ASX ANNOUNCEMENT

Actinogen announces further positive results on depression in the XanCIDD phase 2a trial

Sydney, 26 August 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") announces that on-going analysis of the XanaCIDD phase 2a depression trial data found a consistent benefit of Xanamem® treatment on symptoms of depression in a variety of different endpoints. The consistent benefits observed support the conclusion that a 10 mg Xanamem dose is clinically active in controlling brain cortisol and has clinically significant anti-depressant activity.

Highlights of the updated results are:

- MADRS[1] depression score improvement confirmed ($p < 0.05$) and positive effects were observed in five of six pre-specified subgroups, indicating broad effect in the population studied
- Analysis of further data from a second, well-validated endpoint for clinical function in depression, called the Patient Global Impression of Severity (PGI-S)[2], reveals consistent Xanamem benefits that corroborate MADRS observations
- New MADRS responder analyses underscore MADRS benefit at Week 10 with a 50% higher rate of remission of depression[3]
- Maximal benefits on depression for all endpoints at Week 10, four weeks after the end of treatment, indicate a durable therapeutic effect resulting from controlling brain cortisol
- Xanamem's durable therapeutic effect is consistent with the known pharmacology of cortisol to modify gene expression and consequent protein synthesis and thus Xanamem may be controlling underlying "stress" biological processes for an extended period
- The XanaCIDD data indicate that Xanamem's novel mechanism has clinically significant activity for the treatment of Major Depressive Disorder (MDD) and we are exploring the path forward in MDD with regulators, global thought leaders and potential strategic partners.

Management will discuss the depression data and what the trial results reveal about Xanamem's cortisol control mechanism in a webinar at 11am (AEST) on Thursday, August 29. Click here to pre-register or simply register and attend on the day.

Presentation slides for the webinar will be released in an ASX announcement prior to the webinar.

[1] MADRS (The Montgomery-Asberg Depression Rating Scale) is a structured psychiatric interview evaluating MDD symptoms
[2] Patient Global Impression of (depression) Severity(PGI-S) is a self-assessment of depression severity on a 7-point scale
[3] Remission of depressive symptoms defined as MADRS < 10 points

Dr Steven Gourlay, Actinogen's CEO said:

"The data on depression are incredibly good news for Actinogen and for the many patients who may benefit from Xanamem in the future. This trial shows that Xanamem's mechanism of cortisol control in the brain has major clinical impact.

"This trial confirms our conclusion that a 10 mg daily dose of Xanamem is clinically active in the brain and has the potential to be an effective anti-depressant with a novel mechanism. While the anti-depressant market is competitive, Xanamem's safety profile stands it apart from the competitors and the durability of benefit seen is intriguing.

"Anti-depressant activity would also be a beneficial feature of Xanamem treatment for Alzheimer's disease, where depressive symptoms often occur. Our current primary objective remains enrolment of the XanaMIA Phase 2b trial designed to measure Xanamem's ability to slow or halt Alzheimer's disease progression over 36 weeks. Interim data are anticipated in mid 2025."

Details of the additional XanaCIDD trial findings from further exploration of secondary endpoints and subgroups are:

- Not only did MADRS depression score improvement in all 165 patients favour Xanamem over placebo ($p < 0.05$, Cd = 0.4 at Week 10)[4] but it did so in five of the six pre-specified subgroups (Cd ≥ 0.3 at multiple timepoints)
- Benefits on a newly analysed secondary endpoint called PGI-S showed consistent and clinically significant benefits for Xanamem (Cd = 0.3 at Week 10), corroborating the observations from the MADRS depression endpoint
- Analysis of depression "responders" (MADRS < 10 points) confirmed maximal Xanamem effect at Week 10 with 50% higher rate of remission of depression seen (Xanamem 26% vs. placebo 17%)
- Benefits on depression for all endpoints were maximal at Week 10, four weeks after finishing the 6-week course of treatment, pointing to a durable therapeutic effect resulting from controlling brain cortisol
- Xanamem's durable therapeutic effect is consistent with the known pharmacology of cortisol to modify gene expression and protein synthesis and thus Xanamem may be altering underlying biological "stress" processes in the brain for an extended period.

Details of the design of the XanaCIDD phase 2a trial are:

- Randomized, double-blind, exploratory, proof-of-concept, placebo-controlled, parallel group, six-week trial in 167 patients with persistent MDD and measurable cognitive impairment at baseline (165 patients had at least one efficacy assessment)
- Xanamem 10mg or placebo was added to the existing stable anti-depressant therapy (n = 134), or used as monotherapy in patients with a previous history of anti-depressant treatment (n = 31)
- The primary endpoint was the computerized Cogstate "Attention Composite" test battery, measuring attention and working memory
- The key secondary endpoint was the MADRS which is a structured psychiatric interview evaluating MDD symptoms. The MADRS is the commonly used endpoint for major MDD trials and regulatory approvals of anti-depressant medications
- The Patient Global Impression-Severity (PGI-S) is a patient-reported assessment of their assessment of depression severity on a 7-point scale
- The three subgroups pre-specified for efficacy analyses were patients with or without background anti-depressant therapy, patients with higher vs. lower levels of baseline depression, and patients with higher vs. lower levels of baseline cognitive dysfunction

[4] P values are 2-sided, Cd: Cohen's d statistic of effect size – > 0.25 - 0.3 regarded as clinically significant in depression

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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 cognition & depression trial** is a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 167 patients. Participants are evenly randomized to receive Xanamem 10 mg once daily or placebo, in some cases in addition to their existing antidepressant therapy, and effects on cognition and depression are assessed. Positive topline results on depression were announced 12 August CY2024.

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 effects on cognition, function and progression of Alzheimer's disease are assessed. Thus, Xanamem is being assessed in this trial for its potential effects as a both a cognitive enhancer and a disease course modifier. Initial results from an interim analysis of the first 100 participants are anticipated in mid 2025.

About Xanamem

Xanamem's novel mechanism of action is to block the production of cortisol inside cells through the inhibition of the 11β-HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease and excess cortisol is known to be toxic to brain cells. Cognitive impairment is also a feature in Depression and many other diseases. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 300 volunteers and patients, so far finding a statistically significant improvement in working memory and attention, compared with placebo, in healthy, older volunteers

in two consecutive trials and clinically significant improvements in functional and cognitive ability in patients with biomarker-positive mild AD. Previously, 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. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterize Xanamem's therapeutic potential.

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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