ASX ANNOUNCEMENT

Actinogen randomizes first US participant in XanaMIA phase 2b/3 Alzheimer's disease trial

Sydney, 9 December 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce the first participant randomized and treated on Friday in the United States in the XanaMIA phase 2b/3 clinical trial in patients with biomarker-positive mild to moderate Alzheimer's disease (AD).

The trial is designed to select 220 participants with a progressive clinical profile, determined by elevated levels of the blood biomarker pTau181. It measures the effects of a Xanamem® 10 mg daily dose versus placebo over a 36-week treatment period on multiple clinical endpoints of function and cognition.

With the opening of 10 new clinical sites in the US in addition to the existing 15 Australian sites, screening activities and patient enrolments are expected to accelerate to deliver interim results next year and final results in 2026. Enrolment updates will be routinely provided in the Company's quarterly reports.

Dr Steven Gourlay, Actinogen's CEO and MD, said:

"We are pleased to announce the first participant treated in the US in our phase 2b/3 trial in patients with Alzheimer's disease. The ten new sites in the US will bolster the already active recruitment from our Australian sites.

"Based on the encouraging safety and clinical activity seen in multiple prior trials of Xanamem in both AD and major depressive disorder (MDD), we are confident that the trial will confirm clinically and statistically meaningful results.

"Xanamem's unique ability to control brain cortisol levels as a once-a-day pill sets it apart from other approaches to AD treatment."

The primary endpoint for the XanaMIA AD trial is the Clinical Dementia Rating – Sum of Boxes scale (CDR-SB), a validated combined cognitive and functional measure, recognized by the FDA and used by many companies as a primary endpoint for regulatory approval. Previously, in an analysis of biomarker-positive patients with mild AD treated with Xanamem, a clinically significant mean benefit vs. placebo of 0.6 points was seen on the CDR-SB endpoint after 12 weeks treatment.

A variety of secondary endpoints will be used for the trial including the Amsterdam Activity of Daily Living scale, which measures the ability to perform everyday tasks and a cognitive test battery comprising seven different digital assessments common to the field.

An interim analysis is planned for Q3 2025 when approximately 100 patients reach 24 weeks of treatment, with final results anticipated in H2 2026.

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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 Q3 2025 and final results H2 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 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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