ASX ANNOUNCEMENT

Positive Xanamem® phase 2a biomarker trial published in the *Journal of Alzheimer's Disease* demonstrating potential Xanamem efficacy in patients with elevated blood pTau

Sydney, 26 June 2024. Actinogen Medical ASX:ACW ("ACW" or "the Company") is pleased to announce the peer-reviewed publication of its phase 2a biomarker trial entitled "Plasma pTau181 Predicts Clinical Progression In A Phase 2 Randomized Controlled Trial of the 11β-HSD1 Inhibitor Xanamem for Mild Alzheimer's Disease" in the 100th edition of the *Journal of Alzheimer's Disease*.

Highlights of the publication include:

- Participants comprised 72 patients from the previous XanADu phase 2a trial of mild Alzheimer's disease (AD) who had available stored plasma (blood) samples and gave informed consent for the new trial
- Patients with elevated pTau181 had much more rapid progression than patients with lower levels in four key clinical endpoints: ADCOMS ($p<0.001$), CDR-SB ($p<0.001$), MMSE ($p=0.12$) and ADAS-Cog14 ($p=0.19$)[1]
- In the 34 patients with elevated pTau181 a potentially large and clinically meaningful Xanamem treatment effect compared to placebo was seen in the CDR-SB (LS[2] mean difference 0.6 units, $p=0.09$) and positive trends were observed in a Neuropsychological Test Battery of cognition (LS mean difference 1.8 units, p=NS).

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

"To our knowledge Xanamem is the first drug of this class to have such compelling data. The previously published PET study highlighted just how effective Xanamem is at reaching its target enzyme in the brain at safe and well tolerated doses of 5 and 10 mg/day. No other inhibitor of 11β-HSD1 has ever demonstrated robust central nervous system (CNS) target engagement in this direct way.

"This new peer-reviewed publication reports that Xanamem 10 mg potentially slows AD progression in patients with high plasma pTau181. The other trends toward benefit on cognition are consistent with our two, prior phase 1b studies in older healthy volunteers which showed improved attention and working memory.

"Further data on cognition are anticipated when the XanaCIDD trial of cognitive impairment and major depressive disorder reports results next quarter. The XanaMIA phase 2b trial in 220 patients with mild to moderate AD is on-going."

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[1] ADCOMS: Alzheimer's Disease Composite Score; CDR-SB: Clinical Disease Rating Scale – Sum of Boxes; MMSE: Mini Mental State Examination; ADAS-Cog14: Alzheimer's Disease Assessment Scale – Cognition version 14

[2] Least squares

The original article can be accessed here.

Details of the trial, findings and implications

The biomarker trial was conducted as a stand-alone, prospective, double-blind trial using newly generated plasma biomarker data and clinical data on file from the XanADu phase 2a trial in patients with a clinical diagnosis of mild AD. The protocol and statistical analysis plan were pre-defined and data were analyzed in a blinded manner. No trial or laboratory personnel knew the treatment assignment of the participants until the final analysis results were generated.

The 72 participants in the trial had been treated with Xanamem 10mg or placebo once daily for 12 weeks. The panel of biomarkers was analyzed by a leading laboratory in Sweden, the Clinical Neurochemistry Laboratory, University of Gothenburg, who were "blinded" to treatment assignment, and included pTau181, amyloid beta1-40 and -42, glial fibrillary acidic protein, and neurofilament light.

The placebo group had 34 participants with analyzable plasma pTau181 levels. Those with elevated pTau181 (n=18) showed more rapid clinical progression than patients with lower levels (n=16) in four key clinical endpoints: ADCOMS (*d*=0.55, p<0.001), CDR-SB (*d*=0.63, p<0.001), MMSE (*d*=0.52, p=0.12) and ADAS-Cog14 (*d*=0.53, p=0.19).[3]

The Cohen's *d* statistics (the effect of high/low pTau181 as a proportion of the baseline standard deviation) were quite large and participants with low pTau generally did not worsen during the 12 week trial. This confirms that the original XanADu trial population contained a high proportion of non-progressive patients, many of whom may have had an alternative diagnosis to AD (there was no routine use of biomarker or imaging confirmation of the diagnosis of AD at the time the trial was designed).

The results from this trial are consistent with emerging data from other trials and recently updated international guidelines that consider elevated plasma pTau as a viable diagnostic option for AD. We believe plasma pTau is particularly useful as an alternative or adjunct to amyloid PET brain scans for the selection of patients with progressive disease in AD trials. The on-going XanaMIA phase 2b Alzheimer's disease trial is using elevated plasma pTau181 levels to select patients in whom a Xanamem treatment effect is more likely to be demonstrable over the 36-week treatment period.

The primary evaluation of the efficacy of Xanamem was conducted in the high pTau181 group (n=34) who were considered to have biomarker-confirmed AD. A large and potentially clinically meaningful Xanamem treatment effect compared to placebo was seen in the CDR-SB (LS mean difference 0.6 units, *d*=0.41, p=0.09). Positive trends were also seen in a Neuropsychological Test Battery of cognition (LS mean difference 1.8 units, *d*=0.26, p=NS) but not for other endpoints.

These results suggest that the potential cognitive enhancement and disease-slowing benefits of Xanamem may be sensitively detected with the CDR-SB endpoint, which is an 18-point score that rates both functional and cognitive abilities. Using the cognitive findings from this trial and prior trials showing benefit on attention and working memory, a cognitive composite has been designed for use in future Xanamem trials. This cognitive composite and the CDR-SB are key endpoints in the on-going XanaMIA phase 2b trial in participants with mild to moderate AD whose diagnosis will be confirmed by elevated pTau181 levels.

ENDS

[3] *d*: Cohen's *d* is a measure of effect size vs. placebo as a proportion of baseline standard deviation

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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. Results are due to be reported early in Q3 2024.

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. Interim results are due to be reported in mid 2025 with final results in 2026.

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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