Actinogen Medical

Investor Newsletter - November 2019

HIGHLIGHTS OF THIS NEWSLETTER

A Message from the CEO - Dr Bill Ketelbey Chief Executive Officer

Dear Shareholders,

The last few months have been particularly notable for Actinogen. In October we reported impressively positive results from the XanaHES trial which showed, for the first time, Xanamem's clear and statistically significant effect on improving cognition in humans. We now have firm evidence from human trials that Xanamem works as designed – it gets into the brain in concentrations that inhibit the 11β-HSD1 enzyme and suppresses cortisol production, leading to an improvement in cognition.

The results not only enhance the current Xanamem dataset, but fundamentally shape our drug development strategy. As shareholders will know, while the XanADu results in May showed that Xanamem 10mg daily was safe and altered the cortisol pathway in patients with mild Alzheimer's, it didn't demonstrate adequate efficacy in improving cognition. The combined XanADu and XanaHES results now provide Actinogen with clear evidence that a higher dose of Xanamem at 20mg daily has the potential to be a therapeutic dose and this helps clarify the outcomes of XanADu.

With the XanaHES results, and results from the ongoing Target Occupancy and longer-term toxicology studies, we now have a deeper understanding and greater clarity of Xanamem's efficacy and safety profile, as well as its potential benefit in a number of different disease areas. Given there are some ongoing studies generating data, we will review the totality of these results over the next few months to best inform the next steps in Xanamem's clinical development.

Outside of our clinical news, the Company has continued its efforts to engage investors and potential partners in the pharmaceutical industry. This included attending various conferences including AusBiotech, AAIC and the recent Australian Microcap Conference.

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A Message from the CEO (cont.)

We will also attend the upcoming annual J.P. Morgan Healthcare Week in January 2020, the largest healthcare investment meeting of its kind. As we continue to build out Xanamem's dataset in the coming months, we will also continue our conversations and explore potential partnerships with the pharmaceutical and biotech communities, at partnering meetings like J.P. Morgan's.

I would like to thank all shareholders for their continued support of the Company, as well as the Actinogen Medical team and Board for their hard work the last number of months. We are making great progress with the development of Xanamem and we can all look forward to a very exciting year ahead as we initiate the next series of Xanamem studies on the back of the outstanding positive results generated over the past few months.

Sincerely,
Dr Bill Ketelbey
Chief Executive Officer

XanaHES Study: Xanamem demonstrates improvement in cognition

While the XanaHES trial was primarily designed as a study to investigate the safety profile of 20mg Xanamem in healthy elderly subjects, it also included an exploratory cognition assessment to evaluate the cognitive efficacy of Xanamem using the Cogstate Cognitive Test Battery.

The results from XanaHES showed a statistically significant improvement in cognition in trial participants dosed with Xanamem 20mg daily for 12 weeks. These results are all the more striking as they were seen after treating only 30 subjects in the trial. Additionally, the results demonstrated a statistically significant reduction in serum cortisol and that Xanamem exhibited a good safety profile, with no serious treatment-related adverse events reported throughout the trial.

Xanamem showed improvement in three of the six cognitive domains measured by Cogstate, as shown in the table below:

COGNITIVE EVALUATION (Test)	P value	Effect Size: Cohen's d			
		Week 2	Week 4	Week 8	Week 12
WORKING MEMORY (One Back Test)	<0.01*	0.64#	0.78#	0.64#	0.83Δ
VISUAL ATTENTION (Identification Test)	0.05*	0.19	0.67#	0.62#	0.67#
PSYCHOMOTOR FUNCTION (Detection Test)	0.09	0.47	0.65#	1.12Δ	0.76#

Notes: * statistical significance achieved;
effect size >0.5 (medium treatment effect);
Δ effect size >0.8 (large treatment effect)

These results demonstrate a very encouraging efficacy signal in the cognitive domains that are core to cognitive evaluation across many diseases.

Commenting on the results, Actinogen Medical's Clinical Advisory Board member, Professor Jeff Cummings from the Cleveland Clinic in the US said: "These results from the XanaHES study provide Actinogen with evidence of Xanamem's ability to enhance cognition and inhibit cortisol production. Considering the broad array of medical conditions presenting with cognitive impairment and an associated raised cortisol, these promising results provide many opportunities for the ongoing development of the drug."

XanADu Study: Sub-analyses completed

As communicated in May this year, Xanamem 10mg daily was safe and altered the cortisol pathway in patients with mild Alzheimer's, although it did not demonstrate adequate efficacy in improving cognition. The Company rigorously analysed the dataset for XanADu and whilst several signals have been identified, including positive trends favouring males within some sub-groups, the results are in-line with those observed in XanaHES: that a higher dose of drug is required to demonstrate statistically significant therapeutic efficacy.

The XanADu data, together with the data generated from the XanaHES and Target Occupancy studies, will enable the Company to refine the strategic development plan for Xanamem and initiate the next suite of clinical studies.

Ongoing studies

Target Occupancy Studies: Phase 1 PET study and homogenate binding studies

Actinogen is currently undertaking a series of Target Occupancy studies designed to measure the effect of different Xanamem doses on inhibiting the 11β-HSD1 enzyme in the brain to help confirm the optimum dosing regimen for Xanamem in future clinical trials. These studies include Phase 1 PET and in-vitro homogenate binding studies.

Preliminary results from the Phase 1 PET study demonstrate that 10-30mg Xanamem significantly binds to the 11β-HSD1 enzyme in the brain, achieving between 50 to 85 per cent enzyme occupancy, depending on the brain region, Xanamem dosage and study subjects. Further results are expected in the coming weeks.

The Target Occupancy homogenate binding studies are in-vitro studies designed to confirm and enhance the Phase 1 PET data. Results from these studies are expected before the end of 2019 and will be used alongside the Phase 1 PET data to inform the dose regimen of Xanamem for future clinical studies.

Pre-clinical Toxicology Studies

Prior to the commencement of studies with dosing durations beyond 12 weeks, regulatory authorities require long-term toxicology studies.

The Company is pleased to report these long-term toxicology studies have reported no substantial safety issues and expects that human trials beyond 12 weeks will be approved by the regulators in the future.

Clinical Development Plan

On the back of positive data and study results over the past few months, the Company is urgently working towards consolidating a revised clinical development plan for Xanamem. This plan, which is being developed with the assistance of world-leading therapeutic advisors, includes:

- The next Xanamem study in Alzheimer's disease
- Evaluating the use of Xanamem in mood disorders and/or schizophrenia
- Revisiting the potential benefit of Xanamem to improve cognition in type 2 diabetes
- Availability and validity of using non-dilutive grants to fund some of these potential studies
- Improved manufacturing process for Xanamem, with Actinogen partnering with Corden Pharma

Additional information regarding the Company's Clinical Development Plan will be communicated in due course.

Further research supports Xanamem's cortisol hypothesis

Supporting our ongoing work, a recent study published in the *Journal of Alzheimer's Disease* demonstrated an association between both raised cortisol levels in cerebrospinal fluid (CSF) and amyloid-β abnormalities on the development of Alzheimer's disease. It also suggested that a high cognitive reserve may reduce the associated progression risks of the disease.

Titled 'Cortisol, amyloid-β, and reserve predicts Alzheimer's disease progression for cognitively normal older adults' (*Udeh-Momoh et al, 2019)*, the study evaluated data from a subset of participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

The study determined baseline measurements for each participant by examining cortisol and amyloid-β levels in 91 cognitively normal individuals aged between 55 and 90 years.

After a median follow-up time of 84 months, 19 of the 91 subjects progressed from being 'cognitively normal' to having 'mild cognitive impairment', while another 10 subjects progressed to Alzheimer's disease.

The study builds on the increasing body of evidence linking persistently elevated cortisol levels with cognitive impairment and Alzheimer's disease, and supports the cortisol hypothesis underlying the development of Actinogen's lead candidate, Xanamem, for the treatment of Alzheimer's disease.

Actinogen at AAIC, AusBiotech and MicroCap Conference

Over the last few months, Actinogen presented at a number of industry and investor conferences, including:

AAIC Presentation – September

Actinogen's Vice President Drug Development & Strategy, Tamara Miller, presented a poster at the Australian Satellite Symposium for the Alzheimer's Association International Conference (AAIC). The poster detailed the history of Xanamem, from the early research performed at Edinburgh University, up to the findings of the XanADu, XanaHES, and Target Occupancy clinical studies. The event was attended by Alzheimer's experts and dementia researchers from across the region and allowed the Company to provide an update of its progress and add to the ongoing literature and knowledge surrounding Alzheimer's disease. Click here to view the poster.

AusBiotech – October

Actinogen CEO Dr Bill Ketelbey attended this year's AusBiotech conference as a panelist and presenter across two conference days. Dr Ketelbey appeared alongside other industry experts on a panel discussing the critical role of consistent communication and messaging when developing a drug candidate asset. Additionally, Dr Ketelbey presented a Company update to a large investor audience, as part of the conference's 'AusBiotech Invest' segment.

AusBiotech is the largest life sciences conference in Australia and was attended by investors, pharmaceutical company representatives and biotech companies, both local and international. Dr Ketelbey used the opportunity to conduct a number of meetings with potential pharmaceutical industry partners.
Click here to watch *90 Seconds with Dr Bill Ketelbey* at AusBiotech Invest.

Australian MicroCap conference – October

Actinogen CEO Dr Bill Ketelbey also participated in the 10th Annual Australian Microcap Investment Conference held in Melbourne and presented Actinogen to an investor audience. Regarded as one of Australia's largest and most comprehensive emerging company investment events, the conference featured a number of upcoming growth companies listed on the ASX and was well attended by institutional investors, retail investors and brokers.
Click here to watch the presentation.

Future investor and scientific conferences

Actinogen Medical will participate in a number of upcoming conferences to educate the scientific community, key opinion leaders, potential partners and investors about the company and the recent positive study results. These include:

- **CTAD 2019 | Dec 2019 | San Diego**
- **SACHS Neuroscience Innovation Forum | Jan 2020 | San Francisco**
    - Dr Bill Ketelbey will be presenting at the conference, and participating as part of a panel discussion entitled '*Advances in Alzheimer's & Other Cognitive Disorders*'
- **38th J.P. Morgan Healthcare Conference | Jan 2020| San Francisco**

Actinogen Medical in the media

Largely driven by the successful XanaHES trial, Actinogen appeared in a range of media outlets over the past few months. Outlined below is a small selection of some recent media coverage.

Morgans Senior Healthcare Analyst Scott Power interviewed Actinogen CEO Dr Bill Ketelbey for the 'Under the Microscope' podcast series to discuss the XanaHES results and what it means for the Company. Click here to listen to the interview.

Australian digital investment publication *Small Caps* wrote a long form article detailing the recent XanaHES results and how they will affect the future development of Actinogen's lead drug candidate, Xanamem. Read more here.

On the day the XanaHES results were released, Actinogen's share price rose more than 400 per cent. Australian investment publication *The Motley Fool* covered the news and detailed the substantial increase in share price. This article was also circulated in other publications such as *Yahoo 7*. Read the article here.

Australian small cap publication *Stockhead* produced a feature article on Actinogen, outlining the breakthrough XanaHES results and interviewed CEO Dr Bill Ketelbey. In the article, Dr Ketelbey discussed why the traditional way of targeting amyloid for Alzheimer's may not be working and that the XanaHES trial results showed researchers and investors that there are novel approaches worth investigating. Read the full piece here.