
- ✓ Brain-penetrant at low doses (5-10mg)
- ✓ Potentially disease-modifying in AD
- ✓ Anti-depressant activity in phase 2
- ✓ Low drug interaction potential ideal for combination therapy



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

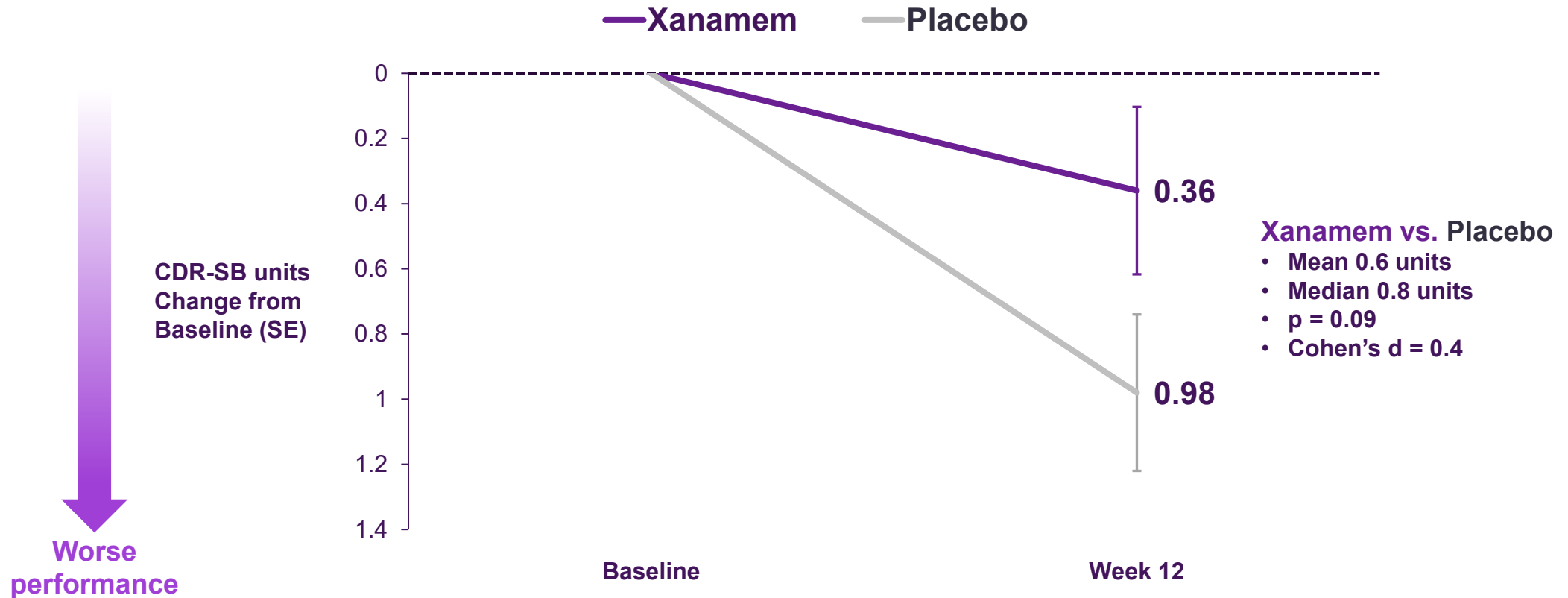
Distribution of cortisol synthesis enzyme 11β -HSD1 shown in left panel



Reduction in tracer signal (loss of color) indicates high 11β -HSD1 occupancy
Strong target occupancy observed across evaluated clinical doses

Large Xanamem benefit¹ in high pTau181² patients (1)

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



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 placebo¹

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

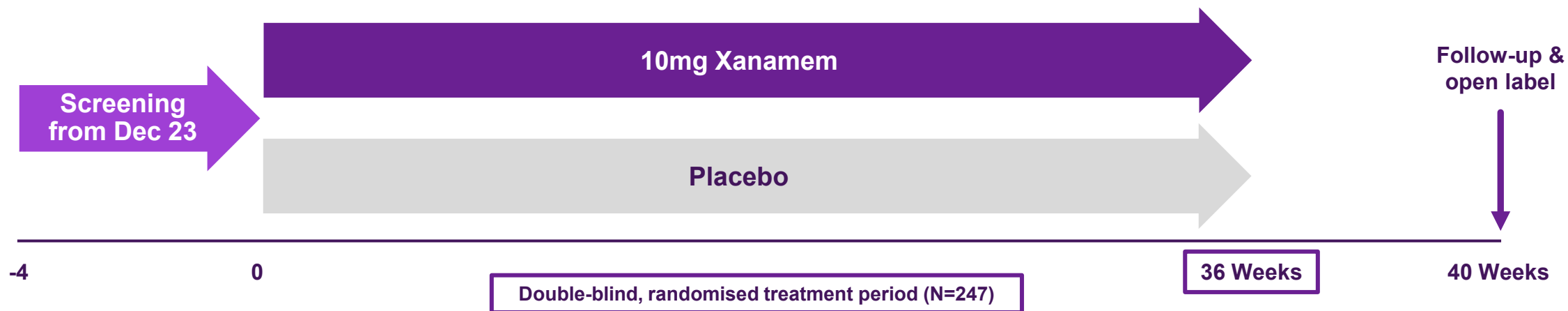
Large effect size vs. placebo of 0.6 – 0.8 units over 12 weeks

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

Xanamem for the treatment of Major Depressive Disorder (MDD)

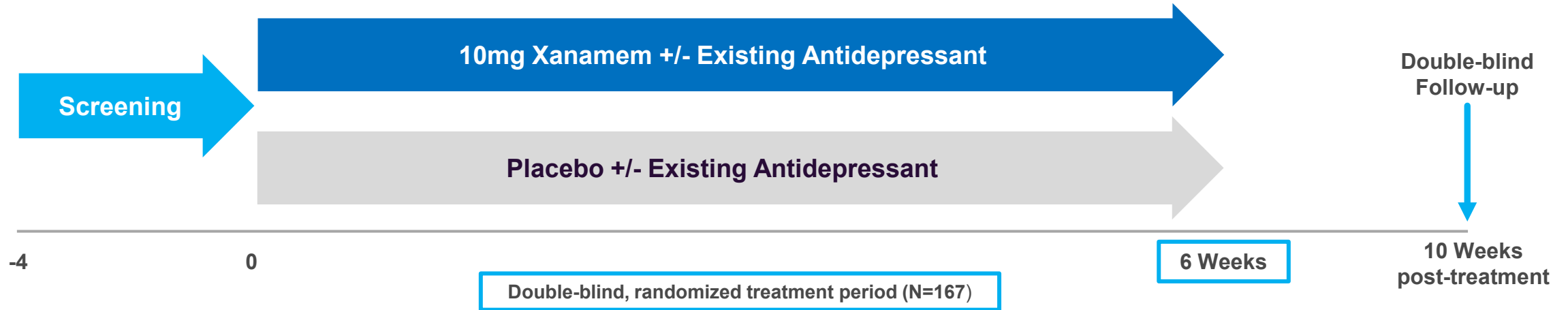
Phase 2 study of difficult-to-treat MDD patients with:

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



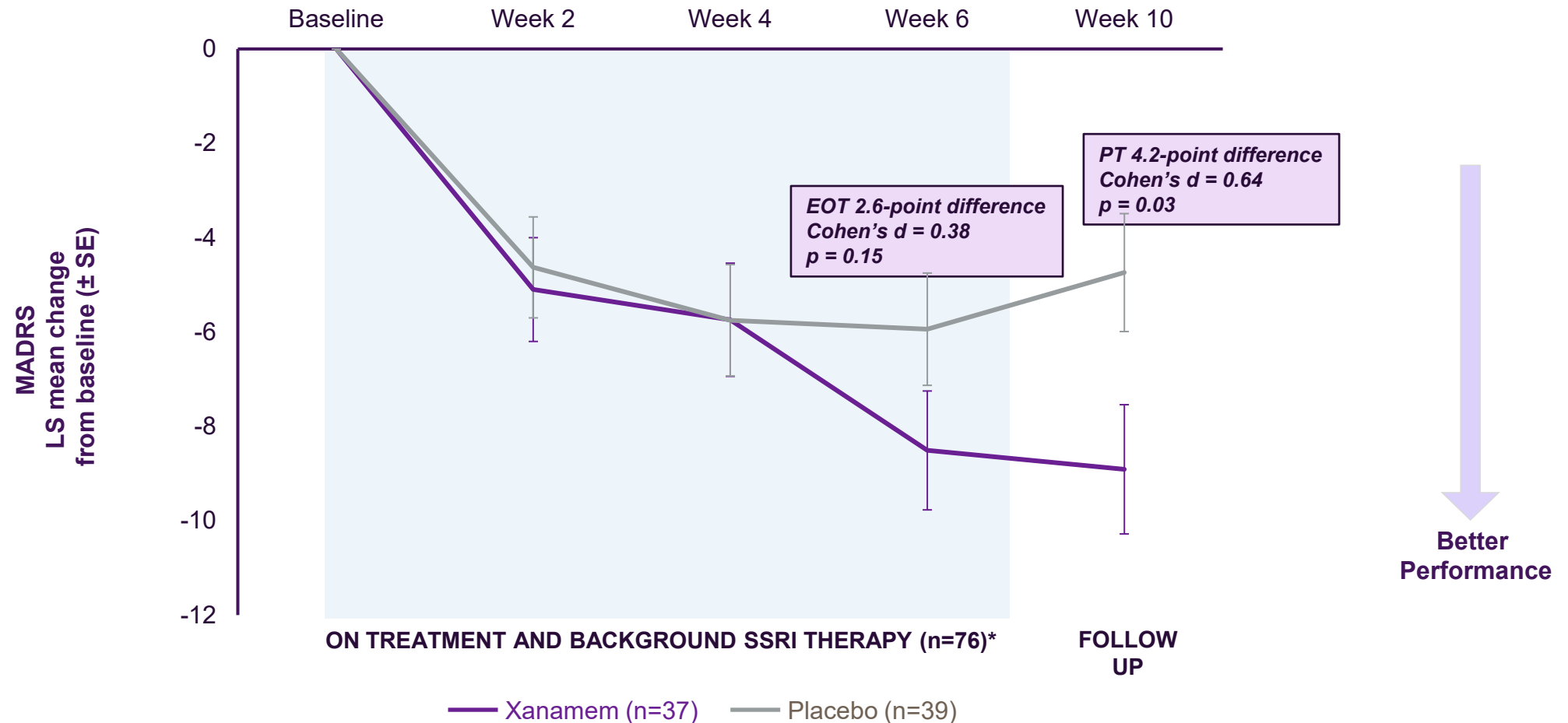
Phase 2, double-blind, proof-of-concept controlled trial to assess safety and efficacy
Enrolled MDD patients that have both depression and measurable cognitive deficit



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*



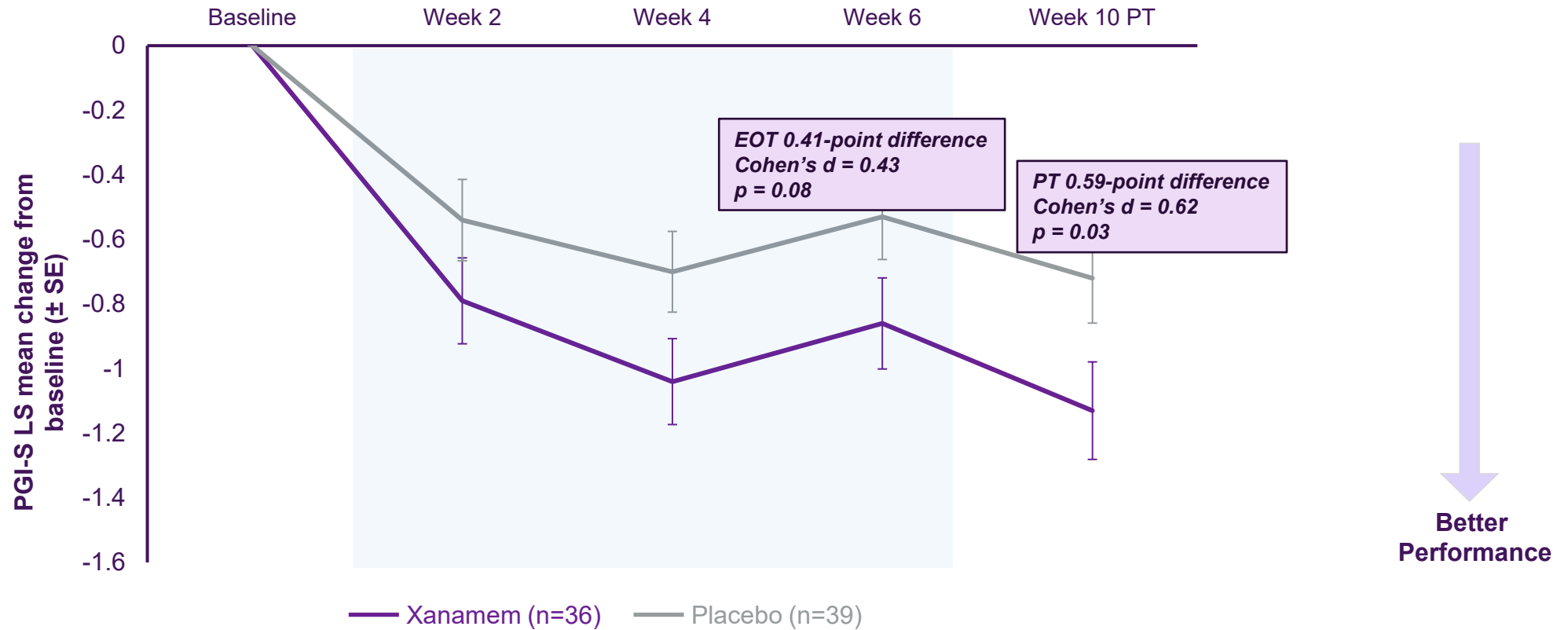
Abbreviations: SSRI, selective serotonin reuptake inhibitor.

*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)



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 11 β -HSD1 inhibitor

- ✓ *Xanamem is a selective 11 β -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

Dana C Hilt MD
CMO, Actinogen Medical Limited
Sydney, Australia
Dana.Hilt @actinogen.com.au