ASX ANNOUNCEMENT

Actinogen CEO presents at Pitt Street Research Conference

Sydney, 19 September 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its CEO, Dr Steven Gourlay, will be a speaker today at the Pitt Street Research Conference in Sydney.

Dr Gourlay's presentation is titled *Oral Xanamem:® Controlling brain cortisol to treat depression and slow progression in Alzheimer's disease - a novel therapeutic mechanism in late phase trials* and outlines the attractive therapeutic profile of ACW's novel small molecule drug Xanamem in treating neurological conditions by controlling brain cortisol and the positive outlook for the Company as it enters late-phase clinical trials.

Dr Gourlay's conference presentation is attached to this announcement.

ENDS

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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.

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.

Disclaimer

This announcement and attachments may contain certain "forward-looking statements" that are not historical facts; are based on subjective estimates, assumptions and qualifications; and relate to circumstances and events that have not taken place and may not take place. Such forward looking statements should be considered "at-risk statements" - not to be relied upon as they are subject to known and unknown risks, uncertainties and other factors (such as significant business, economic and competitive uncertainties / contingencies and regulatory and clinical development risks, future outcomes and uncertainties) that may lead to actual results being materially different from any forward looking statement or the performance expressed or implied by such forward looking statements. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Actinogen Medical does not undertake any obligation to revise such statements to reflect events or any change in circumstances arising after the date hereof, or to reflect the occurrence of or non-occurrence of any future events. Past performance is not a reliable indicator of future performance. Actinogen Medical does not make any guarantee, representation or warranty as to the likelihood of achievement or reasonableness of any forward-looking statements and there can be no assurance or guarantee that any forward-looking statements will be realised.

ACTINOGEN MEDICAL ENCOURAGES ALL CURRENT INVESTORS TO GO PAPERLESS BY REGISTERING THEIR DETAILS WITH THE DESIGNATED REGISTRY SERVICE PROVIDER, AUTOMIC GROUP.

Actinogen

Oral Xanamem®

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

Pitt Street Research Conference

19 September 2024

Disclaimer

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Overview

Novel mechanism and attractive oral profile

- Xanamem is a unique brain-penetrant tissue cortisol synthesis inhibitor (11β-HSD1 enzyme)
- Once-daily oral therapy with potential efficacy, safety and ease of use greater than competitors
- More than 380 people treated with promising safety profile and low drug interaction risk

Large and growing market opportunities with significant unmet need

- Significant benefits in major depressive disorder (MDD) in phase 2a trial, phase 2b/3 in planning
- Disease-modifying activity to slow Alzheimer's disease (AD) in phase 2a data, phase 2b/3 on-going
- Trials potentially read through to bipolar disease, other dementias including Parkinson's

Patent protection

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

Capital Raising of $11.1m led by $1 million investment from CEO, clinical milestones funded

- Current raise announced 18 September for $11.1m via a $8.1m Placement and $3m SPP at $0.03 per share, three for four option with exercise price $0.05 and three-year expiry date
- Funds raised will be used for XanaMIA phase 2b/3 trial - interim data mid 2025, final data mid 2026
- Post capital raising the company will have a cash runway through mid 2026

Experienced board and management team

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

Dana Hilt
Chief Medical Officer
MD

Will Souter
Chief Financial Officer
BComm, LLB

Cheryl Townsend
VP Clinical Operations
RN, M Health Law

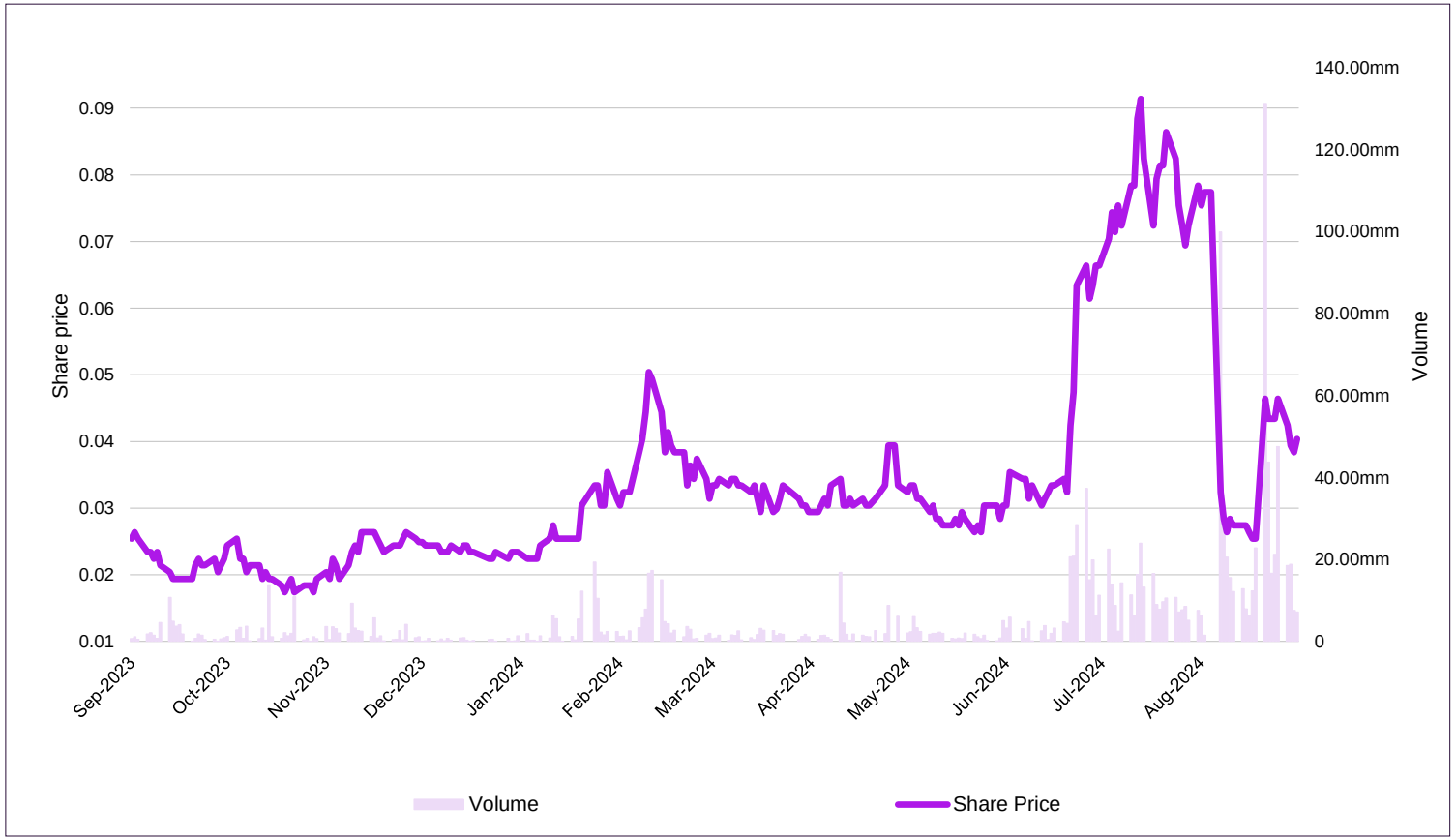
Fujun Li
Head of Manufacturing
PhD

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

* Invested ~$2m post raise on personal account

Stock price and key shareholders*

ASX: ACW – Last 12 months



Key data

52 Week Range	$0.015 - $0.099
YTD CY24 change	+75%
Shares on issue	2.7Bn
Unlisted options	349m
Closing price	$0.035
Closing market cap*	$94.9m
30 June cash balance	$9.45m

Key Shareholders

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

*Data as at 16 September 2024; market cap undiluted (excludes options); cash balance excludes options converted post 30/6 and R&D tax rebate of $9m expected in Q4 FY2024

Healthy neuroscience acquisition and IPO activity

Lead Drug(s)	TRPML1	KarXT	Emraclidine	ALTO-100	PIPE-307 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, 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

PD: Parkinson's disease; **MDD**: major depressive disorder; **MS:** multiple sclerosis; **BPD:** bipolar disorder
* Upfront and milestones combined

Alzheimer's disease phase 2b/3

Recent developments increase confidence in XanaMIA

XanaMIA Alzheimer's disease trial moving to full enrolment and full phase 2b/3 design

- Recently released data showing clinically and statistically significant improvement in depression symptoms validate Xanamem's mechanism of action and 10 mg dose to control brain cortisol
- Lack of superiority over placebo for cognitive enhancement in *depression* prioritizes disease-modification and functional endpoints as the primary evaluation tool in *Alzheimer's disease*
- XanaMIA in patients with AD is established as one of two potential "pivotal" trials by:
  - Continuous enrolment of the full 220 participants in Australia and US to speed enrolment
  - CDR-SB as the primary endpoint (used for Eisai's Leqembi's FDA approval)
  - Independent Data Monitoring Committee to conduct interim analysis similar to market precedents
  - "Phase 3-standard" statistical methods
    - Full statistical power for primary endpoint ($p < 0.05$)
    - Sequential examination of secondary endpoints after primary ($p < 0.05$)
  - Additional quality oversight and auditing of trial sites, vendors and procedures
  - Use of commercial tablet formulation

Alzheimer's disease

Strong scientific rationale to address huge unmet medical need

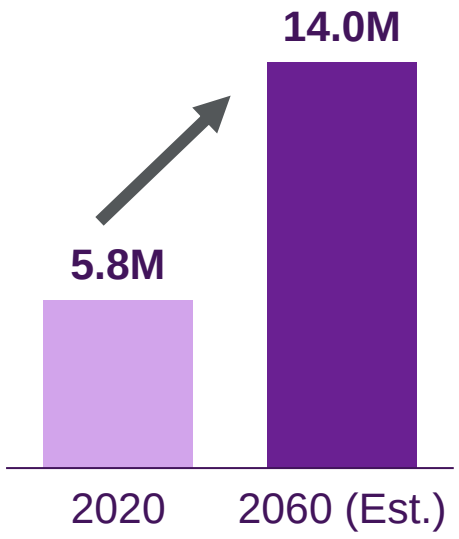
Scientific rationale

- 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 11β-HSD1 provides full neuroprotection
- AD Phase 2a trial shows slowed disease progression in biomarker-positive patients
- MDD Phase 2a trial shows benefits in depression

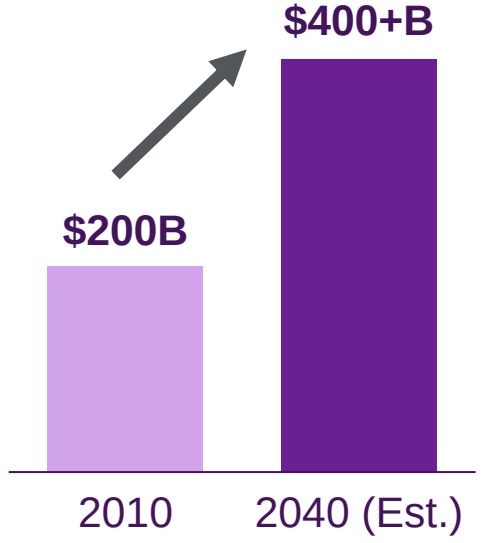
Alzheimer's Disease market – U.S.

Large unsatisfied and growing market

# of patients



Cost to treat



Controlling brain cortisol[1] has durable benefits

Xanamem inhibits local tissue production of cortisol in key regions of the brain via 11β-HSD1[2]

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

Human PET study shows full target engagement

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

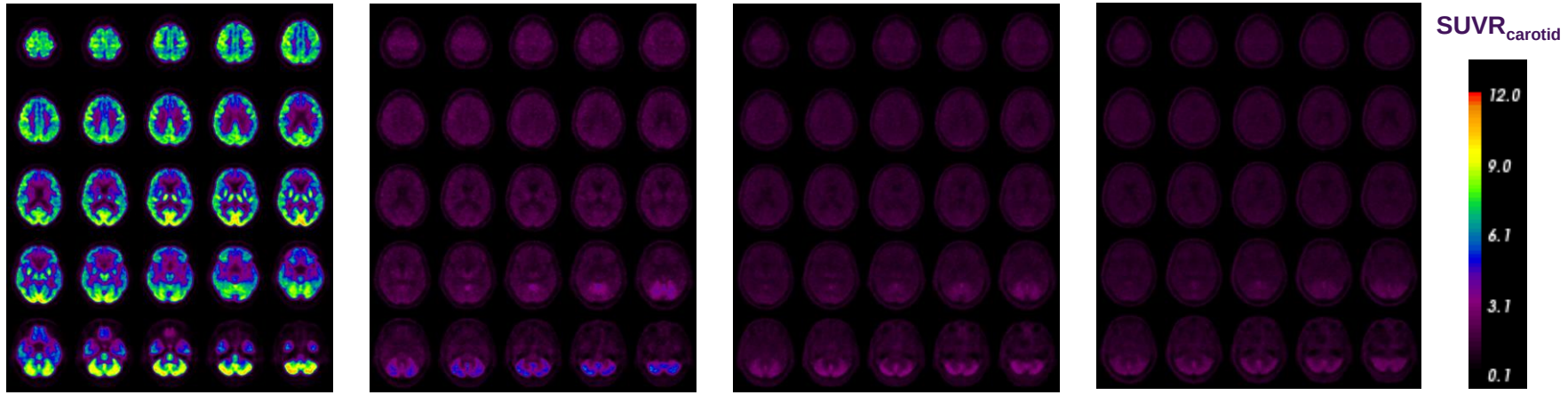
Baseline

After 7 days of daily dosing

5 mg Xanamem

10 mg Xanamem

20 mg Xanamem



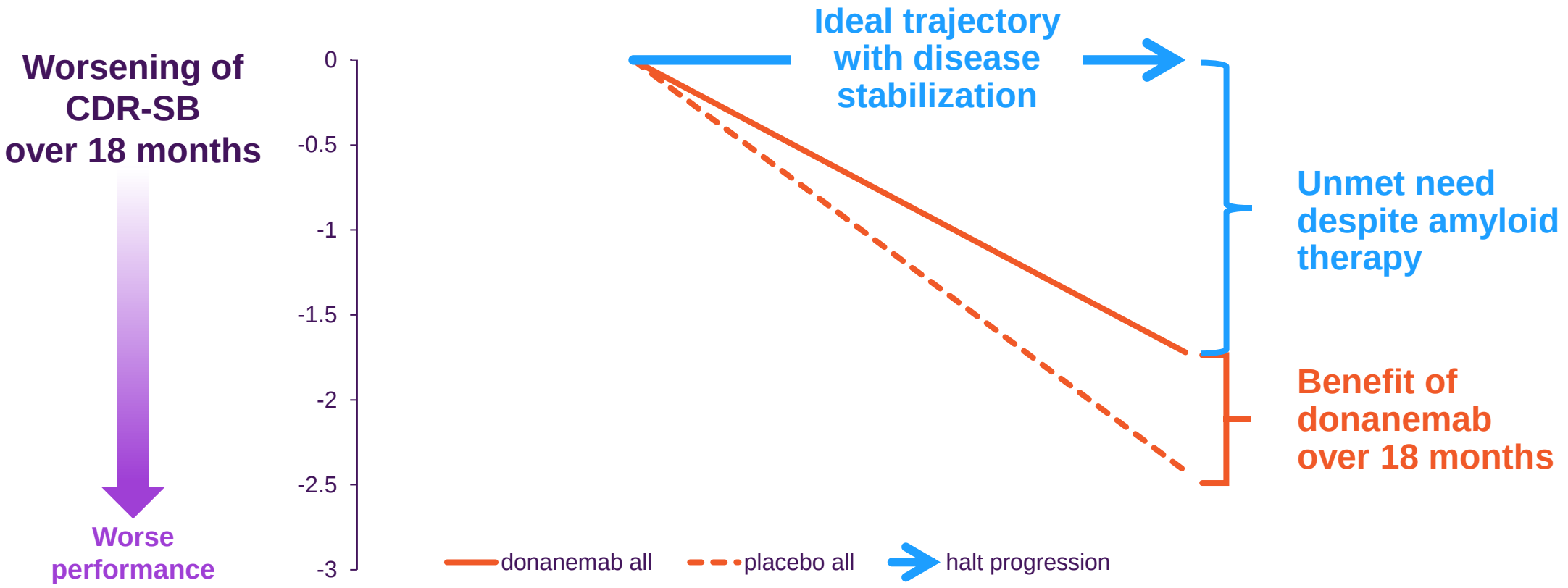
Xanamem extensively binds to the 11β-HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.

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

Validates 10mg dose in efficacy trials

Anti-amyloid therapy modestly slows AD progression

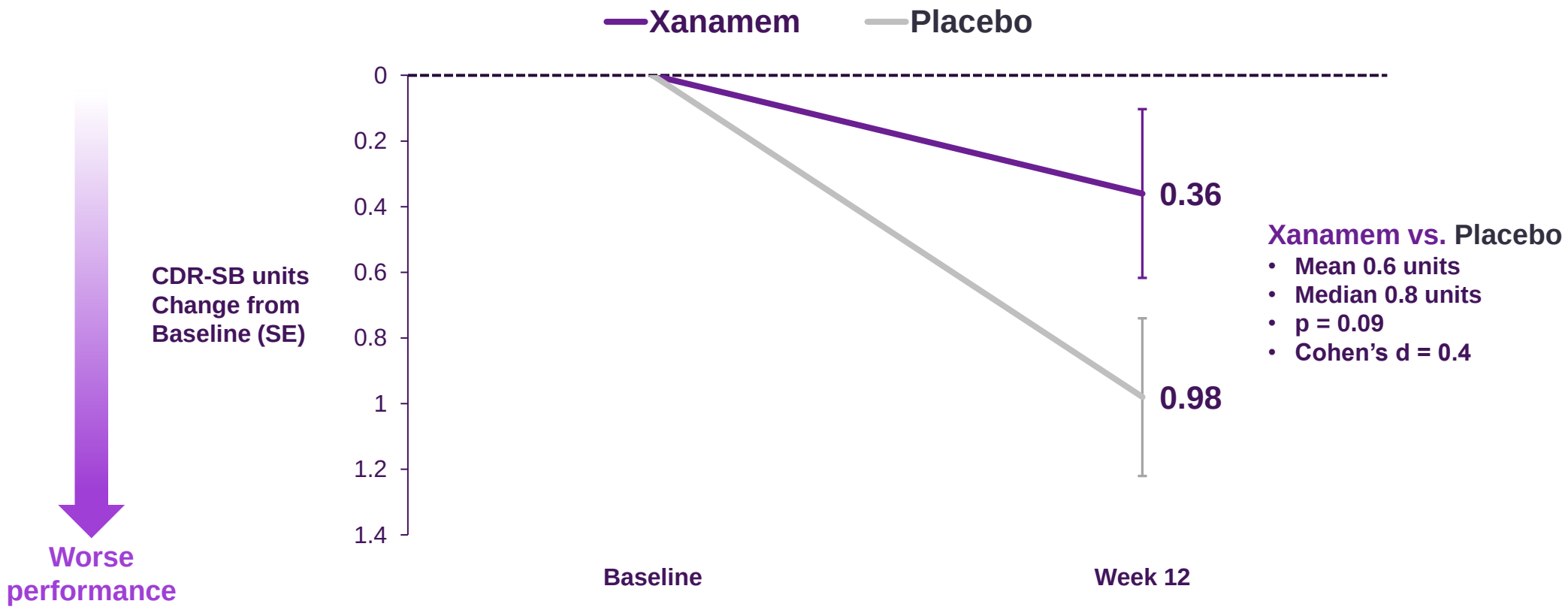
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanamem are needed

Xanamem slows AD progression markedly

Phase 2a data in biomarker-positive patients with mild AD (n=34)[1]

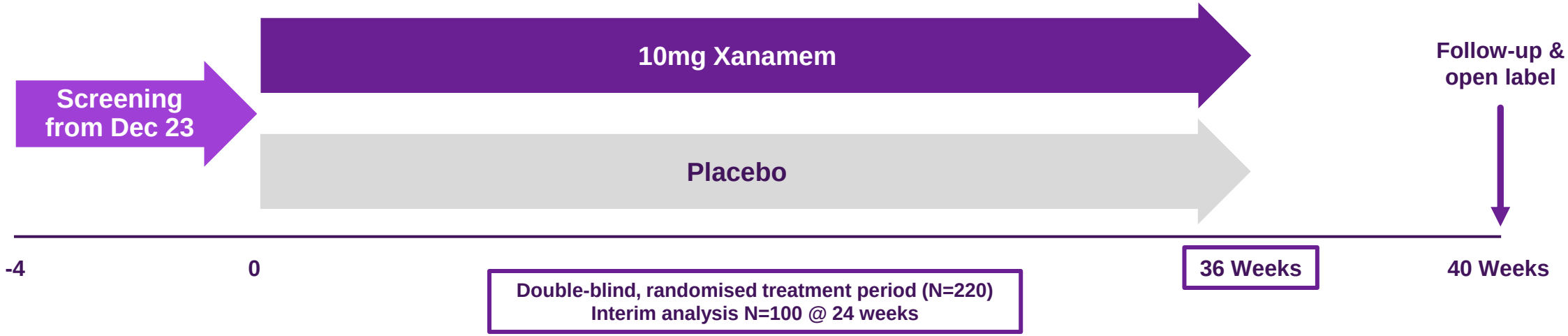


Xanamem benefits extrapolated to 18 months would be ~8x anti-amyloid drugs

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



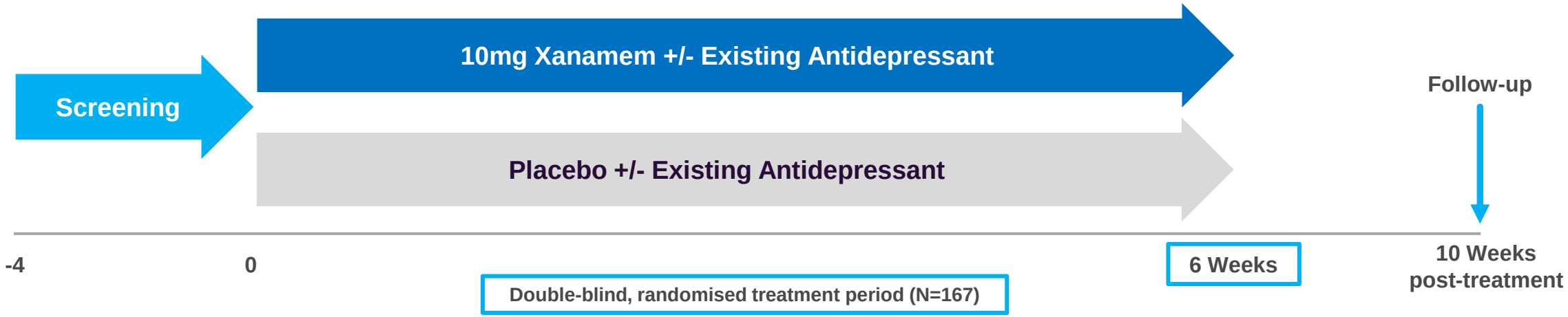
Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
• Blood pTau biomarker positive • Mild-moderate Alzheimer's by NIA-AA criteria	• **CDR-SB (functional and cognitive measure)**	• Amsterdam Activity of Daily Living (functional measure) • Cognitive Test Battery (7 cognitive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

Positive phase 2a depression data

XanaCIDD trial design

Phase 2a, 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)** • Executive Function Cognitive Composite **(EFC)** • Memory Function Cognitive Composite **(MC)**

XanaCIDD statistical methods

Statistical methods reflect industry standard for proof-of-concept trials

- Primary & secondary endpoints analyzed using a standard Mixed Model for Repeated Measures (MMRM)
- Three pre-specified subgroups for efficacy: current anti-depressant therapy (yes/no), baseline depression severity (lower/higher) and degree of cognitive impairment (lower/higher)
- p values shown are 2-sided hypothesis tests unless stated otherwise
- Effect sizes were calculated using the Cohen's d (Cd) statistic representing the effect as a % of the baseline population variability or standard deviation. This metric is frequently used in the cognition field[1] and is useful in depression[2]:
  - **> 0.2** = Potentially clinically meaningful effect size
  - **≥ 0.3** = Clinically meaningful effect size
  - **≥ 0.5** = Large and clinically meaningful effect size

1. Cohen et al. 1992; 2. Hengartner et al. 2020

Typical, broad, moderate depression trial population

All XanaCIDD patients were either on, or previously treated with, anti-depressants

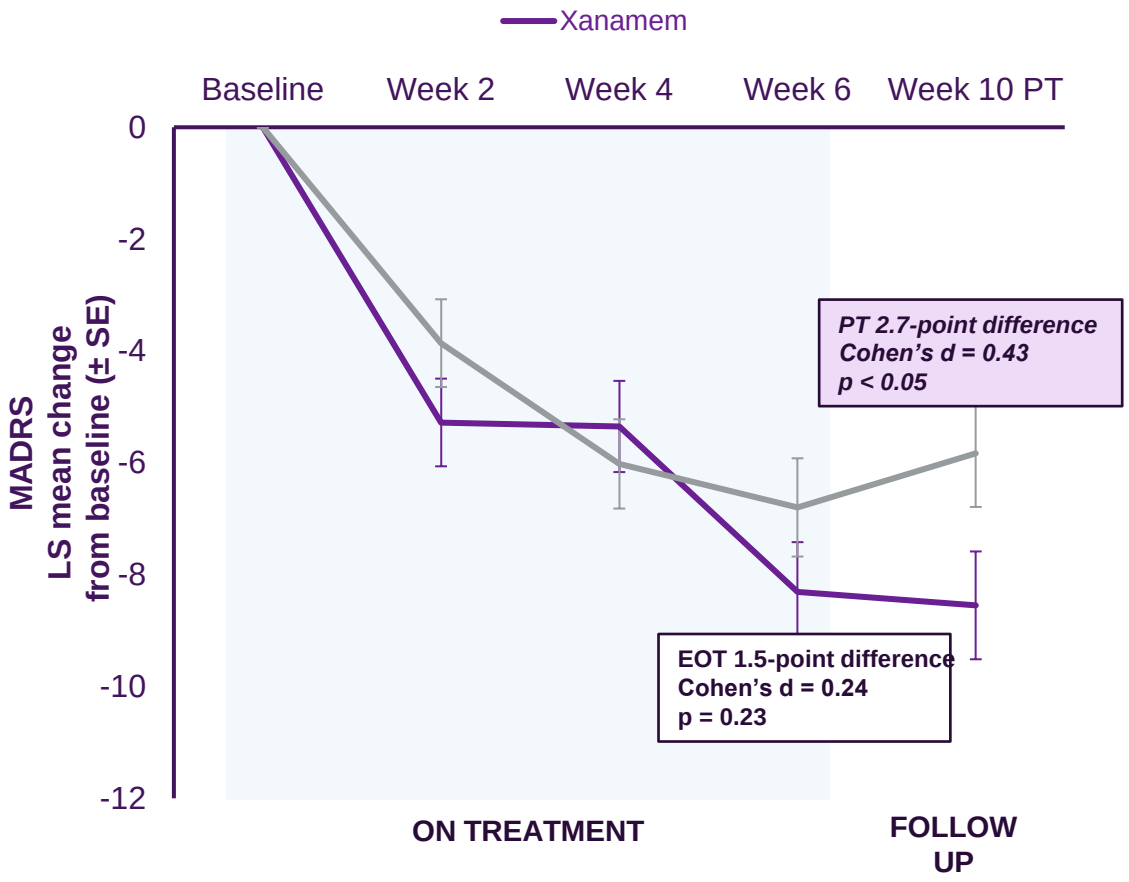
	Xanamem (n=82)	Placebo (n=83)
Mean age (SD)	49 (13)	49 (15)
% female	63	61
Mean screening HAM-D depression score (SD)	21 (3)	21 (3)
Mean MADRS (SD)	24 (6)	26 (7)
% on anti-depressant therapy	77%	86%
Mean cognition – screening Boxfiller (SD)	22 (5)	21 (6)
Mean cognition – Attention Composite (SD)	0.11 (0.77)	-0.10 (0.98)

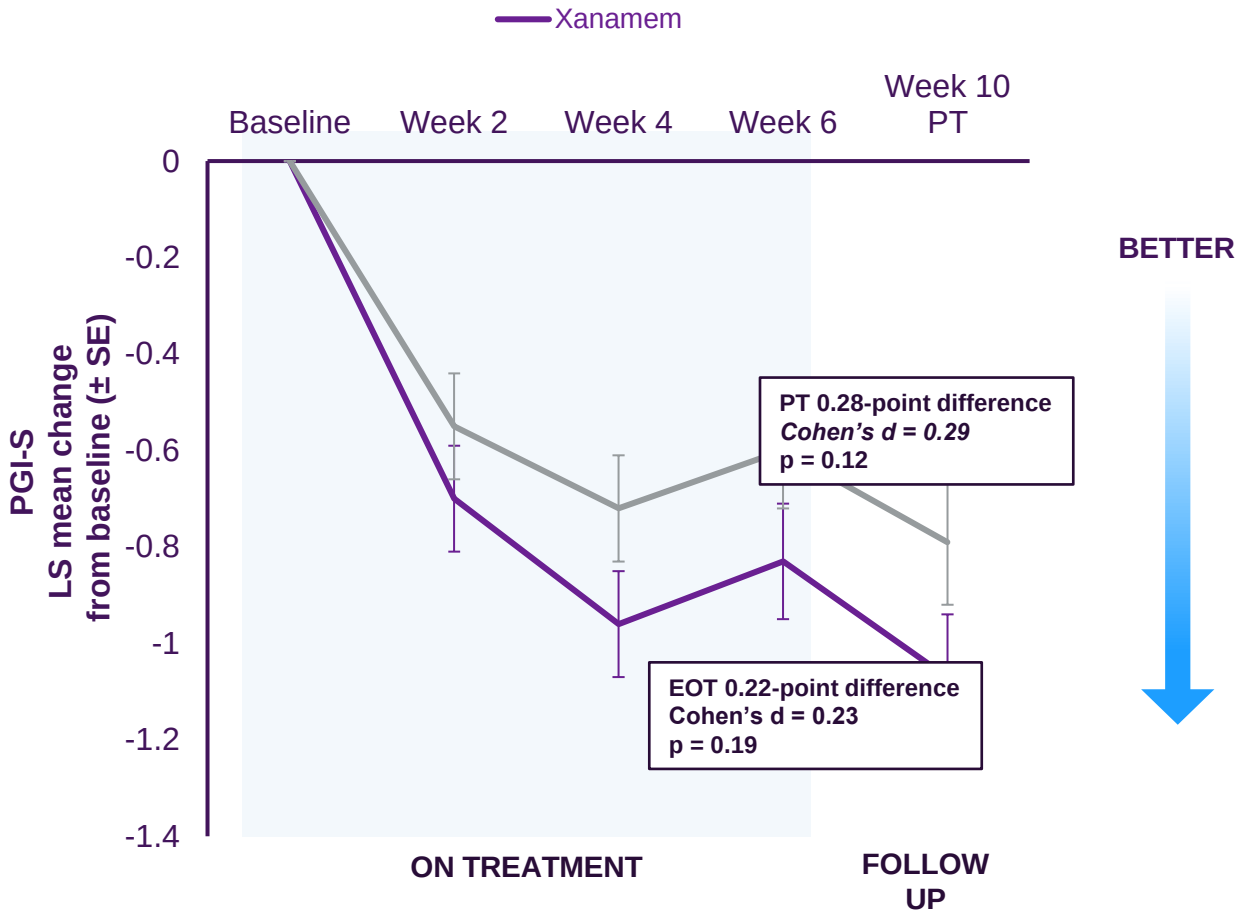
Results summary

- ***Clinically and statistically significant treatment benefits on depression symptoms measured in three different ways***
- Cognition improved markedly in both Xanamem and placebo groups without evidence of greater Xanamem benefit vs. placebo
- Xanamem was safe and well tolerated (n=165 treated)
- The trial was well-conducted, with excellent data quality, no major differences between Australia and the UK or at high enrolling clinical sites

MADRS & PGI-S depression scores favor Xanamem

All randomized participants (n = 165)

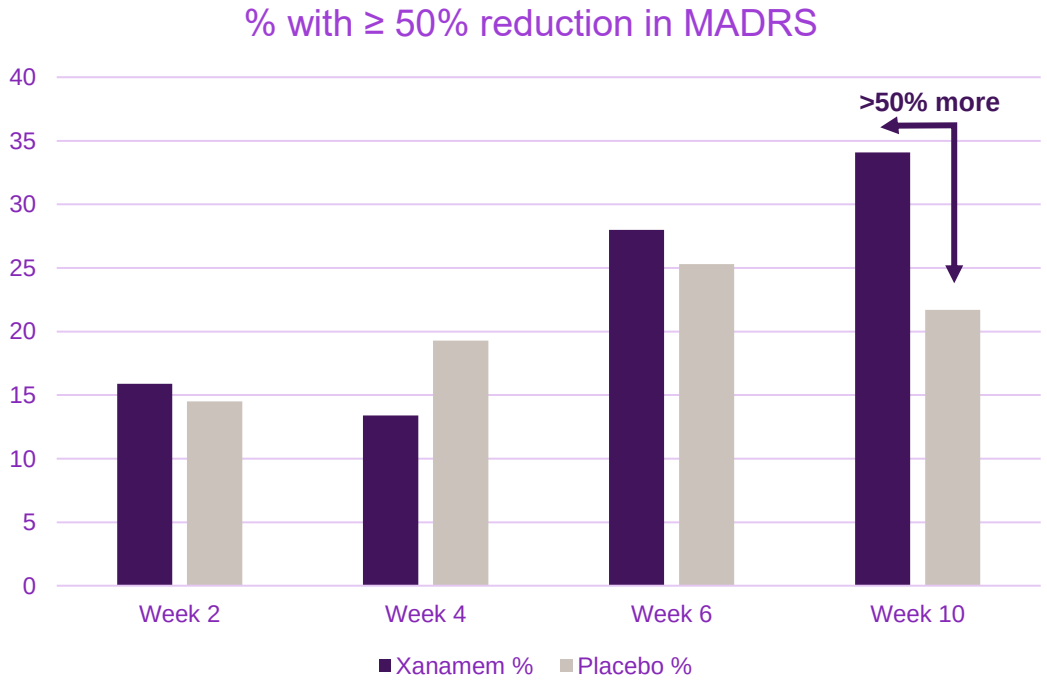


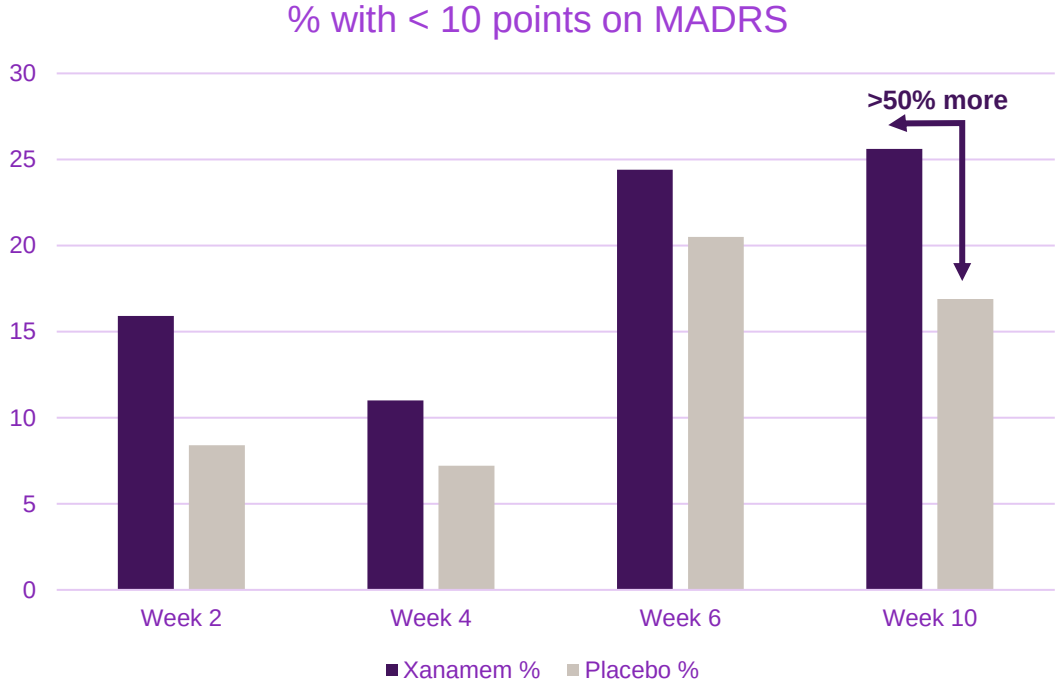


Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

Xanamem major improvement in depression response

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





Broad & durable subgroup effects - MADRS & PGI-S

Measured at Weeks 2, 4, 6 & 10 (green favors Xanamem, red placebo)

Response/variable	All (n=165)	*No anti-D (n=31)	Yes anti-D (n=134)	*MADRS < 26 (n=81)	MADRS ≥ 26 (n=83)	*Cog. < 0.07 (n=82)	Cog. ≥ 0.07 (n=82)
MADRS (Cd ≥ 0.3) (week)	10	2,6	10	2,6,10	(4),10	2,6,10	-
MADRS (p < 0.05) (week)	10	-	10	6	-	2,10	-
PGI-S (Cd ≥ 0.3) (week)	-	6,10	4,6,10	4,6,10	6,10	4,6,10	-
PGI-S (p < 0.05) (week)	-	-	10	-	-	10	-
Selected demographics:							
Mean age (SD)	49 (14)	50 (13)	49 (14)	49 (14)	50 (13)	53 (13)	45 (13)
% female	62%	45%	66%	62%	63%	66%	59%
Mean HAM-D (SD)	21 (3)	21 (4)	21 (3)	20 (3)	23 (3)	22 (3)	21 (3)
% on anti-D therapy	81%	0%	100%	79%	83%	79%	83%
Mean boxfiller (SD)	21 (5)	22 (6)	21 (5)	22 (5)	21 (6)	20 (5)	23 (5)

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%)

There remains significant unmet need in depression

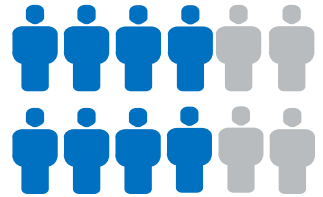
Xanamem's unique mechanism and safety differentiate it from older drugs

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***

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 adults with MDD episodes receive treatment with existing drugs (that have many side effects)
- ≥365 M prescriptions per year

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

3. Ding et al 2021

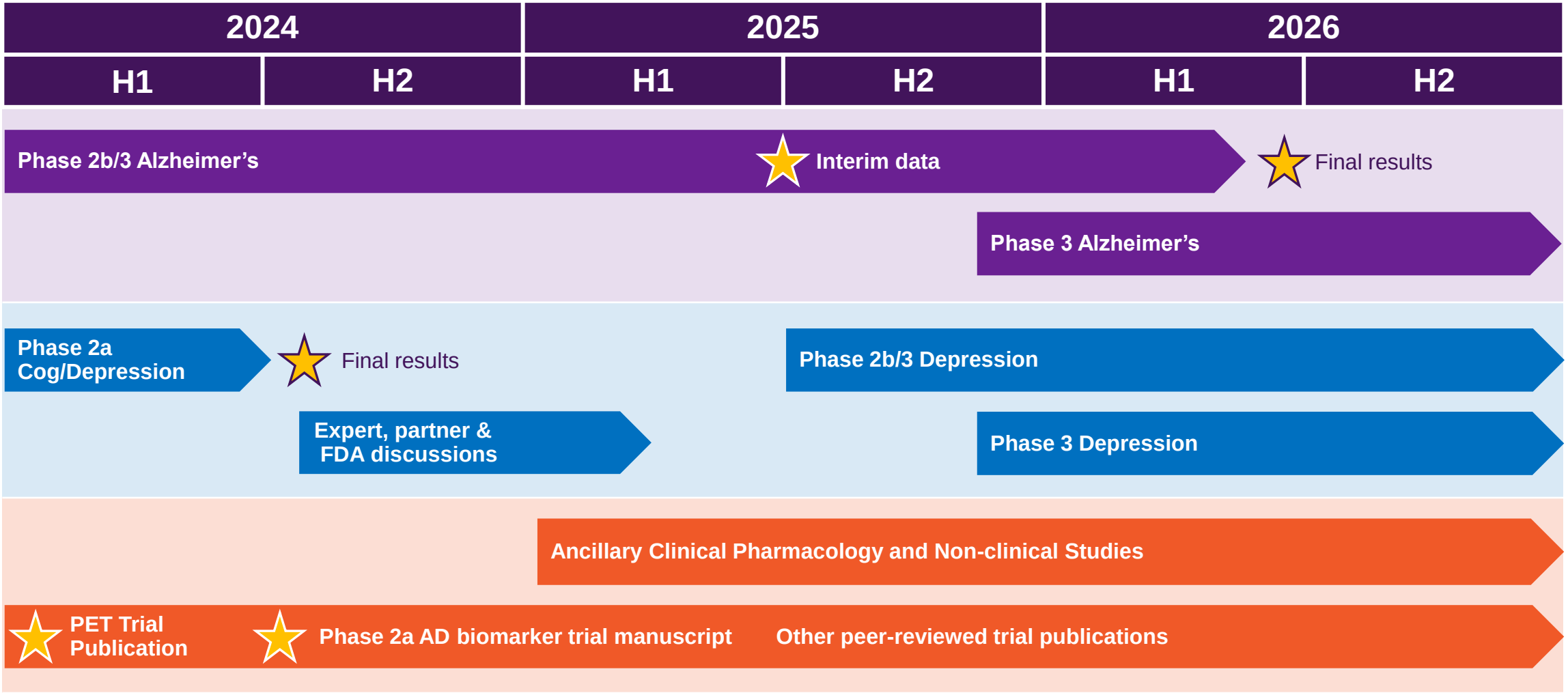
Conclusions

Controlling brain tissue cortisol really works

Proof of 11β-HSD1 as a therapeutic target is a *major scientific and clinical advance*

- Clinically, statistically significant and durable treatment benefits on depression
- Xanamem is safe and well tolerated; no significant safety issues were observed
- Durability of Xanamem benefits on depression for four weeks after the end of treatment suggests underlying biological modification due to cortisol control has occurred
- Strongly positive phase 2a data on CDR-SB endpoint in biomarker-positive patients with Alzheimer's used to design phase 2b/3 design
- Positive depression data support the likelihood of success for Alzheimer's disease

Two promising late-phase clinical programs



Appendix – references

Key references

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

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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
- **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
- **Tau –** A brain protein
- **Ttau –** Total tau levels including both phosphorylated and non-phosphorylated tau

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