ASX ANNOUNCEMENT

Actinogen CEO presents on emerging oral Alzheimer's Disease therapies at the National Dementia Conference, Melbourne

Sydney, 21 June 2023. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its Chief Executive Officer and Managing Director, Dr Steven Gourlay, will present at the **Annual National Dementia Conference** in Melbourne today in the *Cognitive Decline Emerging Treatments & Trends* conference forum.

Dr Gourlay's keynote presentation topic is titled *Novel small molecule therapeutics in development for Alzheimer's Disease*. This presentation is an updated review of oral therapeutics in mid and late-stage clinical trials, such as Xanamem.®

It focuses on the relatively small number of oral non-amyloid mechanism drugs that have potential to solve for the gap between the 25-30% slowing of disease progression with newer amyloid antibody intravenous infusions, and the remaining 70-75% needed to entirely halt disease progression.

The presentation slides are attached to this announcement.

Dr Steven Gourlay, Actinogen CEO and MD, commented:

"While recent positive data on new anti-amyloid antibody infusions give Alzheimer's patients hope, these drugs do not halt disease progression, underscoring the importance of on-going efforts in academia and industry to find more effective and safe therapies that will likely work via non-amyloid mechanisms."

ENDS

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

Investors

Michael Roberts
Investor Relations
M: +61 423 866 231
E. michael.roberts@actinogen.com.au

Announcement authorised by the Board of Directors of Actinogen Medical

® Xanamem is a registered trademark of Actinogen Medical Limited

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.

About Xanamem

Xanamem's novel mechanism of action is to block the production of cortisol inside cells through the inhibition of the 11β-HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease and excess cortisol is known to be toxic to brain cells. Cognitive impairment is also a feature in Depression and many other diseases. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 300 volunteers and patients, so far finding a statistically significant improvement in working memory and attention, compared with placebo, in healthy, older volunteers in two consecutive trials and clinically significant improvements in functional and cognitive ability in patients with biomarker-positive mild AD. Previously, 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. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterize Xanamem's therapeutic potential.

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.

® Xanamem is a registered trademark of Actinogen Medical Limited

Actinogen

Novel oral therapeutics in development for Alzheimer's Disease

There is reason to believe that one or more novel, oral medications will emerge soon

Dr Steven G Gourlay MBBS PhD, CEO & MD Actinogen Medical

Cognitive Decline Emerging Treatments & Trends Forum, Melbourne June 21, 2023

Disclaimer

This presentation has been prepared by Actinogen Medical Limited. ("Actinogen" or the "Company") based on information available to it as at the date of this presentation. The information in this presentation is provided in summary form and does not contain all information necessary to make an investment decision.

This presentation does not constitute an offer, invitation, solicitation or recommendation with respect to the purchase or sale of any security in Actinogen, nor does it constitute financial product advice or take into account any individual's investment objectives, taxation situation, financial situation or needs. An investor must not act on the basis of any matter contained in this presentation but must make its own assessment of Actinogen and conduct its own investigations. Before making an investment decision, investors should consider the appropriateness of the information having regard to their own objectives, financial situation and needs, and seek legal, taxation and financial advice appropriate to their jurisdiction and circumstances. Actinogen is not licensed to provide financial product advice in respect of its securities or any other financial products. Cooling off rights do not apply to the acquisition of Actinogen securities.

Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, no representation or warranty, express or implied, is made as to the fairness, accuracy, completeness or correctness of the information, opinions and conclusions contained in this presentation. To the maximum extent permitted by law, none of Actinogen its officers, directors, employees and agents, nor any other person, accepts any responsibility and liability for the content of this presentation including, without limitation, any liability arising from fault or negligence, for any loss arising from the use of or reliance on any of the information contained in this presentation or otherwise arising in connection with it.

The information presented in this presentation is subject to change without notice and Actinogen does not have any responsibility or obligation to inform you of any matter arising or coming to their notice, after the date of this presentation, which may affect any matter referred to in this presentation.

This presentation is not for general distribution or third party reliance or use.

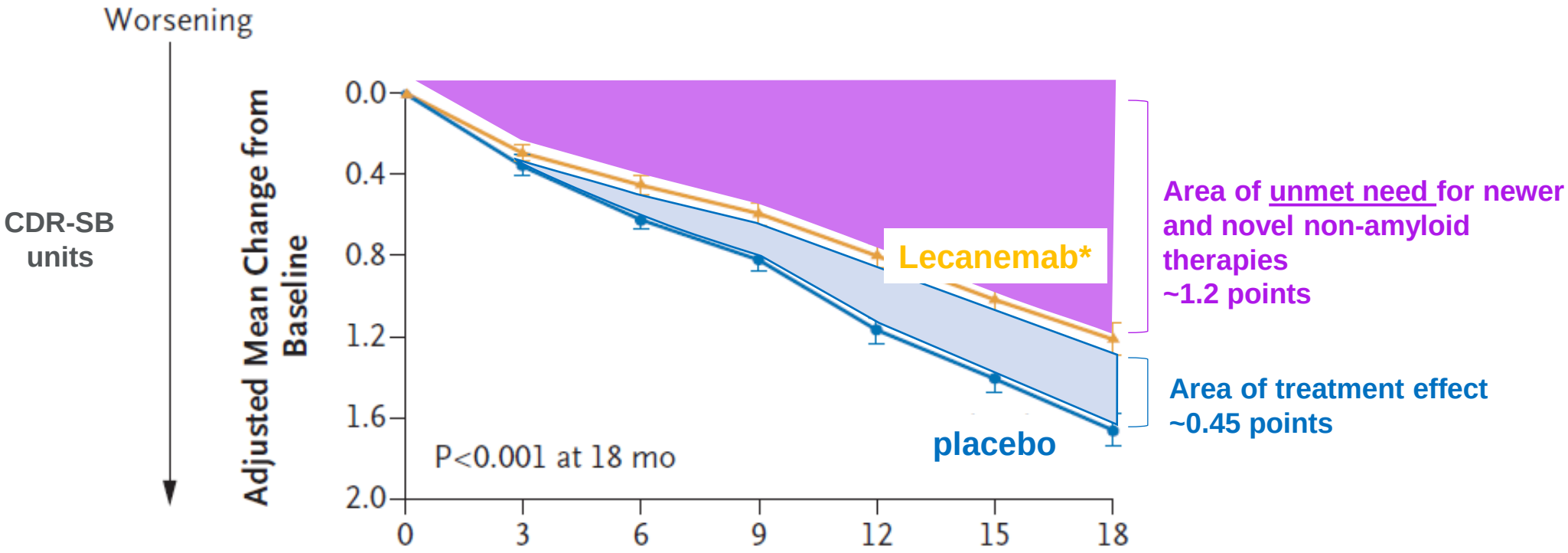
This presentation contains certain budget information, forecasts and forward looking statements that are based on the Company's management's beliefs, assumptions and expectations and on information currently available to management in respect of which there is **NO guarantee of future performance**. Such budget information, forecasts and forward looking statements involve known and unknown risks, uncertainties, and other factors which may cause the actual results or performance of Actinogen to be materially different from the results or performance expressed or implied by such forward looking statements. These risks and uncertainties include, but are not limited to the performance of Actinogen in its clinical trials including whether it's technology proves to be a safe and effective treatment, market penetration, competition from any other similar products, intellectual property risks (including securing rights in technology and patents) and global economic conditions. Furthermore, Actinogen's research, product development, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. There is no guarantee that Actinogen will obtain the required approvals, licences and registrations from the relevant authorities in jurisdictions in which it operates. Actinogen or others could identify product and efficacy issues relating to the safety of our technology. Accordingly, all forward looking statements are based on numerous assumptions regarding the Company's present and future business strategies and the political and economic environment in which Actinogen will operate in the future, which are subject to change without notice. Past performance is not necessarily a guide to future performance and no representation or warranty is made as to the likelihood of achievement or reasonableness of any forward looking statements or other forecast. There is no guarantee that Actinogen will achieve its stated objectives/milestones, that any of its forecasts will be met or that forward looking statements will be realised. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

Neither Actinogen nor any other entity or person in or associated with Actinogen guarantee any return (whether capital or income) or generally the performance of Actinogen or the price at which its securities may trade. Any investment in Actinogen is subject to investment risks including the possibility of loss of capital invested and no return of income or payment of any dividends.

To the maximum extent permitted at law, Actinogen and all of its representatives, directors, officers, partners, employees or professional advisers (**Parties**) exclude all direct and indirect liability arising out of or in connection with any use or reliance of the information contained or described within this presentation. Other than to the extent required by law (and only to that extent), the Parties do not make any representation or give any assurance, guarantee or warranty (express or implied) as to, nor assume any responsibility or liability for, the authenticity, origin, validity, accuracy, suitability or completeness of, or any errors in or omissions from, any information, statement or opinion contained in this presentation or any accompanying, previous or subsequent material or presentation.

Defining the biology of Alzheimer's is a bit like Michelangelo bringing out a human form from stone

New anti-amyloid antibodies slow but do not halt AD progression



Drugs targeting non-amyloid mechanisms are needed

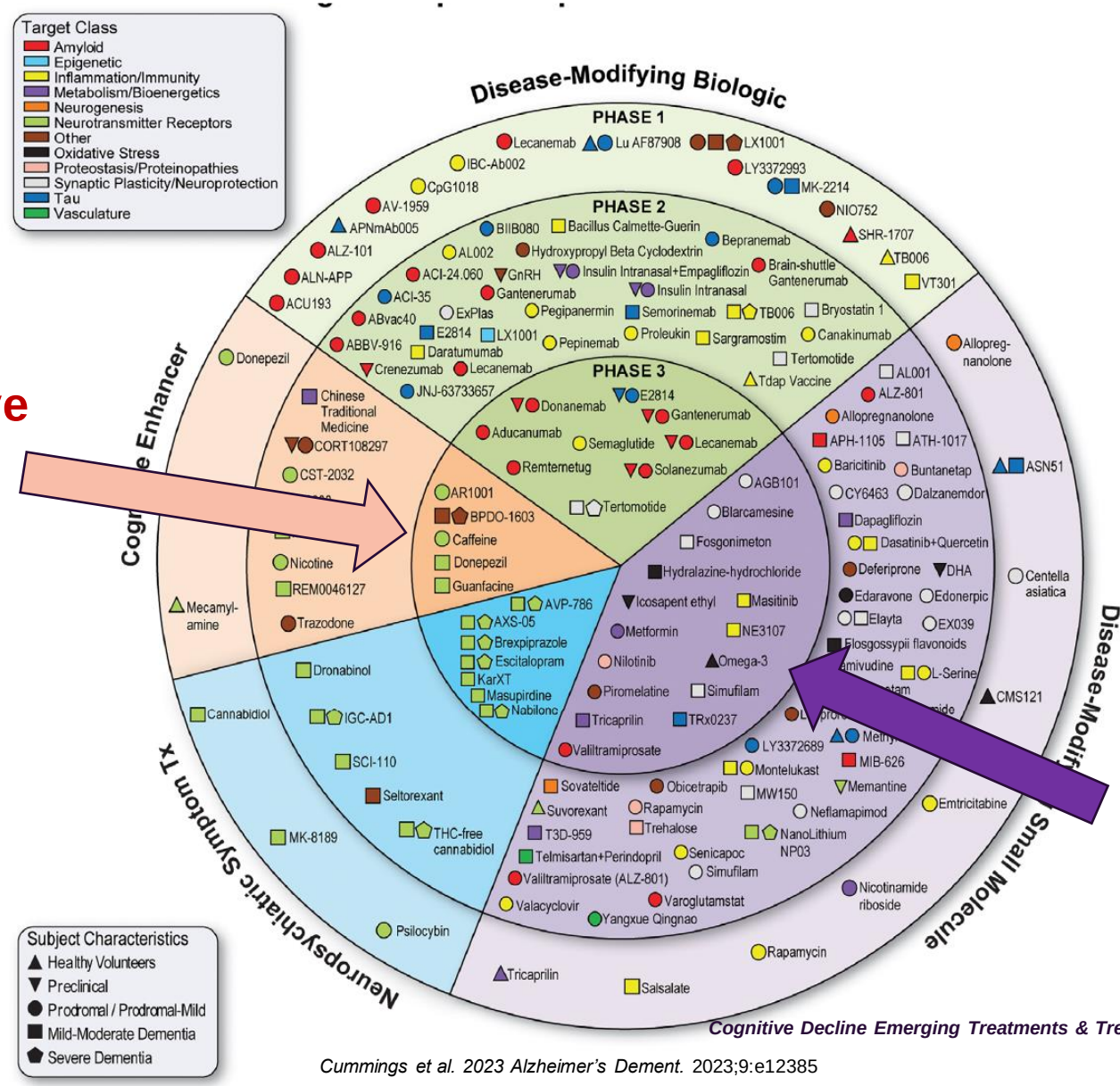
Anti-amyloid therapies are not the entire answer

* IV treatment every two weeks: Leqembi USPI & van Dyck et al. 2022; DOI: 10.1056/NEJMoa2212948 n=1795)

Of the hundreds of candidates, what are some of the most promising oral medication programs?

Actinogen

Promising cognitive enhancers of any mechanism

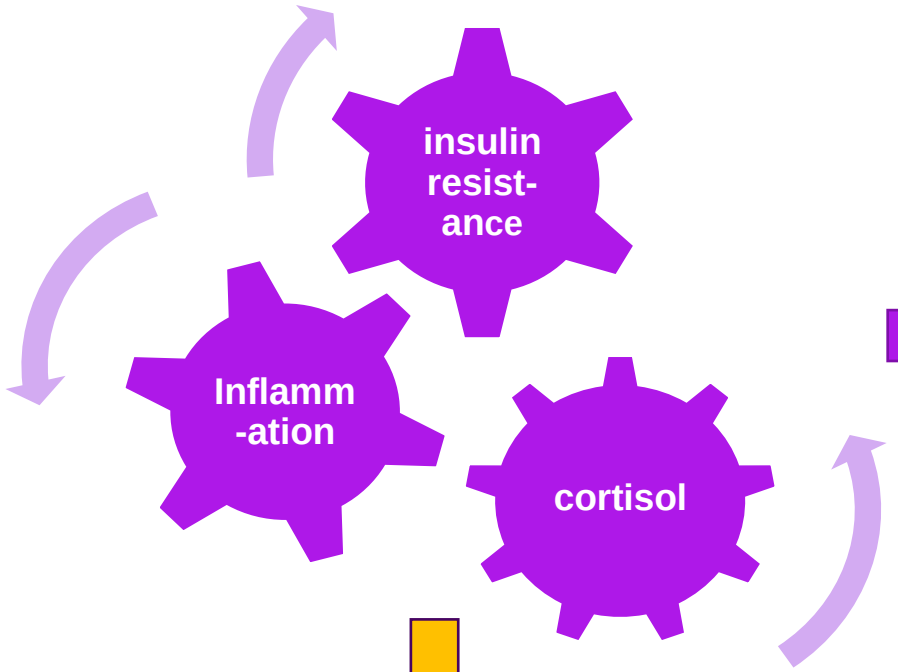


Promising disease-modifiers with non-amyloid mechanisms

Cummings et al. 2023 Alzheimer's Dement. 2023;9:e12385

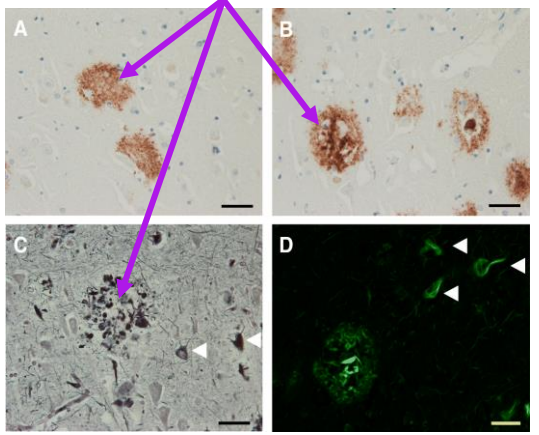
Neuroinflammation, abnormal cell signaling, and insulin resistance

Amyloid and tau deposition may be secondary to these other processes



- Memory impairment
- Difficulty solving problems
- Difficulty functioning
- Language problems

Amyloid plaques



Tau tangles

There are relatively few novel oral cognitive enhancers with evidence of cognitive benefit

Any mechanism

Non-prescription

- **Caffeine & nicotine- have brief effects**

Prescription

- **Acetylcholinesterase prescription drugs like donepezil (Aricept and others), rivastigmine, galantamine**
- **NMDA antagonist memantine**
- **Amphetamine-like drugs e.g. for ADHD**

In Phase 3 clinical trials

- **Novel formulations of older drugs like donepezil and memantine**
- **Guanfacine (an ADHD drug)**

In Phase 2 clinical trials

- **Xanamem® brain cortisol synthesis inhibitor, cognitive enhancement in 3 trials**

There is some potential in the non-amyloid field for oral disease-modifiers

Where there is some credible clinical data

Non-prescription

- None although curcumin has been used in South Asian medicine

Prescription

- GV-971/oligomannate (China only), mechanism certain

In Phase 3 clinical trials

- Semaglutide and other GLP-1 antagonist drugs (reduced risk of dementia onset in patients with Type 2 diabetes)

In Phase 2 clinical trials

- Blarcamasine, a sigma-1 receptor agonist (reduced progression in one trial)
- Xanamem®, inhibitor of brain cortisol synthesis (trends towards slower progression in biomarker-positive patients with mild AD in one trial)

Amyloid-mechanism oral disease-modifiers with credible cognitive data are few

With pro-cognitive data in a randomized trial

Non-prescription

- **None**

Prescription

- **None**

In Phase 3 clinical trials

- **Simufilam (Improved cognition and biomarkers, one 28-day trial)**

In Phase 2 clinical trials

- **Varoglutamstat (some cognition & biomarkers, one 12-week trial)**

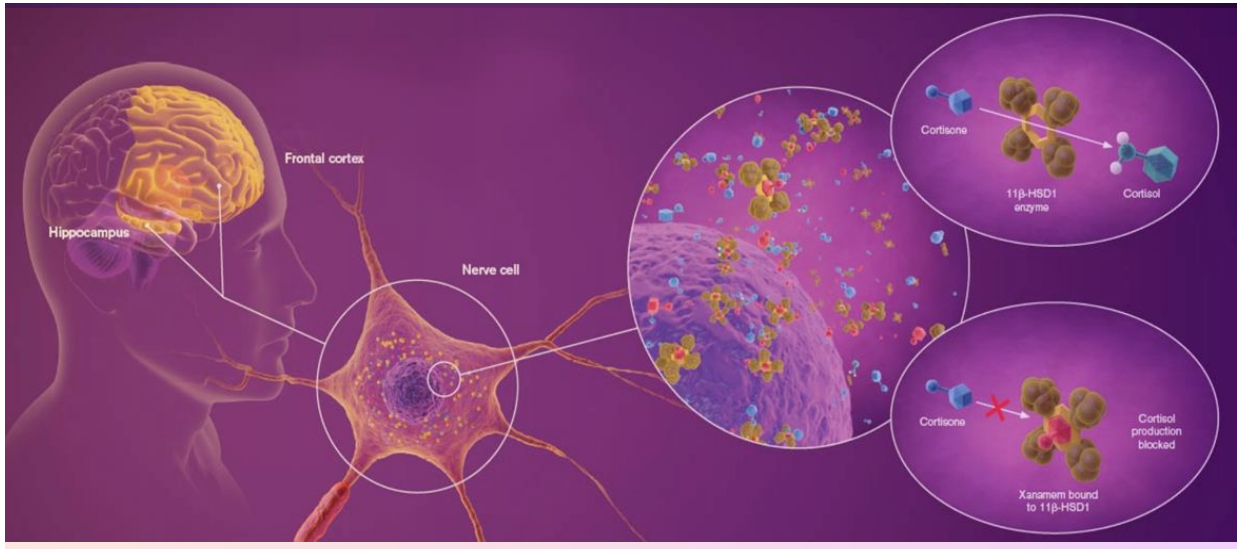
Xanamem: oral, low-dose, once-a-day treatment with a unique, non-amyloid/tau mechanism

Rodent experimental studies & clinical trials validate cortisol target for treatment of AD[1-4]

Brain penetrant 11β-HSD1 small molecule enzyme inhibitor discovered at the University of Edinburgh **reduces cortisol inside brain** cells[3,4] - modulating signalling pathways and underlying disease processes

Potential to be:

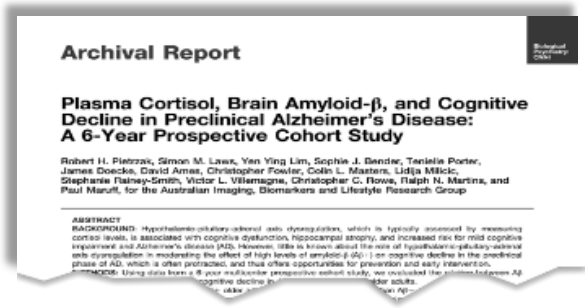
- Rapidly **cognitive enhancing**
- **Disease-modifying** (slow or halt progression) in AD[1,3]
- **Anti-depressant**



1. Sooy et al. 2015 showing effects on amyloid plaque reduction in an aged mouse model after 28 days associated with increases in insulin degrading enzyme – at 13 month cognitive protection was independent of continued amyloid deposition; 2. Popoli et al. 2011 microglial cell modulation in rats, effects on glutamate, cannabinoid and other signalling pathways; 3. Hilt, D. Oral symposium AD/PD International Conference 2023; Actinogen website: Actinogen – News; 4. based on human PET scan evidence (data on file), Webster et al. 2017 Selection and early clinical evaluation of the brain-penetrant 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor UE2343 (Xanamem™)

Many studies support the association between elevated cortisol and AD development and progression[1-9]

- Higher cortisol levels in human aging are associated with hippocampal atrophy[1,2]
- Chronic corticosteroid medication is associated with hippocampal and amygdalar atrophy and cognitive impairment[3]
- Higher plasma cortisol leads to a much greater risk of developing AD[4,5] and accelerated effect of Aβ+ on decline in global cognition, episodic memory, and attention[6,7]
- Higher CSF cortisol levels in AD patients are associated with more rapid clinical worsening and cognitive impairment[3]
- Individuals at high risk of AD due to the APOE-ε4 allele have higher CSF cortisol[9] and lecanemab showed no treatment effect in ε4/ε4 patients[10]


Archival Report

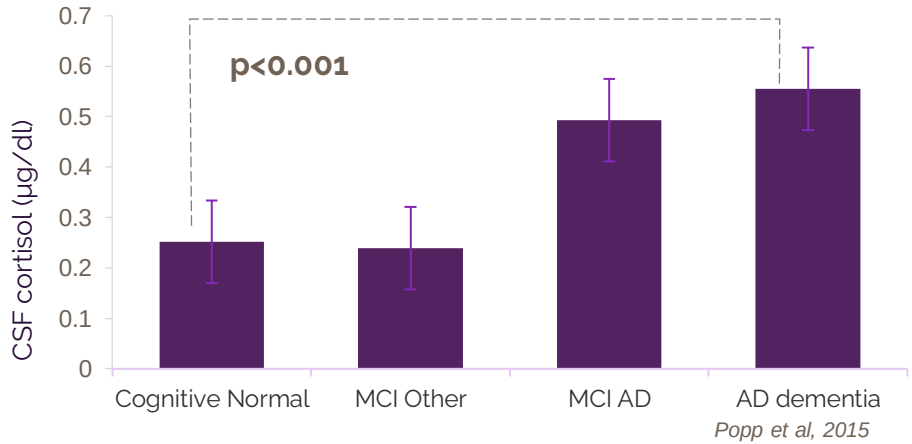
Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study

Robert H. Pietrzak, Simon M. Laws, Yen Ying Lim, Sophie J. Bender, Tenielle Porter, James Doecke, David Ames, Christopher Fowler, Colin L. Masters, Lidija Milicic, Stephanie Rainey-Smith, Victor L. Villemagne, Christopher C. Rowe, Ralph N. Martins, and Paul Maruff, for the Australian Imaging, Biomarkers and Lifestyle Research Group

aibl

The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing

MEAN CSF CORTISOL LEVELS



Popp et al, 2015

1. Geerlings et al., 2015, Neurology 85: 1-8; 2. Lupien et al., 1998, Nat Neurosci 1:69–73; 3. Shorey et al. 2023 https://doi.org/10.1016/j.brainres.2022.148157; 4. Lehallier et al., 2016, JAMA Neurology 73(2), 203-212; 5. Ennis et al., 2017, Neurology 88(4):371-378; 6. Pietrzak et al., 2017, Biol Psychiatry: Cognitive Neuroscience and Neuroimagery, 2:45-52; 7. Csernansky et al., 2006, Am J Psychiatry 163:2164-2169; 8. Popp et al., 2015, Neurobiol. Aging 36:601–607; 9. Peskind et.al. 2001 Neurology 56(8):1094-8; 10. van Dyck et al. N Engl J Med 2023; 388:9-2.

PET data shows full target engagement in the brain at low doses

Previous enzyme inhibitors[1] have not achieved adequate brain concentrations

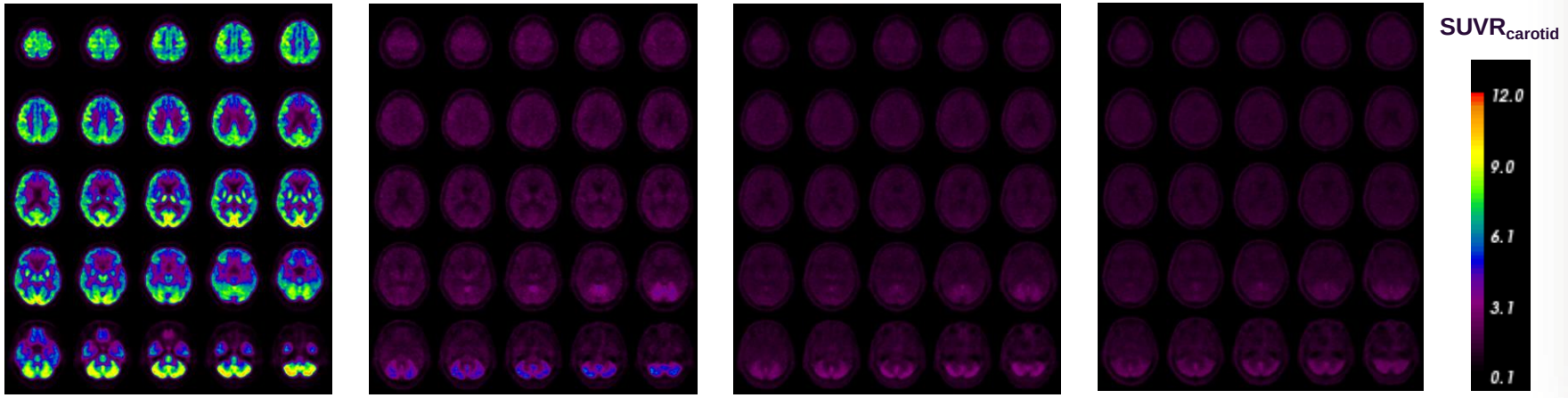
Baseline

After 7 days of daily dosing

5 mg Xanamem

10 mg Xanamem

20 mg Xanamem



PET data[2] demonstrates that 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.

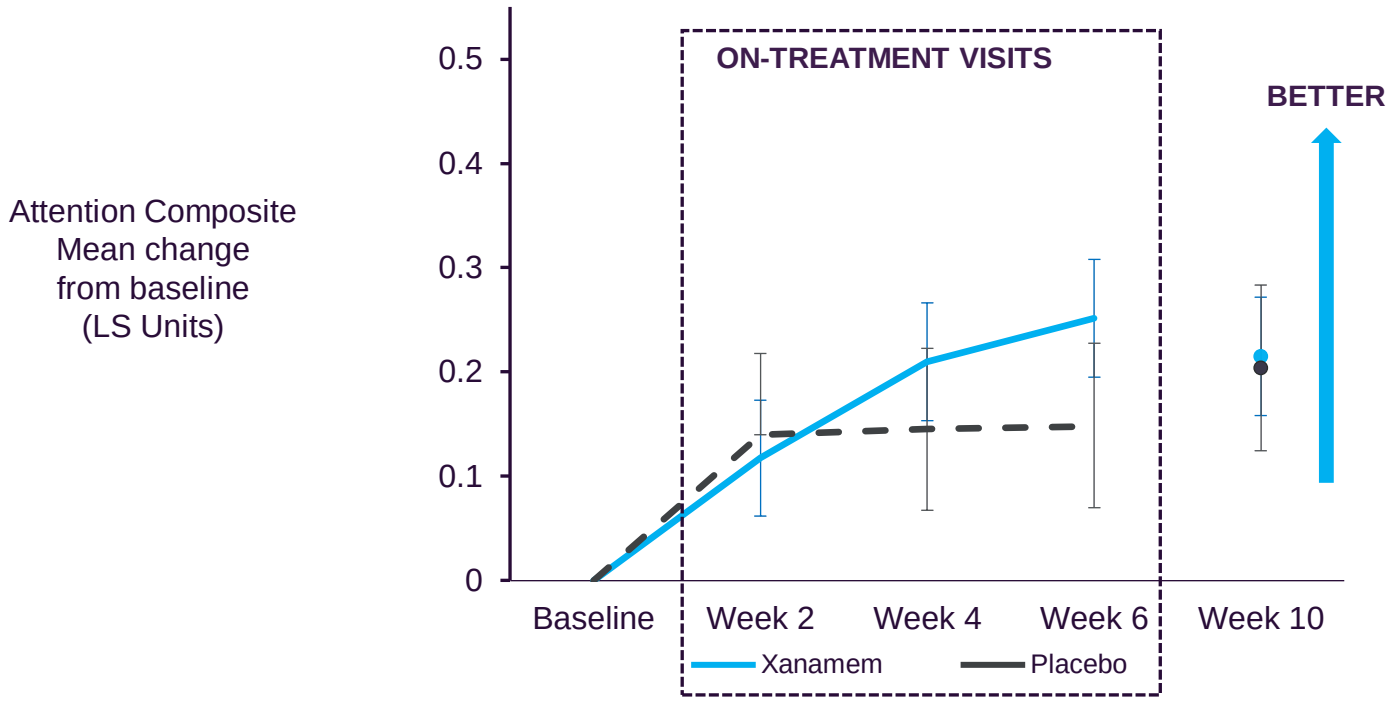
This is consistent with full hormonal pharmacodynamic activity seen with 10 mg in clinical trials. 5 and 10 mg show excellent clinical tolerability and safety.

1. ABT-384 was claimed to have brain penetrant ability based on likely hepatic effects on deuterated cortisol (Katz et al. 2013), negative 12-week AD trial (Marek et al. 2014)
2. Study population consisted of ~50% healthy older subjects who were cognitively normal and ~50% with Alzheimer's disease. Subjects dosed for seven days.
Baseline: Mean of baseline scans of patients in that dose group; After dose: Mean of post-dosing (7 days) scans in that dose group.

Second trial confirms improved attention/working memory at 4-6 weeks using lower doses of 5 – 10 mg

Computerized cognitive testing in cognitively normal older people, 5, 10 mg daily vs. placebo

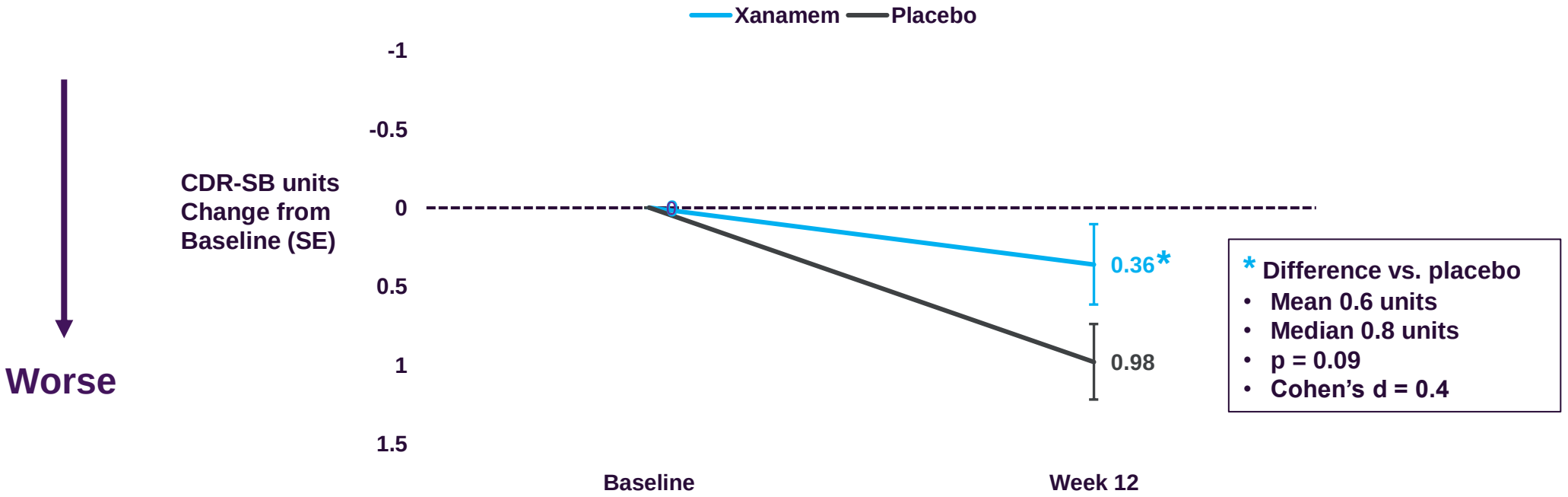
XanaMIA Phase 1b trial (n=107, Xanamem 10 mg & 5 mg combined)



Pro-cognitive effects of Xanamem confirmed in second randomized trial

Xanamem slows the rate of CDR-SB (functional) decline in mild AD*

Patients with elevated plasma pTau181 indicating progressive, amyloid-positive disease (n=34)

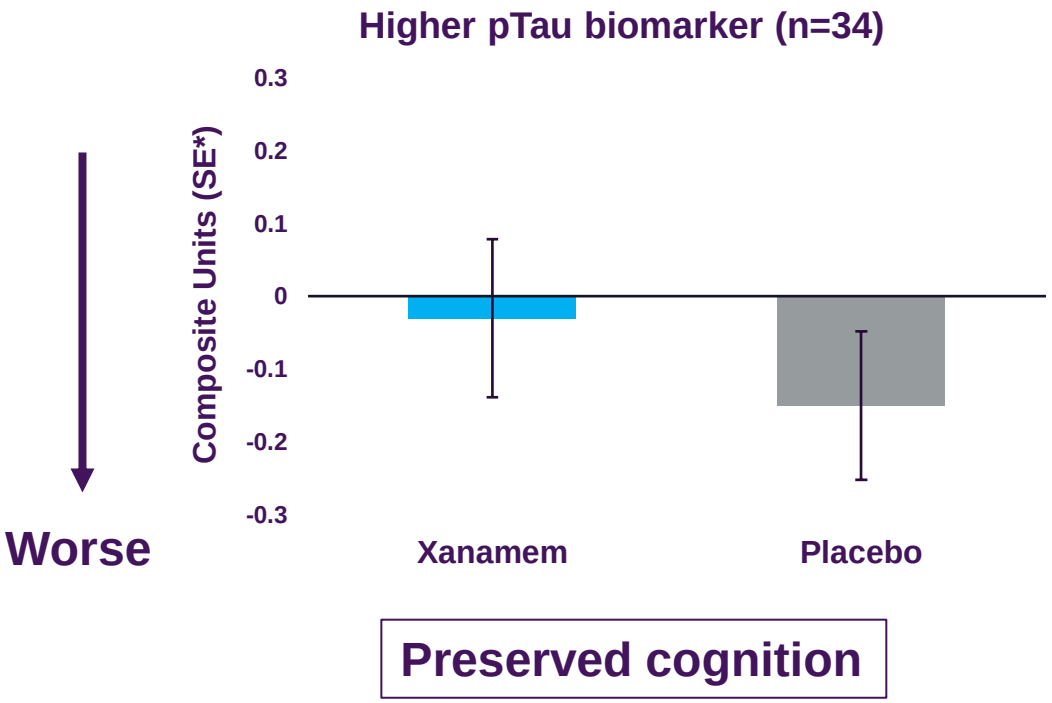


Extrapolated to 18 months effect size would be more than 3 points

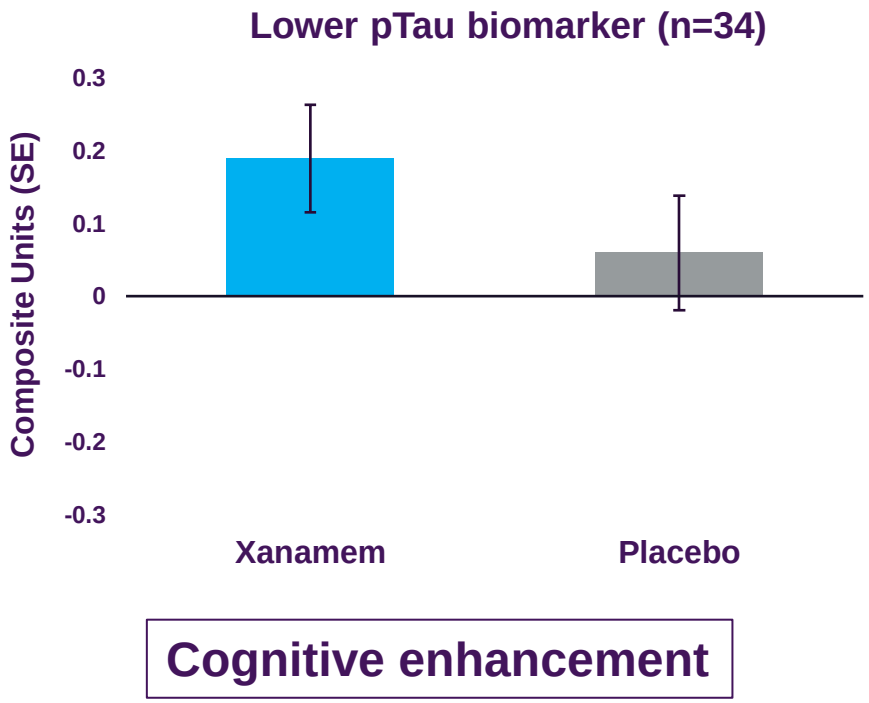
* Patients with a pre-treatment plasma pTau181 level greater than the pre-specified median of 6.74 pg/mL to indicate AD pathology and likelihood of progressive disease; similar effect size for pTau >10.2 pg/mL cutoff; effect size 8-10 times greater than 0.4-0.45 reported for lecanemab (USPI Leqembi 2023 & van Dyck et al. 2022; DOI: 10.1056/NEJMoa2212948) if extrapolated to 18 months

Cognitive composite scores suggest potential clinical benefit across dementia patient sub-types*

Positive trends in both high and low plasma pTau biomarker groups



Preserved cognition



Cognitive enhancement

Consistent with Xanamem activity as a cognitive enhancer & disease-modifier

* Post hoc analysis of composite of word recall & recognition, CFT & COWAT tests (p=NS), error bars show Standard Error of the Mean; low pTau patients less likely to have amyloid-positive disease, results consistent with volunteer data

Timetable for trial results for oral AD therapies

Actinogen

Year	Drug or company	Target	Steve's probability of success
2023	deferiprone	Iron	Low
	TauRx	Tau*	Low
	NE3107	ERK1/2	Low
	simufilam	Filamen A*	Low-Medium
2023	**varoglutamstat**	**pglu-Aβ/QC***	**Medium**
	CT1812	Sigma-2*	Low
2024	Valiltramprosate	Amyloid form.*	Low-Medium
	LY337268	OGA*	Low
2025	**Xanamem**	**cortisol**	**Medium-High**
2026	**semaglutide**	**GLP-1**	**Medium**

* Amyloid or tau protein-related mechanisms

Oral medication AD trials are recruiting in Australia

Actinogen

Phase 3

- **Statin drugs (STAREE trial)**
- **Semaglutide EVOKE (GLP-1 antagonist, diabetes and weight loss treatment)**
- **Simufilam (Filamen A)**

Phase 2

- **MK-1942 (unknown mechanism)**
- **LY3372689 (preventing tau tangle formation)**
- **Probucol (anti-lipid)**
- **SAMe (methionine, anti-inflammation)**
- **CT1812 (sigma-2 antagonist)**
- **Pending: Xanamem (tissue cortisol inhibitor)**

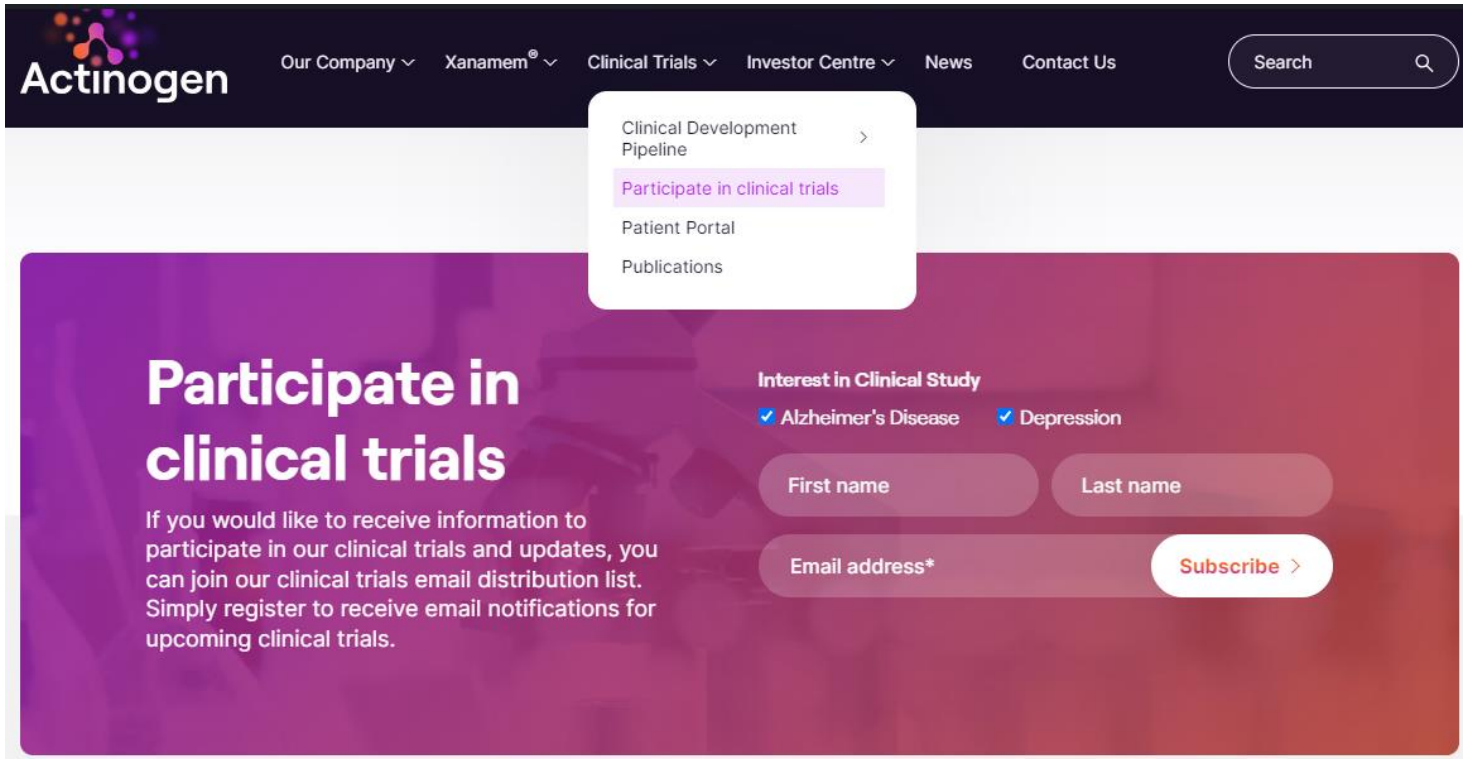
Contact Actinogen

How to access our Xanamem phase 2 trial in Alzheimer's disease

Subscribe

To receive information about our clinical trials: Subscribe

or: https://actinogen.com.au/clinical-development-pipeline/#patient-portal



Contact Us

Web: actinogen.com.au

Phone: +61 2 8964 7401

Email: clinicaltrials@actinogen.com.au

Follow Us

LinkedIn: @Actinogen Medical

Facebook: @ActinogenMedical

Twitter: @ActinogenMed

The answers to Alzheimer's Disease are emerging….

clinicaltrials.gov
anzctr.org.au
actinogen.com.au