



**Oral Xanamem®**

**A new class of cognitive enhancer for depression  
with disease modifying potential in Alzheimer's**

Corporate Presentation July 2024

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## Novel mechanism and attractive oral profile

- Xanamem is a unique brain-penetrant tissue cortisol synthesis inhibitor (11 $\beta$ -HSD1 enzyme)
- Once-daily oral therapy with potential efficacy, safety and ease of use greater than competitors
- More than 350 people treated with promising safety profile and low drug interaction risk



## Large and growing market opportunities with significant unmet need

- Rapidly acting oral therapy with dual action on **cognitive impairment / depression**
- Demonstrated **cognitive enhancement** and potential disease-modifying in **Alzheimer's disease**
- Trials read through to cognitive impairment in schizophrenia, other dementias and Parkinson's disease



## Patent protection

- Composition of matter protection to 2031 – to 2036 with extensions in major markets
- Additional recent patents protect against future competition



## Near-term phase 2 milestones funded

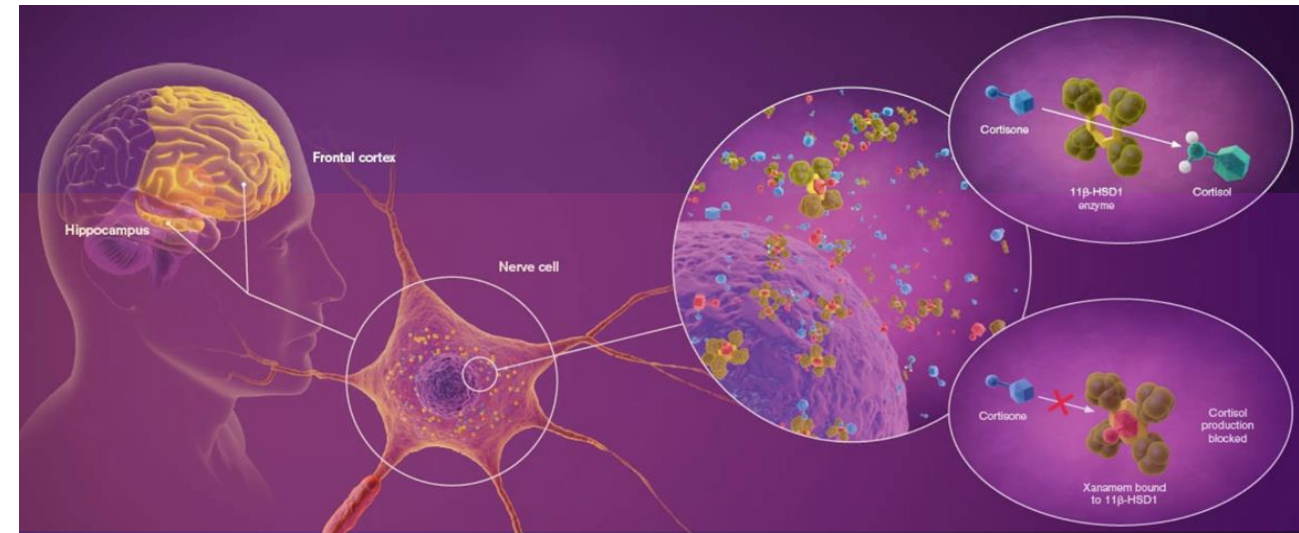
- Cash runway through late 2025
- Phase 2a cognitive impairment in depression results early August 2024 (n=167)
- Phase 2b Alzheimer's disease interim data mid 2025 (n=100)

# Once-daily oral treatment with a unique mechanism



Xanamem is a small molecule tissue cortisol synthesis inhibitor (11 $\beta$ -HSD1 enzyme)

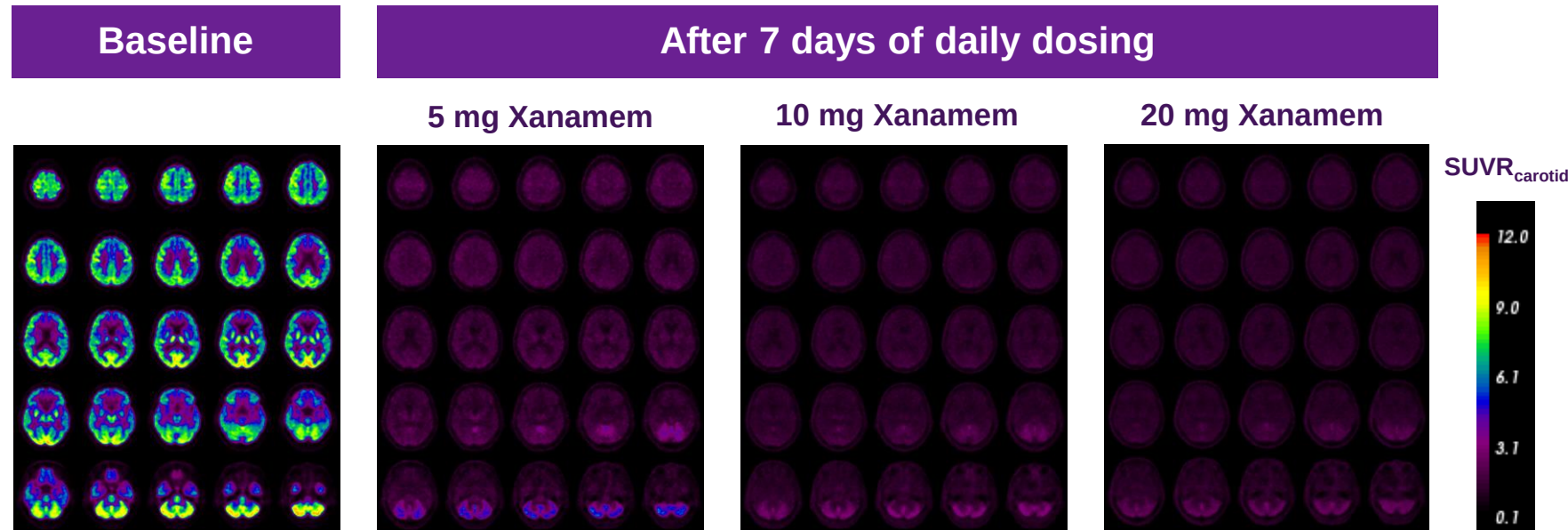
- ✓ Good safety profile in >350 treated
- ✓ Brain-penetrant at low doses
- ✓ Potentially disease-modifying
- ✓ Pro-cognitive within 2–4 weeks
- ✓ Low drug interaction potential ideal for combination therapy



**Mouse experimental studies, brain cortisol levels & human clinical trials validate cortisol as a target for the treatment of AD**

# Human PET study shows full target engagement

Other 11 $\beta$ -HSD1 enzyme inhibitors have not achieved adequate brain levels



Xanamem extensively binds to the 11 $\beta$ -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.

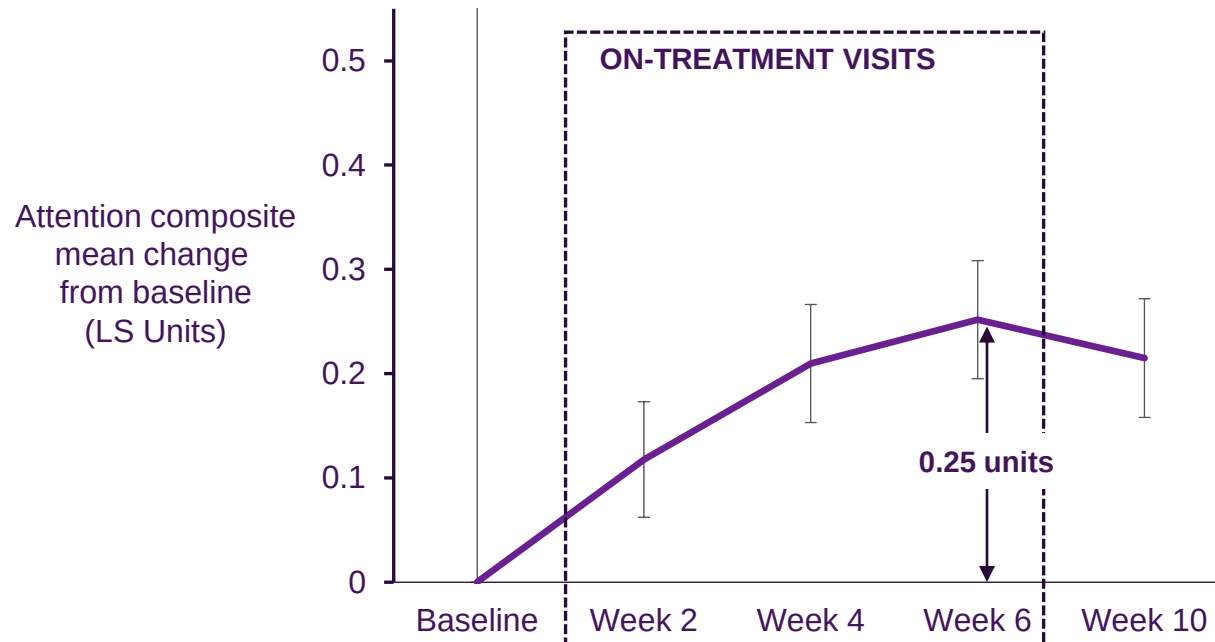
Validates 10mg dose in efficacy trials

# Positive Xanamem effects on cognition in two prior trials

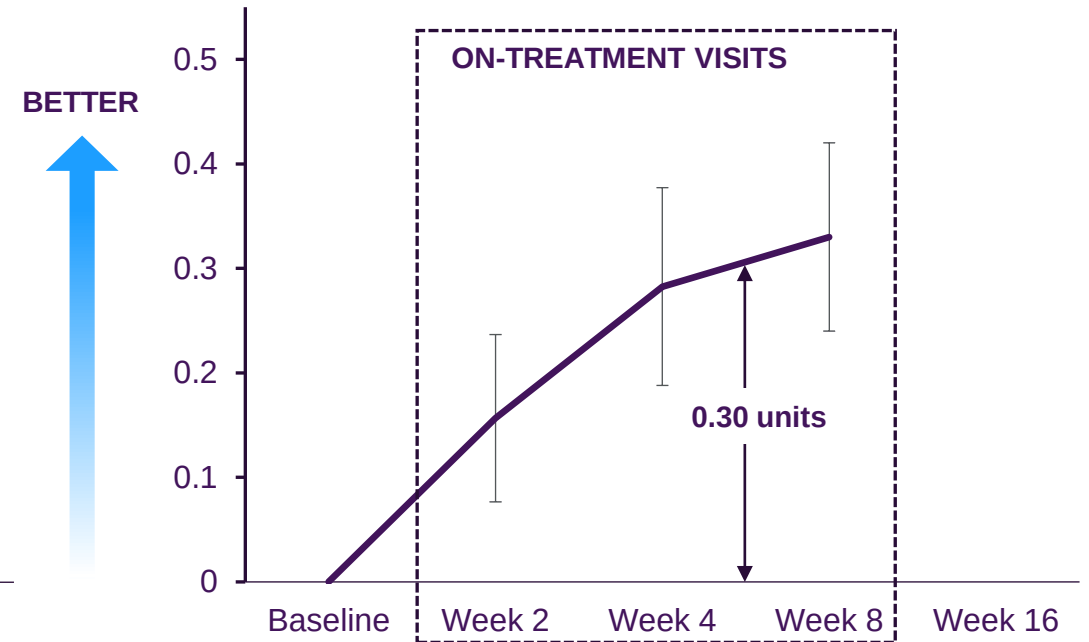


Consistent Cogstate improvements in older, cognitively normal people\*

XanaMIA Phase 1b trial (n=107, 5 and 10mg combined)



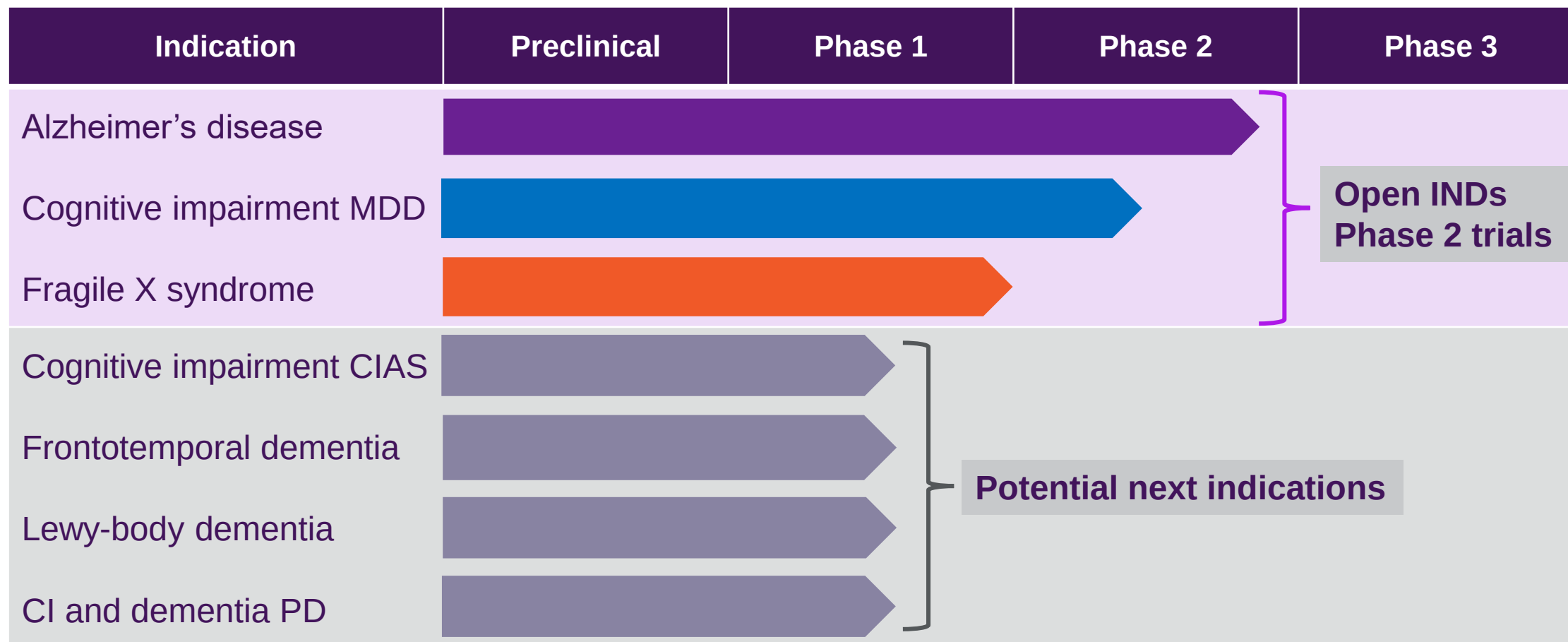
XanaHES Phase 1b trial (n=42, Xanamem 20 mg)<sup>2</sup>



BETTER

\*Placebo groups not shown: XanaMIA slight improvement in placebo group to Week 2, XanaHES worsening in placebo group at all timepoints

# Xanamem pipeline



# Experienced board and management team

## Board of Directors



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# Stock price and key shareholders\*



## ASX: ACW – YTD CY24



## Key Data

|                      |                   |
|----------------------|-------------------|
| 52 Week Range        | \$0.015 – \$0.099 |
| YTD CY24 change      | 291%              |
| Shares on issue      | 2.7b              |
| Unlisted options     | 367m              |
| Closing price        | \$0.081           |
| Closing market cap*  | \$218m            |
| 30 June cash balance | \$9.45m*          |

## Key Shareholders

|                            |       |
|----------------------------|-------|
| Biotech Value Fund         | 9.2%  |
| CEO Steven Gourlay         | 3.6%  |
| Top 20 (ex BVF/Management) | 22.8% |

\*Data as at 19 July 2024; market cap undiluted (excludes options); cash balance excludes options converted post 30/6 and R&D tax rebate expected in Q4 FY2024

# Cognitive impairment & depression



# Cognitive impairment & depression

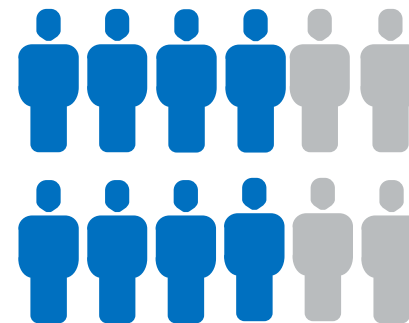
Strong scientific rationale to address the large unmet medical need

## Scientific rationale

- Elevated cortisol associated with severe, melancholic depression
- Cortisol levels associated with treatment outcomes, relapse, & cognition
- Majority of MDD patients report neurocognitive symptoms
- Cognitive symptoms often persist during remission
- Positive effects with glucocorticoid receptor antagonism with mifepristone
- Xanomem has improved human cognition in 2 trials with same cognitive endpoint used for the current XanaCIDD trial

## U.S. Depression market large unmet need

- 21M patients have had  $\geq 1$  MDD episode

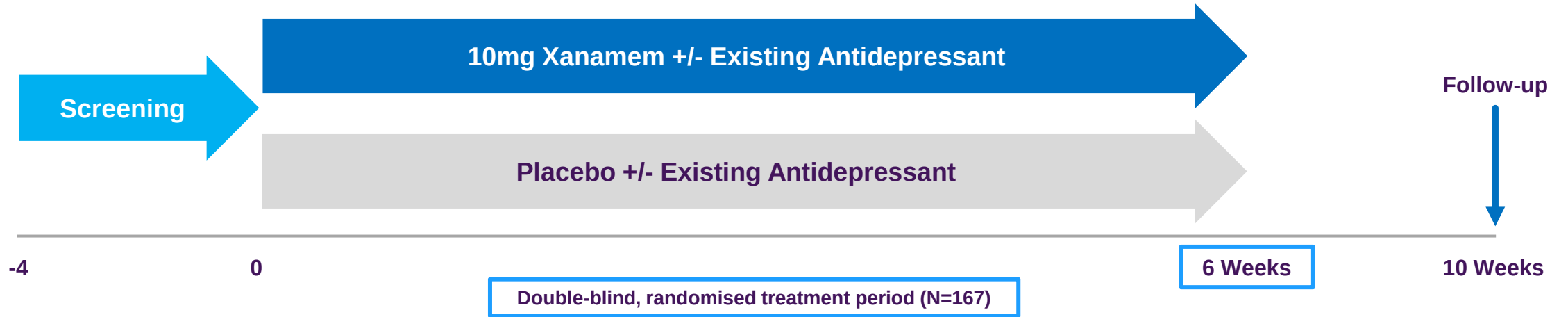


- Two-thirds with an episode **with severe impairment** in the past year
- 61% of all adults with MDD episodes receive treatment
- $\geq 365$  M prescriptions per year

# XanaCIDD phase 2a trial cognitive impairment & MDD



Results early Q3 2024, primary endpoint validated in prior trials of Xanamem



## Primary Endpoint

- **Cogstate Cognitive Test Battery Attentional Composite** (attention and working memory)\*

## Key Secondary Endpoints

- Montgomery-Åsberg Depression Rating Scale (**MADRS**)
- Executive Function Cognitive Composite
- Memory Function Cognitive Composite

# XanaCIDD trial data trending positively

Pooled blinded data trending in the right direction with final results due early August 2024



## Observations

- Assessment of data quality found no concerning trends by country or clinical site
- Clinical safety profile remains excellent, with no serious adverse events related to Xanamem
- Improvement seen in **all three computerized tests** that make up the primary endpoint “Attention Composite”
  - Improvements greater than in prior trial placebo groups
  - Improvements of  $\geq 30\%$  of a baseline standard deviation are potentially clinically significant in the field of cognition
- Improvement in MADRS scores: change of 32% is in the range reported for active & placebo groups in prior trials

# Alzheimer's disease



# Alzheimer's disease

Strong scientific rationale to address huge unmet medical need

## Scientific rationale

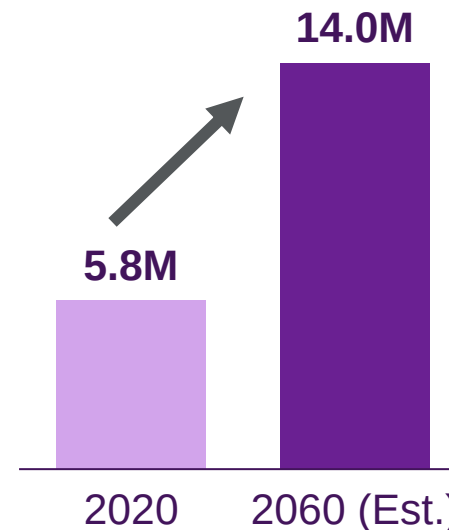
- Cortisol levels are elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11 $\beta$ -HSD1 provides full neuroprotection
- 3 trials show Xanamem activity on cognition
- Phase 2a trial shows slowed disease progression in biomarker-positive patients with mild AD

## Alzheimer's Disease market – U.S.

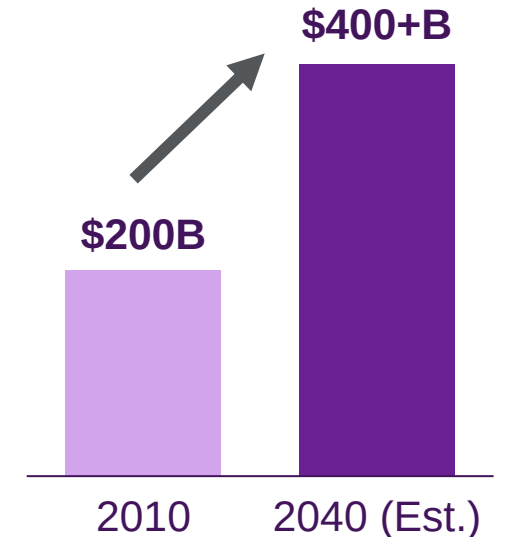
Large unsatisfied and growing market



# of patients



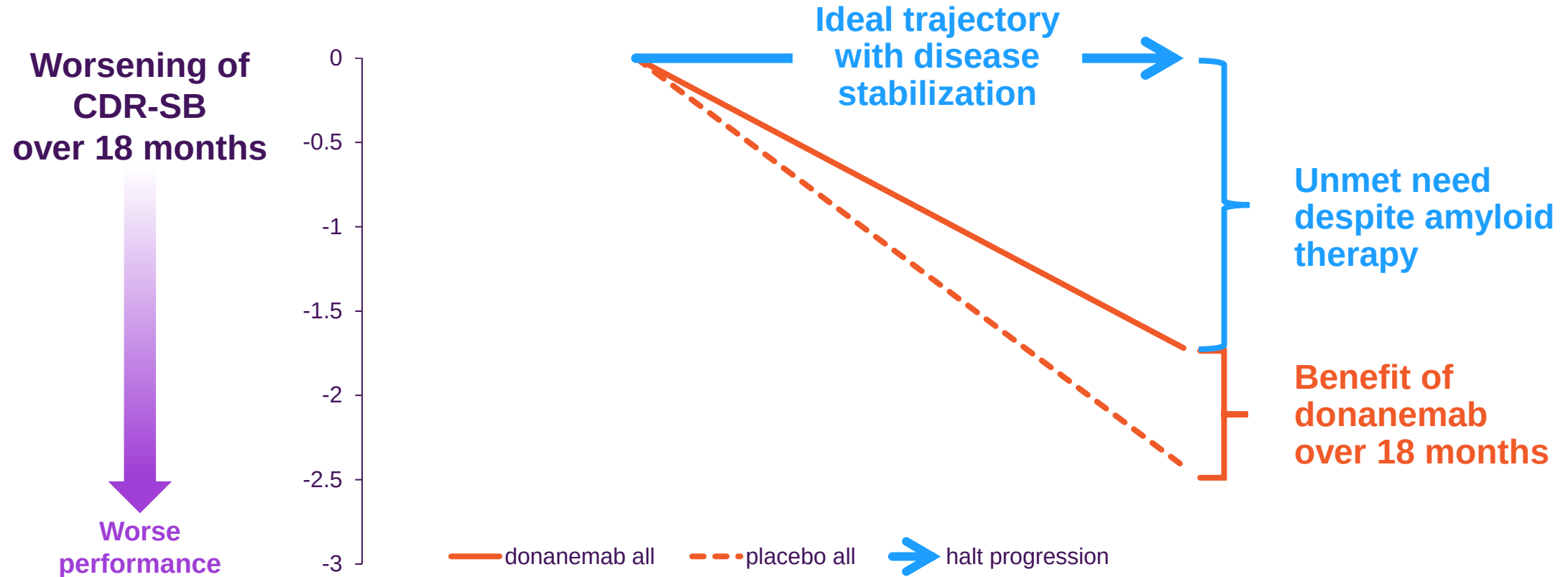
Cost to treat



# Anti-amyloid therapy modestly slows AD progression



Ideally patients with AD would not worsen on treatment at all

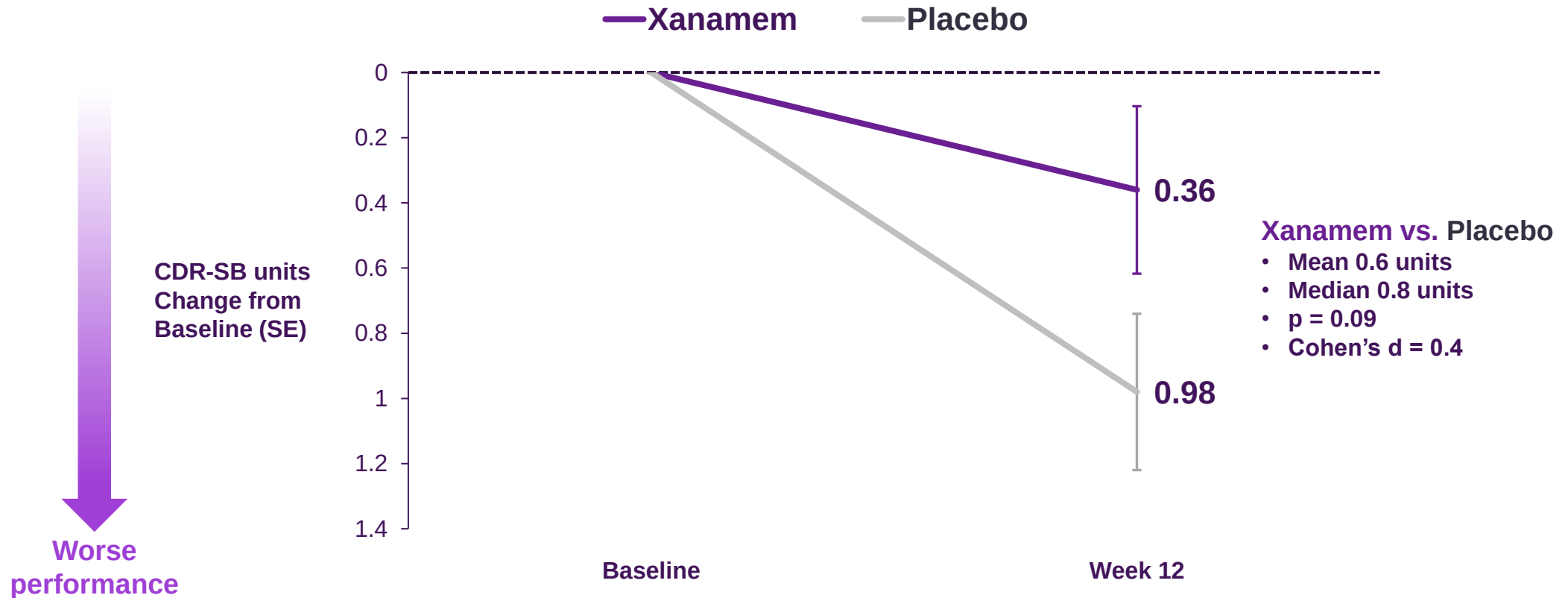


Drugs targeting other mechanisms like Xanamem are needed

# Xanamem in pTau181-positive patients with mild AD



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

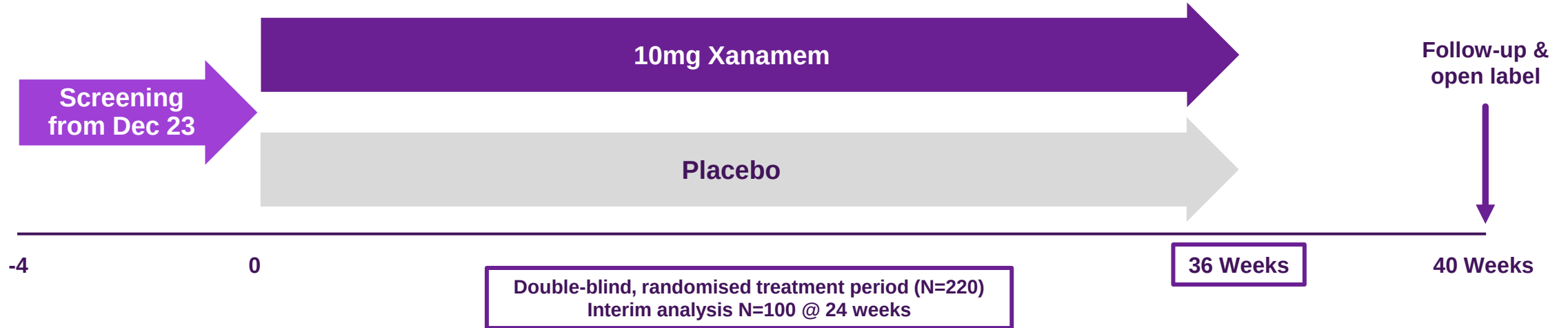


Xanamem benefits extrapolated to 18 months would be ~8x anti-amyloid drugs

# XanaMIA phase 2b trial in Alzheimer's disease



Initial, interim results in mid 2025, final results H1 2026



| Key Inclusion Criteria                                                                                                             | Primary Endpoint                                                                              | Key Secondary Endpoints                                                                                                                                   | Implementation                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>Blood pTau biomarker positive</li><li>Mild-moderate Alzheimer's by NIA-AA criteria</li></ul> | <ul style="list-style-type: none"><li>Cognitive Test Battery (7 cognitive measures)</li></ul> | <ul style="list-style-type: none"><li>CDR-SB (functional and cognitive measure)</li><li>Amsterdam Activity of Daily Living (functional measure)</li></ul> | <ul style="list-style-type: none"><li>Enrolment at 15 Australian sites</li><li>Expanding to US</li><li>Interim analysis when 100 people complete 24 weeks</li></ul> |

# Recent transactions in neuroscience



# Recent neuroscience acquisitions and IPOs



| Lead Drug(s) | TRPML1          | KarXT         | Emraclidine   | ALTO-100 | PIPE-307<br>PIPE-791 | RAP-219                       |
|--------------|-----------------|---------------|---------------|----------|----------------------|-------------------------------|
| Phase        | Preclinical     | Phase 3       | Phase 2       | Phase 2  | Phase 2              | Phase 1                       |
| Lead asset   | PD, other neuro | Schizophrenia | Schizophrenia | MDD      | MS & MDD             | Epilepsy, BPD,<br>other neuro |
| Transaction  | Acquisition     | Acquisition   | Acquisition   | IPO      | IPO                  | IPO                           |
| Amount       | US\$610m*       | US\$14.0b     | US\$8.7b      | US\$148m | US\$110m             | US\$174m                      |
| Date         | 23-Nov          | 23-Dec        | 23-Dec        | 24-Feb   | 24-Apr               | 24-Jun                        |

# Active licensing for clinical neuroscience assets

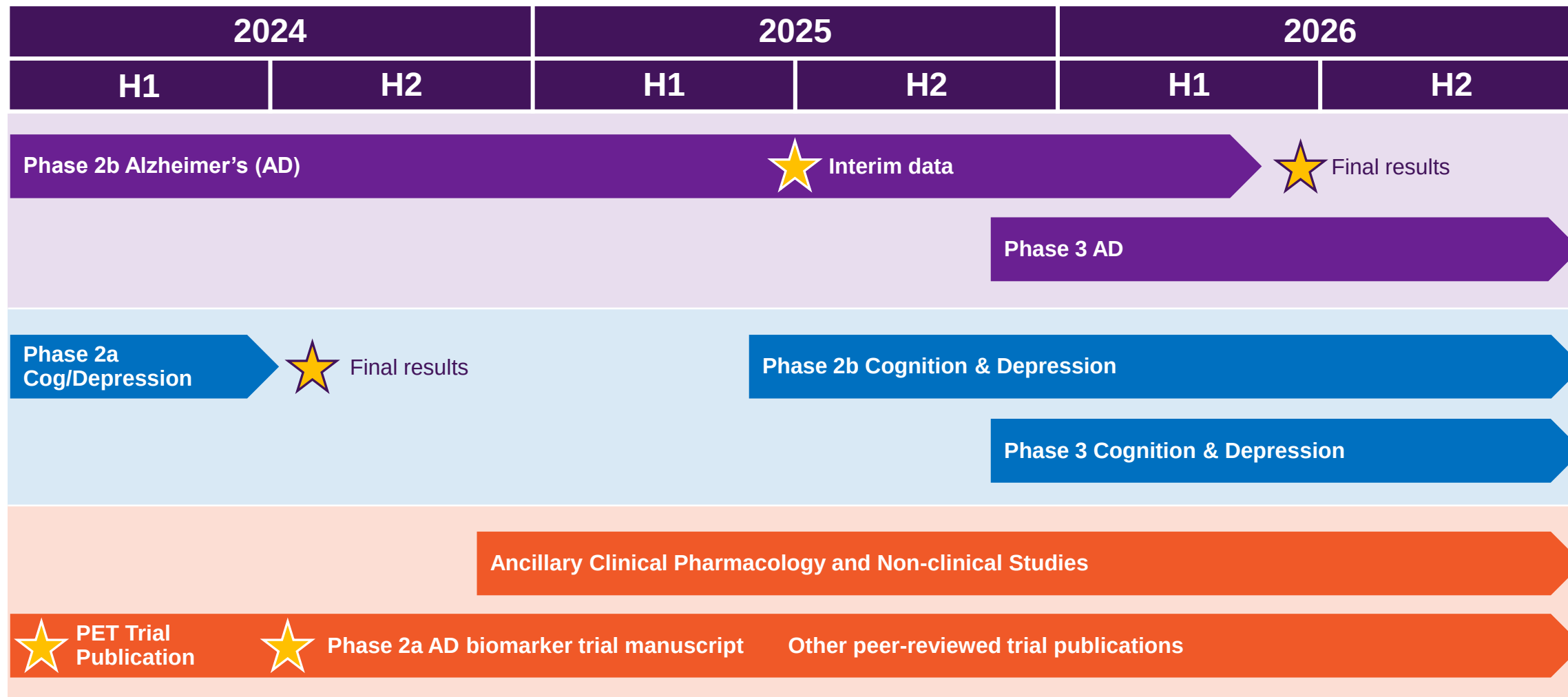


| Drug                   | ACI – 24.060                              | PRX-005                        | NBI-1117567   | ulotaront,<br>SEP- 378614<br>and others | AL-001                               | BIIB-124   | Bepranemab                               |
|------------------------|-------------------------------------------|--------------------------------|---------------|-----------------------------------------|--------------------------------------|------------|------------------------------------------|
| Phase                  | Phase 1b/2                                | Phase 1                        | Phase 2       | Phase 3                                 | Phase 3                              | Phase 3    | Phase 1                                  |
| Indication             | Alzheimer's<br>(amyloid beta<br>antibody) | Alzheimer's<br>(tau antibody)  | Schizophrenia | Schizophrenia/<br>Depression            | Dementias<br>(progranulin<br>target) | Depression | Alzheimer's<br>Disease<br>(tau antibody) |
| Deal Type              | Exclusive<br>Option & License             | Exclusive<br>Option & License* | License       | License                                 | License                              | License    | License                                  |
| Upfront                | US \$100m                                 | US\$100m                       | US\$100m      | US\$300m                                | US\$700m                             | US\$1.5b   | US\$100m                                 |
| Earnout                | US \$2.1b                                 | US\$2.1                        | US\$2.6b      | US\$0.6b                                | US\$1.5b                             | US\$UNK    | US\$2.0b                                 |
| Total<br>Consideration | US\$2.2b                                  | US\$2.2b                       | US\$2.7b      | US\$0.9b                                | US\$2.2b                             | >US\$1.5b  | US\$2.1b                                 |
| Date                   | May-24                                    | Jun-21/Oct-23                  | 21-Nov        | 21-Sep                                  | 21-Jul                               | 20-Nov     | 20-Jun                                   |

\* By exercise of previously negotiated option agreement during early development

# Milestones & summary

# Upcoming milestones & catalysts



# Summary

## Unique oral treatment for patients with neuropsychiatric diseases and dementia



- Rapidly acting oral therapy with potential dual action on cognitive impairment and other depressive symptoms
- Cognitively enhancing and potentially disease modifying oral therapy for all stages of Alzheimer's disease
- Excellent activity and safety profile in more than 350 people treated
- Large clinical opportunities with high unmet medical need in the dementias and neuropsychiatry
- Two phase 2 clinical trials due to read out in early Q3 2024 and mid 2025
- Composition of matter IP protection, expanding patent portfolio
- Cash runway to late 2025

# Appendix



# Key references



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

## Preclinical 11 $\beta$ -HSD1 inhibition

- Cognitive and disease-modifying effects of 11 $\beta$ -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 11 $\beta$ -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 11 $\beta$ -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, Kassiof 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 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -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

## CDR-SB parameters

- CDR-SB Clinical Dementia Rating Scale – Sum of Boxes is an 18-point, 6-domain measure of patient cognition and function and is a common endpoint used by regulators. Patients in the Xanamem biomarker phase 2a analysis had a baseline of approximately 4 points, similar to that in the donanemab phase 3.

## Alzheimer's disease and cortisol

- Plasma Cortisol, Brain Amyloid- $\beta$ , and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study Pietrzak RH, Laws SM, Lim YY et. al. for the Australian Imaging, Biomarkers and Lifestyle Research Group 2017. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2017; 2(1):45-52
- Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease Starkman, M. N., Giordani, B., Gebarski, S. S., Berent, S., Schork, M. A., & Schteingart, D. E. 1999. *Biol psych*, 46(12), 1595-1602.

## Depression and cortisol

- Effect of glucocorticoid and 11 $\beta$ -hydroxysteroid-dehydrogenase type 1 (11 $\beta$ -HSD1) in neurological and psychiatric disorders Dodd S, Skvarc D R, Dean OM, Anderson A, Kotowicz M, Berk M *Int J Neuropsychopharmacol* 2022; 25(5):387-398
- Depression and Hypothalamic-Pituitary-Adrenal Activation: A Quantitative Summary of Four Decades of Research Stetler C, Miller GE *Psychosom Med* 2011; 73(2):114-26

## Market & cost of treatment estimates

- Matthews, K. A., Xu, W., Gaglioti, A. H., Holt, J. B., Croft, J. B., Mack, D., & McGuire, L. C. (2018). Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged  $\geq 65$  years. *Alzheimer's & Dementia*. <https://doi.org/10.1016/j.jalz.2018.06.3063>
- Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *NEJM*. 2013;368(14):1326-34.
- <https://www.cdc.gov/aging/aginginfo/alzheimers.htm#treated>
- <https://www.nimh.nih.gov/health/statistics/major-depression>
- Symphony Health and ICON plc Company, Metys® database full year 2023

## Currencies

- Currencies are in Australian dollars unless otherwise stated

# Selected Glossary 1

- **11 $\beta$ -HSD1** – 11 beta HydroxySteroid Dehydrogenase-1 enzyme. Selectively expressed in brain, liver, adipose.
- **A $\beta$**  – Amyloid beta – a type of amyloid protein associated with Alzheimer's Disease, 42 and 40 are different forms
- **ACTH** – Adrenocorticotrophic hormone that regulates blood levels of cortisol
- **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 Fibrillary 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
- **Tau** – A brain protein
- **Ttau** – Total tau levels including both phosphorylated and non-phosphorylated tau

# Contacts

## Michael Roberts

Investor Relations

P: +61 2 8964 7401

M: +61 423 866 231

E. [michael.roberts@actinogen.com.au](mailto:michael.roberts@actinogen.com.au)

## Steven Gourlay

CEO & Managing Director

P: +61 2 8964 7401

E. [steven.gourlay@actinogen.com.au](mailto:steven.gourlay@actinogen.com.au)