ASX ANNOUNCEMENT

Actinogen CMO presents academic poster at Alzheimer's & Parkinson's diseases 2025 conference

Sydney, 2 April 2025. 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 *19th International Conference on Alzheimer's & Parkinson's Diseases and Related Neurological Disorders* (AD/PD™25) today and tomorrow in Vienna, Austria.

Dr Hilt's poster is titled *Plasma pTau181 predicts clinical progression in mild Alzheimer's Disease in a randomised controlled trial*.

A copy of the poster is attached to this announcement.

The poster details the promising benefits of Xanamem® treatment over 12 weeks in patients with elevated blood pTau181. It also reports that higher levels of blood pTau181 can identify patients with Alzheimer's disease (AD) who have more rapid clinical progression.

Taken together, these data inform the design of the new AD phase 2b/3 pivotal trial[1] using the pTau181 plasma biomarker for selection of patients and the choice of its key endpoints of CDR-SB,[2] cognition and activities of daily living.

The XanaMIA phase 2b/3 AD trial is currently recruiting participants in Australia and the USA to evaluate the benefits of 10mg Xanamem in mild and moderate AD patients with elevated plasma pTau181. An interim analysis is expected in Q4 2025 once around 100 patients have reached six months of treatment. Final results for all 220 patients are expected in H2 2026.

Dr Hilt commented:

"Actinogen is delighted to present a summary of the positive data from the previous phase 2a Alzheimer's disease (AD) trial which showed a large treatment benefit for Xanamem in biomarker-positive patients. It was a one of the first to show that the pTau blood biomarker is a highly effective method for selection of patients with a progressive form of early-stage AD. These data give us confidence in our patient selection criteria, duration of treatment and endpoints for the design of the latest Phase 2b/3 AD trial, which is currently enrolling patients in Australia and the USA."

ENDS

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[1] A "pivotal trial" refers to a late-stage trial that will produce a key dataset for a marketing approval application. It is customary to have two well-designed pivotal trials to achieve approval by regulators such as the FDA for common diseases such as AD and depression.

[2] CDR-SB is the *Clinical Dementia Rating – Sum of Boxes*, a measure of patient functional abilities and a composite of cognitive tests of mental abilities considered a measure of executive function. It is an FDA approved rating scale and almost universally used in modern AD trials

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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.

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.

Plasma pTau181 predicts clinical progression in mild Alzhiemer's Disease in a randomised controlled trial

Jack Taylor[1], Mark Jaros[2], John Harrison[3, 4], Christopher Chen[5], Dana Hilt[1]

[1] Actinogen Medical, Sydney, Australia; [2] Summit Analytical, [3] King's College, London, United Kingdom; [4] Alzheimercentrum, AUmc, Amsterdam, The Netherlands; [5] Memory Aging and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Background

Plasma pTau181 is a biomarker with high diagnostic accuracy, disease sensitivity, and correlation with pathologically proven Alzheimer's Disease (AD) as well as rate of future progression.

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), converts intracellular cortisone to cortisol and is highly expressed in brain regions such as the hippocampus. Chronically elevated plasma and CSF cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD). Thus, reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of AD.

The Phase 2a XanADu biomarker trial aimed to identify patients with elevated plasma pTau181 and explore the natural histories of their clinical progression and potential efficacy of Xanamem in these patients.

Methods

The XanADu biomarker trial used a prespecified, double-blind analysis. 72 participants with clinically diagnosed AD and available plasma samples from baseline and/or Week 12 of the "XanADu" phase 2a trial of Xanamem vs. placebo. The analysis prespecified plasma pTau181 > median to identify patients more likely to have progressive AD.

The objectives of the 12-week biomarker trial were to:

1. observe the natural history of disease progression in low (L; pTau181≤6.74 pg/mL) and high (H; pTau181 > 6.74 pg/mL) pTau181 groups over 12 weeks;
2. analyze the efficacy of Xanamem in the H pTau181 subgroup

Efficacy variables assessed included four clinical scales: ADAS-Cogv14, ADCOMS, CDR-SB, and MMSE. Endpoint scores were z-transformed to control for the varying scoring properties of each clinical scale. Other endpoints included measures cognitive performance and behaviour. Cohen's d (d) of ≥ 0.2 defined potential clinical significance.

Elevated plasma pTau181 predicts progressive AD

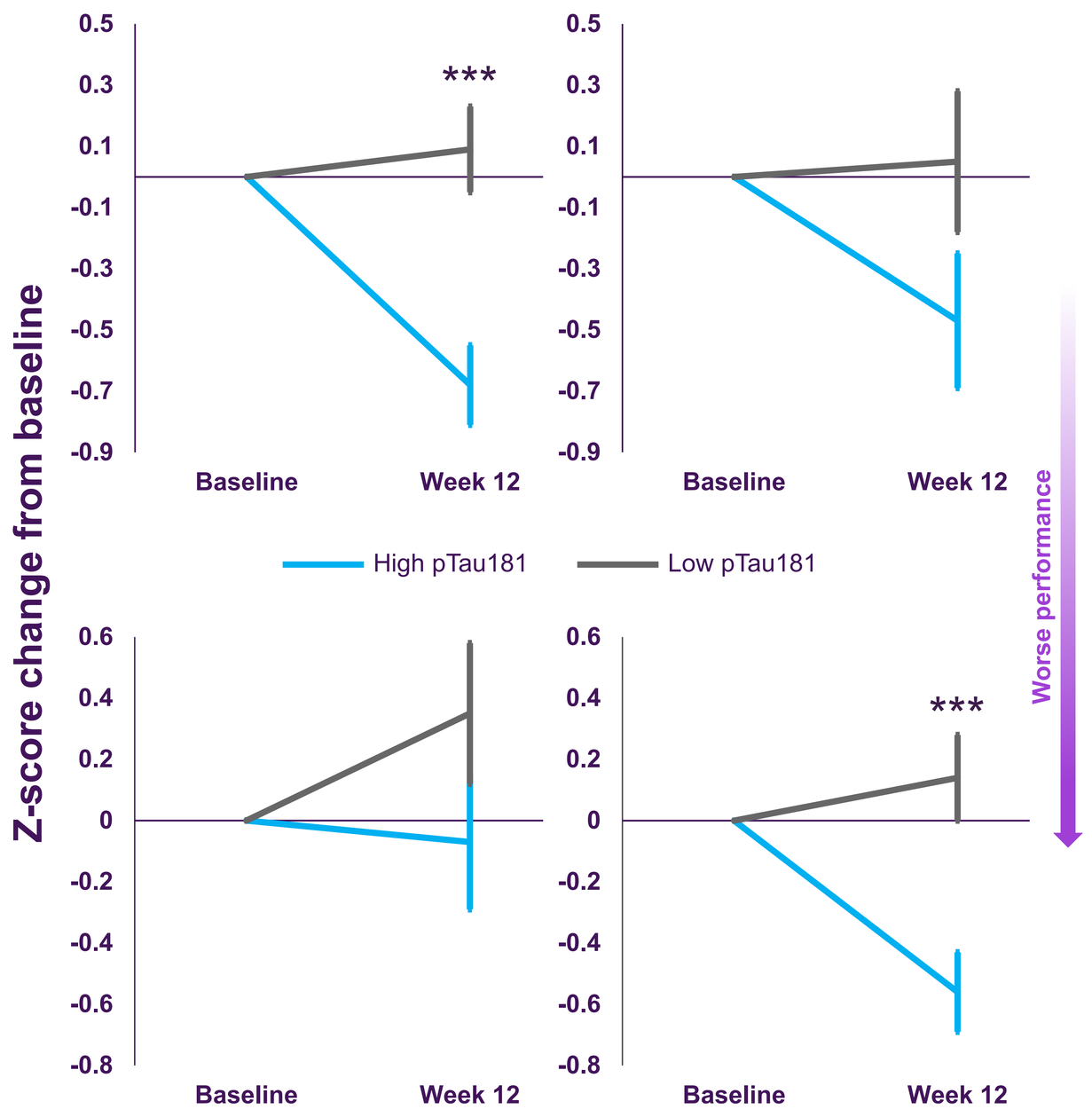

Fig 1: Elevated plasma pTau181 (> median of 6.7 pg/mL) predicts clinical progression over 12 weeks in the placebo group (n = 34). Z-score change from baseline scores (LS mean ± SE) were compared in the high pTau181 and the low pTau181 subgroup on the CDR-SB (*d* = 0.63, ***p < 0.001; Upper left), MMSE (*d* = 0.52, p = 0.12; Upper right), ADAS-Cog (*d* = 0.53, p = 0.19; lower left), and ADCOMS (*d* = 0.55, ***p < 0.001; lower right). The directionality of scores was reversed for the ADAS-Cog and the CDR-SB such that lower scores indicate worse clinical condition

Conclusions

- **Elevated plasma pTau181 may have utility for patient enrichment in future AD trials of patients with mild AD. Enrichment in this way may reduce sample size, cost, and duration of AD clinical trials**
- **Xanamem showed evidence of potentially clinically meaningful benefits in plasma pTau181-elevated patients that will be further explored.**
- **The XanaMIA Phase 2b/3 randomized controlled trial is currently recruiting in Australia and USA to evaluate the benefits of 10mg Xanamem in mild and moderate AD patients with elevated plasma pTau181 (NCT06125951).**

Xanamem slows clinical progression

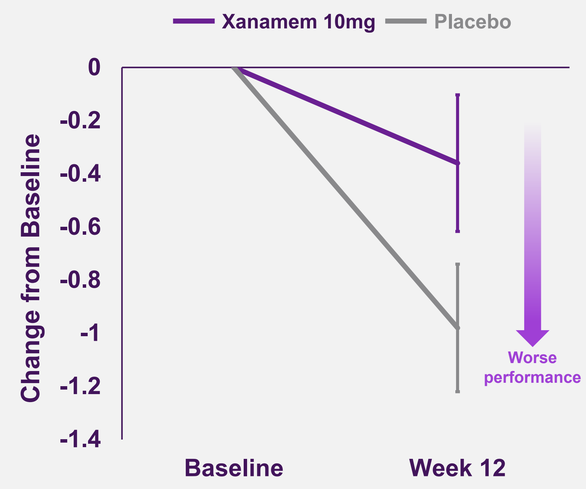

Fig 2: Least Squares (LS) mean change from baseline in CDR-SB in high plasma pTau181 subgroup demonstrating large clinical effect size vs placebo. Mean difference vs placebo 0.6 units (*d* = 0.41) Lower scores represent worse clinical condition. Error bars represent ± SE.

Xanamem has positive Executive function effects

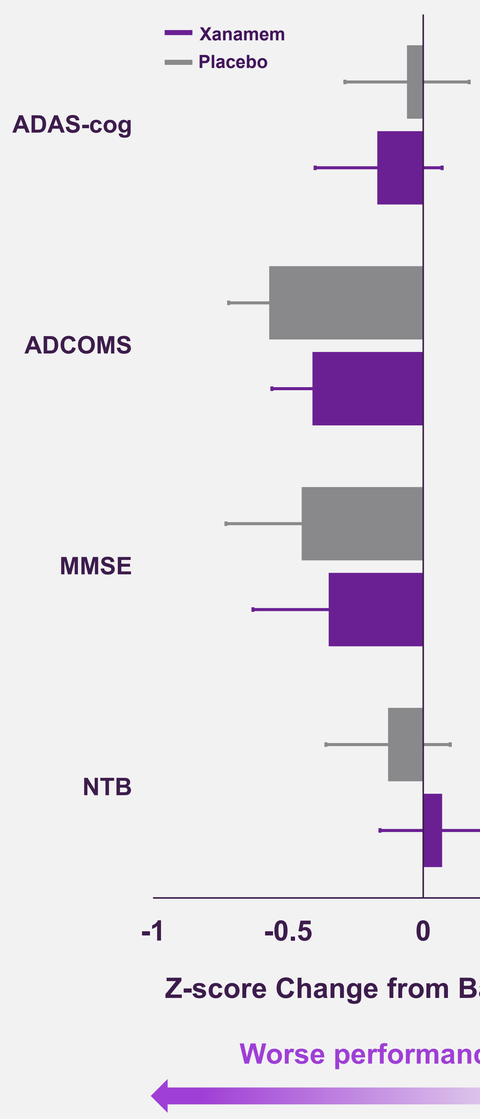

Fig 3: Z-score change from baseline on ADAS-Cog, ADCOMS, MMSE, and NTB-Exec in the prespecified high p-tau181 group. Error bars represent ± SE. p = ns

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