ASX ANNOUNCEMENT

Peer-reviewed clinical pharmacology manuscript for Xanamem (emestedastat) published in Clinical Pharmacology in Drug Development journal

Sydney, 6 February 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce the publication of its most recent peer-reviewed journal article entitled *Clinical Pharmacology and Approach to Dose Selection of Emestedastat, a Novel Tissue Cortisol Synthesis Inhibitor for the Treatment of Central Nervous System Disease* in Clinical Pharmacology in Drug Development, the journal associated with the American College of Clinical Pharmacology.

The review confirms the utility of the 10 mg daily dose of Xanamem being used in current clinical trials. From a drug development perspective, it demonstrates the value of using central pharmacodynamics (PD), including positron emission tomography (PET) and computerized cognitive testing, to supplement pharmacokinetic (PK) and endocrine-based PD for determining the target dose range for clinical efficacy testing.

Earlier PK modeling suggested that 20 mg daily would be optimal to maintain cerebrospinal fluid concentrations above the brain half maximal inhibitory concentration. However, subsequent PET scanning suggested that Xanamem doses of 10 mg or even 5 mg daily may be sufficient to adequately inhibit its 11β-HSD1 enzyme target. With once-daily doses of 5-20 mg in cognitively normal, older volunteers, a consistent pattern of pro-cognitive benefit, without dose-response, was seen as improvement in attention and working memory but not episodic memory. Taken in combination, this confirms that the target dose range for Xanamem therapeutic activity is ≤ 10 mg daily and not higher.

The journal article can be accessed here.

The Company's Chief Medical Officer, Dr Dana Hilt, said:

"The detailed and thorough drug development steps taken by Actinogen to confirm the target dose range of ≤ 10 mg daily demonstrate the value of careful and stepwise clinical pharmacology testing and use of measures of direct brain effects."

"Paired with the positive effects on depressive symptoms seen in the XanaCIDD phase 2a trial with a 10 mg dose, we have full confidence in the design and 10 mg dose being used in our current XanaMIA phase 2b/3 Alzheimer's trial."

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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).

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.

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