## ASX ANNOUNCEMENT

# Actinogen CMO presents academic poster at Alzheimer's Association International Conference in Philadelphia

**Sydney, 29 July 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company")** is pleased to announce that its Chief Medical Officer, Dr Dana Hilt MD is presenting an academic poster at the Alzheimer's Association International Conference (AAIC) today in Philadelphia, USA. AAIC is a global forum to advance dementia science.

The Actinogen academic poster is titled *Development of Xanamem, a specific inhibitor of 11β-HSD1, as a procognitive and disease modifying treatment for mild/moderate Alzheimer's disease. A pharmacodynamic and biomarker driven approach*. An image of the poster is attached to this announcement.

The presentation summarizes the comprehensive clinical pharmacology approach used by Actinogen integrating data from multiple clinical trials to determine the target dose range for Xanamem. Data types used in the analysis included blood and cerebrospinal fluid levels of Xanamem,® blood levels of the cortisol regulating hormone ACTH, PET nuclear imaging of the brain, functional cognitive testing and clinical trial evidence of reduced disease progression in patients with biomarker-positive mild Alzheimer's disease.

**Dr Dana C Hilt, Actinogen's Chief Medical Officer, said:**

*"Thanks to the extensive data pointing to an active target dose range of 5 to 10mg daily, we are confident that the current phase 2 clinical trials studying 10mg daily vs. placebo can generate the confirmatory data needed to progress into further pivotal trials and toward eventual regulatory approvals."*

**ENDS**


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***Announcement authorised by the Board of Directors of Actinogen Medical***

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## 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 cognition & depression trial** is a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 167 patients. Participants are evenly randomized to receive Xanamem 10 mg once daily or placebo, in some cases in addition to their existing antidepressant therapy, and effects on cognition and depression are assessed. Results are anticipated in the first half of August CY2024.

The **XanaMIA Phase 2b Alzheimer's disease trial** is a double-blind, 36-week treatment, placebo-controlled, parallel group design trial in 220 patients with mild to moderate AD and progressive disease, determined by clinical criteria and confirmed by an elevated level of the pTau181 protein biomarker in blood. Patients receive Xanamem 10 mg or placebo, once daily, and effects on cognition, function and progression of Alzheimer's disease are assessed. Thus, Xanamem is being assessed in this trial for its potential effects as a both a cognitive enhancer and a disease course modifier. Initial results from an interim analysis of the first 100 participants are anticipated in mid 2025.

## 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.**

# Development of Xanamem, a specific inhibitor of 11-βHSD1, as a procognitive and disease modifying treatment for mild/moderate Alzheimer's disease. A pharmacodynamic and biomarker driven approach

Paul Rolan[1,2], Jack Taylor[1], Jonathan Seckl[3], John Harrison[4,5,6], Christopher Li-Hsian Chen[7], Colm Farrell[8], Paul Maruff[9,10], Michael Woodward[11], Dana Hilt[1]

## Background

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol. Elevation of CNS cortisol has been associated with impaired cognition, neuroinflammation and neuronal death.

Xanamem is under clinical development as a pro-cognitive and disease modifying drug for Alzheimer's. One of the biggest challenges for development of CNS-targeted drugs, like Xanamem, is the selection of optimal dosage.

We describe Xanamem's clinical pharmacology, including the approach to dose selection and proof-of-concept studies. By combining conventional PK, PD, and tolerability studies with CNS PET occupancy data, and quantitative cognitive testing, dosage for Phase 2 programs can be determined with sufficient confidence.

## Methods

The clinical pharmacology analysis included plasma PK, endocrine measures, target occupancy PET imaging, and cognitive assessment evaluated over a daily dose range of 5 mg to 70 mg in 6 clinical trials.

- PK was summarized by a population PK model using data from 4 clinical trials.
- A PET imaging trial used the displacement of a 11C-TARACT tracer to measure target occupancy in the brain after 7 days of Xanamem therapy with doses of 5mg to 30mg daily in patients with AD and cognitively normal individuals.
- Detailed hormonal assessment of the hypothalamic-pituitary-adrenal axis (HPA) was conducted with doses of 10mg to 70mg daily.
- Computerized cognitive testing (Cogstate) with doses of 5mg to 20mg daily in healthy older participants for 6 and 12 weeks. The test battery included tests of attention, working memory, episodic memory, executive function.
- A prespecified, double-blind analysis was conducted using stored plasma. samples of 72 participants from the "XanADu" trial with clinically diagnosed AD. It explored clinical progression and potential efficacy of Xanamem in those with elevated levels of plasma pTau181.

## PET and quantitative cognitive testing guide dose selection

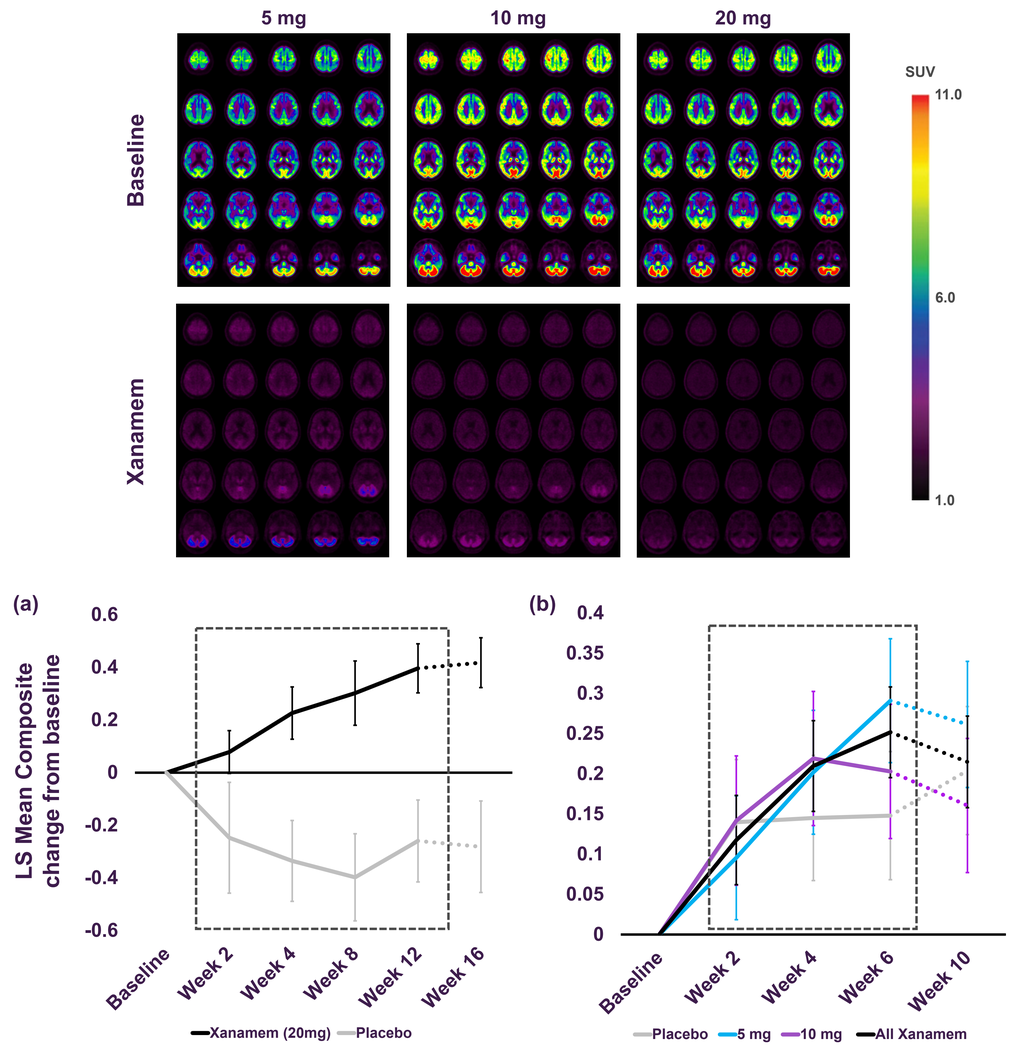


**Fig 4: Upper:** Composite 11C-TARACT images at baseline and with increasing Xanamem dosage. **Lower:** Least squares (LS) mean change from baseline in scores in the attention composite of a cognitive test battery in healthy older participants in trials **(a)** XanaHES and **(b)** XanaMIA-DR. Error bars represent ± SE. Boxes represent on-treatment visits.

## HPA axis peripheral PD

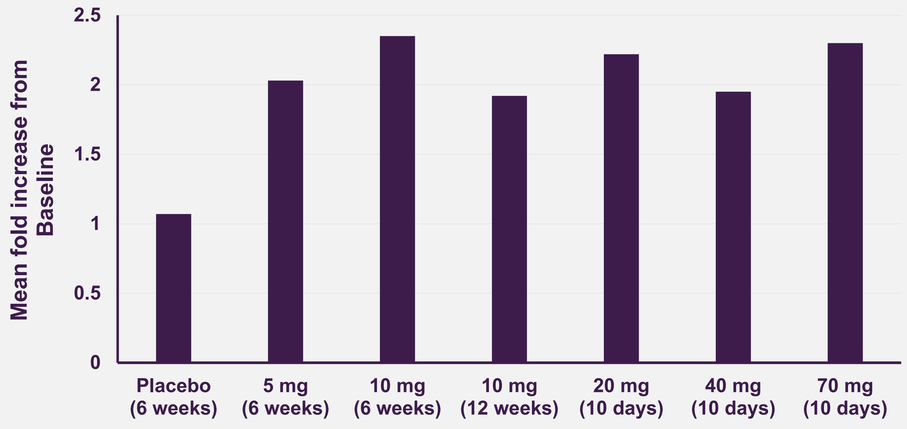


**Fig 1:** Mean fold increase from baseline in ACTH levels at end of treatment across multiple dose trials. ACTH levels were measured at end of treatment in trials for 10 days (20 mg, 40 mg, and 70 mg), 12 weeks (10 mg), and 6 weeks (placebo, 5 mg, and 10 mg).

## Plasma pTau181 predicts clinical progression

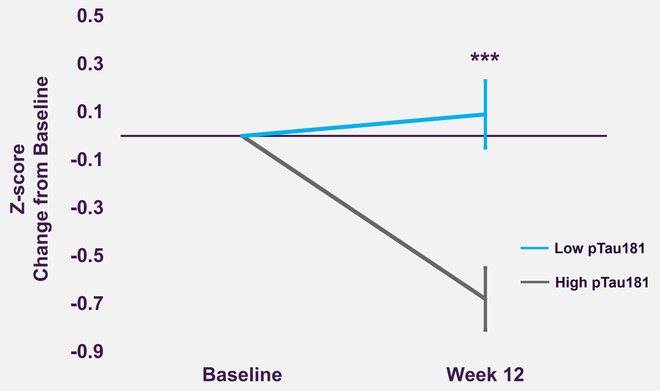


**Fig 2**: Elevated plasma pTau181 (> median of 6.7 pg/mL) predicts clinical progression over 12 weeks in the placebo group (n=34) on the CDR-SB (Cohen's d =0.63, ***p<0.001).

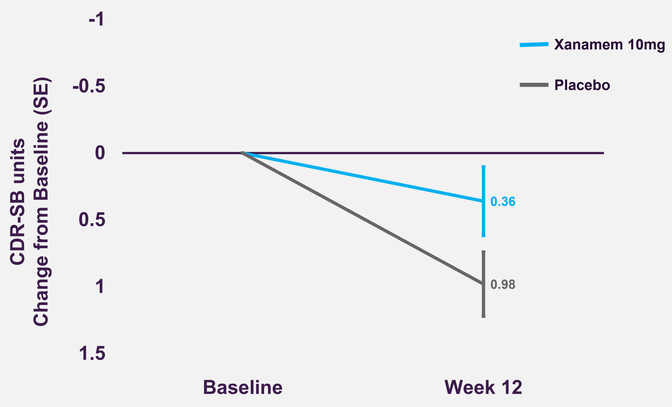


**Fig 3:** XanADu phase 2 biomarker trial: Least Squares (LS) mean change from baseline in CDR-SB in high p-tau181 subgroup demonstrating large clinical effect size vs placebo. Mean difference vs placebo 0.6 units (Cohen's d = 0.4) Error bars represent ± SE

## Conclusions

- **A series of clinical trials demonstrates the utility of quantitative cognitive testing and PET imaging to support conventional methods for optimal dose selection.**
- **Xanamem 10mg showed potential clinical and pro-cognitive treatment benefit in the high pTau181 group**
- **There is a high degree of confidence that ≤ 10mg daily will be pharmacologically active at the target in the CNS**
- **A larger Phase 2b trial in patients with early AD is now underway with a daily dose of 10 mg.**

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