Actinogen

Oral Xanamem® (emestedastat)

Controlling brain cortisol to slow progression in Alzheimer's disease and treat depression

Corporate Presentation

February 2025

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Overview

Xanamem is now in advanced stages of development

Novel 11β-HSD1 cortisol control mechanism, oral, attractive safety profile

- Brain cortisol has long been proposed as a pathogenic mechanism in Major Depressive Disorder (MDD) and Alzheimer's (AD)
- Unique brain-penetrant tissue cortisol synthesis inhibitor that leaves adrenal cortisol synthesis unaffected
- Approximately **400 people** treated to date with excellent safety profile and low drug interaction risk

Positive phase 2 clinical data de-risk clinical program

- **Disease-modifying activity on CDR-SB** in phase 2a trial in biomarker-positive Alzheimer's patients
- **Phase 2a MDD trial showing clinically & statistically significant activity - benefits across multiple endpoints**
- Positive data from both trials read through to other indications in psychiatry and the dementias

Patent/data protection and advanced manufacturing

- **Composition of matter protection** to 2031, and 2036 with extensions in major markets, newer patents in process
- **Data exclusivity protects Xanamem data** from use by others for 5 to 10 years from approval e.g. 10 years in EU
- **Manufacturing process scaled up and patented**, contractors Asymchem (China) & Catalent (US)

Large clinical and commercial opportunities

- **No other brain-penetrant cortisol control molecules are in development, first 11β-HSD1 inhibitor awarded INN name[1]**
- Anti-depressant market is currently ~$20 billion, with major opportunities for novel mechanisms & better-tolerated drugs
- Alzheimer's market likely to be $20 billion by 2030, with major opportunity for a safe & effective oral agent

1. Xanamem's International Nonproprietary Name (INN) , emestedastat, was awarded by a naming committee of the World Health Organization: "-stedastat" chosen for the first time for all 11β-HSD1 inhibitors

Experienced board and management team

Board of Directors

Dr. Geoff Brooke
Chairman
MBBS; MBA

Dr. Steven Gourlay
CEO & MD
MBBS; FRACP; PhD; MBA

Mr. Malcolm McComas
Non-Executive Director
BEc, LLB; FAICD; SF Fin

Dr. George Morstyn
Non-Executive Director
MBBS; PhD; FRACP CD

Dr. Nicki Vasquez
Non-Executive Director
PhD

Management Team

Dr. Steven Gourlay
CEO & MD

Dr. Dana Hilt
Chief Medical Officer
MD

Will Souter
Chief Financial Officer
BComm, LLB

Andrew Udell
Chief Commercial Officer
MBA

Cheryl Townsend
VP Clinical Operations
RN, M Health Law

Fujun Li
Head of Manufacturing
PhD

Michael Roberts
Head of IR & Comms
B.Ec (Hons), CPA, FFIN

Corporate snapshot

ASX-listed company founded in 2014

- Market Cap ~$100 million
- **Cash balance of $22.9 million at Dec 31 2024 provides runway to at least mid 2026**
- Conducted three phase 1 (Australia) and four phase 2 trials (Australia, US and UK)

Key shareholders

- Biotech Value Fund (BVF) ~7%
- **CEO Steve Gourlay ~5% (including via ~$2 million invested personally)**
- Top 20 ex BVF & Gourlay ~23%

Phase 2b/3-stage clinical programs are the “sweet spot” for partnering

- **Alzheimer’s disease phase 2b/3 ongoing – interim Q4 2025, final results H2 2026**
- **Major depressive disorder phase 2a completed – seeking partner(s)**
- Type C meeting with FDA to discuss approval requirements for AD Q2-3 2025

Fundraising history

- Initially Wellcome Trust support for University of Edinburgh
- 2014 merger of U Edinburgh spinout Corticrine with Actinogen ASX-listed shell
- Equity raises on ASX and Australian R&D tax incentive cash rebates (e.g. $9 million received in 2024)

Advancing Xanamem programs

First-in-class INN name awarded by the WHO, “emestedastat” with the unique suffix “-stedastat” that highlights Xanamem’s unique mechanism of action and the lack of direct competition for CNS cortisol control

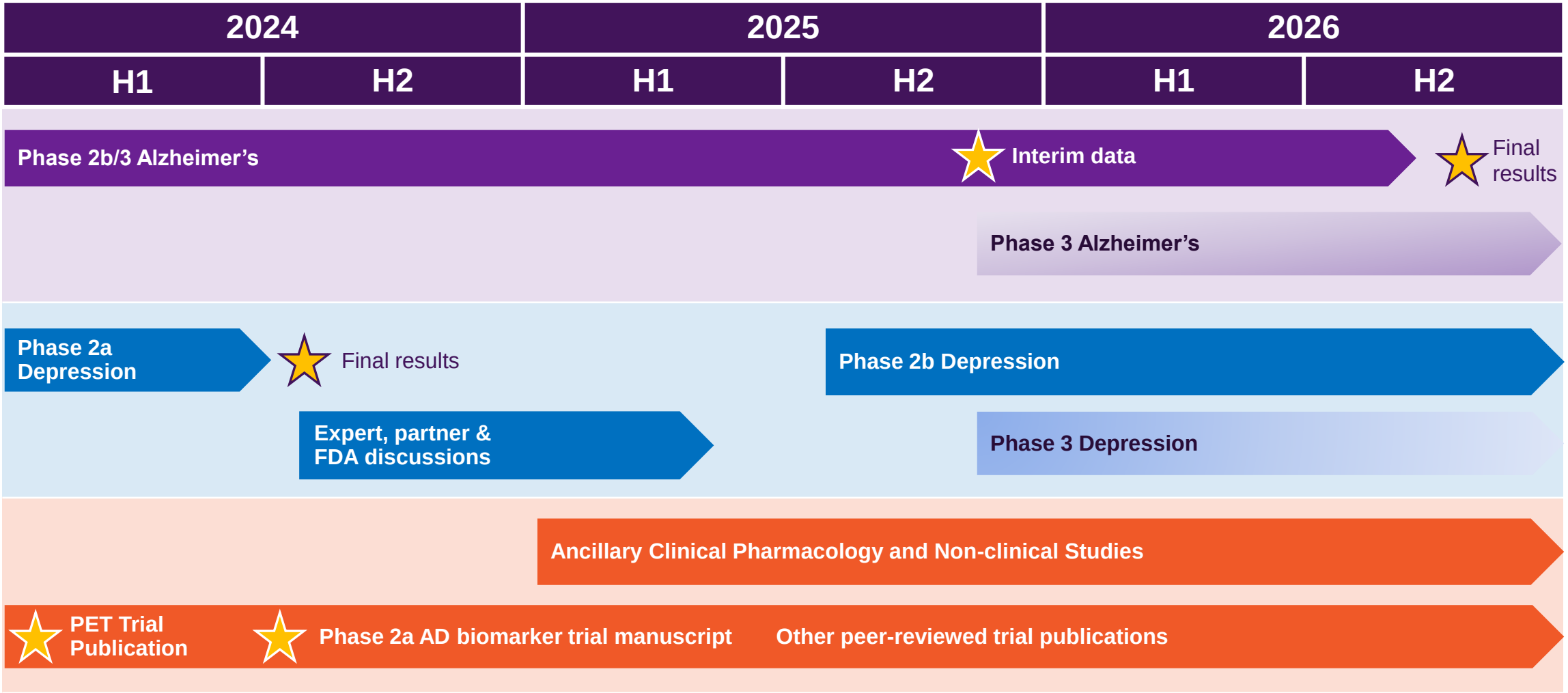
Evidence of durable benefit on depression from control of brain cortisol validates the Xanamem program in terms of:

- ✓ “Cortisol control” mechanism of action aka the “cortisol hypothesis”
- ✓ 10 mg daily proof-of-concept dose being used in Alzheimer’s phase 2b/3 trial
- ✓ 10 mg daily dose is also suitable for next depression trial

Clinical activity on depression with the 10 mg dose supports the likelihood of seeing a disease-modifying effect in Alzheimer’s disease over 36 weeks in current XanaMIA phase 2b/3 trial

FDA meeting on MDD this quarter to define marketing approval requirements to be followed by a similar meeting on AD. EMA meetings also to be scheduled

Xanamem – AD and MDD Program Timelines*



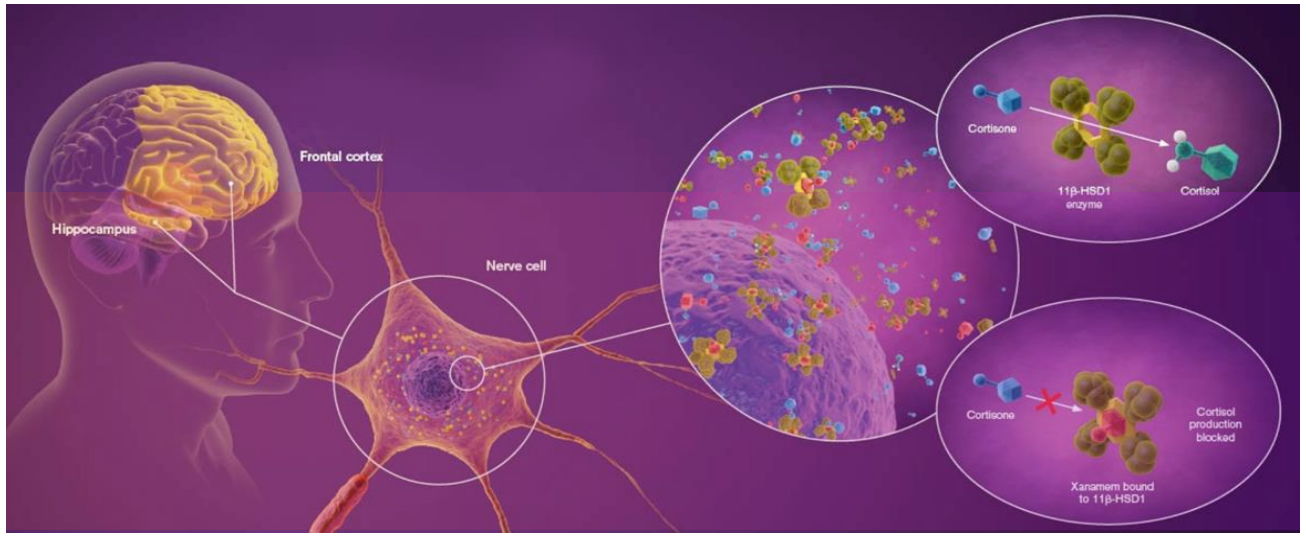
* Seeking partnership(s) and other sources of non-dilutive funding for Phase 2b depression and Phase 3 AD trials

Xanamem

Once-daily oral treatment with a unique mechanism

Xanamem is a small molecule tissue cortisol synthesis inhibitor (11β-HSD1 enzyme)

- Good safety profile in ~400 treated
- Brain-penetrant at low doses
- 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 controls cortisol by inhibition of 11β-HSD1[1]

Controlling brain cortisol[2] has potential durable benefits

Reduction of "stress response" in brain

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

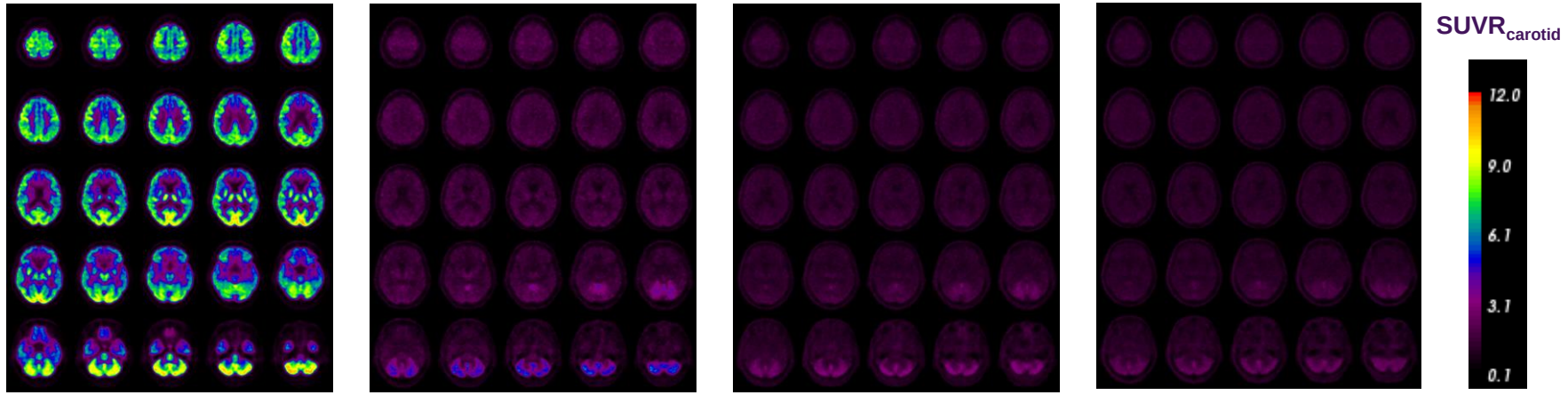
Human PET study shows full target engagement

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 color) 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.

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

Intellectual property protection

Protection from patents and “data exclusivity”

Core “composition of matter” patent granted worldwide to 2031 **with standard extensions to at least 2036 in major markets**

Additional protection is afforded from patents in the “national phase” of approvals covering the treatment of cognitively normal people, manufacturing process and the treatment of depression, with additional patents continuing to be filed

Independent of patent protection, data exclusivity protections stem from Xanamem being a “new chemical entity”, such that Actinogen’s nonclinical and clinical data cannot be used by another party for a period dating from Xanamem’s first marketing approval e.g.:

- US and Australia 5 years
- China and Canada 6 years
- EU 10 years

Alzheimer’s disease program

Alzheimer's disease

Strong cortisol control scientific rationale to address huge unmet medical need

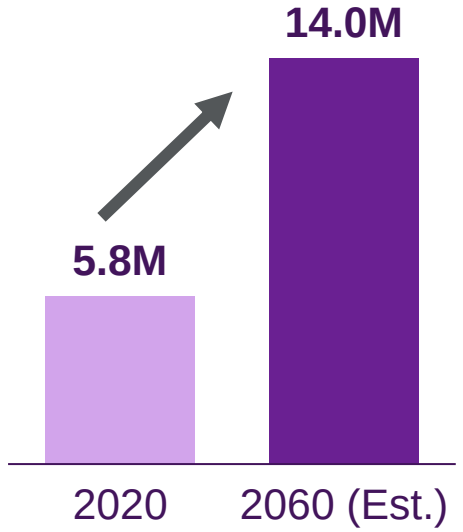
Rationale

- Cortisol levels are elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11β-HSD1 provides full neuroprotection
- AD Phase 2a trial shows slowed disease progression in biomarker-positive patients
- ***Safe & effective oral therapy is "holy grail"***

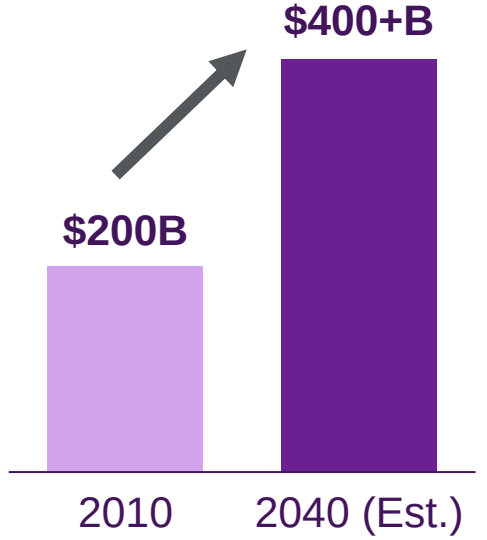
Growing Alzheimer's Disease market – U.S.

Large, unsatisfied and growing market

# of patients

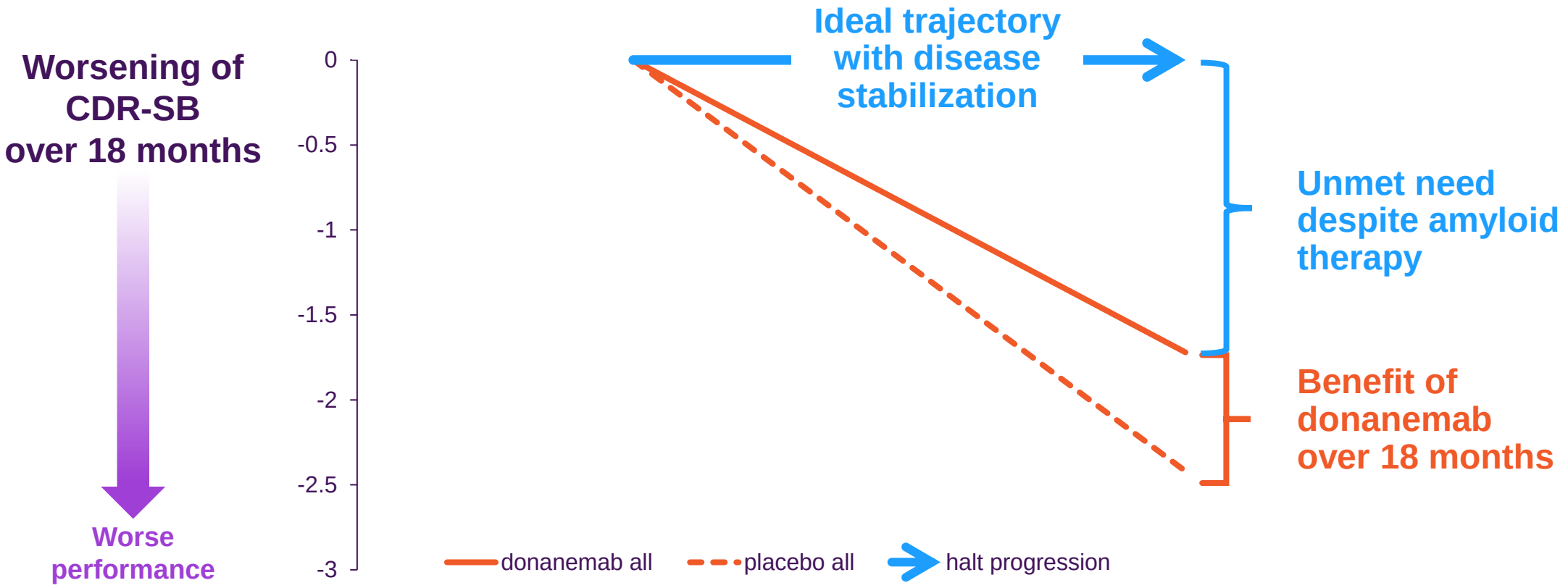


Cost to treat



Anti-amyloid therapy modestly slows AD progression

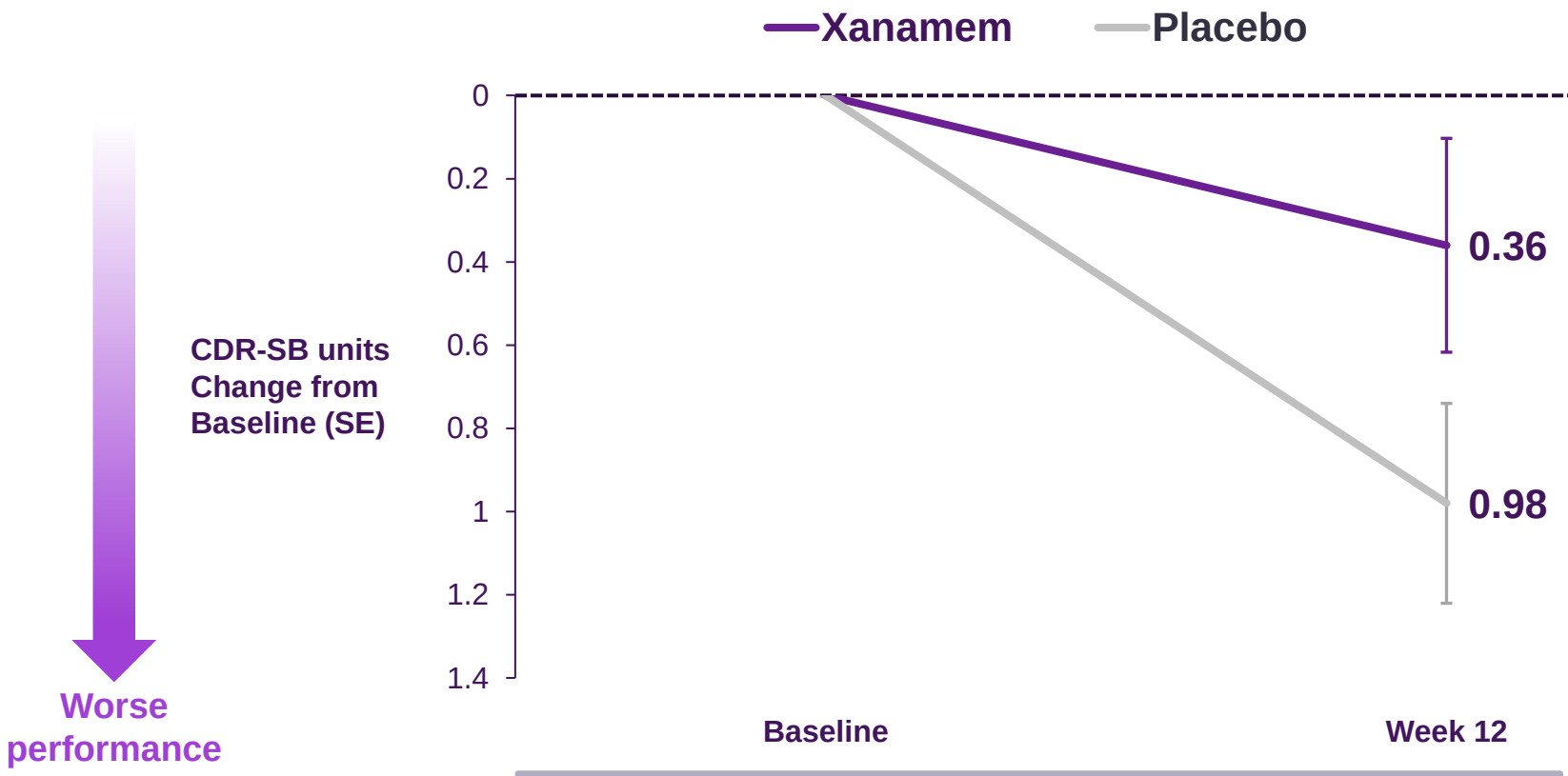
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanamem are needed

Xanamem benefit in pTau181-positive AD patients

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



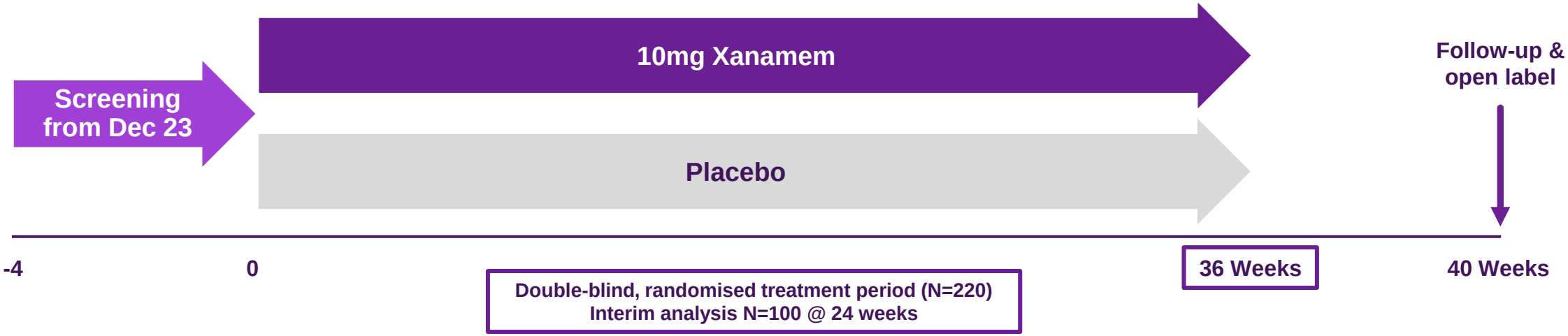
Xanamem vs. Placebo

- **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

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

Initial, interim results in Q4 2025, final results H2 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)	• Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field) • Amsterdam Activity of Daily Living (functional measure)	• Enrolment at 15 Australian & 10 US sites • Interim analysis planned when ~100 people complete 24 weeks

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

Depression program

There remains significant unmet need in depression

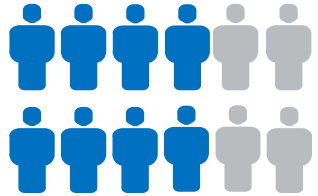
Xanamem's unique mechanism and safety differentiate it from older drugs

Scientific rationale

- More than 50 years of research associates cortisol with depression
- Elevated CSF and plasma cortisol levels associated with diagnosis, treatment outcomes and relapse
- Positive effects of cortisol receptor antagonism reported with mifepristone[3]
- ***Now positive phase 2a data on depressive symptoms for Xanamem (MADRS, PGI-S)***

U.S. Depression market large unmet need

- 21M patients have had ≥ 1 MDD episode



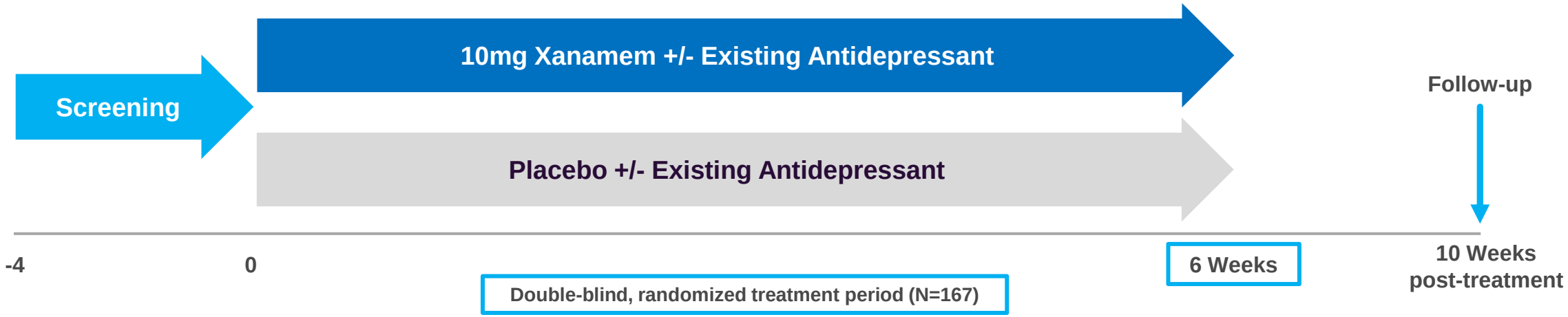
- Two-thirds with an episode **with severe impairment** in the past year
- 61% of all adults with MDD episodes receive treatment
- ≥365 M prescriptions per year

A safe, durably effective and combinable small molecule is a very attractive product profile for depression

3. Ding et al 2021

XanaCIDD trial design and methods – completed CY2024

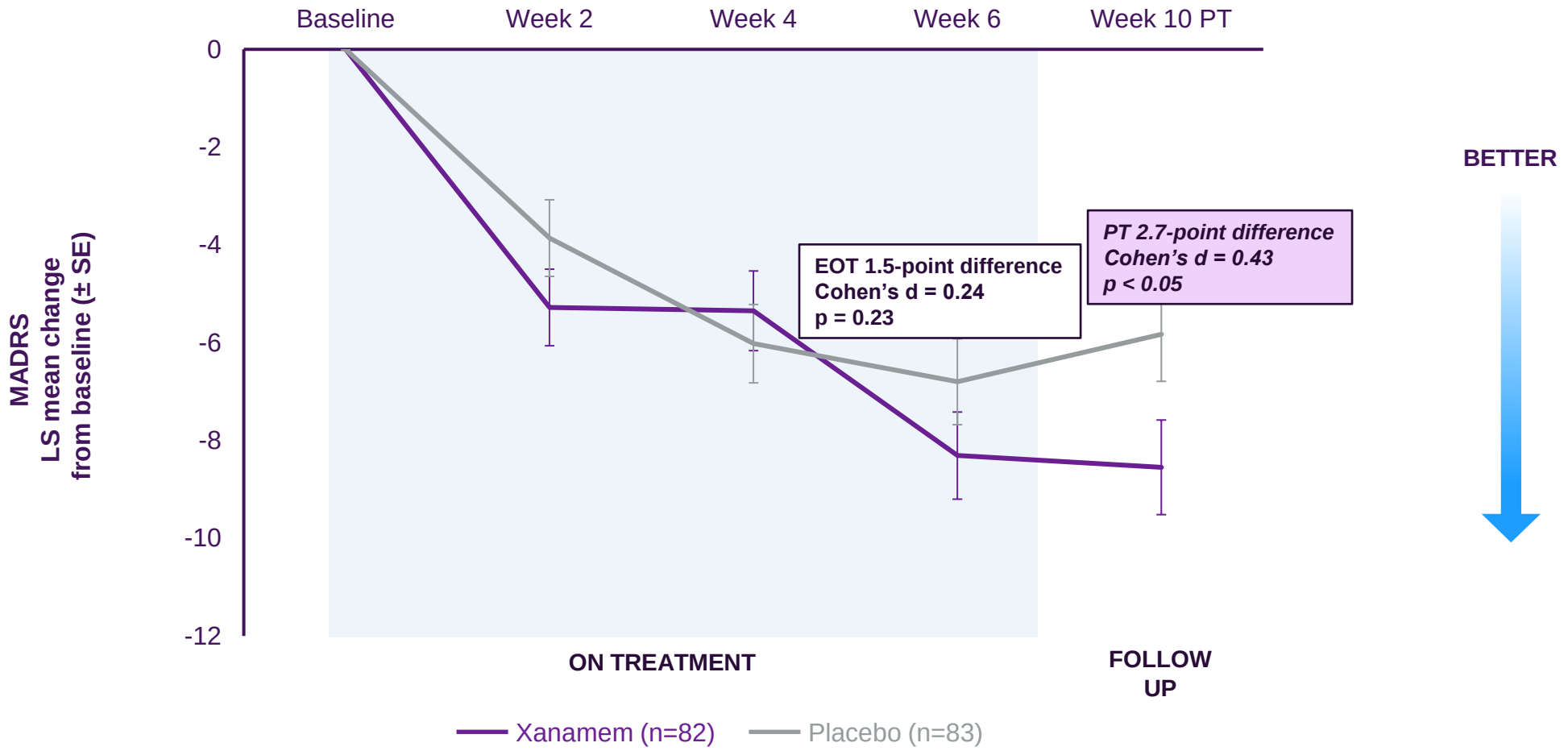
Phase 2, double-blind, proof-of-concept controlled trial to assess safety and efficacy



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

Xanamem MADRS separation from Week 6 (n=165)

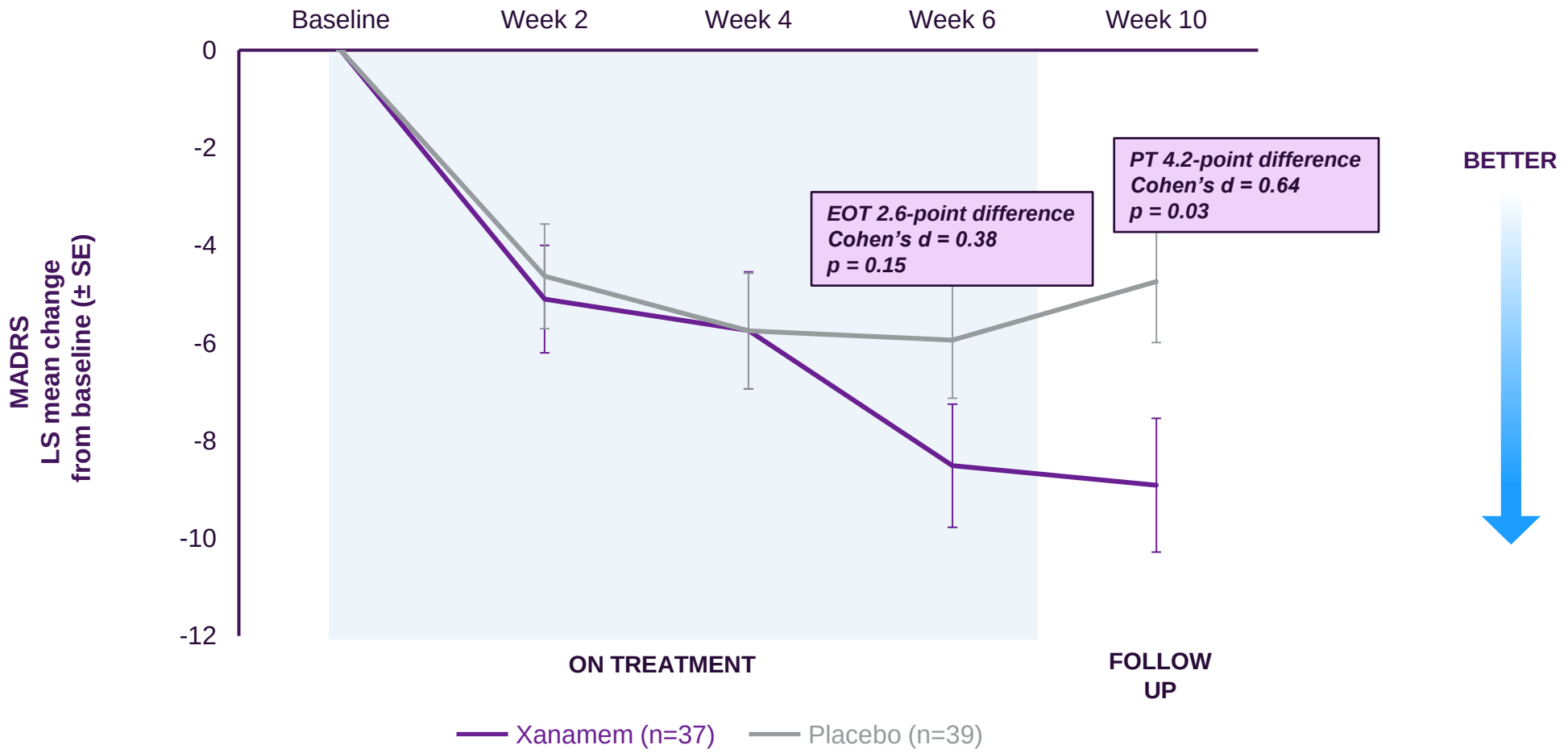
All randomized participants



Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

MADRS in patients taking concurrent SSRI (n=76)

Largest co-treatment subgroup



Abbreviations: SSRI, selective serotonin reuptake inhibitor

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	70 (85.4%)	67 (80.7%)	137 (83.0%)
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%)

Depression phase 2a: key findings & next steps

- ***Clinically and statistically significant treatment benefits on depressive symptoms for MADRS and patient-reported outcome of severity***
- Heavily pre/co-treated population with moderate MDD
- 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
- Funding for the next depression trial being investigated with potential partners and/or granting bodies

Further XanaCIDD phase 2a depression trial result available in the Appendix

Conclusion

Building positive momentum

Evidence of durable benefit on depression from control of brain cortisol validates the Xanamem program in terms of:

- ✓ “Cortisol control” mechanism of action
- ✓ 10 mg daily proof-of-concept dose being used in Alzheimer’s phase 2b/3 trial
- ✓ 10 mg daily dose is also suitable for next depression trial
- ✓ Likelihood of seeing a disease-modifying effect in Alzheimer’s disease over 36 weeks in current XanaMIA trial
  - ✓ Interim results Q4 2025
  - ✓ Final results H2 2026

Positive phase 2a MDD data support further clinical development in MDD

Company funded to at least mid 2026

Multiple value-add milestones in coming 12 months

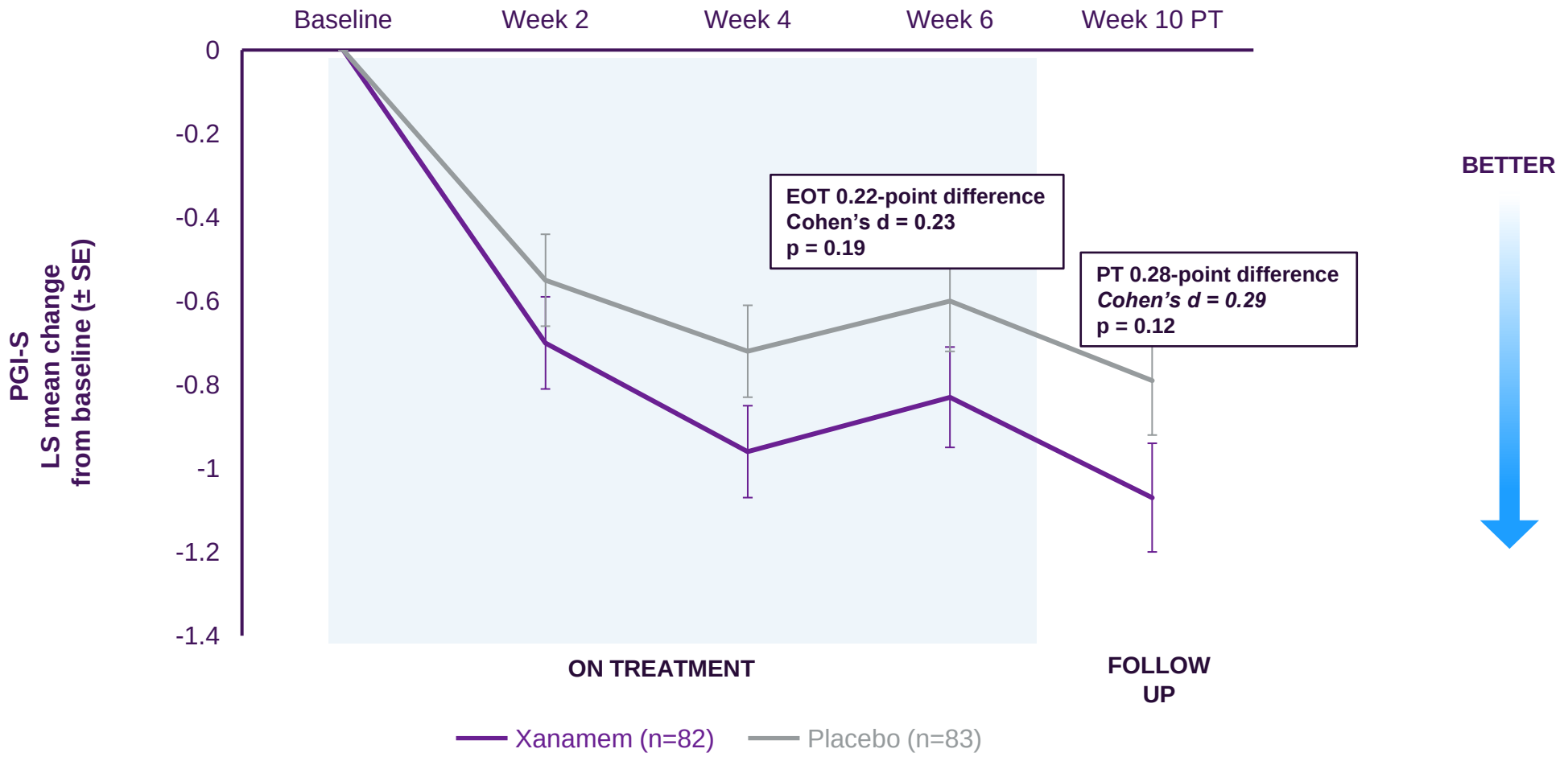
Selected upcoming milestones

Milestone	Likely Timing
First patient randomized and treated in US, XanaMIA trial	Q4 24
Meetings at JP Morgan Healthcare conference week, San Francisco	Q1 25
Clinical pharmacology manuscript peer-reviewed publication	Q1 25
FDA Type C meeting for MDD	Q1 25
Clinical Trials Science Forum – focus on commercial planning	Q1 25
100th patient enrolled, XanaMIA trial	Q2 25
XanaCIDD MDD peer-reviewed journal publication	Q3-4 25
ADPD conference AD presentation in Vienna	Q2 25
American Psychiatric Association MDD presentation, Los Angeles	Q2 25
FDA Type C meeting for AD	Q2-3 25
Interim analysis, XanaMIA trial	Q4 25
Full enrolment, 220 patients with AD, XanaMIA trial	Q4 25
AAIC conference AD presentation in Toronto	Q3 25
CTAD conference AD presentation in San Diego	Q4 25

Appendix

XanaCIDD results - Xanamem PGI-S separation from Week 2 (n=165)

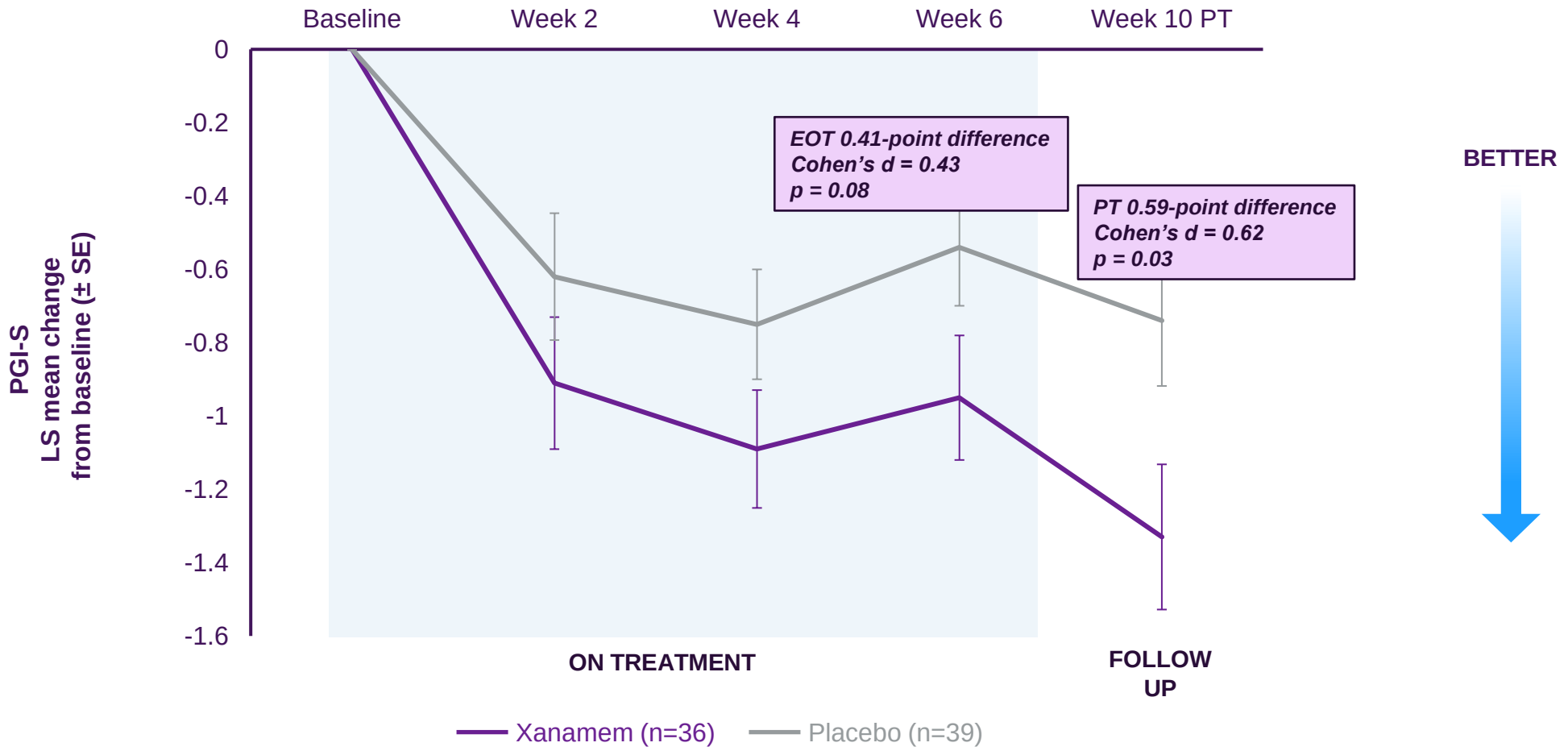
All randomized participants



Abbreviations: PGI-S = Patient Global Impression of Severity – a patient-reported outcome

XanaCIDD results - PGI-S benefit in patients taking SSRI (n=75)

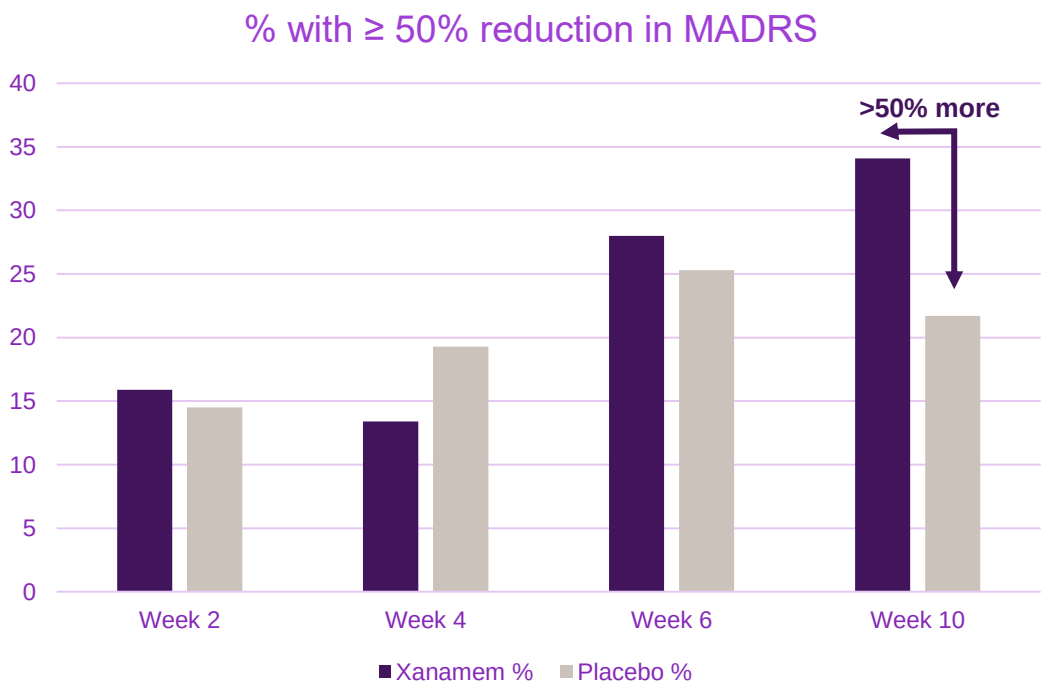
Largest co-treatment subgroup

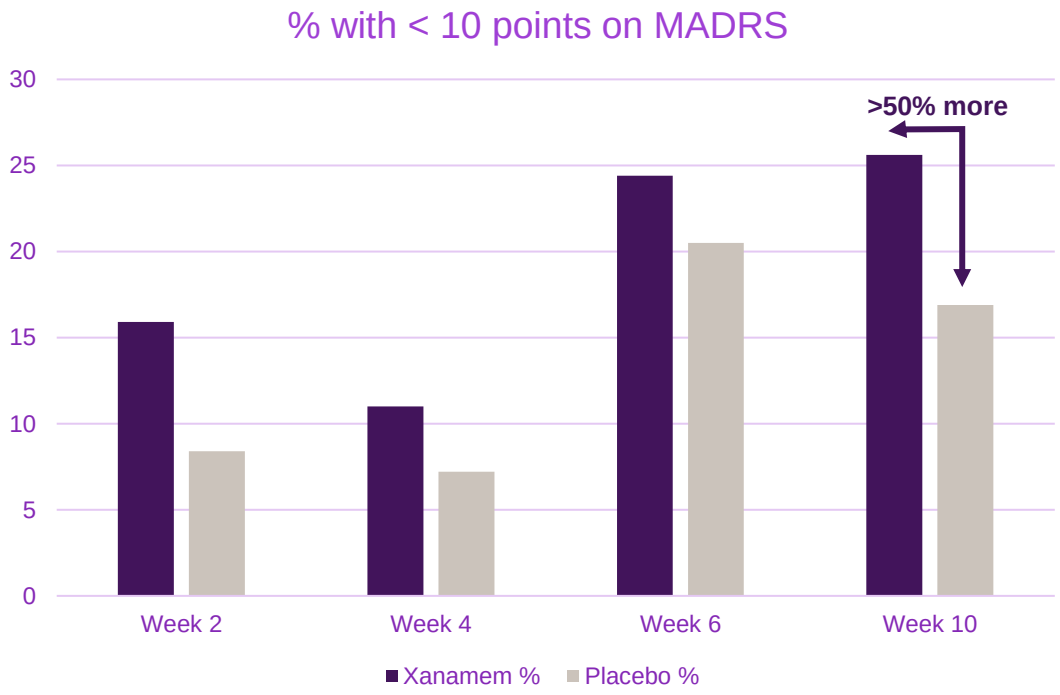


Abbreviations: PGI-S = Patient Global Impression of Severity – a patient-reported outcome

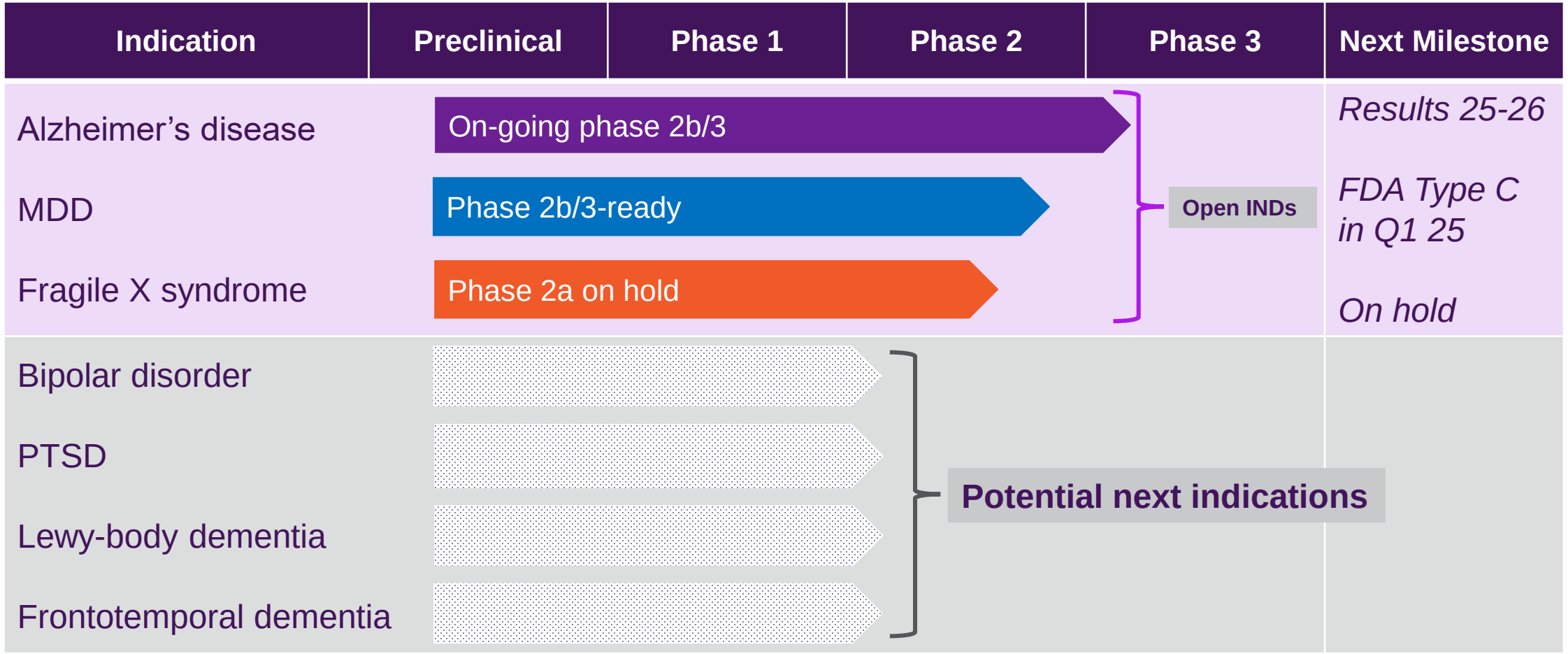
XanaCIDD results - Xanamem improves MADRS response rates (n=165)

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





Xanamem - Pipeline



MDD: Major depressive disorder

Key references

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

11β-HSD1 inhibition

- Seckl J. 11β-Hydroxysteroid dehydrogenase and the brain: Not (yet) lost in translation. J Intern Med. 2024 Jan;295(1):20-37. doi: 10.1111/joim.13741. Epub 2023 Nov 8. PMID:37941106. https://onlinelibrary.wiley.com/doi/10.1111/joim.13741
- 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*
- Brain 11-Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamem™ Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals Villemagne VL, Dore V, Chong L, Kassiouf M, Mulligan, R, Feizpoura A, Taylor J, Roesner M, Miller T, Rowe CC *J Alz Dis 2024: 97: 1463–1475*
- 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.*
- Various podium and poster presentations on website

Technical references

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Currencies

- Currencies are in Australian dollars unless otherwise stated

Selected Glossary 1

- **11β-HSD1 –** 11 beta HydroxySteroid Dehydrogenase-1 enzyme. Selectively expressed in brain, liver, adipose.
- **Aβ –** Amyloid beta – a type of amyloid protein associated with Alzheimer's Disease, 42 and 40 are different forms
- **ACTH –** Adrenocorticotropic hormone that regulates blood levels of cortisol
- **AD –** Alzheimer's disease
- **ADAS-Cog –** Alzheimer's Disease Assessment Score - Cognition
- **ApoE4 –** Apoprotein genotype associated with genetic risk of Alzheimer's Disease
- **ATN –** Amyloid, Tau, Neurodegeneration
- **Clinical Scales –** Measure how a patient feels, performs and functions
- **CDR-SB –** Clinical Dementia Rating "Sum of Boxes" scale measuring cognition and function on an 18-point scale (high worse)
- **CNS –** Central nervous system
- **CSF –** Cerebrospinal fluid
- **CTAD –** Clinical Trials on Alzheimer's Disease (conference)
- **CTB –** Cognitive Test Battery of computerized tests
- **Double-blind –** Investigators, participants and company do not know who has active vs placebo treatment during a trial
- **EMA –** European Medicines Agency
- **FDA –** US Food & Drug Administration
- **Filamen A –** A protein believed to relate to amyloid toxicity
- **GFAP –** Glial Fibrilliary Acidic Protein – a marker of microglial cell activation in the brain
- **IDSST –** International Digit Symbol Substitution Test of cognition

Selected Glossary 2

- **IQCODE –** Informant Questionnaire on Cognitive Decline in the Elderly
- **MCI –** Mild Cognitive Impairment – memory, executive function deterioration with retained functional abilities
- **MDD –** Major Depressive Disorder
- **MMSE –** Mini Mental State Examination – a 30-point scale of simple questions to assess mental abilities
- **NfL –** Neurofilament Light – a nerve protein in the brain and rest of the body too
- **NIA-AA –** National Institutes of Aging and Alzheimer's Association
- **NMDA –** A type of receptor for glutamate in the brain
- **NPI –** Neuropsychiatric Inventory to assess psychiatric symptoms
- **NTB –** A Neurologic Test Battery, in this presentation one designed to measure executive function aspects of cognition
- **PET –** Positron Emission Tomography – a type of body scan
- **Placebo controlled –** Non-active treatment for double-blind design
- **p-Tau181 or 217 AD –** Biomarker of phosphorylated Tau protein
- **QPCT –** Glutaminyl-peptide cyclotransferase is an enzyme proposed to create toxic amyloid species
- **RAVLT –** Rey Auditory Visual Learning Test
- **RBANS –** Repeatable Battery for the Assessment of Neuropsychological Status (a test of mental abilities)
- **ROC AUC –** Receiver Operating Curve Area Under the Curve (1.0 ideal) – a type of statistical test to compared two methods of measurement
- **SSRI –** selective serotonin reuptake inhibitor
- **Tau –** A brain protein
- **Ttau –** Total tau levels including both phosphorylated and non-phosphorylated tau

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