ASX ANNOUNCEMENT

Actinogen presents academic poster at Alzheimer's and Parkinson's diseases 2024 conference

Sydney, 6 March 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its Chief Medical Officer, Dr Dana Hilt MD is presenting an academic poster at the *International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders* (ADPD™ 2024) today and tomorrow in Lisbon, Portugal.

A copy of the poster is attached to this announcement.

Dr Hilt has been invited to present Actinogen's drug trial data on Xanamem® as a poster presentation during the ADPD™ 2024 Congress. The presentation, titled *Design of a state-of-the-art Phase 2b trial to evaluate the efficacy of a specific inhibitor of 11β-HSD1, Xanamem®, in mild and moderate Alzheimer's Disease*, integrates the trials that have been conducted to date with Xanamem in both older normal volunteers and in patients with Alzheimer's disease (AD).

The poster details the utility of selecting patients with progressive AD using elevated levels of the pTau181 blood biomarker. It displays the positive cognition effects observed in normal volunteers and patients with AD and benefit observed on a commonly used clinical endpoint of function in AD trials called the CDR-SB.[1] Taken together, these data inform the design of the new AD Phase 2b trial using the pTau181 plasma biomarker for selection of patients and key endpoints of cognition and the CDR-SB.

The phase 2b trial has been activated in Australia with a plan to enrol the first 100 patients to an interim analysis expected to be announced in the first half of 2025. A total of 220 patients will be enrolled in the full trial.

Dr Hilt commented:

"Actinogen is excited to present a summary of the positive data from several trials and the design of the new Phase 2b Alzheimer's Disease (AD) trial, which is enrolling patients in Australia. The previous phase 2a AD trial was one of the first to show that the pTau blood biomarker is a highly effective method for selection of patients with a progressive form of early-stage AD. These data give us confidence in our patient selection criteria, duration of treatment and endpoints for the new trial."

The company's clear priority for the next 18 months is to deliver high quality results from its two clinical trials - the phase 2a Xanamem trial in 160 patients with depression, which will read out results in just a few months, and the phase 2b trial in 220 patients with Alzheimer's disease which will provide initial results in H1 2025.

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[1] CDR-SB is the *Clinical Dementia Rating – Sum of Boxes*, a measure of patient functional abilities and a composite of cognitive tests of mental abilities considered a measure of executive function. It is an FDA approved rating scale

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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 and Upcoming Clinical Trials

The **XanaCIDD Phase 2a depression trial** is a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 160 patients. Patients 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.

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.

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 350 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.

Disclaimer

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ACTINOGEN MEDICAL ENCOURAGES ALL CURRENT INVESTORS TO GO PAPERLESS BY REGISTERING THEIR DETAILS WITH THE DESIGNATED REGISTRY SERVICE PROVIDER, AUTOMIC GROUP.

Design of a state-of-the-art Phase 2b trial to evaluate the efficacy of a specific inhibitor of 11β-HSD1, Xanamem®, in mild and moderate Alzheimer's Disease

Dana Hilt[1], Jack Taylor[1], Tamara Miller[1], John Harrison[2, 3, 4] , Christopher Chen[5], Craig Ritchie[2]

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Background

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), converts intracellular cortisone to cortisol and is highly expressed in brain regions such as the hippocampus. Elevated plasma and CSF cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD). Thus, reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of AD.

Effects of Xanamem on cognition have been assessed in 3 independent placebo-controlled, double-blind trials.

The XanaHES (n= 42, 20 mg) and XanaMIA (n=105, 5 & 10 mg) Phase 1b trials used the computerised Cogstate system to assess cognition in normal, older volunteers. A pattern of clinically significant improvements was observed in attention and working memory compared to placebo in the Xanamem groups, with Cohen's d up to 1.27 (Fig. 1 & 2).

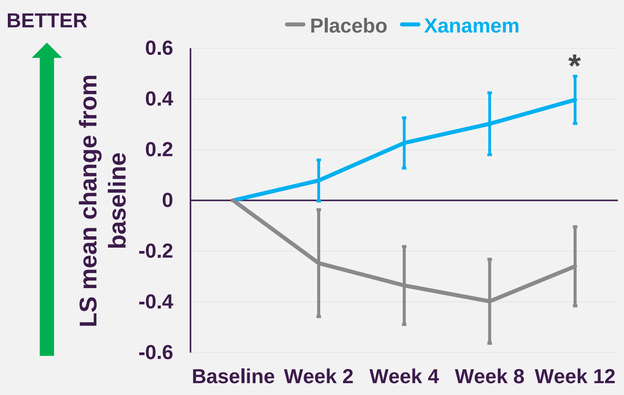


Fig 1: XanaHES: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE. * **Cohen's d = 1.27**.

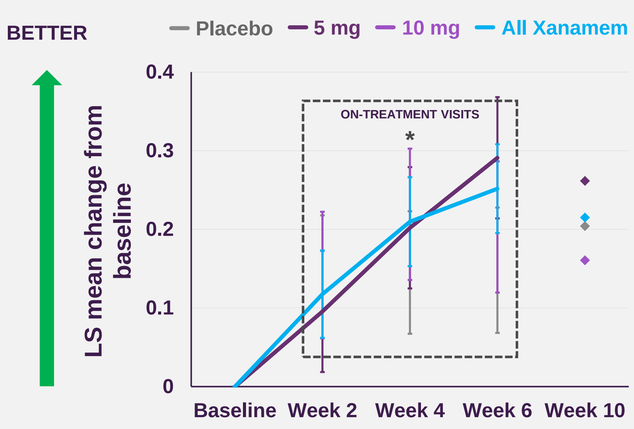


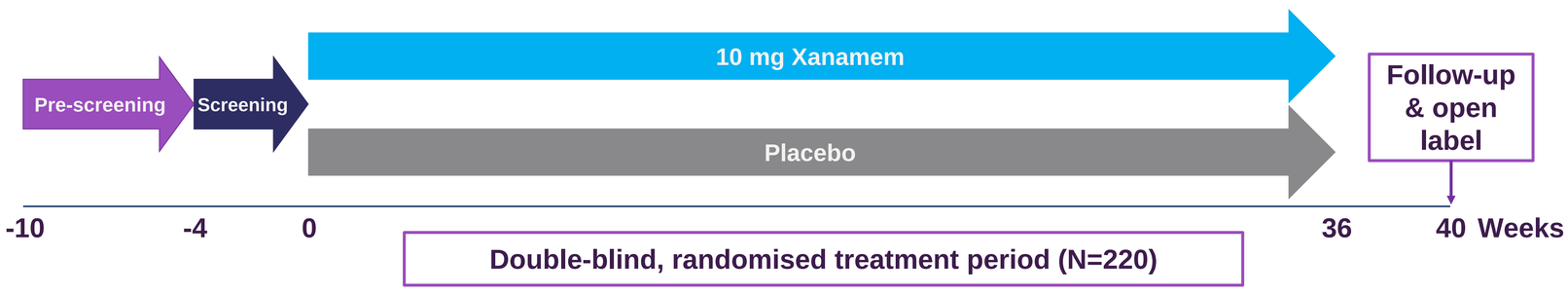
Fig 2: XanaMIA-DR: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE. * **p = 0.05, Cohen's d = 0.32**

The XanADu-X biomarker extension study (n=72, 10 mg) explored clinical and cognitive outcomes in subgroups (n=34 each) of the XanADu Phase 2a AD trial with higher (H) or lower (L) plasma p-tau181 in a new prospective analysis. Xanamem largely prevented clinical progression over 12 weeks, displaying a clinically significant benefit (Cohen's d of 0.41) on the CDR-SB compared to placebo in the H group (Fig. 3). In H group, improvements were also seen favouring Xanamem in tests of executive function (Cohen's d=0.34 and 0.26, respectively) and the MMSE (Cohen's d=0.32 and 0.16, respectively).

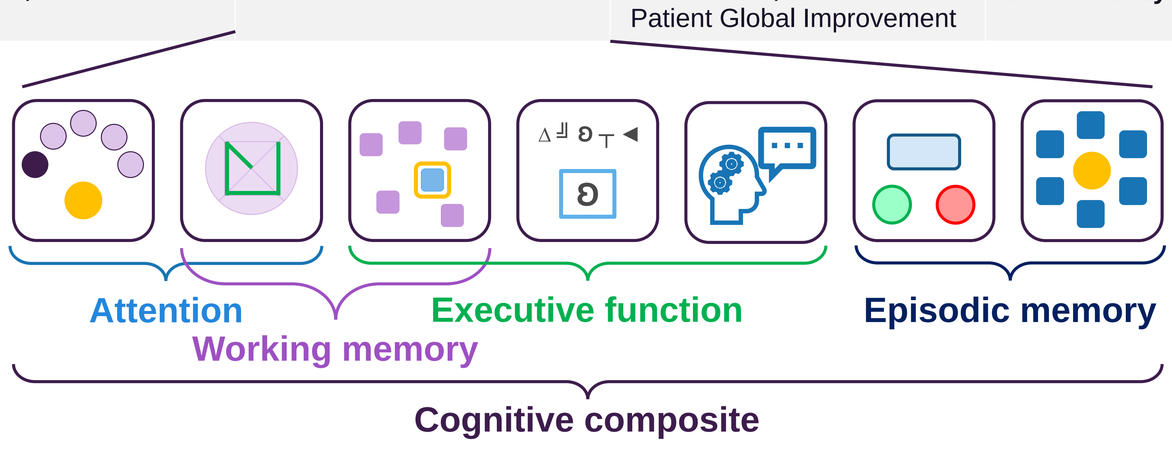
Objective

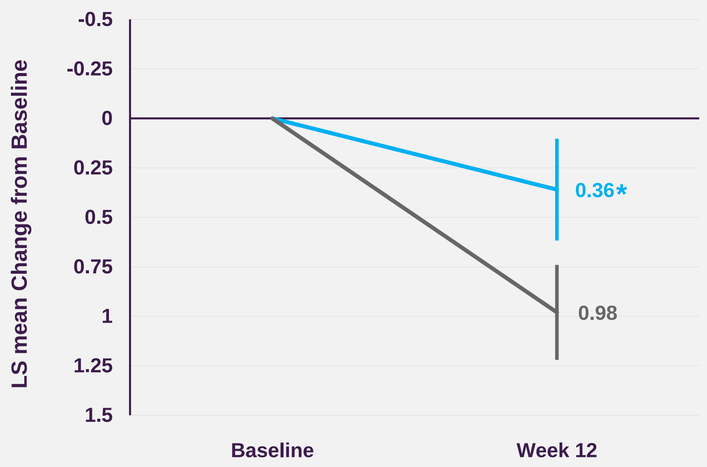
The XanaMIA aims to Phase 2b trial to evaluate the cognitive and clinical benefits of Xanamem

XanaMIA Phase 2b trial design



Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
• Clinical diagnosis of **mild to moderate dementia** due to AD (NIA-AA, MMSE 18-26) • Blood **p-tau181** to confirm progressive AD diagnosis • Cognitive impairment test	• **Cognitive Test Battery** (Global cognition composite)	• **CDR-SB** • **Amsterdam Activity of Daily Living** scale • Executive Function & Episodic Memory Function Composites • Care Giver questionnaire / Patient Global Improvement	• **No PET, MRI, or CSF** • **Global** trial sites including US, AU, Asia, EU and other • Actinogen "hands-on" operational model • **Interim analysis H1 CY25**





* Diff. vs. placebo: Cohen's d = 0.4, Mean 0.6 units, Median 0.8

Fig 3: XanADu phase 2 biomarker trial: Least Squares (LS) mean change from baseline in CDR-SB in high p-tau181 subgroup demonstrating large clinical effect size vs placebo. Error bars represent ± SE.

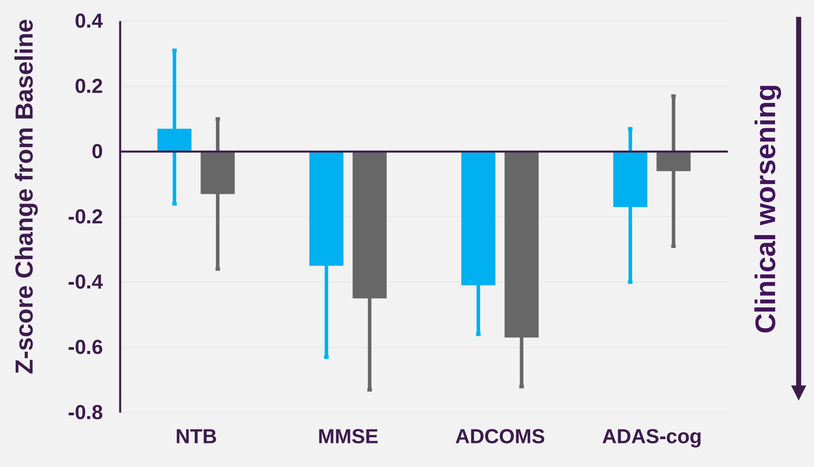


Fig 4: XanADu phase 2 biomarker trial: Z-score change from baseline on NTB, MMSE, ADCOMS, and ADAS-Cog in the prespecified high p-tau181 group. Error bars represent ± SE.

Conclusions

- **Xanamem displays activity in multiple domains of cognition including attention, working memory, and executive function with clinically meaningful effects in normal subjects and in patients with p-tau181-elevated mild AD.**
- **The XanaMIA Phase 2B trial is a robustly designed study using contemporary, treatment-sensitive endpoints, and patient enrichment strategies to demonstrate the procognitive and disease-course modifying benefits of Xanamem.**
- **The initial results of the XanaMIA Phase 2B trial are expected in H1 2025.**

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