ASX ANNOUNCEMENT

Xanamem® (emestedastat) phase 2 depression proof-of-concept trial published in the British Journal of Psychiatry demonstrates meaningful anti-depressant activity in a difficult-to-treat population

Sydney, 20 July 2026. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that results from its proof-of-concept trial, entitled "*A phase 2 randomised, double-blind, placebo-controlled trial of emestedastat in patients with major depressive disorder (MDD) and cognitive impairment (CI)*" have just been published as a peer-reviewed article in the prestigious British Journal of Psychiatry.

The article can be accessed for free via this link: https://tinyurl.com/ckm63z63

The British Journal of Psychiatry is a leading international journal in behavioural and psychiatric medicine.

Key conclusions from the article:

1. Xanamem (emestedastat) may be a novel antidepressant and worthy of further investigation (further Xanamem trials in MDD will depend on future funding and partnership arrangements)
2. In contrast to the previously held belief that cognition improves along with depressive symptoms, there was no correlation of improvement in cognition with improvement in depression.

Other trial highlights:

- Unique trial design studied participants with both measurable cognitive impairment and depression to assess potential Xanamem benefit on both - in other aspects the trial was a standard phase 2a design for MDD using a six-week treatment period with a further four weeks of blinded follow up
- Enrolled 165 participants characterized as having "difficult-to-treat" MDD, with clinically significant residual MDD and measurable CI, most of whom were on another anti-depressant in addition to the trial treatment
- Anti-depressant benefit vs. placebo was maximal at Week 10 (2.7 MADRS[1] points, $p < 0.05$) during the blinded follow up phase. A similar benefit was seen in key subgroups including the 46% of patients who were on background SSRI[2] medication (4.2 MADRS points, $p < 0.05$)
- The observed "lag" in Xanamem benefit to improve depression scores is consistent with the known timeframe of onset and reversal of chronic cortisol-related side effects, e.g. when starting or stopping chronic prednisolone treatment
- A larger placebo group improvement in CI symptoms than previously reported was observed, with no evidence of Xanamem treatment benefit
- Xanamem was safe and well-tolerated.

® Xanamem is a registered trademark of Actinogen Medical Limited
[1] MADRS: Montgomery-Asberg Depression Rating Scale
[2] SSRI: Selective Serotonin Reuptake Inhibitors are the commonest class of anti-depressant in use

Professor Michael Berk AO, academic psychiatrist and co-author, said:

"These results are highly encouraging for the Xanamem 10 mg daily dose that is also being used in the Alzheimer's disease program. The trial demonstrates that the drug penetrates the brain and there is a signal of clinically meaningful activity to improve depression symptoms in a difficult-to-treat MDD patient population. There remains a significant unmet medical need for therapies such as Xanamem that have a novel mechanism of action and can be safely combined with existing depression treatments."

Dr Dana Hilt, the company's Chief Medical Officer, said:

"Depressive symptoms also occur frequently in patients with Alzheimer's disease. Anti-depressant activity may be a useful feature of Xanamem treatment for Alzheimer's disease and help to improve well-being and quality of life in these patients. The first pivotal phase 2b/3 trial of Xanamem in Alzheimer's disease is due to report topline results in November 2026 including initial evaluation of its effects on psychiatric symptoms."

View this announcement on our InvestorHub: https://investors.actinogen.com.au/link/rvnV4r

ENDS

	Investors	**Media**
Dr Steven Gourlay CEO & Managing Director P: +61 2 8964 7401 E. steven.gourlay@actinogen.com.au	**Michael Roberts** Investor Relations M: +61 423 866 231 E. michael.roberts@actinogen.com.au	**George Hazim** Media & Public Affairs Australia M: +61 417 516 262 E: georgehazim@mediaaffairs.com.au

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. It has also conducted a phase 2 trial in patients with cognitive impairment and depression and may 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 247 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 and is now closed to participant recruitment. It has passed an independent Data Monitoring Committee safety and efficacy futility review and final topline results are expected in November 2026.

The XanaMIA-OLE Alzheimer's disease open-label extension is an open-label phase of up to 25 months treatment where all participants will receive active Xanamem 10 mg once daily. The trial evaluates safety and a limited number of

efficacy endpoints such as the CDR-SB. The trial commenced in March 2026 and is 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 is to control elevated levels of cortisol (aka the "stress hormone") in the brain through the inhibition of the cortisol synthesis enzyme, 11β-HSD1, without affecting production of cortisol by the adrenal glands which is essential for the body's normal functioning. Xanamem is a first-in-class, once-a-day pill designed to deliver high levels of cortisol control in key areas of the brain related to Alzheimer's and other diseases such as the hippocampus and frontal cortex. To view Xanamem's two-minute Mechanism of Action animation, 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, further validating the cortisol control mechanism for the Xanamem 10 mg oral daily dose.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 500 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.