ASX ANNOUNCEMENT

Actinogen presents academic poster demonstrating clinical validation of Xanamem® activity in the brain at the Alzheimer's Association International Conference in Toronto

Sydney, 28 July 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its Chief Medical Officer, Dr Dana Hilt MD and Senior Clinical Scientist, Dr Jack Taylor, will be presenting an academic poster at the Alzheimer's Association International Conference (AAIC 2025) today in Toronto, Canada. AAIC is the largest international conference on dementia research and a global forum for distinguished researchers, clinicians and dementia professionals to advance dementia science.

The Actinogen poster is titled *Validating the cortisol hypothesis: Xanamem demonstrates positive clinical effects by lowering CNS cortisol in MDD* and describes the clinically and statistically significant benefits of Xanamem in patients with moderately severe major depressive disorder (MDD). An image of the poster is attached to this announcement.

Xanamem (emestedastat) is an oral, selective 11β-HSD1 enzyme inhibitor designed to reduce production of the "stress hormone", cortisol, in key areas of the brain believed to be important for memory, critical thinking and mood. The positive results on depressive symptoms from the recent XanaCIDD phase 2a trial in patients with MDD validate Xanamem's enzyme target and functional importance.

These data further validate the hypothesis that controlling CNS tissue cortisol production with a daily dose of 10 mg of Xanamem can be beneficial for the treatment of brain diseases such as MDD and Alzheimer's disease.

In addition to the poster presentation, Actinogen will be exhibiting at AAIC 2025 with a sponsored booth (#643) open throughout the five main conference days. Chief Commercial Officer Mr. Andy Udell will be joining Dr Hilt and Dr Taylor at the event, where all three will be available at the booth to engage with clinicians, neurologists, geriatricians, and other healthcare leaders. The booth offers a valuable opportunity to discuss Actinogen's late-stage clinical program and explore the latest developments in dementia research, diagnosis, and care.

Dr Dana C Hilt, Actinogen's Chief Medical Officer, said:

"The positive results from the XanaCIDD depression trial of Xanamem validate Xanamem's mechanism of action and 10 mg daily dose. We are confident that the current phase 2b/3 XanaMIA trial studying 10mg daily vs. placebo in participants with progressive mild to moderate Alzheimer's disease can generate the confirmatory data needed to support future global regulatory approvals."

ENDS

® Xanamem is a registered trademark of Actinogen Medical Limited

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Announcement authorised by the Managing Director 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 triggered by the 100th participant reaching 24 weeks of treatment 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.

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.

Validating the cortisol hypothesis: Xanamem demonstrates positive clinical effects by lowering CNS cortisol in MDD

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

Background

Xanamem™ (Emestedastat) is an oral, selective 11β-HSD1 inhibitor designed to reduce cortisol production in the brain under development for the treatment of AD.

Clinical trials have demonstrated adequate target engagement by PET, improvements in cognitive performance in healthy older adults, and attenuation of decline in pTau181-elevated clinically diagnosed AD patients at doses of 10mg daily. The recent positive results from the XanaCIDD trial in Major Depressive Disorder (MDD) validate the target as well as the 10mg daily dose of Xanamem.

Methods

XanaCIDD was a Phase 2, proof-of-concept trial of 10 mg Xanamem daily in MDD patients with a current depressive episode (HamD > 17) and a cognitive deficit (DSST at least 0.5 SD below age and educational norms). Participants were randomized in a double-blind design 1:1 to Xanamem 10mg or placebo for 6 weeks (Week 6), with 4 weeks follow-up (Week 10).

The primary endpoint was a customized Cogstate test battery (CTB) comprising three tests of attention and working memory at Week 6. Secondary endpoints included assessment of depression with the MADRS and Participant Global Impression of Severity scores (PGI-S).

Clinical effect sizes were described by the Cohen's d statistic (Cd) with ≥ 0.2 considered to be clinically meaningful.

Xanamem displays clinically significant improvements in depression

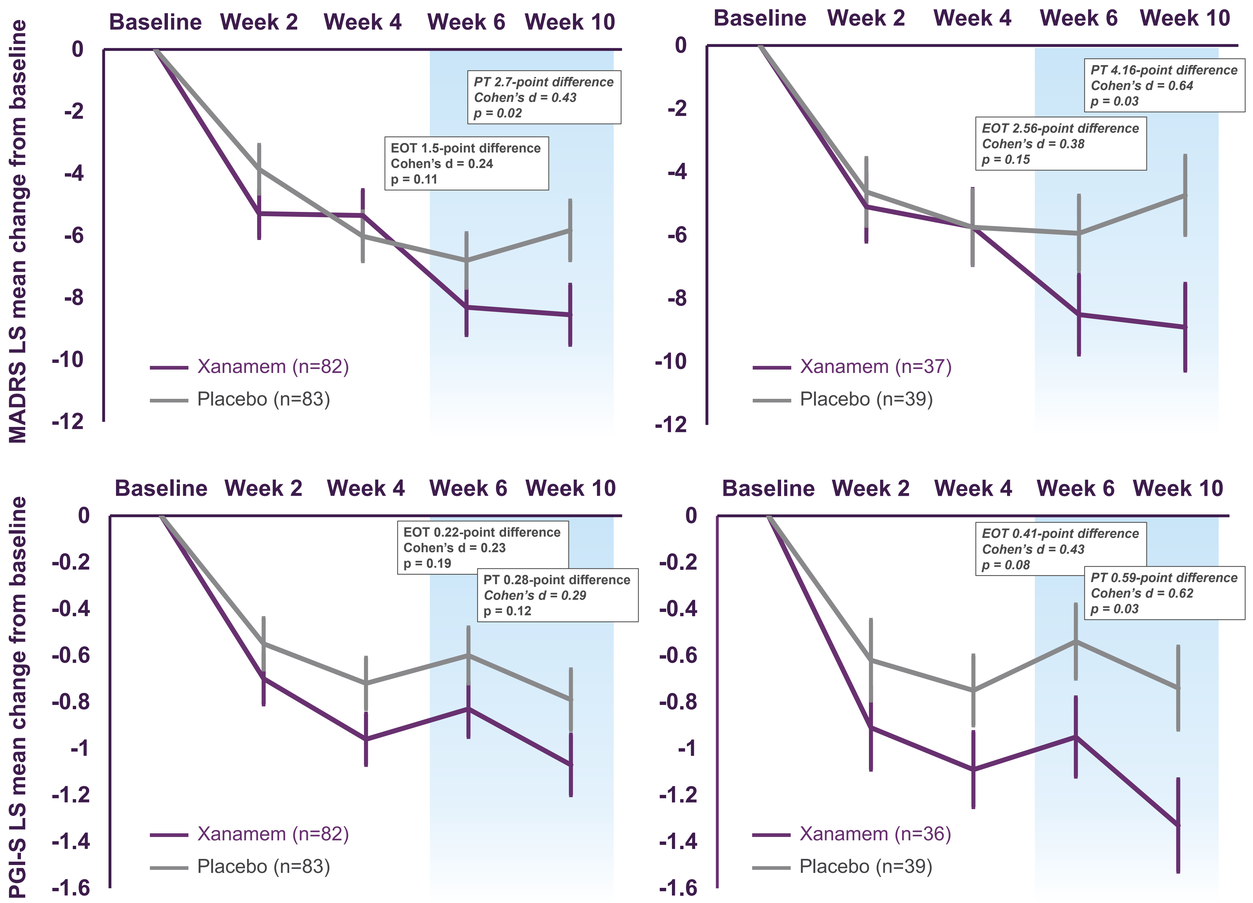

Fig 1: Change from baseline in MADRS (top panels) and PGI-S (bottom panels) scores in the mITT population (left panels) and in the subgroup of participants taking concurrent SSRI therapy (right panels). Blue shaded boxes indicate 4-week blinded post-treatment period. Error bars represent ± SE.

Improvements in cognition in both treatment groups

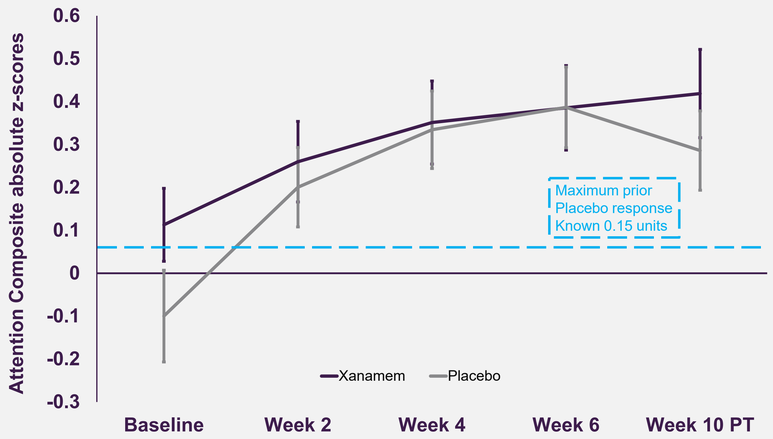

Fig 2: Performance on the Attention Composite in the Xanamem and placebo groups over 6 weeks treatment and 4 weeks follow up. The Attention Composite comprises the Detection, Identification, and One Back tests of the Cogstate battery. Individual tests were combined into z-scores with equal weighting. Higher z-scores in the Attention Composite indicate better performance. Error bars represent ±SE.

Conclusions

- **Xanamem displays a clinically meaningful MADRS benefit, and improvements in PGI-S compared to placebo**
- **Xanamem was safe and well tolerated**
- **Depression is a major risk factor for AD and often coexists with AD**
- **These data suggest validation of the hypothesis that controlling CNS tissue cortisol production may be beneficial for the treatment of AD as well as MDD**

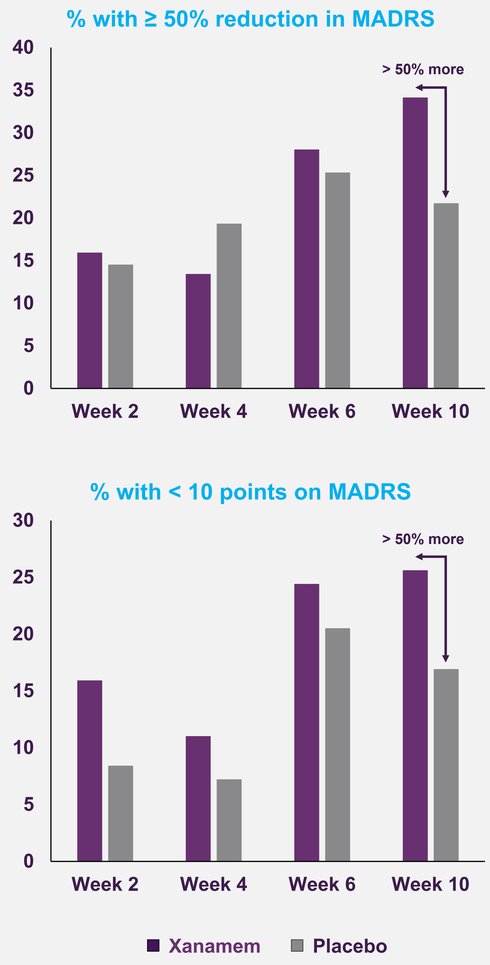

Fig 3: Increased rates of clinically meaningful improvements in depressive symptoms (upper panel) and remission (lower panel) observed in the Xanamem treatment group.

Table 2: Summary of Treatment-Emergent Adverse Effects

	Xanamem N = 82	Placebo N = 83
Any TEAE	70 (85.4%)	67 (80.7%)
TEAE related to trial drug	27 (32.9%)	24 (28.9%)
Serious adverse event	0	1 (1.2%)
Related TEAE discontinuation or interruption of drug	3 (3.7%)	1 (1.2%)
TEAEs with incidence ≥ 5% overall		
Headache	11 (13.4%)	16 (19.3%)
Fatigue	6 (7.3%)	5 (6.0%)
Nasopharyngitis	4 (4.9%)	6 (7.2%)
Upper respiratory tract infection	5 (6.1%)	5 (6.0%)

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