



Issue on Excess Cortisol this and Alzheimer's disease.

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XanADu Update **US FDA Enhances** Trial Design

Actinogen Medical in the United Kingdom

Actinogen in the News



### **Key Investment Highlights:**

ASX: ACW Market cap: Approximately \$36m

- Alzheimer's: a significant unmet need in a huge and growing alobal market.
- Xanamem<sup>™</sup>, a promising research drug for Alzheimer's.
- Xanamem<sup>™</sup>: novel mechanism of action, targeting the "stress hormone" cortisol - a key differentiator.
- Cortisol hypothesis backed by strong preclinical and clinical evidence.
- XanADu: Phase II trial in mild Alzheimer's disease initiated.
- XanADu regulatory filings underway (including IND). Patient recruitment in second half 2016.
- Patent protection to 2031.

## Message from the CEO

A century ago, Louis Pasteur was famously quoted as saying, "Fortune favours the prepared mind". Nothing could be truer in medical research.

So much in medical research is about having a mind prepared for that serendipitous observation that was not expected or predicted - a mind prepared to take that finding to the next phase. The unexpected observation by the University of Edinburgh that cognition was enhanced through inhibiting the  $11\beta$ -HSD1 enzyme in the brain led to 10 years of research that culminated in Xanamem<sup>™</sup>. So too, an observation that elderly healthy subjects with higher anxiety scores appeared to be at greater risk of cognitive decline, led the CSIRO funded AIBL research team in Australia to evaluate cortisol levels in their healthy elderly cohort. While AIBL demonstrated no apparent link between anxiety scores and cortisol, there was a clear association between excess cortisol levels in the blood and the development of Alzheimer's disease. Both of these observations coincidently led to papers presented at AAIC 2016 in Toronto this past July, which is a testament to the prepared minds of both research teams and the fortune that flows from them.

A chance observation at the University of Edinburgh could lead to a major breakthrough in our understanding of the development and treatment of Alzheimer's disease

It's been some months since our last update on Actinogen Medical and the development program for Xanamem<sup>™</sup>. Over this time we've made significant progress in harmonisation of the Phase II XanADu protocol and we have every expectation that all approvals for the study will be in place with the first patients recruited by the end of the year. It's clear that through the recent interaction with the US Food & Drug Administration (FDA) we have a better, more comprehensive protocol that will

provide a stronger data-set for Xanamem™ in the treatment of mild Alzheimer's disease.

Probably, the most significant development over the past few months has been the launch of Xanamem<sup>™</sup> onto the world stage. Fundamental to any medical research, and to any investment decision made on the back of that research, is that the research is peer-critiqued in open forum. Until now, we have had limited data to present at medical congresses, or to publish in medical journals. Starting with the AAIC in Toronto this past July, we initiated a broad-based promotional program of our data to ensure its wide dissemination. Our data has already been accepted for presentation at 4 major medical congresses in 2016 alone, and we expect publication of the full clinical paper in a major peer-reviewed medical journal within months. Add to that the endorsement of the cortisol hypothesis by AIBL in their AAIC presentation and paper, and we expect to see cortisol inhibition and Xanamem<sup>™</sup> move into the mainstream of Alzheimer's research in the months to come. Until now, our research has been invisible to the Alzheimer's research community - from July on, we take up our rightful place on the global Alzheimer's research stage!

We now move to the next important milestone for ACW and Xanamem<sup>™</sup> - the final regulatory approval for XanADu across all 3 geographies (including from the US FDA) where the study will run, and the initiation of dosing patients, before the year end.

We look forward to updating you on these very positive developments in the weeks and months to come.

Thank you again for your ongoing investment in ACW and your continued commitment to supporting medical research on this critically important disease.

Dr Bill Ketelbev Chief Executive Officer 🔰 @billketelbey



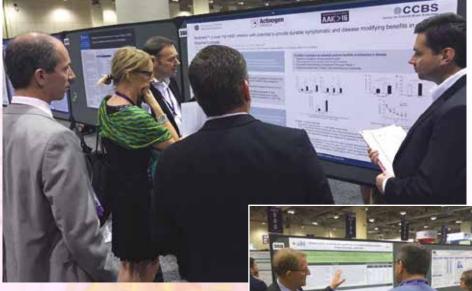
# Landmark Research on Excess Cortisol and Alzheimer's disease: Xanamem<sup>™</sup>'s Global Introduction

In July 2016, Actinogen Medical was ready to present Xanamem<sup>™</sup> to the Alzheimer's research world.

Since acquiring the compound from the University of Edinburgh in December, 2014, we have been working to identify and fill any gaps in the products research database, in preparation for the all-important Phase II study with Xanamem<sup>™</sup>. Most developmental research, while critical to achieving regulatory approval to move into Phase II, is not particularly newsworthy to the medical community. It's when a drug under development moves into dosing in humans in Phase I and beyond, that most congresses and medical journals begin to show real interest.

"To my eyes, AIBL has provided the most important validation to date for controlling excess cortisol production in individuals at risk for developing dementia. Development of new therapies to inhibit cortisol can show us the impact of blocking this mechanism on disease progression," commented Prof. Jeffrey Cummings, M.D., Director, Cleveland Clinic, USA.

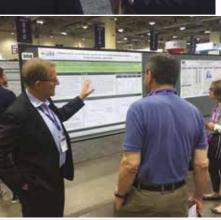
Having completed the Xanamem<sup>™</sup> Phase I studies late last year and the write up of the data for publication, we were ready to present the results to the wider medical world. A paper, **"Selection and early clinical evaluation of the CNS-penetrant 11**β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor UE2343 (Xanamem<sup>™</sup>)", was submitted for publication to a high impact medical journal and very significantly, the paper was accepted for presentation at the Alzheimer's Association International Conference (AAIC 2016) in Toronto.



Top: Craig Ritchie presenting Xanamem<sup>™</sup> paper. Right: Bill Ketelbey speaking about AIBL data.

"In the Xanamem<sup>™</sup> study, we saw clear signals of an effect through the substantial inhibition of cortisol. We are also excited to see clear evidence of delivery through the blood-brain barrier, which we believe has hampered programs targeting this mechanism in the past. We believe this is a promising compound, and we are excited to see the progress into Phase II testing," commented Prof. Craig Ritchie, M.D., PhD, University of Edinburgh.

AAIC is the world's largest Alzheimer's medical and scientific congress, showcasing Alzheimer's research from around the world, and making it the most appropriate forum for us to present Xanamem<sup>™</sup> to the Alzheimer's world. Prof. Craig Ritchie, Professor of the



Psychiatry of Ageing and Director of the Centre for Dementia Prevention at the University of Edinburgh and Chair of our Xanamem<sup>™</sup> Clinical Advisory Board, presented the paper. Most significantly from the event was the universal endorsement we received for this research. It's clear that excess cortisol's link to the development and progression of Alzheimer's disease is becoming widely accepted, and our development of Xanamem<sup>™</sup> as a cortisol inhibitor was welcomed by the audience.

Our Xanamem<sup>™</sup> paper was further endorsed by an independent study from the AIBL research team in Australia. The AIBL study which is part-funded by the CSIRO and a number of universities, followed 416 healthy elderly Australians over nearly 6 years, while regularly undertaking specialised brain scans and an array of cognition and blood tests. Results were compared between those subjects who developed Alzheimer's with those who remained well, and the

# XanADu Trial Update: US FDA Enhances XanADu Trial Design

conclusion from the study was clear. Those subjects with a higher blood cortisol when well, had a much greater chance of developing Alzheimer's disease. The final recommendation from AIBL was that we should look to ways of inhibiting excess cortisol to prevent the development of Alzheimer's disease. Here was independent endorsement of the development of Xanamem<sup>™</sup>, through its ability to inhibit excess cortisol in the brain!

Not only was the Xanamem<sup>™</sup> data very well received, we also received significant endorsement from a totally independent study funded in part by the CSIRO, for the whole cortisol hypothesis that underpins the development of Xanamem<sup>™</sup>! AAIC 2016 was a huge success for Actinogen and Xanamem<sup>™</sup>.

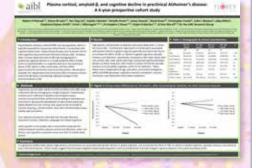
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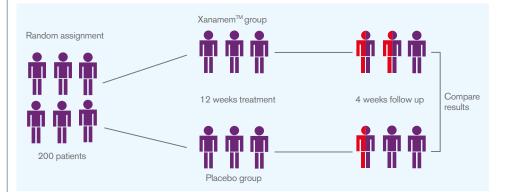
#### Xanamem<sup>™</sup> Poster

http://bit.ly/XanamemPoster



AIBL Poster http://bit.ly/AIBLposter





On 8th June this year, we provided an update on the productive progress we were making with the FDA on XanADu, in our announcement "US FDA feedback enhances Alzheimer's study". We continue to make excellent progress towards securing IND (Investigational New Drug) approval from the FDA. We expect to have approval and to start treating patients in the US within the next few months.

Regulatory approval is required to run any study in any country and while we have previously undertaken Phase I studies on Xanamem<sup>™</sup> in both the UK and Australia, XanADu will be the first human study using Xanamem<sup>™</sup> to run in the US. Achieving this first approval in the US was always going to be more complex and time-consuming. The FDA feedback has now been included in the study design, and the research protocol and documentation have been harmonised across all the 3 geographies where the study will run - the USA, UK and Australia. Harmonisation was crucial to ensure we have exactly the same protocol running in all 3 countries so we end up with one uniform study data-set that will allow data analysis across the whole study. We welcome the FDA input, as it has enhanced the protocol and potentially the value of the data generated from the trial. Everything is now on track to achieve all the regulatory and ethical approvals for XanADu, and to start treating patients on the trial before the end of 2016.

The harmonised XanADu protocol is titled: *A Phase II, Double-Blind,* 12-Week, Randomised,

#### Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Xanamem<sup>™</sup> in Subjects with Mild Dementia due to Alzheimer's disease (AD). But what does all that mean?

A Phase II study is most often the proofof-concept stage of drug research, where the drug is first given to actual patients suffering from the condition being treated, such as Alzheimer's disease. Until then, the only human studies would have been Phase I studies that are usually conducted on healthy volunteers. While the emphasis in Phase I is on safety, the emphasis in Phase II is on effectiveness. XanADu aims to prove the effectiveness of Xanamem<sup>™</sup> in treating patients with mild Alzheimer's disease.

A double-blind study is the gold-standard of clinical trials. It means that neither the patient nor the doctor know whether the study drug given to the patient is Xanamem<sup>™</sup> or a placebo. This trial design aims to eliminate any potential bias from the study. Half of the 200 patients on XanADu are chosen at random according to a computer-generated schedule to receive Xanamem<sup>™</sup>, and the other half will receive placebo. The downside to this is that no results will be known until the randomization code is broken at the end of the trial.

Twelve weeks is the duration that the patient will receive the study treatment. The reason for such a short treatment, is that in earlier animal and human trials, it was demonstrated that cognitive improvement from inhibiting cortisol in the brain can occur within 4 weeks.



# Xanamem<sup>™</sup> – A New Approach to Treating Alzheimer's

# STATISTICS ON ALZHEIMERS

# Increasing with age

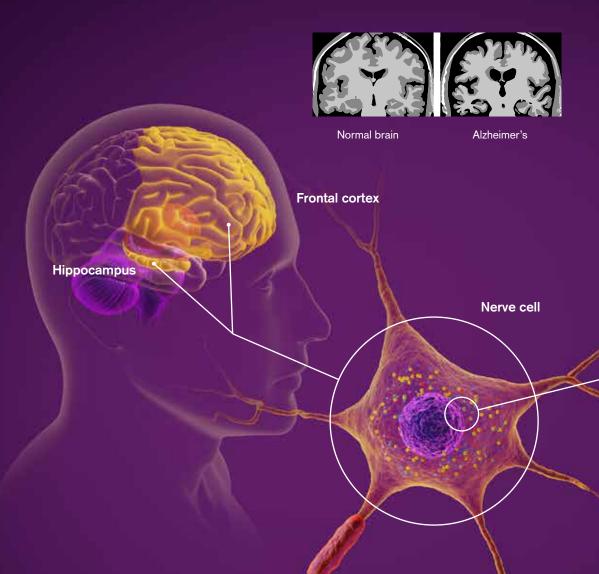
Affects 11% over 65 and 32% older than 75

# A leading cause of death

Contributes to 1 in 3 deaths globally – 1:2 in Australia

# Doubling every 20 years

47m people currently living with dementia globally and set to double every 20 years



## **Stress raises cortisol**

Stress causes production of cortisone from the adrenal glands. Cortisone, following activation to cortisol by the  $11\beta$ -HSD1 enzyme, binds to receptors in the hippocampus and frontal cortex of the brain.

# FAQs

### What is AD?

It usually starts with short-term memory loss. Symptoms then include problems with language, disorientation, mood swings, motivation, self-care and behaviour.

### What causes AD?

A mix of genetic and environmental factors appear to be involved. There is now growing evidence that chronic stress with elevated cortisol plays a part.

#### Is it different from dementia?

Alzheimer's disease is the most common form of dementia, representing about 70% of cases.

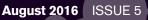
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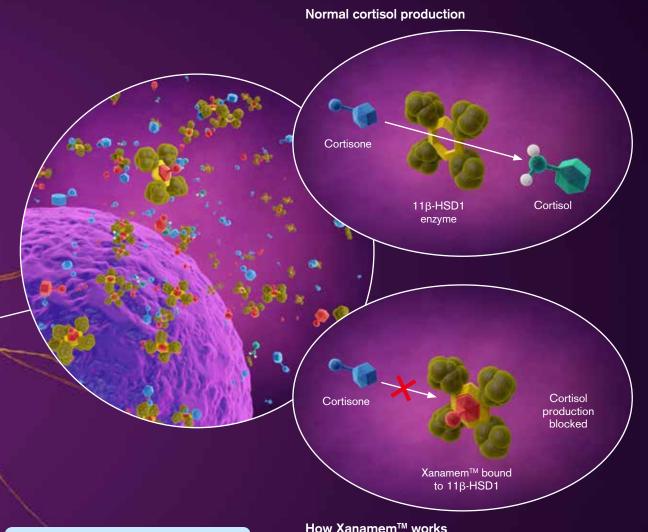
## Xanamem<sup>™</sup> targets the stress hormone cortisol

Actinogen Medical is focused on a new approach to treating Alzheimer's disease. Xanamem<sup>™</sup>, our lead candidate under development, very effectively blocks the enzyme  $11\beta$ -HSD1, which activates cortisone to form cortisol, the stress hormone. High levels of cortisol, have been shown in human and animal models to produce clinical signs and symptoms very similar to Alzheimer's disease.

These include impaired memory, amyloid plaques and nerve death on the brain. The effects are seen particularly in the hippocampus and frontal cortex, the areas of the brain most affected by Alzheimer's, especially early Alzheimer's.

Blocking production of cortisol has been shown to reverse the negative effects of high cortisol levels in the brain.





## Stress – the link with **Alzheimer's**

There is growing evidence that chronic stress and elevated cortisol, the stress hormone, leads to changes in the brain including the development of amyloid plagues and nerve death in the brain with shrinkage of the brain - the hallmarks of Alzheimer's

#### How Xanamem<sup>™</sup> works



### Why is it increasing?

Increasing age is the biggest risk factor, and with the developed world life expectancy approaching 85 years, 1 in 3 will develop Alzheimer's.

#### How is it treated?

There are only four medications currently available but their benefit is limited. No medication clearly delays or stops the progression of the disease.



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# **Actinogen Medical in the United Kingdom**

In July 2016, Actinogen Medical held a series of highly productive research meetings at the University of Edinburgh and with various research partners. The visit coincided with the official opening of Edinburgh's world-class Centre for Dementia Prevention (CDP).

The CDP is an institute 'without walls' and brings together social sciences, basic sciences, drug discovery and clinical expertise in efforts to understand and tackle the key risk factors that underlie dementia. Professor Craig Ritchie, Professor of the Psychiatry of Ageing, leads the clinical arm of the CDP.

At the CDP opening, Dr. Bill Ketelbey, CEO and Managing Director of Actinogen Medical, was introduced to Her Royal Highness Princess Anne who officially opened the CDP in her capacity as Chancellor of the University of Edinburgh. The two discussed Alzheimer's disease and the collaboration between the University of Edinburgh and Actinogen Medical in developing Xanamem<sup>™</sup>. Princess Anne was extremely well informed on Alzheimer's and Xanamem<sup>™</sup>, particularly as Xanamem<sup>™</sup> represents a shining example of successful research and development undertaken at the University.

#### Actinogen meets Her Royal Highness Princess Anne



Left: Actinogen clinical research members Vincent Ruffles and Kerrie Boyd meet Princess Anne. Right: Dr. Bill Ketelbey, Prof. Brian Walker (Co-Inventor of Xanamem<sup>™</sup>), and Prof. Craig Ritchie discuss Actinogen and Xanamem<sup>™</sup> with Princess Anne.

#### Important dates to follow as the Actinogen Medical story unfolds:

Key Conferences & Events		
31 August – 04 September, 2016	International Congress of Endocrinology, Beijing, China	
15 September, 2016	Wholesale Investor Life Sciences Showcase, Sydney, Australia	
21 September, 2016	Understanding Alzheimer's Symposium, Novotel Melbourne, Australia	
18 – 19 October, 2016	Microcap Investment Conference, Sofitel Melbourne, Australia	
24 – 27 October, 2016	BioFest - AusBiotech, Melbourne Convention Centre, Australia	
14 – 16 November, 2016	Mastering Medicinal Chemistry, Lisbon, Portugal	
8 –10 December, 2016	Clinical trials on Alzheimer's Disease, San Diego, California, USA	

# To Find Out More...

## Actinogen in the News

# Announcements

Landmark Research http://bit.ly/Cortisol-and-Alzheimers

US Patent Granted http://bit.ly/USPatentACW

Cortisol Hypothesis http://bit.ly/CortisolHypothesis

FDA Feedback http://bit.ly/EnhancesADstudy

# News

The Australian http://bit.ly/ACWoffershope

IT Wire http://bit.ly/ACWlandmark

Business Wire http://bit.ly/ExcessCortisolResearch

Herald Sun http://bit.ly/ACWandCM http://bit.ly/ACWandBK

# Understanding Alzheimer's The Brains Behind Saving Yours

Alzheimer's disease is one of the greatest health issues of our time. Join us on **World Alzheimer's Day** to hear from leading experts in Alzheimer's research and individuals experienced in coping with the burden of the disease. They will be discussing all aspects of Alzheimer's including the progress being made in developing effective treatments for this devastating condition.

#### Speakers

Dr. Bill Ketelbey CEO & Managing Director, Actinogen Medical

**Professor Colin Masters** 

The Florev Institute &

University of Melbourne

Anne Fairhall Carer Advocate, Alzheimer's Australia Vic

**Professor Ralph Martins** McCusker Foundation & Edith Cowan University

#### **Event Details**



## Understanding Alzheimer's Symposium 2016

#### Professor Colin L. Masters MD

Laureate Professor of Dementia Research Head, Neurodegeneration Division The Florey Institute, The University of Melbourne

#### Professor Ralph Martins AO

Inaugural Chair Alzheimer's and Ageing Edith Cowan University Director, Centre of Excellence for Alzheimer's Disease Research and Care Director of Research, McCusker Alzheimer's Research Foundation

# Engagement

Meet the CEO & Chairman (Perth) https://www.youtube.com/ watch?v=50T7cXXw5p8

NextBiotech Features http://bit.ly/MajorMilestoneACW http://bit.ly/NetxBiotechBK http://bit.lyNextBiotechXanamem

**FinFeed Features** http://bit.ly/FINFeedCortisol http://bit.ly/FinFeedUSA http://bit.ly/FinFeedNewDawn

YouTube Features https://www.youtube.com watch?v=VO7DNk3AoK0 https://www.youtube.com/ watch?v=Q06oCg44NIM

RedChip Research Report http://bit.ly USPatentACW

## **Call for Emails**

In April, 2016, Actinogen moved our investor registry to Link Market Services. We encourage all investors to complete their electronic registrations if they wish to receive consistent email news and updates from Actinogen and Link. Please follow the link provided to both register with Link and to subscribe to the Actinogen Medical paperless newsletter.

https://investorcentre. linkmarketservices.com.au/Login/ Login

We encourage all website visitors to lodge any suggestions, questions or concerns, along with subscriptions, directly with the company by emailing <u>info@actinogen.com.au.</u>

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## **Actinogen Medical**

For further information, please contact:

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Ph: 02 8964 7401

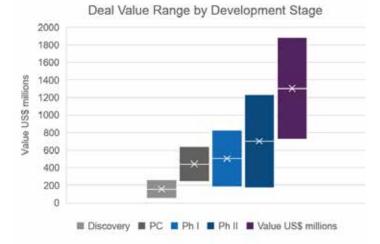
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- A: Level 9, Suite 1 68 Pitt Street Sydney NSW 2000 AUSTRALIA
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#### **Board of Directors**

Martin Rogers	Chairman
Dr. Bill Ketelbey	CEO & Managing Director
Dr. Jason Loveridge	Non-Executive Director
Dr. Anton Uvarov	Non-Executive Director
Management:	
Vincent Ruffles	Vice President of Clinical Research
Christine Drpich	Business Operations Manager
Kerrie Boyd	Clinical Research Operations Manager
Bridget Rooney	Clinical Trials Assistant

#### **Alzheimer's Asset Deal Valuation Trends**

ACW is currently in Phase II with a market cap of approximately \$36m



"Independent validation is clearly emerging that excess cortisol is a key target for treating Alzheimer's disease and our XanADu trial aims to demonstrate that inhibiting cortisol in the brain with Xanamem<sup>™</sup> is an effective treatment option for patients with mild Alzheimer's disease. It's particularly exciting to receive this [AIBL] endorsement of Xanamem<sup>™</sup>'s novel mechanism of action as Alzheimer's is a disease where new approaches to its management are desperately needed to help millions of people worldwide," said Dr. Bill Ketelbey, CEO of Actinogen Medical.

