ASX ANNOUNCEMENT

Actinogen 2024 AGM – Chair's address and CEO's presentation

Sydney, 14 November 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to release the Chair's address and CEO's slide presentation to this morning's Annual General Meeting commencing at 11am (AEDT) in Sydney.

The AGM will be held at the offices of K&L Gates, Level 31, 1 O'Connell Street', Sydney NSW 2000. This AGM is an in-person only meeting.

The Chair's address and CEO's presentation slides are 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, treatment-resistant 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. Trial results were reported in August 2024 and showed clinically and statistically significant benefits on depression symptoms with positive effects on the MADRS scale (a validated scale of depression symptom measurement) and the PGI-S (a valid patient reported assessment of depression severity).

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). The trial is being conducted in Australia and the US. 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.

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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.

14 November 2024

Actinogen 2024 AGM Chair's Address

Good morning, everyone. My name is Geoff Brooke, and I am the Chair of Actinogen Medical Limited. On behalf of the Board of Directors and staff of the Company I welcome shareholders to our 2024 Annual General Meeting.

We continue to make compelling progress in the execution of our strategy, focused on "following the science" in the successful development of our novel small molecule drug Xanamem® for illnesses such as Alzheimer's disease and depression. We believe that Xanamem's mechanism of "tissue cortisol control" to reduce excess cortisol inside brain cells has the potential to have a major impact on the lives of the countless patients and their families around the world suffering from many neurological and neuropsychiatric conditions.

In addition to our own successes in the last year, it was great to witness gradually improving conditions in the biotech market from the start of 2024, especially as key licensing and M&A activity signalled a change in sentiment from the very challenging market headwinds of 2023, particularly in the small-cap biotech sector.

A year of achievement

The Company enjoyed a productive financial year with the achievement of several major milestones including the management of two phase 2 trials running concurrently during the second half. It takes significant effort to get a trial to the starting line, let alone manage the complexities of running two sizeable trials across different jurisdictions simultaneously.

The XanaCIDD phase 2a depression trial completed its final patient treatment on 1 July 2024, having recruited 167 patients in 16 months – a tremendous effort from our staff, collaborators and the trial participants. An unexpectedly high placebo effect impacted our ability to see a potential Xanamem effect in the cognition primary endpoint. However, in the targeted secondary endpoint, we were very pleased to see positive benefits on depression, providing further evidence to support Xanamem as an effective cortisol control mechanism.

Patient recruitment and enrolment activities are ramping up in the XanaMIA phase 2b/3 Alzheimer's disease trial with four US sites now active in addition to 15 sites in Australia. A further six US sites will be activated before the end of the year, and we expect enrolment to accelerate in the coming months as a result.

Another highlight was the approval from the UK Medicines and Healthcare products Regulatory Agency of a UK Innovation Passport, which is the UK version of the FDA's "breakthrough" designation. This represents a significant independent endorsement by an international regulator of the potential medical importance of the Xanamem program for Alzheimer's disease. The team has also continued to work diligently to complete two academic manuscripts that were published in the peer-reviewed journal, the *Journal of Alzheimer's Disease* in the second half of the financial year, with further academic papers planned.

Executive leadership

CEO Dr Steven Gourlay has continued to lead the executive team with distinction. He has the relevant experience needed of a biotech CEO for a company in the mid-late stage of clinical development with a view to commercialisation.

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Steve leads a small but innovative, high calibre executive leadership team with complementary skills that produces results. We added to the team's skillset this year with the appointment in February of the Company's first full-time Chief Financial Officer, Will Souter, and the recent appointment of Andy Udell as our inaugural Chief Commercial Officer. I also take this opportunity to acknowledge and thank the wider executive leadership team and the Actinogen workforce, as well as key contractors, who all work so diligently to manage a very effective and efficient clinical development program and corporate functions required of a listed biotech. What they are undertaking is no mean feat. They are to be thanked and congratulated.

Board, corporate governance and advisory boards

I thank my fellow board members for their contributions during a productive year which has necessarily required a significant planning agenda for the next stages in the Company's development.

We maintain a robust corporate governance framework to support the management and execution of our long-term strategy and annual strategic priorities and we will continue to assess our corporate board skillsets and responsibilities including evaluating the Board skills matrix to identify gaps and opportunities for improvement.

We also continue to utilise world-leading advisors on our advisory boards to help drive our strategic initiatives and ensure the success of our clinical development program. I thank all our esteemed independent external advisory board and committee members for their important contributions to the success of the Company in FY2024.

Capital management

The Company successfully completed two capital raisings totalling $18.9 million during the 2024 financial year. In addition, further funding has been received from the conversion of options associated with previous capital raisings.

We also recently completed an $11.1 million capital raising comprising an $8.1 million placement and a $3.0 million share purchase plan (SPP) following approval by shareholders at a General Meeting last week. I thank shareholders for your strong support for all our capital raisings during the past 18 months. A further $9.0 million related to the 2024 R&D tax incentive rebate was received earlier this week bringing our cash balance as at 13 November 2024 to $24.5 million. We estimate that the company is funded to at least mid 2026.

Notably, Steve Gourlay's investment of $1 million in the last funding round, which brings his total personal investment in the company to around $2 million, is a clear indication of his belief in the continued success of the Xanamem program.

Outlook

A key focus in FY2025 will be on progressing our XanaMIA phase 2b/3 Alzheimer's disease clinical trial as we activate further sites in the USA and ramp up patient screening and enrolments at all locations, ahead of a planned interim analysis in mid 2025.

We will also be planning our follow-on activities in our depression trial program by completing the data analysis and exploring the path forward into larger trials in MDD with regulators, global thought leaders and potential strategic partners.

The Board looks forward with confidence to a very exciting 2025 financial year. As always, we remain vigilant in our governance and proactive in our management as we deliver on our strategic priorities.

On behalf of the Board, I would like to thank you, our shareholders, for your ongoing support, and we look forward to updating you on our progress during the coming year.

Actinogen

Oral Xanamem®

Controlling brain cortisol to treat depression and slow progression in Alzheimer's disease – increasing clinical validation from phase 2 trials

AGM CEO Presentation, Steve Gourlay

14 November 2024

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Program and 2024's achievements

Xanamem is now significantly de-risked

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

- **Phase 2a MDD[1] trial showing clinically & statistically significant activity - benefits across multiple endpoints**
- Disease-modifying activity on CDR-SB in AD[2] phase 2a trial in biomarker-positive AD patients 0.6 points over 12 weeks
- Positive data from both trials read through to other indications in psychiatry and the dementias

Patent protection and manufacturing

- Composition of matter protection to 2031 – to 2036 with extensions in major markets
- **Additional recent patents protect further** against future competition e.g. use patent for MDD
- **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**
- 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. MDD: Major depressive disorde0r 2. Alzheimer's disease

Accomplishments since June 30 2023

Actinogen is in a strong position

Trial & regulatory progress

Commenced enrolment in XanaMIA phase 2b/3 in patients with pTau-positive AD

Opened 15 Australian clinical sites and 4 US sites for XanaMIA with 6 more US in the pipeline

Completed XanaCIDD phase 2a with positive benefit on depression symptoms

“Innovation passport” status from UK MHRA for AD, FDA protocol approvals

Key hires

Will Souter, CFO

Andy Udell, CCO

Publications & presentations

Two peer-reviewed manuscripts in the Journal of Alzheimer’s Disease

1. Xanamem benefit in pTau-positive patients
2. Human PET study showing full target engagement at low doses

Presented at more than ten scientific and partnering meetings

Strengthened financial position with ~ $44m[1]

Cash on hand $24.5m[2] - runway to at least mid 2026

$30m of equity raised across three rounds

R&D tax rebate cash received of $13.8m ($4.8m FY23 & $9.0m FY24)

1. Unless stated otherwise, all financial data is in Australian dollars
2. As at 13 November 2024

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

Company now in late-stage trials

ASX-listed company founded in 2014

- Market Cap $75 million
- **Cash runway to mid 2026**
- Conducted three phase 1 (Australia) and four phase 2 trials (Australia, US and UK)

Key shareholders

- Biotech Value Fund (BVF) ~8%
- **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 (AD) phase 2b/3 on-going – interim ~mid 2025, final results ~mid 2026**
- **Major depressive disorder (MDD) phase 2a just completed**
- Type C meeting with FDA to discuss approval requirements early 2025

Fundraising history

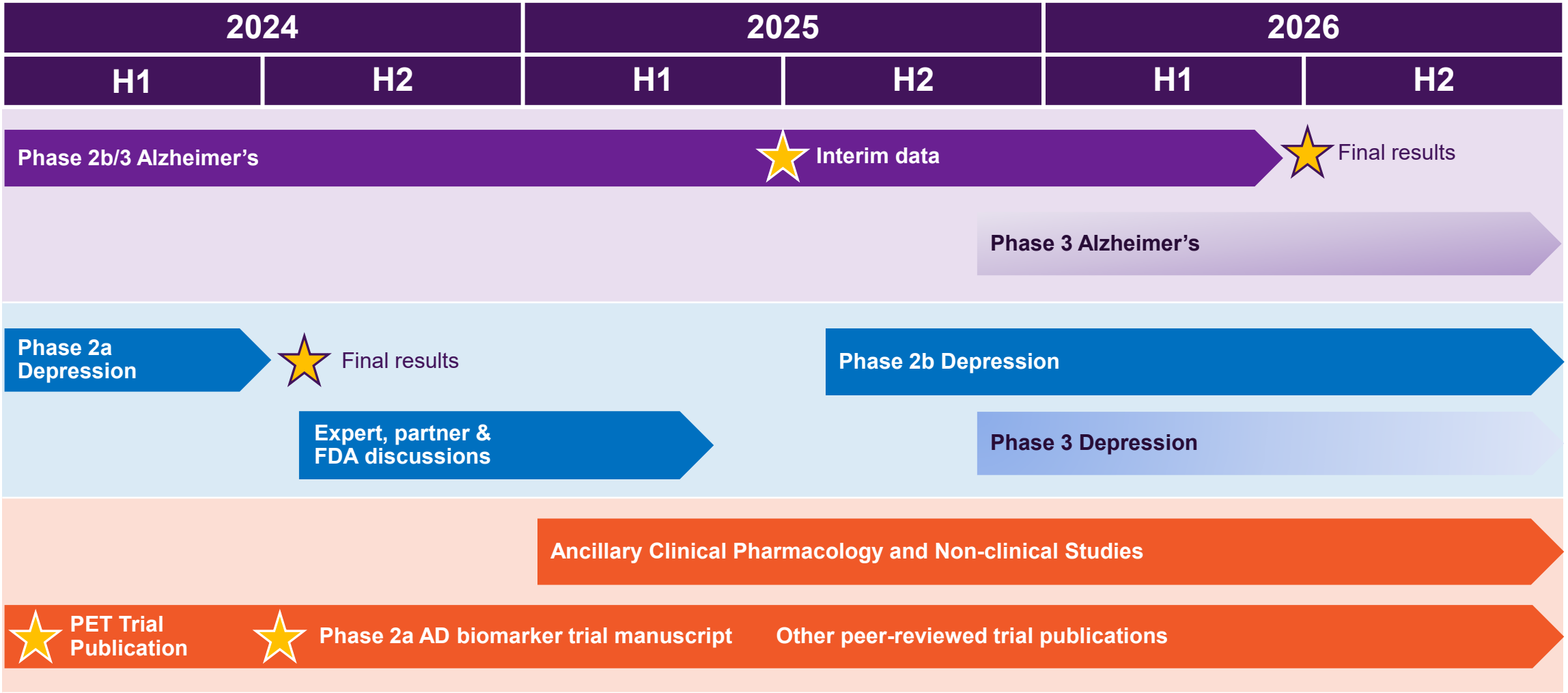
- Initially Wellcome Trust support for University of Edinburgh
- 2014 merger of U Edinburgh spinout Corticrine with Actinogen ASX-listed shell
- Equity raises on ASX and Australian R&D tax incentive cash rebates (eg $9 million received this year)

Xanamem - Pipeline

Indication	Preclinical	Phase 1	Phase 2	Phase 3	Next Milestone
Alzheimer's disease (AD)	On-going phase 2b/3			Open INDs	*Results 25-26*
MDD	Phase 2a complete, Phase 2b/3 in planning				*FDA Type C in Q1 25*
Fragile X syndrome	Phase 2a on hold				*On hold*
Bipolar disorder	Potential next indications				
PTSD					
Lewy-body dementia					
Frontotemporal dementia					

MDD: Major depressive disorder

Xanamem – AD and MDD Program Timelines*



* Seeking partnership(s) for Phase 2b depression and Phase 3 AD trials which are currently unfunded

Xanamem is in a class of its own

Xanamem controls cortisol by inhibition of 11β-HSD1[1]

Controlling brain cortisol[2] has potential durable benefits

"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

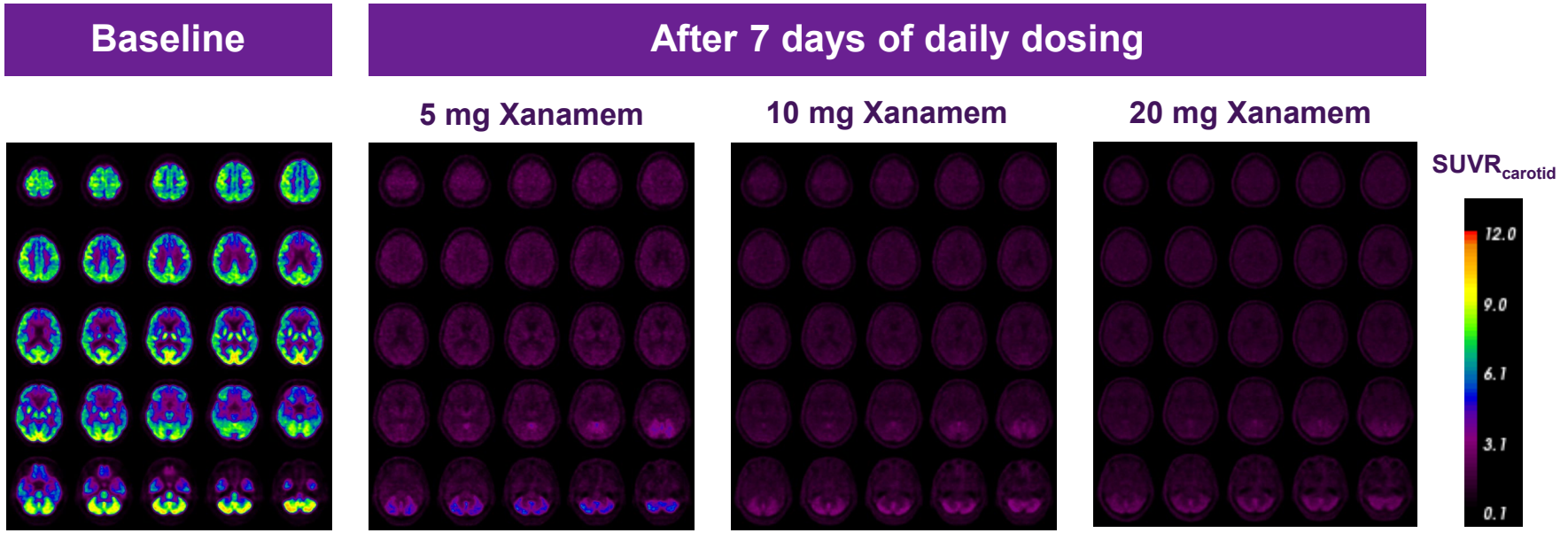
"Lower stress" longer term e.g.

- Improving neural circuitry
- Generating new brain cells
- Ideal receptor configurations

1. 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 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.

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

Conclusions

Positive depression data a boost to both AD and MDD

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

Phase 2a MDD data support further clinical development in MDD

Clinical activity on depression supports the likelihood of seeing a disease-modifying effect in Alzheimer’s disease over 36 weeks

What to look forward to in the rest of FY 2025

Xanamem has the potential to be a first & best-in-class treatment for MDD and AD

- Regulatory interactions on both MDD and AD with the FDA
- Partnering interactions on new MDD data
- Accelerating XanaMIA enrolment towards the interim analysis in mid 2025
- Further peer-reviewed publications
- Multiple scientific and partnering presentations
- Company is now funded to at least mid 2026

Q & A

Appendix

Key references

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

11β-HSD1 inhibition

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- 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*
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- Various podium and poster presentations on website

Technical references

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Alzheimer's disease and cortisol

- Plasma Cortisol, Brain Amyloid-β, 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
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Depression and cortisol

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- Effect of glucocorticoid and 11β-hydroxysteroid-dehydrogenase type 1 (11β-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
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Market & cost of treatment estimates

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- 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

- **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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