Alzheimer’s Treatment Needs a New Approach – Xanamem™

Bill Ketelbey – September 2018
Singapore
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Xanamem™ - novel approach to Alzheimer’s dementia
Xanamem, Actinogen’s lead compound, in development for the treatment of Alzheimer’s disease (AD) and cortisol-associated cognitive impairment

Xanamem, a novel differentiated mechanism of action: prevents the production of excess brain cortisol

Persistently raised cortisol in the brain is associated with the development and progression of AD

First-in-class, brain penetrant, orally active, inhibitor of 11βHSD1 enzyme, reducing conversion of cortisone to cortisol

Experienced board and management; expert clinical and scientific advisory boards

### STOCK METRICS

<table>
<thead>
<tr>
<th>ASX CODE</th>
<th>ACW</th>
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<tbody>
<tr>
<td>Market Capitalisation</td>
<td>$63.1m</td>
</tr>
<tr>
<td>Enterprise Value</td>
<td>$53.1m</td>
</tr>
<tr>
<td>52-week High/Low</td>
<td>$0.039-$0.066</td>
</tr>
<tr>
<td>Top 20 Shareholdings</td>
<td>61%</td>
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### TOP 10 HOLDERS

<table>
<thead>
<tr>
<th>Rank</th>
<th>Name</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HSBC Custody Nominees</td>
<td>24.34%</td>
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<tr>
<td>2</td>
<td>National Nominees Ltd</td>
<td>4.49%</td>
</tr>
<tr>
<td>3</td>
<td>Edinburgh Technology Fund Limited</td>
<td>4.43%</td>
</tr>
<tr>
<td>4</td>
<td>JK Nominees Pty Ltd</td>
<td>3.68%</td>
</tr>
<tr>
<td>5</td>
<td>Citicorp Nominees</td>
<td>2.12%</td>
</tr>
<tr>
<td>6</td>
<td>CS Fourth Nominees</td>
<td>2.04%</td>
</tr>
<tr>
<td>7</td>
<td>Warambi Sari</td>
<td>2.01%</td>
</tr>
<tr>
<td>8</td>
<td>BNP Paribas Nominees Pty Ltd</td>
<td>1.93%</td>
</tr>
<tr>
<td>9</td>
<td>Mr Martin Rogers</td>
<td>1.84%</td>
</tr>
<tr>
<td>10</td>
<td>Sunset Capital Management Pty Ltd</td>
<td>1.84%</td>
</tr>
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</table>

In May 2018, Actinogen raised $16.5m via an institutional placement and SPP that saw leading US biotech investor, BVF Partners LP take a 19.9% holding and leading Australia-based institutional investors Australian Ethical and Platinum Asset Management join the register.
Commercially experienced, globally recognised

Board of Directors

Dr. Geoff Brooke
Chairman

Dr. Bill Ketelbey
CEO & MD

Dr. Jason Loveridge
Non-Executive Director

Dr. George Morstyn
Non-Executive Director

Xanamem Clinical Advisory Board

Prof. Craig Ritchie
Chair

Prof. Colin Masters

Prof. Jeffrey Cummings

GBS

Pfizer

JAFCO

AMGEN

Cleveland Clinic

The Westmead Institute

GENABLE

Symbio

morphosys

Cancer Therapeutics CRC

The Florey

The Royal Melbourne Hospital

The University of Edinburgh

The University of Melbourne
A foundation of cutting edge research and translation

Scientific Advisory Board

Prof Jonathan Seckl
Vice Principal
University of Edinburgh

Prof Brian Walker
Pro-Vice- Chancellor
Research Strategy and Resources
University of Newcastle

Prof Scott Webster
Professor of Medicines Discovery
University of Edinburgh

- Combining deep understanding of endocrinology, 11βHSD1 and drug discovery
- Conducted seminal research linking cortisol with cognitive decline
- Actively engaged in the progress and development of Xanamem
Inhibiting cortisol production in the brain with carbenoxolone improves cognitive function in healthy elderly men & type 2 diabetics

**Human pilot studies (2004) - Cortisol inhibition improves cognition**

**VERBAL FLUENCY – Study 1***

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>40.6</td>
<td>12.4</td>
</tr>
<tr>
<td>Treatment</td>
<td>44.2</td>
<td>10.6</td>
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</tbody>
</table>

**VERBAL MEMORY – Study 2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55.2</td>
<td>8</td>
</tr>
<tr>
<td>Treatment</td>
<td>58.8</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Study 1 = 10 healthy subjects Age 55-75 (Mean Age = 65.5 ± 5.5) receiving 100mg carbenoxolone 3 times daily compared to placebo for 4 weeks, in a double-blind randomised crossover study.

**Study 2 = 12 type 2 diabetics (m=9; f=3) Age 52-70 (Mean Age = 60 ± 4.9) receiving 100mg carbenoxolone 3 times daily compared to placebo for 6 weeks, in a double-blind randomised crossover study.

**Significant improvement in verbal fluency and verbal memory after only 4 and 6 weeks treatment**

11β-Hydroxysteroid dehydrogenase inhibition improves cognition function in healthy elderly men and type 2 diabetics
Sandeep et al., 2004 PNAS (vol. 101, no. 17) 6734-6739
Robust animal data with new candidate

Symptomatic and disease modifying effects in mouse models – AUD $25 million invested pre-licensing by ACW

**COGNITION:** treatment 28 days

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to enter dark compartment (seconds)</td>
<td>43 ± 21</td>
<td>172 ± 28</td>
</tr>
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</table>

\[ P = 0.004 \]

**AMYLOID CLEARANCE:** treatment 28 days

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Number of Plaques / brain area (total)</td>
<td>38 ± 3</td>
<td>22 ± 5</td>
</tr>
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</table>

\[ P = 0.01 \]

Significant improvement in cognition after only 28 days treatment, continuing out to 41 weeks

UE2316 in Tg2576 rodent model of Alzheimer’s disease.
Soo, et al., 2015. Endocrinology 156 (12) 4592-4603

Xanamem™ - novel approach to Alzheimer’s dementia
Xanamem™ - novel approach to Alzheimer's dementia
Mechanism of action

Inhibition of 11βHSD1, reducing brain cortisol production
Xanamem

• Actinogen’s lead compound

• A novel, first in class, potent, orally bioavailable, brain-penetrant, 11βHSD1 inhibitor

• Differentiated mechanism of action: blocking cortisol production in the brain

• Symptomatic and disease modifying effects in vivo

• Well-tolerated – dosed >100 patients/subjects: acceptable clinical safety, toxicity and PK/PD profile

• Effective human brain concentrations demonstrated

• XanADu – phase II clinical study underway, dosing subjects with mild AD dementia in USA, UK, AU
  • Fully funded following completion of ~A$5.3 million capital raise in Nov 2017.

• Planning ongoing for additional studies and clinical indications

• A range of additional studies adequately funded following completion of ~$16.5 million capital raising in May-July 2018

• Composition of matter IP coverage ≥ 2031, patents granted in all major markets

1. Webster et al., 2017, British J Pharmacol 174:396-408
Cortisol: a validated biomarker and target for AD

Cortisol and Alzheimer’s

• Recent independent studies support the association between cortisol and AD development and progression1-5
• Cognitive impairment in patients with neuroendocrine dysfunction6-9
• Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017)5
  • Subjects with higher plasma cortisol at much greater risk of developing AD
  • Accelerated effect of Aβ+ on decline in global cognition, episodic memory and attention

Xanamem

• Data presented at four major international medical congresses in 2016 – AAIC Toronto; CTAD San Diego; ICE Beijing; MMC Lisbon
• Pre-clinical and Phase I data published10-11

Cortisol, cognitive decline and AD: a growing body of literature

Recent relevant reviews:
• Cortisol: Mediator of association between Alzheimer's disease and diabetes mellitus? (Notarianni, 2017, Psychoneuroendocrinology)
• Unified theory of Alzheimer's disease (UTAD): implications for prevention and curative therapy. (Nehls 2016, J Mol Psychiatry)
• Is Dysregulation of the HPA-Axis a Core Pathophysiology Mediating Co-Morbid Depression in Neurodegenerative Diseases? (Du and Pang, 2015; Front Psychiatry)
• The impact of stress and glucocorticoids on memory. (Tatomir et al. 2014; Clujul Med.)
• Contribution of glucocorticoids and glucocorticoid receptors to the regulation of neurodegenerative processes. (Vyas and Maatouk, 2013; CNS Neurol Disord Drug Targets)
• Stress-induced cytokines and neuronal dysfunction in Alzheimer's disease. (Ricci et al., 2012; J. Alzheimer’s Dis.)
• Local amplification of glucocorticoids in the aging brain and impaired spatial memory (Yau and Seckl, 2012; Front. Aging Neuroscience)
XanADu – Phase II Trial
XanADu – Xanamem in Alzheimer's disease

Phase II double blind, randomised, placebo-controlled study to assess the efficacy and safety of Xanamem in participants with mild Alzheimer's disease*

- 145 patients enrolled (83% of total study cohort) and more than 101 patients already completed study**
- On track for last patient enrolled in Q4 2018 and top line results in Q2 2019

Xanamem treatment course

12 weeks

Xanamem 10mg daily for 12 weeks vs placebo

174
Mild Alzheimer’s patients

Trial conducted at 20 sites in

AUS, USA and UK

Primary and secondary endpoints are standard and experimental cognitive outcome measures used in Alzheimer's research: ADASCog14, ADCOMS, CDR-SOB, MMSE, RAVLT, NTB-ED

* Registered on Clinicaltrials.gov: NCT02727699
**As at 10 Sept 2018
Interim analysis – DSMB recommendation to continue trial without modification*

- Conducted on data from first 50 evaluable XanADu trial patients. Additional 37 patients’ safety data included in the analysis
- Safety and efficacy data reviewed
- Interim Analysis undertaken by independent Data Safety Monitoring Board (DSMB)
- Recommendation by DSMB to continue trial without modification
- No treatment related serious adverse events
- Recommendation affirms the positive benefit-risk safety profile of Xanamem 10mg daily
- Supports progression of study as planned
- Underpins further development in other indications
- 22nd August 2018 - DSMB safety analysis of 125 patients reaffirmed continuation without modification.

* Announced 23 May 2018
Recognises potential and endorses strategy

- Positive interim analysis catalyses significant $15M investment through Placement

- Leading investors enter register:
  - USA specialist biotech investor Biotechnology Value Fund L.P.
  - Australian institutions Platinum Investments Management and Australian Ethical Investment

- Strong endorsement - Placement price represents an **13.4% premium** to the 5-day VWAP

- **BVF cornerstones Placement** - largest shareholder with a **19.97% holding**

- Funding to advance the development plan through additional Xanamem studies.

* Announced 23 May 2018
New Xanamem studies – funded through May ‘18 capital raising

Enhancing value, broadening scope, strengthening data-set

New funding to advance Company’s development plan

Focus on enhancing the data-set for Xanamem, broadening scope of use and adding substantial value to asset

• **A Target Occupancy Study.** A highly specialised study that aims to accurately demonstrate the effect different doses of Xanamem has on the 11B-HSD1 enzyme in the human brain. The initial work on the Target Occupancy Study underway, with the results anticipated in Q2 2019.

• **A higher dose safety study.** To expand the safety data-set for Xanamem and allow for higher doses of the drug to be used, if required, including in non-Alzheimer’s applications. This human study is expected to initiate in Q4 2018.

• **Additional safety toxicology studies.** To allow for longer treatment periods, as normally required by global regulatory authorities in the development of any drug. Likewise, these studies are expected to initiate in Q4 2018.

• **Market expansion opportunities – multiple new indications** to expand the potential use of Xanamem beyond Alzheimer’s under evaluation - review of all potential indications will complete in the next few months.
  
  • diseases with possible cortisol induced cognitive impairment, including diabetes, depression, Parkinson’s disease, schizophrenia
  
  • as well as conditions like post-traumatic stress disorder (PTSD) and post myocardial infarction
Market and Investment Opportunity

Xanamem™ - novel approach to Alzheimer’s dementia
Large opportunity for Xanamem patient uptake in AD

• Huge commercial opportunity

• Peak sales potential >US$5bn (base case, mild AD), assuming:
  • US launch 2024, ex-US (EU5, JP) 2025
  • 30% penetration (470,000 in US) of target mild AD in 5 yrs
  • $19/day gross price in US at launch

• Upside potential for earlier use:
  • Prodromal AD
  • Prophylactic use
    • at-risk “cortisol-high” – 50% over 65yrs

Xanamem™ - novel approach to Alzheimer’s dementia
Peer comparison

What big pharma companies are paying for acquisition of drug developers in the Alzheimer’s space

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<th>PH I</th>
<th>PH II</th>
<th>PH III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value US$ Millions</td>
<td>400</td>
<td>1200</td>
<td>1800</td>
</tr>
</tbody>
</table>

Xanamem™ - novel approach to Alzheimer Dementia
Xanamem™ - summary
Summary

A huge market with a significant unmet medical need

Xanamem
- Differentiated, with a novel mechanism of action
- Small molecule - oral
- Numerous studies underway/in planning
- Solid IP out to at least 2031
- Potential utility in other indications

XanADu
- Fully funded to completion of XanADu
- Additional studies funded with May 2018 capital raise
- Interim Analysis – continue study without modification
- On track for last patient enrolled before end 2018
- 145 patients enrolled (83% of total); 101 completed

Substantial independent support for cortisol/Alzheimer's hypothesis
Highly experienced Board
Growing interest in Xanamem from pharma partners
A compelling investment opportunity

Highly experienced Board
Growing interest in Xanamem from pharma partners
A compelling investment opportunity
Let’s not forget Alzheimer’s

Remember to wear purple on 21st September World Alzheimer’s Day!
Dr. Bill Ketelbey
CEO & Managing Director
☎ Main: +61 2 8964 7401
Email: bill.ketelbey@actinogen.com.au

www.actinogen.com.au
Xanamem journey of discovery

11β-HSD1 enzyme discovered

1970

11β-HSD1 is highly expressed in regions important for cognition

Xanamem™ - novel approach to Alzheimer's dementia

2001

Carboxoxolone is shown to enhance cognitive function in elderly men and type II diabetics Sandep et al., 2004

First patent filed

2004

11β-HSD1 knockout mice are protected against age-related cognitive dysfunction

Development of selective 11β-HSD1 inhibitors that cross the blood brain barrier

First human study

2009

Xanamem development commences

ACW acquires rights to Xanamem

Xanamem crosses blood brain barrier

2011

Xanamem data published Webster et al., 2017

PHASE I

2013

Webster et al., 2017

PHASE II

2014

XanADu FIRST Subject In

2015

Successful Interim Analysis

2016

XanADu Top Line results Q2 19

2017

XanADu last patient in Q4 18

2018

XanADu FDA IND Approval

2019

CANDIDATE OPTIMISATION

NON-CLINICAL

wellcome trust funded

Actinogen investor funded

2014 2018 2019

2010 2012

2011 2015

2007 2009

2004 2007

2001 2004

2004 2007

2001 2004

2001 2004

2001 2004
Xanamem pipeline of indications, back-up compounds*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
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<tr>
<td>Diabetes Cognitive Impairment &amp; other diseases with possible cortisol induced Cognitive Impairment</td>
<td>[ ]</td>
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</tr>
<tr>
<td>Post Traumatic Stress Disorder</td>
<td>[ ]</td>
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</tr>
<tr>
<td>Post Myocardial Infarction</td>
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* Back-up compounds to Xanamem, licenced from Edinburgh University