Actinogen

Oral Xanamem® (emestedastat)

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

Corporate Presentation

October 2025

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Overview

Xanamem: Clear pathway to Alzheimer's approval

Phase 2b/3 trial on track, FDA agreement streamlines development

- FDA confirms development pathway to US marketing approval using one additional pivotal trial of 10 mg vs. placebo and open-label safety studies
- Clear guidance on minimal ancillary nonclinical and clinical pharmacology work
- Agreement on key manufacturing items
- Ongoing XanaMIA clinical trial:
  - Brisk enrolment at 35 clinical centers in US and Australia
  - Excellent safety profile maintained
  - Interim analysis of safety and efficacy futility in Jan 2026
  - On-track for final results in late 2026
- Phase 3 planning commencing in parallel with discussions re potential partnerships

First-in-class therapy with strong IP and large market potential

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

- Brain cortisol has been proposed as pathogenic mechanism in Alzheimer's & major depressive disorder
- Unique brain-penetrant tissue cortisol synthesis inhibitor that leaves adrenal cortisol synthesis unaffected

Large clinical and commercial opportunities

- **No other brain-penetrant cortisol control drugs in development**
- **Multiple clinical trials showing treatment benefits**
- **First to be awarded INN and USAN names**[1]
- 2025 estimated 7.2 million Alzheimer's patients in the US alone with the cost to treat $384 billion[2]

Patent/data protection and advanced manufacturing

- **Composition of matter protection** to 2036 in all major markets, newer patents to 2044
- **Data exclusivity protects Xanamem data** from use by others for 5 to 10 years from approval
- **Manufacturing process scaled up and patented**, tablets manufactured in US by Catalent

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; USAN (United States Adopted Name)
2. U.S. burden of Alzheimer's disease, related dementias to double by 2060 | CDC Online Newsroom | CDC and The Cost of Dementia in 2025 - April 23, 2025 - USC Schaeffer

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 runway to at least mid 2026**
- Seasoned Board and Management team with a track-record of success

Key shareholders

- **CEO Steve Gourlay ~5% (including via ~$2 million invested personally)**
- Top 20 ex-Gourlay ~23%

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

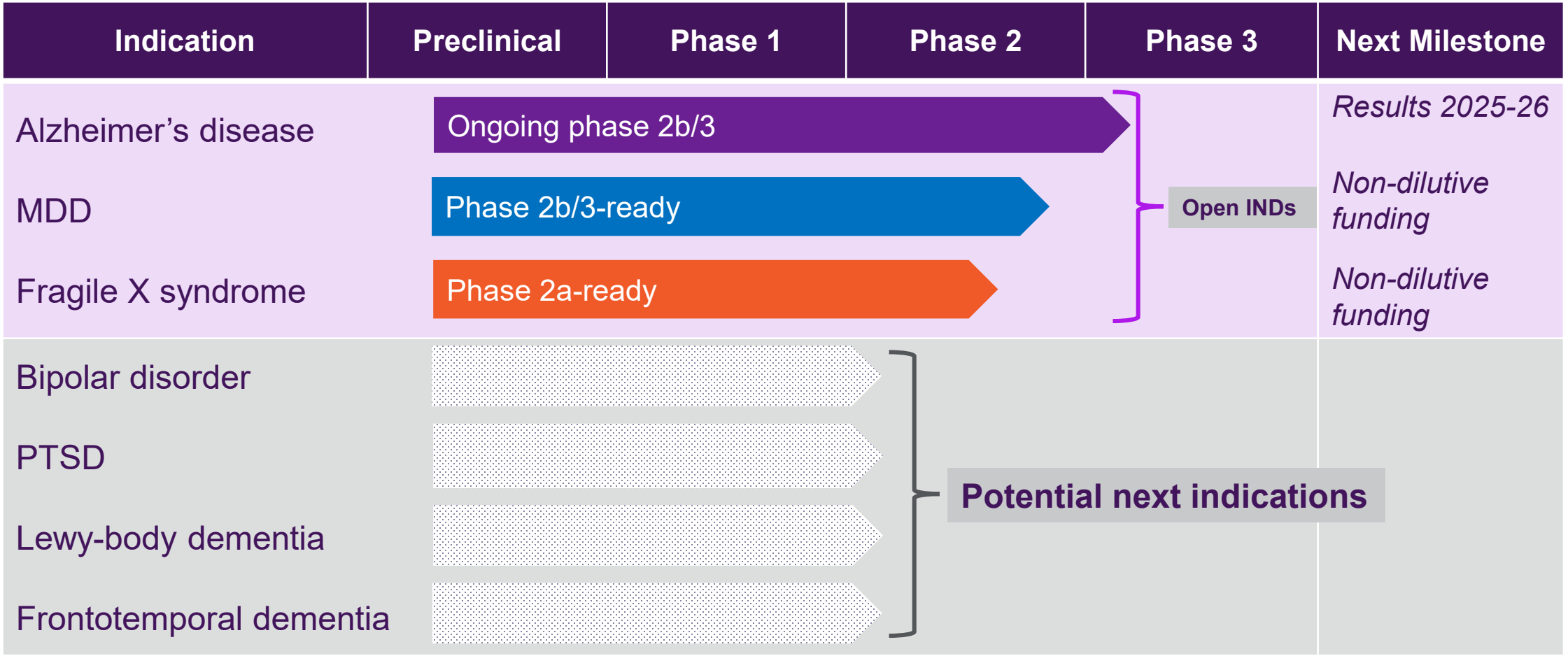
- **Alzheimer’s disease phase 2b/3 ongoing – interim January 2026, final results Q4 2026**
- **Positive depression trial phase 2a completed, peer-review publication pending**
- FDA confirms development pathway to US marketing approval (Type C meeting, Sept 2025)

Fundraising history

- Merger of U Edinburgh spinout Corticrine with Actinogen ASX-listed shell (2014)
- Equity raises on ASX and Australian R&D tax incentive cash rebates (e.g. $9 million received in 2024)
- Option exercise funds (2024-25)

Xanamem – Pipeline focused on Alzheimer's as lead

Depression phase 2a results support further development

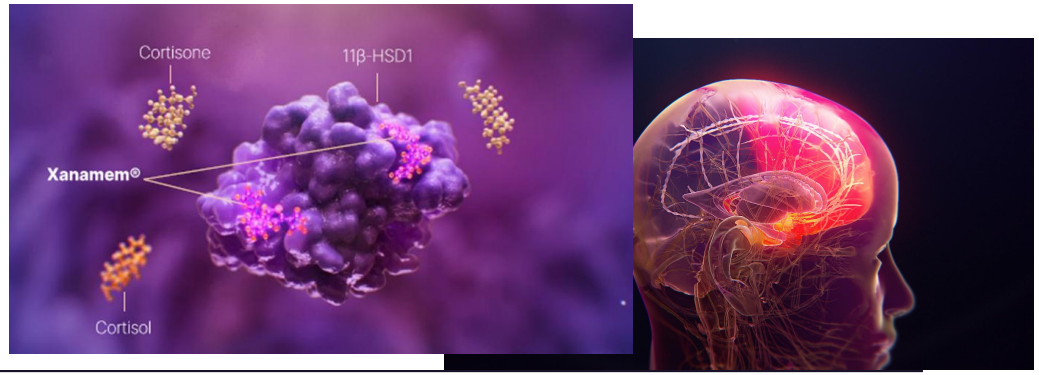


MDD: Major depressive disorder

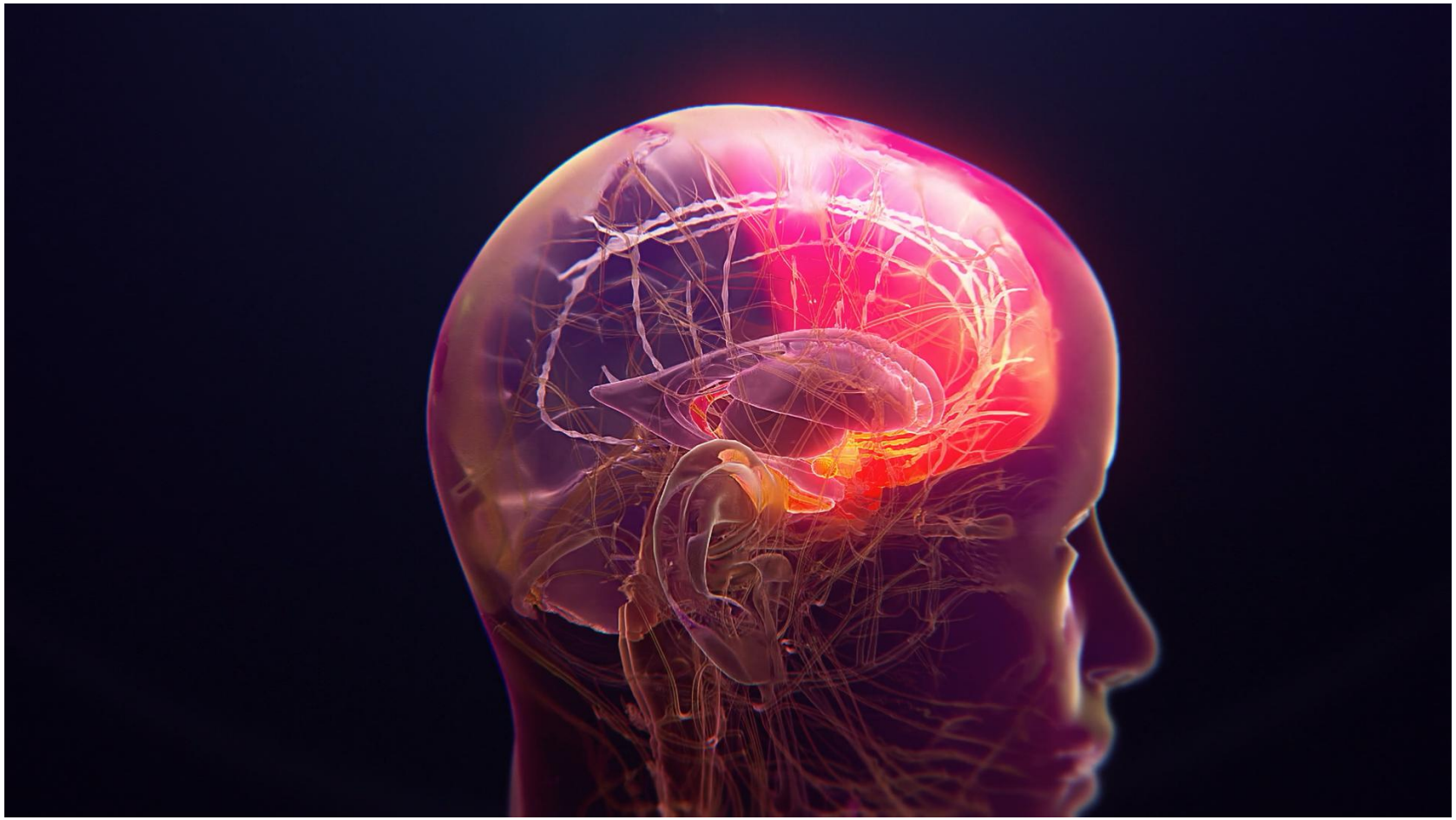
Xanamem

Clinically validated and differentiated Alzheimer's program

- ✓ Mouse experimental studies, brain cortisol levels & human clinical trials validate cortisol as a target for the treatment of AD
- ✓ Excellent safety profile, 400+ patients treated, no related serious adverse events
- ✓ Fully brain-penetrant oral therapy clearly demonstrated on brain PET scan imaging
- ✓ Positive clinical data demonstrated in phase 2 trials in patients with biomarker-elevated Alzheimer’s and moderately severe depression
- ✓ Differentiated from antibody drugs: oral pill, suitable for general practice use, no invasive monitoring
- ✓ Open INDs and collaborative FDA engagement



Xanamem's unique mechanism of action animation



Click here for animation video

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

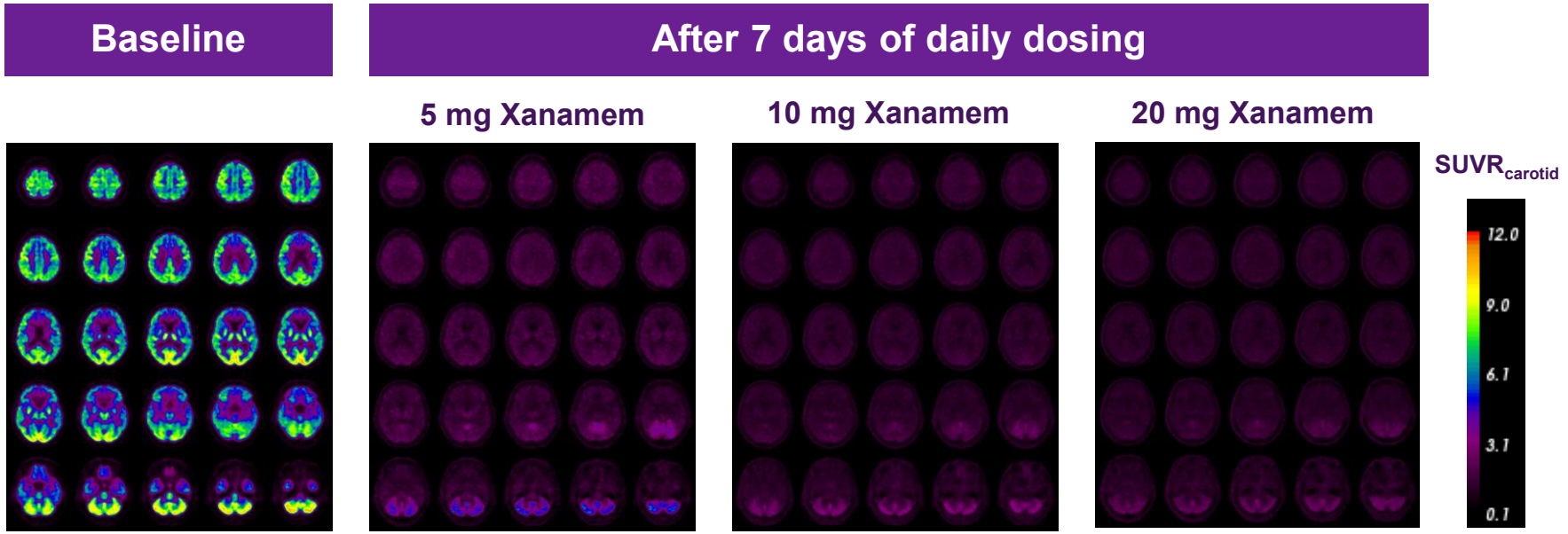
"Lower stress" longer term e.g.

- 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



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

Alzheimer’s disease program

Alzheimer's disease market is large and growing

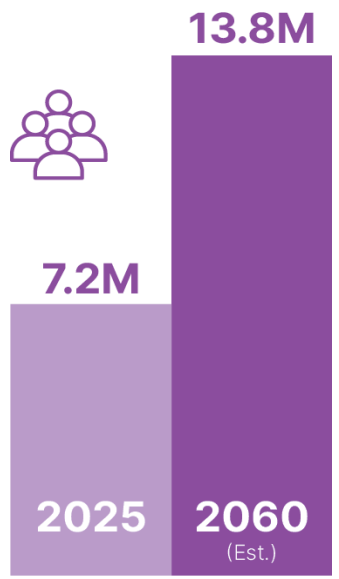
Strong cortisol control scientific rationale to address huge unmet medical need

Rationale

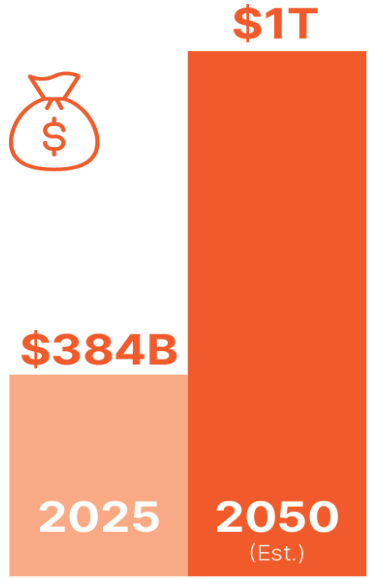
- Cortisol levels elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11β-HSD1 provides full neuroprotection
- 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



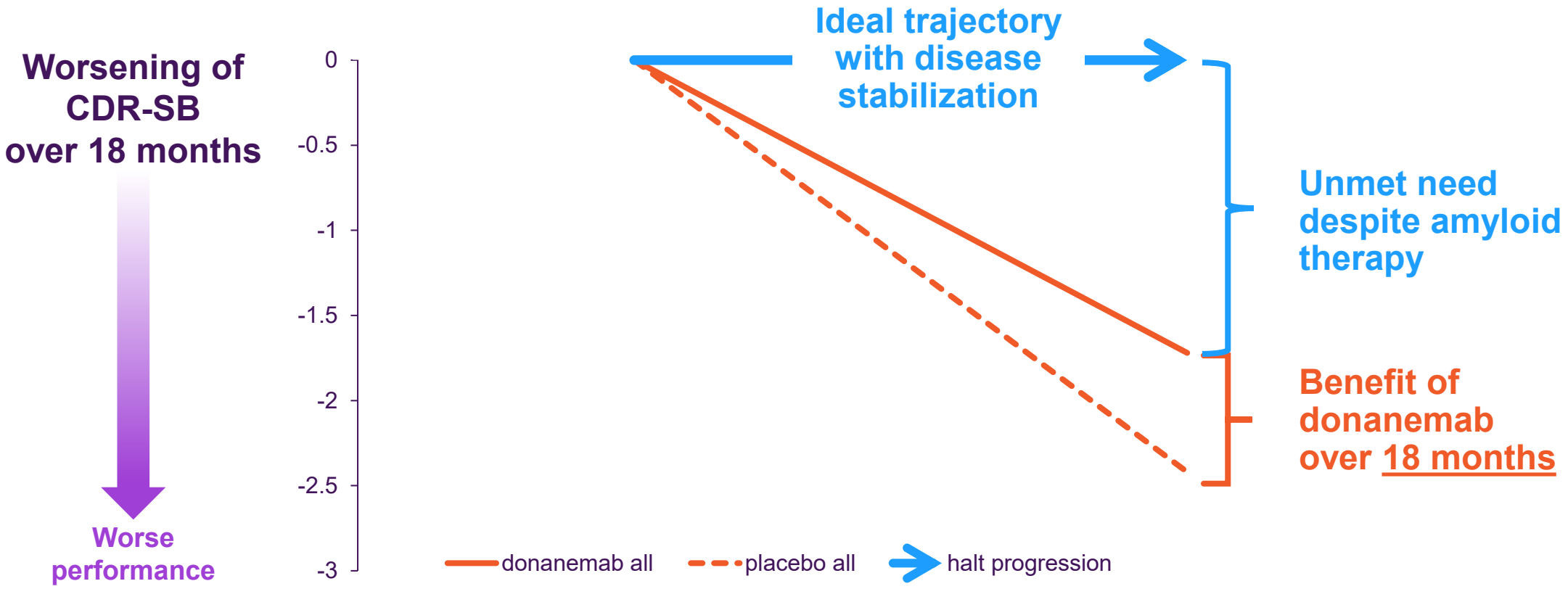
Number of patients (65+ years old)



Cost to treat (USD)

Anti-amyloid therapy modestly slows AD progression

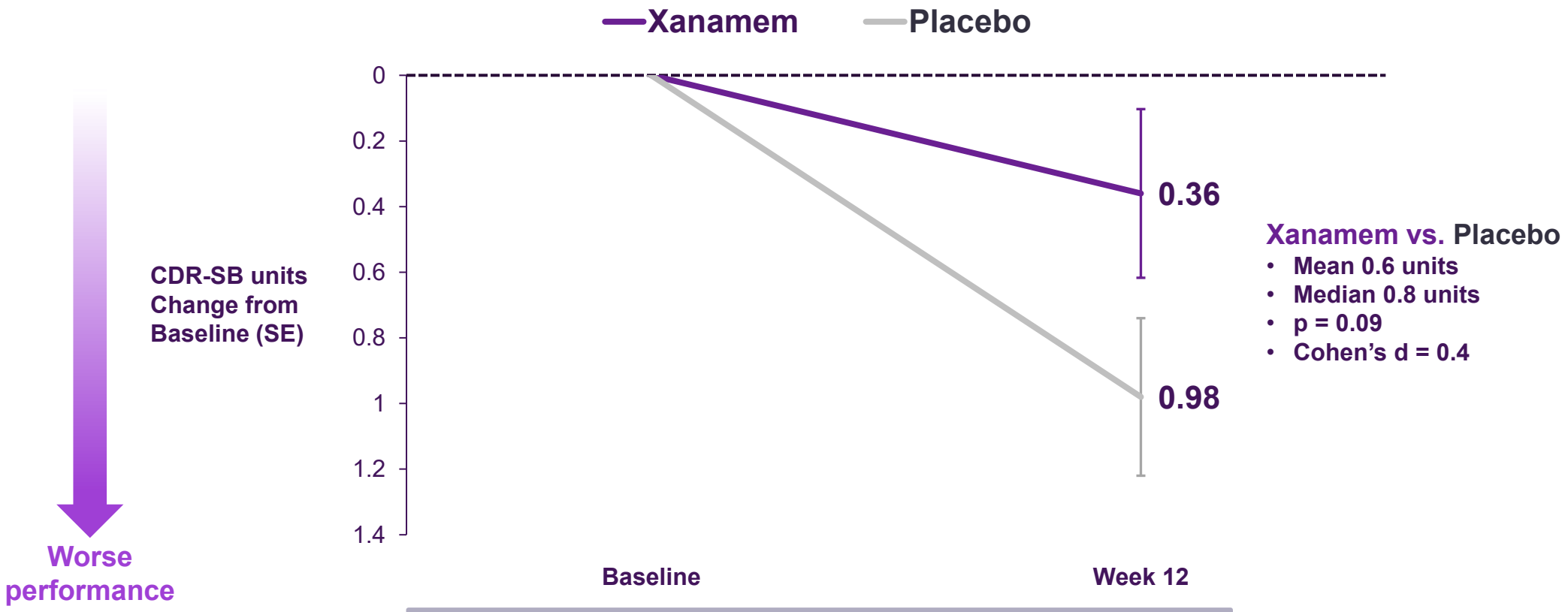
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanamem are needed

Large Xanamem benefit in high pTau181 patients

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



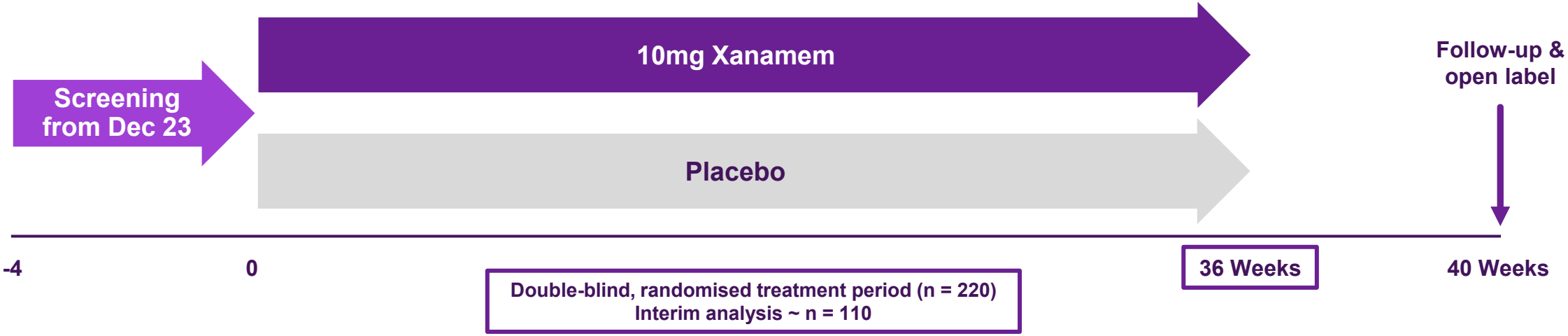
Xanamem vs. Placebo

- **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

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

Initial, interim results January 2026, final results Q4 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) @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 • Interim analysis planned when ~100 people complete 24 weeks (efficacy, futility and safety)

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

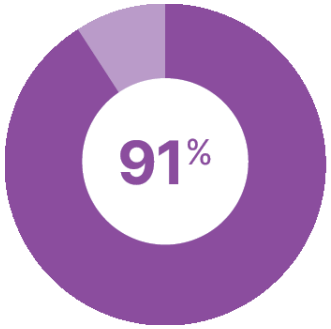
Commercial readiness

Direct insights from the front line of Alzheimer's care

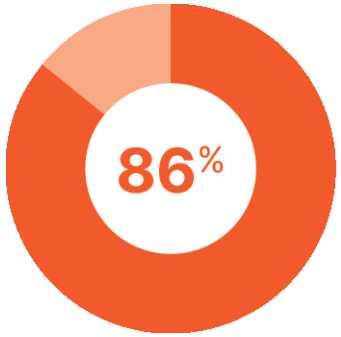
Physician perspectives on current practice, unmet needs, and future therapies*

- Market research with over 100 general neurologists and dementia/geriatric specialists
- Representative of the AD-treating physician population as it relates to geography and practice type, and:
  - 18 mean years in practice
  - 94% of time in clinical practice setting
  - Mean of 222 Alzheimer's patients (median: 175) under personal care (per physician)

Current Market Perceptions:



of neurologists agree there is a **high unmet need** for **DMTs for early AD**



of neurologists expect their **approach to treating early AD** will **change over the next 5 years** as **novel DMTs** launch

*"I think eventually what will happen is that we're **not going to be just treating patients with an amyloid remover**, but also **anti-neuroinflammation**, **mitochondrial enhancers**, **synaptic enhancers** and so on and so on, in order to actually stop or substantially **slow down the progression of the disease**."*

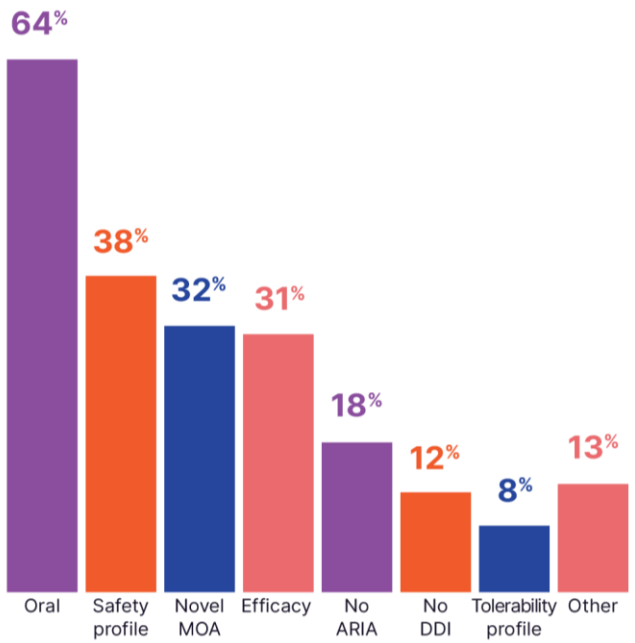
* Spherix Global Insights: Market Dynamics and Custom Research 2025

Strong physician response to Xanamem's target profile

Over half of their current AD patients fall within Xanamem's addressable market

Positive reaction to Xanamem's potential advantages per clinician feedback

Advantages of Xanamem (Unaided) % of respondents



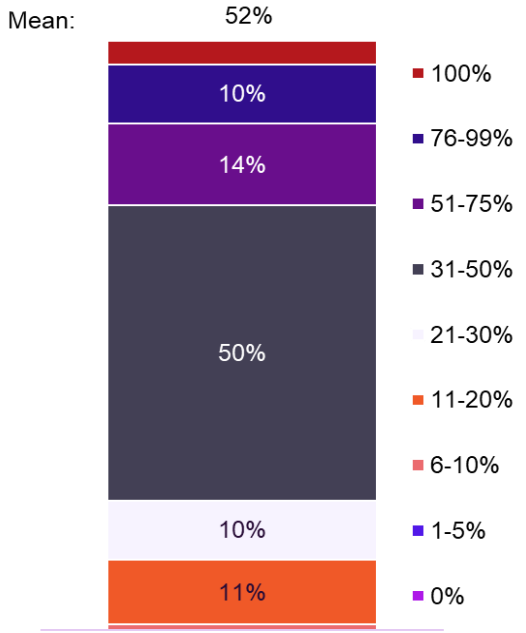
"Oral agent with distinctive mechanism of action, no safety concern."

"More efficacious, oral, no concern for ARIA, can be used in more advanced AD."

"It appears to be quite safe. There is little work to be done on the part of the clinician or the patient (dosing, labs, titration, etc.)"

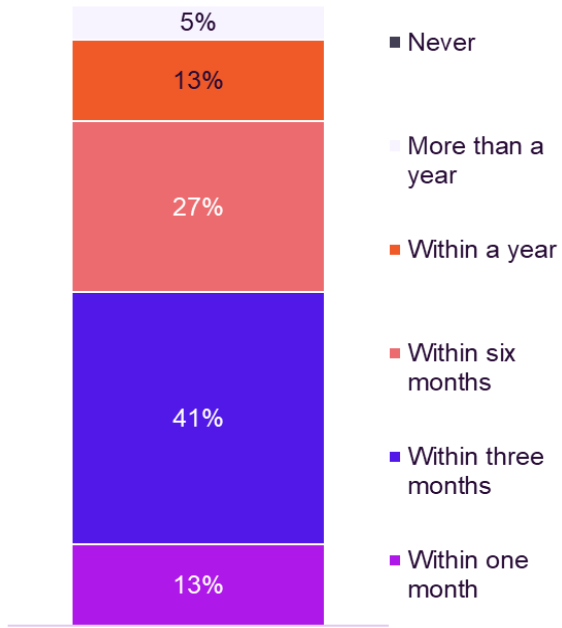
Xanamem Patient Candidacy

% of respondents



Anticipated Timeline to Prescribe

% of respondents



Above and right: Spherix Global Insights: Market Dynamix Early Alzheimer's Disease (US) Q2 2025 (n=101) and Custom Quantitative Analysis (US) July/August 2025 (n=91)

DMTs: Disease modifying therapies
ARIA: Amyloid-related imaging abnormalities

Driving awareness of Xanamem and cortisol biology

Expanding education, engagement and visibility

- **Educational need identified**: Qualitative research and advisory boards revealed limited physician understanding of the role of cortisol in the brain and its link to Alzheimer's pathology
- **Action taken**: Developed a concise two-minute animation explaining Xanamem's unique "cortisol control" mechanism of action
- **Scientific presence**: Active participation at major Alzheimer's conferences, including a booth at AAIC and presence at CTAD and other key global meetings
- **KOL engagement**: Ongoing collaboration with leading neurologists and psychiatrists through advisory boards, 1:1 discussions, and planning for future review papers and publications
- **Broader awareness**: Continuing to elevate Xanamem's visibility and differentiation through consistent medical, scientific, and educational initiative

Depression program

There remains significant unmet need in depression

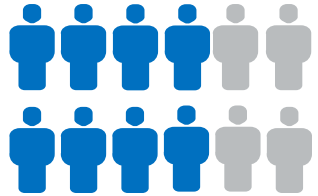
Xanamem's unique mechanism and safety differentiate it from older drugs

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 AND Alzheimer's

3. Ding et al 2021

Phase 2a depression symptom benefits (2024) - major scientific and drug development achievement

Data support further MDD development and are a positive for Alzheimer's too

- ***Clinically and statistically significant treatment benefits on depressive symptoms***
- Predominantly co-treated population with moderate MDD
- Consistent depression efficacy across subgroups
- Xanamem was safe and well tolerated (n=165 treated) with no observed suicide risk or withdrawal syndrome
- The trial was well-conducted with no major differences between Australia and the UK or at high enrolling clinical sites
- Benefits on depression are a desirable feature for an Alzheimer's drug
- Funding for the next depression trial being investigated with potential partners and/or granting bodies

Further XanaCIDD phase 2a depression trial results shown in the Appendix

Conclusion

On track to deliver transformative Alzheimer's data

Multiple catalysts ahead as Xanamem advances towards pivotal results

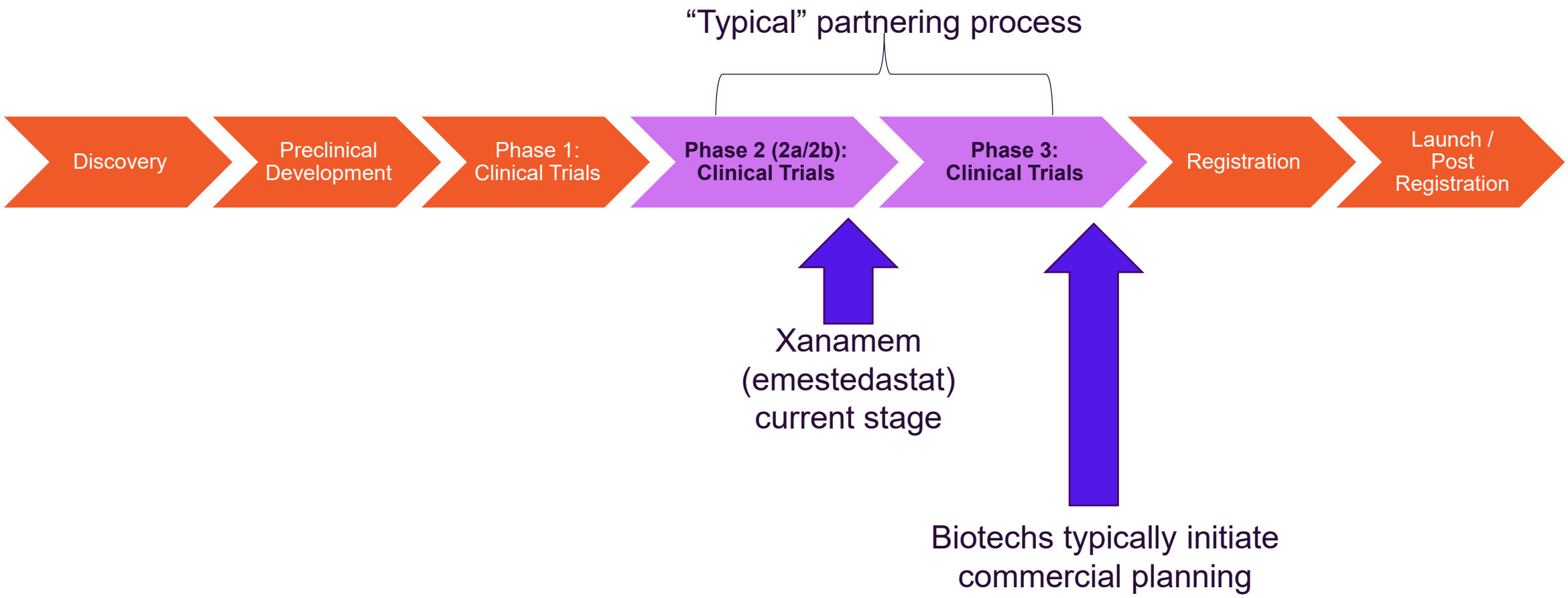
- ***On-track with XanaMIA trial in patients with mild-moderate Alzheimer's disease***
  - ✓ FDA confirms development pathway to US marketing approval
  - ✓ Full enrolment of 220 participants in Q4 2025
  - ✓ Formal interim analysis of safety and efficacy futility January 2026, final results Q4 2026
- ***Positive phase 2a depression data validates Xanamem clinical activity in the brain***
  - ✓ Clinical benefit of unique "cortisol control" mechanism of action and 10 mg dose
  - ✓ Reinforces the likelihood of seeing a disease-modifying effect in Alzheimer's disease
  - ✓ Peer-reviewed journal publication pending
- ***Company funded to at least mid 2026***
- ***Commercial & partnership planning underway***
- ***Other trial, regulatory, publication and presentation milestones***

Multiple near-term milestones in coming year

Milestone	Likely Timing
Screening activities close, XanaMIA AD trial	Q4 25
Full enrolment, 220 patients with AD, XanaMIA AD trial	Q4 25
XanaCIDD MDD peer-reviewed journal publication	Q4 25 / Q1 26
CTAD conference AD presentation in San Diego	Q4 25
Meetings at JP Morgan Healthcare conference week, San Francisco	Mid Jan 26
Interim analysis XanaMIA AD trial	Late Jan 26
ADPD conference AD presentation in Copenhagen	Q1 26
EMA Scientific Advice meeting for AD	Q2 26
Clinical Trials Science Forum – focus on commercial planning	Q2 26
BIO conference in San Diego	Q2 26
AAIC AD conference in London	Q3 26
Final results, XanaMIA AD trial	Q4 26

Appendix

Early commercial planning drives strategy and impact



Current Alzheimer's treatments

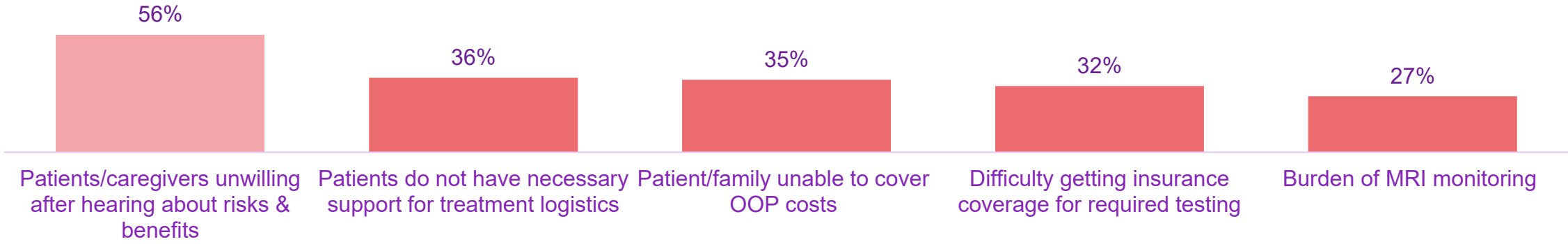
Significant unmet need persists despite two approved anti-amyloid mAbs

Though acknowledging advance of current DMTs, neurologists remain cautious.

- Neurologists are conscious of the advances current DMTs offer in a field that has seen sparse innovation for decades and they acknowledge the potential benefits these DMTs offer.
- However, both neurologists and patients/caregivers remain cautious about the current generation of DMTs, leaving ample opportunity for new entrants to capture both prescribers and brand share.

Top Barriers to Prescribing Anti-Amyloid DMTs

% of respondents



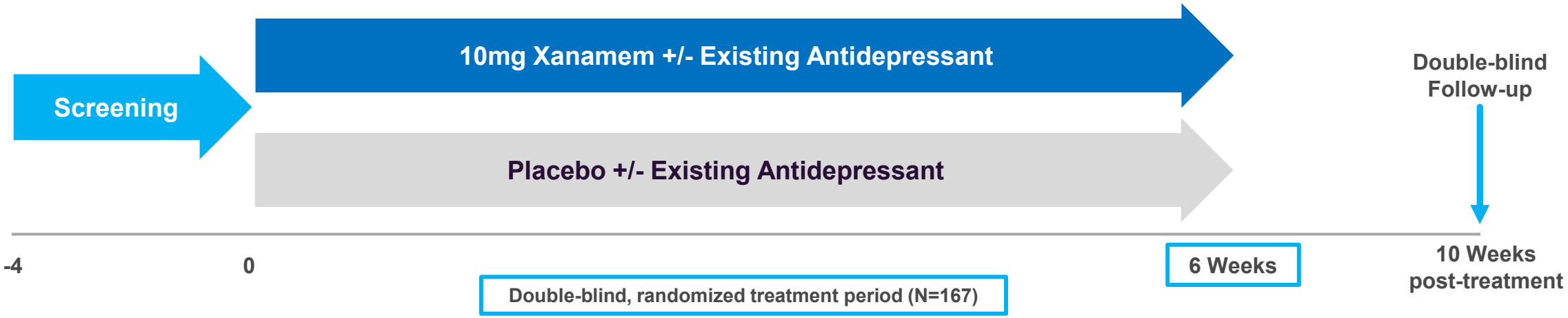
AD Pipeline: Opportunity for differentiated therapies

Combination approaches likely needed for meaningful impact

- Amyloid-targeting therapies: Demonstrated limited efficacy; market differentiation remains modest
- Anti-Tau programs: Many early candidates have not achieved clinical success, highlighting development challenges
- GLP-1 therapies: Upcoming Q4 2025 trial results are highly anticipated; physician feedback has been mixed, though success could broaden interest in novel MoAs aligned with Xanamem
- Pipeline outlook: No single “silver bullet” anticipated; as with other chronic diseases, effective treatment may require complementary therapies

XanaCIDD trial design and methods – completed CY2024

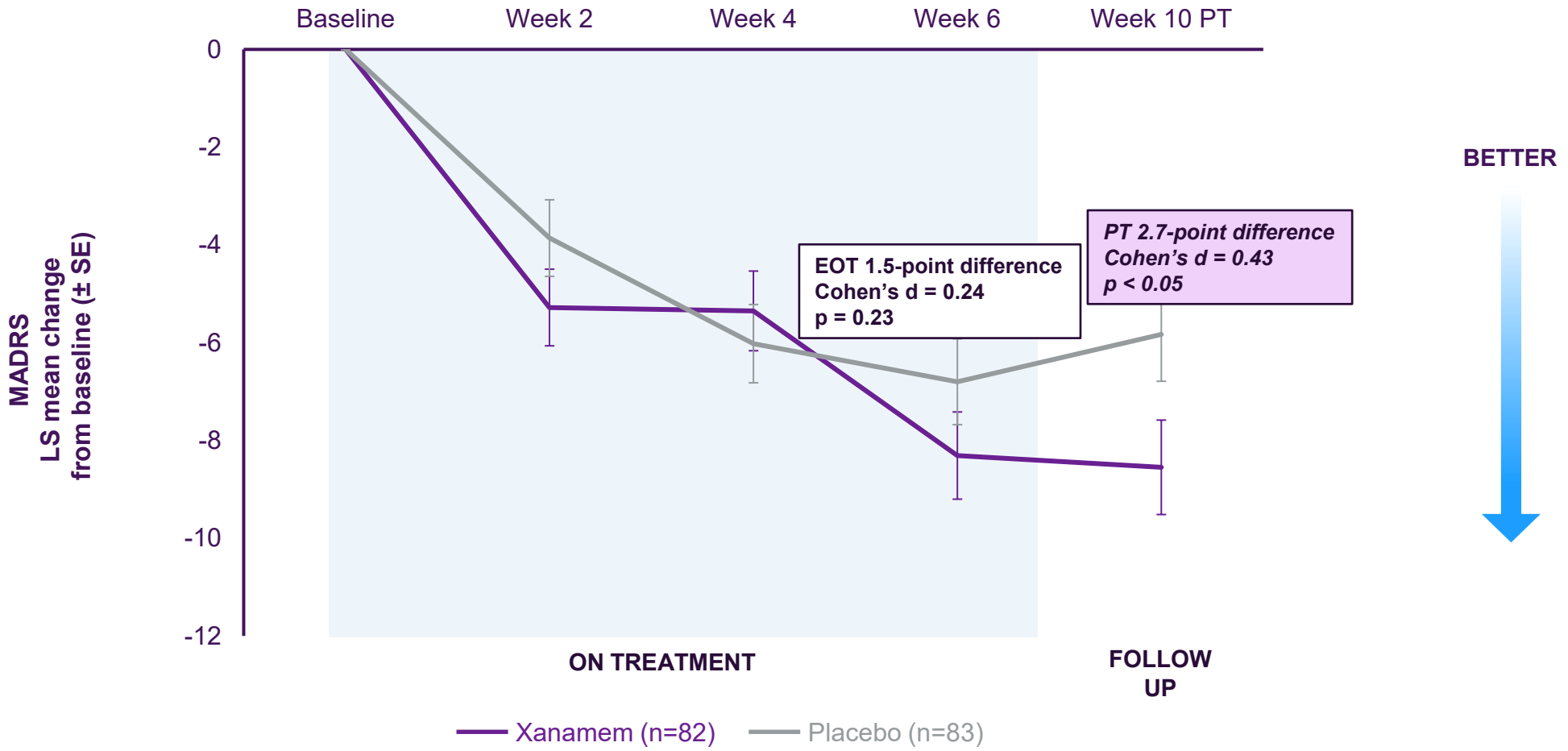
Phase 2, double-blind, proof-of-concept controlled trial to assess safety and efficacy



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 improvement from Week 6 (n=165)

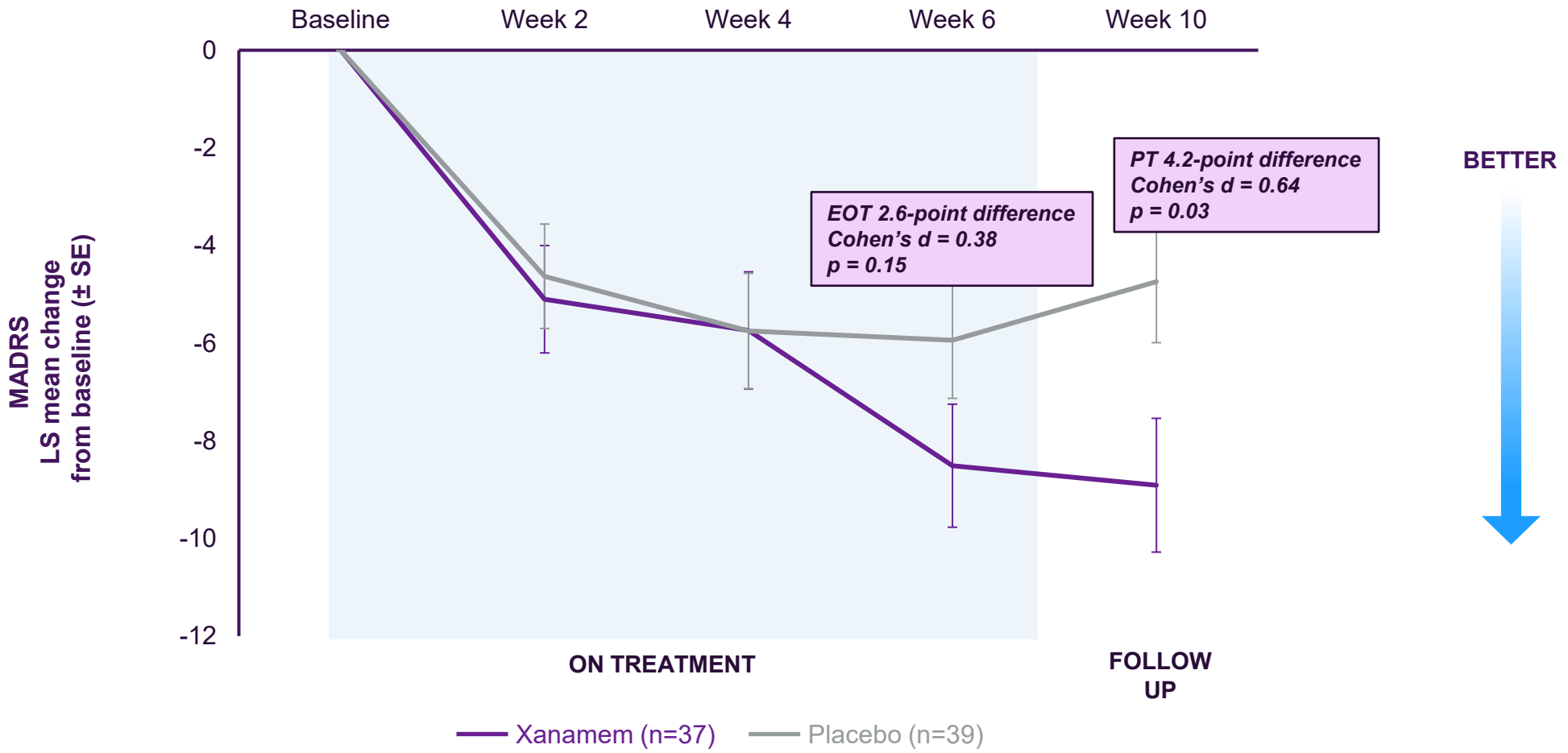
All randomized participants



Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale – a structured interview to assess depression severity

MADRS benefit in patients also taking SSRI (n=76)

Largest co-treatment subgroup



Abbreviations: SSRI, selective serotonin reuptake inhibitor

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
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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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