ASX ANNOUNCEMENT

Actinogen achieves agreement with the FDA in a Type C meeting written response on the manufacturing, clinical and nonclinical activities required for a future US marketing approval of Xanamem for Alzheimer's disease

Sydney, 15 September 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce the successful conduct of its scheduled Type C meeting (written response) on Alzheimer's disease (AD) with the US Food & Drug Administration (FDA).

Actinogen and the FDA reached a common understanding of the pathway to marketing approval in AD - meaning agreement on regulatory starting materials in drug substance synthesis, the design of one additional pivotal clinical trial and the limited number of ancillary clinical pharmacology trials and nonclinical studies required. Key understandings include the:

1. 'Regulatory starting materials' for the commercial manufacturing of Xanamem® (emestedastat) drug substance
2. General design of the interim analysis for XanaMIA
3. Design of one additional, well-controlled, pivotal (phase 3) trial to support a positive XanaMIA pivotal trial
4. Single emestedastat dose design (10 mg vs placebo) for the planned pivotal Phase 3 trial
5. Number of people to be treated with Xanamem to be described in the New Drug Application (NDA) – that is, the makeup of the planned safety database consistent with FDA guidelines
6. Small number of ancillary clinical pharmacology trials to be conducted
7. Nonclinical studies required to further characterize the metabolism and excretion pathways of Xanamem.

The outcome reached at this meeting with the FDA's Neurology-I Division represents a major milestone for Actinogen as the Company prepares for the earliest possible NDA submission in the US and submissions to other global regulators. It provides important clarity for ongoing discussions with potential development and marketing partners.

A similar meeting for Alzheimer's disease (AD) will be held with European Medicines Agency in 2026 and subsequently with the UK MHRA[1] and other regulators. Actinogen's FDA agreement is consistent with the desire of regulators worldwide to find safer and more effective therapies for AD, given the limited effectiveness of currently available treatments.

The Company can now confidently move forward following agreement from the FDA on the planned program.

Dr Steven Gourlay, the Company's CEO and MD, said:

"We are pleased with the clear guidance from the FDA that confirms our plans for streamlined development of Xanamem in Alzheimer's disease. Importantly, the Agency agreed with our approach for only one additional, pivotal trial using a single 10 mg Xanamem dose design vs. placebo to support a marketing application for Alzheimer's in the US."

® Xanamem is a registered trademark of Actinogen Medical Limited
[1] The UK MHRA is the United Kingdom Medicines and Healthcare products Regulatory Agency

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Announcement authorised by the Disclosure Committee of Actinogen Medical Limited

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 are anticipated in January 2026 and final results Q4 2026.

The XanaMIA-DUR Alzheimer's disease open-label extension trial is an open-label trial of up to 24 months where all participants will receive active Xanamem 10 mg once daily. The trial will evaluate safety and a limited number of efficacy endpoints such as the CDR-SB. The trial will commence in Q1 2026 and be open to all former and current participants in the XanaMIA Phase 2b/3 trial.

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. To view Xanamem's two-minute Mechanism of Action video, click here.

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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