First-in-class/best-in-class Phase 2 oral drug candidate for Alzheimer’s Disease & Depression

Four trials validate Xanamem® as a novel, differentiated, safe and efficacious candidate

Corporate Presentation June, 2023

Non-confidential
Dr Steven G Gourlay, CEO
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Actinogen (ACW.AX) & Xanamem Summary

- Xanamem is an oral treatment with rapid onset of clinical activity
- Cortisol target validation in animal models and by cognitive benefit shown in multiple controlled trials of Xanamem
- Excellent safety profile, low drug interaction potential
- Commercial tablet formulation developed
- Intellectual property protection including composition of matter
- Phase 2a proof-of-concept trial in Depression associated with Cognitive Impairment (n=160, results H1 2024)
- Phase 2b confirmatory trial in mild-moderate AD (n=330, interim analysis late 2024/early 2025, final results H2 2025)
- Experienced team based in Australia, US and UK
Targeting large clinical opportunities with unmet need

Current clinical focus:

- Alzheimer’s Disease global prevalence: 33 million patients
- Major Depressive disorder: 280 million patients, 70% associated with cognitive impairment

Potential future indications:

- Other neurodegenerative diseases such as Frontotemporal dementia & Lewy-Body dementia: 17 million patients
- Schizophrenia-associated cognitive impairment: 24 million patients
- Cognitive impairment in bipolar disease: 46 million patients
Xanamem: oral, low-dose, once-a-day treatment with a unique, non-amyloid/tau mechanism

Mouse experimental studies & clinical trials validate cortisol target for treatment of AD\textsuperscript{1-4}

Brain penetrant \(11\beta\)-HSD1 small molecule enzyme inhibitor reduces cortisol inside brain cells\textsuperscript{3,4} - modulating signalling pathways and underlying disease processes

Potential to be:

- **Rapidly cognitive enhancing**
- **Disease-modifying** (slow or halt progression) in AD\textsuperscript{1,3}
- **Anti-depressant**

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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 \(11\beta\)-hydroxysteroid dehydrogenase type 1 (\(11\beta\)-HSD1) inhibitor UE2343 (Xanamem™)
PET data shows full target engagement in the brain at low doses

Previous enzyme inhibitors\(^1\) have not achieved adequate brain concentrations

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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.

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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.
### Actinogen
**Oral Xanamem**
- Safely targets **brain tissue cortisol**
- 2 trials: improved attention & working memory
- 1 trial: trends to reduce AD progression, improve cognition
- Low drug interaction potential – good combination candidate

### Eisai-Biogen
i.v. infusion of lecanemab
- Approved on ability to reduce **brain amyloid**
- Potential to cause brain swelling and bleeding
- 2 trials reduced progression modestly
- Will need to be combined with other therapies

### Lilly
i.v. infusion of donanemab
- Full approval expected ~8 months, reduces **brain amyloid**
- Potential to cause brain swelling and bleeding
- 2 trials reduced progression modestly
- Will need to be combined with other therapies

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1 Companies claiming efficacy based on uncontrolled data, biomarkers or imaging not included in this comparison

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Newer anti-amyloid antibodies shown to slow but not halt progression of AD

Lecanemab is an anti-amyloid antibody given as an intravenous infusion every 2 weeks and largely clears brain of amyloid by 12 months, accelerated approval given by the US FDA based the ability of the drug to clear amyloid, full approval pending. Used (CDR-SB) with an effect size reported of 0.4-0.45 points at 18 months; Leqembi USPI & van Dyck et al. 2022; DOI: 10.1056/NEJMoa2212948 n=1795

Drugs targeting other mechanisms like Xanamem are needed
Xanamem clinical activity data

- Phase 1b (n=42)
- Phase 1b (n=107)
- Phase 2a (n=185)
- Phase 2a-pTau (n=34)
Attention/Working Memory improved by 4 weeks*

Cogstate computerized testing in cognitively normal older, 20 mg daily vs. placebo

* XanaHES trial, n = 30 Xanamem 20mg vs n = 12 Placebo; no treatment effects on three other tests of episodic memory (Actinogen data on file)
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)

![Graph showing change in CDR-SB units from Baseline to Week 12 for Xanamem and Placebo groups.]

- Xanamem: Mean 0.6 units, Median 0.8 units, p = 0.09, Cohen's d = 0.4
- Placebo: Mean 0.36 units

**Difference vs. placebo**
- Mean 0.6 units
- Median 0.8 units
- p = 0.09
- Cohen's d = 0.4

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

June 2023
Cognitive composite scores suggest potential clinical benefit across dementia patient sub-types*

Positive trends in both high and low plasma pTau biomarker groups

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
Well-demonstrated, excellent safety profile

No emerging safety signals

<table>
<thead>
<tr>
<th>TEAE term ACW0002*</th>
<th>Xanamem (n=91)</th>
<th>Placebo (n=94)</th>
<th>Total (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5 (5.5%)</td>
<td>2 (2.1%)</td>
<td>7 (3.8%)</td>
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<tr>
<td>Dizziness</td>
<td>4 (4.4%)</td>
<td>3 (3.2%)</td>
<td>7 (3.8%)</td>
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<tr>
<td>Diarrhea</td>
<td>1 (1.1%)</td>
<td>4 (4.3%)</td>
<td>5 (2.7%)</td>
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<tr>
<td>Fatigue</td>
<td>3 (3.3%)</td>
<td>1 (1.1%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Nerve conduction abnormal</td>
<td>1 (1.1%)</td>
<td>3 (3.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (1.1%)</td>
<td>3 (3.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (2.2%)</td>
<td>0 (0.0%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

* TEAEs reported by more than one patient in any group in the largest clinical study to date

✓ No treatment-related Serious Adverse Events in clinical program

Xanamem AD & Depression programs

Building on three independent Phase 1 and 2 studies showing safety and procognitive activity

Prior Phase 1 & 2a studies
Safety, cognition, clinical activity demonstrated (n~300 patients)

Phase 2b (n=330)
Alzheimer’s Disease (AD)
Interim 24/25, final results H225

Phase 2a (n=160)
Cognitive Impairment in Depressive Disorder (CIDD)
Final results H124

Phase 3
Alzheimer’s Disease with focus on cognitive enhancement

Phase 3
Cognitive Impairment in Depression

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Upcoming catalysts

2023
- Phase 2b trial in AD to commence
- Results of FDA End-of-Phase 2, EMA, UK regulatory interactions
- pTau Phase 2a and Phase 1b peer-reviewed publications
- AAIC and CTAD (AD) presentations

2024
- Depression Phase 2a trial results H1
- Phase 2b AD interim analysis late H2 / early 2025

2025
- Commence Depression Phase 3
- Phase 2b AD results H2
Summary

Xanamem

• Oral treatment with rapid onset of clinical activity
• Cortisol target validation from cognitive benefit shown in multiple clinical trials
• Encouraging safety profile suited to mono- or combination therapy
• Intellectual property protection including composition of matter

Alzheimer’s Disease

• Fully simulated Phase 2b design in mild AD patients suggests large clinical effect
• Interim results in late 2024/2025, final results H2 2025

Depression-associated Cognitive Impairment

• Phase 2a proof-of-concept trial with results H1 2024
Appendix
Phase 2b trial in Alzheimer’s Disease
Matching patients and endpoints used in the positive Ph 2a analysis

Key inclusion/exclusion criteria
- Clinical diagnosis of mild to moderate dementia due to AD (NIA-AA, MMSE 18-26)
- Blood p-tau181 to confirm progressive AD diagnosis
- Cognitive impairment test

Primary Endpoints
- Cognitive Test Battery (cognitive measures)

Key Secondary Endpoints
- CDR-SB (functional measure)
- Amsterdam Activity of Daily Living scale
- Executive Function & Episodic Memory Function Composites
- Care Giver questionnaire / Patient Global Improvement

Key Implementation Features
- Global trial sites including US, AU, Asia, EU and other
- Actinogen “hands-on” operational model
- FPI H2 CY23
- Interim analysis late CY24/25
- Final results CY25

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

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XanaCIDD proof-of-concept trial in Depression

Key inclusion/exclusion criteria
- Primary diagnosis of MDD
- Persistent depressive symptoms despite existing therapy
- Cognitive impairment relative to demographic norms

Primary Endpoints
- Cogstate Cognitive Test Battery Attentional Composite (attention and working memory)

Key Secondary Endpoints
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Executive Function Cognitive Composite
- Memory Function Cognitive Composite

Key Implementation Features
- Australia & UK trial sites
- Actinogen “hands-on” operational model
- First patient treated Dec 22
- Final Results H1 CY24

Double-blind, randomised treatment period (N=160)
Many studies support the association between elevated cortisol and AD development and progression\textsuperscript{1-9}

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

\textsuperscript{1.} Geerlings et al., 2015, Neurology 85: 1-8
\textsuperscript{2.} Lupien et al., 1998, Nat Neurosci 1:69–73
\textsuperscript{3.} Shorey et al. 2023 https://doi.org/10.1016/j.brainres.2022.148157
\textsuperscript{4.} Lehallier et al., 2016, JAMA Neurology 73(2), 203–212
\textsuperscript{5.} Ennis et al., 2017, Neurology 88(4):371–378
\textsuperscript{6.} Pietrzak et. al. 2017, Biol Psychiatry: Cognitive Neuroscience and Neuroimagery, 2:45–52
\textsuperscript{7.} Csernansky et al., 2006, Am J Psychiatry 163:2164–2169
\textsuperscript{8.} Popp et al., 2015, Neurobiol Aging 36:601–607
\textsuperscript{9.} Peskind et al. 2001 Neurology 56(8):1094–8
\textsuperscript{10.} van Dyck et al. N Engl J Med 2023; 388:9-2
Methods for double-blind, prospective assessment of biomarker-positive mild AD patients in Phase 2a¹

A simulation of the Phase 2b XanaMIA trial

Phase 2a trial (XanADu²)
- 185 people with mild AD treated for 12 weeks with 10 mg or placebo

72 patients with stored blood samples
- Blinded laboratory and company staff
- N=34 with elevated pTau

Measure disease biomarkers Week 0 & 12
- pTau181
- Amyloid 42/40 ratio
- GFAP
- Assess change over time

Assess efficacy trends on clinical endpoints
- Effects in biomarker-positive patients
- Endpoints including CDR-SB, executive function, ADAS-Cog
- Cohen’s d to measure clinical effect size

¹ Used a pre-specified protocol and statistical analysis plan, blinded laboratory and company personnel
Experienced Leadership and Management

Extensive drug development and commercial experience, two new key appointments in 2023

Experienced Board of Directors...

Dr. Geoff Brooke
Chairman
MBBS; MBA

• 30+ years experience in the healthcare investment industry
• Founder and MD of Medvest Inc and GBS Ventures, Chairman of Cynata Therapeutics, Board Member of Acrux

Dr. George Morstyn
Non-Executive Director
MBBS; PhD; FRACP; MAICD

• 25+ years experience in biotech investment and drug development
• Board member of Cancer Therapeutics and Symbio

Mr. Malcolm McComas
Non-Executive Director
BSc, LLB; FAICD; SF Fin

• 25+ years experience in the financial services industry
• Chairman of Pharmaxis and Fitzroy River Corporation

Dr. Nicki Vasquez
Non-Executive Director
PhD

• 25+ years experience in biopharmaceutical discovery research and development
• Chief Portfolio Strategy & Alliance Officer at Sutro Biopharma

...with a talented management team in place

Dr. Steven Gourlay
CEO & MD
MBBS; FRACP; PhD; MBA

• 30+ years experience in development of novel therapeutics
• Former founding CMO at US-based Principia Biopharma Inc

Jeff Carter
Chief Financial Officer
B. Fin Admin; M. App. Fin; CA

Tamara Miller
SVP Product Development
M.Med Sci; BSc; MSc; PMP; CPPM

Dana Hilt
Chief Medical Officer
MD

Cheryl Townsend
VP Clinical Operations
RN, M Health Law

Dr Christian Toouli
Head of Business Development
PhD; GAICD

See full team and bios at: https://actinogen.com.au/about-us/

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Preeminent global thought-leaders in clinical trials for assessment of cognition

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- Chartered psychologist with two PhDs and author/co-author of more than 80 books and scientific articles
- Principal Consultant at Metis Cognition, which advises on selection and integration of cognitive testing into therapeutic development programs

Dr Dana C. Hilt (CMO)
- 25+ years of drug development experience, primarily of Central Nervous System (CNS) drugs
- Deep experience in Phases 1 to 4 drug development
- CMO at Frequency Therapeutics and has held senior management positions as Chief Medical Officer at various pharmaceutical companies

Dr Christina Kurre Olsen
ORPHA ZYME
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- Strong hands-on knowledge across drug development value chain and a passion for cognition
- Medical Director at Orphazyme A/S

Prof. Paul Maruff
Cogstate
- Chief Innovation Officer at Cogstate Ltd
- Professor in Neuroscience at the Florey Institute of Neuroscience and in Psychology Monash University, Melbourne Australia
- Senior management committee of the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of Alzheimer’s Disease
- Involved in the development and approval of 13 new drugs that affect cognition including most recently esketamine for treatment resistant depression

A/Prof Christopher Chen
- Senior Clinician-Scientist, Associate Professor at the Departments of Pharmacology and Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, and Director of the Memory Aging and Cognition Centre, National University Healthcare System.
- Major research and clinical interests are in neuroimaging, molecular biology and treatment of stroke and dementia.
- President of the Asian Society Against Dementia, Secretary-Treasurer of the Asian & Oceanian Association of Neurology.

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International Scientific Advisory Boards

Preeminent thought-leader academics involved in the development of Xanamem

Alzheimer’s Disease Clinical Advisory Board

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- World-leading authority on dementia; senior investigator on 30+ drug trials
- Chair of the Scottish Dementia Research Consortium; Professor of the Psychiatry of Ageing; Director of the Centre for Dementia Prevention (University of Edinburgh)

Prof. Colin Masters AO
- 35+ years research on Alzheimer’s Disease and other neurodegenerative diseases
- Laureate Professor of Dementia Research and Head, Neurodegeneration Division at The Florey Institute (UniMelb)

Prof. Jeffrey Cummings
- World-renowned Alzheimer’s researcher and leader of clinical trials
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- Recognised for his work through various awards

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- Senior VP at the university of Edinburgh; Chaired Panels for MRC, Innovate UK and Wellcome Trust
- MBBS UCL, PhD (London)

Prof. Brian Walker
- 20+ years research in the area of disease
- Extensive experience advising for pharmaceutical R&D
- Pro Vice Chancellor for Research Strategy & Resources at Newcastle University, UK

Prof. Scott Webster
- Chair of Medicines at the Centre of Cardiovascular Science, University of Edinburgh
- Former positions across both biotech and academia
- Founder and Chief Scientific Officer at Kynos Therapeutics

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