ASX ANNOUNCEMENT

Actinogen CEO 2022 review and outlook

Sydney, 22 December 2022. Actinogen Medical Ltd ASX: ACW ("ACW" or "the Company") is pleased to attach a copy of a letter sent to shareholders today from the Company's CEO and MD, Dr Steven Gourlay.

This announcement is issued in accordance with Listing Rule 3.17.1.

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Investors

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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.

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 its capsule.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease, and Xanamem has shown the ability to enhance cognition in healthy, older volunteers. 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 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.

22 December 2022

Dear shareholders,

ACW 2022 review and outlook

Holiday greetings from all the team at Actinogen Medical.

It has certainly been a productive and pivotal year for ACW, and we are pleased to reflect on our successful clinical trial results for our small molecule drug, Xanamem® and a series of other significant milestones achieved in 2022.

Data from two positive clinical trials

In April, we achieved our first major milestone for the year of strongly positive results for safety and cognition from the **XanaMIA Part A Alzheimer's Disease (AD) trial.** The results confirmed Xanamem's ability to rapidly enhance attention and working memory (referred to as cognition – the ability to think and remember things) at 5 mg and 10 mg dose levels in healthy older volunteers, confirming the low dose range indicated by high target occupancy in our earlier human PET scan study. It also replicated the pattern of improvement in cognition seen in the prior **XanaHES** trial at a 20 mg dose.

In October, we achieved our second major milestone of positive results in the **Phase 2a AD clinical biomarker study.** By demonstrating a strong clinical effect on an FDA-approved measure in patients with mild AD selected by a blood test for a protein called pTau181, we successfully simulated the planned Phase 2b trial. The results showed:

1) that selecting patients with elevated blood pTau as a diagnostic for AD is an excellent alternative to more complicated brain scan methods, and
2) Xanamem has a large clinical effect on the FDA-approved endpoint for early AD of Clinical Dementia Rating – Sum of Boxes (CDR-SB) in these patients.

These two results are a major validation of the science behind the Xanamem program and the *cortisol hypothesis* for AD. The large effect seen on CDR-SB was considerably greater than that recently reported for anti-amyloid antibodies. CDR-SB will be a key endpoint in the upcoming Phase 2b trial of 330 patients with mild AD due to commence in H1 CY2023. With confirmation in the Phase 2b trial, a large effect size on CDR-SB would establish Xanamem as a leading treatment for AD. Xanamem continues to have a promising safety profile for use alone or in combination with other therapies.

Cognitive impairment in depression trial commenced in December

Earlier this month we announced that the first patient was randomized and treated in the **XanaCIDD Phase 2 Depression** clinical trial of 160 patients who are inadequately treated by their anti-depressant medication and

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have both depressive symptoms and cognitive impairment.[1] The trial will measure the effects of Xanamem on safety, cognitive performance and depression. Results are expected to read out in late 2023 or early 2024.

Manufacturing of commercial 5 mg and 10 mg tablet formulations

During the year our US-based manufacturing team was busy improving manufacturing processes and developing new Xanamem tablets for commercial use. These Xanamem tablets will be used in the upcoming XanaMIA Phase 2b AD trial so that the trial may be considered one of the pivotal trials for marketing approval.

Expanding the team

We were very pleased to announce the establishment of two new Xanamem clinical advisory boards during the year, including one for Cognition and Depression. This panel of renowned global thought leaders has already provided expert guidance and advice for our upcoming trials.

We have also continued to fill vital organisational and technical consultant roles to drive strategic initiatives and ensure the success of our clinical development program and other operational requirements. In addition, we have made strategic appointments to our Executive Leadership Team and key consultant appointments.

Business development & communication activities

Despite the ongoing impact of the COVID pandemic, we made significant efforts to attend and participate in major international conferences and meetings during 2022, including key biopartnering conferences. These events are important for developing partnering relationships as well as raising the profile of Xanamem and the *cortisol hypothesis*.

We have also been very focused on improving our corporate communications including clear and relevant announcements in plain English, while maintaining scientific integrity, both of which are important for a company like ours that is dealing with very technical information. I encourage all shareholders if you haven't yet seen it to look at our ***Clinical Trials Science Forum*** webinar held on 3 August this year. The presentations from world-leading authorities on cognition trials and key senior members of the Actinogen management team explore in more depth the science behind Xanamem and ACW's clinical trials program.

This year we launched our new corporate brand, logo, and website early in the year and continue to add functionality and patient access features to the website. If you or your friends or family have an interest in participating in any of our trials, please register on our website.

An exciting 2023 ahead

Our three priorities continue to be:

1) accelerating clinical development
2) creating value from partnerships
3) forward planning for marketing approval (for example, regulatory planning, manufacturing and ancillary clinical and nonclinical studies).

We now enter an exciting period with continued enrolment of the XanaCIDD Phase 2a trial in Depression, with a view to possibly having results as early as the end of the year, and the commencement of the XanaMIA Phase 2b Alzheimer's Disease trial in 330 patients with early-stage disease.

[1] The XanaCIDD Phase 2 Depression trial is a 6-week proof-of-concept, placebo-controlled parallel group designed trial in approximately 160 patients with persistent MDD and cognitive impairment despite a standard course of anti-depressant therapy

We will kick off partnering discussions in the new year in San Francisco by attending a series of meetings at the JP Morgan Healthcare Conference week and by presenting at the Sach's Neuroscience conference on January 8. We will continue to present our data and have a major presence at international AD meetings throughout the year. Several peer-reviewed journal articles on Xanamem are due to be published.

On behalf of the management team and Board, we wish you a safe and happy holiday season and thank you for your continued support and interest in Actinogen. We look forward to updating you on our progress during the coming year.

Yours sincerely,

Dr. Steven Gourlay
CEO & Managing Director

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