ASX ANNOUNCEMENT

Actinogen CEO presents at Dementia Trials Australia Annual Scientific Meeting in Sydney

Sydney, 11 October 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its CEO, Dr Steven Gourlay, will present at the Dementia Trials Australia Annual Scientific Meeting in Sydney today, which is focused on the theme ***The new era in AD therapies***.

Dr Gourlay's presentation is titled "*Oral Xanamem:® How Xanamem's benefit on depressive symptoms translates to possible efficacy in Alzheimer's disease".*

The presentation outlines the encouraging data showing clinically and statistically significant anti-depressant activity in ACW's latest phase 2a trial. He discusses the important validation this provides for Xanamem's mechanism of action to control cortisol in the brain, and for the 10 mg daily dose also being used in the Alzheimer's program.

Dr Gourlay's presentation slides are attached to this announcement.

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Announcement authorised by the Board of Directors of Actinogen Medical

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.

® Xanamem is a registered trademark of Actinogen Medical Limited

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 and Depression and hopes to 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.

Current Clinical Trials

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 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. Positive topline results on depression were announced 12 August CY2024 and updated 26 August CY2024.

The **XanaMIA Phase 2b Alzheimer's disease trial** is a double-blind, 36-week treatment, placebo-controlled, parallel group design trial in 220 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). Initial results from an interim analysis of the first 100 participants are anticipated in mid 2025 and final results mid 2026.

About Xanamem

Xanamem's novel mechanism of action is to control the level of cortisol in the brain through the inhibition of the cortisol synthesis enzyme, 11β-HSD1, without affecting production of cortisol by the adrenal glands. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing.

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.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 380 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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Actinogen

Oral Xanamem®

Controlling brain cortisol to treat depression and slow progression in Alzheimer's disease - a novel therapeutic mechanism in late phase trials

How Xanamem's benefit in depression translates to possible efficacy in Alzheimer's

Dementia Trials Australia Annual Scientific Meeting 2024

11 October 2024

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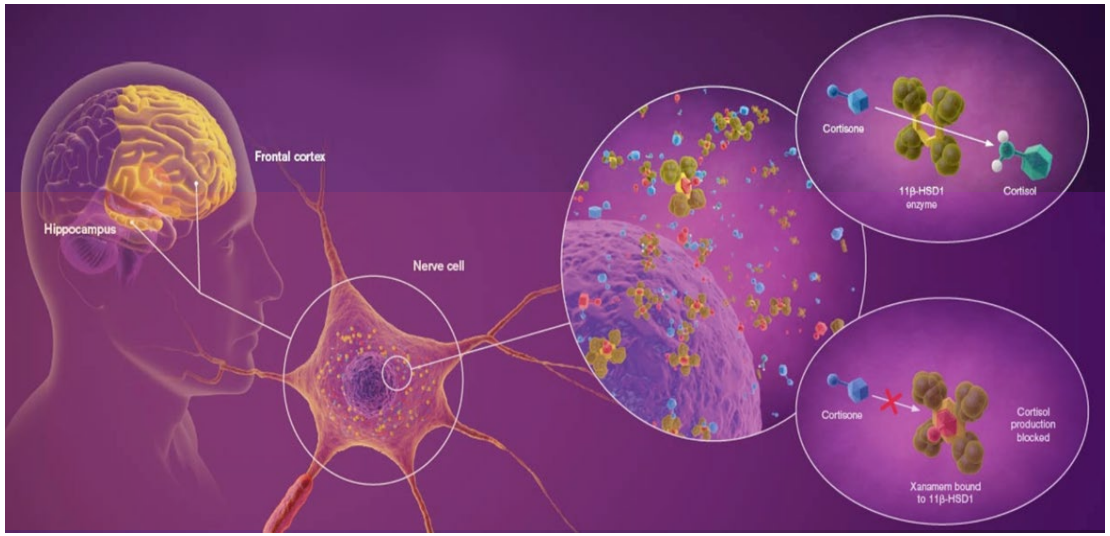
Once-daily oral treatment with a unique mechanism

Xanamem controls tissue cortisol via inhibition of the 11β-HSD1 enzyme

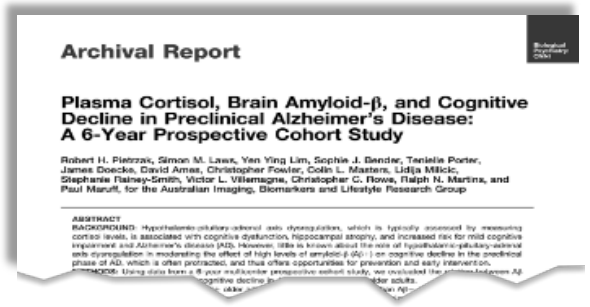
- Knockout mice protected against age-related cognitive decline
- Memory improvements shown in mice with 27-60% enzyme inhibition
- Murine AD model with 30% enzyme inhibition showed complete cognitive protection over 13 months independent of amyloid
- Reduced hippocampal inflammation



Mouse studies, human brain cortisol levels and now Xanamem clinical trials validate brain cortisol control for the treatment of AD and MDD

Cortisol: guilty by association in humans in many ways

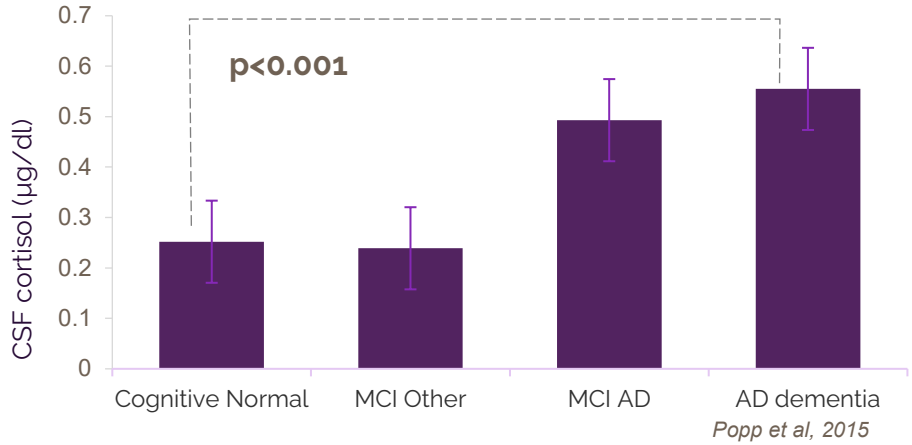
- Multiple studies support the association between cortisol and AD development and progression[1-5]
- Cognitive impairment in patients with neuroendocrine dysfunction[6-9]
- Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017)[5]
  - Higher plasma cortisol leads to a much greater risk of developing AD
  - 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 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

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 controls cortisol by inhibition of 11β-HSD1[1]

Controlling brain cortisol[2] has potential durable benefits

"STRESS" in the brain becomes "CHILL"

RAPID changes in kinases, cell function, neurotransmitters over hours to days lead to short-term "low stress" settings

"Lower stress" shorter term e.g.

- Reducing inflammation
- Improving neurotransmitter balance
- Decreasing cell death

SLOW changes in gene expression and protein synthesis over days to weeks lead to durable "low stress" settings

"Lower stress" longer term e.g.

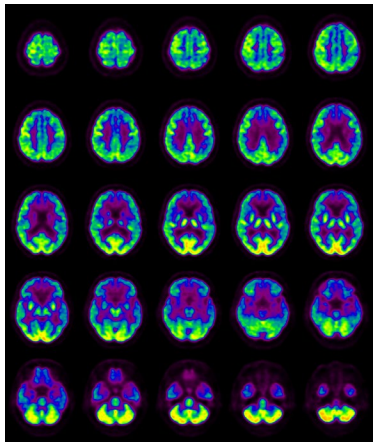
- Improving neural circuitry
- Generating new brain cells
- Ideal receptor configurations

1. For a comprehensive review of 11β-HSD1 see Seckl J. 2024 2. Ramamoorthy & Cidlowski 2016

Human PET study shows full target engagement

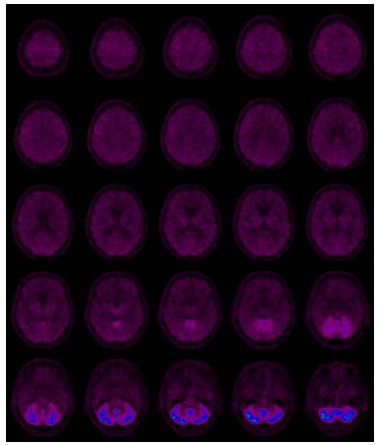
Other 11β-HSD1 enzyme inhibitors have not achieved adequate brain levels

Baseline

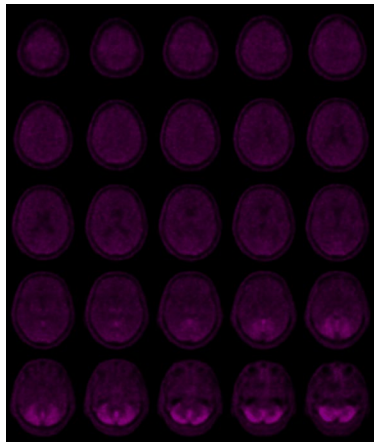


After 7 days of daily dosing

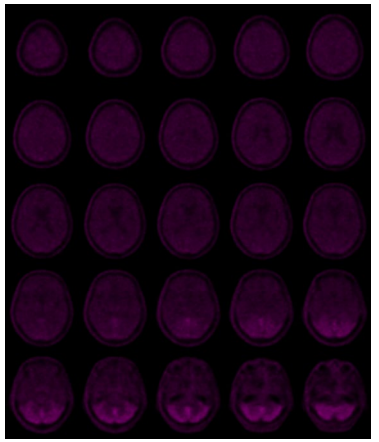
5 mg Xanamem

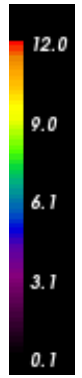


10 mg Xanamem



20 mg Xanamem



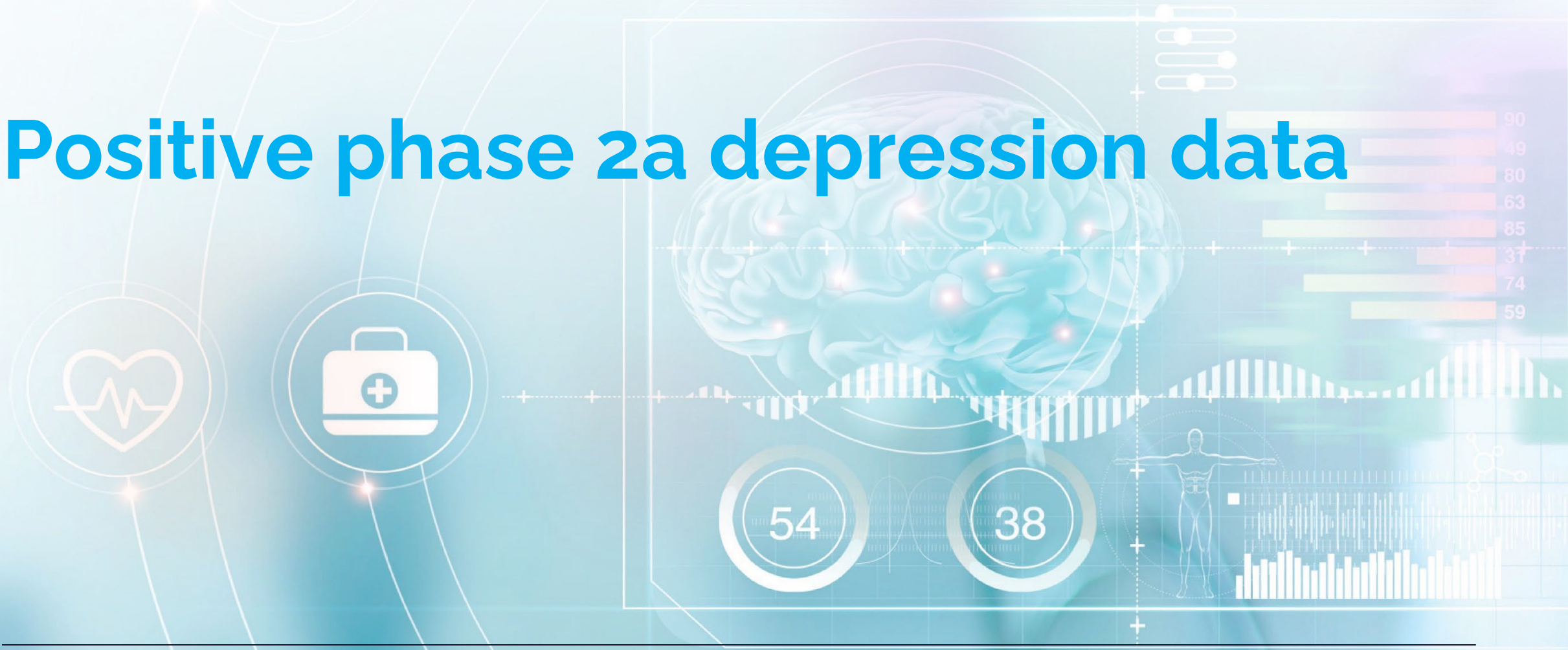


Xanamem extensively binds to the 11β-HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.

This is consistent with full hormonal pharmacodynamic activity seen in clinical trials with doses as low as 5 mg.

Validates 10mg daily dose in efficacy trials

Positive phase 2a depression data



Background to development in depression

Xanamem's unique mechanism and safety differentiate it from other anti-depressants

Scientific rationale

- More than 50 years of research associated cortisol with depression
- Elevated CSF and plasma cortisol levels associated with diagnosis, treatment outcomes and relapse[1-3]
- Positive effects of cortisol receptor antagonism reported with mifepristone[4]

Promising Xanamem clinical data

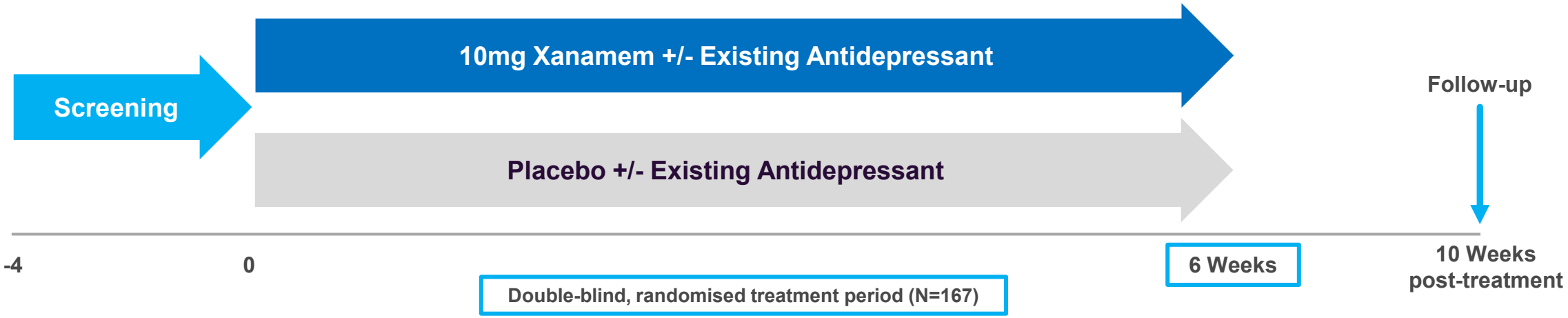
- Good tolerability 5mg to 70mg daily
- Once-a-day, half-life ~12 hours
- Human PET study confirms dose range of 5-10mg
- Positive effects at 5, 10 and 20mg daily on attention and working memory in older volunteers
- Large potential benefits in patients with AD

A safe, effective and combinable small molecule is an attractive product profile for depression

1. Quantitative summary of four decades of research, Stetler & Miller 2011 2. Depression literature review, Malhi & Mann 2018; HPA axis in major depression, 3. Keller et al. 2016
4. A meta-analysis Ding et al. 2021

XanaCIDD trial design

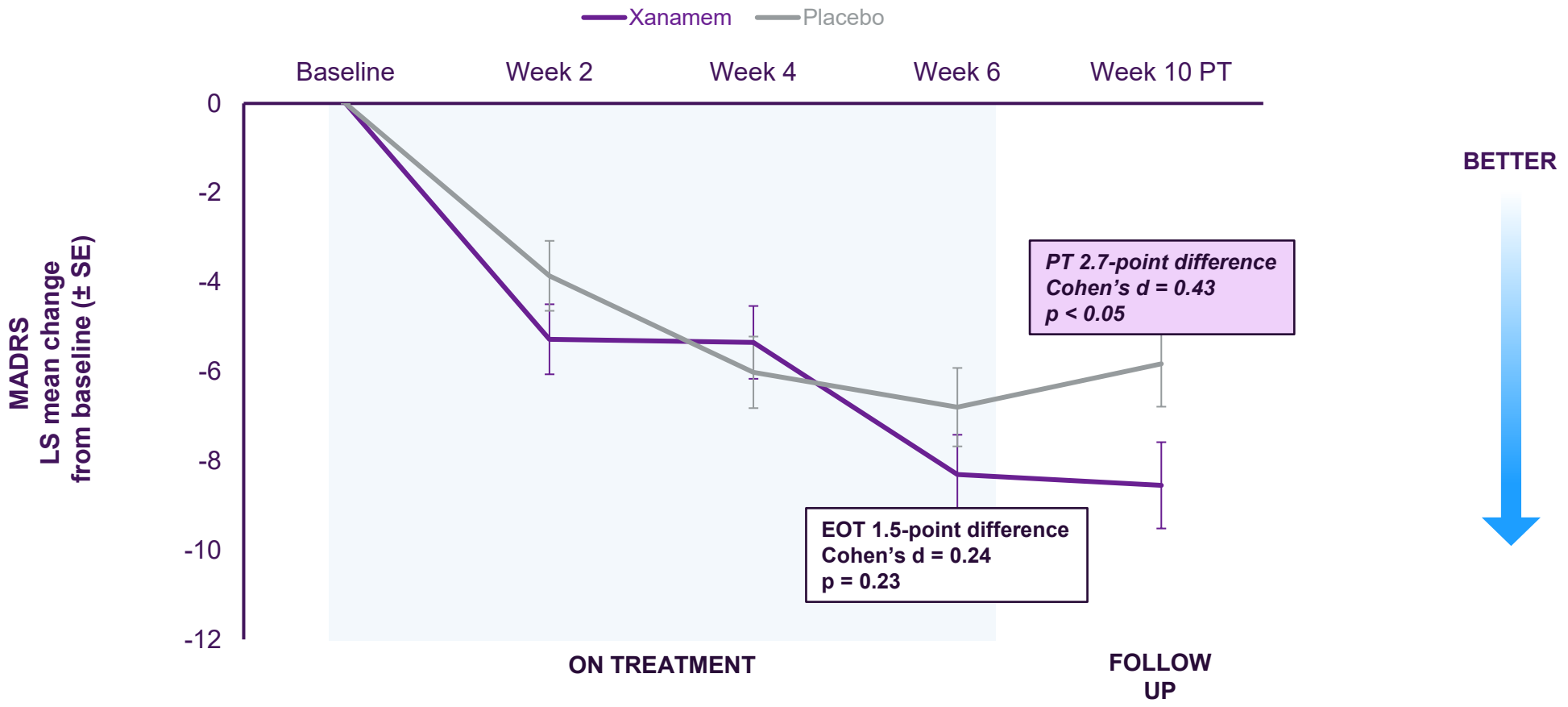
Standard phase 2a design with 6 weeks treatment



Primary Endpoint	Key Secondary Endpoints
• **Cogstate Cognitive Test Battery Attention Composite** (attention and working memory as used in prior trials)	• Montgomery-Åsberg Depression Rating Scale (**MADRS**) • Patient Global Impression-Severity **(PGI-S)** • Executive Function Cognitive Composite **(EFC)** • Memory Function Cognitive Composite **(MC)**

Xanamem MADRS separation from Week 6

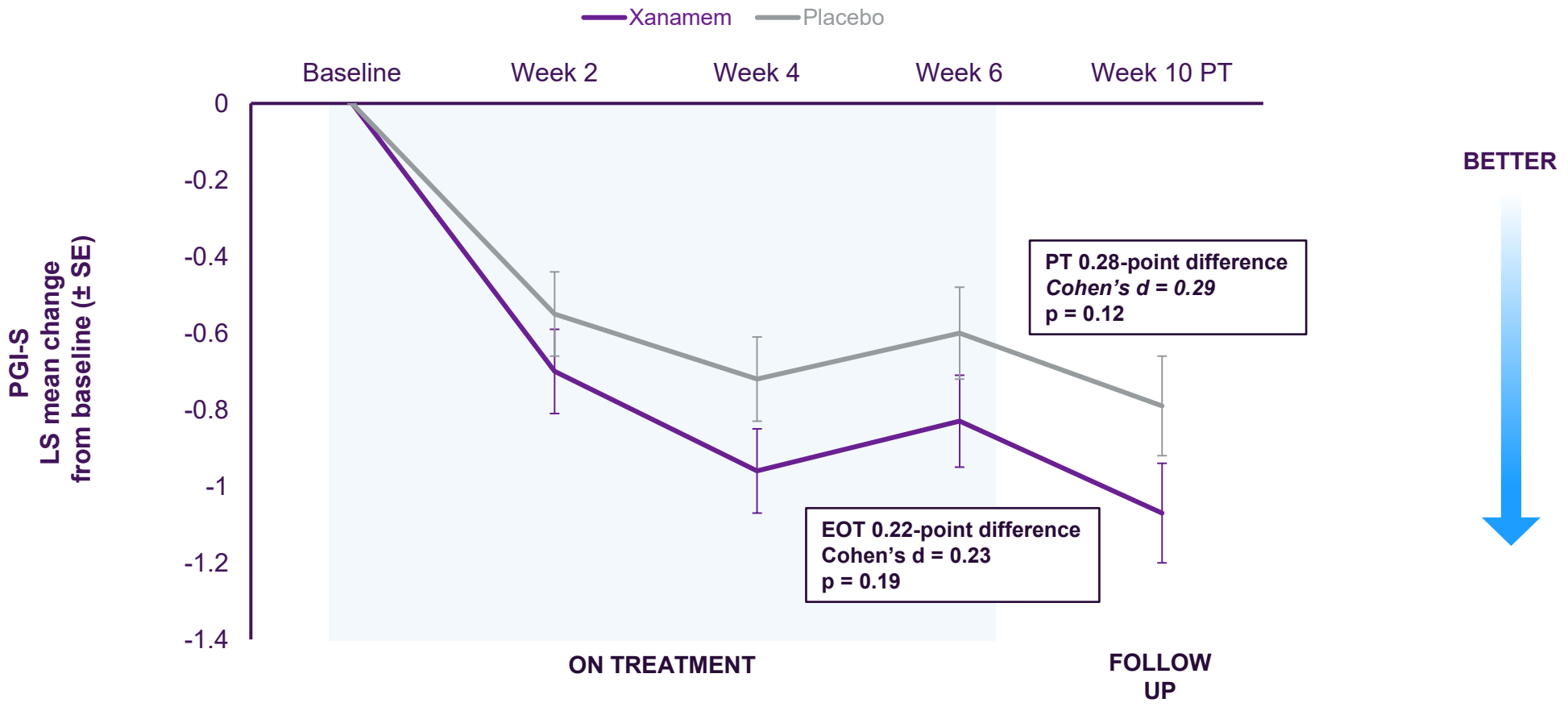
All randomized participants (n = 165)



Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

Xanamem PGI-S separation from Week 2

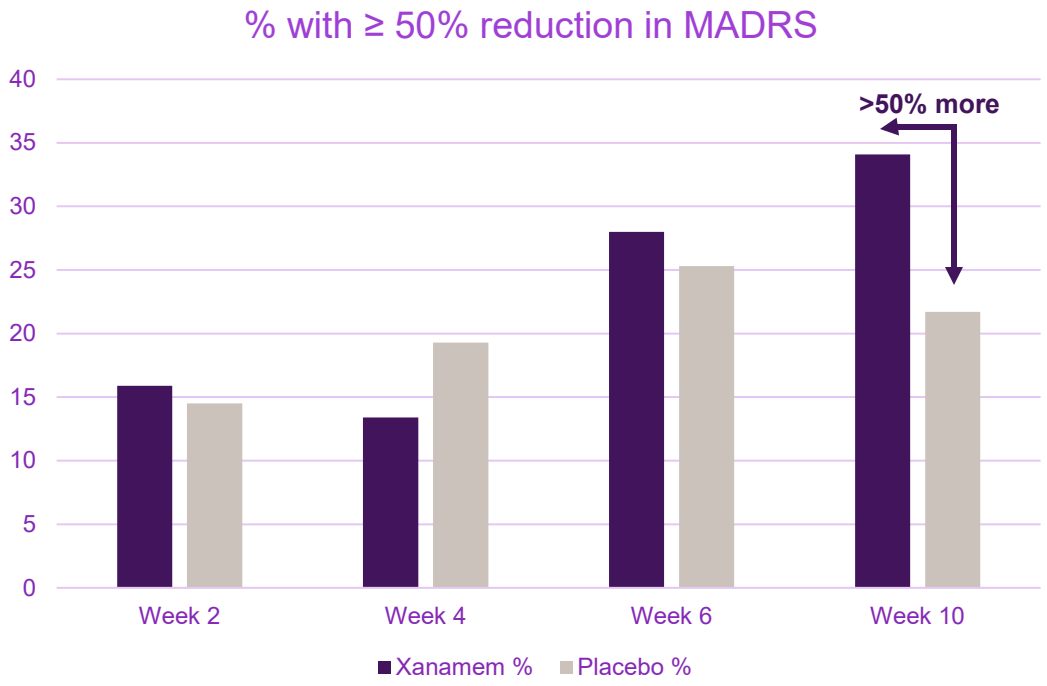
All randomized participants (n = 165)

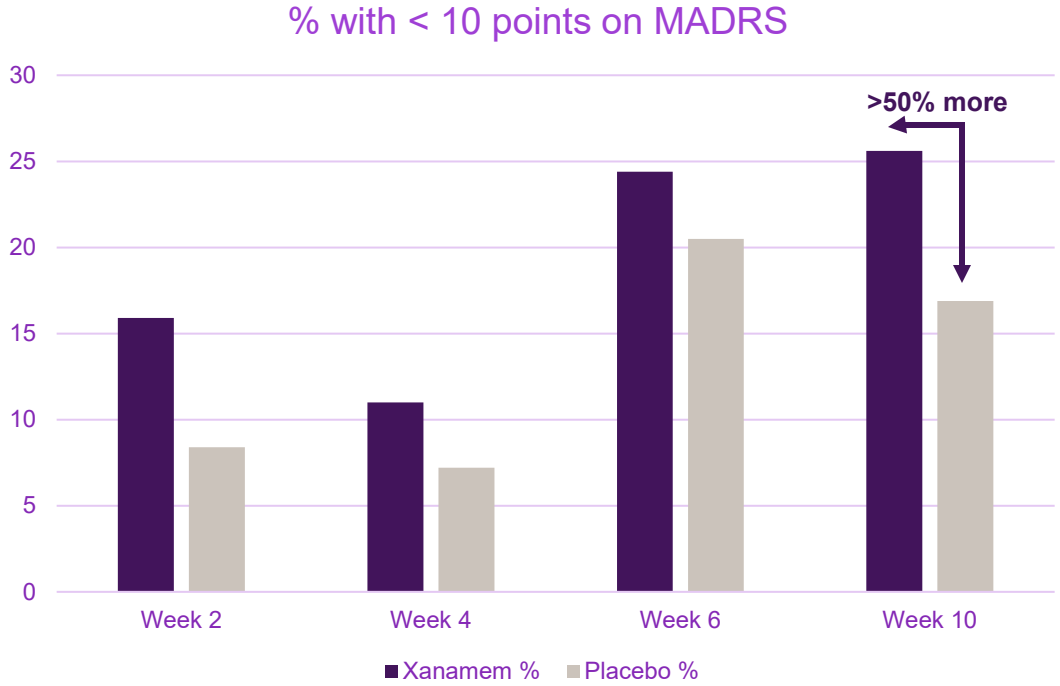


Abbreviations: PGI-S = Patient Global Impression of Severity

Xanamem major improvement in depression response

Increased rates of remission (MADRS < 10) and large (50%) improvements





Excellent safety profile consistent with prior trials

Summary of Treatment-Emergent Adverse Effects (TEAE)

	Xanamem N = 82	Placebo N = 83	Overall N = 165
Any TEAE	69 (84.1%)	67 (80.7%)	136 (82.4%)
TEAE related to trial drug	27 (32.9%)	24 (28.9%)	51 (30.9%)
Serious adverse event	0	1 (1.2%)	1 (0.6%)
Related TEAE discontinuation or interruption of drug	3 (3.7%)	1 (1.2%)	4 (2.4%)
TEAEs with incidence ≥ 5% overall			
Headache	11 (13.4%)	16 (19.3%)	27 (16.4%)
Fatigue	6 (7.3%)	5 (6.0%)	11 (6.7%)
Nasopharyngitis	4 (4.9%)	6 (7.2%)	10 (6.1%)
Upper respiratory tract infection	5 (6.1%)	5 (6.0%)	10 (6.1%)

Clinically and statistically significant benefits

Depression phase 2a summary

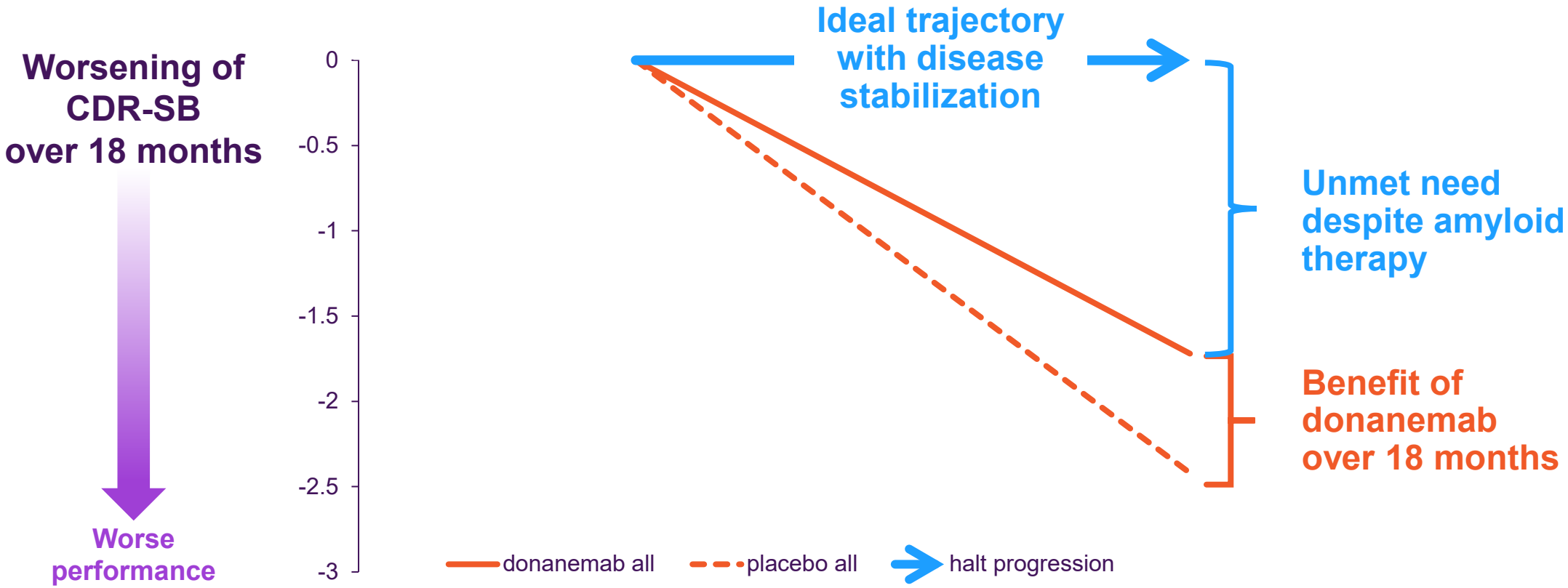
- Heavily pre/co-treated population with moderately severe MDD
- Treatment benefits on depressive symptoms for MADRS and patient-reported outcome of severity
- Consistent depression efficacy across subgroups
- Cognition improved markedly in both Xanamem and placebo groups without evidence of greater Xanamem benefit vs. placebo (data not shown)
- Xanamem was safe and well tolerated (n=165 treated) with no suggestion of suicide risk or withdrawal syndrome
- The trial was well-conducted, with excellent data quality, no major differences between Australia and the UK or at high enrolling clinical sites

Anti-depressant clinical activity validates Xanamem's cortisol control mechanism and supports the likelihood of success in AD trial at 10 mg dose

Alzheimer's disease phase 2b/3

Donanemab only modestly slows AD progression

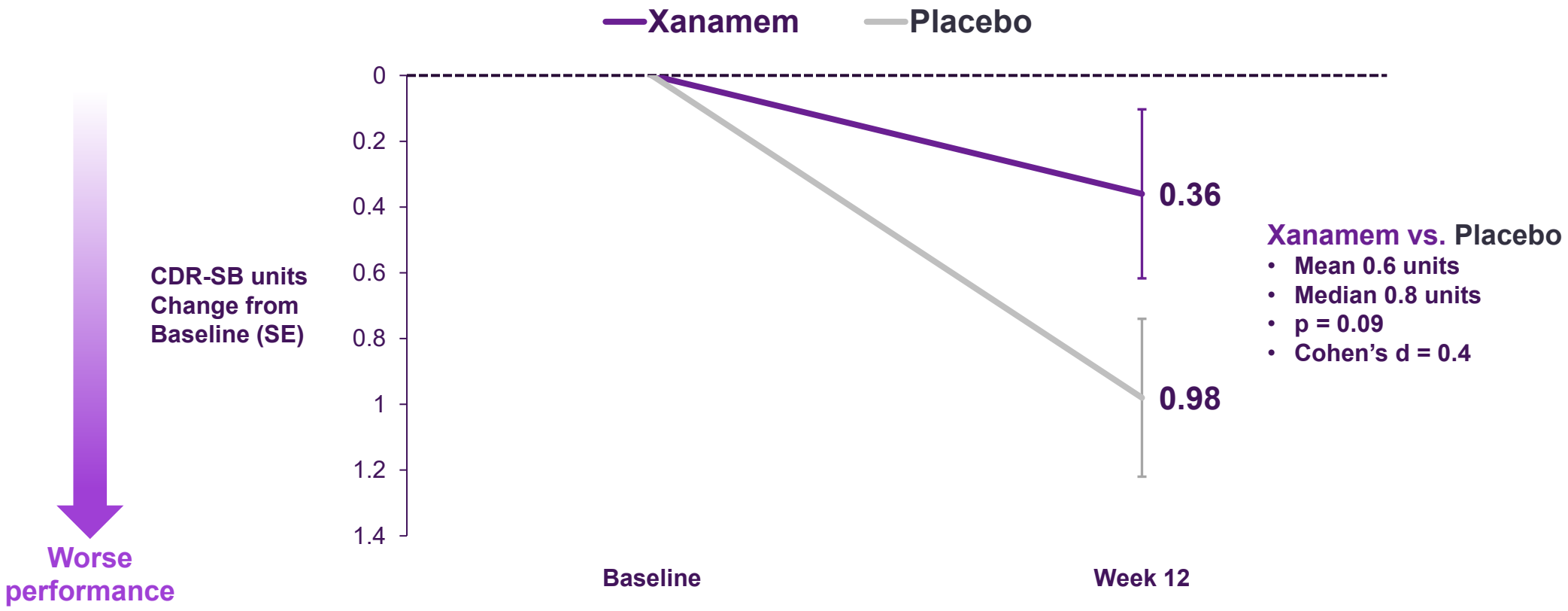
Ideally patients with AD would not worsen on treatment at all



New or combination treatment needed to stabilize AD without progression

Xanamem slows AD progression markedly over 12 weeks

Phase 2a data in biomarker (pTau181)-positive patients used to design next AD trial (n=34)[1]

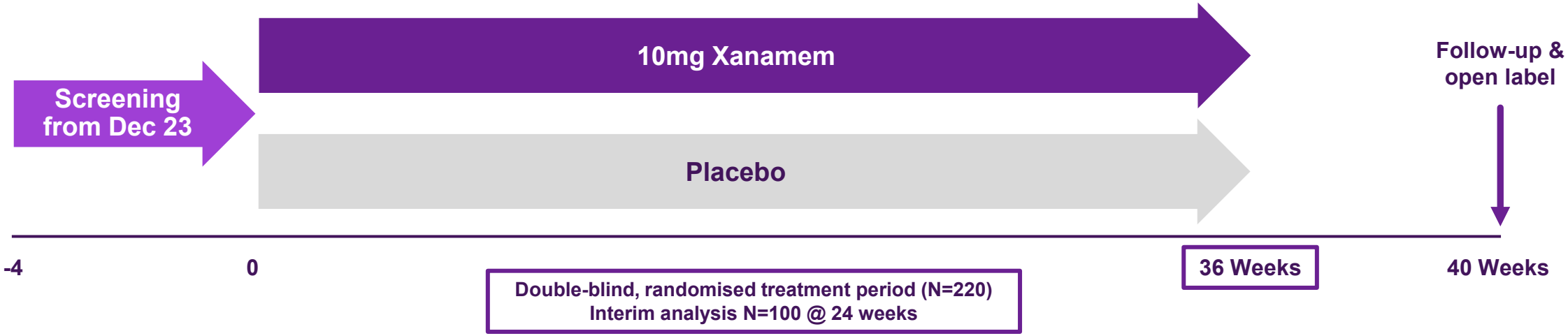


pTau-positive patients enrolling in new XanaMIA trial without PET scanning

1. Taylor et al. 2024, biomarker is pTau181 measured in blood

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

Interim results mid 2025, final results mid 2026



Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
• Blood pTau biomarker positive • Mild-moderate Alzheimer's by NIA-AA criteria	• **CDR-SB (functional and cognitive measure)**	• Amsterdam Activity of Daily Living (functional measure) • Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field)	• **To-be-marketed tablet formulation** • Enrolment at 15 Australian sites • Currently **expanding to 10 sites in US** • Interim analysis when 100 people complete 24 weeks

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

Conclusions

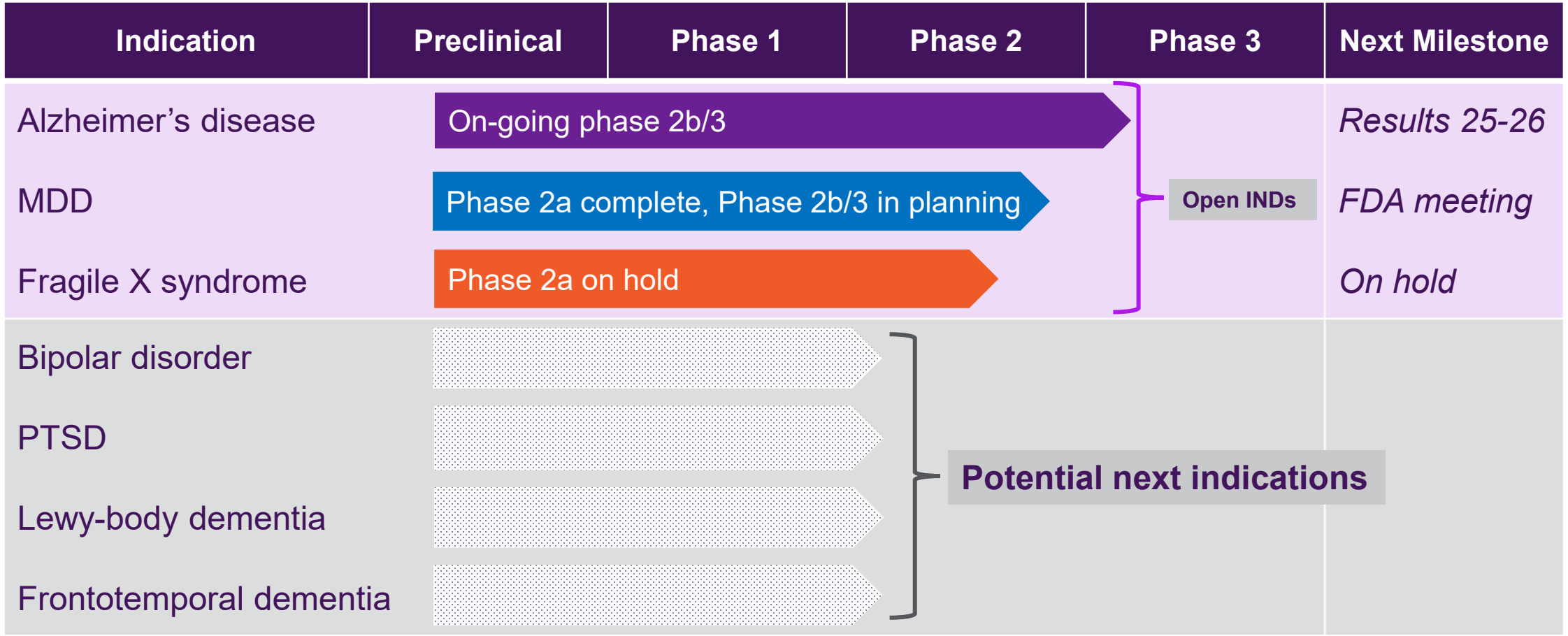
Validation of cortisol mechanism supports AD program

XanaMIA Alzheimer's disease trial implemented as a pivotal, phase 2b/3 design

- ***XanaMIA AD trial is now being conducted as one of two potential "pivotal" trials by:***
  - CDR-SB amended as the primary endpoint
  - 220 participants gives full statistical power on CDR-SB and cognition
  - Fully Independent Data Monitoring Committee
  - "Phase 3-standard" statistical methods
    - Full statistical power for primary endpoint ($p \leq 0.05$)
    - Sequential examination of secondary endpoints after primary ($p \leq 0.05$)
  - High standard of quality oversight and auditing of trial sites, vendors and procedures
- ***Interim results mid 2025, final results mid 2026***

Appendix

Xanamem pipeline



MDD: Major depressive disorder; **CIAS:** Cognitive impairment associated with schizophrenia; **CI:** Cognitive impairment; **PD:** Parkinson's disease

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Key references

Other references see also https://actinogen.com.au/xanamem

11β-HSD1 inhibition

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- Cognitive and disease-modifying effects of 11β-hydroxysteroid dehydrogenase type 1 inhibition in male Tg2576 mice, a model of Alzheimer's Disease: Sooy, K., Noble, J., McBride, A., Binnie, M., Yau, J. L. W., Seckl, J. R., Walker, B. R., & Webster, S. P. 2015. *Endocrinology, 1-12.*
- Partial deficiency or short-term inhibition of 11β-hydroxysteroid dehydrogenase type 1 improves cognitive function in aging mice Sooy, K., Webster, S. P., Noble, J., Binnie, M., Walker, B. R., Seckl, J. R., & Yau, J. L. W. 2010. *Journal of Neuroscience, 30(41), 13867-13872.*

Xanamem clinical trials

- Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11β-HSD1 Inhibitor Xanamem® for Mild Alzheimer's Disease Taylor J, Jaros M, Chen C, Harrison J, Hilt D *J Alz Dis 2024; 100: 139-150*
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- Selection and early clinical evaluation of the brain-penetrant 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor UE2343 (Xanamem™) Webster, S. P., Ward, P., Binnie, M., Craigie, E., McConnell, K. M., Sooy, K., Vinter, A., Seckl, J.R. & Walker, B. R. 2007. *Bioorganic & medicinal chemistry letters, 17(10), 2838-2843.*
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Technical references

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Alzheimer's disease and cortisol

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Currencies

- Currencies are in Australian dollars unless otherwise stated

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