ASX ANNOUNCEMENT

Actinogen September 2022 Quarterly Activity Report and Appendix 4C

Sydney, 28 October 2022. Actinogen Medical ASX: ACW ("ACW" or "the Company") announces the release of its quarterly activity report and Appendix 4C for the three-month period ended 30 September 2022.

Key Highlights

- **Accelerating Xanamem® clinical development:**
    - Reported positive Phase 2a clinical data from an Alzheimer's Disease (AD) biomarker study, which validates the Company's Xanamem program and use of a blood biomarker called pTau to select patients in the next clinical trials[1]
    - Solid progress in preparations for upcoming Phase 2 trials:
        - XanaMIA Phase 2b AD trial, which will be a placebo-controlled, 6-month, parallel group design, measuring the effects of Xanamem on safety and cognitive performance in patients with early stages of AD. Trial commencing in H1CY2023
        - XanaCIDD Phase 2 Depression trial, which will be a placebo-controlled, 6-week, parallel group design, measuring the effects of Xanamem on safety, cognitive performance and depression in patients who are inadequately treated by their anti-depressant medication and have both depressive symptoms and cognitive impairment. Trial commencing this year.
    - Signed contracts with suppliers worth approximately US$3 million to provide clinical research services for the XanaCIDD Phase 2 trial.
- **Continued to scale-up drug substance manufacturing with Corden Pharma and tablet manufacturing with Metrics Contract Services. The to-be-marketed tablet formulation will be used in the XanaMIA Phase 2b AD trial to allow the trial to be considered a pivotal trial for product registration**
- **Appointed Associate Professor Christopher Chen BMBCh (Oxon), MRCP (UK), as a Singapore-based clinical advisor to the ACW Depression and Cognition Advisory Board**
- **Initiated the *Actinogen Clinical Trials Science Forum* in August to inform and educate a broad audience, including those from non-technical backgrounds, on the science behind Xanamem and ACW's clinical trials program**

® Xanamem is a registered trademark of Actinogen Medical Limited

[1] Announced 10 October 2022

- **Cash balance of $12.98 million at 30 September 2022.[2] On 20 October 2022, the Company received a $4.17 million research and development (R&D) tax Incentive cash rebate relating to the 2022 financial year.**

Dr Steven Gourlay, Actinogen CEO and MD, commented:

"We were pleased to announce strongly positive clinical data for patients with biomarker-positive, mild Alzheimer's Disease in early October. The results extend findings of therapeutic effects on cognition in two prior trials of cognitively normal, older volunteers to patients with early Alzheimer's Disease. The data also validate the dose range planned for our upcoming trials in Alzheimer's Disease and Depression.

"Xanamem has the potential to be a novel daily oral medication for Alzheimer's Disease and other conditions that could be safely used alone or in combination with other therapies. The results affirm our confidence in the upcoming clinical trials that will confirm if Xanamem can make a significant improvement in the lives of patients and their families living with serious neurological and psychiatric conditions."

Large clinical benefit shown in AD biomarker study - validates Xanamem program

On 10 October 2022, the Company announced positive Phase 2a clinical data from its Alzheimer's Disease biomarker study.

The biomarker analysis has validated and de-risked Actinogen's AD program by showing:

- Clinical activity in a third clinical trial
- Large clinical effect size in patients with mild AD and elevated blood pTau on the CDR-SB endpoint (Clinical Dementia Rating – Sum of Boxes) used to approve anti-amyloid antibodies by the FDA
- Utility of blood pTau levels to select suitable patients with early-stage AD for the Phase 2b trial

The biomarker study was conducted in 72 patients with available blood biomarker samples from the prior Phase 2a placebo-controlled XanADu study of 185 patients. Patients in the original trial had a clinical diagnosis of mild AD,[3] and were treated with Xanamem 10 mg or placebo once daily for 12 weeks. The trial was conducted in the US, UK and Australia. The average age of patients was 71 years, 57% were female and baseline mean CDR-SB score was 3.9.[4]

The biomarker analysis was 'double-blind' and 'pre-specified' meaning the results were generated according to an analysis plan where the biomarker laboratory and company personnel were unaware of which treatment patients had used. This method is standard in the biopharmaceutical industry to avoid bias in the results. Key blood biomarkers studied were phosphorylated tau (pTau) and amyloid levels.

Findings

Xanamem doubled the rate of disease stabilization in Alzheimer's Disease patients with a positive biomarker profile:[5]

- Twice as many patients in the Xanamem group had stable or improved disease compared with placebo[6].
- Represented a 60-80% relative reduction of disease progression versus placebo over 12 weeks.

[2] Unless stated otherwise, all financial data is in Australian dollars
[3] Measured by a Mini Mental State Examination (MMSE) score of 20 to 26. MMSE is a 30-point scale of simple questions to assess mental abilities
[4] Biomarker study: Baseline mean CDR-SB of 3.9 (with 1.6-point standard deviation); original XanADu study mean was 3.8 (SD 1.7)
[5] Identified by pTau-positive biomarker level above median value, n=34
[6] Where CDR-SB decreased or was unchanged - Xanamem 9 of 16 (56%) vs. Placebo 5 of 18 (28%)

Blood pTau levels above the median value of 6.74 pg/mL (n=34) or 10.2 pg/mL (n=9) identified patients who had a clinically significant therapeutic benefit from Xanamem with an average effect size of **0.6 to 0.8 points** on the CDR-SB scale, measuring cognition and function, which is widely used in modern trials of early-stage AD (Cohen's d = 0.41, p = 0.09).

The size of the effect seen with Xanamem is considerably greater than that reported for anti-amyloid antibodies.

The findings also confirm that the CDR-SB is a suitable primary endpoint for measuring Xanamem's therapeutic effect in trials of biomarker-positive AD patients over relatively short periods such as 12 or 24 weeks. Consequently, the use of this endpoint in future trials is anticipated to be straightforward and uncontroversial.

For further detailed information, please refer to the detailed biomarker study results announcement along with the associated webcast slide presentation released to the ASX on 10 October 2022. Alternatively, please refer to the *ASX announcements* section in the *Investor Centre* on the Actinogen website www.actinogen.com.au.

Phase 2 trials in Alzheimer's Disease and Major Depressive Disorder

Preparations continue for the upcoming Phase 2 trials in AD and MDD:

- The **XanaMIA Phase 2b AD trial** is a six-month dose-ranging, placebo-controlled trial in approximately 330 patients with early stages of AD, selecting patients on the basis of clinical characteristics and elevated blood pTau levels. Effects of 5mg and 10mg Xanamem dose levels on cognition will be measured using the CDR-SB rating scale, the Cogstate Cognitive Test Battery (CTB, as used in the XanaMIA Phase 1b trial) and other endpoints. Results are expected in H2CY2024.
- The **XanaCIDD Phase 2 Depression trial** is a six-week proof-of-concept, placebo-controlled trial in approximately 160 patients with persistent MDD and cognitive impairment despite a standard course of anti-depressant therapy. Xanamem 10 mg daily or placebo will be added to the existing anti-depressant therapy and effects on cognition, using the Cogstate CTB, and depression, using the Montgomery Asberg Depression Rating Scale, will be assessed. Results are expected in late 2023 or H1CY2024.

Signed clinical services contracts for XanaCIDD Phase 2 Depression trial

From 1 July 2022 to the date of this announcement the Company has signed a Letter of Intent (LOI) and Statement of Work (SOW) contracts worth approximately US$3 million in total to provide clinical research services for the XanaCIDD Phase 2 trial. Services under these and future contracts for the trial are predominantly paid for as they are fulfilled.

Clinical Advisory Board

The Company recently appointed the esteemed clinical expert in dementia Associate Professor Christopher Chen to its Depression and Cognition Advisory Board.

A/Prof. Chen is a senior clinician-scientist and is an Associate Professor at the Departments of Pharmacology and Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, and Director of the Memory Aging and Cognition Centre, National University Healthcare System.

The Company welcomes Singapore-based A/Prof. Chen who joins Professor John Harrison, Dr Dana Hilt and Ms Christina Kurre Olsen on this world-renowned expert advisory board.

Cash position

Actinogen's cash balance at 30 September 2022 was $12.98 million. Shortly after the end of the September quarter the Company received a $4.17 million R&D tax Incentive cash rebate from the Australian Tax Office for the 2022 financial year.

Net operating cash outflow for the quarter was $3.38 million, primarily related to R&D spend of $2.29 million, staff costs of $0.84 million and administration and corporate costs of $0.36 million.

The increase in R&D spend for the September quarter ($2.29 million) compared to the June quarter ($1.84 million) was primarily associated with the costs of the successful biomarker study (results announced 10 October 2022) and the progressive ramp-up of activities associated with the upcoming Phase 2 trials in AD and Depression.

The increase in staff costs spend for the September quarter ($0.84 million) compared to the June quarter ($0.48 million) was primarily due to the payment of annual bonuses to staff as accrued in the 30 June 2022 accounts ($0.26 million).

Consistent with ASX Listing Rule 4.7c.3, item 6 of the attached Appendix 4C of the cashflow report for the quarter included payments to Related Parties of approximately $0.27 million, comprising the salary for the CEO/Managing Director, fees paid to Non-Executive Directors and superannuation.

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.

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.

Appendix 4C

Quarterly cash flow report for entities subject to Listing Rule 4.7B

Name of entity

ACTINOGEN MEDICAL LIMITED

ABN	**Quarter ended ("current quarter")**
14 086 778 476	30 September 2022

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (3 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers		
1.2	Payments for		
	(a) research and development	(2,287)	(2,287)
	(b) product manufacturing and operating costs		
	(c) advertising and marketing		
	(d) leased assets		
	(e) staff costs	(836)	(836)
	(f) administration and corporate costs	(357)	(357)
1.3	Dividends received (see note 3)		
1.4	Interest received	46	46
1.5	Interest and other costs of finance paid	(5)	(5)
	Income taxes paid		
1.7	Government grants and tax incentives		
1.8	Other (working capital movements)	57	57
1.9	**Net cash from / (used in) operating activities**	**(3,382)**	**(3,382)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities		
	(b) businesses		
	(c) property, plant and equipment	(8)	(8)
	(d) investments		
	(e) intellectual property		
	(f) other non-current assets		

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
2.2	Proceeds from disposal of:		
	(a) entities		
	(b) businesses		
	(c) property, plant and equipment		
	(d) investments		
	(e) intellectual property		
	(f) other non-current assets		
2.3	Cash flows from loans to other entities		
2.4	Dividends received (see note 3)		
2.5	Other (provide details if material)		
2.6	**Net cash from / (used in) investing activities**	**(8)**	**(8)**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of equity securities (excluding convertible debt securities)		
3.2	Proceeds from issue of convertible debt securities		
3.3	Proceeds from exercise of options		
3.4	Transaction costs related to issues of equity securities or convertible debt securities		
3.5	Proceeds from borrowings		
3.6	Repayment of loan shares by Managing Director		
3.7	Transaction costs related to loans and borrowings		
3.8	Dividends paid		
3.9	Other		
3.10	**Net cash from / (used in) financing activities**		

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	16,370	16,370
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(3,382)	(3,382)
4.3	Net cash from / (used in) investing activities (item 2.6 above)	(8)	(8)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
4.4	Net cash from / (used in) financing activities (item 3.10 above)	-	-
4.5	Effect of movement in exchange rates on cash held	3	3
4.6	**Cash and cash equivalents at end of period**	**12,983**	**12,983**

5.	Reconciliation of cash and cash equivalents at the end of the quarter (as shown in the consolidated statement of cash flows) to the related items in the accounts	Current quarter $A'000	Previous quarter $A'000
5.1	Bank balances	983	4,370
5.2	Call deposits	12,000	12,000
5.3	Bank overdrafts		
5.4	Other – restricted cash re office lease		
5.5	**Cash and cash equivalents at end of quarter (should equal item 4.6 above)**	12,983	16,370

6.	Payments to related parties of the entity and their associates	Current quarter $A'000
6.1	Aggregate amount of payments to related parties and their associates included in item 1	266
6.2	Aggregate amount of payments to related parties and their associates included in item 2	

Note: if any amounts are shown in items 6.1 or 6.2, your quarterly activity report must include a description of, and an explanation for, such payments.

7.	**Financing facilities** *Note: the term "facility' includes all forms of financing arrangements available to the entity.* *Add notes as necessary for an understanding of the sources of finance available to the entity.*	**Total facility amount at quarter end $A'000**	**Amount drawn at quarter end $A'000**
7.1	Loan facilities		
7.2	Credit standby arrangements		
7.3	Other (please specify)		
7.4	**Total financing facilities**		

7.5	**Unused financing facilities available at quarter end**	
7.6	Include in the box below a description of each facility above, including the lender, interest rate, maturity date and whether it is secured or unsecured. If any additional financing facilities have been entered into or are proposed to be entered into after quarter end, include a note providing details of those facilities as well.	

8.	**Estimated cash available for future operating activities**	**$A'000**
8.1	Net cash from / (used in) operating activities (item 1.9)	(3,382)
8.2	Cash and cash equivalents at quarter end (item 4.6)	12,983
8.3	Unused finance facilities available at quarter end (item 7.5)	
8.4	Total available funding (item 8.2 + item 8.3)	12,983
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	3.84

Note: if the entity has reported positive net operating cash flows in item 1.9, answer item 8.5 as "N/A". Otherwise, a figure for the estimated quarters of funding available must be included in item 8.5.

8.6 If item 8.5 is less than 2 quarters, please provide answers to the following questions:

8.6.1 Does the entity expect that it will continue to have the current level of net operating cash flows for the time being and, if not, why not?

Answer: N/A

8.6.2 Has the entity taken any steps, or does it propose to take any steps, to raise further cash to fund its operations and, if so, what are those steps and how likely does it believe that they will be successful?

Answer: N/A

8.6.3 Does the entity expect to be able to continue its operations and to meet its business objectives and, if so, on what basis?

Answer: N/A

Note: where item 8.5 is less than 2 quarters, all of questions 8.6.1, 8.6.2 and 8.6.3 above must be answered.

Compliance statement

1 This statement has been prepared in accordance with accounting standards and policies which comply with Listing Rule 19.11A.

2 This statement gives a true and fair view of the matters disclosed.

Date: 28 October 2022

Authorised by: By the Board
(Name of body or officer authorising release – see note 4)

Notes

1. This quarterly cash flow report and the accompanying activity report provide a basis for informing the market about the entity's activities for the past quarter, how they have been financed and the effect this has had on its cash position. An entity that wishes to disclose additional information over and above the minimum required under the Listing Rules is encouraged to do so.

2. If this quarterly cash flow report has been prepared in accordance with Australian Accounting Standards, the definitions in, and provisions of, *AASB 107: Statement of Cash Flows* apply to this report. If this quarterly cash flow report has been prepared in accordance with other accounting standards agreed by ASX pursuant to Listing Rule 19.11A, the corresponding equivalent standard applies to this report.

3. Dividends received may be classified either as cash flows from operating activities or cash flows from investing activities, depending on the accounting policy of the entity.

4. If this report has been authorised for release to the market by your board of directors, you can insert here: "By the board". If it has been authorised for release to the market by a committee of your board of directors, you can insert here: "By the [*name of board committee – eg Audit and Risk Committee*]". If it has been authorised for release to the market by a disclosure committee, you can insert here: "By the Disclosure Committee".

5. If this report has been authorised for release to the market by your board of directors and you wish to hold yourself out as complying with recommendation 4.2 of the ASX Corporate Governance Council's *Corporate Governance Principles and Recommendations*, the board should have received a declaration from its CEO and CFO that, in their opinion, the financial records of the entity have been properly maintained, that this report complies with the appropriate accounting standards and gives a true and fair view of the cash flows of the entity, and that their opinion has been formed on the basis of a sound system of risk management and internal control which is operating effectively.