Actinogen Medical – Best Risk vs Reward Play in Alzheimer’s Dementia

Baker Young Stockbrokers met again with the Australian Biotechnology company Actinogen Medical (‘Actinogen’ or ‘ACW’) management to discuss the Company’s lead compound Xanamem™, its past research and the initiation of XanADu, its Phase II trial in Alzheimer’s disease (‘AD’). There is growing evidence that chronic stress and elevated cortisol (the “stress” hormone) levels are associated with changes in the brain, leading to cognitive decline and the development of amyloid plaques and neural death – the hallmarks of Alzheimer’s disease. Xanamem™ targets the 11b-HSD1 enzyme blockage the production of excess cortisol and thereby reducing these negative effects of elevated cortisol. Importantly, this hypothesis has been supported by a recent Australian CSIRO and university funded AIBL study linking excess cortisol and Alzheimer’s disease, as announced by the Company in July.

We maintain coverage of Actinogen Medical with a BUY recommendation and we value ACW $0.39 per share base case and $1.12 per share optimistic case using the probability weighted DCF methodology. Our target price of $0.39 sits in the low point of our valuation range. We have increased our valuations across the board in light of a) successful Phase 1 safety results b) Initiation of Phase II trial and c) the recent Australian CSIRO and university funded AIBL study supporting the link between excess cortisol and Alzheimer’s disease.

We see XanADu, the Phase II trial of Xanamem™ for the treatment of mild Alzheimer’s disease positioning Actinogen amongst significantly larger peers (see Table inside report). Going forward Actinogen has a strong cash position to progress through the pivotal Phase II clinical trial, which the company hopes will show Xanamem™ to be an effective and safe treatment for mild Alzheimer’s disease. We believe positive results from this Phase II trial will likely result in a significant partnering transaction (potential for a total deal size of up to $18 upfront & milestones + royalties) given the current unmet market need, comparable similar transactions and Big Pharma’s desire to bring new effective treatments for dementia to market. We believe ACW at current levels represents compelling value on a risk-reward basis.

Novel Mechanism of Action in Alzheimer’s – New way of trying to solve the problem Xanamem™ mechanism of action blocks the excess production of cortisol (the stress hormone) in the brain. Excess cortisol has been associated with memory loss, amyloid plaques and neural death – hallmarks of AD (see inside report for details). Importantly, Xanamem™’s novel mechanism of action sets it apart from many other biotech and pharmaceutical companies trialling potential Alzheimer’s treatments that have recently failed in the clinic.

Australian CSIRO and university funded AIBL study support the ‘Cortisol Hypothesis’ Actinogen recently presented its successful Phase I data at the Alzheimer’s Association International Conference in Toronto. The Company’s research was also accompanied by the AIBL Research Group, which presented their independent study, which showed a clear link between elevated cortisol in the blood of a healthy aged population and the subsequent development of Alzheimer’s disease in these individuals. When individuals also evidenced a broad build-up of beta-amyloid plaques in the brain, their chances of developing Alzheimer’s disease increased even further. The AIBL study (n=416) concluded that targeting ways to lower excess cortisol should be undertaken in battling Alzheimer’s disease in the elderly. This is very encouraging for Actinogen as the Cortisol Hypothesis is the foundation for the development of Xanamem as a treatment for Alzheimer’s disease.

Considerable Upside on Positive Phase II Data in Alzheimer’s Companies developing treatments for AD are valued highly in the market due to the enormous upside in the event they bring a new drug to the market. Aricept™, the market-leading Alzheimer’s disease drug at its peak was generating over US$4.4 Billion in annual sales in the United States, which accounts for approximately 50% of global sales. Recent success by Biogen’s (BIIB) and last year’s IPO of Axovant Sciences (AXON) have rekindled investors’ interest in AD drug discovery. Axovant, which have a single Phase II/III AD drug in development, currently has a market capitalisation of US$1.55 Billion after initially peaking at ~US $3 Billion. Phase II Xanamem Data Expected in late 2018 Successful results from XanADu, the Phase II trial in mild AD will provide the basis for entering into a significant licensing agreement with a larger pharmaceutical company (see figure 15). Given the large unmet patient need, the patent expiry of existing drugs and sheer size of the addressable global market, we see Xanamem™ being highly sought after, assuming positive results are shown in the Phase II trial. We believe the market will gain interest in Actinogen long before these results are due, as has been the case with many other biotechs with upcoming AD trial results, and therefore early investors will be rewarded along the way and before headline results are announced.
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10 Reasons to invest in Actinogen Medical

Extremely large, yet substantially unsatisfied, Global Market – There are currently only 4 routinely prescribed drugs (3 cholinesterase inhibitors and 1 NMDA receptor blocker) approved to treat the symptoms of Alzheimer’s disease, and none that can significantly alter the course of the disease. New treatments are badly needed. The current worldwide cholinesterase inhibitor market (Alzheimer’s market) is estimated to be approximately $11-14Bn annually.⁴

It is estimated that the total annual cost of treating AD in the US is $236 billion alone, quadrupling to around $1 trillion by 2050.

Dementia Medicine and Alzheimer’s disease is a ‘hot’ area in the biotechnology market – Companies developing treatments for dementia and in particular AD are valued highly in the market because investors recognise the enormous upside in the event a company does develop a new effective treatment. Xancept™, the market-leading Alzheimer’s disease drug was generating over US$4.4 Billion in annual US sales at its peak, and it is potential annual sales like this that companies and investors alike are chasing. In what is traditionally a difficult area to develop effective treatments (length and expense of trials and high failure rate) Biogen’s (BIIB) recent clinical success has led to increased optimism (see inside report for more details). In a recent example of investor interest in this space, Axovant Sciences (AXON), which has a single drug in Phase III development for AD and Phase II development for Lewy Body disease, currently has a market capitalisation of US$1.55 Billion after peaking at ~US$3 Billion post its highly publicised IPO on the NYSE. We note, however, that with high reward comes high risk and clinical failure often results in substantial destruction of shareholder wealth.

Novel Mechanism of Action & Early development funded by the Wellcome Trust – There have been many costly failures by Big Pharma in the search for effective treatments for Alzheimer’s disease and Actinogen is focussed on a new approach in this respect. Dementia is progressive memory loss with Alzheimer’s as the most common type. It results in progressive cognitive impairment affecting memory, reason, judgement and language. The neuropathology of the disease includes the development of amyloid plaques, neurofibrillary tangles, and brain cell degeneration particularly affecting the frontal cortex and hippocampus, the areas of the brain most associated with memory, and behaviour and personality. There is growing evidence that chronic stress and elevated cortisol (the “stress” hormone) levels are associated with changes in the brain, leading to cognitive decline and the development of amyloid plaques and neural death – the hallmarks of Alzheimer’s disease. Xanamem™, targets the enzyme 11β-HSD1 blocking the production of excess cortisol and thereby reducing these negative effects of elevated cortisol. In pre-clinical studies, treatment with Xanamem™ has resulted in cognitive improvement and reduction in the size and number of amyloid plaques.

The Wellcome Trust in the UK, invested $25m over seven years in the pre-clinical and clinical development (including a Phase I single ascending dose study) of Xanamem™. The Wellcome Trust is a global charitable foundation supporting early biomedical research and is highly regarded for rigorous selection of medical innovation breakthroughs globally.

Actinogen’s ‘Cortisol Hypothesis’ is supported by the AIBL study funded by the Australian CSIRO and various universities. The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), sponsored by the CSIRO and a number of Australian universities, highlighted the correlation between elevated cortisol in the blood of a healthy population and the consequent progression to Alzheimer’s disease in these individuals. It is believed that a broad accumulation of beta-amyloid plaques in the brain further increases the likelihood of developing Alzheimer’s disease. The AIBL study concluded that investigation into ways to lower excess cortisol should be a focus for the battle against Alzheimer’s disease in the elderly.

Leading up to late-2018 Phase II Trial Data will provide the opportunity for a significant licensing agreement – Successful results from XanADu, the pivotal Phase II clinical trial in patients with mild Alzheimer’s disease, will provide the basis for entering into a significant licensing agreement with a larger pharmaceutical company (see figure 10). Given the huge unmet patient need, the patent expiry of existing drugs and sheer size of the addressable global market, we see Xanamem™ being highly sought after, assuming positive results are shown in the Phase II trial. We believe the market will gain interest in Actinogen long before these results are available, as has been the case with many other biotechs with upcoming AD trial results. Early investors will be rewarded along the way and before headline results are announced.

Thomson Reuters rated Xanamem™ as a Top 5 Global Drug during Phase I – In late 2014, respected financial research firm Thomson Reuters published a list of the Top 5 drugs in development globally, sourced from pharmaceutical and biotechnology companies. Xanamem™ (UE2343) was rated as one of the top 5 drugs to watch coming out of phase I development. It was highlighted as a potential promising new treatment for Alzheimer’s disease for its novel approach on the inhibition of the “stress” hormone cortisol in the brain.

There are currently only 4 approved drugs to treat Alzheimer’s, none of which alter the course of the disease.

The Alzheimer’s market is estimated to be between $11-14 Billion annually.

Alzheimer’s is a Hot’ Area in the biotechnology market, fuelled by the fact there is no solution to a rapidly growing global problem.

The AIBL study concluded that investigation into ways to lower excess cortisol should be a focus for the battle against Alzheimer’s disease in the elderly.

Successful Phase II Trial data is likely to lead to a significant licensing agreement with a large pharmaceutical company.

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¹ Mark Schoenbaum, MD (2015) Axovant Initiation Slides. Available at: https://www.isihmail.com/distribution.ashx?f=rSofsbg5gOtRPe9C98TJSNTL

² Wu11Dm7Qn0ksJ6aJw5B7r1K9fQw+VATg+YUHlbrEC0c+c=1HHyocCN06EJ6hba85sIDQ2tdb=+nNh7SK7KE28MPhtYto2A2.
10 Reasons to invest in Actinogen Medical – Continued

**Xanamem™ has a long patent life with 15 years patent protection until 2031**

A long patent life, to 2031, gives Actinogen a substantial window to benefit from a successful commercialisation before the patent expires and generic versions are launched. This long patent life will be very attractive to big pharmaceutical companies as patents on all current Alzheimer’s disease therapies have expired. In July 2016, Actinogen received official notification from the United States Patent Office, granting the most comprehensive patent for Xanamem™. This patent increases the comprehensive cover for Xanamem™ through to 2031.

Specifically, the patent applies to Xanamem™ for the composition of matter and for the use in Alzheimer’s dementia and other related diseases which are linked to the inhibition of the 11beta-hyroxysteroid dehydrogenase (11β-HSD1) enzyme. It is notable that the patent cover until 2031 comes on top of preceding approvals in other significant markets, including all European countries and the UK, Australia, Japan and China. The final hurdle of US Patent approval is particularly important as the US accounts for in excess of 50% of the global Alzheimer’s disease treatment market.

A highly experienced Board and Management team with invaluable expertise in drug development, commercialisation and clinical research. We are confident that this team are capable of delivering the full potential of their lead candidate, Xanamem™. Dr Bill Ketelbey as Chief Executive Officer, brings a wealth of commercialisation and clinical research expertise with more than 30 years’ experience in the industry. This includes senior medical and management roles at global pharmaceutical giant, Pfizer in Australia and the APAC region. Dr Ketelbey was responsible for leading the development of a number of best-in-class medicines in the region in a broad range of therapeutic areas and was in charge of developing Aricept™, the market-leading Alzheimer’s disease drug.

Actinogen has a highly regarded Advisory Board of global Alzheimer’s experts, which has helped guide Xanamem™’s clinical development through the optimal design of a Phase II efficacy trial in mild Alzheimer’s disease. XanADu, as the Phase 2 trial is branded, will begin patient enrolment and treatment later this year.

Multiple Potential Indications for Xanamem™ have been identified. The Company believes that there are a number of potential indications for diseases of the central nervous and endocrine/metabolic system, which substantially increases the scope of Xanamem™’s developmental pipeline. Each of these indications are commercially very attractive on their own. The first two are already well advanced in planning:

- Diabetes – cognitive dysfunction
- Cognitive dysfunction and sleep disorders in Parkinson’s disease
- Cognitive dysfunction in schizophrenia, depression
- Post-myocardial infarction

Xanamem™ is expected to be used in combination with other AD therapies – Given Xanamem’s™ Mechanism of Action and its safety profile, the Company is confident that it will be able to be used in combination with drugs currently being marketed, or those under development. The use of combination therapies appears to be the direction that the treatment of Alzheimer’s disease is heading.
Company Overview

Actinogen Medical ("Actinogen" or "the Company") is focused on the treatment of Alzheimer's disease and is developing its lead candidate drug Xanamem™, to treat this condition and other age-related neurodegenerative diseases. The Company has completed all Phase I and preclinical trails and has initiated XanADu, its Phase II trial in mild Alzheimer’s disease. First patients are expected to be on study later this year, with final results due in late-2018.

About Xanamem™

Actinogen's lead treatment candidate, Xanamem™ was discovered in 2007 by Professor Brian Walker and Dr. Scott Webster at the University of Edinburgh, where development of this drug was supported by funding from the Wellcome Trust. Xanamem™, very effectively blocks the enzyme 11β-HSD1, which activates cortisone to form cortisol, the stress hormone. Xanamem is designed to primarily block the 11β-HSD1 enzyme in the hippocampus and frontal cortex of the brain, the areas most affected by Alzheimer’s disease. High levels of cortisol, have been shown in human and animal models to be associated with the development and progression of Alzheimer’s disease. This includes the developments of impaired memory, and amyloid plaques and neural death in 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. Actinogen has completed all pre-clinical toxicology and safety pharmacology studies on Xanamem™, including two Phase 1 studies. The data helped inform the optimum design of XanADu, the Phase II trial in mild Alzheimer’s disease Patients are expected to be recruited to the study later in 2016.

History

In December 2014, Actinogen signed a sale and purchase agreement to acquire 100% of Corticrine Limited ("Corticrine"), a pharmaceutical company, which focused on the development of new therapies for Alzheimer’s dementia. The acquisition of Corticrine Ltd, transformed Actinogen into a clinical stage company with a truly innovative asset, in a multi-billion dollar market.

Corticrine was a spin-out from ‘Edinburgh BioQuarter’, the commercialisation arm of the College of Medicine and Veterinary Medicine of the University of Edinburgh in the United Kingdom. Corticrine had gained worldwide development and commercialisation rights from the University of Edinburgh to UE2343 (Xanamem™), which it had progressed through to clinical development for Alzheimer’s disease.

The University of Edinburgh received substantial support from the ‘Wellcome Trust’, to successfully complete a Phase I single ascending dose (SAD) study of UE2343 (Xanamem™) in healthy human volunteers. The results from this Phase I study revealed Xanamem™ to be safe and well tolerated in humans with no serious adverse events.

The Transaction

125 million shares were issued to shareholders of Corticrine (including the University of Edinburgh) on condition of successfully completing a $2m capital raise to fund the initial stages of the program. On completion of the acquisition the University of Edinburgh became a substantial shareholder (~11%) of Actinogen, however, following the recent $11m Placement and SPP the University of Edinburgh now holds ~8% of Actinogen.

There is a multi-billion dollar boom in Alzheimer’s drug development right now.

Pre-clinical and Phase I studies have been completed for Xanamem™ and Phase II results are due in late 2018.

The results from this Phase I study revealed Xanamem™ to be safe and well tolerated in humans with no serious adverse events.

Figure 1: Actinogen’s Journey of Discovery

Source: Company Presentation
Market Overview

Disease Prevalence and Statistics

Alzheimer’s disease (AD) is the most common type of dementia, representing about 70% of dementia cases. It is characterised by progressive cognitive impairment affecting memory, reason, judgement and language. The neuropathology of the disease includes the development of amyloid plaques (caused by an abnormal build-up of beta-amyloid protein in the brain), and brain cell degeneration particularly affecting the hippocampus and frontal cortex, the areas of the brain most associated with memory, and behaviour and personality.

It is widely considered to be the future major public health crisis globally, across all societies.

Worldwide, there are more than 44 million people with dementia today, and expected to triple to around 135 million by 2050. What is most concerning these figures may be understated due to the fact only 1 in 4 people with Alzheimer’s disease have been diagnosed. Australian statistics do not appear any better (see numbers below). It is estimated that the global cost of Alzheimer’s and dementia is in excess of $605 billion, which is equivalent to 1% of the entire global GDP.

The alarming growth in the AD numbers reflects the global aging population and public health success in managing most other major diseases, like infectious diseases, cardiovascular disease and cancer (Figure 2).

Australian Statistics and Impact

- Currently there over 342,800 Australians living with dementia. This number is predicted to exceed 400,000 in less than ten years.
- In the absence of a medical breakthrough, the number of people diagnosed with dementia in Australia is estimated to triple to 900,000 by 2050.
- Every week, there are over 1,800 new cases of dementia diagnosed in Australia, approximately one every six minutes. By 2050 this number is expected to grow to 7,400 new cases each week.
- Dementia is the second leading cause of death in Australia.
- Dementia is the leading cause of disability in elderly Australians (65+) and the third greatest cause of overall disability burden.
- The Australian expenditure in 2009-2010 on direct health and aged care system related to dementia exceeded $4.9 billion.
- In 2011 it was assessed that more than 50% of residents in Australian Government-subsidised aged care facilities have dementia (85,227 out of 164,117).

Alzheimer’s disease (AD) is the most common neuropathologic type of dementia (70%).

Actigen is focussed on a new approach. Xanamem targets the enzyme 11β-HSD1, blocking the production of cortisol, the stress hormone.

There are more than 44 million people worldwide living with dementia. This number is expected to reach 135 million by 2050.

Currently there over 342,800 Australians living with dementia. This number is predicted to exceed 400,000 in less than ten years.
What is Alzheimer’s Disease?

Dementia is a broad term for decline in cognitive function, the ability to think, reason, and remember. Alzheimer’s disease is the leading cause of dementia – around 70% of dementia is Alzheimer’s. As people are living longer, populations are aging and as Alzheimer’s is an age related disease, the number of patients diagnosed with Alzheimer’s disease is expected to grow exponentially. This will have a substantial impact on society.\(^6\)

Alzheimer’s disease is identified by synapse loss (i.e. connections between brain cells) in conjunction with distinctive β amyloid protein plaques and neurofibrillary tangles, composed mainly of tau protein\(^7\) throughout the brain. The pathological diagnosis of AD in a given patient is made by evaluating the location, distribution, and abundance of these characteristic brain lesions.

Detailed autopsy and neuropathological examination of the brain, continues to be considered the gold standard for the diagnosis of AD. However, the clinical diagnosis is commonly based on neuropsychological testing (i.e. ability to perform certain mental tasks), in conjunction with specialised imaging and pathology examinations. See the summary of current diagnostic methods below.

**Figure 3:**
A normal brain compared to a brain affected by Alzheimer’s disease – with functional areas highlighted

Source: Actinogen Medical

**Figure 4:**
Current diagnostic procedures for Alzheimer’s disease

<table>
<thead>
<tr>
<th>Method</th>
<th>Measures</th>
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<tr>
<td>Neurologic and neuropsychological examination of the subject</td>
<td>Emphasizes mental status, memory storage and retrieval</td>
</tr>
<tr>
<td>Neuroimaging (structural) MRI</td>
<td>Ventricular enlargement</td>
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<td>Thinning of the cortex</td>
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<td>Hippocampal atrophy/enlargement of the temporal horn of the lateral ventricle</td>
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<td>Brain microbleeds (for cerebral amyloid angiopathy)</td>
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<tr>
<td>Neuroimaging (metabolic) PET scan</td>
<td>Pittsburgh compound B (PiB), labelled with (^{18})F or (^{11})C: imaging for amyloid Tau markers</td>
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<td>(See Figure 5)</td>
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<tr>
<td>Cerebrospinal fluid testing for abnormal protein levels.</td>
<td>Amyloid beta 1-42</td>
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<td></td>
<td>Total tau and phosphorylated-tau</td>
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<tr>
<td>Blood test – genetic profiling</td>
<td>Apolipoprotein E isoforms</td>
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Source: Vinters, 2015

**Figure 5:**
MRI and PET Scan Images

Source: Actinogen Investor Presentation July 2015

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\(^{6}\) Shurkin, J. 2015. The Oncoming Medical Disaster... With No Cure In Sight. Inside Science. 1 Available at: http://www.insidescience.org/content/oncoming-medical-disaster%2E%2Fno-cure-sight/2716

While performance in neurophysiological tests (based on questionnaires and tasks) is commonly used, it is not very effective in the diagnosis of early stage disease. Clinically, AD is marked by minor onset of cognitive loss, which gradually progresses from mild, short-term memory impairment to total decline, typically over a course of years. In addition to memory loss, AD typically involves many other symptoms. The progression of AD will completely debilitate speech and language, basic daily functions, the ability to recognise familiar people, places and objects. Most patients also undergo significant changes in personality, sleep and behaviour.³

What Happens on Molecular Level?

Figure 6 illustrates some of the molecular and cellular processes presumed to participate in the development of Alzheimer’s disease. Aβ proteins produced by the neurons and other brain cells aggregate and impair the functioning of the synapses and neuronal dendrites. Build-up of the Aβ plaques is thought to be due to either increased production or decreased clearance mechanisms. ApoE4 genes and tau proteins (the main constituent of the abnormal neurofibrillary tangles – another hallmark of AD) appear to promote Aβ neuronal injury, as well as having their own independent adverse effects. Microglial cells are the immune cells in the brain. This multifactorial scenario leads to progressive disintegration of the neural circuits, loss of neurons and neurological failure.

As mentioned above, amyloid beta and tau proteins are normally associated with Alzheimer’s disease development and progression. The Alzheimer’s peptide Aβ is a natural cleavage product released within neuronal cells. Its function is not completely understood.⁵

If misfolded (shaped incorrectly inside the cell), Aβ forms distinctive structures that are susceptible to aggregation, first into oligomers (see Figure 6), then into progressively larger structures called amyloid plaques. It is widely believed that Aβ oligomers are the toxic form of the peptide that leads to impairment of basic neuronal processes like the communication between nerve cells, well before clinical symptoms appear.¹⁰

How Alzheimer’s Develops in Humans

There are a number of forms of Alzheimer’s: a somewhat rare form that runs in families, an early-onset type that appears mid-life (about 5%), and the most common form known as sporadic, which appears with age, usually between 70s and 80s:¹¹

Once the first pathological changes of brain tissue occur, it can take several years, in some cases decades for patient’s mental and cognitive symptoms to appear. The time lag between the initiation of the disorder and the symptoms is partly due to the plasticity of the brain. The plasticity of the brain causes it to compensate when the amyloid is doing its damage. If one neural pathway isn’t functioning, the brain will formulate a detour.¹² This process will continue until there are no more detours available and the damage becomes apparent to the patient (see symptoms mentioned above).

Recent studies suggest that two people can have the same damage to their brain tissue, although one can be affected with mental symptoms, whilst the other may not. The reasoning for this disparity is believed to be due to a person’s ‘cognitive reserve’. Suggesting that people who have active brains, are well educated and use analysis in their work, are less likely to be affected by amyloid pathology.

Amyloid beta and tau proteins are normally associated with Alzheimer’s disease development and progression.

There are a number of forms of Alzheimer’s disease. Sporadic is the most common, which is related to aging.

Once the first pathological changes of brain tissue occur, it can take several years, in some cases decades for patient’s mental and cognitive symptoms to appear.
Stages of Alzheimer’s and Dementia

It is common for everyone to experience cognitive changes with age. The common changes that arise due to aging include, slower recall of information, increased difficulty to learn and store new information, heightened susceptibility to distraction, slower processing of new information, and increased difficulty multi-tasking.\footnote{UCI Mind http://www.alz.uci.edu/alzheimers-disease/what-is-alzheimers/mild-cognitive-impairment/} Once these symptoms start to become more apparent and have an impact on others, the cognitive decline indicates the onset of Alzheimer’s.

There are three stages in the development and progression of Alzheimer’s disease (Figure 7.)

1. **Pre-clinical or pre-symptomatic phase** is the silent stage where plaques begin to accumulate in the brain, but are not substantial enough to cause noticeable symptoms.

2. **Mild Cognitive Impairment (MCI)** is where symptoms become evident as they begin to affect the individual and their close relations, although everyday activities are not impeded.

3. **Dementia** is the final stage, where there is a significant loss of intellectual ability, memory and basic cognitive function; these impairments have a severely detrimental effect on the individual’s everyday activities.\footnote{Ibid.}

Actinogen Medical is focused on developing a therapy for early stage disease (i.e. mild) AD. The consensus thinking amongst Alzheimer’s specialists is that patients should be diagnosed and treated as early as possible (see below) as the individuals brain is most responsive to therapy in early disease.

There are three stages in the development and progression of Alzheimer’s disease:

1. Pre-clinical or pre-symptomatic
2. Mild Cognitive Impairment
3. Dementia

![Stages of Alzheimer's and Dementia](image-url)
Current and Future Therapies for Alzheimer’s Disease

Xanamem™ – A likely Combination Therapy

Xanamem™ is not competitive to other Alzheimer’s treatments. Its unique mechanism of action through the inhibition of cortisol means it likely could be used in combination with other Alzheimer’s drugs.

Current – A lack of effective treatment options

There are 5 drugs approved to treat Alzheimer’s disease, however, only 4 are routinely used. Cognex, the 5th drug exhibits too many side-effects. None of these drugs work very effectively – they appear to slow the progression of the disease for some people for a while, but then stop working.16

There are two groups of medications available to treat Alzheimer’s Disease:

1. Cholinesterase Inhibitors (Aricept®, Cognex®, Exelon®, Razadyne® which is branded as Reminyl® In Australia

Cholinesterase inhibitors, protect against the depletion of acetylcholine, a neurotransmitter involved in the communication between brain cells that play a part in memory and learning. Alzheimer’s disease disrupts the communication process between these brain cells.17 Cholinesterase inhibitors may slow the progression of the symptoms in about 50% of people, but only for a limited amount of time, on average around 6 months.

- **Aricept®** (donepezil) is the only treatment approved by the FDA for all stages of Alzheimer’s disease: mild, moderate, and severe.
- **Cognex®** ( tacrine) was the first of these drugs to be FDA approved, but it is has a very limited use these days due to its poor safety profile.
- **Exelon®** (rivastigmine) is approved for use in mild to moderate Alzheimer’s dementia and is available as a skin patch, capsules and liquid form.
- **Razadyne®** (galantamine) also known as Reminyl®, is approved for mild to moderate Alzheimer’s dementia and is available as an extended-release capsule, immediate-release tablet, and liquid forms.18

Common adverse effects for cholinesterase inhibitors are usually mild and include diarrhea, vomiting, nausea, fatigue, insomnia, loss of appetite, and weight loss. Cognex® may cause liver damage, so liver function tests are performed in these patients.19 Importantly Cognex®, Exelon® and Razadyne®/Reminyl® seem to help only those with mild or moderate symptoms of Alzheimer’s disease.

2. Agents regulating the activity of Glutamate in the Brain

- **Namenda®** (memantine) is also known under the brand-name Ebixa is approved to treat moderate-to-severe Alzheimer’s disease. Namenda is thought to play a protective role in the brain by regulating the activity of glutamate, which also plays a role in learning and memory. Alzheimer’s patients have too much glutamate, which overstimulates nerve cells. Namenda® may improve mental function and performance of daily activities for some people and it may have increased benefit when used in conjunction with Aricept®, Exelon®, Razadyne®/Reminyl®, or Cognex®. Adverse effects of Nameda/Ebixa (memantine) include tiredness, dizziness, confusion, constipation, and headache.20

- Namzaric® (a Fixed-Dose Combination of Memantine Extended-Release and Donepezil Hydrochloride) is a sixth drug that was FDA approved in December 2014. Despite lack of effectiveness of the current drugs on the market, the latest estimates demonstrate that Alzheimer’s global market is today valued at $11 - $14B in annual sales.21 The bestselling product, Aricept (Pfizer) had peak sales of $4.48 22 US per annum in the United States, which accounts for approximately 50% of global sales.

The unique mechanism of action of Xanamem™, makes it likely it will be used in combination with other Alzheimer’s drugs.

There are 5 drugs approved to treat Alzheimer’s, although none work very effectively.

There are two groups of medications to treat Alzheimer’s disease:

1. Cholinesterase Inhibitors
2. Agents regulating the activity of Glutamate in the Brain

The bestselling Alzheimer’s treatment, Aricept (Pfizer) had peak sales of US$4.4B per annum in the United States, which accounts for approx 50% of global sales.
Why Current Therapies Are Not Effective? Implications for Future Drugs

An analysis of aggregated results from 10 placebo-controlled clinical trials of the cholinesterase inhibitors for mild-to-moderate AD demonstrated only about half of the subjects show evidence of a benefit.

The clinical problems experienced with the available assessment tools is reflected in their subjectivity. There are currently limited adequate objective biomarkers for diagnosis and management of Alzheimer’s disease.

Psychometric instruments, such as rating scales and questionnaires, are the most commonly used measurements tools. Some of the more commonly used instruments, include:

- **ADAS-Cog** - The Alzheimer Disease Assessment Scale–Cognitive is a battery of tests commonly used in pharmaceutical research. It consists of 14 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD;
- **MMSE** - The Mini-Mental State Examination is a cognitive test used in both research and clinical practice. It is a 30-point measure of orientation, short-term memory, attention, naming, speech, visual–spatial skills, and reading and writing;
- **Clinical Dementia Rating (CDR) – Sum of Boxes** - CDR is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and dementia. These domains include memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care.

**NPI** - The Neuropsychiatric Inventory (NPI) is a clinician-rating scale that measures psychiatric symptoms.

It is necessary to use psychometric testing due to the lack of any suitable biomarker and the symptomatic nature of the available treatments. However, the choice and design of these tests may not encompass all critical aspects of the disease (e.g. functions of daily living), which can result in an overestimate of treatment effects.

Future – Despite Failures, Drug Development Remains Focused on treating β-amyloid (Aβ)

Currently the leading hypothesis in AD research stipulates that β-amyloid (an abnormal protein) disposition in the brain is the principle cause of the disease. To date there has been significant research and development of therapies based on this hypothesis, but no drugs have yet been able to successfully target amyloid or tau, producing disappointing clinical trials.

**July 2012** - Johnson & Johnson and Pfizer learned that their biological drug bapineuzumab (monoclonal antibody against Aβ) had failed to show any benefit in two large Phase III trials.

**August 2012** - Eli Lilly announced that its drug solanezumab (monoclonal antibody against Aβ) had not hit its goal of significantly slowing the memory decline and dementia that characterize Alzheimer’s disease.

**December 2014** - Basel-based Roche said it was terminating a phase 3 trial of gantenerumab, also a monoclonal antibody against Aβ, in prodromal patients, based on the outcome of an interim futility analysis. All of these failed drugs targeted amyloid-β.

**July 2016** - Tau-Rx announces that LMTX misses co-primary endpoints of LMTX® as add-on therapy, and shows no beneficial effects in combination therapy. LMTX® as monotherapy did however demonstrate significant reductions in disease progression in mild and moderate Alzheimer’s disease.

Following their initial setbacks, Lilly re-evaluated their data in more depth and have initiated further studies on their compound. Currently there are three major ongoing late stage clinical programs focused on targeting amyloid beta. Lilly (solanezumab) and Roche (crenezumab, highly homologous to solanezumab) target soluble monomeric Aβ, while Biogen Idec’s BiB037 (aducanumab, see below) appears to have an effect on soluble oligomeric Aβ.

Alzheimer’s Renaissance? Biogen’s Data Spurs More Investments into the Space

Despite setbacks, rather than abandoning the amyloid hypothesis, big pharma companies are focusing on trying to develop new innovative clinical-trial designs and diagnostics that enable the compounds to be tested earlier in the disease.

Researcher’s hard work eventually paid off when Biogen Idec presented its highly favourable interim data from PRIME, its phase 1b study of the antibody drug aducanumab (monoclonal antibody against Aβ).

The release of that data in early 2015 sparked a renaissance in the Alzheimer field and renewed the interest among investors towards AD drug development. It also revived hopes in the Alzheimer’s disease community that a treatment based on targeting amyloid-beta, a hallmark of Alzheimer’s disease, could be realised.

23. David A. Casey, MD, Demetra Antimisiaris, PharmD, and James O’Brien, MD Drugs for Alzheimer’s Disease: Are They Effective? P&T April 2010 Vol. 35 No. 4
24. David A. Casey, MD, Demetra Antimisiaris, PharmD, and James O’Brien, MD Drugs for Alzheimer’s Disease: Are They Effective? P&T April 2010 Vol. 35 No. 4
25. David A. Casey, MD, Demetra Antimisiaris, PharmD, and James O’Brien, MD Drugs for Alzheimer’s Disease: Are They Effective? P&T April 2010 Vol. 35 No. 4
Initial Interim Analysis From Biogen’s Phase 1b PRIME Study Added $40B US to Biogen’s Market Cap

In 2015 interim analysis of PRIME reflected data from 166 patients at week 54 on treatment. The results from the higher doses showed significant slowdown of disease progression (source: Biogen Idec, 2015) and a statistically significant reduction of amyloid plaque. In the period after the data release Biogen Idec (NASDAQ: BIIB) added almost $40B to its market cap.27

Interim Analysis - September 2016

Recent interim analysis published in Nature (vol 537) demonstrated that aducanumab penetrates the brain and decreases Aβ in patients with AD in a time and dose dependent manner. It also highlighted that the cognitive results for CDR-SB and MMSE (see above) provide support for the clinical hypothesis that reduction of brain Aβ confers a clinical benefit. These results effectively confirmed that efficacy and safety data were consistent with results previously reported.

It was noted that “the clinical study results provide robust support to the biological hypothesis that treatment with aducanumab reduces brain Aβ plaques and, more importantly, to the clinical hypothesis that Aβ plaque reduction confers clinical benefit.”

Reasons for Biogen’s Success

Target

If aducanumab is effective, its success could be attributed to the discovery approach implemented by Neurimmune, the Zurich based company that licensed the molecule to Biogen in 2007. Aducanumab was discovered by screening healthy elderly individuals that did not suffer from Alzheimer’s disease for potential protective antibodies.28 Neurimmune discovered that aducanumab effectively targeted fibrils and oligomers, enabling it to break up plaque and clean up oligomers. Additionally, aducanumab does not attach to soluble amyloid in the vasculature (unlike solanezumab, for example, which attacks soluble Aβ).29

Timing

Timing is the main challenge for diagnosing and treating Alzheimer’s disease. Individuals that have just begun to show symptoms could have had Alzheimer’s for over 20 years. A person with Alzheimer’s disease will compensate for their abated cognitive function until the disease is well progressed. Therefore, Alzheimer patients seek medication at a later stage, where there is already significant damage to their neurons.30 The recent failures in AD Phase III studies uncovered that the key to successfully developing an Alzheimer’s treatment is to diagnose and treat patients as early as possible (i.e. Biogen focused on patients with prodromal early symptomatic or mild disease). Similarly Actinogen is recruiting mild AD patients into XanADu, its Phase II study.

Right Patient Population and Enrolment Criteria

In recent failed AD trials, 22% of the patients who participated in the studies didn’t have significant levels of amyloid plaque in their brains, while the majority of drugs in development that failed targeted the plaque formation process (see above).31 Therefore the trials were testing drugs on patients that did not have the pathology that the drugs were designed to treat.32 These failures have led a much greater focus on perfect enrolment criteria and clinical study design.

Learning from these mistakes, Biogen enrolled 166 people, whose early Alzheimer’s diagnosis was confirmed by way of a positive PET scan for amyloid , ensuring the correct diagnosis.

Actinogen appears to have leveraged on mistakes and successes of these earlier studies in Alzheimer’s disease, and has recruited the assistance of a world class clinical Advisory Board to ensure they optimise the design of XanADu, their Phase II trial in Alzheimer’s disease.

Increased interests in assets and companies that do not target Aβ

In the midst of substantial failures, biotech and pharmaceutical companies remain committed to finding a new drug to treat AD. Six months after private company Axovant acquired a discarded Alzheimer’s drug from GlaxoSmithKline for a mere $5 million ( in late 2014), the company mounted the biggest biotech IPO in recent times raising $315M US by promoting the blockbuster potential for new drugs that make it to the regulatory finish line in Alzheimer’s.33

Recent AD Phase III failures highlighted the critical need to diagnose and treat patients as early as possible.

Actinogen will be recruiting mild AD patients into XanADu, its Phase II study.

Actinogen has leveraged on mistakes and successes of earlier studies in Alzheimer’s disease to optimise their Phase II trial.
In January 2015 Johnson & Johnson licensed AC Immune’s (Swiss based) tau-targeting therapeutic vaccine ACI-35 in a deal potentially worth $509 million.\textsuperscript{34}

In December 2014, Eli Lilly and AstraZeneca began the process of recruiting 1,500 patients diagnosed with early-stage Alzheimer’s disease for a critical phase 2/3 trial of γ-secretase cleaving enzyme (BACE) inhibitor AZD3293 (LY3314814).\textsuperscript{35} Given the hype of the biotechnology market in general and reinvigorated interest in Alzheimer’s disease, we believe this is the best time for small cap biotechs focused on Alzheimer’s therapies to attract institutional interest and a significant premium in valuation(s).

**Why Invest in Actogen Medical?**

Current therapies (cholinesterase inhibitors and NMDA antagonists) for dementia are poorly efficacious, non-disease modifying, and provide only limited benefit to patients.

We believe that Xanamem\textsuperscript{TM}, an 11β-HSD1 enzyme inhibitor has the following advantages over other drug classes:

- **Low toxicity at therapeutic doses.** Two Phase I studies of Xanamem have successfully completed, with 70 of 88 trial subjects dosed with Xanamem in doses of up to 70mg per day, without any unusual or unexpected safety signals identified. The conclusion from these studies is that Xanamem is safe and well tolerated at doses of up to 35mg twice daily.

  Other selective 11β-HSD1 inhibitors have progressed to Phase I and 2 clinical trials for type 2 diabetes with the only target related toxicity being modest elevation of the adrenal androgen levels, as predicted from enhanced metabolic clearance rate for cortisol. A Phase II study of ABT-384 (11β-HSD1 inhibitor developed by AbbVie) showed that the most common (> 5%) side effects of treatment were headaches. The study of ABT-384 was halted when the selective 11β-HSD1 inhibitor ABT-384 failed to show non-inferiority against donepezil for the primary endpoint of ADAS-Cog score\textsuperscript{36}. It remains uncertain whether ABT-384 inhibited 11β-HSD1 adequately in the brain.

- **Potential for disease modification in Alzheimer’s disease.** The striking reduction in amyloid plaque burden in Tg2576 mice following Xanamem\textsuperscript{TM} analogue (UE2316) administration, on top of the clear cognition benefit demonstrated, represents a substantial potential benefit over existing therapies. Importantly, however, unlike well-publicised recent failures of therapies targeted exclusively at amyloid plaque reduction, 11β-HSD1 inhibitors have symptomatic effects which are independent of any disease-modifying effect, justifying progression to the trial of symptomatic efficacy in the current proposal.

- **Added value for metabolic and cardiovascular risk factors.** Selective 11β-HSD1 inhibitors in Phase II studies have reduced plasma glucose, blood pressure, and body weight and improved lipid profile. These systemic risk factors also influence progression of dementia.

Investment View

Since our initiation report was released in August 2015, Actinogen has successfully completed the second Phase I Safety Study of Xanamem and has now initiated XanADu, their pivotal Phase II study. Phase II is a key milestone in the life of a biotech company.

The completion of their Phase I trial confirmed that Xanamem™ is safe in humans, crosses the blood-brain barrier and is effectively administered to the brain, its primary site of action in Alzheimer's disease. This is important as it verifies that orally administered Xanamem successfully reaches the brain in concentrations, which is believed will very effectively inhibit 11β-HSD1, the enzyme in the brain that produces cortisol, 'the stress hormone'.

In March 2016, the Company announced the initiation of XanADu, their pivotal, global Phase II clinical trial to investigate the efficacy of Xanamem™ as a treatment for mild Alzheimer's disease. The much deliberated protocol design for XanADu, was designed with significant input from the Company’s highly regarded Clinical Advisory Board, the US FDA and the key stakeholders from the Edinburgh University and so we have confidence that the trial won’t be let down by its design – something that negatively effects many junior Australian biotech companies.

The recruitment of the first of 200 patients is expected to be initiated by year end 2016 and we believe this will be a key catalyst for the share price. Patients will be recruited in Australia, the UK and the US under a US FDA Investigational New Drug (IND) application (in the process of being completed) with results from the trial expected in late 2018.

Actinogen recently presented the results of their Phase I Xanamem studies at the AAIC, the world’s leading Alzheimer’s Dementia meeting. The results, demonstrated that the orally administered 11β-HSD1 inhibitor significantly inhibited the production of cortisol in healthy volunteers and successfully crossed the blood-brain barrier.

Of particular note, Actinogen’s cortisol hypothesis was supported by a separate study, conducted by the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), sponsored by the CSIRO and a number of Australian universities, which highlighted the correlation between elevated cortisol in the blood of a healthy population and the consequent progression of Alzheimer’s disease in these individuals. It is believed that a broad accumulation of beta-amyloid plaques in the brain further increases the likelihood of developing Alzheimer’s disease. The AIBL study concluded that investigation into ways to lower excess cortisol should be a focus for the battle against Alzheimer’s disease in the elderly.

 Naturally, Actinogen’s Management were very encouraged by these ABIL results with “the findings from the AIBL study, linking excess cortisol with the development of Alzheimer’s disease, providing further strong validation of our ongoing development of Xanamem™,” said Dr. Bill Ketelbey, CEO of Actinogen Medical. “Independent validation is clearly emerging that excess cortisol is a key target for treating the disease and our XanADu trial aims to demonstrate that inhibiting cortisol in the brain with Xanamem™ is an effective treatment option for patients with mild Alzheimer’s disease. It’s particularly exciting to receive this endorsement of Xanamem™’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.”

Thus we are very interested in Actinogen’s novel approach to treating AD and Dementia as there have been many spectacular failures around the anti-amyloid drugs. We see compelling logic to Actinogen’s differentiated approach.

We feel that should Actinogen be successful in proving that Xanamem™ is an effective treatment for mild AD in their proposed Phase II trial, it will be viewed as an additional valuable treatment solution for AD. Given the complexity of the disease we don’t foresee Xanamem™ being the silver bullet, but it could well be another weapon with which to combat AD.

Biotechnology investing is often considered high risk/high reward. Success with pivotal clinical trials can lead to the development of clinically significant advances in healthcare and commercial success, with commensurate reward to the investors. Failed trails often require further costly research with additional investment, or the complete abandonment of the development opportunity and drug candidate with substantial realised losses.

The unmet clinical need, sheer market size and potential economic opportunity of finding an effective treatment for AD significantly incentivises both junior drug discoverers and large Pharma to devoting large amounts of time and capital to this cause. Inevitably any compound demonstrating clinical promise becomes very sought after by larger industry players. We believe Actinogen ticks all the necessary boxes to be positioned to enter partnering discussions, assuming Phase II clinical success.

The recruitment of the first of 200 patients under the Phase II Trial will be a key catalyst for the share price.

AIBL study highlights the correlation between elevated cortisol in the blood of a healthy population and the consequent progression of Alzheimer’s disease in these individuals.

The AIBL study concluded that investigation into ways to lower excess cortisol should be a focus for the battle against Alzheimer’s disease in the elderly.

We see logic with Actinogen’s differentiated approach as there have been many spectacular failures around the anti-amyloid drugs.

Xanamem™ may be a part of the solution to treating and potentially curing AD.
Key differentiators for Xanamem include:

- Hypothesis backed by good pre-clinical and clinical data
- Successful completion of Phase I – Establishing safety and confirming adequate brain penetration and enzyme inhibition.
- Novel mechanism of action, targeting the stress hormone cortisol;
- Long patent life (to 2031) of Xanamem;
- The Wellcome Trust funding early development to the tune of $25m provides us with additional confidence around the pre-clinical and clinical data;
- The company is confident that Xanamem™ will be able to be used in combination with other AD therapies (in market and under development);
- A number of very significant additional indications are being evaluated for development in parallel, which will increase the overall attractiveness of Xanamem™; and
- Being a small molecule, Xanamem™ is not an expensive drug to make and importantly can be taken orally thus increasing its marketability.
- A route of synthesis has been developed providing acceptable cost of goods, and GMP (good manufacturing practice) batches have been manufactured for optimal formulation and administration in the Phase II human studies.

All of this is tied together by a highly experienced Board of Directors/Management and Clinical Advisory Board. The company is led by CEO Dr Bill Ketelbey who is a highly experienced and successful healthcare and pharmaceutical sector professional. Dr Ketelbey has a solid track record of product development leading to the successful registration, launch and commercialisation of numerous market leading medicines in a broad range of therapeutic areas, including in Alzheimer’s disease. Importantly at Pfizer, Dr Ketelbey led the Australian/New Zealand clinical development, and was involved in the launch and commercialisation of Aricept™ (donepezil), an acetylcholinesterase inhibitor (ACHEI), the market leading Alzheimer’s disease therapy locally and globally. More recently he was involved in developing monoclonal antibodies directed at amyloid plaques, a hallmark of Alzheimer’s. Actinogen’s Chairman, Martin Rogers has extensive experience in identifying unique compounds, obtaining the requisite capital to fund development and provides the necessary corporate governance. Dr Loveridge and Dr Uvarov have extensive experience in drug development/commercialisation.

Actinogen’s Advisory Board consists of world experts in AD, which have helped design the optimum Phase II efficacy trial for Xanamem™ in early Alzheimer’s disease. Prof. Craig Ritchie is a Professor of Psychiatry of Aging, at the University of Edinburgh and notably a Senior Investigator in over 30 Alzheimer’s clinical trials whose work on dementia has been published extensively. Prof. Colin Masters (University of Melbourne, Australia) is an Executive Director of Mental Health Research Institute and Senior Deputy Director of the Florey Institute of Neuroscience and Mental Health. Prof. Jeffrey Cummings is a Professor of Medicine (Neurology), Cleveland Clinic, Ohio and Nevada, USA and is also the Chair of the Neurological Institute of Cleveland Clinic. Prof. Cummings has edited 39 books and published over 650 papers.

From an investor viewpoint the key attractiveness for Actinogen is the increasing attention and interest in the cortisol hypothesis that underlies the development of Xanamem, and the ongoing Phase II trial in mild Alzheimer’s disease. The Phase II Trial results in mild AD patients will ultimately determine the near term value for ACW stock, however we anticipate there will be an inevitable growing investor interest in ACW shares as the date for release of the Phase II results approaches.

We believe there are two primary strategies that investors should follow:

1. Invest early and take profits along the way and have a minimal position upon the read out of Trial results; or
2. Invest early and take your largely unchanged original position into the announcement of results.
Naturally, strategy 1 is lower risk than strategy 2 and allows the investor to have conserved their capital (and even made profits) without taking on the binary outcome risk of the trial announcement. However, strategy 2 can lead to extraordinary returns in the event that the trial is successful. In the case of PBT, one could speculate that the share price could have risen to $2.00-2.50 on the back of a positive phase II trial results announcement and ensuring partnering discussions. The most important theme from these two investment strategies is that of investing early and not investing late i.e. too close to the read out trial results.

The recent hype around Axovant Sciences which is no doubt indicative of increasing investor interest in the AD space highlights the returns available to biotech investors. A 29 year old hedge fund manager founded Axovant Sciences and acquired worldwide rights to RVT-101 from GlaxoSmithKline (GSK) in 2014 for $5m + 12.5% royalty on sales and other milestones. RVT 101 had failed several mono-therapy trials and had received a muted response (missed one primary endpoint but hit secondary endpoints) from its last combination trial with Aricept. GSK shelved RVT101 for 4 ½ years until selling the drug late last year. Axovant raised $315m via an IPO on the NYSE and the company commenced trading on the 12th June 2015 with a market capitalisation of ~US$3B. Axovant is currently undertaking a phase III combination trial with Aricept.

For the reasons outlined above we think Actinogen’s Xanamem™ will provide investors with the opportunity for a significant licensing event upon the release of successful Phase II trial results and we feel the best way to play this type of investment is investing early, whilst the company represents good value compared to other drug discovery companies in the AD space. We are confident the management/board have the requisite skills to design and carry out the required trial and that the company has adequate funds to progress the trial through into 2018. The only variable is the actual trial results – but this is the case with every biotech investment and hence why investors can achieve extraordinary returns (i.e. multiples on their initial investment).

Given the inherent difficulty in arriving at a current value for Actinogen we have used the probability weighted DCF methodology of what Xanamem™ and hence Actinogen would potentially be worth in the market place. We therefore arrive at a present day valuation range of $0.39 to $1.12 assuming successful Phase II trial results and a partnering (or takeover) transaction of US$1.05-1.8B. We note that Prana Technology had valuation of circa $600m before the release of its Phase II results and that Axovant is currently worth US$1.55B.

The extraordinary IPO of Axovant Sciences, highlights the interest in the Alzheimer’s space.

Actinogen’s Xanamem™ is expected to receive a significant licensing event upon a successful Phase II trial.
Actinogen – a novel approach to treating Alzheimer’s

Actinogen’s lead candidate Xanamem™ (UE2343) is a small molecule inhibitor of the 11β-hydroxysteroid dehydrogenase (11β-HSD1) enzyme. 11β-HSD1 is a steroid converting enzyme, found predominantly in the liver, adipose and brain that reduces cortisone to the active hormone cortisol (see Figure 7 below). Cortisol activates glucocorticoid receptors and is known as a stress hormone. Chronically elevated cortisol is believed to be among the major triggers for Alzheimer’s disease.

Mechanism of Action - How Stress Could Lead to Cognitive Impairment

Part I – Regulation of Cortisol (stress hormone) levels.

The body’s response to stress includes the activation of the autonomic nervous system and the hypothalamic-pituitary-adrenocortical (HPA) axis. Activation of the HPA axis results in the release of cortisone from the adrenal cortex. Cortisone, in its active state cortisol, mediates the effects of stress, memory and behaviour on brain.

Levels of cortisol circulating in the blood are tightly regulated. Active cortisol circulates mostly bound to a protein, CBG (corticosteroid binding globulin) such that only ~4% is free to enter tissues. The inactive form, cortisone, circulates unbound to plasma proteins so is available to enter tissues.

Once cortisone gets into the cell, there is another level of control by the presence of 11β-HSD1 (found mainly in specific cells in the adult brain such as in hippocampus and cortex, and other tissues such as liver and adipose tissue). 11β-HSD1 regenerates active cortisol from inactive cortisone thereby effectively amplifying intracellular levels of active glucocorticoids before they bind to their receptors (depending on brain region). The activated receptors then translocate into the nucleus to activate the transcription of target genes that affect behaviour and memory. (See figure 9)

Part II – Effect of Cortisol on Cognition

A range of diseases including Alzheimer’s disease, Cushing’s syndrome, obesity, diabetes, hypertension, high cholesterol, major depressive disorder, osteoporosis and glaucoma have been associated with excess levels of the stress hormone cortisol.

In the brain, 11β-HSD1 is highly expressed in regions such as the hippocampus, frontal cortex and cerebellum. These regions are important for cognition and the hippocampus, in particular, has high expression of glucocorticoid receptors. There is substantial evidence for a role of glucocorticoids and hypothalamus-pituitary–adrenal axis dysfunction in Alzheimer’s disease that includes both cortisol-induced neurotoxicity on the hippocampal formation and acute ongoing impairment of cognition. Reducing glucocorticoid action in the CNS via inhibition of 11β-HSD1 has therefore emerged as an important therapeutic goal in the treatment of age-associated cognitive impairment and Alzheimer’s disease.

38. Ibid
39. Ibid
41. (Bill Ketelbey, CEO, Actinogen Limited, Feb. 2015)

Figure 9:

Source: Joyce and Seckl, 2012

A number of medical conditions are linked to excess levels of the ‘stress hormone’ cortisol.
Strong Scientific Rationale – Medical Evidence Supports 11β-HSD-1 Inhibition as a Treatment for Neurodegeneration and Alzheimer’s disease

Key scientific evidence supporting Xanamem™:

• 11β-HSD1 is highly expressed in regions of the adult brain that underpin memory. These include in particular the hippocampus and cortex.42

• Independent of circulating glucocorticoids, the local regeneration of active steroids by 11β-HSD1 influences memory deficits with aging.43

• 11β-HSD1 expression in the mouse hippocampus and cortex increases with age, correlating with impaired memory.

• Mice genetically deficient in 11β-HSD1 resist age-dependent cognitive decline.44

• Short-term pharmacologic inhibition of 11β-HSD1 reverses memory deficits in aged mice.45 Significantly, this has been demonstrated with Xanamem analogues (Fig 12)

• Short-term treatment with a nonselective 11β-HSD1 inhibitor, carbonoxolone, improved aspects of memory in a small cohort of elderly humans and subjects with type 2 diabetes.46

• Small molecule inhibition of 11β-HSD1 (with Xanamem™ analogue) reduces Aβ plaque burden in animal AD models. It was also shown experimentally that stress induces production of Aβ by neural cells and that stress can promote hyperphosphorylation of tau protein (“bad” tau).47 (Fig 12)

• Conversely, it was demonstrated that administration of the cortisol-like compounds increased brain tau and Aβ pathology in a mouse model of AD and induces a dose-related impairment of memory within several weeks of administration. This suggests that increased glucocorticoids may not simply be a result of the disease process, but rather a contributing factor towards the development of Alzheimer’s.48

• On a genetic level, it was demonstrated that an increased risk of AD arises from mutations affecting cortisol production. A study in a population of 814 AD patients and unrelated control subjects showed that a rare mutation in the gene encoding 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) was associated with a 6-fold increased risk for sporadic AD.49

Recent publications confirm association between cortisol and Alzheimer’s


Strong endorsement of cortisol’s association with the development and progression of Alzheimer’s disease in humans comes from a number of recently published studies(Figure 10), including a multi-centre study out of Germany. In this study, the levels of cortisol measured in cerebrospinal fluid (CSF) were increased in the subjects with AD dementia or mild cognitive impairment due to AD (MCI-AD) compared with subjects with mild cognitive impairment due to other reasons (MCI-O) or normal cognition.50 It is evident that higher baseline CSF cortisol levels were found to be associated with faster clinical worsening and cognitive decline in MCI-AD and AD (see Figure 11 below) thus providing a strong proof-of-concept to the Xanamem™ mechanism of action.
The strongest endorsement of the association between cortisol and Alzheimer’s disease and the development of Xanamem as a cortisol inhibitor, comes from the very recently presented Australian AIBL (Figure 10). This CSIRO and university funded study links excess cortisol and Alzheimer’s disease and concluded that “in cognitively healthy older adults, high plasma cortisol levels are associated with greater decline in global cognition, and accelerates the effect of Aβ+ on decline in global cognition, episodic memory, and attention over a 54-month period. These results suggest that therapies targeted toward lowering plasma cortisol and Aβ levels may help mitigate cognitive decline in the pre-clinical phase of AD.”

Xanamem™’s Clinical Development

To date a number of studies have been completed on Xanamem™ and its analogues, including safety pharmacology, 28-day toxicology pre-clinical studies, 3-month toxicology pre-clinical studies, a Phase I single ascending dose (SAD, 48 participants), and a Phase I study that included a multiple ascending dose study in 24 participants, a fed/fasted study of 12 participants and a CNS pharmacokinetics study in 4 participants.

Xanamem was administered to 70 of the 88 Phase I study participants, and the drug is well tolerated in humans with no serious adverse events. It has potent effects on pharmacodynamic biomarkers consistent with substantial inhibition of 11β-HSD1. Xanamem™ was considered safe and well tolerated even at the highest does tested – 35mg twice a day.

Short term administration of Xanamem™ analogue (UE-2316) to mice with age-related cognitive impairment leads to an improvement in cognition as measured by a spatial memory test (Y-maze) and a fear-related memory test (passive avoidance test). One month administration of Xanamem™ analogue in a rodent model of Alzheimer’s disease (the TG2576 mouse) also leads to an improvement in memory (passive avoidance test). This was accompanied by a reduction in amyloid plaque number in the post-mortem brain as demonstrated by histopathological staining of brain slices (see Figure 12, source Sooy 2015).

Xanamem™ is well tolerated in humans with no serious adverse events.

Pre-clinical studies indicate both symptomatic and disease modifying efficacy in dementia.

Figure 11: Cortisol and Alzheimer’s disease
Source: Company Presentation

Figure 12: Xanamem – Symptomatic and Disease modifying effects in mouse models
Source: Company Presentation
This pre-clinical study indicates both symptomatic (cognitive testing) and disease-modifying (plaque burden reduction) efficacy in dementia.

**PHASE I – COMPLETION/RESULTS**

Actinogen completed its final Phase I clinical trial in September 2015, confirming that Xanamem™ crosses the blood-brain barrier and is effectively delivered to the brain, its primary site of action in Alzheimer’s disease.

To assess the amount of Xanamem™ reaching the brain, trial participants were required to undergo lumbar punctures. The results are very encouraging as they verify that oral administration of Xanamem successfully reaches the brain in concentrations, which is believed will very effectively inhibit 11β-HSD1, the enzyme in the brain that produces cortisol the ‘stress hormone’.

Professor Brian R. Walker of the University of Edinburgh commented on the results “Unlike other 11β-HSD1 inhibitors in development for type 2 diabetes, Xanamem™ was designed with the explicit goal of maximising penetration of the drug into the brain. These results confirm that this goal has been achieved in humans. Xanamem™ is therefore an excellent drug with which to evaluate the benefits of 11β-HSD1 inhibition in patients with memory loss.”

The results further endorse the underlying design principles of Xanamem™, demonstrating that Actinogen remains on tract to develop a promising new effective treatment for Alzheimer’s disease.

With these results, Actinogen Medical is ready to move to a Phase II trial to demonstrate the effectiveness of Xanamem™ in treating patients suffering from mild Alzheimer’s disease.

“We are particularly pleased with these much anticipated results showing that Xanamem™ effectively crosses the blood-brain barrier. Our entire team is passionate about this novel new treatment for Alzheimer’s dementia, as it’s a disease where a new treatments are desperately needed, to help millions of patients worldwide,” said Actinogen Medical CEO, Dr Bill Ketelbey.

**XanADu – PHASE II**

In March 2016, the Company announced the initiation of XanADu, their pivotal, global Phase II clinical trial to investigate the efficacy of Xanamem™ as a treatment for mild Alzheimer’s disease. The much deliberated protocol design for XanADu, was formed with significant input from the Company’s highly regarded Clinical Advisory Board and the inventors of Xanamem™ at Edinburgh University.

Actinogen is working with the US Food and Drug Administration to further enhance the protocol design of XanADu, the pivotal Phase II trial of the lead Alzheimer’s drug candidate, Xanamem™. Working with the FDA is key to securing final US FDA approval under an Investigating New Drug (IND) for the Phase II study.
A US focussed study and protocol design is important in order to promote wider value creation, due to the fact the US is the largest market for Alzheimer’s drugs. The Company will implement the enhanced protocol across US, Australian and UK study sites, with the first enrolment of patients expected in late 2016.

The recruitment of the first of 220 patients is expected to be initiated in the current quarter. Patients will be recruited in Australia, the UK and the US under a US FDA Investigational New Drug (IND) application.

Results from the trial are expected in late 2018. Some basic design features are laid out in figure 14.

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<th>Design Feature</th>
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<tr>
<td>Primary End Point</td>
<td>ADAS-Cog and ADCOMS</td>
</tr>
<tr>
<td>Secondary End Points</td>
<td>Multiple, including MMSE, CDR, NTP, NPI, RAVLT &amp; CSF Ab and Tau</td>
</tr>
<tr>
<td>First Patient Enrolment</td>
<td>Expected Q4, CY2016</td>
</tr>
</tbody>
</table>

Figure 14 - XanADu Trial Design
Valuation Methodology

Given the inherent difficulty in valuing junior biotech companies we have had to make a series of assumptions and use the probability weighted valuation methodology which we feel is most appropriate for a company like Actinogen.

- We have assumed a Weighted Average Cost of Capital (WACC) of 16% in line with industry standard for early stage drug discovery companies.
- Market size and sales are predicted in US$ but revenues to ACW are converted to AU$ using a AUD:USD exchange rate of 0.75
- We have assumed Xanamem™ will be used as a combination therapy in conjunction with the market leading AD treatments ACHEI, like Aricept™. We feel comfortable with this view as evidence suggests that AD treatments going forward will most likely be combination therapies – as discussed earlier. Similarly to Aricept™, Xanamem™ is QD (once a day dosing) for all patients.
- We have modelled the potential market of Xanamem on that of Aricept for the following reasons:
  - Aricept™ (and donepezil its generic) is by far the market leading drug for the treatment of AD and has several advantages:
    - QD for all patients
    - Only currently approved therapy indicated for ALL AD patients (mild, moderate and severe)
    - First mover advantage (1996 vs next drugs 2000-03)
    - Post-Aricept™ drugs are not markedly different in efficacy, safety or price.
    - We strip out Namenda™ from our graph because majority who take it, use it with an ACHEI therapy.
  - Not listed on the chart, but today’s ACHEI market shares are similar;
    - Aricept™ (81%), Exelon™ (15%), Razadyne™ (4%)
  - Therefore we have modelled the addressable market, in terms of size, as being that of the various ACHEI treatments currently on market.
  - Alz.org estimates 5.3 million Americans of all ages have AD in 2015 and that by 2050 there number of people age 65 and older with AD may nearly triple to 13.8 million – this implies a CAGR of ~3%
  - However using IMS supplied data regarding number of ACHEI pills sold we arrive at a 2014 patient population of 1.4m in the US ($11,235,735 pill divided by 365 days in the year)
  - Global ex-US patient population is ~90% of US

| Acetylcholinesterase Inhibitors (ACHEI) Global Market ($) – Using 2014 Pricing |
|---------------------------------|---------------------|
| ACHEI # Pills (on a QD basis)   | 511,235,735         |
| Days/Year                       | 365                 |
| Number of Patients on ACHEI 2014 in US only | 1,400,646       |
| ex-US is 90% of US              | 90%                 |
| Total ex-US patient population in 2014 | 1,260,581       |
| Total Current Global ACHEI market | 2,661,227    |
| Approximate Total Current ACHEI market value at ~$5,000 p.a. | 13,306,135,555 |
| CAGR                            | 3.0%                |
| Number of Patients on ACHEI 2031 in US Only | 2,247,625     |
| Total ex-US patient population in 2031 | 2,022,863     |
| TOTAL Global patient population in 2031 | 4,270,488    |
| Xanamem™ total market penetration - assume 10% of total Market in 2031 | 427,049 |
| Cost of Treatment p.a. for Xanamem™ | $5,000-$10,000 |
| Total Global Peak Sales for Xanamem™ in prodromal & mild AD in 2031 | $2,135,244,141 | $4,270,488,281 |

It is estimated that 5.3 million Americans have AD in 2015 and it is estimated to increase to 13.8m by 2050.

Figure 15:
Source: Evercore ISI, Axovant Report, Roche, IMS, Alz.Org, BYS Estimate

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Valuation Methodology Continued

- Therefore we estimate the total number of patients being treated in the US market is estimated to be 1.4m and the number of patients being treated ex-US is 1.26m (addressable market 2.66m) and estimate this will grow to ~4.2m patients by 2031 (date of patent expiry) – this is our estimate for the target market for Xanamem™.

- Based on the above sales of AD drug launches we assume to following growth rates. Note these sales are from the United States, which accounts for approximately 50% of global sales per annum.

<table>
<thead>
<tr>
<th>Year Sales</th>
<th>Percentage of Xanamem Peak Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.0%</td>
</tr>
<tr>
<td>2</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>34%</td>
</tr>
<tr>
<td>5</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>56%</td>
</tr>
<tr>
<td>7</td>
<td>67%</td>
</tr>
<tr>
<td>8</td>
<td>78%</td>
</tr>
<tr>
<td>9</td>
<td>89%</td>
</tr>
<tr>
<td>10</td>
<td>100%</td>
</tr>
</tbody>
</table>

- We assume Xanamem™ will achieve peak sales/class penetration of 10% of the addressable market (using CAGR of 3%) in 2031 which equates to annual sales of $2,135,244,141-54,270,488,281 using pricing range below.

- As Aricept is currently priced at ~$5,500\(^5\) / patient / year on a WAC basis we believe Xanamem™ will be priced between $5,000 and $10,000 per patient per year or $13.70 to $27.40 per day.

- We apply a probability weighting of 20% on net gross sales

- We estimate that R&D and Overheads to be minimal and a company tax rate of 30%.

- We assume Actinogen will have pivotal Phase II results in late 2018 Calendar year. Based on the successful result Management would seek to partner Xanamem™. Actinogen and their partner would then commence and complete a Phase III trial before registering the drug thus we estimate sales will commence in 2021.

- Utilising the data presented across both Figure 17 & 18 we assume a License Agreement with a large Pharmaceutical company will be US$1.05-1.8B total deal size + 15% royalties on sales

- As a market measure that gives us comfort in our probability weighted valuation of ACW we note that:

  On the low end:
  - Bionomics was able to licence their pre-clinical CNS Ion Channel Modulator compound BNC375 to Merck in 2014 for $526m total deal size and Prana Biotechnology was valued by the market at Circa $500-600m in the lead up to its Phase II AD results.\(^56\)

  On the high end:
  - Axovant Sciences is valued ~US$1.7B with a Phase II, Phase III ready AD compound
  - Lundbeck licensed Lu AES8054 to Otsuka for US$825m (inc $150m upfront)\(^57\)
  - January Johnson & Johnson licensed AC Immune’s (Swiss based) tau-targeting therapeutic vaccine ACI-35 in a deal potentially worth $509 million.\(^58\)

Source: Evercore ISI, Axovant Report – Annual Sales in US (Approx 50% of global sales) (Note: Exelon (rivastigmine) not included. Namenda is also known as Ebixa in Australia, and Razadyne as Reminyl)

We estimate the total addressable market to be 2.66m growing to ~4.2m by 2031.

Source: Evercore ISI, Axovant Report

---


Peer Comparison Chart

**DEAL COMPARABLES: Asset partnered prior to completion of Ph II**

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Investor/Partner</th>
<th>Year</th>
<th>Phase @ deal signing</th>
<th>Deal Value (US$ m)</th>
<th>Upfront (US$ m)</th>
<th>Milestone Fees (US$ m)</th>
<th>Upfront Equity</th>
<th>Molecule</th>
<th>Target</th>
<th>Royalty structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC Immune SA</td>
<td>Janssen</td>
<td>2015</td>
<td>Ph Ib (on-going)</td>
<td>$509</td>
<td>$509</td>
<td>n/a</td>
<td>AC135</td>
<td>immunostimulant - anti-phospho-Tau mAb syruncinein, alpha (SNVCA) inhibitor</td>
<td>tiered royalties</td>
<td></td>
</tr>
<tr>
<td>Neurimmune</td>
<td>Biogen</td>
<td>2010</td>
<td>Ph I</td>
<td>$427.50</td>
<td>$60</td>
<td>n/a</td>
<td>aducanumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evotec</td>
<td>Roche</td>
<td>2011</td>
<td>Ph I</td>
<td>$830</td>
<td>$10</td>
<td>n/a</td>
<td>EVT302</td>
<td>MAO-B inhibitor</td>
<td>double-digit</td>
<td></td>
</tr>
<tr>
<td>AFFiRIS AG</td>
<td>GSK</td>
<td>2008</td>
<td>Ph I</td>
<td>$555</td>
<td>$526</td>
<td>n/a</td>
<td>ADD1, ADD2, ADD3 amyloid beta peptide epitope</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoMents, Inc.</td>
<td>Astellas</td>
<td>2008</td>
<td>Ph I</td>
<td>$760</td>
<td>$680</td>
<td>$20 m</td>
<td>CTX21666</td>
<td>beta-secretase inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transition Therapeutics, Inc.</td>
<td>Elan Corp</td>
<td>2006</td>
<td>Ph I</td>
<td>$206.50</td>
<td>$16.50</td>
<td>$185</td>
<td>n/a</td>
<td>ELND005 beta-amyloid aggregation inhibitor</td>
<td>8-15%</td>
<td></td>
</tr>
<tr>
<td>Bionomics</td>
<td>MSD</td>
<td>2014</td>
<td>pre-clinical</td>
<td>$526</td>
<td>$506</td>
<td>Yes</td>
<td>BNC-375</td>
<td>a7NACHR -modulator</td>
<td>double-digit royalties</td>
<td></td>
</tr>
<tr>
<td>AC Immune Primal Healthcare</td>
<td>Roche</td>
<td>2012</td>
<td>pre-clinical</td>
<td>$421</td>
<td>undisclosed</td>
<td>n/a</td>
<td>anti-Tau antibody candidate selection</td>
<td>anti-Tau</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alectos Therapeutics</td>
<td>Merck &amp; Co</td>
<td>2010</td>
<td>pre-clinical</td>
<td>$289</td>
<td>$289</td>
<td>n/a</td>
<td>multiple leads</td>
<td>O-GlcNAcase: O-linked N-acetylglucosaminidase</td>
<td>tiered royalty</td>
<td></td>
</tr>
<tr>
<td>Vitea Pharmaceuticals</td>
<td>Boehringer Ingelheim</td>
<td>2009</td>
<td>pre-clinical</td>
<td>$242</td>
<td>$200</td>
<td>n/a</td>
<td>BI1147560, VTP37948 BACE-Inhibitor</td>
<td>7-12%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DEAL COMPARABLES: Asset partnered post- Ph II results**

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Partner/Investor</th>
<th>Year</th>
<th>Phase @ deal signing</th>
<th>Deal Value (US$ m)</th>
<th>Upfront (US$ m)</th>
<th>Milestone Payments (US$ millions)</th>
<th>Upfront Equity</th>
<th>Molecule</th>
<th>Target</th>
<th>Royalty structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundbeck</td>
<td>Otsuka</td>
<td>2013</td>
<td>Ph II</td>
<td>$825</td>
<td>$150</td>
<td>$675</td>
<td>n/a</td>
<td>LuAE58054</td>
<td>5-HT6 anagonist</td>
<td>royalties</td>
</tr>
<tr>
<td>Acadia Pharmaceuticals</td>
<td>Valeant</td>
<td>2009</td>
<td>Ph II</td>
<td>$395</td>
<td>$30</td>
<td>$365</td>
<td>n/a</td>
<td>ACP103 primavaserin tartrate PRX03140; plus 3 assets in discovery program</td>
<td>5-HT2A inverse agonist 15-20%</td>
<td></td>
</tr>
<tr>
<td>EPIX Pharmaceuticals, Inc.</td>
<td>GSK</td>
<td>2006</td>
<td>Ph II</td>
<td>$1,235</td>
<td>$35</td>
<td>$1,200</td>
<td>n/a</td>
<td>crenezumab MABT5102A</td>
<td>5-HT4 receptor partial agonist</td>
<td></td>
</tr>
<tr>
<td>AC Immune SA</td>
<td>Genentech Inc</td>
<td>2006</td>
<td>Ph II</td>
<td>$300</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
<td>Beta amyloid hMab</td>
<td></td>
</tr>
<tr>
<td>VTV Therapeutics</td>
<td>Pfizer</td>
<td>2006</td>
<td>Ph II</td>
<td>$173</td>
<td>$18</td>
<td>n/a</td>
<td>n/a</td>
<td>TTP4000, TTP488 RAGE modulator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catalyst Biosciences, Inc. (formerly Targacept Inc.)*</td>
<td>AstraZeneca</td>
<td>2005</td>
<td>Ph II</td>
<td>$300</td>
<td>$57</td>
<td>$73</td>
<td>n/a</td>
<td>AZD3480, AZD1446 (+ TC5619, TC6683, non AD assets)</td>
<td>NN1 agonisit, (64b2 neuronal nicotinic receptor (ADZ3480 a.k.a TC1734, TC6683); and a7 neuronal nicotinic receptor agonist (TC6616)</td>
<td>step-up double digit royalty</td>
</tr>
</tbody>
</table>

**Shareholders**

<table>
<thead>
<tr>
<th>Top Ten Shareholders</th>
<th>% of Total Shares</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Edinburgh Technology Fund Limited</td>
<td>7.94%</td>
</tr>
<tr>
<td>2 Tisia Nominees Pty Ltd</td>
<td>5.43%</td>
</tr>
<tr>
<td>3 JK Nominees Pty Ltd</td>
<td>5.36%</td>
</tr>
<tr>
<td>4 Webinvest Pty Ltd</td>
<td>4.20%</td>
</tr>
<tr>
<td>5 Mr Martin Rogers</td>
<td>4.12%</td>
</tr>
<tr>
<td>6 Warmbi SARLN</td>
<td>3.61%</td>
</tr>
<tr>
<td>7 Mr Jason Peterson &amp; Mrs Lisa Peterson</td>
<td>3.21%</td>
</tr>
<tr>
<td>8 Denlin Nominees Pty Ltd</td>
<td>2.52%</td>
</tr>
<tr>
<td>9 Oaktone Nominees Pty Ltd</td>
<td>2.43%</td>
</tr>
<tr>
<td>10 Bannaby Investments Pty Limited</td>
<td>2.07%</td>
</tr>
</tbody>
</table>
QuintusFinancial Summary

Actinogen Medical Ltd (ACW)

Date: 27-Sep-16
Share Price ($A): $0.057
Year End: 30-Jun-17

Profit & Loss (A$mn) - year ended 30 June FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
Revenue 0.00 0.00 0.00 0.00 0.00
Other Income 0.00 0.00 0.00 0.00 0.00
Total Revenue 0.00 0.00 0.00 0.00 0.00
Total Operating Expenses 3.70 4.25 5.50 8.60 9.93
EBITDA -3.70 -4.25 -5.50 201.81 -8.95
Depreciation & Amortisation 0.00 0.00 0.00 0.00 0.00
Share based payments 0.00 0.00 0.00 0.41 0.42
EBIT -3.70 -4.25 -5.50 201.81 -9.37
Interest Revenue 0.02 0.10 0.02 4.04 2.00
Net Interest Expense 0.00 0.00 0.00 0.00 0.00
Net Profit Before Tax -3.78 -4.15 -5.48 205.85 -7.37
Income Tax Expense 0.00 0.00 0.00 54.00 0.00
Net Profit After Tax -3.70 -4.15 -5.48 151.85 -7.37

Balance Sheet (A$mn) FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
Current Assets Cash 9.80 4.75 0.17 151.85 144.48
Receivables 0.00 0.00 0.00 0.00 0.00
Inventories - - - - -
Other 0.00 0.00 0.00 0.00 0.00
Total Current Assets 9.80 4.75 0.17 151.85 144.48
Non Current Assets Property, Plant and Equipment 0.08 0.08 0.10 0.15 0.15
Intangibles 0.10 0.15 0.20 0.25 0.25
Other 0.00 0.00 0.00 0.00 0.00
Total Non Current Assets 0.18 0.23 0.30 0.35 0.40
Total Assets 9.98 4.98 0.47 152.20 144.88
Current Liabilities Trade and other Payables -0.05 -0.05 0.00 0.00 0.00
Other - Deferred Income 0.00 0.00 0.00 0.00 0.00
Total Current Liabilities -0.05 -0.05 0.00 0.00 0.00
Non-Current Liabilities Borrowings 0.00 0.00 0.00 0.00 0.00
Total Non Current Liabilities 0.00 0.00 0.00 0.00 0.00
Total Liabilities -0.05 -0.05 0.00 0.00 0.00
Net Assets 9.93 4.93 0.47 152.20 144.88
Contributed Capital 20.10 20.10 22.00 22.00 22.00
Other component of equity Accumulated Losses -11.00 -15.15 -20.63 131.22 123.85
Total Equity 9.10 4.95 3.37 153.22 145.85

Cash Flow (A$mn) FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
Cash at Start 2 4.75 0.60 -3.78 148.07
Cash Flow From Ops -3.70 -4.15 -5.48 151.85 -7.37
Cash Flow From Investing 0.50 0.00 0.00 0.00 0.00
Cash Flow From Financing/Options 11.00 0.00 1.10 0.00 0.00
Net Cash Flow 7.80 -4.15 -4.38 151.85 -7.37
Cash At End 4.75 0.60 -3.78 148.07 140.70

Shares on Issue 606,158,558 Un-Diluted Current Mkt Cap $34.5m
Share + Options + Rights 661,858,558 Fully Diluted Mkt Cap $37.7m
Share Price $0.057
Rating: Buy
Price Target $0.39 per Share
Valuation: $1.12/0.39 DCF WACC 16%
Valuation Method Probability Weighted DCF
Risk 584%

EARNINGS FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
EPS - Basic -0.006 -0.007 -0.009 0.251 -0.012
EPS - Diluted -0.006 -0.006 -0.008 0.227 -0.011
EPS Growth (%) n/a 12.16% 32.05% -2870.92% -104.85%
DPS 0 0 0 0 0
Franking (%) 0% 0% 0% 0% 0%
Payout Ratio (%) 0% 0% 0% 0% 0%

Valuation FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
P/E (x) -9.34 -8.33 -6.30 0.23 -4.69
EVEBIT (x) -6.68 -7.00 -6.24 -0.58 11.74
EVEBITDA (x) -6.68 -7.00 -6.24 -0.58 12.29
Dividend Yield (%) 0% 0% 0% 0% 0%
Price/Book (x) 3.53 7.27 203.24 0.23 0.24
Price/NTA (x) 3.50 7.15 127.97 0.23 0.24
Price/Cash/Flow per Share (x) n/a -8.33 -7.89 0.23 -4.69

Growth FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
Total Rev. Growth (% pcp) n/a n/a n/a n/a -100%
Op. Exp. Growth (% pcp) n/a -15% -29% 56% 4%
EBITDA Growth (% pcp) n/a -15% -29% -3769% -104%
EBIT Growth (% pcp) n/a -15% -29% -3769% -105%
NPBT Growth (% pcp) n/a -12% -32% 3856% -104%
NPAT Growth (% pcp) n/a -12% -32% 2871% -105%

Margins & Returns FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
EBITDA Margin (%) n/a n/a n/a 96% n/a
EBIT Margin (%) n/a n/a n/a 96% n/a
NPBT Margin (%) n/a n/a n/a 96% n/a
ROIC(%)**NO DEBT*** -41% -84% -400% 99% -5%
ROE (%) -41% -84% -400% 99% -5%
ROA (%) -37% -83% -116% 100% -5%
Effective Tax Rate (%) n/a n/a n/a n/a n/a

Gearing FY15/16E FY16/17E FY17/18E FY18/19E FY19/20E
Net Debt (A$mn) 0
Net Debt/Equity (%) n/a n/a n/a n/a n/a
Board and Management

Mr. Martin Rogers
Non-Executive Chairman

A well-recognized Australian biotechnology entrepreneur and executive, Mr. Rogers has a depth of experience in incubating companies and publicly listed organisations, with degrees in Chemical Engineering and Science.

Experienced in all aspects of financial, strategic and operational management, he has helped raise over $100m cash equity. Both an investor and senior executive in a private funded advisory business, he was instrumental in significantly increasing the value of investments in the science and biotechnology sectors.

Dr. Bill Ketelbey
CEO & Managing Director

Dr Bill Ketelbey is a highly experienced and successful healthcare and pharmaceutical sector professional, with over 30 years’ experience in the industry, including most recently in senior medical and management roles with global pharmaceutical giant, Pfizer. Prior to joining Actinogen Medical, Dr Ketelbey was Regional Vice President of Medical Affairs for Pfizer’s Primary Care Business Unit for Australia and New Zealand, Japan, Canada, Korea and Country Medical Director for Pfizer Australia and New Zealand.

Dr Ketelbey has a solid track record of product development over his years in the industry leading to the successful registration, launch and commercialisation of numerous market leading medicines in a broad range of therapeutic areas, including in Alzheimer’s disease. At Pfizer, Dr Ketelbey led the Australian/New Zealand clinical development, and was involved in the launch and commercialisation of Aricept™ (donepezil), an acetylcholinesterase inhibitor, and the market leading Alzheimer’s disease therapy locally and globally. More recently he was involved in developing monoclonal antibodies directed at amyloid plaques, a hallmark of Alzheimer’s.

Dr Ketelbey is a medical graduate from the University of the Witwatersrand, South Africa, a Fellow of the Faculty of Pharmaceutical Physicians from the Royal College of Physicians in the UK, has an MBA from Macquarie Graduate School of Management, Australia and is a Graduate of the Australian Institute of Company Directors.

Dr. Jason Loveridge
Non-Executive Director

Dr. Loveridge has been working in the biomedical technology industry for over 20 years and has extensive experience in developing clinical stage biotechnology companies. As a venture investor with JAFCO Nomura, Dr. Loveridge participated and invested in the start-up of over 24 companies in Europe, the US and Israel. Since leaving the investment arena in 2005, he has been directly involved in the management of a number of small innovative companies in the medical field, specifically in restructuring, refinancing and in product commercialisation.

Dr. Loveridge is currently a Non-Executive Director of Resonance Health Ltd (ASX: RHT), an Australian healthcare company specialising in the development and commercialisation of magnetic resonance imaging (MRI) related technology.

Dr. Anton Uvarov
Non-Executive Director

Dr. Uvarov has significant experience as an equity analyst in the healthcare industry with a focus on biotechnology sector, both domestically and internationally. Prior to moving to Australia he was with Citigroup Global Markets where he spent two years as a member of New York based biotechnology team that has been continuously ranked top 4 for Biotechnology in the All-America Institutional Investor survey. Dr. Uvarov’s scientific expertise and company knowledge spreads across variety of therapeutic areas and spectrum of market capitalizations with his particular interest in early stage biotechnology companies.

Dr. Uvarov holds a PhD degree in Biochemistry and Medical Genetics from the University of Manitoba, Canada and an MBA degree from the University of Calgary, Canada. He is currently a Director of Actinogen Medical (ASX:ACW) – an Australian clinical stage biotechnology company developing therapies for Alzheimer’s and other neurodegenerative diseases, and Imugene Limited (ASX:IMU) – an Australian immuno-oncology company.

Vincent Ruffles
Vice President of Clinical Research

Mr. Ruffles has over 20 years of experience in the pharmaceutical and biotechnology industries, and has worked across all phases of the drug development cycle. Mr. Ruffles began his career in the UK at Hoechst-Roussel (now Sanofi) and relocated to Geneva, Switzerland to work for Serono (now Merck Serono). After returning to the UK to work at Procter & Gamble and then Amgen, Vincent moved to Sydney, Australia in 2008.

He has worked on several drugs taking them through clinical development and has extensive experience in Alzheimer’s disease and related therapeutic areas. Mr Ruffles’ recent role in a global contract research organisation has given him great exposure to the Asia Pacific region and a variety of companies and their needs including local start-up pharmaceutical companies with limited resources but significant potential and multinational clients.

Mr. Ruffles will be responsible for implementing the overall strategy, scientific and regulatory oversight and direction of clinical programs of Xanamem™.

Peter Webse
Company Secretary

Peter has over 25 years’ company secretarial experience and is the managing director of Platinum Corporate Secretariat Pty Ltd, a company specialising in providing company secretarial, corporate governance and corporate advisory services. Mr Webse is a non-executive director of Cynata Therapeutics Limited.
**Key Risks**

We have identified the following risks for Actinogen:

**Dependence on a partnership to drive value:** Actinogen must engage strategic partnering deals for its lead drug Xanamem™ in order to execute its business model and receive notable cash flows. Failure to enter a favourable partnership will have detrimental consequences.

**Poor Design of the Phase II Study:** It is imperative that the correct personnel are in place to optimally design the Phase II clinical trial. As many biotech companies have experienced, an incorrectly designed study will inevitably lead to detrimental results, which will adversely affect our valuation and forecasts.

**Actinogen derives its value from Xanamem™,** which entered Phase II trials in CY2016. Unsuccessful Phase II results and a subsequent failure to attract a partnering deal will significantly adversely impact the valuation and forecasts we have formulated for Actinogen.

**Diversification Risk,** currently Xanamem™ is Actinogen’s lead compound and the value in the company is heavily skewed towards the success of this compound in Alzheimers. While there is a platform of additional potential indications for Xanamem, Actinogen does not possess a diversified drug pipeline at this stage.

**Timing Risks:** The company will be looking to partner at the completion of their upcoming phase II trial. Delay in timelines may inhibit optimal potential partnerships. Furthermore, once partnered, timeline delays will affect milestone payments as well as long-term revenues.

**Funding Risks:** A delay in achieving a partnership and subsequent upfront/milestone payments may have an impact on Actinogen’s funding capabilities.

**Intellectual property risks:** Actinogen does have registered patents, registrable designs and other statutory registrations, which form the base for intellectual property rights however we cannot guarantee that this will not be challenged nor can we guarantee that another company will not usurp this IP.

**Competition Risks:** The emergence of new competitors in the market or advancements in the treatment of AD may render Xanamem™ redundant or mean that the compound is no longer novel. This may affect the commercial value of the compound.

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