ASX ANNOUNCEMENT

Actinogen CMO presents poster at Clinical Trials on Alzheimer's Disease (CTAD) 2024 conference

Sydney, 31 October 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its Chief Medical Officer, Dr Dana Hilt, and Senior Clinical Scientist, Jack Taylor, will present an academic poster at the 17th annual CTAD conference in Madrid, Spain today.

The academic poster is titled: *Plasma pTau181 predicts clinical progression in mild Alzheimer's Disease in a randomized controlled trial*.

The poster presents data to show that elevated plasma pTau181 is useful in predicting clinical decline in patients with mild, clinically diagnosed Alzheimer's disease (AD). The analysis provides evidence that plasma pTau181 has utility as a patient enrichment methodology with the potential to reduce sample size, cost and duration of clinical trials in AD. This trial was the first to describe the natural history of a mild AD population with elevated plasma pTau181. It also demonstrated a large clinical effect of Xanamem® in those patients, as reported in the Journal of Alzheimer's Disease earlier this year (Click here to access JAD paper).

The Company's ongoing XanaMIA phase 2b/3 randomized, placebo-controlled trial is utilising plasma pTau181 to select patients with progressive AD and is recruiting participants in Australia and the USA. It is evaluating the ability of Xanamem 10 mg to slow progression of disease over a 36-week period of treatment. Initial results for the trial are expected in mid-2025 with final results due in mid-2026.

A copy of the poster is attached to this announcement.

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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.

Current Clinical Trials

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).

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 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 mid 2025 and final results mid 2026.

About Xanamem

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 designed to get into the brain after it is absorbed in the intestines upon swallowing.

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 more than 380 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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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.

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Plasma pTau181 predicts clinical progression in mild Alzheimer's Disease in a randomized controlled trial

Dana Hilt[1], Jack Taylor[1], Mark Jaros[2], Christopher Li-Hsian Chen[3], John Harrison[4,5,6]

Background

Evidence suggests plasma pTau181 is a useful biomarker in the staging of AD. Prospective longitudinal studies can elucidate the relationship between plasma pTau181 and clinical progression.

Xanamem® is a brain-penetrant inhibitor of 11β-HSD1, which acts to reduce brain cortisol. Chronically elevated cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD).

The Phase 2a XanADu biomarker trial identified patients with elevated plasma pTau181 and explored their clinical progression and potential efficacy of Xanamem.

Methods

A prespecified, double-blind analysis was conducted using stored plasma samples of 72 participants from the "XanADu" trial with clinically diagnosed AD. 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-Cog v14, ADCOMS, CDR-SB, and MMSE. Endpoint scores were z-transformed to control for the varying scoring properties of each clinical scale. Other endpoints included NPI, NTB-Exec, and RAVLT. A potentially clinically meaningful improvement was defined by a Cohen's d (*d*) statistic ≥ 0.2

Elevated plasma pTau181 predicts progressive AD

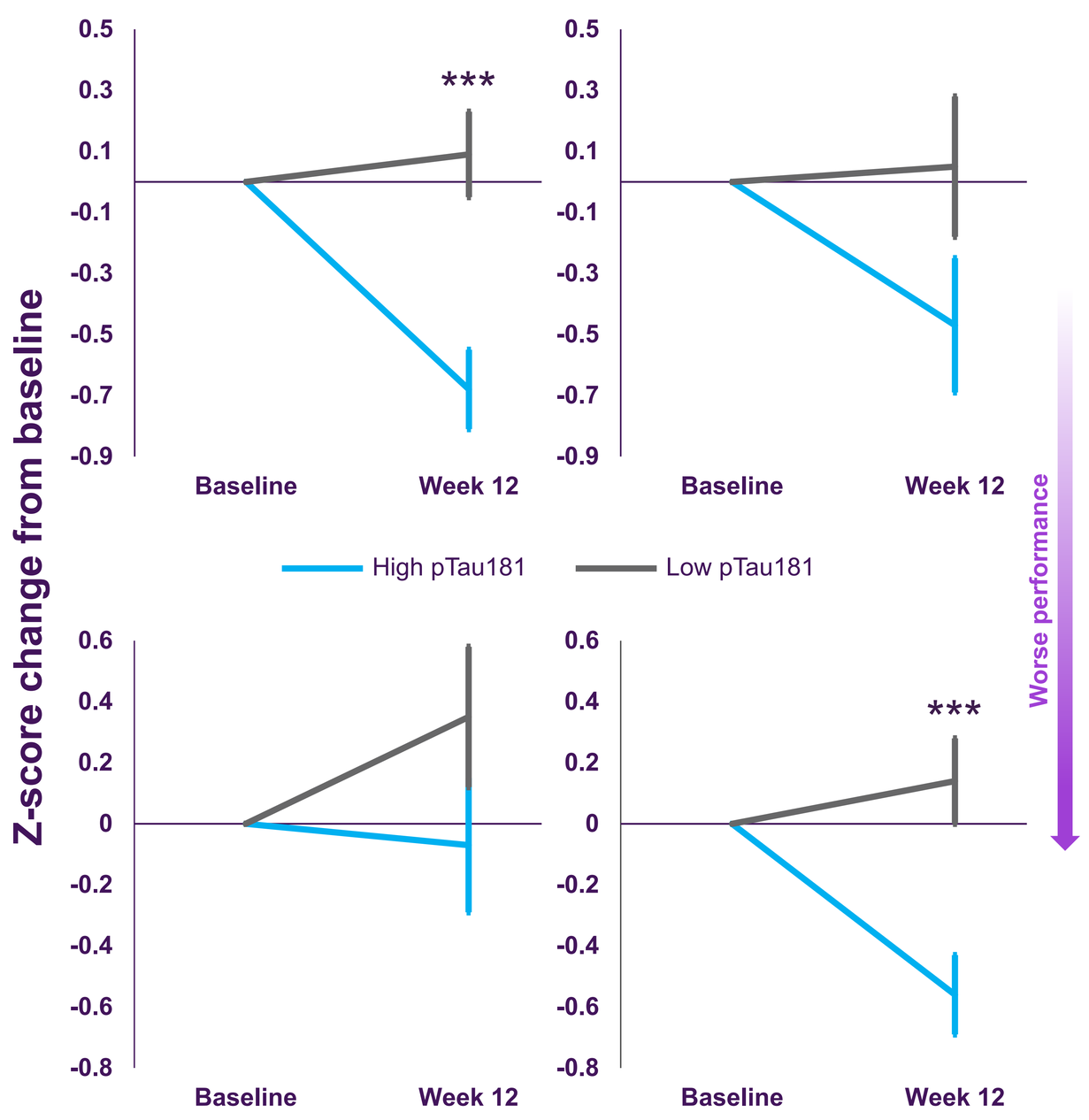

Fig 1: Elevated plasma pTau181 (> median of 6.7 pg/mL) predicts clinical progression over 12 weeks in the placebo group (n = 34). Z-score change from baseline scores (LS mean ± SE) were compared in the high pTau181 and the low pTau181 subgroup on the CDR-SB (*d* = 0.63, ***p < 0.001; Upper left), MMSE (*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 AD trials of patients with mild AD.**
- **Enrichment in this way may reduce sample size, cost, and duration of clinical trials.**
- **Xanamem showed evidence of potentially clinically meaningful benefits in these patients with elevated plasma pTau181.**
- **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 attenuates clinical progression

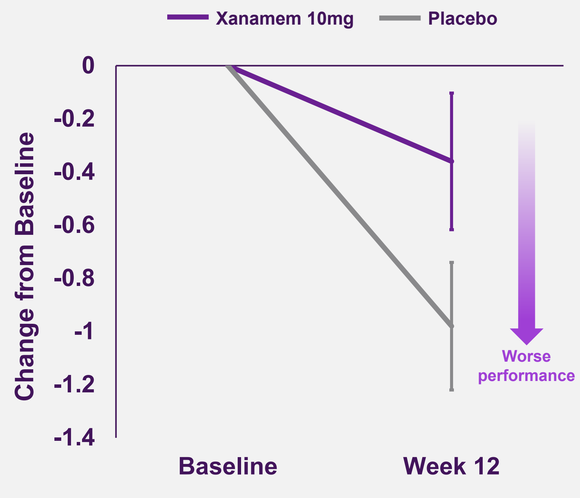

Fig 2: Least Squares (LS) mean change from baseline in CDR-SB in high plasma pTau181 subgroup demonstrating large clinical effect size vs placebo. Mean difference vs placebo 0.6 units (*d* = 0.41) Lower scores represent worse clinical condition. Error bars represent ± SE.

Xanamem has positive Executive function effects in AD

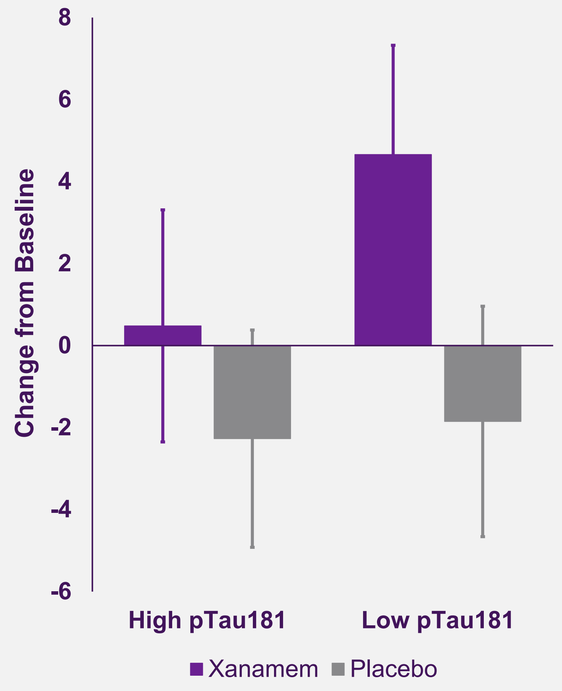

Fig 3: Xanamem vs placebo LS mean change from baseline score in both high and low pTau181 subgroups for a Neuropsychological test battery—Executive function. The NTB comprised the COWAT and CFT. In both High and Low pTau181 groups, improvements were seen favoring Xanamem (*d* = 0.26 and 0.34, respectively).

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