NDF RESEARCH

Providing independent research coverage of ASX-listed Life Science companies

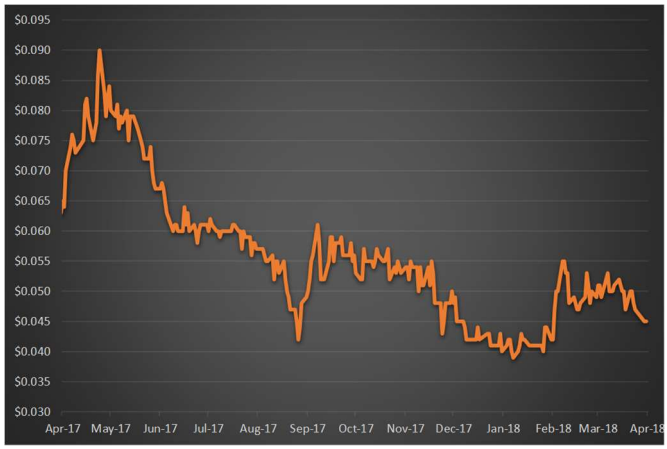
Actinogen Medical (ASX: ACW)

Initiation of Coverage – Tuesday 10 April 2018

Breaking the long dry spell in Alzheimer's treatment

20 years ago, a diagnosis of cancer was often considered a death sentence; today the majority of patients survive for more than five years through significant advances in diagnosis and treatment. 25 years ago, the first treatment for Alzheimer's disease was brought to market; yet today the prognosis for Alzheimer's disease has changed very little. The few drugs that are available provide only marginal benefit and the need for new effective therapies has never been more urgent. In the US alone, there are over 5 million Alzheimer's sufferers, and in Australia, it's the leading cause of death for women and second only to cardiovascular disease for men. These current grim statistics are due in large part to the few approved treatments providing only symptomatic relief, and that there has not been a new FDA-approved Alzheimer's treatment since 2003. Age is the biggest risk factor for Alzheimer's and the aging population is resulting in more and more of our loved ones being diagnosed with the disease each year. The challenge is to develop new treatments that result in a shift in Alzheimer's disease prognosis comparable to the substantial progress seen with cancer. The company that successfully brings a drug to market will have access to a global market in the tens of billions of dollars and the potential to create the next Alzheimer's blockbuster. Actinogen Medical aspires to be part of that shift. The company's unique focus is on the development of Xanamem, a drug that targets cortisol (rather than amyloid plaques). This target has strong published scientific support indicating a promising chance of success. Actinogen's Phase 2 trial of Xanamem, entitled XanADu, is expected to complete in 2019. On this basis, we value the company at 10 cents per share base case and 26 cents per share optimistic case. Our target price of 18 cents per share sits at the midpoint of our valuation range. We see Actinogen being re-rated by the progress of the XanADu trial, particularly with an interim analysis due in May/June 2018 prior to the full results in the second quarter of 2019.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.044	$0.18



Stock details

Daily Turnover: ~A$41,000
Market Cap: A$32.9m
Shares Issued: 747.2m
52-Week High: $0.09
52-Week Low: $0.039

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About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX), most of which are headquartered in Australia and New Zealand. ASX hosts one of the world's premier equity markets for biotech and medical device companies and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

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Ferry at the end of a rainbow on Sydney Harbour, August 2014

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Introducing Actinogen, ASX: ACW

Actinogen, with Xanamem, may have the first new Alzheimer's drug since 2003. In this report we present the specifics behind why Xanamem, now in Phase 2, has the potential to become a successful treatment for mild Alzheimer's disease. Such a claim might be considered bold due to Alzheimer's clinical trials eliminating hundreds of drug candidates since the last approved drug, Namenda, came on the market in 2003. Given the urgent need for new Alzheimer's drugs, if Xanamem yields favourable data in its Phase 2 – and top-line results are expected in the first half of 2019 – the Sydney-based Actinogen will be worth significantly more than their current US$25m market capitalisation.

Xanamem, an '11β-HSD1 inhibitor', represents a new treatment approach for Alzheimer's. Observers of the Alzheimer's space will have become used to hearing about drugs in research that target amyloid beta, or tau, or 5-HT6, none of which, to date, have proven successful. Xanamem can potentially treat cognitive impairment in Alzheimer's and other neurodegenerative diseases by reducing excess cortisol production in the brain. It does this by targeting an enzyme called 11β-HSD1 and this mode of action, as a treatment pathway for Alzheimer's, is new. To provide clinical proof of this mode of action – coined the Cortisol Hypothesis – Actinogen commenced a Phase 2 study of Xanamem called 'XanADu' in mild Alzheimer's in mid-2017. The company expects to complete recruitment for this study by the end of 2018 and read out top-line data from this study in the first half of 2019.

ACTINOGEN'S DRUG REPRESENTS A NEW TREATMENT APPROACH FOR ALZHEIMER'S

What is 11β-HSD1 and why is it considered an important drug target in Alzheimer's? The enzyme 11β-hydroxysteroid dehydrogenase type 1, or 11β-HSD1 for short, converts cortisone to cortisol inside cells. Cortisol is a steroid hormone vital among other things for the body's production of energy. Excess cortisol has historically been associated with a range of chronic health conditions[1], and a large body of research has now established a link between elevated brain levels of cortisol and the cognitive decline seen in Alzheimer's disease. Moreover, it has been shown *in vivo* that this decline improves once excess cortisol production is reduced. Research on cortisol, 11β-HSD1, and Alzheimer's was conducted at the University of Edinburgh, where a drug discovery effort ultimately resulted in Xanamem. In 2014, Actinogen acquired the company that was developing Xanamem.

What is the evidence to date of Xanamem's effectiveness in Alzheimer's? The Edinburgh scientists, which we call the Edinburgh Group, gathered and published considerable *in vivo* evidence on the effectiveness of their 11β-HSD1 inhibitors in Alzheimer's disease, which we evaluate in this report. In one important 2015 paper they noted a marked increase in cognition and reduction in amyloid plaques in an animal model of Alzheimer's when 11β-HSD1 inhibitors are used[2]. Actinogen confirmed, in Phase 1 studies in healthy volunteers, high bioavailability of Xanamem at therapeutic levels leading to concentrations in the brain adequate to inhibit the 11β-HSD1 enzyme and reduce the production of cortisol. The company has now progressed into Phase 2, with its XanADu clinical trial.

What is XanADu and what are Xanamem's prospects in that study? XanADu is a 174-patient double blind, placebo-controlled Phase 2 study of Xanamem in mild Alzheimer's disease in which the patients are randomised

[1] Clin Endocrinol (Oxf). 2009 Dec;71(6):779-86. Epub 2009 Feb 18.
[2] Endocrinology. 2015 Dec;156(12):4592-603. Epub 2015 Aug 25.

1:1 to either 10 mg daily Xanamem or placebo for twelve weeks. The study is being conducted in 20 sites in the US, the UK and Australia. The co-primary endpoints are improvements in two standard measures of Alzheimer's severity called 'ADAS-Cog 14' and 'ADCOMS'. In addition, numerous secondary outcome measures are being used, increasing the likelihood of clinical success. A 2013 guidance document released by the FDA on Alzheimer's drugs outlined that for mild Alzheimer's disease, changes in cognition are considered clinically relevant even without any associated functional changes; this raises the chances that Actinogen's drug can show meaningful therapeutic benefit. The FDA released an update to this guidance document in February 2018, further consolidating the adaptable approaches to approving Alzheimer's treatments that are being established by global regulatory authorities.

If Actinogen is so good, why is it only capitalised at A$32.9m/US$25.2m? It's fair to say that Alzheimer's has been something of a 'drug developer's graveyard' over the last decade and a half, which has made investors reluctant to give too high a market capitalisation to Actinogen at this stage of Xanamem's development. That said, the 'Cortisol Hypothesis' is fresh in the Alzheimer's drug development field, when compared to the historical approach of targeting the amyloid beta and tau proteins. The Cortisol Hypothesis has significant patient population data behind it, most notably with the recent AIBL study which verified the hypothesis in >400 patients over six years[3]. Actinogen can re-rate markedly should an interim analysis of the XanADu study in mid-2018 recommend that the trial proceed as planned.

Ten reasons to look at Actinogen

1) **Actinogen is working on a differentiated mechanism of action in Alzheimer's and dementia**. Whilst most drug development efforts in Alzheimer's have historically focused on targeting amyloid beta and tau, the approach of inhibiting cortisol production in the brain has yet to be explored as deeply. Numerous independent findings in recent years, including a number derived from clinical evidence, suggests the Cortisol Hypothesis has merit.
2) **The data on cortisol inhibition and on Xanamem is exciting**, with many published papers, reporting both human and animal data, that show that it is possible to improve cognition via inhibiting cortisol in the brain.
3) **The commercial potential of a new Alzheimer's drug is immense**. Whilst numerous drugs in development have failed over the last decade, the demand for new Alzheimer's drugs continues to grow as populations age. In America alone an estimated 5.5 million people have Alzheimer's disease[4]. Any drug that is successful in clinical trials is likely to be a blockbuster.
4) **The regulatory environment for new Alzheimer's drugs is favourable**. A 2013 guidance from the FDA means that drugs developed for earlier-stage Alzheimer's patients only, must improve cognition rather than function where improvement is difficult to measure. This notionally makes it easier for drugs like Xanamem, which is being studied in mild Alzheimer's, to ultimately gain approval.

THE COMMERCIAL POTENTIAL OF A NEW ALZHEIMER'S DRUG IS IMMENSE

[3] Biol Psychiat: Cog Neurosci Neuroimaging. 2017; 2: 45-52.
[4] Alzheimers Dement. 2016 Apr;12(4):459-509.

5) **Xanamem has a good safety profile,** with the drug having been well-tolerated in over 100 clinical trial subjects and patients in Single and Multiple Ascending Dose studies, as well as in the current XanADu Phase 2 trial.
6) **Xanamem is now recruiting in Phase 2**. The initiation of the XanADu study in June 2017[5] puts Actinogen on track to potentially complete recruitment for this Phase 2 trial before the end of 2018 and read out top-line results in 2019.
7) **Actinogen is funded for its next stage of development**. A late 2017 raising of A$5.3m at 4 cents per share provided the necessary capital to finish the XanADu study, which we believe can lead to a significant deal with a major pharmaceutical partner in the event of favourable data.
8) **Xanamem is a 'pipeline in a product'**. The evidence to date has suggested that Xanamem could have utility across a range of conditions characterised by raised cortisol and cognitive decline. Actinogen intends to prioritise Diabetes-Associated Cognitive Impairment (DACI) for its second indication. Post-traumatic stress disorder (PTSD) and post-myocardial infarction (post-MI), among others, are also under consideration.
9) **Actinogen has an accomplished management team**. CEO Dr Bill Ketelbey has many years of experience in medical affairs and drug development with Big Pharma and knows the Alzheimer's space well, having been involved in the development of Aricept, the market leading Alzheimer's treatment. Backing Ketelbey is a board with all the requisite knowledge and skills to build an early-stage Life Sciences company including recent appointees, Drs Geoff Brooke, one of Australia's most credentialed biotechnology venture capitalists, and George Mostyn, whose >25 years' experience in the biotechnology industry included being Senior Vice President of Development and Chief Medical Officer at Amgen.
10) **Actinogen is undervalued on our numbers**. We value Actinogen at 10 cents per share base case and 26 cents per share optimistic case. Our target price of 18 cents per share sits at the midpoint of our valuation range. We see a significant re-rating in Actinogen stock should the XanADu trial read out positive top-line results in 2019.

[5] See the Actinogen market release dated 22 June 2017 and headlined '*First US patients treated in landmark Alzheimer's disease trial*'.

2018 – A changing of the guard in Alzheimer's research

To properly understand the investment opportunity presented by Actinogen, it's necessary to understand the various hypotheses that have historically been employed in Alzheimer's drug development strategies. The lack of success of most of these hypotheses to date opens the way for Actinogen's Cortisol Hypothesis.

ACTINOGEN MAY HELP BREAK A 14 YEAR DRY SPELL IN ALZHEIMER'S DRUG DEVELOPMENT

Existing Alzheimer's therapies are inadequate – this is Actinogen's opportunity. Alzheimer's disease is a chronic brain disease in which the patient's memory, intellectual abilities, and personality gradually erode. The disease today is a high prevalence one in all advanced industrial countries, with around 11% of people over the age of 65 suffering Alzheimer's dementia[6]. That translates to >5 million patients in the US alone[7]. Despite this huge market opportunity, there are a paucity of drug treatment options available. We noted on the front page of this report that the first treatment for Alzheimer's disease was brought to market 25 years ago. That was Tacrine, the first of the cholinesterase inhibitors, developed by Warner-Lambert and FDA-approved in September 1993.That drug was something of a false start, because it caused liver damage in many patients[8] and was eventually withdrawn from the market. Three subsequent cholinesterase inhibitors gained FDA approval between 1996 and 2001 - Aricept[9], Exelon[10] and Razadyne[11] - and showed similar effectiveness in Alzheimer's but without the liver damage. How effective in treating the Alzheimer's? Not much – they provide around 6 months benefit on average. Cognition initially improves but has typically returned to baseline at or before the 36-week mark[12], which was not a great outcome given that patients could expect to live close to eight years after the start of therapy[13]. The story of patients on Namenda[14], a NMDA receptor antagonist, is similar, with the drug merely slowing the decline across most measures over 28 weeks[15].

No new drug has been approved in Alzheimer's disease since 2003 – this, too, is Actinogen's opportunity. Namenda was the last Alzheimer's drug to gain FDA approval, in October 2003. All we've had since then are clinical failures, many at Phase 3, which we profile in Appendix I of this note. Indeed, one recent paper tracked 413 different Alzheimer's drug studies between 2002 and 2012 and found a 99.6% failure rate![16]. As with new drugs under development for any disease, the failure of Alzheimer's drug candidates could be attributed to what we didn't know about Alzheimer's biology 10 or 15 years ago[17]. That said, as we note in Appendix I, part of the dry

[6] Source: The Alzheimer's Association, 2017 Alzheimer's disease Facts and Figures. The Alzheimer's Association sources data from Neurology. 2013 May 7;80(19):1778-83. Epub 2013 Feb 6.
[7] It's interesting to note that widespread public awareness of Alzheimer's in the Western world really only started in the 1970s.The turning point was probably 1976, when the American neurologist Robert Katzman (1925-2008) published an editorial in the journal *Archives of Neurology* (Arch Neurol. 1976 Apr;33(4):217-8) arguing that Alzheimer's was the fourth or fifth most common cause of death in the United States, not just a normal process of ageing.
[8] JAMA. 1994 Apr 6;271(13):992-8.
[9] Generic name donepezil, developed by Pfizer and Eisai and FDA approved in December 1996.
[10] Generic name rivastigmine, developed by Novartis and FDA approved in April 2000.
[11] Generic name galantamine, developed by J&J and FDA approved in February 2001. The drug, identified in daffodil bulbs, has its origins in Homer's Odyssey (true story!) and several decades of pharmacological work in Eastern Bloc countries in the 20th Century AD – see *Slivers of Science in Homer's 'The Odyssey'* by Matt Kaplan, Discover Magazine, November 2015.
[12] CNS Drugs. 2010 Feb;24(2):163-76
[13] BMC Neurol. 2014 Apr 11;14:83.
[14] Generic name memantine, developed by Forest Laboratories (which was acquired by Actavis in 2014).
[15] See N Engl J Med. 2003 Apr 3;348(14):1333-41.
[16] Alzheimers Res Ther. 2014 Jul 3;6(4):37. The first author on this paper is Professor Jeffrey Cummings of the Cleveland Clinic, who serves on Actinogen's Clinical Advisory Board.
[17] See *Why coming up with a drug for Alzheimer's is so devilishly hard* by Carolyn Y. Johnson, The Washington Post, 12 January 2018.

spell has had to do with poor clinical trial construction, the lessons of which Actinogen's management team has heeded as it designed the XanADu trial. The scarcity of drug approvals for Alzheimer's can also be partly blamed on the unsuccessful single-minded focus on targeting two proteins considered hallmarks of Alzheimer's disease, amyloid and tau; the disillusionment and disappointment of that focus opens the way for Actinogen and Xanamem.

ACTINOGEN BENEFITS FROM THE DECLINE IN POPULARITY OF THE AMYLOID HYPOTHESIS

Alzheimer's drug research has evolved over the years through a series of hypotheses that have guided drug research. Alzheimer's may have been first described by the German psychiatrist Alois Alzheimer (1864-1915) in 1906[18], but the first potential drug targets for the condition weren't developed for another seven decades, when scientists started generating hypotheses about what caused the disease at the molecular level. There are now at least seven hypotheses:

THE AMYLOID HYPOTHESIS HAS BEEN AROUND SINCE THE 1980s

- **The cholinergic hypothesis**. The first significant approach, developed in the 1970s, held that deficiencies in a neurotransmitter[19] called acetylcholine, essential for processing memory and learning, was involved in the development of Alzheimer's[20]. That approach ultimately led to the abovementioned cholinesterase inhibitor drugs, which work by stopping the acetylcholinesterase enzyme from breaking down acetylcholine in the brain.
- **The amyloid and tau hypotheses**. The pathology of Alzheimer's had been relatively easy to describe in autopsies from Alois Alzheimer onwards – a shrunken brain, numerous plaques in the brain of protein deposits, and tangled bunches of 'fibrils' (ie thin fibres) within brain cells. However, the soluble building blocks of the plaques and the neurofibrillary tangles weren't elucidated until the 1980s – amyloid beta for the plaques, in 1984[21], and tau, for the tangles, around 1986[22]. This led to substantial drug development interest on the assumption that targeting these two abnormal proteins would be 'disease modifying' for Alzheimer's disease.
- **The inflammation hypothesis**. The observation from about 1986 that immune cells were present in the brains of Alzheimer's patients[23] led to the view that inflammation may be a major cause of nerve cell destruction in the disease.
- **The glutamatergic hypothesis**. In the late 1980s[24] several groups linked the cognitive decline seen in Alzheimer's to an excess of a neurotransmitter in the brain called glutamate. This hypothesis led to Namenda, which blocks the N-methyl-d-aspartate (NMDA) receptors to which glutamate binds.
- **The oxidative stress hypothesis**. In this view, which originated in the mid-1990s[25], reactive oxygen species from a variety of sources such as metals, when not neutralised with antioxidants, proceed to damage brain cells[26].

[18] J Med Biogr. 2011 Feb;19(1):32-3.
[19] Neurotransmitters are chemicals that neurons use to communicate with each other.
[20] Brain. 1976 Sep;99(3):459-96.
[21] Biochem Biophys Res Commun. 1984 May 16;120(3):885-90.
[22] Proc Natl Acad Sci U S A. 1986 Jul;83(13):4913-7. The protein was named after the 19th letter of the Greek alphabet. Its function in healthy brain cells is to form the 'railway ties' that hold the microtubule 'tracks' in place. Microtubules, in turn, route nutrients and molecules around the cell.
[23] See, for example, Virchows Arch B Cell Pathol Incl Mol Pathol. 1986;51(3):247-54.
[24] Neurobiol Aging. 1989 Sep-Oct;10(5):593-602.
[25] Am J Clin Nutr. 2000 Feb;71(2):621S-629S.
[26] A prominent feature of the complementary medicine scene since the 1980s has been the recommended use of antioxidants as prophylactics or therapeutics for various diseases. When we breathe, the oxygen taken in by our bodies is processed to produce energy, however in the process various 'free radicals' are created including 'reactive oxygen species', that is, molecules with an oxygen component where there are unpaired electrons. A free radical must combine with a complementary molecule to achieve chemical stability. If it bonds with a positively charged molecule, its charge is neutralised. If not, the oxygen component of the free radical can damage cells in the body in a process called oxidative stress. Reactive oxygen species

- **The vascular hypothesis**. This hypothesis, also from the mid-1990s[27], suggests that a weakening of the blood vessels feeding the brain deprive it of valuable nutrients, leading to the development of the plaques and tangles.
- **The cholesterol hypothesis**. This hypothesis originates in part from the fact that Apolipoprotein E is a cholesterol transport protein, and presence of the E4 allele[28] of the gene (ApoE4) in patients is associated with a higher incidence of late-onset Alzheimer's disease [29].

Up until recently the amyloid hypothesis has dominated. Of all these hypotheses, the one that has captured the most research interest to date has, by a substantial margin, been the amyloid hypothesis, where the build-up of toxic amyloid beta protein in the brain is held to cause the disease, and drugs that target amyloid beta are believed to be the most promising approach to treat the disease[30]. The amyloid hypothesis rose to be the prevailing paradigm in Alzheimer's research because: the amyloid plaques are the dominant pathology seen in Alzheimer's; the genes that were discovered which were involved with familial Alzheimer's tended to work through amyloid beta[31]; and amyloid deposition appears to lead to early-onset dementia in Down Syndrome in many cases[32]. The amyloid hypothesis has led to numerous drug candidates being developed for clinical research. Some of the drugs developed act directly on the amyloid beta protein, and others target auxiliary proteins required for amyloid beta, such as the secretases[33]. So far however, none of these drugs have proved successful in hundreds of clinical trials.

The failure of the drugs developed using the amyloid hypothesis necessitates a widened search for drugs with a different mode of action, including Actinogen's. These high-profile drug failures have increasingly led researchers to explore other mechanisms where amyloid beta is perhaps an effect of the disease rather than a cause[34]. We call this 'the changing of the guard' in Alzheimer's and the Cortisol Hypothesis may be one such approach that attracts more adherents as thought leaders in the field start to widen their horizons[35].

THE NEXT SUCCESSFUL ALZHEIMER'S DRUG OPENS UP THE WHOLE FIELD

The next successful drug – and it could be Actinogen's – opens up the whole field. The amyloid hypothesis hasn't died yet. Indeed, there's a reasonable chance that a drug like Roche's gantenerumab or Biogen's adacanumab at the right dose could verify the hypothesis. However, before the amyloid hypothesis achieves its first clinical verification, there is potential for Actinogen to be the first company to achieve significant success if Xanamem is proven effective.

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are widely believed to cause or aggravate various diseases such as neurodegenerative diseases, cancer and stroke. Antioxidants are assumed to counteract the oxidative stress involved

[27] Neurol Res. 1993 Jun;15(3):146-53.

[28] In genetics an allele is one of a number of alternative forms of a gene resulting in different gene products. A single allele for each gene locus is inherited separately from each parent.

[29] Neurology. 1993 Aug;43(8):1467-72. The gene for APOE had been mapped in 1992 to a region on chromosome 19.

[30] Tau regulation is directly downstream of amyloid beta (JAMA Neurol. 2014 Apr;71(4):505-8) so the tau hypothesis had less chance historically of capturing the same level of belief as the amyloid hypothesis.

[31] Biochem J. 2012 Sep 1;446(2):165-77.

[32] Alzheimers Dement. 2016 May;12(5):538-45. Epub 2015 Sep 9. Note, the genes for the Amyloid Precursor Protein and for Down Syndrome are both on Chromosome 21.

[33] Amyloid beta results when Amyloid Precursor Protein (APP) is cut by a secretase enzyme. Amyloid beta 40, an amyloid beta protein which is 40 amino acids in length, is the more common, however a slightly longer protein called amyloid beta 42, which as the name suggests is 42 amino acids long, tends to aggregate into plaques more easily. The main secretases that do the APP cleaving are the beta- and gamma-secretases, while alpha-secretase cleavage on APP prevents amyloid beta deposition.

[34] Acta Neuropathol Commun. 2014 Sep 18;2:135.

[35] It's interesting to note that as early as 2011 researchers at Abbott Laboratories, now AbbVie, were working on 11β-HSD1 inhibitors – see J Neurosci. 2011 Apr 6;31(14):5406-13.

The Cortisol Hypothesis in Alzheimer's and why it has significant merit

Persistently raised cortisol production may be a significant factor in the dementia associated with Alzheimer's disease. Whenever you experience stress, a hormonal cascade begins in the brain that passes through a succession of glands called the 'hypothalamic–pituitary–adrenal axis' or HPA axis and produces the hormone called cortisol. This steroid hormone, one of a class of hormones called the glucocorticoids, has a function in our bodies that goes far beyond stress. Most cells in the body have cortisol receptors, allowing the hormone to play an important role in regulating metabolism and inflammation, amongst other things. Indeed, it was the role of cortisol in modulating inflammation that led to the development of the glucocorticoid anti-inflammatory drugs such as prednisone[36]. Cortisol is, however, best associated in the public mind with the body's stress response[37] because in these conditions it helps to increase heart rate, blood pressure, blood glucose, respiration and other physiological responses the body needs in response to stress. Too much cortisol for too long, however, can lead to a range of problems including impaired immune function[38] and lower bone density[39], weight gain[40], high blood pressure,[41] and high cholesterol[42]. Significantly, high cortisol levels are toxic to the brain and are known to be associated with learning and memory problems[43], with evidence building for some time that the stress hormone may play a role in cognitive decline and ultimately with the development and progression of Alzheimer's dementia.

HIGH CORTISOL IS ASSOCIATED WITH LEARNING AND MEMORY PROBLEMS

The evidence supporting the Cortisol Hypothesis has been building for 25 years. Way back in 1968 Bruce McEwan at Rockefeller University in New York discovered that there were adrenal steroid receptors in the hippocampus[44], the region of the brain responsible for memory. The implication was that cortisol may interfere with memory formation and retention, and by the 1990s there was evidence in humans to demonstrate this. The science leading to that point begins in the late 1980s when scientists at McGill University in Montreal described an important link between cortisol and cognitive impairment in rats[45]. In 1990 a related group showed the link in primates[46]. In the 1990s the McGill scientists, whose research interests include a focus on how stress impacts cognition and mental health over time[47], followed a cohort of 51 elderly people for five years and showed that 30% had elevated cortisol levels, which was associated with poorer memory function[48] and atrophy (shrinkage) of the hippocampus[49]. That the memory worsening was related to Alzheimer's was suggested by 2001 studies performed

THE CORTISOL HYPOTHESIS EVIDENCE HAS BEEN BUILDING FOR 25 YEARS

[36] Work on corticosteroids won the American scientists Philip Hench (1896-1965) and Edward Kendall (1886-1972) a share of the 1950 Nobel Prize in Physiology or Medicine with the Swiss Tadeus Reichstein (1897-1996).
[37] First proposed by the Canadian endocrinologist Hans Selye (1907-1982) in the mid-1930s – see Nature, Volume 138, Issue 3479, pp. 32.
[38] Med Hypotheses. 1991 Mar;34(3):198-208.
[39] Calcif Tissue Int. 2005 Sep;77(3):134-8. Epub 2005 Sep 8.
[40] Domest Anim Endocrinol. 2016 Jul;56 Suppl:S112-20. Epub 2016 Mar 31.
[41] Clin Exp Pharmacol Physiol Suppl. 1998 Nov;25:S51-6.
[42] J Am Geriatr Soc. 1995 Dec;43(12):1345-9.
[43] Ann N Y Acad Sci. 2006 Jul;1071:434-7.
[44] Nature. 1968 Nov 30;220(5170):911-2.
[45] Science. 1988 Feb 12;239(4841 Pt 1):766-8.
[46] J Neurosci. 1990 Sep;10(9):2897-902.
[47] Nat Rev Neurosci. 2009 Jun;10(6):434-45. Epub 2009 Apr 29.
[48] Neurobiol Aging. 1996 Jan-Feb;17(1):95-105.
[49] Nat Neurosci. 1998 May;1(1):69-73. Interestingly, in 2002 the McGill team showed that simply inhibiting cortisol secretion by the administration of a drug called metyrapone wouldn't improve memory in test subjects with high cortisol - see J Clin Endocrinol Metab. 2002 Aug;87(8):3798-807.

at the VA Puget Sound Health Care System in Seattle, where scientists found higher cortisol levels in the cerebrospinal fluid was associated with the afore-mentioned ApoE4 Alzheimer's gene[50]. In 2005 the laboratory of Professor Jonathan Seckl at the University of Edinburgh showed that high plasma cortisol levels correlated with worsening cognition in healthy older men[51]. The following year came two seminal findings related to Alzheimer's – one from the University of California Irvine showing cortisol contributing to amyloid beta and tau pathology in mouse models of the disease[52], and one from Washington University in St. Louis showing from patient data that the severity of Alzheimer's dementia correlated with levels of cortisol[53].

More recent evidence supporting the Cortisol Hypothesis. In 2015 a network of German psychiatric researchers showed that when elevated cortisol levels were observed in the early stages of Alzheimer's, the faster the disease progressed[54]. That same year researchers evaluating a large database of elderly people in Iceland found a link between cortisol and brain volume[55]. In 2016 researchers associated with the Alzheimer Disease Neuroimaging Initiative, which looks for biomarkers as predictors of Alzheimer's, named cortisol among six other biomarkers which when used together could reliably predict disease status three years from the time of sample collection[56]. Shortly after this paper was published, another group tracking older people in the US city of Baltimore were able to show that cortisol in urine could predict the onset of Alzheimer's around three years before diagnosis[57].

The evidence from Cushing's syndrome. An easier way to test the Cortisol Hypothesis is to look at how treatment for Cushing's disease reduces the incidence of dementia. Cushing's is a rare[58] disorder of cortisol overproduction characterised by weight gain around the midsection and fatty deposits around the face and upper back. It also tends to cause dementia-like symptoms if left untreated. In 1999 a team at the University of Michigan looked at patients with Cushing's and found that treatment which successfully reduced the overproduction of cortisol resulted in increased hippocampal volume[59]. That study didn't evaluate memory changes or improvement. In dementia, however, hippocampal volume and memory tend to move together[60].

The 2016 evidence from 'AIBL' provided major validation to the Cortisol Hypothesis. The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) is a study funded by the CSIRO[61] seeking to discover biomarkers and other factors that would predict the development of Alzheimer's disease. In 2017 the AIBL researchers reported data from 416 test subjects tracked over 6 years showing a significant link between elevated cortisol and Alzheimer's dementia. The study authors proposed that therapies targeted towards lowering cortisol may be helpful in slowing the cognitive decline in Alzheimer's disease. This work was presented at the Alzheimer's Association International Conference in Toronto in July 2017.

THE AIBL STUDY HAS VALIDATED THE CORTISOL HYPOTHESIS

[50] Neurology. 2001 Apr 24;56(8):1094-8.
[51] Psychoneuroendocrinology. 2005 Jun;30(5):505-15. Epub 2005 Jan 25. The same cohort for this study had previously been used to show a link between brain size and cognition – see Neurology. 2002 Jul 23;59(2):169-74.
[52] J Neurosci. 2006 Aug 30;26(35):9047-56.
[53] Am J Psychiatry. 2006 Dec;163(12):2164-9.
[54] Neurobiol Aging. 2015 Feb;36(2):601-7. Epub 2014 Oct 31.
[55] The link was cortisol in saliva when measured in the evening – see Neurology. 2015 Sep 15;85(11):976-83. Epub 2015 Aug 19.
[56] JAMA Neurol. 2016 Feb;73(2):203-212. Epub 2015 Dec 14.
[57] Neurology. 2017 Jan 24;88(4):371-378. Epub 2016 Dec 16.
[58] That is, annual incidence of 2 or 3 per million people – see Neuroendocrinology. 2010;92 Suppl 1:1-5. Epub 2010 Sep 10.
[59] Biol Psychiatry. 1999 Dec 15;46(12):1595-602.
[60] Brain. 2010 Apr;133(Pt 4):1163-72.
[61] The Commonwealth Scientific and Industrial Research Organisation, an Australian government agency for scientific research.

The evidence from Actinogen and its academic collaborators. The Edinburgh Group led by Professors Jonathan Seckl and Brian Walker have performed extensive pre-clinical development on molecules that work to inhibit cortisol. This developmental work is expanded upon in the next section. Currently XanADu represents the only clinical trial being conducted in Alzheimer's disease using a drug based on the Cortisol Hypothesis.

The evidence that Xanamem can treat Alzheimer's

One of the most notable merits of the Cortisol Hypothesis is that it has attracted significant backing in the research community since the 1990s. Between 2001 and 2014 the Wellcome Trust, the pre-eminent UK medical research charity, invested around US$23m supporting the team at the University of Edinburgh in the development of 11βHSD1 inhibitors to target excessive cortisol production in the brain. Actinogen has now inherited the scientific evidence that guided the Wellcome Trust. One could assert that the Actinogen opportunity is undervalued to the extent that the company's current market capitalisation isn't much more than the money the Wellcome Trust initially invested.

THE WELLCOME TRUST SPENT US$23M ON DEVELOPMENT WORK THAT LED TO XANAMEM

Xanamem is an 11βHSD1 inhibitor, Actinogen's answer to the Cortisol Hypothesis. Xanamem, originally designated UE2343, is the product of many years of research on the link between cortisol and cognitive impairment at Edinburgh University. Back in 1995, for example, the Seckl lab had shown, *in vivo,* that antidepressant therapy, by increasing glucocorticoid receptors in the brain, could improve memory[62]. As Seckl and colleagues considered whether drugs could act on glucocorticoids to improve memory, they started looking at whether 11β-hydroxysteroid dehydrogenase type 1, an enzyme better known as 11β-HSD1, might be a target of interest. 11β-hydroxysteroid dehydrogenase had been known about since 1953[63] as an enzyme that could convert cortisone to cortisol, and in 1989 it had been cloned, that is, produced using the standard tools of genetic engineering[64]. By 1994 the Seckl lab had helped establish that there were in fact two 11β-HSDs[65], and the 1989 clone, now called Type 1, performed, in the brain, the cortisol-regenerating function originally identified in the 1950s[66]. Significantly, in 2001 the Edinburgh Group were able to show that 11β-HSD1 knockout mice, which lacked the gene to make the enzyme and therefore couldn't naturally produce intracellular cortisol, didn't experience cognitive impairment[67]. This opened the door for a potential drug therapy. Acting directly on the HPA axis wasn't an option because that would impair the ability for patients to mount a normal stress response. Acting on 11β-HSD1 in the neurons in the brain, however, was considered more likely to succeed because this enzyme was highly concentrated in regions of the brain important for cognition, like the hippocampus[68]. The key was to discover and develop drugs that would specifically target the type 1 enzyme, and that would cross the blood-barrier in adequate concentrations to be active within the brain[69].

[62] Neuroscience. 1995 Jun;66(3):571-81.
[63] J Clin Endocrinol Metab. 1953 Sep;13(9):1125-6.
[64] J Biol Chem. 1989 Nov 15;264(32):18939-43.
[65] Part of their contribution was the 1993 discovery of the type 2 isozyme – see Endocrinology. 1993 Jun;132(6):2614-21.
[66] J Neuroendocrinol. 1994 Jun;6(3):285-90.
[67] Proc Natl Acad Sci U S A. 2001 Apr 10;98(8):4716-21. Epub 2001 Mar 27.
[68] Endocrinology. 1990 Sep;127(3):1450-5.
[69] For a review of the science just described see Front Neuroendocrinol. 2011 Aug;32(3):265-86. Epub 2010 Dec 7.

The Edinburgh Group showed that 11βHSD inhibition could improve cognition, as early as 2004. The first step towards exploring the validity of the 11β-HSD1-inhibition approach in cognition was to investigate carbenoxolone, a drug derived from the root of the liquorice plant, *Glycyrrhiza glabra* and clinically studied in the treatment of ulcers since the 1960s[70]. Carbenoxolone was known to be a nonselective 11β-HSD inhibitor. Two small crossover studies were run by the Edinburgh Group in elderly men, each randomised, double-blinded, and placebo-controlled. In the first, using 100 mg of carbenoxolone three times per day improved verbal fluency after four weeks. In the second the same dosage improved verbal memory in 12 men with Type 2 Diabetes. Each outcome was statistically significant ($p<0.01$). This data was published in the *Proceedings of the National Academy of Sciences* in April 2004[71]. Having demonstrated the validity of cortisol inhibition in a pilot study in humans, the Edinburgh Group commenced a full development programme that resulted in Xanamem.

ACTINOGEN BENEFITS FROM OVER 10 YEARS OF EDINBURGH SCIENCE

The Edinburgh Group dedicated ten years from 2004 to 2014 to developing the science behind Xanamem. The Edinburgh Group proceeded to develop more specific inhibitors of 11β-HSD1 that could penetrate the blood-brain barrier[72] and be tested in animal models. A key 2010 paper showed how 11β-HSD1 knock-out mice, that lack the enzyme and therefore can't make cortisol, have much better memories than aged normal mice, and that treating these normal aged mice with an Edinburgh-developed 11β-HSD1 inhibitor could improve memory similar to the levels seen in the knockouts[73]. They also found, in a six-year longitudinal study in men over 65, that measures of systemic levels of 11β-HSD1 could predict cognitive decline and brain atrophy[74]. In 2015 the Edinburgh Group applied their compounds specifically to Alzheimer's in an animal model of the disease[75] and showed, remarkably, that their compounds could not only improve memory, but also be disease-modifying by decreasing amyloid plaque accumulation in the brain[76]. The US$23m Wellcome Trust money noted above, which came from its Seeding Drug Discovery Programme, had funded the development of these compounds. By 2014 the Edinburgh/Wellcome programme had developed UE2343 (Xanamem), the drug that Actinogen licenced later that year. The final development study undertaken by Edinburgh in 2014 was a 48-subject Phase 1 Single Ascending Dose study[77] in healthy volunteers.

[70] See Doll. et. al., *Clinical trial of a triterpenoid liquorice compound in gastric and duodenal ulcer*. Lancet, 2, 793-796. Sir Richard Doll (1912-2005), the British epidemiologist, is famous for the British Doctors Study which provided convincing statistical proof that smoking increased the risk of lung cancer.
[71] Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6734-9. Epub 2004 Apr 7. In this paper the Edinburgh Group also show, from post-mortem tissue, that 11B-HSD1 is the active enzyme in the human brain, not 11B-HSD2.
[72] Bioorg Med Chem Lett. 2007 May 15;17(10):2838-43. Epub 2007 Feb 25.
[73] J Neurosci. 2010 Oct 13;30(41):13867-72. Around the same time as this finding the Edinburgh Group demonstrated that 11β-HD1 inhibition could potentially be disease-modifying, finding that 11β-HD1 in the brain, but not circulating corticosterone levels nor tissue corticosteroid receptor expression, correlated with lower cognition in aged mice (see J Neurosci. 2010 May 19;30(20):6916-20). A later paper showed, mechanistically, how the memory impairment of high cortisol would work: by saturating all the mineralocorticoid receptors in the brain so that the cortisol spilled over to activate the glucocorticoid receptors – see J Neurosci. 2011 Mar 16;31(11):4188-93.
[74] Neurobiol Aging. 2012 Jan;33(1):207.e1-8. Epub 2010 Oct 18.
[75] The model was Tg2576, created in the mid-1990s using the so-called 'Swedish mutation' of the Amyloid Precursor Protein gene (Science. 1996 Oct 4;274(5284):99-102).
[76] Endocrinology. 2015 Dec;156(12):4592-603. Epub 2015 Aug 25. This data was gathered using a compound called UE2316. The mechanism of amyloid clearance appears to involve action on an enzyme called the 'insulin degrading enzyme', which in turn regulates amyloid beta.
[77] See NCT01770886 at www.clinicaltrials.gov.

Actinogen licensed the 11β-HSD1 project in August 2014. Professors Jonathan Seckl and Brian Walker, with colleague Professor Scott Webster, formed a University of Edinburgh spinout company around the 11β-HSD1 project called Corticrine Ltd, which was granted worldwide commercialisation rights to UE2343 (Xanamem). Xanamem was licensed into Actinogen in August 2014[78] and became that company's primary interest[79].

THE MULTIPLE ASCENDING DOSE STUDY FOR XANAMEM WAS A SUCCESS

Actinogen completed a successful Phase 1 Multiple Ascending Dose of Xanamem in 2015. Actinogen's first task following the licensing of Xanamem in late 2014 was to prepare the drug for its first Phase 2 clinical study. To that end a Multiple Ascending Dose (MAD) study was conducted to confirm the pharmacodynamics in healthy volunteers. In this MAD study[80] 40 healthy volunteers were used to test the safety and pharmacokinetics of 10, 20 and 35 mg twice-daily doses. Also completed within the MAD study were two sub-studies. The first evaluated whether taking Xanamem with or without food had an effect on its mode of action. The second was a pharmacokinetic study of Xanamem in cerebrospinal fluid. The MAD study was completed in August 2015, and it provided critical confirmation that Xanamem was safe and penetrated the brain in concentrations adequate to inhibit the enzyme and decrease the production of cortisol in the brain[81]. The results of that successful trial, and the earlier Single Ascending Dose study, were reported in the *British Journal of Pharmacology* in January 2017[82].

XanADu – testing the Cortisol Hypothesis

THE XANADU STUDY IS RECRUITING PATIENTS WELL

XanADu initiated in mid-2017. Having completed all the necessary preliminary studies, Actinogen was able to plan a definitive proof-of-concept Phase 2 study of Xanamem in the treatment of Alzheimer's disease. XanADu[83] is a 174-patient double blind, placebo-controlled Phase 2 study of Xanamem in mild Alzheimer's in which the patients are randomised 1:1 to either 10 mg daily Xanamem or placebo for twelve weeks[84]. The study is being conducted at 20 study sites in the US, the UK and Australia. Actinogen's Investigational New Drug (IND) application to the FDA was cleared in January 2017 and similar regulatory approvals were received to conduct the study in the UK and Australia over the next few months. The first XanADU patient was dosed in mid-2017. By late November 2017 forty-four patients had been enrolled and as at mid-March 2018, this number had reached 87, the half-way point in the study.

XanADu will reach an interim data analysis point in mid-2018. In late November 2017 Actinogen announced a protocol amendment to XanADu introducing an interim efficacy and safety analysis, that would be managed by an independent Data Safety Monitoring Board (DSMB) once the first 50 evaluable patients have completed 12 weeks of dosing and a further 4 weeks follow-up. Actinogen expects that, at the present rate of recruiting, this

[78] For A$2.5m, settled with 125 million ordinary shares at 2 cents per share.
[79] Actinogen, originally a developer of new generation antibiotics, had done its IPO on the ASX in October 2007. The company's original intention was to bioprospect for actinomycetes in a natural product library sourced in Western Australia. These actinomycetes were expected to allow the creation of new drugs to treat MRSA, that is, Methicillin-Resistant *Staphylococcus Aureus*. Actinogen subsequently used its library to go looking for compounds that were active against cancer stem cells. These bioprospecting activities were shelved after the Corticrine acquisition, which was completed in December 2014.
[80] See NCT02616445 at www.clinicaltrials.gov.
[81] See the Actinogen market release dated 29 September 2015 and headlined '*Positive trials results for Alzheimer's drug Xanamem*'.
[82] Br J Pharmacol. 2017 Mar;174(5):396-408. Epub 2017 Jan 25.
[83] See NCT02727699 at www.clinicaltrials.gov.
[84] Actinogen may have left the impression that XanADu would dose patients in the treatment arm at 35 mg twice daily, which is what the Multiple Ascending Dose study had suggested would work (see Actinogen's 15 July 2016 presentation, slide 15). However, an analysis of all the available data, both *in vivo* and from human subjects, suggested that 10 mg once daily was the most effective appropriate dose.

interim analysis will take place in the first half of calendar 2018. Due to the importance of maintaining the double-blind nature of XanADu, the DSMB analysis will not provide detailed safety or efficacy data. However, a recommendation from the DSMB that the study should continue as planned will signal to Actinogen that Xanamem has not presented any safety concerns in Alzheimer's patients and that XanADu is progressing in a statistically acceptable manner. What the interim analysis may mean for investors, however, is this: before initiating XanADu, Actinogen's consulting biostatisticians evaluated the available data and calculated that 174 patients would be sufficient to demonstrate a treatment effect with statistical significance. For Actinogen to report to the market that XanADu is progressing in a statistically acceptable manner would be very encouraging, particularly given that, at the present rate of recruitment, XanADu will potentially enrol its 174 patients before the end of 2018 and be in a position to read out top-line data in 2019.

XanADu will track multiple efficacy measures. The primary outcome measures for XanADu will be improvements in two measures of Alzheimer's severity called 'ADAS-Cog14' and 'ADCOMS'. There are also four secondary outcome measures. It's worth looking at all XanADu's efficacy measures in turn to appreciate the multitude of ways in which the XanADu investors can capture, analyse, and translate patient data. The large spread of measurements increases the likelihood of a favourable outcome for Actinogen.

- **ADAS-Cog**, short for 'Alzheimer's disease Assessment Scale-cognitive subscale', is considered the gold standard in terms of measuring 'cognition', a term which covers multiple aspects of mental function such as memory, language, praxis[85], and orientation.[86] ADAS-Cog was first published in 1984[87] and has been used to achieve FDA approval for most Alzheimer's drugs to date. The Xanamem investigators will use ADAS-Cog14, a 14-item scale developed in 1997[88].
- **ADCOMS**, short for 'Alzheimer's disease Composite Score', is a relatively recent measure developed in 2016[89] which takes the most sensitive domains from ADAS-Cog, MMSE and CDR-SOB and provides a composite score; it is arguably the most sensitive measure currently available. The idea behind this measure is to be able to show meaningful changes in patients with very early stage disease where there is relative little cognitive impairment and almost no functional impairment. XanADu is one of the first Alzheimer's clinical studies in the world to have ADCOMS as a primary endpoint.
- **CDR-SOB.** CDR, short for Clinical Dementia Rating, was developed in the early 1980s[90] as a way of staging dementia patients. CDR has a global score as well as a 'Sum of Boxes' score, and while both have been found to be adequate staging tools, the higher score available using the SOB approach allows a better chance for a patient to register an improvement in an Alzheimer's drug trial[91]. A key advantage of CDR-SOB is that it is a single scale that measures both cognition and function.
- **MMSE**, short for 'Mini-Mental State Examination', has been around since 1975 as a general-purpose screening tool for dementia[92]. In MMSE, test subjects answer 30 questions designed to evaluate

XANADU IS ONE OF THE FIRST CLINICAL STUDIES TO USE ADCOMS AS AN ENDPOINT

[85] Praxis is the process of getting an idea and initiating and completing a new motor task.
[86] A patient's 'situational awareness' - such as their name and home city or what time of day it is.
[87] Am J Psychiatry. 1984 Nov;141(11):1356-64.
[88] Digit Cancellation, Delayed Word Recall and a Maze test – see Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S13-21.
[89] J Neurol Neurosurg Psychiatry. 2016 Sep;87(9):993-9. Epub 2016 Mar 23.
[90] Br J Psychiatry. 1982 Jun;140:566-72.
[91] Arch Neurol. 2008 Aug;65(8):1091-5.
[92] J Psychiatr Res. 1975 Nov;12(3):189-98.

capabilities such as: writing a short sentence that is grammatically correct, or; correctly identifying the current date. In the resulting score out of 30, 20-26 represents mild cognitive impairment, 10-19 is 'moderate impairment' and 0-9 is 'severe impediment'. XanADu will enrol patients with MMSEs between 20 and 26.

- **RAVLT**, short for Rey's Auditory Verbal Learning Test[93], has been used in tests of cognition for many years[94]. It is a is a measure of episodic memory, where the examiner reads aloud a series of lists of 15 words at the rate of one per second, and the subject must recall what words they can remember from prior lists and whether they have heard words before. RAVLT has proved over the years a reliable tool tracking the underlying pathology of Alzheimer's[95].
- **NTB-ED**. The Neuropsychological Test Battery was developed in 2007[96] as an alternative to ADAS-Cog and designed to be able to detect small changes in Executive Function, that is, the ability to develop plans that help organised thought processes. The Xanamem investigators are using the components from NTB specifically associated with Executive Function rather than memory.

Actinogen benefits from changes in the way the regulators view Alzheimer's treatment outcomes. Historically, an Alzheimer's drug could only be approved if it registered a statistically significant improvement in both cognition and function. By 2013 the FDA realised that drugs that work in early stage patients would be most beneficial, but that functional measurements might not be the ideal way to track efficacy in such patients, since typically early stage patients still had good Executive Function. To address this issue the Agency issued a landmark February 2013 guidance document headlined '*Alzheimer's disease: developing drugs for the treatment of early stage disease'*.[97] Here, the FDA indicates that it will accept cognition-only improvements and is more flexible about how these improvements are tracked, hence Actinogen's choice of multiple outcome measures. In February 2018 an encouraging update of this guidance document[98] from the Agency proposed additional pathways to approval based on the inclusion of acceptable Alzheimer's biomarkers as clinical trial endpoints that could provide valuable secondary proof that a drug is effective.

If XanADu works, what next? Given that Alzheimer's is such a significant area of unmet medical need globally, if XanADu meets either of its co-primary endpoints the drug could advance into a single pivotal study for US registration purposes. Allowing 3-4 years for this pivotal trial to complete and an NDA to be filed, Xanamem could potentially gain expedited FDA approval by 2022. It is expected that Actinogen would complete a significant licence agreement to conduct these registration studies in conjunction with a major Pharma partner.

[93] It was originally developed by the Swiss psychologist André Rey (1906-1965), remembered as an early developer of neuropsychological tests.
[94] Indeed, since 1941 - see Archives de Psychologie, 28, 21.
[95] Neuroimage Clin. 2016 Dec 18;13:415-427.
[96] Arch Neurol. 2007 Sep;64(9):1323-9.
[97] N Engl J Med. 2013 Mar 28;368(13):1169-71. Epub 2013 Mar 13.
[98] Headlined '*Early Alzheimer's disease: Developing Drugs for Treatment - Guidance for Industry'*.

Xanamem: A blockbuster, if the drug works in the clinic

Alzheimer's has turned into a huge global health issue. Alzheimer's is very much a disease of ageing. In America the condition is virtually undiagnosed before the age of 65, at only 0.1% prevalence[99], and it is still relatively rare in the first ten years thereafter, at only 3%. From the age of 75, Alzheimer's becomes commonplace, with 17% of 75-84-year-olds and 32% of people aged 85 and over[100] being diagnosed with Alzheimer's. As a population ages, its Alzheimer's population grows significantly. There are now ~5.5 million Americans with Alzheimer's and by 2030,[101] there are expected to be 8.4 million. Worldwide around 40-50 million people have dementia of some kind, of which around 20 million live in high income countries[102], including >400,000 in Australia[103].

BY 2030, >8 MILLION AMERICANS MAY HAVE ALZHEIMER'S

Older Alzheimer's drugs have been blockbusters[104]. Their long-term effectiveness in treating Alzheimer's may be limited, but Aricept peaked at US$4.2bn in 2010 sales for Eisai and Pfizer; Exelon and the Exelon Patch at just over US$1bn for Novartis in 2011; and Namenda at US$2bn for Forest Laboratories and Lundbeck[105].

Alzheimer's is, prospectively, a US$40bn+ drug market globally. We argue that, once a few new agents have proven successful in clinical trials, Alzheimer's can evolve into a drug market worth at least US$40bn (US$15bn in the US, US$25bn in the rest of the world[106]), based on:

- the size of the patient population;
- the recent pricing dynamics of new agents in other large-market conditions such as cancer; and
- the current mean life expectancy of the patients, which as we noted above can be eight years.

Even US$40bn may prove conservative due to the high cost of aged care – in the US alone Alzheimer's and related dementias cost US$259bn in health care and aged care costs. A new Alzheimer's drug could reasonably be reimbursed at US$20,000-25,000 a year and still be cost-effective[107].

Alzheimer's is just too big a market for Big Pharma to ignore. Traditionally, when a disease turns into a perceived 'drug developer's graveyard', Big Pharma significantly slows or even ceases its R&D investment in the space[108]. Alzheimer's is a little different however - it may have been a drug developer's graveyard since 2003, but Big Pharma has persisted in licensing and trialling candidates, as evidenced as recently as January 2018 when Pfizer, while announcing the closure of their neurodegeneration discovery labs, indicated that it was reallocating the capital to external alliances[109]. We think there are three reasons for Big Pharma's continuing

OLDER ALZHEIMER'S DRUGS HAVE BEEN BLOCKBUSTERS

[99] For background here see Clin Pract Epidemiol Ment Health. 2013 Jun 14;9:88-95.
[100] Source: The Alzheimer's Association, 2017 Alzheimer's disease facts and figures.
[101] That is, under the current priority date. However, Actinogen will be able to apply for patent term extension should Xanamem gained FDA approval, with the years between IND clearance and marketing authorisation being added to the original patent term under the 1984 Waxman-Hatch Act.
[102] Source: World Alzheimer Report 2015.
[103] Source: Dementia Australia, www.dementia.org.au.
[104] For background on the pricing of these drugs see P T. 2015 Apr;40(4):288-9. Note: 'P T' is the journal *Pharmacy and Therapeutics*.
[105] Razadyne was, admittedly, a niche drug, with around US$200m a year in sales in 2008.
[106] The US drug market is roughly 30-40% of the global drug market - see *Why Big Pharma won't get its piece of the $1.2 trillion global drug market* by Matt Herper, Forbes 12 July 2012.
[107] See *Billions saved because FDA didn't rush approval of Alzheimer's drug* by Gene Emery, Reuters, 10 May 2017.
[108] That's more or less what has happened historically for lupus, sepsis, ischemic stroke, pain, obesity and melanoma. Benlysta for lupus, FDA approved in 2011, was the first new agent for lupus in fifty years.
[109] See *Pfizer to cut 300 Jobs as Alzheimer's, Parkinson's research ends* by Jared Hopkins, Bloomberg, 8 January 2018

interest in Alzheimer's. Firstly, the prospective market size is just too big to ignore. Secondly, Alzheimer's is politically important because it could conceivably bankrupt healthcare and aged care systems in the middle of the century[110]. Thirdly, exciting new agents continue to come forward from emerging companies like Actinogen.

The partnering deals in the Alzheimer's space have been significant. Alzheimer's drug candidates from emerging companies generally need to be partnered because of the sheer cost of development – for example, one recent clinical study of 252 patients is understood to have a budget in the order of US$100m[111]. Sometimes Big Pharma just buys the developer outright - witness Bristol-Myers Squibb's April 2014 acquisition of iPierian for $175m, with the potential for additional development and regulatory milestone payments totalling $550m; all to add to its pipeline an anti-tau antibody that was still pre-clinical. More often, however, the programme stays with the developer and is licensed or optioned to a pharma partner at a sometimes-astounding price tag. There have been numerous such deals in Alzheimer's over the last decade[112]. Consider just a few of these, noting as you go that the deals listed were mostly done when the agents were in early stage clinical development, or pre-clinical. We think Actinogen is in line to talk terms like these, or better, once the XanADu data reads out next year.

- **Boehringer Ingelheim / Vitae Pharmaceuticals[113], US$242m, June 2009**. Boehringer Ingelheim paid Vitae US$42m in upfront and near-term payments including an equity investment, for a pre-clinical programme focused on BACE inhibitors. There was US$200m in milestones[114].
- **Merck & Co. / Alectos Therapeutics[115], US$289m, August 2010**. US$289m in total deal value, over a programme targeting the enzyme O-GlcNAcase, represented a Merck bet on the tau hypothesis.
- **Genentech / AC Immune, US$418m, June 2012**. AC Immune licensed a pre-clinical anti-tau programme to Genentech for US$418m in total deal value. The two companies already had a relationship that had started with crenezumab, an amyloid beta antibody now in Phase 3.
- **Otsuka / Lundbeck, US$825m, March 2013**. This deal covered a 5HT6 receptor antagonist then at Phase 2, and involved both companies sharing the development costs, but did see Otsuka pay US$150m upfront to buy in to the programme, indicative of the attractiveness of 5HT6 as a target at that time.
- **Biogen / Proteostasis Therapeutics[116], US$200m, December 2013**. Proteostasis works on drugs that modulate protein 'homeostasis pathways' within cells – the sort of pathway, for example, designed to clear misfolded proteins out of the cell. The company had identified a target called USP14 which pre-clinically could be shown to slow down the aggregation of neurotoxic tau protein. This concept attracted US$200m in total deal value, which included a Biogen equity investment.

[110] For some perspective here see *Where's the War on Alzheimer's?* by T.R. Reid, AARP Bulletin, January/February 2015. AARP is the American Association of Retired Persons, America's peak lobby for the elderly.
[111] For the study, see NCT01998841 at www.clinicaltrials.gov. For the cost estimate, see *Genentech readies for groundbreaking $100m trial of Alzheimer's therapy*, FierceBiotech, 14 December 2012.
[112] Probably the high point for Alzheimer's partnering was in September 2008 when Pfizer licensed, from a San Francisco-based company called Medivation, a former anti-histamine with memory-enhancing properties called Dimebon. Medivation got US$225m upfront and was eligible to up to US$500m in development, regulatory and commercial milestones. This for a drug that failed Phase 3 in 2010! For the 2008 deal see the Pfizer press release dated 3 September 2008 and headlined '*Pfizer and Medivation enter into global agreement to co-develop and market Dimebon for the treatment of Alzheimer's and Huntington's Diseases*'.
[113] Allergan acquired this company in 2016 for US$639m, primarily for its dermatology pipeline.
[114] This collaboration yielded a promising Phase 1-ready drug candidate before it was terminated in 2015.
[115] Burnaby, BC, privately held, www.alectos.com.
[116] Cambridge, Ma., Nasdaq: PTI, www.proteostasis.com.

- **J&J / Orion[117], US$31m upfront, December 2013**. This deal helped fund Orion's Phase 2a programme for an alpha-2C adrenoceptor antagonist to proceed. It is notable because the deal took place not long after the high-profile Phase 3 failure in mid-2012 of J&J's bapineuzumab amyloid beta monoclonal.
- **Eli Lilly / AstraZeneca, US$500m, September 2014**. This deal saw Lilly buy into an AstraZeneca small molecule BACE inhibitor, for US$500m in development and regulatory milestones. This deal was done off the back of Phase 1 data.
- J**&J / AC Immune, US$509, January 2015**. This deal saw AC Immune licensed its anti-tau vaccine to J&J for US$509m in total deal value. The vaccine was then at Phase 1.
- **Biogen / Rodin Therapeutics[118], US$500m, January 2016**. Rodin Therapeutics develops drugs targeting an enzyme called HDAC, believed to be useful in improving synaptic resilience. This concept was worth US$485m in upfronts and milestones to Biogen, which also anchored a US$17m capital raising by Rodin.
- **Allergan / Heptares[119], US$125m, April 2016**. Allergan licensed a portfolio of subtype-selective muscarinic receptor agonists for US$125m upfront and US$665m per product. The most advanced candidate was in Phase 1 at the time.
- **Biogen / Bristol-Myers Squibb, US$710m, April 2017**. Biogen licensed a Phase 2 anti-tau antibody from Bristol-Myers Squibb for US$300m upfront and US$410m in milestones.
- **AbbVie / Alector[120], US$225m, October 2017**. Alector is working on drugs that harness the microglial cells of the brain's immune system to go after amyloid beta and tau. With AbbVie, the company will now look at a portfolio of antibody targets, in return for US$205m upfront and a potential future US$20m equity investment.
- **Takeda / Denali Therapeutics[121], US$240m+, January 2018**. One of Denali's core technologies is the 'Antibody Transport Vehicle' (ATV) to get monoclonal antibody drugs through the blood-brain barrier. Takeda is collaborating with Denali on two drugs for Alzheimer's[122] and another for an unnamed neurodegenerative disease where the drug will be delivered using ATV. Takeda paid US$150m upfront in cash and an equity investment in Denali, plus US$90m in pre-clinical milestones. The total deal value is understood to be >US$1.2bn[123].

[117] Espoo, Finland, Nasdaq Helsinki: ORNBV, www.orion.fi.
[118] Cambridge, Ma., privately held, www.rodintherapeutics.com.
[119] This company, acquired by the Japanese pharma company Sosei in 2015 for US$400m in total deal value, was one of the pioneers of technology to properly characterise G Protein–Coupled Receptors.
[120] South San Francisco, Ca., privately held, www.alector.com.
[121] South San Francisco, Ca., Nasdaq: DNLI, www.denalitherapeutics.com. Denali takes its name from the Alaskan mountain of the same name, also known as Mt McKinley, which is the world's third tallest mountain in the world.
[122] One for the neuro-inflammation target TREM2, another targeting BACE1 and tau.
[123] See *Up-to-$1.2B neurodegenerative disease collaboration launched by Takeda, Denali* by Alex Philippidis, Genetic Engineering and Biology News, 5 January 2018.

Xanamem's pipeline in a product

An impressive capacity of Xanamem is the potential additional indications that Actinogen can develop in subsequent clinical programmes. At this stage Actinogen intends that Diabetes-Associated Cognitive Impairment (DACI) will be its second indication, and there are others that can follow.

Raised cortisol and cognitive decline characterises numerous conditions. Consider:

RAISED CORTISOL AND COGNITIVE DECLINE CHARACTERISE NUMEROUS CONDITIONS

- **Parkinson's disease**. Around a quarter to a third of Parkinson's patients have dementia[124], and investigators have noted that Parkinsonians have elevated cortisol[125]. Possibly there is a link that has to do with the progressive failure of levodopa therapy[126].
- **Schizophrenia and bipolar disorder**. Researchers have noted elevated cortisol in both conditions[127].
- **Depression**. Researchers have long been aware of the presence of elevated cortisol in major depressive disorder, and the role of glucocorticoid receptors in impaired cognition in this setting is now beginning to be understood[128].
- **Post-traumatic stress disorder (PTSD**). In Appendix VI below we list a paper from a Dutch group (Sarabdjitsingh et. al., 2014), with which Edinburgh's Professors Webster, Walker and Seckl collaborated, showing, *in vivo*, how lowering cortisol could be used in the treatment of PTSD.
- **Acute Myocardial Infarction.** From patients with Cushing's syndrome it has been inferred that high cortisol tends to inhibit microvascular formation[129] which, for a patient that has suffered a heart attack, would delay re-vascularisation of the affected heart muscle. Actinogen is interested in exploring whether Xanamem administered shortly after the attack could rectify this. Interestingly, post-AMI, a patient often suffers a period in which cognition is notably worsened. Elevated cortisol is known to be a factor[130].

Xanamem may be a treatment for Diabetes-Associated Cognitive Impairment (DACI). Cognitive impairment has long been known to be a co-morbidity of Type 2 Diabetes[131]. However, the mechanisms have until recently, been uncertain. The Edinburgh Group believes that elevated cortisol is a significant factor. They tracked > 1,000 men and women aged 60-75 with Type 2 Diabetes and reported, in a 2010 paper, that higher morning plasma cortisol was associated with decline in cognition, working memory, and processing speed[132]. There is supporting evidence from other groups, most notably a 2008 paper from scientists at the National Institute on Aging which shows, *in vivo*, that reducing glucocorticoid levels in diabetes prevents cognitive deficits and enhances neurogenesis and synaptic plasticity[133]. Inhibiting cortisol in the brain, using Xanamem, is a credible way to treat the cognitive decline in diabetes.

2-14% OF TYPE 2 DIABETICS WILL BE COGNITIVELY IMPAIRED

[124] Mov Disord. 2005 Oct;20(10):1255-63.
[125] Int J Gen Med. 2011; 4: 561–569.
[126] Clin Neuropharmacol. 2007 Mar-Apr;30(2):101-6.
[127] Psychoneuroendocrinology. 2014 Nov;49:187-206. Epub 2014 Jul 21.
[128] Mol Psychiatry. 2017 Apr;22(4):527-536. Epub 2016 Aug 16.
[129] Endocrine. 2013 Feb;43(1):206-13. Epub 2012 Aug 1.
[130] Cardiovasc Psychiatry Neurol. 2013;2013:340342. Epub 2013 Jan 16
[131] World J Diabetes. 2016 Sep 15;7(17):412-22.
[132] Diabetes Care. 2010 Apr;33(4):714-20. Epub 2010 Jan 22.
[133] Nat Neurosci. 2008 Mar;11(3):309-17. Epub 2008 Feb 17.

The DACI opportunity is a significant one. Further clinical or pre-clinical evidence of the cortisol/cognition link in diabetes would greatly increase the value of Xanamem. Around 2% of type 2 diabetics have dementia[134]. That represents at least 400,000 patients in the US alone, given the epidemic nature of diabetes in that country[135] ~14% of type 2 diabetics will have mild cognitive impairment[136], which is another 2.7 million potential patients in America. The need for a drug to treat cognitive impairment in diabetes is high given that cognitive impairment is known to reduce adherence to diabetes medications[137], and non-adherence can be costly[138].

Valuing Actinogen

We value Actinogen at 10 cents per share base case and 26 cents optimistic case. Our target price of 18 cents per share sits at the midpoint of our valuation range. Our approach was as follows:

- Our WACC was 15.3% (Speculative)[139];
- We modelled a single payoff for Xanamem;
- We valued Xanamem on a probability-weighted DCF approach;
- We model around 15 years of commercial exclusivity for each product, which assumes patent-term extension;
- We modelled a corporate overhead of A$0.4m per month.

Xanamem deal parameters - We assume Actinogen partners this asset after the first Phase 2[140]. We assume:

- US$5-10m more expenditure by Actinogen on the project;
- A 29% probability of the drug ultimately gaining approval, as per the historic success rates for molecules in Phase 2, small and large[141]. While the 14-year dry spell for Alzheimer's may suggest to some that this risk-weighting is too high, balanced against this is the willingness of pharma companies we noted above to continue licensing new candidates; and of the FDA to assist Alzheimer's drug development through more lenient guidance and expediting promising drugs in development.

[134] See PLoS One. 2015; 10(10): e0141325.
[135] Diabetes prevalence is now 8% of the adult population - source: CDC 2009 estimates, which assume that 27% of the total patient population is, as yet, undiagnosed. Another 35% of American adults have 'pre-diabetes', that is, HbA1c in a range of 5.5% to 6.5%, which is higher than normal blood glucose.
[136] Arch Gerontol Geriatr. 2016 Jan-Feb;62:138-42. Epub 2015 Sep 10.
[137] Health Psychol. 2010 Jan; 29(1): 50–55.
[138] Value Health. 2009 Sep;12(6):915-22. Epub 2009 Apr 27.
[139] For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.7%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.
[140] Part of the attraction to a potential licensee being the fact that Xanamem is a small molecule, which will likely allow low cost of goods and high gross profits.
[141] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

- A licensing in FY21 or FY22, for US$40-60m upfront, US$200-400m in milestones (conservative by the standards of some of the deals noted above) and a 12-16% royalty rate. This is conservative because positive XanADu data could lead to a licensing much earlier;
- First product approval in FY23-FY24, after a single pivotal study;
- Peak sales of US$1.7-2.8bn, as per the experience of previous Alzheimer's blockbusters. This assumes a range of new agents coming on the market between now and the late 2030s, and Xanamem gaining a 4-7% market share of the US$40bn market we postulated earlier. It's worth noting that there'll be an increasing number of Alzheimer's patients globally over time, however balanced against this will be budgetary pressures on drug pricing. In Xanamem's favour is the fact that it has a differentiated mechanism of action and favourable safety profile, and as such could quite probably be given in combination with any other future approved drug. Combination therapy is likely in the future irrespective of the approval of other drugs;
- 10% market share post-exclusivity for Actinogen's licensee, with a 3-5% negative terminal growth rate;
- A 30% tax rate.
- A 5% royalty back to the University of Edinburgh[142].

IF IT WORKS CLINICALLY, XANAMEM COULD REASONABLY BECOME A BLOCKBUSTER

Further capital. As at December 2017 Actinogen held A$5.5m with a burn rate over the previous twelve months of A$440,000. The company raised $5.3m at 4 cents per share in December 2017, A$1.6m of which was received in January 2018. For conservatism's sake we modelled a further A$4m raise at 4 cents per share.

	Base	Optim.
Xanamem (A$m)	94.8	263.3
Total programme value	94.8	263.3
Value of tax losses	8.0	8.0
Corporate overhead	-22.0	-22.0
Cash now (A$m)	9.2	9.2
Cash to be raised (A$m)	4.0	4.0
Option exercises (A$m)	10.8	10.8
Total value (A$m)	104.8	273.3
Total diluted shares (million)	1,046.7	1,046.7
Value per share	$0.100	$0.261
Valuation midpoint	$0.181	
Share price now (A$ per share)	$0.044	
Upside to midpoint	310.2%	

[142] See Page 21 of Actinogen's 2014 Notice of Annual General Meeting.

Re-rating Actinogen

We see the following factors helping to re-rate Actinogen towards our target price of 18 cents per share:

- The first interim analysis of XanADu, should the DSMB recommend the trial proceed as planned;
- Further published science from various sources on the Cortisol Hypothesis;
- Initiation of the Diabetes-Associated Cognitive Impairment study;
- Grant funding for further XanADu indications;
- Completion of recruitment for XanADu;
- Top-line Phase 2 results for XanADu;
- Partnering deals or collaboration arrangements between Actinogen and large and medium-sized pharma companies;
- Pharma deals involving Actinogen's peer companies.

WE LOOK FOR FURTHER PUBLISHED SCIENCE ON THE CORTISOL HYPOTHESIS

Solid management

Actinogen in our opinion has a first-class management team that can take the company forward in terms of creating shareholder value.

CEO **Dr Bill Ketelbey**, who joined Actinogen in December 2014, brings to the company many years of experience in Medical Affairs for Pfizer in Australia and the Asia-Pacific region. During his time with Pfizer Dr Ketelbey was involved in the development and commercialisation, with Eisai, of Aricept[143], giving Bill substantial knowledge around the Alzheimer's and dementia space.

The Actinogen board, which includes Ketelbey, was refreshed in 2017. The current board has a range of skills relevant to building an early-stage Life Sciences company.

ACTINOGEN HAS A HIGHLY SKILLED BOARD

- **Dr Geoff Brooke**, who became Chairman in March 2017, brings management skills relevant to early stage biotech companies gained from his years building the respected VC house GBS Venture Partners. That firm has backed numerous Australian Life Science success stories such as Peplin Biotech[144], Spinifex Pharmaceuticals[145] and Elastagen[146].
- **Dr Jason Loveridge**, currently CEO of the German drug developer 4SC[147], brings biotech entrepreneurial and drug development skills gained over numerous early-stage companies.

[143] FDA approval happened in November 1996.
[144] Developer of a natural product for the treatment of skin cancer. This company was sold to Denmark's Leo Pharma for US$287.5m in 2009.
[145] Developer of a potential first-in-class oral treatment for chronic pain without CNS side effects. Spinifex was sold to Novartis in 2015 for US$200m plus milestone payments.
[146] Developer of recombinant tropoelastin, useful in aesthetics, scar remodeling and surgical wound repair. This company was sold to Allergan in February 2018 for US$95m plus contingent commercial payments.
[147] Planegg, Germany, Xetra: VSC, www.4sc.de.

- **Dr George Morstyn,** who was a significant player in the growth of Amgen[148] as Chief Medical Officer in the 1990's and early 2000's[149], brings valuable Big Pharma experience rare for a company of Actinogen's size. Here's what Gordon Binder, CEO of Amgen from 1988 to 2000, said about Morstyn: *'Dr George Morstyn, head of the Ludwig Institute's clinical program, stood out as exceptionally talented. He was also unusual in that he was both a PhD and an MD. We recognised right away that he would make a terrific addition to Amgen. After a year of wooing… – and many thirty-hour plane trips – in 1991 George joined the company'*[150]. George Morstyn joined Actinogen's board in December 2017.

The Actinogen Clinical Advisory Board is also well-stocked with talent. Indeed, we argue that it would be hard to find a better board to advise this company given what each individual has achieved in the Alzheimer's field to date:

ACTINOGEN HAS A WORLD-CLASS CLINICAL ADVISORY BOARD

- Professor **Colin Masters** of the University of Melbourne was one of three men who in effect created the amyloid hypothesis in the 1980s[151] – the laboratory of the late George Glenner[152] discovered one amyloid beta sequence in 1984, while Masters' lab, collaborating with the laboratory of Konrad Beyreuther at the University of Cologne, discovered another in 1985[153], allowing the German and Australian labs to isolate the gene encoding the Amyloid Precursor Protein in 1987[154]. The willingness of Colin Masters to advise a company working on the Cortisol Hypothesis attests to the urgent search for, and openness to, new treatment approaches in Alzheimer's.
- Professor **Craig Ritchie** of the University of Edinburgh, who chairs the Actinogen Clinical Advisory Board, is an authority on Alzheimer's clinical studies. He is also well known in the field of dementia diagnosis and testing, something that is critical to good trial design[155].
- Professor **Jeffrey Cummings** of the Cleveland Clinic invented the dementia rating scale known as the Neuropsychiatric Inventory[156]. Cummings is well known in the Alzheimer's field today primarily for his presence at the treatment coal face (he directs Lou Ruvo Center for Brain Health in Las Vegas), where he directly utilises his profound knowledge of the disease to advocate for new treatment approaches[157] and innovation in clinical trial design[158]. Cummings has authored or edited 39 books and published over 650 peer-reviewed papers.

[148] Amgen is currently the world's 10th largest pharma company, with US$21.9bn in 2016 revenue and US$3.8bn in R&D spend (source: Pharmaceutical Executive magazine).
[149] Morstyn's journey with Amgen began because he was an authority on haemopoietic growth factors - see Cancer Chemother Biol Response Modif. 1999;18:250-67.
[150] That was an excerpt from Binder's book *Science Lessons: what the Business of Biotech Taught Me About Management* (Cambridge: Harvard Business Press, 2008). Binder was CFO of Amgen in its formative years under the legendary George Rathmann (1927-2012) before becoming CEO.
[151] For some good background here, see *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's disease* by Rudi Tanzi (New York: Perseus Books, 2000). Rudi Tanzi is a Professor of Neurology at Harvard. Tanzi was a co-founder of Prana Biotechnology (ASX: PBT). He has been working on the genetics of Alzheimer's since the 1980s.
[152] Glenner (1927-1995) died from senile amyloidosis, a disease on which, as a researcher, he was an authority.
[153] Proc Natl Acad Sci U S A. 1985 Jun;82(12):4245-9.
[154] Nature. 1987 Feb 19-25;325(6106):733-6.
[155] See, for example, Cochrane Database Syst Rev. 2017 Mar 22;3:CD010803 and Cochrane Database Syst Rev. 2014 Jun 10;(6):CD008782.
[156] : Neurology. 1994 Dec;44(12):2308-14.
[157] See, for example, Alzheimers Dement. 2008 Jan;4(1):49-60.
[158] See, for example, Alzheimers Dement. 2011 May;7(3):e13-44. Epub 2011 May 6.

Appendix I – Notable Alzheimer's drug development failures

This Appendix chronicles some of the notable moments in the current dry spell in Alzheimer's drug development. This long list has allowed critics to label Alzheimer's disease as a 'Drug Developer's Graveyard', and it's one reason why Actinogen has in our view a currently low market capitalisation. However, a careful perusal of this list will also show that errors in clinical trial design have also played a part. Also, it's fair to say that an excessive focus on amyloid and tau has guided a considerable number of clinical programmes in the past.

Neramexane, August 2004[159]. This drug was intended to be the second NMDA receptor antagonist after Namenda, however where Namenda succeeded, Neramexane failed.

Phenserine, February 2005[160]**.** This acetylcholinesterase inhibitor was understood from pre-clinical work to be able to inhibit amyloid beta synthesis as well. In Phase 3 the drug beat placebo but not with statistical significance, having been 'confounded by a better than expected ADAS-Cog response in the placebo-treated patients'. There is evidence that this trial had design flaws that compromised what could have been an effective drug[161].

Tramiprosate, August 2007[162]. This drug is a glycosaminoglycan mimetic that, by interacting with amyloid beta peptide, prevents its aggregation. In Phase 3 the drug failed on statistical significance measures but 'a substantial difference observed in hippocampal volume did approach statistical significance' and the data also showed 'significant interference from high between-site variations that complicated the statistical analyses'. The study was probably under-powered[163].

Flurizan, June 2008[164]. This drug, which is a pure R-enantiomer form of the anti-inflammatory drug flurbiprofen, was understood to function as a gamma secretase inhibitor. One paper has suggested that the drug would never had made it to Phase 3 if biomarker data had been used in earlier development stages[165].

***Ginkgo biloba*, November 2008**[166]**.** Extracts from the leaf of the *Ginkgo biloba* tree have long been regarded as effective in memory disorders. A six-year study tracking >3,000 people aged over 75 found no relationship between a twice-daily dose of 120-mg extract of *G. biloba* and placebo in terms of preventing dementia. Other work has suggested that extract of *G. biloba* might have cognitive benefits beyond the cholinesterase inhibitors for patients diagnosed with Alzheimer's[167].

[159] See the Forest Laboratories press release dated 31 August 2004 and headlined '*Forest announces that neramexane did not demonstrate statistical significance in recently completed Phase III trial in patients with moderate to severe Alzheimer's disease*'.
[160] See the Axonyx press release dated 7 February 2005 and headlined '*Axonyx announces that phenserine did not achieve significant efficacy in Phase III Alzheimer's disease trial*'.
[161] J Alzheimers Dis. 2010;22(4):1201-8.
[162] See the Neurochem press release dated 27 August 2007 and headlined '*Neurochem's Tramiprosate North American Phase III clinical trial inconclusive*'.
[163] J Nutr Health Aging. 2009 Jun;13(6):550-7.
[164] See the Myriad press release dated 30 June 2008 and headlined '*Myriad Genetics reports results of U.S. Phase 3 trial of Flurizan in Alzheimer's disease*'.
[165] Clin Transl Sci. 2009 Jun;2(3):242-7.
[166] JAMA. 2008 Nov 19;300(19):2253-62.
[167] Phytomedicine. 2014 May 15;21(6):888-92. Epub 2014 Feb 16.

Dimebon, March 2010[168]. This drug, generic name latrepirdine, was an old Russian anti-histamine that was found to be a low-affinity NMDA receptor antagonist and had shown strong effectiveness data in Alzheimer's in a Phase 2 study in Russia[169]. Dimebon failed at Phase 3 in March 2010, possibly because the mechanism of the drug (it may actually be a 5-HT6 antagonist, or act on mitochondria in some way) was poorly understood[170]. Medivation and its partner from 2008, Pfizer, finally called time on Dimebon in January 2012[171].

Semagecestat, August 2010[172]. Lilly's Phase 3 work found that this drug, a gamma secretase inhibitor, actually worsened cognition and functional ability and was associated with adverse events such as skin cancer and infections[173].

Bapineuzumab, August 2012[174]. This drug, a humanised monoclonal antibody targeting the N-terminal epitope of amyloid beta, may have been the first to act directly on the protein but this direct action didn't lead to an efficacy readout[175].

Intravenous Immunoglobulin, May 2013[176]. Following earlier evidence that IVIG seemed to benefit patients (possibly because it is rich in amyloid beta antibodies as well as other neuro-immune modulators), a pivotal study of this blood product, sponsored by Baxter and the NIH, tracked Alzheimer's patients at two doses over 18 months and found no statistically significant improvement in cognition or functioning. It did, however, find an improvement in two subgroups - moderate patients, and carriers of the ApoE4 genetic marker being administered the higher of the two doses[177].

Gantenerumab, December 2014[178]. This monoclonal antibody to amyloid beta is fully human and binds to both the N-terminal and central regions of the protein. Initially developed by the German antibody engineer Morphosys[179], it failed in the Phase 3 SCarlet RoAD study in prodromal Alzheimer's, that is, Alzheimer's before the appearance of dementia[180]. The gantenerumab programme, however, remains active, with Roche and Morphosys announcing in March 2017 a new pivotal planned in mild to prodromal patients[181] at the higher dose the SCarlet RoAD data suggested would be efficacious[182].

Idalopirdine, September 2016[183]. This was the first of the 5-HT6 receptor antagonist drugs to go to Phase 3. Idalopirdine is a selective 5-HT6 receptor antagonist. The 5-HT6 receptor binds to serotonin, a neurotransmitter

[168] See the Pfizer press release dated 3 March 2010 and headlined '*Pfizer And Medivation announce results from two Phase 3 Studies in Dimebon (latrepirdine) Alzheimer's disease clinical development program*'.
[169] Lancet. 2008 Jul 19;372(9634):207-15.
[170] Drug News Perspect. 2010 Oct;23(8):518-23.
[171] See the Pfizer press release dated 17 January 2012 and headlined '*Medivation and Pfizer announce results from Phase 3 CONCERT Trial of Dimebon in Alzheimer's disease.*'
[172] See the Eli Lilly press release dated 17 August 2010 and headlined '*Lilly halts development of Semagacestat for Alzheimer's disease based on preliminary results of Phase III clinical trials*'.
[173] N Engl J Med. 2013 Jul 25;369(4):341-50.
[174] See the Pfizer press release dated 6 August 2012 and headlined '*Pfizer announces co-primary clinical endpoints not met in second Phase 3 Bapineuzumab study in mild-to-moderate Alzheimer's disease patients who do not carry the APoE4 genotype*'.
[175] BMC Neurol. 2017 Apr 4;17(1):66.
[176] See the Baxter press release dated 7 May 2013 and headlined '*Baxter announces topline results of Phase III study of Immunoglobulin for Alzheimer's disease*'.
[177] J Clin Immunol. 2014 Jul;34 Suppl 1:S74-9. Epub 2014 Apr 24.
[178] See the Roche press release dated 19 December 2014 and headlined '*Roche provides update on gantenerumab development programme*'.
[179] Under a collaboration established in 2000.
[180] In medicine a 'prodrome' (from the Greek prodromos, 'a running before') is an early sign or symptom before the diagnostically specific signs and symptoms appear.
[181] See *Roche is bringing back gantenerumab from the dead, taking another stab at Alzheimer's PhIII* by John Carroll, Endpoints News, 7 March 2017.
[182] Alzheimers Res Ther. 2017 Dec 8;9(1):95.
[183] See the Lundbeck press release dated 27 September 2016 and headlined '*Headline conclusions from the first out of three phase III studies on idalopirdine in Alzheimer's disease*'.

considered therapeutically relevant in Alzheimer's[184]. Lundbeck's thinking with idalopirdine was that the drug would modulate the balance between neuronal excitation (glutamate) and inhibition (GABA) in brain regions that mediate cognition[185], and thereby potentiate the cholinesterase inhibitors. Phase 3 didn't bear this out[186].

Solanezumab, November 2016[187]. This drug, is, like Bapineuzumab, another humanised monoclonal antibody targeting amyloid beta, however its binding site is the central rather than the N-terminal epitope. In Phase 3 the data 'directionally favoured solanezumab', however 'the magnitudes of treatment differences were small'.

Verubecestat, February 2017[188]. This drug went after beta secretase[189]. While it failed in mild-to-moderate Alzheimer's, work on prodromal Alzheimer's continues, which suggests that timing is an important feature of secretase inhibitor therapy[190].

AC-1204, February 2017[191]. This product is a formulation of caprylic triglyceride, a 'ketone body' designed to supplement the lower levels of glucose metabolised by the Alzheimer's brain[192]. Accera blamed AC-1204's Phase 3 failure on a formula modification resulting in lower drug plasma levels than prior formulations.

Intepirdine, September 2017[193]. This drug, another 5-HT6 receptor antagonist, was originally developed by GSK but sold to the newly formed Axovant for US$5m in 2014. In Phase 3 in mild-to-moderate Alzheimer's the drug failed on the ADAS-Cog and ADCS-ADL scales for cognitional and function but did yield a statistically significant improvement in the first key secondary endpoint, CIBIC+. However, after a poor Phase 2b trial in Lewy body dementia, Axovant in January 2018[194] decided to scrap the programme.

[184] ACS Chem Neurosci. 2015 Jul 15;6(7):940-3. Epub 2015 May 26.
[185] Neuropharmacology. 2017 Oct;125:50-63. Epub 2017 Jul 12.
[186] JAMA. 2018 Jan 9;319(2):130-142.
[187] See the Eli Lilly press release dated 27 November 2016 and headlined '*Lilly announces top-line results of Solanezumab Phase 3 clinical trial*'.
[188] See the Merck & Co. press release dated 14 February 2017 and headlined '*Merck announces EPOCH study of Verubecestat for the treatment of people with mild to moderate Alzheimer's disease to stop for lack of efficacy*'.
[189] Also known as BACE1, the Beta-site Amyloid Precursor Protein Cleaving Enzyme 1.
[190] J Med Chem. 2017 Aug 8. [Epub ahead of print]
[191] See the Accera press release dated 28 February 2017 and headlined '*Accera announces results of its first Phase 3 study in mild-to-moderate Alzheimer's disease*'.
[192] Neurotherapeutics. 2008 Jul;5(3):470-80.
[193] See the Axovant press release dated 26 September 2017 and headlined '*Axovant announces negative topline results of Intepirdine Phase 3 MINDSET trial in Alzheimer's disease*'.
[194] See the Axovant press release dated 8 January 2018 and headlined '*Axovant announces negative results for Intepirdine in Phase 2b HEADWAY and pilot Phase 2 Gait and Balance studies; positive trends in efficacy seen in pilot phase 2 Nelotanserin study*'.

Developer	Drug	Mechanism	Date
Forest Laboratories	Neramexane	NDMA-receptor antagonist	Aug-04
Axonyx	Phenserine	Acetylcholinesterase inhibitor	Feb-05
Neurochem	Tramiprosate	Glycosaminoglycan inhibitor	Aug-07
Lundbeck / Myriad Genetics	Flurizan	Secretase inhibitor	Jun-08
NCCIH	*Ginkgo biloba*	Antioxidant	Nov-08
Pfizer	Dimebon	Multiple, including 5-HT6 antagonism	Mar-10
Eli Lilly	Semagacestat	Secretase inhibitor	Aug-10
J&J and Pfizer	Bapineuzumab	Antibodies to amyloid beta	Aug-12
Baxter	Intravenous Immunoglobulin	Auto-antibodies to amyloid beta	May-13
Roche	Gantenerumab	Antibodies to amyloid beta	Dec-14
Lundbeck	Idalopirdine	5-HT6 receptor antagonist	Sep-16
Eli Lilly	Solanezumab	Antibodies to amyloid beta	Nov-16
Merck & Co.	Verubecestat	BACE1 inhibitor	Feb-17
Accera	AC-1204	Improvement in cerebral metabolism	Feb-17
Axovant Sciences	Intepirdine	5-HT6 receptor antagonist	Sep-17

Appendix II – An Actinogen glossary

11β-HSD1 – Short for 11β-hydroxysteroid dehydrogenase type 1, an enzyme that catalyses the intracellular conversion of cortisone to physiologically active cortisol.

AIBL – The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing, a study funded by the CSIRO seeking to discover biomarkers and other factors that would predict the development of symptomatic Alzheimer's disease.

Alzheimer's disease – A brain disorder that affects parts of the brain that control thought, memory, and language. Alzheimer's is understood to afflict between 1 and 2% of the population of the Western world.

Amyloid hypothesis – The hypothesis that amyloid beta protein is the primary cause of Alzheimer's disease.

Bioavailability – The quantity of a drug able to make it to its target once inside the body. High bioavailability is an important component in a drug's prospects for commercial success.

Biomarker – A natural substance used as an indicator of a biological state, especially to detect the presence or severity of disease.

Blockbuster – A pharmaceutical drug with more than US$1bn in annual sales.

Blood-brain barrier – A wall of cells which line the blood vessels in the brain so tightly that only selected substances are permitted to pass through.

Carbenoxolone – An old ulcer drug derived from the root of the liquorice plant, *Glycyrrhiza glabra*. Carbenoxolone has been found to be a 11β-HSD inhibitor.

Central Nervous System (CNS) – The brain and the spinal column, which is mostly made up of nerve cells.

Cerebellum — The part of the brain that controls motor skills, balance and emotions.

Cerebrospinal Fluid (CSF) – A fluid that surrounds the central nervous system. Physicians can check on the levels of amyloid beta in the brain by using a lumbar puncture to assay for the fluid.

Cortisol – A glucocorticoid hormone produced by the adrenal glands that increases the body's fuel supply of carbohydrate, fat, and glucose. Cortisol is involved in the body's physiologic stress response.

Cortisol Hypothesis – The theory that elevated cortisol contributes to the neurotoxicity and subsequent cognitive decline in Alzheimer's disease dementia.

Dementia – The group of brain disorders that seriously affects the patient's ability to carry out daily activities.

DSMB – A Data and Safety Monitoring Board, comprising an independent group of experts that advises the investigators in a clinical trial.

Endpoint – The outcome or outcomes that a clinical trial is designed to evaluate, such as disease progression or death. Generally clinical trials have primary and secondary endpoints.

Enzyme – A protein that helps speed up biochemical reactions in the body. Enzymes generally have the suffix 'ase' in their name.

Frontal cortex – A part of the brain associated with thought processing.

Glucocorticoids – Hormones that help regulate the body's stress response. They are known to dampen an immune response.

Hippocampus – A part of the brain associated with long-term memory and memory recall.

Hormone – A protein produced in the endocrine glands that serves as chemical messenger to regulate tissues throughout the body.

Hypothalamic-Pituitary-Adrenal axis (HPA axis) – A complex system involving the hypothalamus, pituitary gland, and the adrenal gland, that controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. In response to stress, the hypothalamus releases corticotrophin releasing factor (CRF), which triggers the release of adrenocorticotrophic hormone (ACTH) by the pituitary gland, which in turn causes the adrenal gland to release stress hormones, particularly cortisol.

IND – Short for Investigational New Drug application. It is a request filed with the FDA for authorisation to conduct human trials of a new drug or biological product in the United States.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Pivotal trial – A Phase 3 clinical trial to prove that the drug is effective in a large patient group.

Plasma – The white blood cell fraction of blood.

p-value – A measure of statistical significance. Generally, a p-value below 0.05 is considered 'statistically significant'.

Small molecules – Drugs that have a low molecular weight (<500 daltons), making them easier to penetrate cell membranes and the blood-brain barrier.

Statistical significance – The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone.

XanADu – Actinogen's Phase 2 efficacy study of Xanamem, not the location of Kubla Khan's stately pleasure dome. The latter, as Coleridge will attest, was 'A Vision in a Dream'. As NCT02727699 at clinicaltrials.gov shows, Actinogen's XanADu is very real indeed.

Xanamem – Actinogen's lead molecule, an inhibitor of 11β-HSD1. Originally called UE2343.

Appendix III – Actinogen's intellectual property

Actinogen's intellectual property around Xanamem is covered by three main patent families:

Amido-thiophene compounds and their use, WO/2009/112845, priority date 13 March 2008, Invented by Scott Webster, Jonathan Seckl, Brian Walker, Peter Ward, Thomas Pallin, Hazel Dyke and Trevor Perrior.

- This patent application covers the Walker group's original selection of 11β-HSD1 inhibitors.

Amido-isothiazole compounds and their use as inhibitors of 11beta-HSD1 for the treatment of metabolic syndrome and related disorders, WO/2010/146338, priority date 15 June 2009, Invented by Scott Webster, Jonathan Seckl, Brian Walker, Peter Ward, Thomas Pallin, Hazel Dyke and Trevor Perrior.

- This patent application covers the use of the Walker group's 11β-HSD1 inhibitors in treating metabolic syndrome.

3, 3 -disubstituted- (8 - aza - bicyclo [3.2.1] oct- 8 - yl) -[5- (1h - pyrazol - 4 -yl) -thiophen-3 -yl] methanones as inhibitors of 11 (beta) -hsd1, WO2011/135276, priority date 29 April 2010, Invented by Scott Webster, Jonathan Seckl, Brian Walker, Peter Ward, Thomas Pallin, Hazel Dyke and Trevor Perrior.

- This patent application covers the composition of matter for Xanamem.

Appendix IV – Capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code ACW (million)	747.2	78.9%	
Unlisted options (million)	199.5	21.1%	Average exercise price 5.4 cents, average expiry date 26-May-2019
Fully diluted shares	946.7		

Current market cap:	A$32.9 million (US$25.3 million)
Current share price	$0.044
Twelve month range	$0.039 - $0.09
Average turnover per day (last three months)	1.41 million

Appendix V – Major shareholders

Actinogen currently has two substantial shareholders:

- **Edinburgh Technology Fund** (6.4%), a seed capital arm of the University of Edinburgh
- **JK Nominees** (5.4%), representing Perth investor Kim Hogan.

Appendix VI – Papers relevant to Actinogen

Lupien et. al. (1998), *Cortisol levels during human aging predict hippocampal atrophy and memory deficits*. Nat Neurosci. 1998 May;1(1):69-73.

- This paper, from the laboratory of Michael Meaney at McGill University in Montreal, was one of the first to show that elevated cortisol in older people led to smaller a smaller hippocampus and corresponding memory deficits.

Sandeep et. al. (2004), *11β-Hydroxysteroid Dehydrogenase inhibition improves cognitive function in healthy elderly men and Type 2 Diabetics*. Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6734-9. Epub 2004 Apr 7 (full text available for free online).

- This paper, from the Edinburgh 11β-HSD1 Group, was the first to show that it was 11β-HSD1 that is expressed in the human brain, and that 11β-HSD1 inhibition could ameliorate cognitive decline in elderly human subjects.

Csernansky et. al. (2006), *Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia*. Am J Psychiatry. 2006 Dec;163(12):2164-9 (full text available for free online).

- This paper, from a group at Washington University School of Medicine in St. Louis, Mo., showed, in patients with and without Alzheimer-type dementia, that high plasma cortisol was associated with more rapid disease progression in Alzheimer's.

Webster et. al. (2007), *Discovery and biological evaluation of adamantyl amide 11β-HSD1 inhibitors*, Bioorg Med Chem Lett. 2007 May 15;17(10):2838-43. Epub 2007 Feb 25.

- This paper reports in the initial 11β-HSD1 inhibitors developed by the Edinburgh Group.

Holmes et. al. (2010), *11β-Hydroxysteroid Dehydrogenase type 1 expression is increased in the aged mouse hippocampus and parietal cortex and causes memory impairments*. J Neurosci. 2010 May 19;30(20):6916-20 (full text available for free online).

- This paper showed that increased 11β-HSD1 was a factor in the lower cognitive performance of aged mice.

Sooy et. al. (2010), *Partial deficiency of short-term inhibition of 11β-Hydroxysteroid Dehydrogenase type 1 improves cognitive function in aging mice*. J Neurosci. 2010 Oct 13;30(41):13867-72 (full text available for free online).

- In this paper the Edinburgh Group showed, using an 11β-HSD1 inhibitor called UE1961 in mouse models, that only a short-term decrease in 11β-HSD1 activity is needed to alter cognitive function in aged mice.

Yau et. al. (2011), *11β Hydroxysteroid Dehydrogenase type 1 deficiency prevents memory deficits with aging by switching from glucocorticoid receptor to mineralocorticoid receptor-mediated cognitive control*. J Neurosci. 2011 Mar 16;31(11):4188-93 (full text available for free online).

- This paper demonstrated a key mechanism of action of 11β-HSD1 inhibitors – that they sufficiently lower glucocorticoids to allow memory-enhancing mineralocorticoid receptors to be activated.

Mohler et. al. (2011), *Acute inhibition of 11βeta-Hydroxysteroid Dehydrogenase type-1 improves memory in rodent models of cognition*. J Neurosci. 2011 Apr 6;31(14):5406-13 (full text available for free online).

- This paper reported *in vivo* data on 11β-HSD1 inhibitors developed by Abbott Laboratories.

MacLullich et. al. (2012), *11β-Hydroxysteroid Dehydrogenase type 1, brain atrophy and cognitive decline*. Neurobiol Aging. 2012 Jan;33(1):207.e1-8. Epub 2010 Oct 18 (full text available for free online).

- This paper, from the Edinburgh Group, reports a longitudinal study over six years of 41 men to show that 11β-HSD1 was related to brain atrophy and cognitive decline.

Sarabdjitsingh et. al. (2014), *Inhibiting 11ß-Hydroxysteroid Dehydrogenase type 1 prevents stress effects on hippocampal synaptic plasticity and impairs contextual fear conditioning*. Neuropharmacology. 2014 Jun;81:231-6. Epub 2014 Feb 1.

- This paper presents *in vivo* data suggesting that 11β-HSD1 inhibitors can be used in the treatment of PTSD, by reducing cortisol levels in the brain.

Yau et. al. (2015), *Intrahippocampal glucocorticoids generated by 11ß-HSD1 affect memory in aged mice.* Neurobiol Aging. 2015 Jan;36(1):334-43. Epub 2014 Jul 15 (full text available for free online).

- This paper was the first to show *in vivo* that a dynamic link between 11β-HSD1 and corticosterone during learning is associated with subsequent memory impairment.

Popp et. al. (2015), *Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type*. Neurobiol Aging. 2015 Feb;36(2):601-7. Epub 2014 Oct 31.

- This paper, from a network of German psychiatric researchers, shows that cortisol in the cerebrospinal fluid corelated with the level of disease severity in Mild Cognitive Impairment leading to Alzheimer-type dementia.

Kilgour et. al. (2015), *11ß-Hydroxysteroid dehydrogenase activity in brain does not contribute to systemic interconversion of cortisol and cortisone in healthy men*. J Clin Endocrinol Metab. 2015 Feb;100(2):483-9. Epub 2014 Nov 13 (full text available for free online).

- This paper established, using healthy men as test subjects, that cortisol created in brain regions like the hippocampus tended to stay there – indicating that the activity of 11β-HSD1 inhibitors was unlikely to have systemic effects.

Geerlings et. al. (2015), *Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia*, Neurology. 2015 Sep 15;85(11):976-83. Epub 2015 Aug 19 (full text available for free online).

- This paper showed, using subjects living in the Icelandic capital of Reykjavik, that higher levels of cortisol when measured in the evening is associated with smaller brain volume and poorer cognitive functioning.

Sooy et. al. (2015), *Cognitive and disease-modifying effects of 11ß-hydroxysteroid dehydrogenase type 1 inhibition in male Tg2576 mice, a model of Alzheimer's disease*. Endocrinology. 2015 Dec;156(12):4592-603. Epub 2015 Aug 25 (full text available for free online).

- This paper showed, in mouse models, that an Edinburgh-developed 11β-HSD1 inhibitor called UE2316, when administered chronically, could prevent cognitive decline and, in the early stages of treatment, could reduce amyloid plaques.

Webster et. al. (2017), *Selection and early clinical evaluation of the brain-penetrant 11ß- hydroxysteroid dehydrogenase type 1 (11ß-HSD1) inhibitor UE2343 (Xanamem),* Br J Pharmacol. 2017 Mar;174(5):396-408. Epub 2017 Jan 25 (full text available for free online).

- This paper reported the Single Ascending Dose, Multiple Ascending Dose and CNS data from Phase 1 studies of Xanamem.

Appendix VII – Companies to watch

Company	Location	Code	Market cap (USDm)	Web
Voyager Therapeutics	Cambridge, Ma.	Nasdaq: VYGR	581	www.voyagertherapeutics.com
AC Immune	Lausanne, Switzerland	Nasdaq: ACIU	523	www.acimmune.com
Concert Pharmaceuticals	Lexington, Ma.	Nasdaq: CNCE	466	www.concertpharma.com
INSYS Therapeutics	Chandler, Az.	Nasdaq: INSY	460	www.insysrx.com
Axovant Sciences	New York, NY	Nasdaq: AXON	123	www.axovant.com
Probiodrug	Halle, Germany	Euronext Amsterdam: PBD	109	www.probiodrug.de
vTv Therapeutics	High Point, NC	Nasdaq: VTVT	107	www.vtvtherapeutics.com
Anavex Life Sciences	New York, NY	Nasdaq: AVXL	102	www.anavex.com
Pharnext	Paris, France	Euronext Paris: ALPHA	92	www.pharnext.com
Axsome Therapeutics	New York, NY	Nasdaq: AXSM	62	www.axsome.com
Neurotrope Bioscience	Plantation, Fl.	OTCQB: NTRP	61	www.neurotropebioscience.com
Actinogen Medical	**Sydney, Australia**	**ASX: ACW**	**25**	**www.actinogen.com.au**

AC Immune. This company developed Crenezumab, a monoclonal antibody to amyloid beta for Alzheimer's disease partnered to Genentech and now in Phase 3. Peptide-based vaccines for amyloid beta and tau are in Phase 2 and 1 respectively, the latter partnered with Janssen. An anti-tau antibody also partnered with Genentech is at Phase 2.

Anavex Life Sciences. This company, which develops drugs targeting a class of CNS receptor called 'sigma receptors'[195], has completed Phase 2 with Anavex 2-73 in Alzheimer's disease, with favourable two-year data[196].

Axovant Sciences. This company was founded in 2015[197] to pick up GSK's RVT-101, an Alzheimer's candidate that had completed several Phase 2 studies. RVT-101, now called Intepirdine, is a 5-HT_6 receptor antagonist[198]. Intepirdine failed at Phase 3 in mild-to-moderate Alzheimer's in September 2017 and in Lewy Body Dementia in January 2018. The company is now focused on nelotanserin, is a selective inverse agonist of the 5HT2A receptor which may be useful in sleep disorders related to Parkinson's and Lewy Body Dementia.

Axsome Therapeutics. This CNS drug developer is in Phase 3 with AXS-05, which is the cough medicine dextromethorphan[199] plus the antidepressant and smoking cessation aid bupropion[200]. Axsome is testing this

[195] A common protein target of drugs of abuse and addiction – see Expert Rev Clin Pharmacol. 2009 Jul; 2(4): 351–358.
[196] See the Anavex press release dated 4 November 2017 and headlined '*Anavex Life Sciences - new clinical data on Alzheimer's disease*'.
[197] With a good deal of fanfare and some scepticism – see *The 30-year-old CEO conjuring drug companies from thin air* by Nathan Vardi, Forbes, 9 September 2015.
[198] 5HT is 5-hydroxytryptamine, the chemical name for the neurotransmitter serotonin, known to regulate memory, among other things – see Alzheimers Res Ther. 2013; 5(2): 15.
[199] The original anti-pertussive is known to have beneficial effects across a variety of neurological and psychiatric disorders - se. Pharmacol Ther. 2016 Mar;159:1-22. Epub 2016 Jan 28.
[200] GSK marketed this product as Wellbutrin for depression and Zyban for smoking cessation.

combination for treatment-resistant depression and for agitation in Alzheimer's. AXS-02 is a non-opioid pain drug in Phase 3 for knee osteoarthritis associated with bone marrow lesions.

Concert Pharmaceuticals. This company's platform allows deuterium to be used instead of hydrogen in drug compounds, thereby improving their metabolic profile. The lead product from this platform is AVP-786, a deuterated dextromethorphan for Alzheimer's agitation. ABP-786 is now in Phase 3 with the Otsuka unit Avanir Pharmaceuticals[201].

INSYS Therapeutics. This company was built on technology for making drugs available as oral sprays. Its first product was Subsys, a sublingual fentanyl spray for the treatment of breakthrough cancer pain. More recently INSYS has developed novel drugs based on cannabinoids. A cannabinoid called dronabinol, FDA approved for treatment of appetite loss and nausea and vomiting, is being considered as a potential treatment for agitation in Alzheimer's patients[202].

Neurotrope Biosciences. This company is working on the bryostatins, which are Protein Kinase C agonists, for the treatment of Alzheimer's as well as the Orphan Diseases Fragile X Syndrome and Niemann-Pick Type C. Bryostatin 1 for Alzheimer's, which is believed to be able to reverse synaptic loss, is in Phase 2.

Pharnext. This company's Pleotherapy platform allows the discovery of new combinations of existing drugs in areas of unmet medical need. PXT3003, a combination of baclofen, naltrexone and sorbitol, is in Phase 3 for a disorder of the peripheral nervous system called Charcot-Marie-Tooth disease. PXT864, a combination of baclofen and acamprosate designed to rebalance excitatory and inhibitory pathways in the CNS, is in Phase 2 in Alzheimer's.

Probiodrug. This company is working on drugs that target pyroglutamate-modified Aβ (pGlu-Abeta), one of the variants of amyloid beta present in the Alzheimer's brain. PQ912, a small molecule inhibitor of Glutaminyl Cyclase, which helps create pGlu-Abeta, is in Phase 2. PBD-C06, a pGlu-Abeta monoclonal antibody, is pre-clinical.

Voyager Therapeutics. This gene therapy company uses adeno-associated virus (AAV) to deliver therapeutic genes into cells. Voyager's lead program, VY-AADC01, delivering a dopamine precursor to treat advanced Parkinson's Disease, is in Phase 1[203]. VY-TAU01 for Alzheimer's, which involves delivery of an anti-tau antibody, is pre-clinical.

vTv Therapeutics. This CNS drug developer is in Phase 3 with azeliragon for Alzheimer's disease. Azeliragon works by targeting RAGE (Receptor for Advanced Glycation Endproducts), a protein believed to contribute to Alzheimer's pathology through mediating oxidative stress induced by amyloid beta, among other things.

[201] Avanir was acquired by Otsuka in late 2014 for US$3.5bn primarily for Nuedexta. That product is dextromethorphan plus the antiarrhythmic qunidine for the treatment of pseudobulbar affect (uncontrollable crying and/or laughing). Nuedexta gained FDA approval in 2010.
[202] Am J Geriatr Psychiatry. 2014 Apr;22(4):415-9. Epub 2013 Apr 15.
[203] VY-AASX01 is designed to allows an enzyme called L-Amino Acid Decarboxylase (AADC) to be delivered to a part of the brain called the putamen for better production of dopamine, the neurotransmitter that is lacking in Parkinson's.

Risks related to Actinogen

Risks specific to Actinogen. We see five major risks for Actinogen as a company and as a listed stock:

- **Clinical risk**. There is the risk that Xanamem may fail to meet the primary or secondary endpoints in the currently ongoing XanADu clinical trial. Also, there is the risk that the upcoming XanADu interim analysis may suggest abandonment due to safety concerns.
- **Funding risk**. More capital will likely be needed to continue clinical development of Xanamem beyond the XanADu trial.
- **Drug class risk**. Many Alzheimer's drugs which have looked good at Phase 2 failed to translate into meaningful clinical outcomes in Phase 3. There is the risk that this may happen to Xanamem as well.
- **Timing risk.** There is the risk that the XanADu study may take longer than we expect to complete.
- **Regulatory risk.** There is the risk that regulatory decisions may slow or stop the progress of XanADu in to the marketplace.

Risks related to pre-revenue Life Science companies in general.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Actinogen.

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