ASX ANNOUNCEMENT

Actinogen presentation to ASX small & mid-caps conference

Sydney, 26 March 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its CEO, Dr Steven Gourlay, will be a speaker this afternoon at the ASX small & mid-caps conference in Sydney.

Dr Gourlay's presentation is titled *Oral Xanamem®* (emestedastat) *Controlling brain cortisol to slow progression in Alzheimer's disease and treat depression: enrolling pivotal Phase 2b/3 trial in Alzheimer's.* The presentation outlines the attractive therapeutic profile of ACW's novel small molecule drug Xanamem and provides an update as the company approaches critical milestones in its phase 2b/3 Alzheimer's trial.

Register to join online using the following link: https://www.asx.com.au/investors/investment-tools-and-resources/events/smid

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.

Clinical Trials

The **XanaMIA Phase 2b/3 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 Q4 2025 and final results H2 2026.

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). Cognition improved markedly and to a similar extent in both Xanamem and placebo groups.

About Xanamem (emestedastat)

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 a first-in-class, once-a-day pill designed to deliver high levels of cortisol control in the brain.

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 approximately 400 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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ACTINOGEN MEDICAL ENCOURAGES ALL CURRENT INVESTORS TO GO PAPERLESS BY REGISTERING THEIR DETAILS WITH THE DESIGNATED REGISTRY SERVICE PROVIDER, AUTOMIC GROUP.

Actinogen

Oral Xanamem® (emestedastat)

Controlling brain cortisol to slow progression in Alzheimer's disease and treat depression: enrolling pivotal Phase 2b/3 trial in Alzheimer's

ASX SMIDCaps conference

26 March 2025

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Corporate snapshot

ASX-listed company founded in 2014

- Market Cap ~$100 million
- **Cash balance of $22.9 million at Dec 31 2024 provides runway to at least mid 2026**
- Conducted three phase 1 (Australia) and four phase 2 trials (Australia, US and UK)

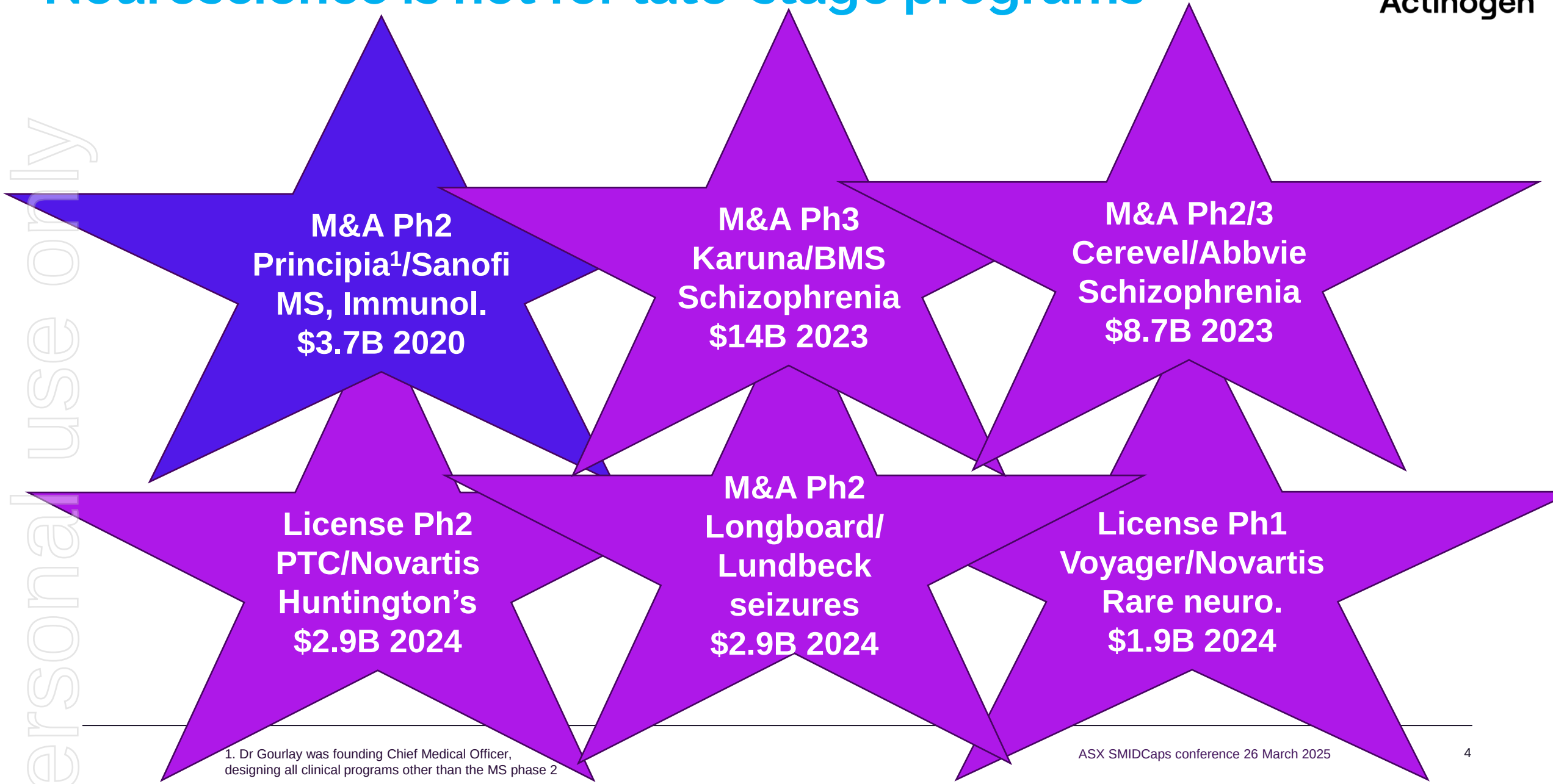
Key shareholders

- Biotech Value Fund (BVF) ~6%
- **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 phase 2b/3 ongoing – interim Q4 2025, final results H2 2026**
- **Major depressive disorder phase 2a completed – seeking non-dilutive funding for phase 2b**
- Type C meeting with FDA to discuss approval requirements for AD Q2-3 2025

Neuroscience is hot for late-stage programs



1. Dr Gourlay was founding Chief Medical Officer, designing all clinical programs other than the MS phase 2

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

Xanamem is now in advanced stages of development

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

- **Disease-modifying activity on CDR-SB** in phase 2a trial in biomarker-positive Alzheimer's patients
- **Phase 2a MDD trial showing clinically & statistically significant activity - benefits across multiple endpoints**
- Positive data from both trials read through to other indications in psychiatry and the dementias

Patent/data protection and advanced manufacturing

- **Composition of matter protection** to 2031, and 2036 with extensions in major markets, newer patents in process
- **Data exclusivity protects Xanamem data** from use by others for 5 to 10 years from approval e.g. 10 years in EU
- **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, first 11β-HSD1 inhibitor awarded INN name**[1]
- 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. Xanamem's International Nonproprietary Name (INN) , emestedastat, was awarded by a naming committee of the World Health Organization: "-stedastat" chosen for the first time for all 11β-HSD1 inhibitors

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

Controlling brain cortisol[2] has potential durable benefits

Reduction of "stress response" in brain

RAPID changes in kinases, cell function, neurotransmitters over hours to days lead to short-term "low stress" settings

"Lower stress" shorter term e.g.

- Reducing inflammation
- Improving neurotransmitter balance
- Decreasing cell death

SLOW changes in gene expression and protein synthesis over days to weeks lead to durable "low stress" settings

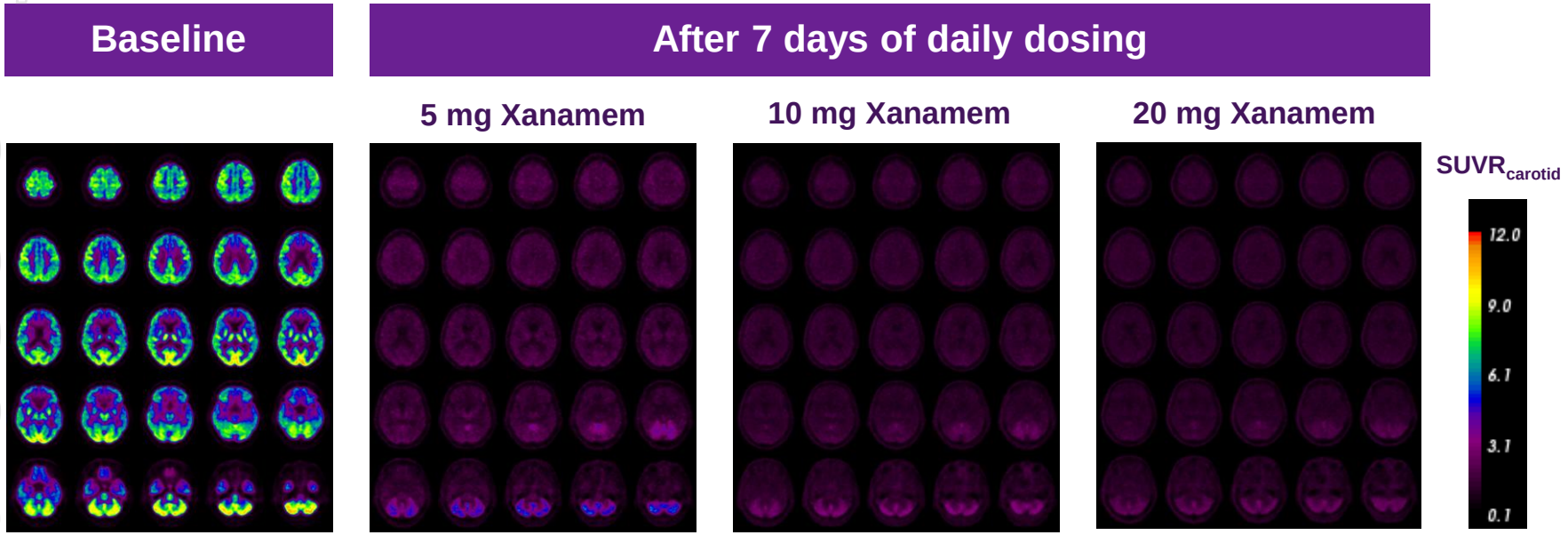
"Lower stress" longer term e.g.

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

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

Human PET study shows full target engagement

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



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

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

Journal of Alzheimer's Disease 97 (2024) 1463–1475
Brain 11-Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamem™ Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals
Victor L. Villemagne, Vincent Dor, Lee Chong, Michael Kassiou, Rachel Mulligan, Azadeh Feizpour, Jack Taylor, Miriam Roesner, Tamara Miller and Christopher C. Rowe

Alzheimer's disease

Strong cortisol control scientific rationale to address huge unmet medical need

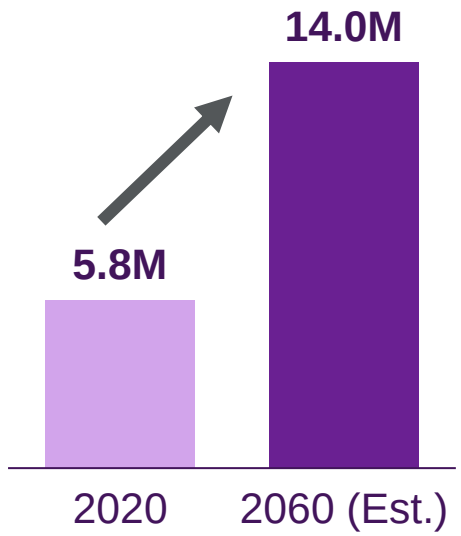
Rationale

- 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
- ***Safe & effective oral therapy is "holy grail"***

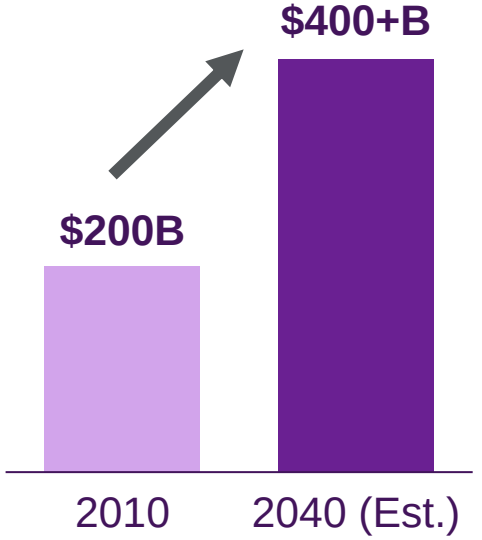
Growing Alzheimer's Disease market – U.S.

Large, unsatisfied and growing market

# of patients

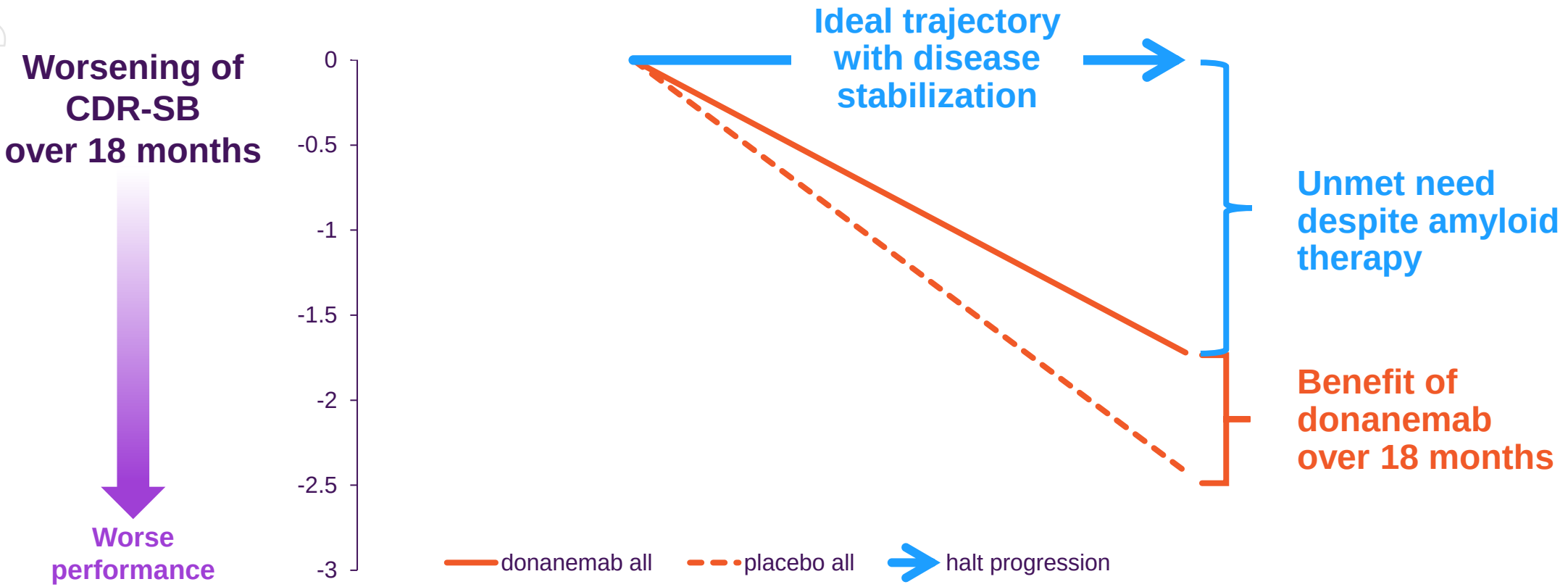


Cost to treat



Anti-amyloid therapy modestly slows AD progression

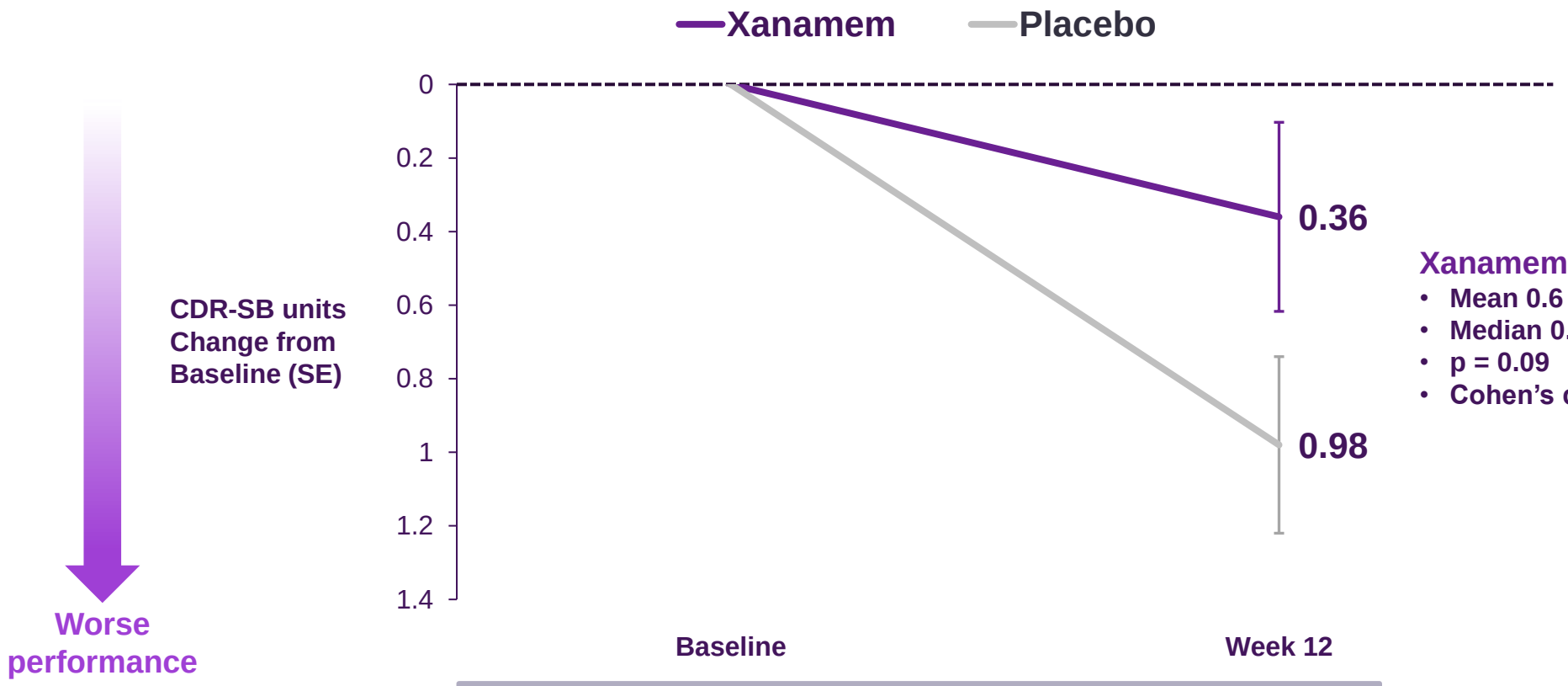
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanamem are needed

Xanamem benefit in pTau181-positive AD patients

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



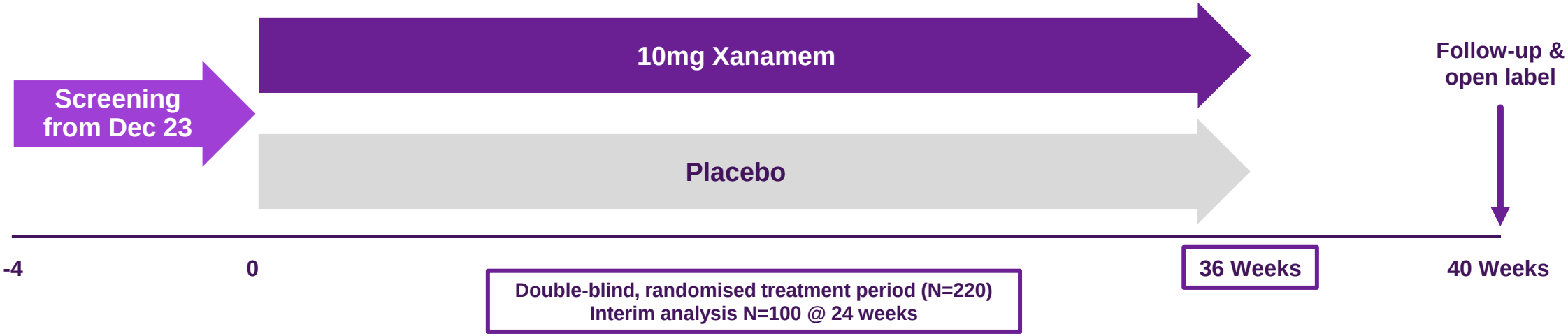
Xanamem vs. Placebo

- **Mean 0.6 units**
- **Median 0.8 units**
- **p = 0.09**
- **Cohen's d = 0.4**

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

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

Initial, interim results in Q4 2025, final results H2 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)	• Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field) • Amsterdam Activity of Daily Living (functional measure)	• Enrolment at 15 Australian & 20 US sites • Interim analysis planned when ~100 people complete 24 weeks

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

Six different datasets validate Xanamem 10mg dose

Data source	Conclusion
Safety data n > 400	No concerning safety signals
Phase 1	Adequate blood levels
Phase 1	Adequate brain fluid levels
Human PET study	High target binding in the brain
Phase 1b	Improved cognition in healthy people
Phase 2a	Slowed Alzheimer's progression (pilot data)[1]
Phase 2a	Improved depression symptoms
Phase 2b/3	Confirmatory Alzheimer's trial in progress

1. Taylor et. al 2024 – positive CDR-SB effect seen in pTau-positive patients

Building positive momentum

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

We have high confidence in a positive, disease-modifying outcome in Alzheimer’s disease over 36 weeks in current XanaMIA trial

- ✓ Interim results Q4 2025
- ✓ Final results H2 2026

Depression is a great alternative indication and anti-depressant effects are also a positive feature for an Alzheimer’s drug label

Company funded to at least mid 2026

Multiple value-add milestones in coming 12 months

A busy 2025 of milestones and announcements

Milestone	Likely Timing
First patient randomized and treated in US, XanaMIA trial	Q4 24
Meetings at JP Morgan Healthcare conference week, San Francisco	Q1 25
Clinical pharmacology manuscript peer-reviewed publication	Q1 25
FDA Type C meeting for MDD	Q1 25
Clinical Trials Science Forum – focus on commercial planning	Q1 25
100th patient enrolled, XanaMIA trial	Q2 25
XanaCIDD MDD peer-reviewed journal publication	Q3-4 25
ADPD conference AD presentation in Vienna	Q2 25
American Psychiatric Association MDD presentation, Los Angeles	Q2 25
FDA Type C meeting for AD	Q2-3 25
Interim analysis, XanaMIA trial	Q4 25
Full enrolment, 220 patients with AD, XanaMIA trial	Q4 25
AAIC conference AD presentation in Toronto	Q3 25
CTAD conference AD presentation in San Diego	Q4 25

Actinogen investment highlights

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

Potential to be the “holy grail” for Alzheimer’s

Positive phase 2a clinical data in two diseases has proven the “cortisol hypothesis”

Phase 2b and 3 trials significantly de-risked

Strong patent/data protection

Advanced manufacturing, nonclinical program and clinical pharmacology

Large clinical and commercial opportunities – Alzheimer’s will be a $20 billion market

Phase 2b/3 trial in Alzheimer’s has an interim readout in late 2025 and final results late 2026

Appendix

Key references

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

11β-HSD1 inhibition

- Seckl J. 11β-Hydroxysteroid dehydrogenase and the brain: Not (yet) lost in translation. J Intern Med. 2024 Jan;295(1):20-37. doi: 10.1111/joim.13741. Epub 2023 Nov 8. PMID:37941106. https://onlinelibrary.wiley.com/doi/10.1111/joim.13741
- 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*
- 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, Kassiouf 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 11β-hydroxysteroid dehydrogenase type 1 (11β-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

Technical references

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- Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155
- Hengartner MP, Jakobsen JC, Sørensen A, Plöderl M (2020) Efficacy of new-generation antidepressants assessed with the Montgomery-Asberg Depression Rating Scale, the gold standard clinician rating scale: A meta-analysis of randomised placebo-controlled trials. PLOS ONE 15(2): e0229381. https://doi.org/10.1371/journal.pone.0229381

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
- 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

- Ding et. al. Front. Pharmacol 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8461240/
- 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
- 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≥ 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

- **11β-HSD1 –** 11 beta HydroxySteroid Dehydrogenase-1 enzyme. Selectively expressed in brain, liver, adipose.
- **Aβ –** Amyloid beta – a type of amyloid protein associated with Alzheimer's Disease, 42 and 40 are different forms
- **ACTH –** Adrenocorticotropic hormone that regulates blood levels of cortisol
- **AD –** Alzheimer's disease
- **ADAS-Cog –** Alzheimer's Disease Assessment Score - Cognition
- **ApoE4 –** Apoprotein genotype associated with genetic risk of Alzheimer's Disease
- **ATN –** Amyloid, Tau, Neurodegeneration
- **Clinical Scales –** Measure how a patient feels, performs and functions
- **CDR-SB –** Clinical Dementia Rating "Sum of Boxes" scale measuring cognition and function on an 18-point scale (high worse)
- **CNS –** Central nervous system
- **CSF –** Cerebrospinal fluid
- **CTAD –** Clinical Trials on Alzheimer's Disease (conference)
- **CTB –** Cognitive Test Battery of computerized tests
- **Double-blind –** Investigators, participants and company do not know who has active vs placebo treatment during a trial
- **EMA –** European Medicines Agency
- **FDA –** US Food & Drug Administration
- **Filamen A –** A protein believed to relate to amyloid toxicity
- **GFAP –** Glial Fibrilliary Acidic Protein – a marker of microglial cell activation in the brain
- **IDSST –** International Digit Symbol Substitution Test of cognition

Selected Glossary 2

- **IQCODE –** Informant Questionnaire on Cognitive Decline in the Elderly
- **MCI –** Mild Cognitive Impairment – memory, executive function deterioration with retained functional abilities
- **MDD –** Major Depressive Disorder
- **MMSE –** Mini Mental State Examination – a 30-point scale of simple questions to assess mental abilities
- **NfL –** Neurofilament Light – a nerve protein in the brain and rest of the body too
- **NIA-AA –** National Institutes of Aging and Alzheimer's Association
- **NMDA –** A type of receptor for glutamate in the brain
- **NPI –** Neuropsychiatric Inventory to assess psychiatric symptoms
- **NTB –** A Neurologic Test Battery, in this presentation one designed to measure executive function aspects of cognition
- **PET –** Positron Emission Tomography – a type of body scan
- **Placebo controlled –** Non-active treatment for double-blind design
- **p-Tau181 or 217 AD –** Biomarker of phosphorylated Tau protein
- **QPCT –** Glutaminyl-peptide cyclotransferase is an enzyme proposed to create toxic amyloid species
- **RAVLT –** Rey Auditory Visual Learning Test
- **RBANS –** Repeatable Battery for the Assessment of Neuropsychological Status (a test of mental abilities)
- **ROC AUC –** Receiver Operating Curve Area Under the Curve (1.0 ideal) – a type of statistical test to compared two methods of measurement
- **SSRI –** selective serotonin reuptake inhibitor
- **Tau –** A brain protein
- **Ttau –** Total tau levels including both phosphorylated and non-phosphorylated tau

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