Actinogen

# Advancing oral Xanamem® in Alzheimer's disease

***Fully enrolled phase 2b/3 pivotal trial | Topline data November 2026***

***Potentially game-changing product profile***

Corporate Presentation

August 2026

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# Corporate and Xanamem highlights

## Potentially game-changing oral therapy for CNS diseases in late-stage trials

### Validated mechanism with differentiated oral profile

- Xanamem is a novel oral therapy targeting elevated brain cortisol, a well-established risk factor for Alzheimer's disease and depression
- Oral administration and favorable safety profile support broad use

NEXT MAJOR VALUE INFLECTION
Pivotal trial topline results
**November 2026**

### Biomarker-enriched pivotal trial with independent validation

- XanaMIA phase 2b/3 pivotal trial (n=247) fully enrolled; open-label extension commenced; topline results November 2026
- January 2026 independent Data Monitoring Committee recommended the trial continue unchanged following unblinded interim review of safety and efficacy futility

### Regulatory clarity in the US and EU

- Current pivotal trial expected to form part of registrational package for Alzheimer's disease
- FDA and EMA guidance support a streamlined marketing approval path requiring only one additional pivotal trial following positive XanaMIA results

### Strong capital position

- Company funded through mid 2027
- Resources focused on execution of the XanaMIA trial and preparation for 2027

# Experienced leadership

## Proven experience in clinical development, manufacturing, regulatory & commercialization

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MD

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**Andrew Udell**
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MBA

**Cheryl Townsend**
**VP Clinical Operations**
RN, M Health Law

**Fujun Li**
**Head of Manufacturing**
PhD

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

# Recent milestones

# Clear regulatory pathway to approval in US and EU

## Regulatory guidance from FDA & EMA supports streamlined late-stage development

### Current trial

- XanaMIA pivotal trial (n=247) expected to form key part of registrational package
- Open-label phase has commenced with high uptake from main trial participants

### Regulatory engagement

- FDA guidance September 2025, EMA May 2026
- Both aligned on clinical, manufacturing and ancillary studies

### Remaining clinical requirements

- One additional single-dose phase 3 trial (10 mg vs placebo) required[1]
- Open-label safety trials
- Limited number of clinical pharmacology and nonclinical studies

1. FDA and EMA may accept a single pivotal trial plus adequate supportive evidence for approvals under certain circumstances

# Positive interim safety, efficacy futility reviews

## Independent Data Monitoring Committee chaired by expert Dr Hans Moebius

**Recommendation:**

- Jan 2026 “non-futile” recommendation to continue the XanaMIA trial without modification
- Jun 2026 positive safety review without futility assessment

**Formal interim review process in January:**

- The Committee was not authorized to recommend early stopping for efficacy in order to preserve the trial’s statistical integrity and alpha
- The Committee confidentially reviewed treatment group data on:
  - ✓ Safety data from all enrolled participants (n=247)
  - ✓ Approximately 37% of the expected final dataset across scheduled timepoints including 52 participants with Week 36 (end of treatment) data

**Independent DMC reviews deliver positive continuation decisions, clearing safety and futility criteria ahead of November 2026 topline results**

# Open-label extension commenced March 2026

## Long-term safety and efficacy durability extension to Phase 2b/3

### Design

- All participants offered active Xanamem 10mg after completion of double-blind phase
- Initiated March 2026 with high initial enrolment (>80% continuation from main trial)

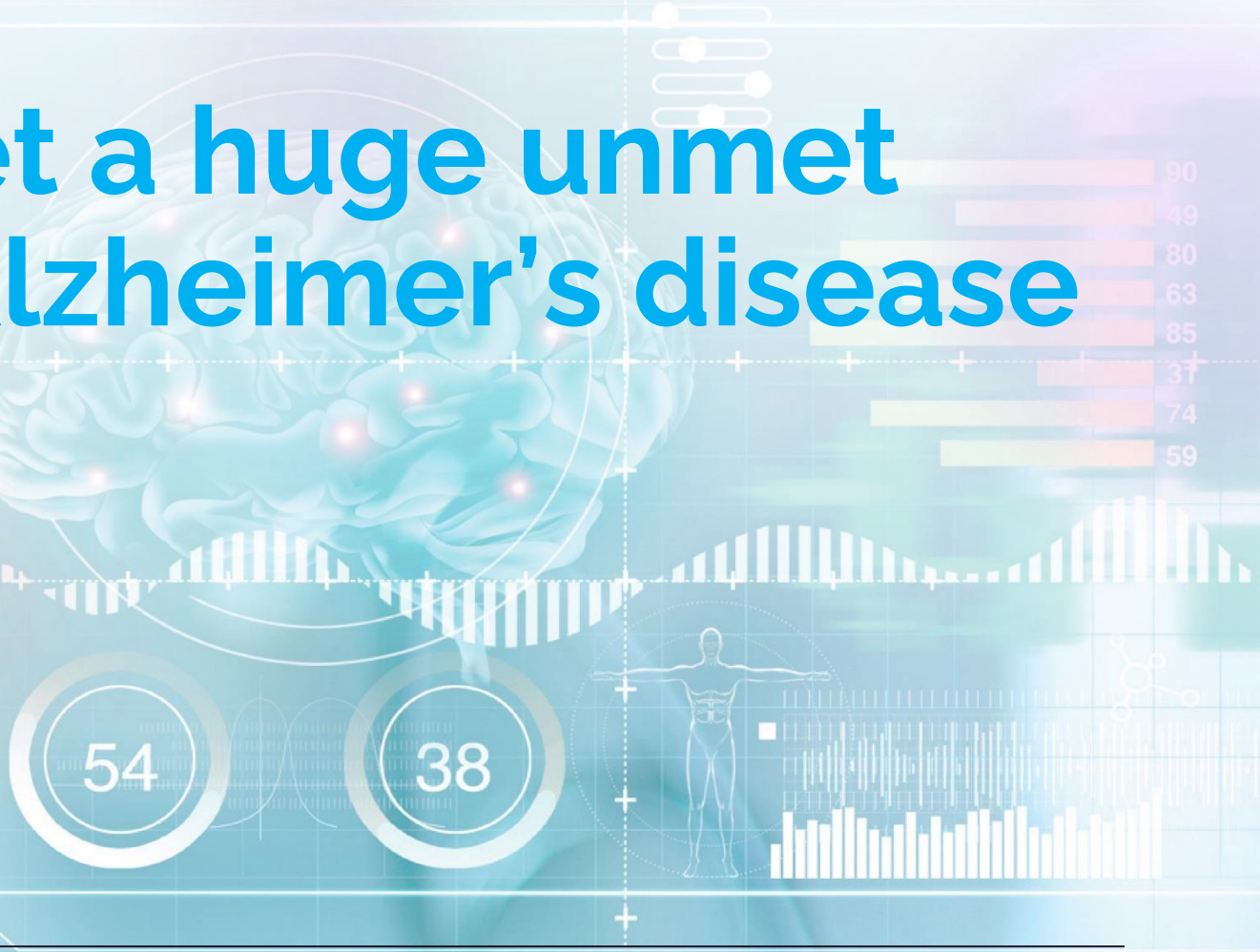
### Data contribution

- ≥14 months additional safety exposure
- Longitudinal assessment of CDR-SB, cognition, and activities of daily living
- Observational comparison of early vs delayed treatment initiation
- Potential to show durability of benefit

### Strategic impact

- Expands cumulative safety database
- Supports regulatory engagement
- Informs durability of clinical effect

# Positioned to meet a huge unmet medical need in Alzheimer's disease



# Strong physician interest and demand for Xanamem

***Global Alzheimer's therapeutic market expected to exceed US$20B by 2030***

**Quantitative survey of 91 U.S. neurologists treating Alzheimer's disease (June 2025)**

*Respondents each manage ~250 AD patients on average*

**Rapid adoption expected**

**~80%** expect to prescribe within 6 months

- 13% within first month
- 41% within three months

Early uptake anticipated among high-volume AD prescribers

**Significant market share potential**

**~50%** projected peak share

- 43% estimate 31–50% peak share
- 14% estimate >50% peak share

Broad eligibility supports substantial utilization

**Expected role in management**

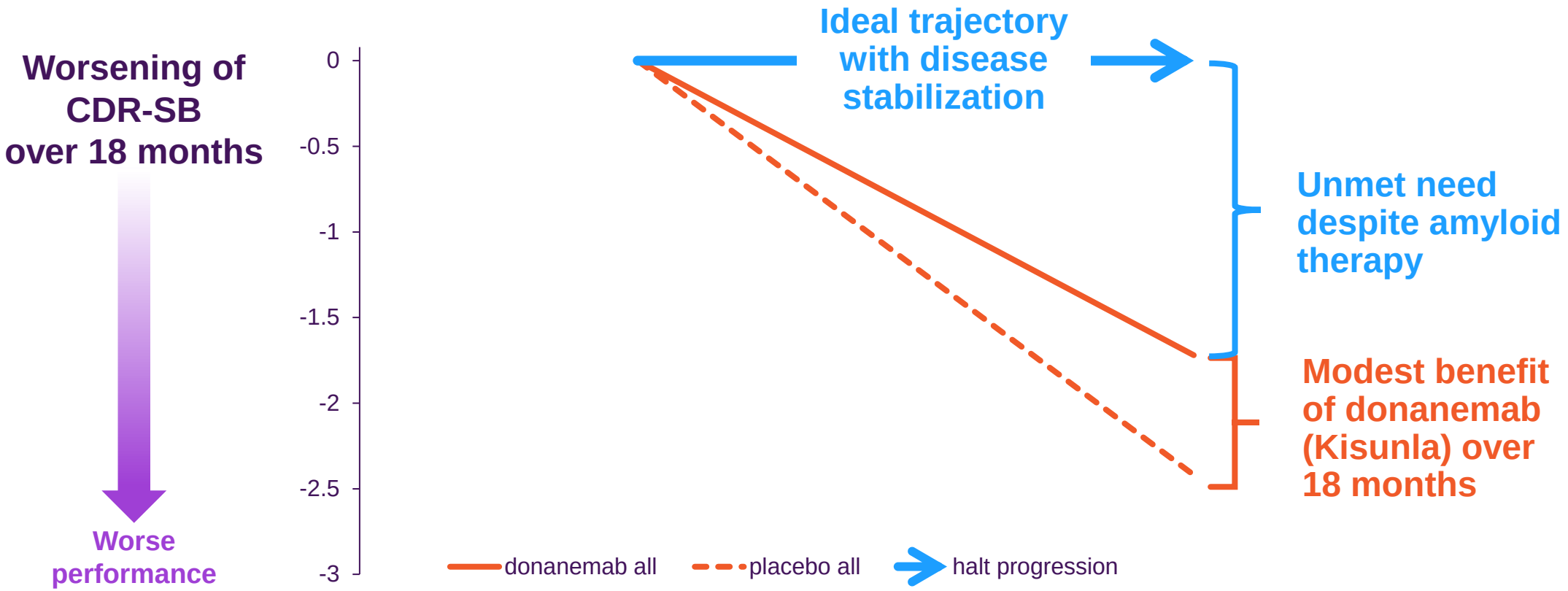
**92%** anticipate leading / definite role

- 30% expect top-two agent
- 0% indicate no role

Oral profile and safety drive enthusiasm

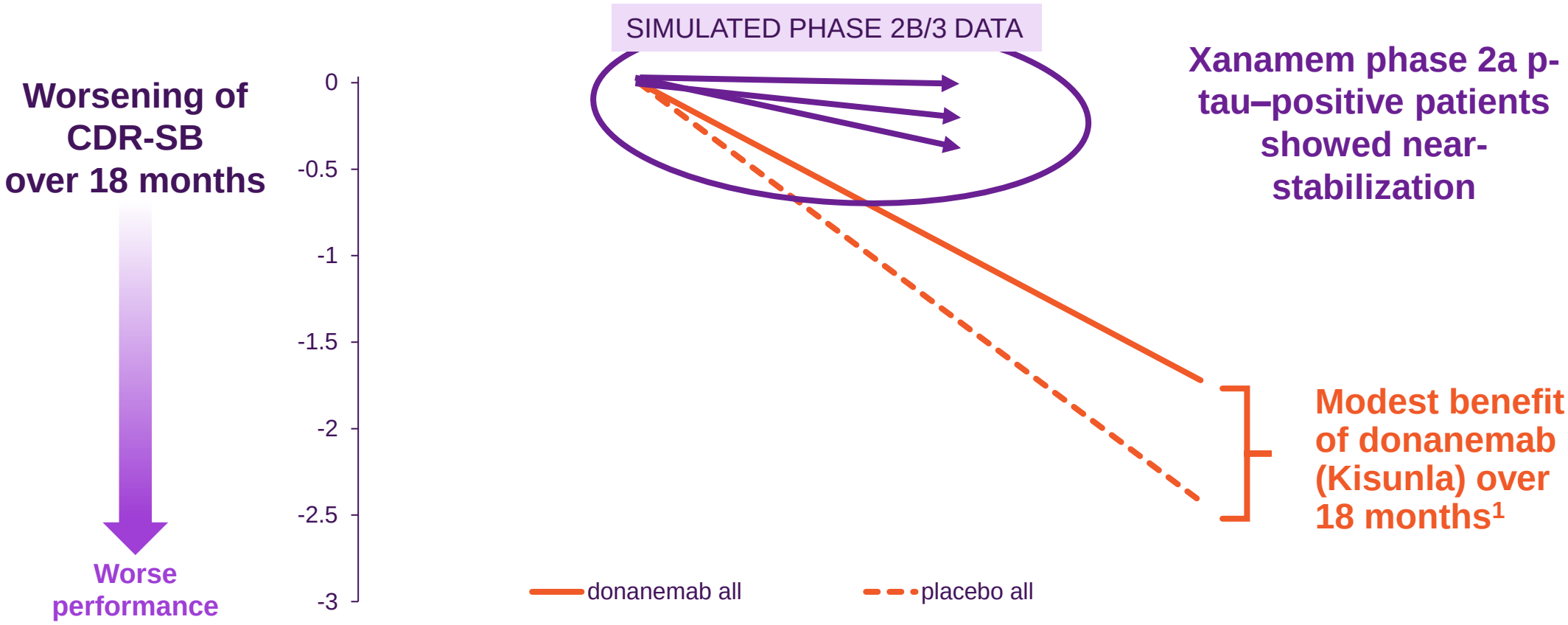
# Anti-amyloid therapies only modestly slow decline

## Disease stabilization represents an important therapeutic aspiration




**Additional therapeutic mechanisms remain an important area of investigation**

# Potential for greater magnitude of effect on CDR-SB




**Xanamem may stabilize or slow CDR-SB progression more than other therapies**

1. Sims et al. JAMA 2023 336(6):512-527

# Summary: commercial and partnering implications

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**Structural Limitations of Anti-Amyloid**

Infusion burden, ARIA risk, and cost limit broad adoption

**Differentiated Oral Profile**

Xanamem is positioned with a favorable risk-benefit and ease-of-use profile

**Potential for Meaningful Stabilization**

Targeting elevated brain cortisol may enable functional impact beyond modest slowing

**XanaMIA as a Value Catalyst**

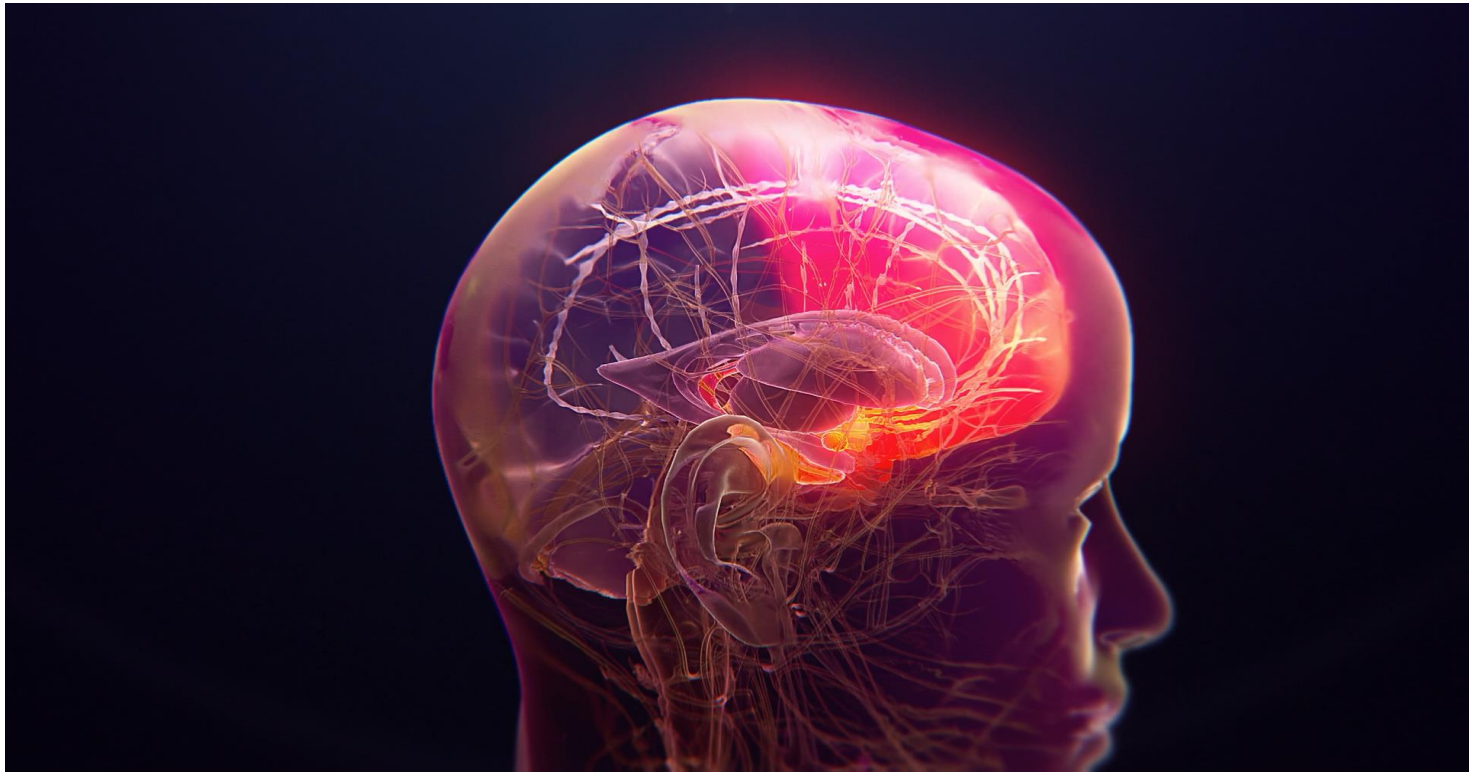
Phase 2b/3 readout is positioned to accelerate commercial and strategic partnering activity

# Positioned for clinical success

# Targeting elevated brain cortisol in Alzheimer's disease

## Xanamem selectively inhibits brain 11β-HSD1 while preserving adrenal cortisol function

## Elevated brain cortisol is associated with cognitive decline and neurodegeneration

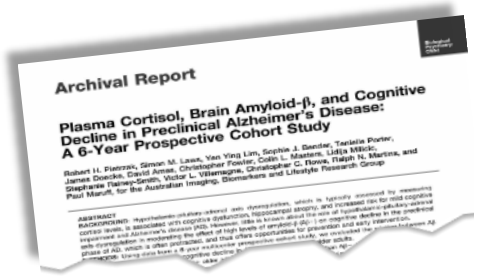


**Watch MOA animation**

# Elevated brain cortisol and Alzheimer's progression

## Human observational and biomarker data support cortisol as a disease driver

- Higher plasma cortisol associated with increased AD risk (AIBL study)
- Cortisol accelerates cognitive decline and interacts with Aβ pathology
- APOE-ε4 carriers exhibit higher CSF cortisol levels
- Elevated CSF cortisol correlates with more rapid clinical worsening

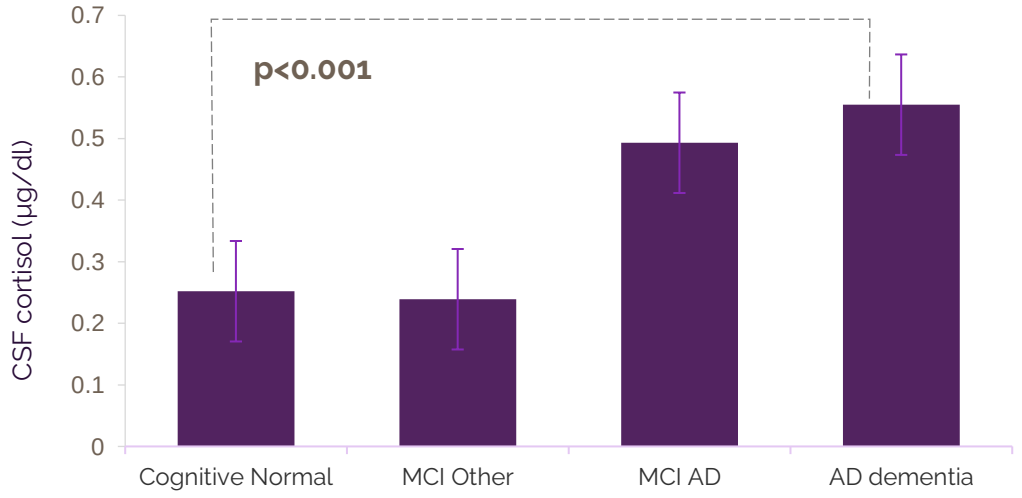

Archival Report

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**

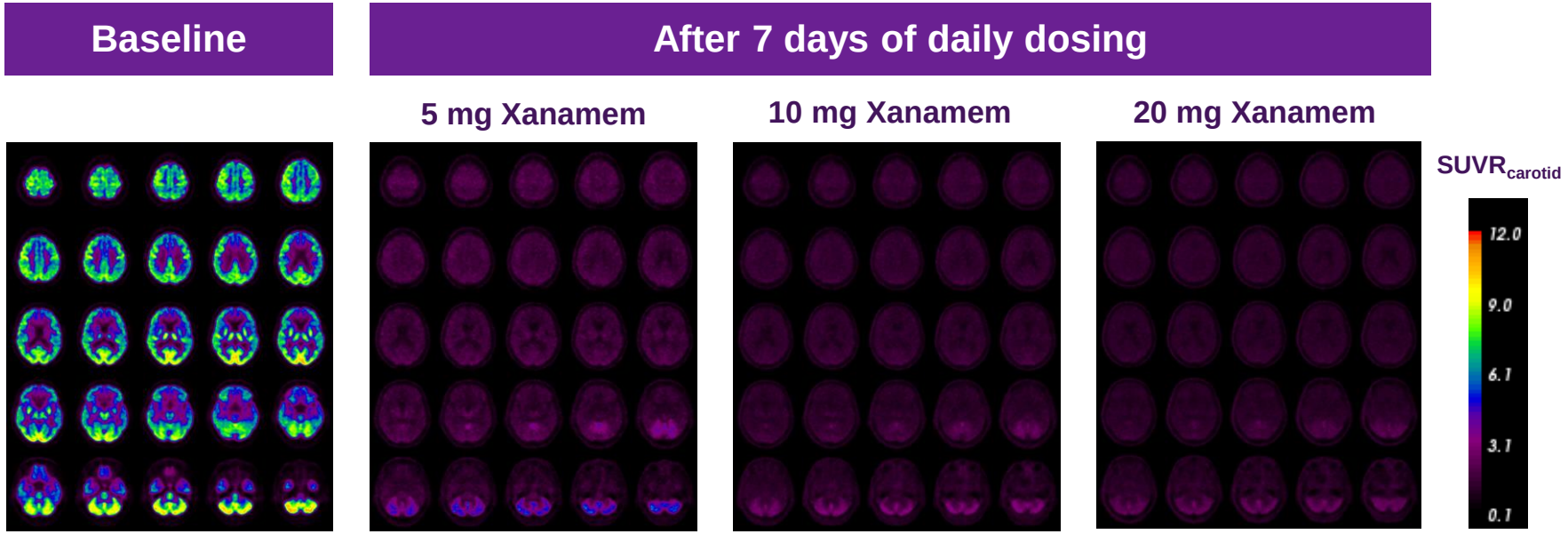



*Popp et al, 2015*

[1] Pietrzak et al., 2017, Biol Psychiatry: Cognitive Neuroscience and Neuroimagery, [2] Lupien et al., 1998, Nat Neurosci 1:69–73; [3] Geerlings et al., 2015, Neurology 85: 1-8; [4] Lehallier et al., 2016, JAMA Neurology 73(2), 203-212; [5] Popp et al., 2015, Neurobiol. Aging 36:601–607; [6] Ennis et al., 2017, Neurology 88(4):371-378; 2:45-52; [6] Lupien et al., 2009, Nat Rev Neurosci 10:434–445; [7] Hinterberger et al., J Am Ger Soc 2013 61(4):648-651; [8] Cernansky et al., 2006, Am J Psychiatry 163:2164-2169; [9] Kornhuber & Jensen, 2015, Neurobiol Aging 36:601-607;

# Xanamem achieves high brain target occupancy

## Human PET imaging confirms brain 11β-HSD1 engagement



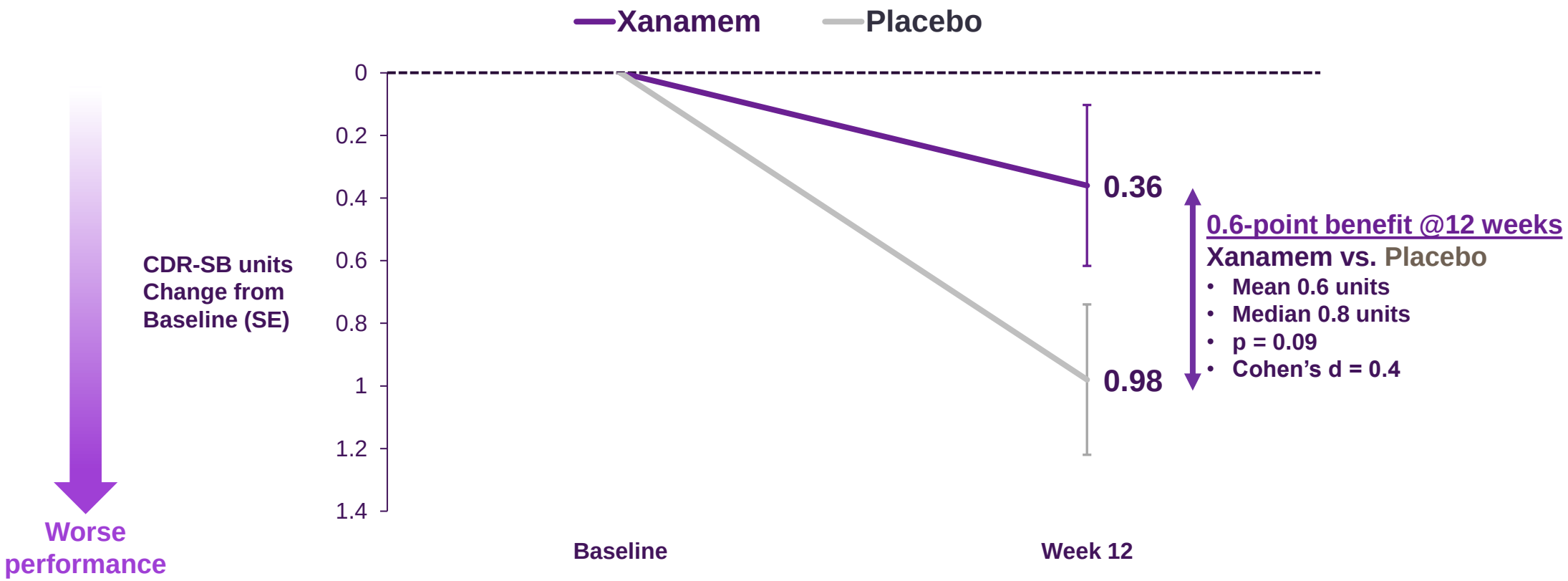

**Reduction in tracer signal (loss of color) indicates high 11β-HSD1 occupancy -**

**Strong 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

# CDR-SB slowed in pTau-positive Alzheimer's

## Phase 2a trial showed slowing of decline over 12 weeks (n=34)

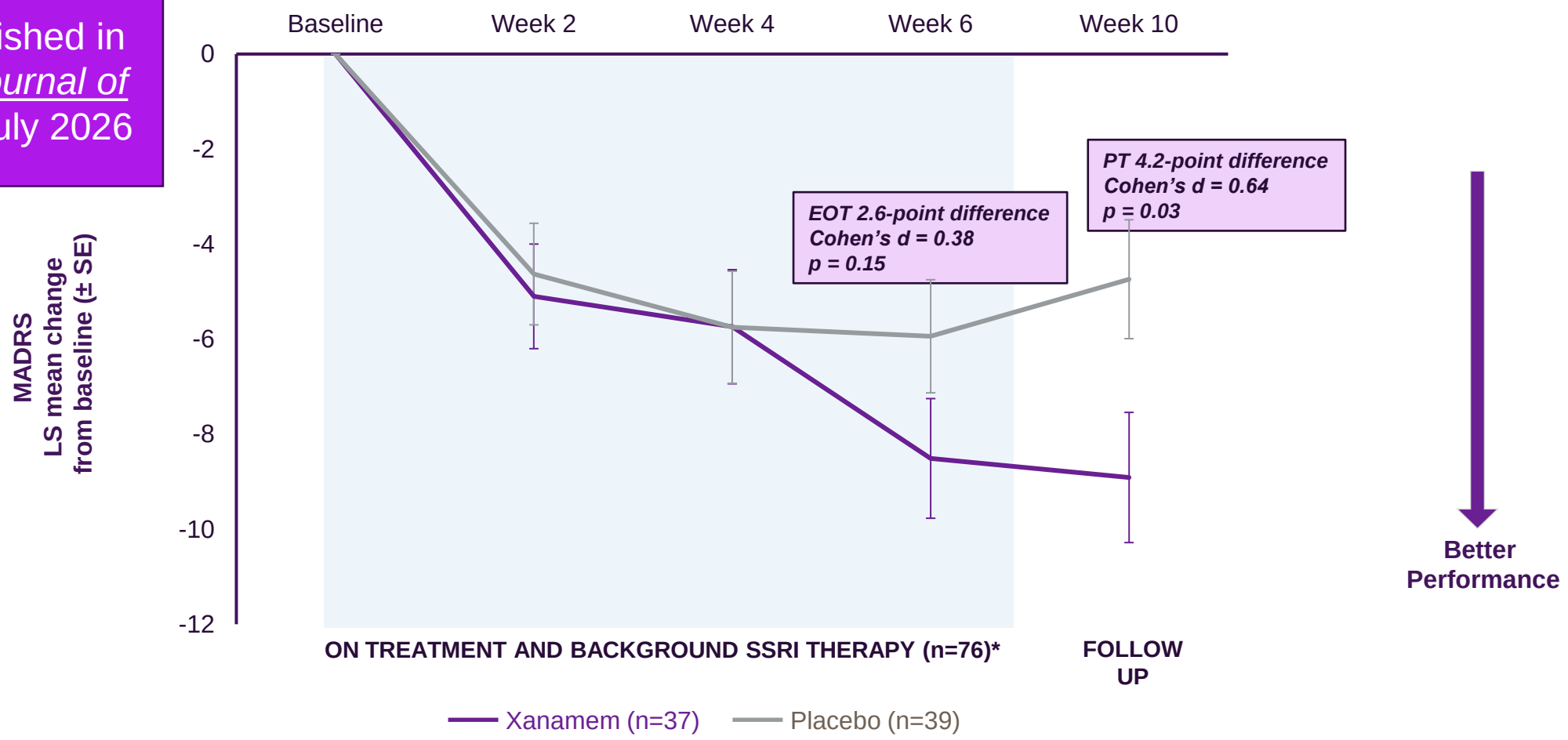



Journal of Alzheimer's Disease 100 (2024) 139–150
Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11-HSD1 Inhibitor Xanamem® for Mild Alzheimer's Disease
Jack Taylor, Mark Jaros, Christopher Chen, John Harrison and Dana Hilt

# Durable activity in phase 2 depression trial

## 10 mg demonstrated separation from placebo overall and on background SSRI therapy

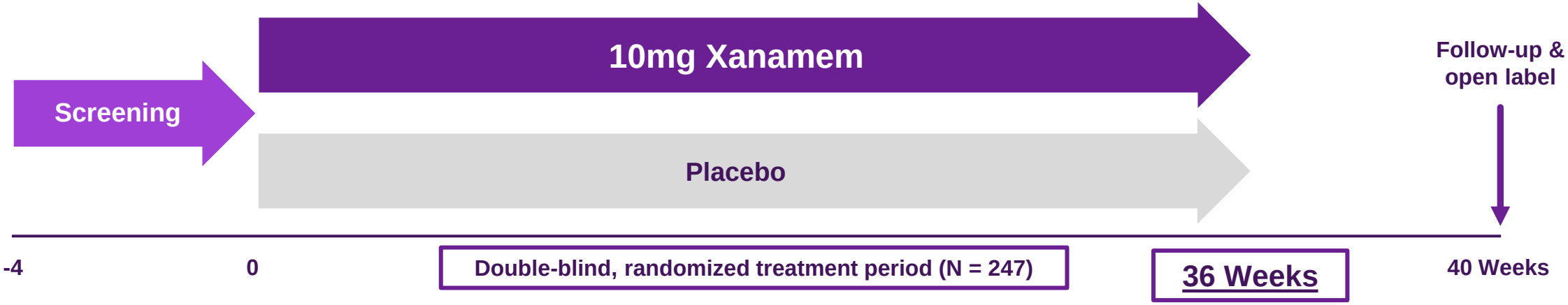
Results published in the *British Journal of Psychiatry*, July 2026




Abbreviations: SSRI, selective serotonin reuptake inhibitor.
*Planned phase 3 population

# Rigorous pivotal trial positioned for success

## Fully enrolled (n=247) across U.S. and Australia; topline results November 2026




| Population | Primary Endpoint | Key Secondary Endpoints | Execution |
|---|---|---|---|
| • Blood pTau biomarker positive<br>• Mild-moderate AD (NIA-AA criteria) | • CDR-SB at 36 weeks (functional and cognitive measure) | • Cognitive Test Battery<br>• Amsterdam Activity of Daily Living | • **Fully enrolled (n=247)**<br>• Independent DMC interim review recommended trial continuation<br>• Open-label ext. commenced<br>• **Topline results November 2026** |

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

# Well-established safety, industry-standard endpoints being used in current pivotal trial

## Safety

- Well-tolerated across clinical program
- No serious adverse events related to Xanamem reported to date (n ~ 500)[1]
- No ARIA signal observed

## Robust XanaMIA endpoints

- CDR-SB at 36 weeks is primary endpoint
- Cognition (validated cognitive measures)
- “Amsterdam” activities of daily living instrument (functional measures)

1. No serious adverse events related to Xanamem have been reported across all clinical trials to date; various other safety data are reported in peer reviewed publications (see Actinogen – Xanamem® (emestedastat)/)

# Summary: positioned for phase 2b/3 success

| Clear Biological Rationale | Demonstrated Brain Target Engagement | Clinical Signal in Enriched Alzheimer's Population | Consistent CNS Activity Across Indications | Rigorous, Fully Enrolled Pivotal Trial |
|---|---|---|---|---|
| Elevated brain cortisol implicated in cognitive decline and neuronal injury | High 11β-HSD1 occupancy confirmed by human PET imaging | CDR-SB slowing in pTau positive patients over 12 weeks | Durable separation from placebo in Phase 2 depression trial | 247 patients; interim continuation; November 2026 readout |

# Summary

# XanaMIA trial positioned as a game-changer

## Operational execution and regulatory alignment ahead of pivotal Alzheimer's data

- **On-track with XanaMIA pivotal trial in patients with mild-to-moderate AD**
  - ✓ Full enrolment of 247 participants achieved
  - ✓ Positive interim analysis Jan 2026 followed by positive June safety review
  - ✓ Topline results expected Nov 2026
  - ✓ Structured as a registrational trial aligned with FDA & EMA guidance

- **Executing on streamlined development path for Alzheimer's disease**
  - ✓ Open-label extension XanaMIA trial phase opened in March 2026
  - ✓ Next pivotal trial in planning - to commence mid 2027
  - ✓ Manufacturing and pre-commercialization activities on-track
  - ✓ Ancillary clinical pharmacology and nonclinical studies to start in 2027

# Commercial and strategic strength ahead of readout

## Leadership, market validation, lifecycle protection, and financial readiness

- **Experienced leadership team with proven track records across development, approval, commercialization, and strategic transactions**
- **Strong physician demand across ~100 U.S. Alzheimer's specialists**
  - ✓ ~80% indicate intent to prescribe within first 6 months of launch
- **Composition of matter protection to 2036 in most markets**[1]
  - ✓ Additional patents extend protection into the 2040s
  - ✓ Regulatory data exclusivity of at least 5 to 6 years from marketing approval dates support protection from generic competition in major markets
- **Increasing strategic interest and engagement as results approach**
- **Funded beyond November 2026 topline Alzheimer's readout**
- **Anti-depressant activity** a good feature for Alzheimer's prescribing information

1. Patent protection extensions for the initial composition of matter patent (2031) of between 5 and 10 years apply in nearly all countries

# Appendix

# 2026 catalysts leading to November Alzheimer's results

| Milestone | Likely Timing |
|---|---|
| Positive interim analysis XanaMIA AD trial of all available data (weeks 12, 24 & 36) | Completed |
| XanaMIA AD open-label extension (OLE) commences & reports initial enrolment data | Completed |
| EMA Scientific Advice meeting for AD | Completed |
| Third Independent Data Monitoring Committee safety review | Completed |
| XanaCIDD MDD peer-reviewed journal publication | Completed |
| AAIC AD conference in London – BD and KOL meetings | Completed |
| Bioshares conference Queenstown, NZ | August 6-7, 2026 |
| Clinical Trials Science Forum – the future of Alzheimer's treatment | August 12, 2026 |
| Last participant assessment visit in XanaMIA pivotal trial | Sept 2026 |
| Final topline results, XanaMIA pivotal AD trial | Nov 2026 |
| Topline results presentation at major AD scientific meeting | TBD |

# AD treatment landscape: meaningful limitations persist

## Recent advances have not eliminated meaningful clinical and practical barriers

| Mechanistic | Admin | Comments |
|---|---|---|
| Older drugs - boosting acetylcholine or glutamate | Oral | • Symptomatic benefit only<br>• Gastrointestinal tolerability limitations |
| Anti-amyloid protein immunotherapies | IV/SubQ | • Modest slowing of decline<br>• ARIA risk and MRI monitoring; variable reimbursement |
| Second-gen anti-amyloid with “brain shuttle” | IV/SubQ | • Late-stage trials aimed at improved vascular safety |
| **Xanamem (emestedastat) control of elevated brain cortisol** | **Oral** | • **Phase 2b/3 pivotal trial (n=247)**<br>• **Oral, once-daily; no ARIA observed**<br>• **Combination-compatible** |
| Blarcamesine SIGMAR1 antagonist to block autophagy | Oral | • Phase 2b/3 trial; EMA rejection<br>• CNS tolerability concerns reported |
| Anti-amyloid formation or toxicity | Oral | • High historic attrition<br>• Subgroup strategies under evaluation |
| Anti-tau protein immunotherapy | IV/SubQ | • Multiple trial failures to date<br>• Development ongoing |
| PDE-5 inhibitor (AriBio/Fosun) | Oral | • Failed phase 2, now phase 3 in different population with different endpoints, due to read out Sept 2026 |

# Contacts

**Will Souter**
CFO & Investor Relations
M: +61 402 035 716
E. will.souter@actinogen.com.au

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

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