ASX ANNOUNCEMENT

Actinogen presents academic poster at Australian Dementia Research Forum 2024 conference

Sydney, 3 June 2024. Actinogen Medical ASX:ACW ("ACW" or "the Company") is pleased to announce that its Clinical Scientist Dr Jack Taylor is presenting an academic poster at the *Australian Dementia Research Forum* (ADRF2024) on the Gold Coast, Australia from 3 to 5 June 2024.

The theme for ADRF2024 is ***Turning the Tide on Dementia***, with particular focus on exciting innovations in the field. The Forum is a meeting place for national and global experts to share the latest developments in dementia research, care and policy.

A copy of the poster is attached to this announcement.

The poster, entitled *Clinical pharmacology and development of Xanamem®, a tissue specific inhibitor of 11β- HSD1*, describes Xanamem's clinical pharmacology, including Actinogen's innovative approach to dose selection. The poster details how traditional pharmacokinetics and pharmacodynamics were paired with PET brain imaging and cognitive testing and other clinical data to confirm a target dose range of ≤ 10 mg daily.

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

"Dr Taylor's presentation summarizes the multiple streams of data supporting the selection of Xanamem doses of ≤ 10 mg for the treatment of cognitive impairment in a number of diseases. Via Inhibition of 11β-HSD1, the enzyme synthesizing cortisol in brain, low doses of Xanamem potentially improve cognition and slow disease progression in patients with AD.

To our knowledge Xanamem is the first drug of this class to have compelling data showing robust central nervous system (CNS) target engagement, and positive procognitive effects in three independent, placebo-controlled trials."

ENDS

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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 anticipated in early Q3 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.

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.

Clinical pharmacology and development of Xanamem, a tissue specific inhibitor of 11β-HSD1

Paul Rolan[1,2], Jack Taylor[1], Jonathan Seckl[3], John Harrison[4,5,6], Christopher Li-Hsian Chen[7], Colm Farrell[8], Paul Maruff[9,10], Michael Woodward[11], Dana Hilt[1]

Background

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol. Elevation of CNS cortisol has been associated with impaired cognition, neuroinflammation and neuronal death.

Xanamem is under clinical development as a pro-cognitive and disease modifying drug for Alzheimer's.
One of the biggest challenges for development of CNS-targeted drugs, like Xanamem, is the selection of optimal dosage.

We describe Xanamem's clinical pharmacology, including the approach to dose selection and proof-of-concept studies. By combining conventional PK, PD, and tolerability studies with CNS PET occupancy data, and quantitative cognitive testing, dosage for Phase 2 programs can be determined with sufficient confidence.

Methods

The clinical pharmacology analysis included plasma PK, endocrine, target occupancy PET imaging, and cognitive assessment evaluated over a daily dose range of 5 mg to 70 mg in 6 clinical trials.

- PK was summarized by a population PK model using data from 4 clinical trials.
- A PET imaging trial used the displacement of 11C-TARACT tracer to measure target occupancy in the brain after 7 days of Xanamem therapy with doses of 5mg to 30mg daily in patients with AD and cognitively normal individuals.
- Detailed hormonal assessment of the hypothalamic-pituitary-adrenal axis (HPA) was conducted with doses of 10mg to 70mg daily.
- Computerized cognitive testing (Cogstate) with doses of 5mg to 20mg daily in healthy older participants for 6 and 12 weeks. The test battery included tests of attention, working memory, episodic memory, executive function.

PET and quantitative cognitive testing guide dose selection

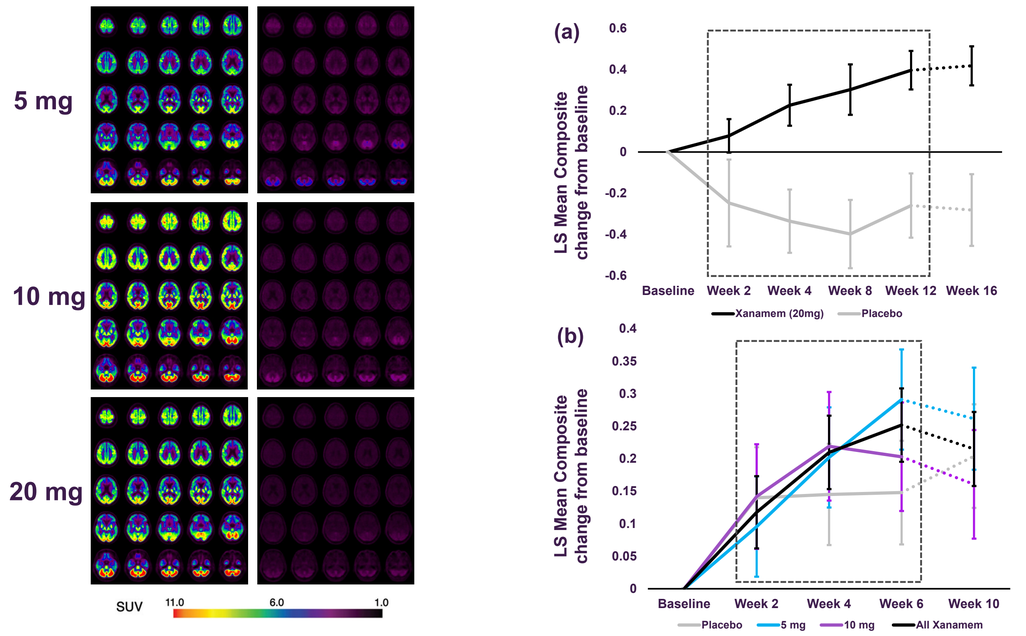

Fig 3: Left: Composite 11C-TARACT images at baseline (left) and with increasing Xanamem dosage (right). **Right:** Least squares (LS) mean change from baseline in scores in the attention composite of a cognitive test battery in healthy older participants in studies (a) XanaHES and (b) XanaMIA-DR. Error bars represent ± SE.

Population PK

Table 1: Population PK parameter estimates for the final population PK model

Model Parameters (Units)	Estimate	%RSE	Lower 95% CI	Upper 95% CI	Between-Participant Variability (CV%)
Structural Parameters					
CL/F ($L.h^{-1}$)	4.76	9.73	3.85	5.67	50.2
V/F (L)	64.3	4.70	58.4	70.2	33.0
k_a (h^{-1})	1.74	92.5	-1.42	4.90	51.5
ALAG (h)	0.900	38.1	0.228	1.57	75.8
Covariates					
WT on V/F	1.00	-	-	-	

Abbreviations: ALAG = absorption lag time; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; F = bioavailability; ka = absorption rate; RSE = relative standard error; V/F = apparent volume of distribution; WT = weight.

HPA axis peripheral PD

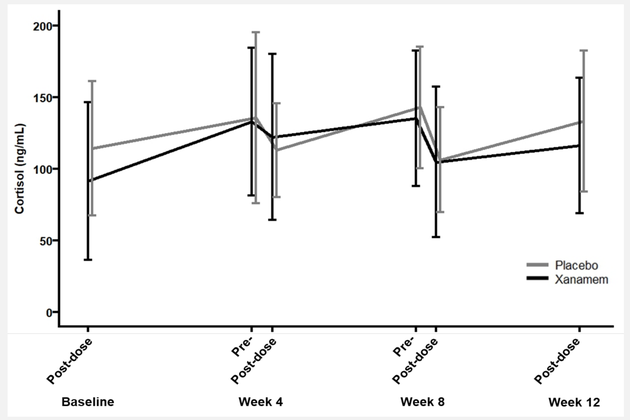

Fig 1: Mean cortisol level (ng/mL) and 95% confidence interval over time, pre- and 3 to 5 hours post-dose, for 10 mg Xanamem (blue line) and placebo (red line) in the XanADu study.

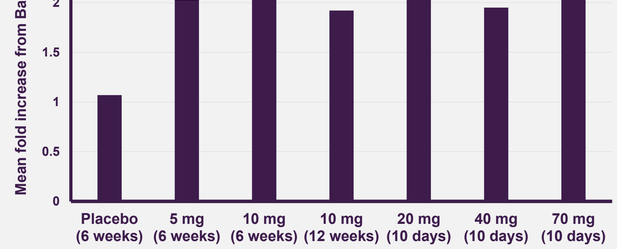

Fig 2: Mean fold increase from baseline in ACTH levels at end of treatment across multiple dose studies. ACTH levels were measured at end of treatment in trials for 10 days (20 mg, 40 mg, and 70 mg), 12 weeks (10 mg), and 6 weeks (placebo, 5 mg, and 10 mg).

Conclusions

- **A series of clinical trials demonstrates the utility of quantitative cognitive testing and PET imaging to support conventional methods for optimal dose selection.**
- **There is a high degree of confidence that ≤ 10mg daily will be pharmacologically active at the target in the CNS**
- **A larger Phase 2b trial in patients with early AD is now underway.**

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