EDISON

Actinogen Medical

Cognitive enhancer targeting key diseases

Company outlook

Pharma and biotech

Actinogen Medical is developing its lead asset, small molecule Xanamem, a selective 11β-HSD1 inhibitor designed to cross the blood-brain barrier and target excess brain cortisol, which has been associated with cognitive impairment (CI). Actinogen is targeting two CI indications: for patients with mild CI (MCI) in the early stages of Alzheimer's disease (AD), and for patients with major depressive disorder (MDD). Positive XanaHES and Phase Ib XanaMIA results in healthy adults demonstrate the drug's initial efficacy, and a recent analysis of biomarker-positive patients using newly available plasma samples from the previous XanADu study in mild AD also showed clinical activity. Actinogen plans to start the Phase IIb portion on XanaMIA in patients with biomarker-confirmed early AD in H1 CY23. The XanaCIDD proof-of-concept Phase II trial in MDD is also planned to start in Q422. Our valuation is A$651m or A$0.36 per share.

Year end	Revenue* (A$m)	PBT** (A$m)	EPS** (A$)	DPS (A$)	P/E (x)	Yield (%)
06/21	2.0	(3.3)	(0.002)	0.0	N/A	N/A
06/22	3.6	(7.9)	(0.005)	0.0	N/A	N/A
06/23e	3.6	(8.7)	(0.005)	0.0	N/A	N/A
06/24e	3.3	(38.7)	(0.022)	0.0	N/A	N/A

Note: *Revenues include tax rebates and financial interest (local GAAP). **PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

11β-HSD1, an untapped target in dementia

Multiple studies have linked excess cortisol with detrimental effects on cognition, which is evident in neurodegenerative and psychiatric diseases. The enzyme 11β-HSD1 converts cortisone to cortisol inside cells and regulates corticosteroid concentrations, and imbalances are associated in the pathogenesis of several diseases. Xanamem was designed to penetrate the brain to target and block the 11β-HSD1 enzyme isoform, and thereby prevent excess cortisol production. Brain-specific 11β-HSD1 inhibition is the only known viable approach for intracellular excess cortisol modulation that minimises disturbance to systemic cortisol levels.

XanaMIA trial studying early AD patients with MCI

Rapid therapeutic effects on working memory and attention tests were reported in April 2022 from the Phase Ib portion on the XanaMIA study, which enrolled cognitively normal older people. The Phase IIb portion will recruit patients with biomarker-confirmed early AD and is scheduled to start in H1 CY23 and report data in CY24. The 2019 XanaHES study showed cognitive benefit in healthy elderly subjects at a higher tested dose. While initial results from the previous XanADu trial in mild AD (2017–19) did not show significant improvements, a new analysis in 34 patients with elevated pTau blood levels, confirming AD diagnosis, provides stronger indications of activity in this population. The second targeted indication, MDD, provides diversification to the R&D pipeline.

Valuation: A$651m or A$0.36 per share

We value Actinogen at A$651m or A$0.36/share, based on a rNPV analysis largely driven by Xanamem for early AD. We use a 10.0% probability of success (PoS) for Xanamem to reach the market in early AD. We apply a 12.5% probability for CI in MDD reflecting the cognitive improvement already shown in healthy patients.

19 October 2022

Price	**A$0.12**
Market cap	**A$215m**
	US$0.69/A$
Net cash (A$m) at 30 June 2022	16.5
Shares in issue	1,795bn
Free float	90%
Code	ACW
Primary exchange	ASX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	40.2	105.4	15.0
Rel (local)	42.7	103.7	28.8
52-week high/low	A$0.19		A$0.04

Business description

Actinogen Medical is an ASX-listed Australian biotech developing its lead asset Xanamem, a specific and selective 11β-HSD1 inhibitor designed to treat cognitive impairment (CI) that occurs in chronic neurodegenerative and neuropsychiatric diseases. Currently, Actinogen is targeting CI in two indications: the early stages of Alzheimer's disease and major depressive disorder.

Next events

Start enrolment for XanaCIDD in MDD	Q422
Start enrolment for XanaMIA Part IIb study in biomarker-confirmed early AD	H123

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Edison profile page

Investment summary

Company description: Targeting cortisol in CI

Headquartered in Sydney, Australia, and listed in the ASX in 2007, Actinogen is a biotechnology company focused on its lead product Xanamem, a novel cognitive enhancer. Xanamem is being developed for CI in neurodegenerative and neuropsychiatric diseases. The groundwork underpinning the cortisol hypothesis and Xanamem's discovery was carried out at the University of Edinburgh, UK, in the 1990s and 2000s. In 2014, Actinogen acquired Corticrine, which had a licence to the technological IP that included Xanamem from the University of Edinburgh. Actinogen initially focused Xanamem development on CI relating to AD, but the company has expanded the pipeline to include CI relating to MDD. Currently, Actinogen is focused on proof-of-concept Phase II trial stages. Following positive safety and cognition data reported in April 2022 in healthy patients in the Phase Ib portion of its XinaMIA study and positive data in biomarker-positive AD patients from XanADu, Actinogen plans to start enrolment in patients with early AD in H1 CY23 in the Phase IIb portion of the XanaMIA trial, with top-line data expected in CY24. It is also scheduled to start the XanaCIDD study assessing the drug's benefit on CI in MDD patients in or around Q422.

Valuation: Blockbuster sales potential in AD

We value Actinogen at A$651m or A$0.36 per share, based on an rNPV analysis including Xanamem in the lead indication, AD (10.0% PoS), and a lower contribution from MDD (12.5% probability). Our slightly higher PoS for MDD reflects the fact that Xanamem has already shown cognitive benefit in the XanaHES and XanaMIA (Phase Ib portion) studies in the healthy adult population, and that the MDD population is much less likely to have any cognitive benefits from the drug (Xanamem) to be confounded by an underlying progressive neurodegenerative disease (as in AD). However, we view the peak sales potential for CI in MDD to be lower than in AD patients, given that MDD patients are less likely to experience the severe progressive neurological decline that impairs autonomy and basic function, as AD patients. We forecast FY34 (near-peak) US Xanamem sales of US$2.6bn in MCI due to early AD, and US$860m in CI relating to MDD.

Financials: Rational expansion of the R&D pipeline

As of 30 June 2022, Actinogen had a cash position of A$16.4m. The company had reported a FY22 net cash burn rate of A$9.5m, up from A$1.7m in FY21, primarily due to costs relating to the XanaMIA clinical trial. We forecast an FY23 cash burn rate of A$9.5m, with costs likely to be higher in H223 as the company will by then start enrolment for both the Phase IIb portion of XanaMIA and the XanaCIDD MDD study. We expect the burn rate to ramp up significantly to A$39m in FY24 to fund the completion of both studies and as Actinogen could then start registration-enabling pivotal studies. We model the company will raise A$20m in FY23 and A$40m in FY24. In total, we forecast A$390m in additional financings will be required before FY29 to fund the development of both programmes, and after which, provided it receives regulatory approval, the company should be able to generate sufficient operating revenues to reach recurring profitability. As per Edison's usual policy, fundraising requirements are modelled as illustrative debt.

Sensitivities: Biotech funding and development risks apply

The main sensitivities are in relation to lead drug candidate Xanamem. Although it has shown safety in Phase I/II trials and demonstrated therapeutic efficacy in terms of cognitive benefit in healthy adults (XanaHES and XanaMIA Phase Ib portion) and in biomarker-positive AD patients (following an analysis using retrospective clinical data), it remains to be seen whether this will translate into a clinical benefit in a prospectively designed randomised trial in patients with MCI

relating to early AD, or in MDD. While the initial results from the Phase II XanADu study in patients with AD did not meet the primary endpoints, a recent analysis using newly available plasma samples showed the subset of patients with biomarker-positive AD (determined through elevated pTau) demonstrated clinical activity that appears to be quantitatively superior to what has been shown with FDA-approved Aduhelm in its EMERGE Phase III pivotal study and by lecanemab in its Phase III Clarity AD study. Further, the upcoming Phase IIb portion of XanaMIA will study a longer-duration treatment period (six months versus 12 weeks) and will study patients with biomarker-positive AD determined using similar criteria to those in the recent XanADu biomarker analysis. Actinogen is also assessing the drug's ability to treat CI in the MDD population, with the XanaCIDD study expected to start in late 2022. The company faces significant financing risks as it will require substantial further capital to advance its programmes in the absence of a co-development or licensing deal. While our model accounts for financing(s) as long-term illustrative debt, Actinogen may need to issue equity instead, at pricing that may not be favourable for current shareholders and could lead to significant dilution.

Xanamem: Differentiated cognitive enhancer

Xanamem is an 11β-HSD (11β-Hydroxysteroid dehydrogenase) type 1 (or, 11β-HSD1) inhibitor designed to reduce excessive cortisol production in the brain. Much scientific literature and existing Xanamem data suggest that excessive cortisol is associated with CI in patients with various chronic conditions.

11β-HSD's role in cortisol metabolism was discovered in the 1950s and in later years two distinct isoforms, 11β-HSD1 and 11β-HSD2, were characterised (Chapman et al, 2013). The origins of the Xanamem compound discovery date back to the 1990s and early 2000s, with research undertaken at the University of Edinburgh, which explored the effect of cortisol on cognition and possible pharmacological interventions. Carbenoxolone, a non-specific 11β-HSD inhibitor, demonstrated promising results in preclinical and early clinical trials. The University of Edinburgh researchers then developed Xanamem, a specific 11β-HSD1 inhibitor designed to cross the blood-brain barrier (BBB). The inventors' research and optimisation work was supported by the Wellcome Trust, with a total investment of c $25m. Clinical development of Xanamem started in 2013 and was continued by Actinogen after it acquired the Corticrine assets, including Xanamem, in 2014.

Cortisol hypothesis and 11β-HSD1

Cortisol, also known as the 'stress hormone', is a steroid hormone (glucocorticoid) that is tightly regulated via feedback loops connecting the hypothalamus, pituitary and adrenal glands. This is also known as the hypothalamic pituitary adrenal (HPA) axis. Most cells in the body have cortisol receptors, so this hormone has profound effects on the body's metabolism. For example, as part of the response to stress, cortisol is a powerful inflammation suppressor, making glucocorticoid anti-inflammatory drugs (eg. prednisone) widely used in many autoimmune or inflammatory diseases.

Chronically elevated cortisol is associated with a variety of conditions characterised by metabolic disturbances. One of the best-recognised syndromes resulting from chronically elevated cortisol is Cushing's syndrome, the main symptoms being central obesity, dyslipidaemia, hypertension and glucose dysregulation.[1]

[1] S. P. Webster et al. Selection and early clinical evaluation of the brain-penetrant 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor UE2343 (Xanamem). British Journal of Pharmacology (2017) 174 396–408.

Several studies demonstrate that increased glucocorticoid exposure in the brain is linked to age-related CI and a person's cortisol level correlates with reduction in hippocampal volumes and memory impairment.[1] Corticosteroid receptors are highly expressed in the hippocampus, as well as in the neocortex, including frontal lobes associated with cognition.

Studies showed that in AD, elevated plasma cortisol was associated with accelerated disease progression, while a high cortisol level in cerebrospinal fluid was associated with a more rapid worsening in patients with mild AD (Csernansky et al, 2006; Popp et al, 2015). Animal models showed that if mice are treated with glucocorticoids, this leads to increased amyloid beta formation, reduced degradation and increased tau expression in the brain (Green et al, 2006).

In January 2017, the Australian Imaging, Biomarker & Lifestyle (AIBL) study (RH Pietrzak et al, 2016) was published. The six-year, multicentre, prospective cohort study evaluated the relationship between amyloid-beta, plasma cortisol and CI in 416 healthy older adults. The study found that subjects with higher plasma cortisol had a much greater chance of developing AD. Another major study (J B Echouffo-Tcheugui et al, 2018) published in 2018 in Neurology, analysed data from the Framingham Heart Study, which is a large study that followed the health of residents of Framingham, Massachusetts, and their families since 1948. In this particular publication, the authors evaluated a group of more than 2,000 men and women with an average age of 48 with no sign of dementia. MRI brain scans, together with psychological evaluation of cognition and blood chemistry, including cortisol levels, were performed at the beginning of the study and after eight years. The authors concluded that participants with the highest levels of serum cortisol had the highest levels of impaired memory and that people with higher cortisol levels had lower brain volumes.

Direct manipulation of the HPA axis is unlikely to be an optimal treatment option for CI or AD, as it would likely compromise the stress response in the long term. The action of glucocorticoid on its intracellular receptors is determined not only by circulating steroid levels, but also by target tissue concentrations. The latter is regulated by 11β-HSD, which in effect 'gates' the access of these steroids to their nuclear receptors.[2] 11β-HSD1 is present predominantly in the liver, adipose tissue and brain, and converts inactive cortisone to cortisol, while 11β-HSD2 is expressed mainly in the kidneys and catalyses the reverse reaction. Therefore, tissue-specific modulation of intracellular cortisol in relevant brain areas (including the hippocampus and frontal lobes) can potentially be achieved by inhibiting the 11β-HSD1 enzyme without adversely affecting the normal regulation of circulating cortisol in other bodily areas.

Discovery of Xanamem and existing data

Researchers at the University of Edinburgh showed that in aged rodents the genetic knockout of 11β-HSD1 or its pharmacological inhibition protected against age-associated cognitive decline.[1] In the first clinical trials this concept was tested using carbenoxolone, which is a non-specific 11β-HSD inhibitor potently inhibiting both 11β-HSD types. Sandeep et al (2004) showed that in healthy volunteer studies (elderly men and patients with type 2 diabetes), treatment with carbenoxolone led to improved memory. More specifically, in two randomised, double-blind studies, administration of carbenoxolone improved verbal fluency (p=0.006) after four weeks in 10 healthy elderly men and improved verbal memory (P=0.005) after six weeks in 12 patients with type 2 diabetes.

Subsequently, the research team worked on developing a specific, brain-penetrant 11β-HSD1 inhibitor. An animal study using Tg2576 mice (AD model) showed that inhibition of 11β-HSD1 with a Xanamem analog led to improved memory and a reduction in amyloid beta plaques after a

[2] S. Webster et al. Discovery and biological evaluation of adamantly amide 11β-HSD1 inhibitors. Bioorganic & Medicinal Chemistry Letters 17 (2007) 2838–2843.

relatively short 28-day treatment period. The cognitive improvement effect was sustained for up to 13 months.[2]

After optimisation, the Xanamem molecule (formerly UE2343) was finalised and the original team of Edinburgh researchers co-founded a company called Corticrine, which in-licensed the rights to Xanamem from the University of Edinburgh. In December 2014, Actinogen acquired Corticrine and continued its development with a number of studies, including a multiple ascending dose Phase I study. No safety issues were detected in the Phase I. Actinogen also confirmed that Xanamem penetrates the BBB and achieves adequate concentration levels in a pharmacokinetics (PK) sub-study.

There have been three subsequent trials studying the drug's effects on cognition. XanADu was a double-blinded Phase II trial assessing the drug versus placebo in 185 mild AD patients between 2017 and 2019, but as explained below, did not demonstrate adequate efficacy. XanaHES was a single-blinded placebo-controlled Phase I study in healthy elderly volunteers (n=42) that started in early 2019 and showed cognitive improvements with the 20mg daily dose. XanaMIA started in July 2021 and is assessing a lower 5mg and 10mg dose, with positive Phase Ib data in healthy volunteers reported in April 2022, and recruitment of the Phase IIb portion (in patients with CI associated with early AD) expected to H1 CY23.

XanADu Phase II study

The Phase II XanADu trial started in March 2017. It was a double-blind, placebo-controlled Phase II trial with mild AD patients (n=185), who received 10mg of Xanamem daily or placebo (1:1) for 12 weeks. Primary endpoints included ADAS-Cog v14 and ADCOMS measures of CI severity. Secondary endpoints included other cognitive measures such as RAVLT, CDR-SB, MMSE, NPI and NTB.

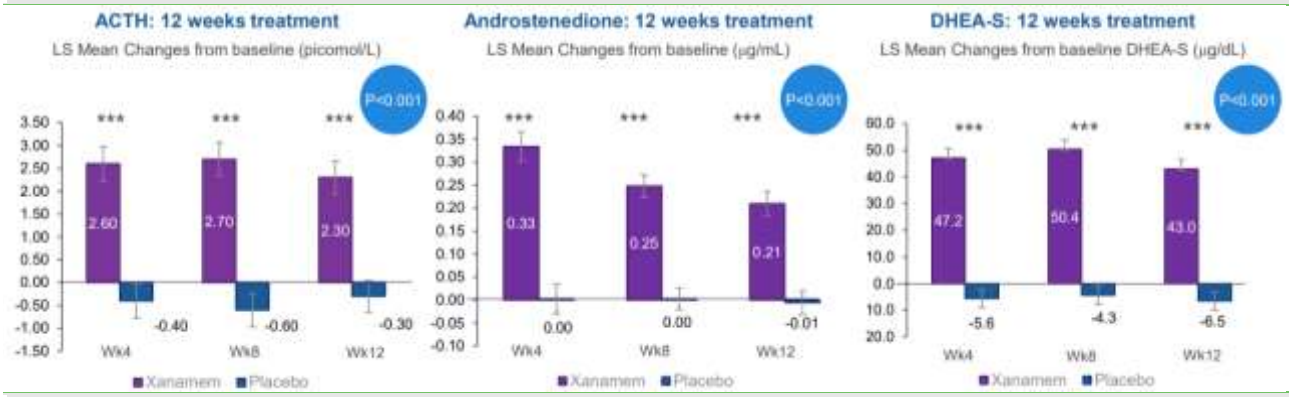
Exhibit 1: Xanamem Phase II study (XanADu) (NCT02727699)

Summary design	Phase II, randomised, double-blind, placebo-controlled proof-of-concept study to assess the safety, tolerability and efficacy of oral Xanamem in mild dementia due to AD
Number of patients	185
Treatment groups	Experimental treatment arm: oral Xanamem 10mg, once daily in conjunction with current standard therapy Placebo once daily in conjunction with current standard therapy
Endpoints	Primary endpoints: ADAS-Cog v14, ADCOMS (change from baseline after 12 weeks) Secondary endpoints: RAVLT, CDR-SOB, MMSE, NPI, NTB (change from baseline after 12 weeks)
Key inclusion criteria	Male or female aged 50+ Diagnosis of mild dementia due to AD (according to National Institute of Ageing and Alzheimer's Association workgroup) MMSE 20 to 26 inclusive Clinical Dementia Rating Scale (CDR) global score of 0.5 to 1.0 On stable dose of acetylcholinesterase (AChEI) and/or memantine (at least three months prior to screening) or treatment-naïve. Initiating AChEIs or memantine during the study will not be permitted
Clinical trial sites	United States, Australia, United Kingdom – 25 sites in total
Timelines	Study start: March 2017; top line results published in May 2019

Source: Actinogen, clinicaltrials.gov. Note: ADAS-cog = Alzheimer's Disease Assessment Scale-Cognition; ADCOMS = AD Composite Score; RAVLT = Rey Auditory Verbal Learning Test; CDR-SOB = Clinical Dementia Rating Scale – Sum of Boxes; MMSE = Mini-Mental Status Examination; NPI = Neuropsychiatric Inventory; NTB = Neuropsychological Test Batteries.

In May 2019, the results of the Phase II XanADu trial showed that Xanamem 10mg daily for 12 weeks was safe and pharmacologically effective, but the efficacy endpoints were missed. Xanamem 10mg daily did effectively inhibit cortisol production, as demonstrated by the expected and maximal increase in adrenocorticotropic hormone (ACTH) and related hormones. ACTH rises as a result of low cortisol and falls as a result of high cortisol. This suggests Xanamem is inhibiting 11β-HSD1.

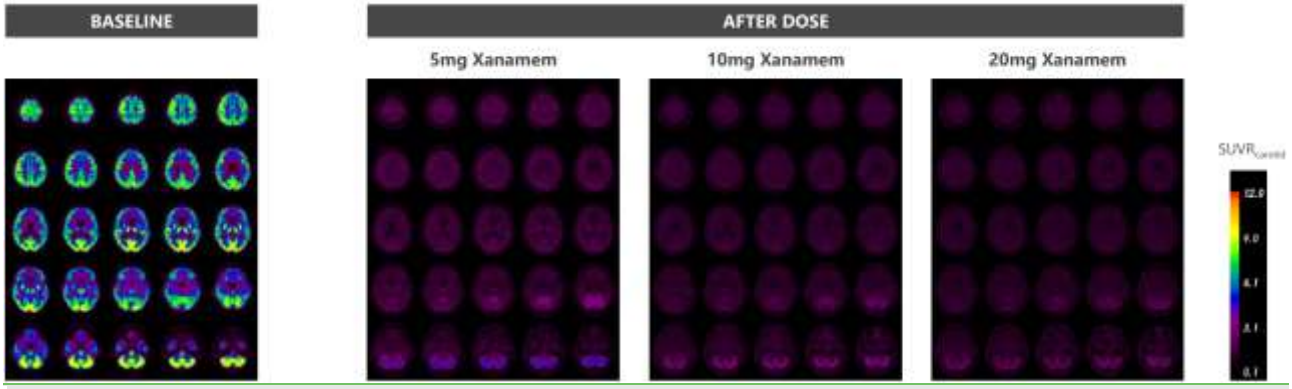
Exhibit 2: XanADu Study – pharmacodynamic results – increase in hormones in Xanamem patients versus placebo group (placebo + standard of care (SoC))



Source: Actinogen Investor presentation June 2019

These pharmacological data were also supported by separate target occupancy studies. Phase I study results (competitive binding with radio-labelled tracer positron emission tomography (PET) imaging assay) showed that Xanamem can achieve 50–85% occupancy, dependent on brain region, dosage and study subject. Based on knockout and enzyme inhibition rodent models, a target inhibition level of 30–60% may provide a therapeutic effect (Sooy et al, 2015).

Exhibit 3: Target occupancy study case (PET imaging)



Source: Actinogen. Note: Study population consisted of ~50% healthy subjects (cognitively normal) and ~50% with AD. Subjects dosed for seven days. Baseline: mean of baseline scans of patients in that dose group. After dose: mean of post-dosing (seven days) scans in that dose group.

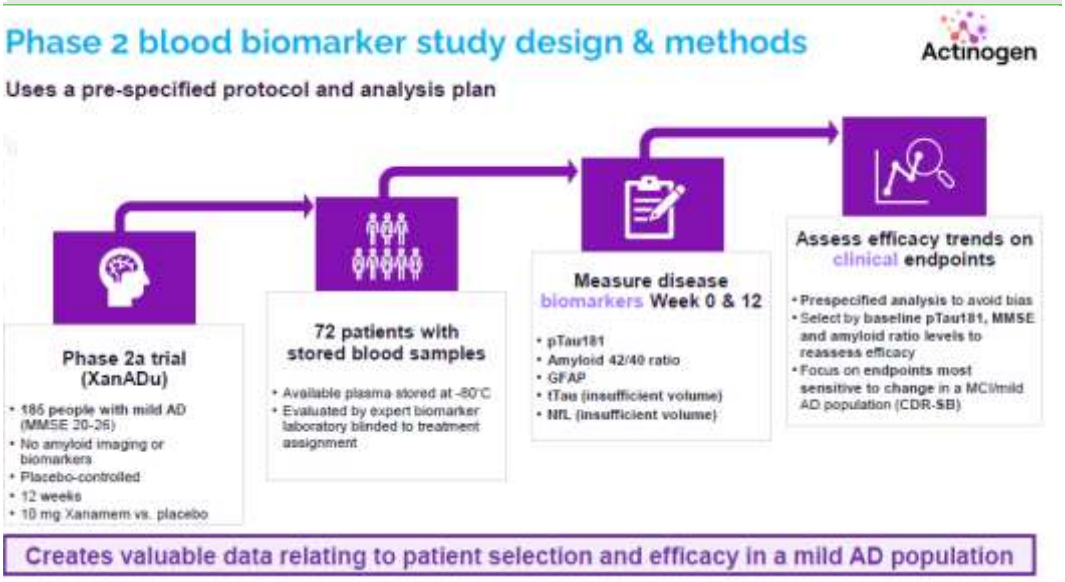
In XanADu, the co-primary efficacy endpoints of ADAS-Cog and ADCOMS were used, which were based on the earlier development of acetylcholinesterase inhibitors and memantine (approved symptomatic AD drugs for later stages of disease). While some trials of those drugs showed efficacy at 12 weeks of treatment, most were at least 24 weeks long. The 12-week treatment period design of the XanADu trial raised the hurdle needed to show efficacy. The selected endpoints to measure the cognitive effects of 11β-HSD1 inhibition in this study were also unproven in the mild AD population studied in XanADU. We note that various secondary endpoints were studied but not computerised cognitive testing such as Cogstate. Cogstate, and similar tests from the Cambridge Neuropsychological Test Automated Battery in the UK, have been used for many years to detect and define cognitive benefits in drug development. The Cogstate Cognitive Test Battery (CTB) was not used as an endpoint in this trial but is being used in subsequent trials, as discussed below.

Subset analysis shows activity in biomarker-positive patients

Actinogen decided to revisit the patients who were enrolled in the XanADu trial and explore the dynamics of biomarkers. Biomarker analysis was not included in the original trial design, but the company studied stored plasma samples from 72 of the 185 original patients in the study (reflecting data at both baseline and at week 12). At the time top line XanADU results were reported in 2019,

blood-based AD biomarker analysis was not available and AD clinical diagnoses was not confirmed by any biomarkers. The recent analysis reported in October 2022 using newly available plasma samples re-ran study analysis in distinct patient subpopulations and found clinical activity and relatively large effect size using the FDA-recognized CDR-SB scale in biomarker-positive AD patients as determined through patients who had elevated phosphorylated Tau (pTau), a recognized AD diagnostic biomarker, at baseline.

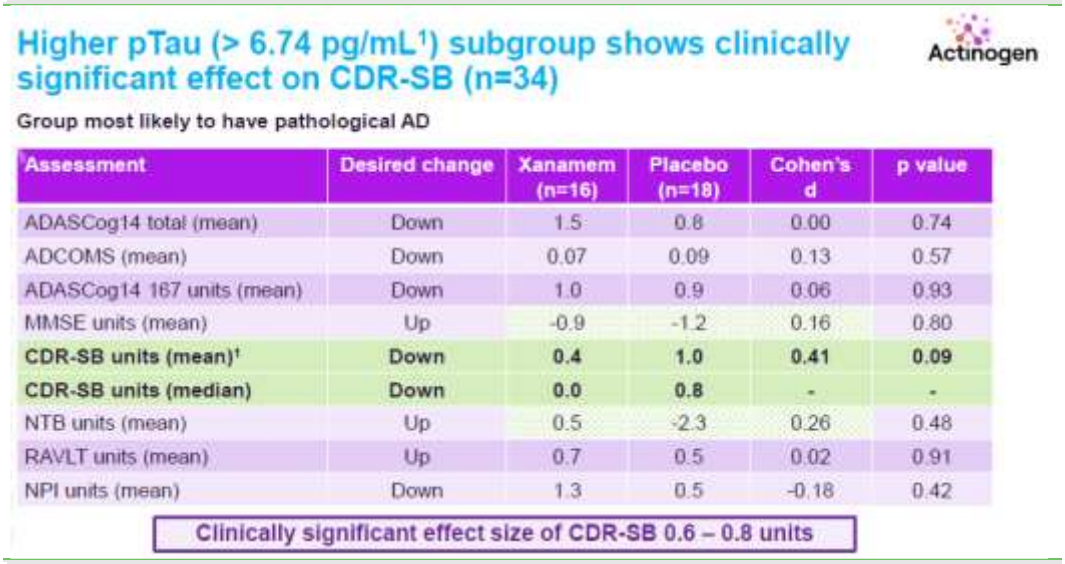
Exhibit 4: Plasma biomarker study design



Source: Company presentation

Patients with elevated pTau (defined as 6.74pg/mL, the median value among patients in the study), representing 34 patients (16 on Xanamem 10mg daily, 18 on placebo) showed a 0.6 mean difference (effect size) on CDR-SB (representing a 60% relative reduction in disease progression versus placebo) at 12 weeks between the placebo and treatment arms. While the effect size was relatively large, given the small sample size, it did not meet statistical significance (p=0.09). Within this elevated pTau group, 56% of Xanamem-treated patients were stable or improved at 12 weeks versus 28% for placebo. Actinogen also reported that among the patients with the highest levels of pTau at baseline (>10.2 pg/mL, n=9 in each of the placebo and treatment arms) the effect size was as high as 0.7–0.8 in the CDR-SB scores between the two arms.

Exhibit 5: Effects on CDR-SB score seen among XanADu patients with elevated p-Tau



Assessment	Desired change	Xanamem (n=16)	Placebo (n=18)	Cohen's d	p value
ADASCog14 total (mean)	Down	1.5	0.8	0.00	0.74
ADCOMS (mean)	Down	0.07	0.09	0.13	0.57
ADASCog14 167 units (mean)	Down	1.0	0.9	0.06	0.93
MMSE units (mean)	Up	-0.9	-1.2	0.16	0.80
CDR-SB units (mean)[1]	**Down**	**0.4**	**1.0**	**0.41**	**0.09**
CDR-SB units (median)	**Down**	**0.0**	**0.8**	**-**	**-**
NTB units (mean)	Up	0.5	-2.3	0.26	0.48
RAVLT units (mean)	Up	0.7	0.5	0.02	0.91
NPI units (mean)	Down	1.3	0.5	-0.18	0.42

Source: Company presentation

We note that these differences in CDR-SB versus placebo exceed the level of CDR-SB improvements shown for Aduhelm in its ENGAGE Phase III study at 78 weeks and for lecanemab as shown in the recent Clarity-AD Phase III study at 18 weeks (both discussed further below). However, we add the caveat that the XanADu biomarker analysis sample size is relatively small and recognize that there may be limitations in forecasting future trial outcomes based on study analyses determined using retrospective clinical data. Nonetheless, we view these biomarker results as highly encouraging in that they demonstrate the potential for meaningful Xanamem clinical activity in biomarker-confirmed AD patients, if replicated in a prospective trial.

No change in blood amyloid or pTau was observed over the 12-week treatment period and the company estimates that a longer study would be required to reveal any possible disease-modification effects from the drug based on blood biomarkers. The company plans to use durability of clinical benefit, based on endpoints like CDR-SB, to assess disease-modification. Following the initial XanADu results in 2019, Actinogen showed positive cognitive effects in healthy adults in two prospective separate studies, XanaHES and the Phase Ib portion of XanaMIA.

Pro-cognitive effects also seen in two other clinical trials

In parallel to the XanADu study, Actinogen was running another trial, XanaHES, and announced the results in Q419. Primarily, this study was designed as a placebo-controlled trial to investigate a higher dose of Xanamem (20mg), compared to the 10mg dose tested in XanADu. The XanaHES cohort included 42 healthy elderly subjects (n=30 active arm, n=12 in placebo arm), who received Xanamem 20mg daily, or placebo for 12 weeks.

Xanamem's effect on cognition was measured using the standard Cogstate Battery. The Cogstate Battery evaluated six domains of cognition and the results of the trial showed that an improvement in two domains reached statistical significance (at 5% level) and trended towards significance in one other domain. More specifically:

- The One Back Test demonstrated improvement in working memory with p<0.01 and an effect size[3] of 0.83.
- The Identification Test showed improvement in visual attention with p=0.05 and an effect size of 0.67.

[3] Effect size describes the magnitude of the result and can be interpreted as effect size >0.5 indicating a medium treatment effect; effect size >0.8 indicating a large treatment effect.

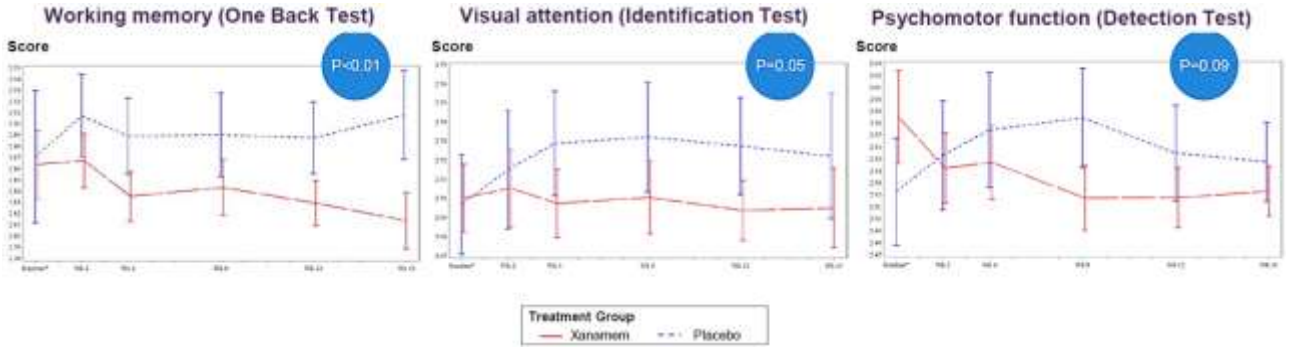
- The Detection Test showed a trend towards improved psychomotor function with p=0.09 and an effect size of 0.76.
- The results confirmed a good safety profile with no reported serious adverse events.

Exhibit 6: Cogstate CTB results in the XanaHES trial

Cognitive Evaluation (Test)	p value			Treatment Effect Size: Cohen's d			
	All	Male	Female	Week 2	Week 4	Week 8	Week 12
Working Memory (One Back Test)	<0.01*	<0.01*	0.03*	0.64#	0.78#	0.64#	0.83Δ
Visual Attention (Identification Test)	0.05*	0.04*	0.60	0.19	0.67#	0.62#	0.67#
Psychomotor Function (Detection Test)	0.09	0.94	0.13	0.47	0.65#	1.12Δ	0.76#
Paired Associate Learning (CPAL[1] Test)	0.21	0.34	0.49	0.87Δ	0.01	0.66#	0.08
Memory (CPAL[1] – Delayed Test)	0.50	0.55	0.21	0.34	0.23	0.06	0.48
Visual Learning (One Card Learning Test)	0.92	0.41	0.64	0.11	0.12	0.60#	0.19

Source: Actinogen. Notes: *Statistical significance achieved; # effect size >0.5 (moderate treatment effect); Δ effect size >0.8 (large treatment effect).

Exhibit 7: Longitudinal data demonstrating Xanamem versus placebo effect on top CTB domains



Source: Actinogen. Note: XanaHES Phase I clinical trial treated healthy older volunteers, aged 50–75 years, with 20mg Xanamem daily (n=30 active, n=12 placebo). p<0.01 strong statistically significant result; p=0.05 statistically significant result; p=0.09 trend towards statistical significance.

Phase Ib portion of XanaMIA study

The XanaMIA Phase Ib portion started in 2021 and was designed to investigate Xanamem in healthy elderly volunteers, similar to the XanaHES study, but using lower doses (5mg and 10mg daily) and by using the same computerised testing endpoints, supplemented with a version of the Digit Symbol Substitution Test (DSST). PET Phase I studies conducted by the company revealed high levels of target occupancy in the brain with doses as low as 5mg daily, which prompted the company to pursue the lower doses (5mg and 10mg) chosen in XanaMIA. With the Phase Ib portion of the XanaMIA study, Actinogen wanted to replicate the positive effects on cognition shown in XanaHES, but using lower doses of Xanamem (10mg or less).

The Phase Ib portion of the XanaMIA study investigated the efficacy of 5mg and 10mg Xanamem doses compared to placebo in 107 older healthy subjects (aged 50–80 years), over six weeks. The primary endpoints were safety, pharmacodynamics of ACTH response and effects on cognition (one

or more cognitive domains showing a clinically meaningful effect size defined as Cohen's d statistic of ≥0.3).

The scales used were Cogstate Neuropsychological Test Battery supplemented by the DSST. The results include:

- The primary efficacy endpoint defined as clinically significant effect size (ES) of Xanamem treatment on cognitive ability versus placebo, measured with well validated tests of attention and working memory from the Cogstate CTB, was met at the end of treatment (week six) in the 5mg group, where the visual attention test achieved a statistically significant effect size ($p < 0.05$).
- Xanamem was safe and well tolerated over the six-week treatment period.
- Both 5mg and 10mg dose levels showed pharmacodynamic activity by raising mean ACTH by 2.03x and 2.35x, respectively, to a similar extent as higher doses in prior studies.
- Cognitive effects on working memory, attention and psychomotor function were consistent with those in XanaHES.

Exhibit 8: Cogstate CTB results in the Phase Ib portion of XanaMIA trial compared to the XanaHES trial

XanaMIA trial Cognitive Evaluation (Test)	Desired improvement	Effect size[1] 5 mg			Effect size[1] 10 mg		
		Week 4 N=35	Week 6 N=35	Follow up N=33	Week 4 N=30	Week 6 N=29	Follow up N=29
Attention Composite	Positive	0.52	1.29	0.51	0.65	0.48	-0.38
Working Memory (One Back Test)	Positive	0.19	1.11	1.11	0.42	0.98	1.07
Visual Attention (Identification Test)	Positive	0.45	1.97[2]	-0.31	-0.48	0.29	-1.99
Psychomotor Function (Detection Test)	Positive	0.95	0.27	0.83	1.61	0.30	0.65

1. Z-score of standardized treatment effect (mean difference in MMRM model change from baseline vs. placebo/standard error of change) ; Z > 0.8 ~ one-sided 80% confidence interval or greater
2. p < 0.05 by MMRM, Cohen's d (raw mean change/pooled raw standard deviation of change) = 0.32

Previous XanaHES trial[3]	Week 4	Week 8	Week 12	Follow up
Attention Composite ES[1]	1.11	1.20	1.27	1.36

3. XanaHES Phase 1 clinical trial treated healthy elderly patients with 20mg Xanamem daily (n=30 active, n=12 placebo). MMRM ES Z-score calculated by a similar model to the XanaMIA trial

Source: Actinogen

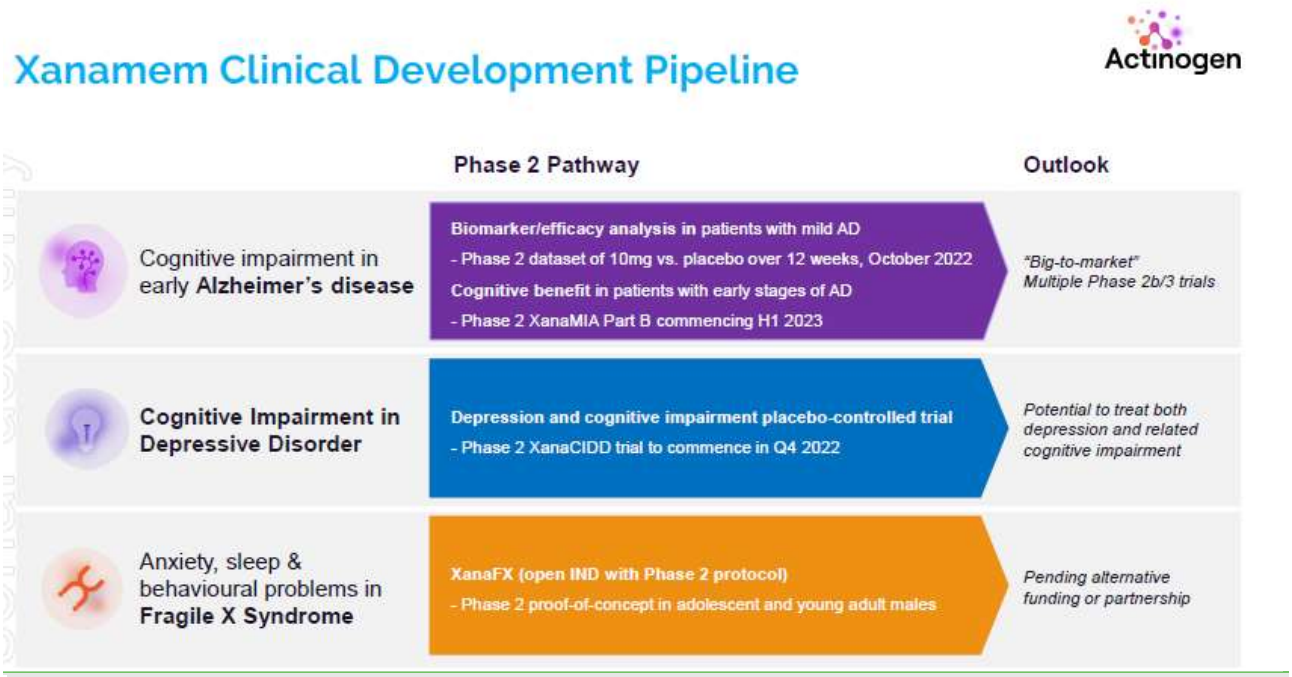
Next steps – XanaMIA Phase IIb portion and XanaCIDD

Actinogen is now pursuing Xanamem development for the treatment of CI in two areas

- Patients with MCI due to Early AD (XanaMIA Phase IIb portion), and
- Patients with MDD suffering from CI (XanaCIDD trial).

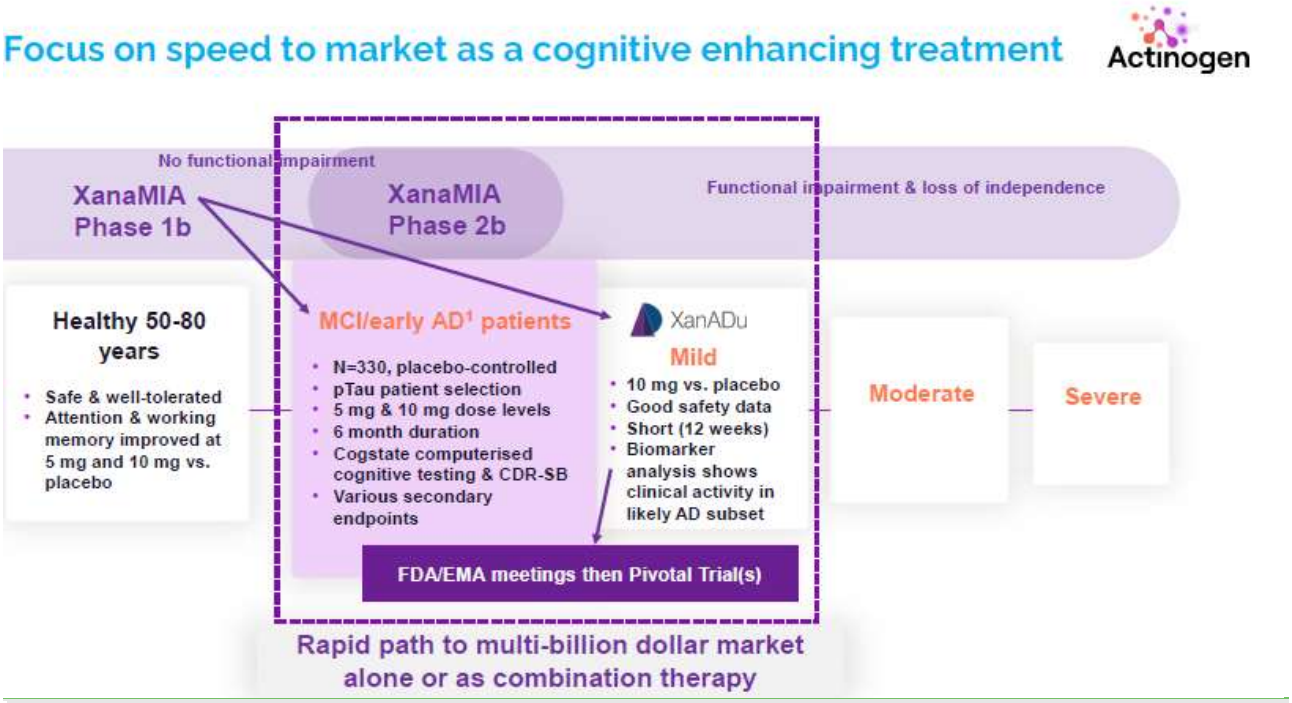
Actinogen is now planning the Phase IIb portion of the XanaMIA trial, with enrolment planned in H1 CY23.

Exhibit 9: Actinogen's R&D pipeline



Source: Actinogen

Exhibit 10: Xanamem's positioning in AD



Source: Actinogen

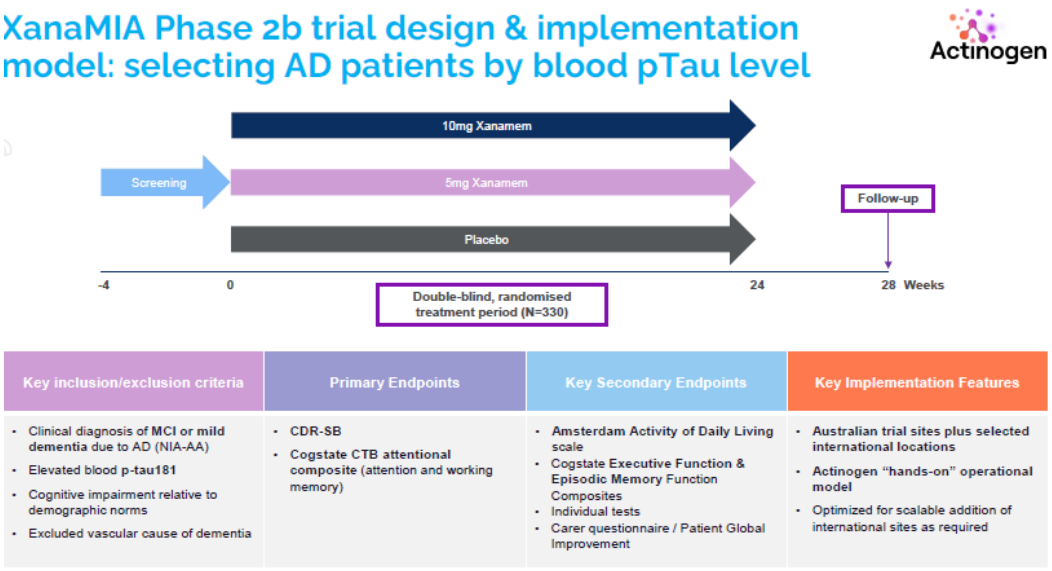
Phase IIb portion of the XanaMIA study

Following the recent biomarker analysis of XanADU and insights gained from the XanaHES study and the Phase Ib portion of XanaMIA, Actinogen now plans to advance to its next AD study, the Phase IIb portion of XanaMIA. The Phase IIb portion of XanaMIA is designed to demonstrate the safety and efficacy of Xanamem in a population of patients with MCI and mild AD who at baseline will have been confirmed as biomarker-positive for AD (as determined through elevated blood

pTau). As a reminder, MCI is an early stage of loss of memory or other cognitive ability that may develop into AD in some individuals, but not in others. The company expect the use of pTau as an entry criteria would select for patients with underlying AD who, in the absence of any treatment, are likely to have disease progression during the trial.

Recruitment is planned to start in H1 CY23 and Actinogen expects to report primary efficacy data in CY24.The XanaMIA Phase IIb study will use the CDR-SB scale as a primary endpoint, in addition to the Cogstate CTB attentional composite. As a reminder, CDR-SB is a validated endpoint that has been used as the basis for Aduhelm FDA approval and in lecanemab pivotal studies.

Exhibit 11: XanaMIA Phase IIb trial plan



Source: Actinogen

The Phase IIb portion of XanaMIA is designed to recruit 330 patients with MCI and AD, as confirmed through elevated pTau, across three arms (Xanamem 10mg daily, Xanamem 5mg daily, and placebo). Primary efficacy data are expected to be reported after 24 weeks of treatment (or placebo).

As it relates to study endpoints, CDR-SB has well-established validity and has been the basis for drug approvals in AD, whereas Cogstate has not been a component of regulatory approvals to date. However, the company has received significant guidance from various sources, including from the FDA itself, which suggests that the agency could consider this parameter and/or other endpoint combinations for a possible approval application provided there is adequate validity, ideally showing cognitive and functional improvements versus placebo (although this may not be a factor for Actinogen if it can demonstrate statistical significance in CDR-SB).

AD: High risk, high reward

The number of people living with dementia worldwide is currently estimated at around 55 million, approximately 60–70% of whom have AD, including about 5.8m persons in the United States. Given the lack of a preventative or curative treatments, this number is set to almost double by 2030 and more than triple by 2050 (World Alzheimer Report 2021). Despite this unmet need, until Aduhelm (approved in 2021, discussed further below), the main available four drugs have been approved by the FDA for AD before 2003 (cholinesterase inhibitors: donepezil, rivastigmine, galantamine; and a NMDA receptor blocker, memantine). However, they provide only symptomatic benefit and do not affect the progression of the disease.

Seismic developments in AD management

The FDA approved the first-ever disease-modifying drug Aduhelm in Q221 (anti-Aβ antibody, aducanumab, Biogen). The final data set supporting the approval was rather controversial (the EMERGE Phase III study reached a 0.39 effect size or 22% relative reduction on the CDR-SB scale at 78 weeks, but the ENGAGE Phase III trial did not meet the primary endpoint). Despite unmet medical need, the launch of this drug was challenging and after Medicare insurance reimbursement in the US was limited to the clinical trial setting only, the company slashed its commercial infrastructure towards the drug. In September 2022, Biogen and partner Eisai reported positive confirmatory Phase III data of its anti-amyloid beta (Aβ) protofibril antibody, lecanemab, for the treatment of MCI due to AD from the Clarity AD study, showing that lecanemab met the primary endpoint and reduced clinical decline on the CDR-SB cognitive and functional scale at 18 months by 27% (effect size of 0.45 points) versus placebo. Eisai had already filed for accelerated approval with the FDA and expects a decision in early 2023. Compared to aducanumab, lecanemab binds smaller Aβ protofibrils (75–5000kDa) more tightly than the larger fibril macromolecules targeted by the former.

Actinogen's approach is differentiated from classic anti-Aβ antibodies and is focused mainly on cognitive enhancement (rather than disease modification) at this stage, which may result in shorter future trials. So, although there is no direct read-across from Aduhelm's story from a technology perspective, we believe the controversial approval from the FDA is a strong indication that regulators are keen to make novel AD treatments available as quickly as possible.

Current treatment practice and AD market

Prior to Aduhelm, Memantine was the last branded therapy approved in 2004. AChEIs are standard first-line therapy and the only approved drugs, although patients with MCI are generally not prescribed these until the disease has progressed to mild or moderate AD. Memantine is approved for moderate to severe AD but is also used off-label in mild disease, usually added to ongoing therapy with AChEIs. Preferences for specific treatment options vary widely across geographies. In addition, the AD drugs have known side effects, especially gastrointestinal (GI)-related.

Exhibit 12: Symptomatic treatments approved for AD

Class	MoA	Product	Company	Proprietary status	Peak sales (pa)
Acetylcholinesterase inhibitors	Inhibit the enzyme that breaks down acetylcholine in the synaptic cleft (acetylcholinesterase) to increase the amount of acetylcholine available at the synapse for cholinergic neurotransmission	Aricept (donepezil)	Pfizer, Eisai	Generic	$3.9bn (2009)
		Exelon (rivastigmine)	Novartis	Generic	$1.1bn* (2011)
		Razadyne (galantamine)	Johnson & Johnson, Takeda	Generic	$0.5bn (2008)
NMDA receptor antagonists	Memantine reduces the amount of glutamate receptor activation and excitotoxic glutamatergic neurotransmission	Namenda (memantine)	Allergan, Lundbeck, Daiichi Sankyo, Merz, Hanmi Pharmaceutical	Generic	$1.2bn (2014)
		Namenda XR (memantine extended-release formulation)	Allergan, Merz, Adamas Pharmaceuticals	Generic	$0.8bn (2015)
Combinations	The two classes of drugs are complementary and can be used in combination	Donepezil + memantine XR (combination capsule)	Allergan, Merz, Adamas Pharmaceuticals	Branded (patent expires 2025/2026)	$0.2bn (2018)

Source: Evaluate Pharma, Edison Investment Research. Note: *Includes sales from Exelon Patch.

With regard to market size, currently the trend of ageing populations and the increasing prevalence of AD is mostly offset by the increasing use of lower-priced generics, as branded drug protection expires. However, due to a high unmet need and the vast patient population, any new, effective drug could disrupt the market. In our view, any new disease-modifying drug with uncontested efficacy and US Centers for Medicare & Medicaid Services (CMS) coverage could achieve peak sales well in excess of the current combined sales of all generic AD drugs. Even an effective new

branded drug providing symptomatic relief, which adds benefit to the current SoC, could achieve blockbuster status or meaningful sales, as was the case with all four existing symptomatic AD drugs prior to generic competition.

Competitive landscape

Several Abeta antibodies remain in late-stage studies, but Xanamem is the only 11β-HSD1 inhibitor in clinical development for CI, to our knowledge. There have been many other drugs with different mechanisms of action in clinical trials at various stages targeting the three specific indications that Actinogen has chosen. Below we highlight some of the drug candidates in advanced development stages for the treatment of AD, including lecanemab discussed previously.

Exhibit 13: Selected emerging drug treatments for AD

Product	Company	Mode of administration	Mechanism of action	2028 predicted sales*	Stage	Notes
Gantenerumab	Roche	Subcutaneous	Anti-amyloid-β monoclonal antibody	$3530m	Phase III	In October 2021, gantenerumab was granted breakthrough therapy designation by the FDA for the treatment of AD. Results from GRADUATE 1 and 2 Phase III studies are expected in Q422. In March 2022 Roche announced that it will conduct another Phase III trial, SKYLINE (n=1200) as a preventative trial in patients who may be susceptible to AD (with amyloid positivity but no CI)
Donanemab	Eli Lilly	Intravenous	Anti-amyloid-β monoclonal antibody	$1599m	Phase III	In June 2021 donanemab received FDA breakthrough therapy designation based on evidence of improved cognition from a Phase II trial, TRAILBLAZER-ALZ. The drug is currently being reviewed by the FDA under an accelerated approval pathway, with a decision expected in Q123. The drug is currently being investigated in a Phase III study, TRAILBLAZER-ALZ 2, which could form the basis for full approval and improve the likelihood for CMS reimbursement
Blarcamesine (ANAVEX 2-73)	Anavex Life Sciences	Oral	Sigma-1 receptor agonist; muscarinic acetylcholine receptor regulator	$1270m	Phase III	Results from the 48-week Phase IIb/III trial in early AD (targeted enrolment of c 450) are expected in Q422. The trial started in 2018 and is assessing cognitive and functional efficacy, measured through ADAS-Cog, ADCS-ADL and CDR-SB scales. Positive results could form the basis of an FDA accelerated approval application
Lecanemab (BAN2401)	Eisai	Intravenous	Anti-amyloid-β monoclonal antibody	$1236m	Phase III	18-month data from the Phase IIb trial showed a reduction in brain amyloid and a consistent reduction of clinical decline in several measures and in biomarkers in mild AD patients. Lecanemab was granted breakthrough therapy and fast-track designations by the FDA in 2021. Readout of the Phase III confirmatory clinical trial recently showed that lecanemab met the primary endpoint and reduced clinical decline on the CDR-SB cognitive and functional scale at 18 months by 27% versus placebo
Simufilam	Cassava Sciences	Oral	Filamin A inhibitor	$1052m	Phase III	Two randomised Phase III studies in mild-to-moderate AD are underway: RETHINK-ALZ, a 52-week study in c 750 patients, and REFOCUS-ALZ, a 76-week trial expected to enrol c 1,000 patients. Both are conducted under an FDA special protocol assessment (SPA). A separate c 200 patient open-label Phase IIb safety trial is underway, with top line data expected near YE22. Interim data from c 100 of these patients showed ADAS-Cog11 scores by an average of c 1.5 points (P<0.05) at 12 months

Source: Edison Investment Research, Evaluate Pharma. Note: *As estimated by consensus forecasts at Evaluate Pharma (assuming regulatory approval).

Successful development or approval of any of the above drugs could help fulfil much unmet need in AD, as none of the currently approved treatments (except Aduhelm, albeit with caveats described above) have shown disease-modifying properties. Theoretically, Xanamem could be used in combination with many of those therapies, for example with amyloid beta drugs or other cognitive enhancers that are in development. In particular, we note that the oral mode of administration for

Xanamem and its favourable safety profile to date, could signal potentially wide commercial reach if approved and successful in XanaMIA Phase IIb and subsequent AD trials.

There have been many attempts in the past to develop 'cognitive enhancers', mostly neurotransmitter strategies aiming to replicate the results seen with donepezil etc, but no notable results have been achieved so far. There are multiple ongoing trials investigating potential cognitive enhancers in patients suffering from AD, and some studies have found that noradrenergic drugs can have benefits on global cognition and apathy in AD patients. Of note is guanfacine, a noradrenergic α2A agonist which is currently being studied in a Phase III trial (NorAD) to assess its effect (in addition to standard cholinergic treatment) on the improvement of CI (in particular attention span) in AD patients. Thus far it has not been shown to have statistically significant effects in AD patients, but the NorAD study is expected to be completed in Q422. In a Phase II trial octohydroaminoacridine, an acetylcholinesterase inhibitor, showed statistically significant improvements ($p<0.01$) in cognitive function in patients suffering from mild-to-moderate AD. It has since been investigated in a Phase III trial, although results are yet to be published.

Two11β-HSD1 inhibitors that did progress into Phase II trials in neurology were AbbVie's ABT-384 and Astellas's ASP3662. Astellas was developing its compound ASP3662 for AD (Phase I) in addition to neuropathic pain (Phase I), and painful diabetic peripheral neuropathy (Phase II). The Phase II study for painful diabetic peripheral neuropathy was terminated at the futility analysis for efficacy stage and there appears to be no further update. AbbVie's ABT-384 did progress into a Phase II study for AD after reporting Phase I safety study results. The Phase II study was conducted in 267 patients with mild-to-moderate AD and results were published in Q414. The study was stopped after futility analysis for efficacy found no benefit from baseline to 12 weeks measured by ADAS-Cog. Webster et al (2017) discussed these results and concluded that ABT-384 had much lower BBB penetration than Xanamem (UE2343). Actinogen has also reported that Xanamem crosses the BBB and has high levels of target inhibition in the brain at doses of 5mg and above.

MDD

Announced in November 2021, Actinogen plans to advance Xanamem as a treatment for CI in patients with MDD. Having demonstrated the ability to improve cognition in XanaHES and XanaMIA (Phase Ib portion) in healthy adults, Actinogen is confident that the drug can exert similar cognitive improvement effects in MDD patients, and it will also explore whether the drug can have effects on depression as well.

MDD is a common disorder, with a c 5% prevalence globally and a one in seven lifetime risk (World Health Organisation, Depression; 2021). Its prevalence has grown substantially in the past decade, with the number of MDD diagnoses in adults in the US increasing from 13.7 million in 2005 to 17.5 million in 2018 (28% increase). The COVID-19 pandemic has further escalated global cases, with an estimated additional 53m global cases in the 12 months leading to January 2021. CI is a feature in most MDD patients and commonly persists even when depression symptoms subside. In a three-year study on 267 patients suffering from depression, CI occurred c 90% of the time during depressive episodes and c 40% of the time when depressive symptoms were in remission. Elevated cortisol levels have been associated with depression (Stetler and Miller, 2011) and modification of brain cell cortisol levels has been proposed as a strategy to treat both depression and its associated CI (Block et al, 2018).

The treatment of depression is very accessible with multiple drug classes available, including selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin-dopamine activity modulators (SDAMs), tricyclic antidepressants, and others. With treatment, about 70–80% of affected individuals achieve a significant reduction in symptoms. However, a study investigating antidepressant discontinuation

rates of 900 patients suffering from MDD found that almost 30% of patients stopped taking their medication within the first month, and almost half within three months.

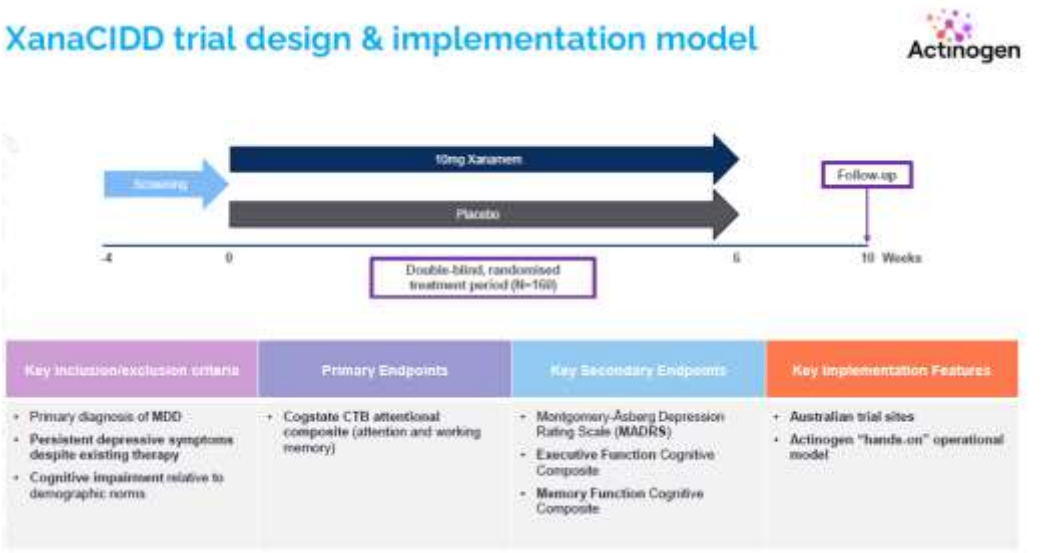
Only one approved antidepressant has shown cognitive effects to date

There is one antidepressant, vortioxetine (Brintellix/Trintellix, Lundbeck/Takeda), with a cognitive benefit claim approved in Europe. Vortioxetine is an SSRI and serotonin receptor modulator antidepressant with a multitarget profile that has several pharmacological actions. To differentiate vortioxetine in what is otherwise a fairly crowded market of antidepressants, Lundbeck conducted a large study on 602 patients with recurrent MDD, which showed significantly improved objective and subjective cognitive function measures in patients with recurrent MDD, which occurred independently of the drug's effect on depressive symptoms. The drug showed a significant improvement ($p<0.001$) in the number of correct responses on the DSST compared to placebo, as well as other significant ($p<0.05$) measures on RAVLT. However, in the US, the largest market for antidepressants, the drug does not have a cognitive benefit claim on its label, although the FDA label does refer to the study cited above and mention that 'patients in the TRINTELLIX group had a statistically significantly greater improvement in number of correct responses on the DSST'.

Clinical programme in CI for MDD

The company plans to start XanaCIDD, a six-week proof-of-concept, placebo-controlled Phase II study in c 160 patients with persistent MDD and cognitive difficulties despite taking SoC antidepressant therapy. Xanamem 10mg daily or placebo will be added to enrolled patients' existing antidepressant therapy, and changes in both cognition and depression will be assessed in the trial. Recruitment will begin in Q422 and top-line results are expected in late 2023 or early 2024. As stated earlier, given the benefits shown in healthy adults in XanaHES and the Phase Ib portion of XanaMIA, we believe it is plausible for cognitive benefits to be shown in patients with persistent MDD.

Exhibit 14: XanaCIDD study design



Source: Company presentation

Exhibit 15 shows a selection of the top selling marketed treatments for MDD with their forecast 2028 sales. Most of these products have a mechanism of action that targets the serotonin (5-HT) transporter, which is distributed throughout the brain. It has been estimated that SSRIs make up c 80% of the antidepressant market.

Exhibit 15: A selection of the top selling marketed treatments for MDD

Product	Company	Mechanism of action	2021 sales	*Forecasted 2028 sales
Rexulti	Otsuka Holdings	SDAM, or 5-HT1A (serotonin) receptor partial agonist; 5-HT2 (serotonin) receptor antagonist; Dopamine D2 receptor partial agonist	$870m	$988m
Trintellix	Lundbeck/ Takeda	5-HT (serotonin) reuptake transporter inhibitor; 5-HT1A (serotonin) receptor agonist; 5-HT1B (serotonin) receptor partial agonist; 5-HT3/5-HT7 (serotonin) receptor antagonist	**$475m (Lundbeck) and $591m (Takeda)	$456m (Lundbeck) and $427m (Takeda)
Cymbalta	Eli Lilly	5-HT (serotonin) & norepinephrine reuptake inhibitor (SNRI)	$582m	$158m
Lexapro	Lundbeck	Selective 5-HT (serotonin) reuptake inhibitor (SSRI)	$316m	$243m
Effexor XR	Viatris	5-HT (serotonin) & norepinephrine reuptake inhibitor (SNRI)	$317m	$309

Source: Evaluate Pharma, annual reports. Note: *According to Evaluate Pharma; **for Trintellix Lundbeck markets ex-US and co-promotes in Japan; Takeda markets US and co-promotes in Japan.

Our view is that if the XanaCIDD study is successful in showing CI improvement, the company will then move to advance it into pivotal studies, likely starting in CY24. We expect two pivotal studies would be needed to gain market approval. Given that no US-approved antidepressant has a CI label, we believe there is a significant opportunity for Xanamem in this market if it can demonstrate CI in this population, even if the drug itself does not demonstrate much effect on depressive symptoms, given that we would expect it be taken on top of SoC antidepressant therapy.

Sensitivities

The main sensitivities surround drug development and regulatory risks relating to lead drug candidate Xanamem. Although it has shown safety in Phase I/II trials and demonstrated therapeutic efficacy in terms of cognitive benefit in working memory and attention in healthy adults (XanaHES and XanaMIA Phase Ib portion) and clinical activity in XanADu (in AD patients with elevated pTau as determined in a recent analysis using newly available biomarker data), it remains to be seen whether this will translate into a clinical benefit in prospectively designed randomised trials in patients with CI related to early AD, or in MDD. For AD, in particular, despite cognitive improvement shown in healthy adults, the complex pathology of AD and degenerative nature of the condition could potentially outweigh or confound any therapeutic benefit from cortisol inhibition resulting from the drug.

While the initial results from the Phase II XanADu study in patients with AD did not meet the primary endpoints, a recent analysis showed that the subset of patients with biomarker-positive AD (as determined through elevated pTau) demonstrated encouraging clinical activity that appears to be quantitatively superior to what has been shown with FDA-approved Aduhelm in its EMERGE Phase III pivotal study and lecanemab in its Clarity AD study. However, we add a caveat about the relatively small sample size and note the limitations in using findings determined using retrospective clinical data as a basis for forecasting future clinical outcomes. The upcoming Phase IIb portion of the XanaMIA study will study a longer-duration treatment period (six months versus 12 weeks) and will study patients with biomarker-positive AD (as determined through elevated pTau at baseline).

Actinogen also faces significant financing risks as it will require substantial further capital to advance its programmes in the absence of a co-development or licensing deal. We expect the burn rate to increase substantially starting in CY24 should any or both of the two CI programmes advance to pivotal studies. We expect that each of the programmes would require two separate Phase III studies in their respective indications, prior to a possible FDA regulatory approval filing. While the Phase IIb portion of XanaMIA may potentially qualify as one of the pivotal studies required for approval in early AD, our base case forecasts assume that two additional AD studies will be required for approval (although we may revisit our forecasts once the Phase IIb study is completed and/or further information on the AD development plan becomes available). While our model accounts for financing(s) as long-term illustrative debt, the company may need to issue

equity instead, at pricing that may not be favourable for current shareholders and could lead to significant dilution. Difficulties or challenges in obtaining funds could affect the timing or progression of Actinogen's programmes. If Actinogen's expenditures are higher than forecast and/or if revenue is below our expectations, it many need to raise further capital beyond our current expectations.

Valuation

We value Actinogen at A$651m or A$0.36 per share, based on a rNPV analysis, which includes A$16.5m in net cash at the end of June 2022 (no debt, Actinogen raised net A$12.4m in December 2021). The breakdown of our rNPV valuation, which uses a discount rate of 12.5%, is shown below. Our valuation only includes Xanamem in the two lead indications. We use a PoS of 10.0% for Xanamem to reach the market in the AD project and 12.5% in the MDD project. Our PoS for AD is in the lower range of historical sector averages for Phase II stage level drug candidates in neurological disorders, as we believe a minor discount for AD is warranted given that this is a highly challenging condition (with many historical drug development failures) to treat due to its complex pathophysiology, with very few product approvals in recent years as discussed above.

We view the biomarker-differentiated XanADu results as highly encouraging in that they demonstrate the potential for meaningful Xanamem clinical activity in biomarker-confirmed AD patients. However, we add the caveat that the XanADu biomarker analysis sample size is relatively small (n=34 among the elevated pTau group) and recognize that there may be limitations in forecasting future trial outcomes based on study analyses using retrospective clinical data, as reflected in our PoS assumption. Our current model does not assume that Xanamem would demonstrate any specific disease-modifying effects as we view its usage primarily for improving cognition in the early to mid-stage AD population (rather than decelerating disease progression), and this assumption is reflected in our US gross pricing assumption at launch of US$7,500 per year (we believe a disease-modifying therapy could command a much stronger price), and we assume an average c 30% discount to this price for EU5 and Australia. Our model assumes two Phase III trials will commence in H125 (H2 CY24), which could lead to FDA approval and launch in H2 CY27. Our 2034 US sales estimate of US$2.6bn assumes a 5% market share within the US AD population, which is currently estimated at 5.8 million persons.

For CI related to MDD, our slightly higher PoS of 12.5% for reflects the fact that Xanamem has already shown cognitive benefit in the XanaHES and XanaMIA (Phase Ib portion) studies in the healthy adult population, and that the MDD population is much less likely to have any cognitive benefits from drug (Xanamem) to be confounded by an underlying progressive neurodegenerative disease (as in AD). However, we view the peak sales potential for CI in MDD to be lower than in AD patients, given that MDD patients are less likely to experience the severe progressive neurological decline that impairs autonomy and basic function, as AD patients. We assume similar pricing for the MDD indication as in AD, and while the current US prevalence of MDD is c 21m individuals, we assume the target treatment population as being much smaller (c 5 million), as we assume only 80% of MDD patients have cognitive effects, and that only 30% of these would consider seeking treatment. Within this group we assume a peak US market share of 7.5%, and that the average treated patient will take the drug for three months during the year, resulting in peak US FY34 sales of US$860m in the indication. We model generic erosion in both indications starting in FY37.

Exhibit 16: Actinogen rNPV valuation

Product	Market	Launch	Sales in FY34 (A$m)	NPV (A$m)	PoS (%)	rNPV ($Am)	rNPV/basic share (A$)
Xanamem in CI related to AD	US	H2 CY27	3,820	3,555.4	10.0%	317.0	0.18
Xanamem in CI related to AD	EU5 and Australia	H2 CY27	1,808	1,721.1	10.0%	172.1	0.10
Xanamem in CI related to MDD	US	H2 CY27	1,245	1,037.3	12.5%	109.4	0.06
Xanamem in CI related to MDD	EU5 and Australia	H2 CY27	726	629.0	12.5%	78.6	0.04
Corporate costs				(42.3)	100%	(42.3)	(0.02)
Net cash at 30 June 2022				16.5		16.5	0.01
Total equity value				**6,917.0**		**651.4**	**0.36**

Source: Edison Investment Research

Financials

As of 30 June 2022, the company had a cash position of A$16.4m, and reported a A$3.6m note corresponding to an annual R&D tax rebate which it expects to receive as payment from the Australian government before end-CY22. Actinogen had reported a FY22 net cash burn rate of A$9.5m, up from A$1.7m in FY21, primarily due to costs relating to the XanaMIA clinical trial. We forecast an FY23 cash burn rate of A$9.5m, with costs likely to be higher in H223 as the company will by then start enrolment for both the Phase IIb portion of the XanaMIA study, and the XanaCIDD MDD study. We expect the burn rate to ramp up significantly to A$39m in FY24 to fund the completion of both studies and as the company could then start registration-enabling pivotal studies. We model the company will raise A$20m in FY23 and A$40m in FY24. In total, we forecast A$390m in additional financings will be required before FY29 to fund the development of both programmes, and after which, provided it receives regulatory approval, the company should be able to generate sufficient operating revenues to reach recurring profitability. We forecast potential approval in both indications (CI related to AD and MDD) in H2 CY27 (or H128). As per Edison's usual policy, fundraising requirements are modelled as illustrative debt.

Exhibit 17: Financial summary

A$'000s	2020	2021	2022	2023e	2024e
30-June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	3,516	1,984	3,640	3,573	3,278
Cost of Sales	0	0	0	0	0
Gross Profit	3,516	1,984	3,640	3,573	3,278
Sales, General & Administrative	(2,962)	(3,111)	(4,558)	(4,200)	(4,410)
Net Research & Development	(5,537)	(2,406)	(8,215)	(7,536)	(36,232)
EBITDA	(4,983)	(3,533)	(9,133)	(8,163)	(37,364)
Amortisation of intangible assets	(314)	(313)	(313)	(313)	(313)
Depreciation & other	(99)	(74)	(88)	(226)	(267)
Normalised Operating Profit (ex. amort, SBC, except.)	(4,888)	(3,318)	(7,933)	(8,388)	(37,631)
Operating profit before exceptionals	(5,396)	(3,920)	(9,533)	(8,701)	(37,943)
Exceptionals including asset impairment	0	0	0	0	0
Other	0	0	0	0	0
Reported Operating Profit	(5,396)	(3,920)	(9,533)	(8,701)	(37,943)
Net Finance income (costs)	65	5	36	(269)	(1,025)
Profit Before Tax (norm)	(4,822)	(3,313)	(7,897)	(8,657)	(38,655)
Profit Before Tax (FRS 3)	(5,331)	(3,915)	(9,497)	(8,970)	(38,968)
Tax	0	0	0	0	0
Profit After Tax and minority interests (norm)	(4,822)	(3,313)	(7,897)	(8,657)	(38,655)
Profit After Tax and minority interests (FRS 3)	(5,331)	(3,915)	(9,497)	(8,970)	(38,968)
Average Basic Number of Shares Outstanding (m)	1,118.0	1,405.2	1,717.1	1,795.6	1,795.6
EPS - normalised (A$)	(0.004)	(0.002)	(0.005)	(0.005)	(0.022)
EPS - normalised and fully diluted (A$)	(0.004)	(0.002)	(0.005)	(0.005)	(0.022)
EPS - (IFRS) (A$)	(0.005)	(0.003)	(0.006)	(0.005)	(0.022)
Dividend per share (A$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	3,772	3,287	2,889	3,427	3,917
Intangible Assets	3,346	3,033	2,720	2,908	3,095
Tangible Assets	19	17	13	363	666
Investments in long-term financial assets	408	237	156	156	156
Current Assets	8,164	15,091	20,417	30,909	31,452
Short-term investments	0	0	0	0	0
Cash	5,040	13,457	16,370	26,863	27,405
Other	3,123	1,634	4,047	4,047	4,047
Current Liabilities	(744)	(755)	(1,480)	(1,480)	(1,480)
Creditors	(744)	(755)	(1,480)	(1,480)	(1,480)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(304)	(165)	(87)	(20,087)	(60,087)
Long term borrowings	0	0	0	(20,000)	(60,000)
Other long term liabilities	(304)	(165)	(87)	(87)	(87)
Net Assets	10,889	17,458	21,740	12,770	(26,198)
CASH FLOW STATEMENT					
Operating Income	(5,396)	(3,920)	(9,533)	(8,701)	(37,943)
Movements in working capital	(3,591)	(1,513)	(3,143)	0	0
Net interest and financing income (expense)	65	5	36	(269)	(1,025)
Depreciation & other	99	74	88	226	267
Taxes and other adjustments	5,966	3,630	3,035	313	313
Net Cash Flows from Operations	(2,856)	(1,724)	(9,517)	(8,432)	(38,388)
Capex	(23)	(6)	(3)	(1,076)	(1,070)
Acquisitions/disposals	0	0	0	0	0
Interest received & other investing activities	0	0	0	0	0
Net Cash flows from Investing activities	(23)	(6)	(3)	(1,076)	(1,070)
Net proceeds from share issuances	0	10,195	12,491	0	0
Net movements in long-term debt	0	0	0	20,000	40,000
Dividends	0	0	0	0	0
Other financing activities	282	(84)	(71)	0	0
Net Cash flows from financing activiities	282	10,111	12,420	20,000	40,000
Effects of FX on Cash & equivalents	0	0	49	0	0
Net Increase (Decrease) in Cash & equivalents	(2,596)	8,381	2,949	10,493	542
Cash & equivalents at beginning of period	7,637	5,040	13,422	16,370	26,863
Cash & equivalents at end of period	5,040	13,422	16,370	26,863	27,405
Closing net debt/(cash)	(5,448)	(13,694)	(16,527)	(7,019)	32,439
Lease debt	390	236	165	165	165
Closing net debt/(cash) inclusive of IFRS 16 lease debt	(5,058)	(13,458)	(16,361)	(6,854)	32,604
Free cash flow	(2,878)	(1,730)	(9,520)	(9,507)	(39,458)

Source: Actinogen Medical accounts, Edison Investment Research

Contact details	Revenue by geography
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Key team members

CEO and Managing director: Dr Steven Gourlay	SVP Product Development : Tamara Miller
Dr Gourlay has more than 30 years' experience in the development of novel therapeutics. Formerly founding chief medical officer (CMO) at US-based Principia Biopharma, he was responsible for the supervision of multiple clinical trial programmes in orphan immunological diseases, multiple sclerosis and cancer. Principia Biopharma was acquired by Sanofi for US$3.7bn in 2020. Before that, Dr Gourlay was a partner at GBS Venture Partners, the Australian specialist life sciences and healthcare venture capital firm. He is based in Sydney and holds a Bachelor of Medicine, Bachelor of Surgery (MB, BS) from the University of Melbourne, a PhD in Medicine from Monash University and an MBA from Macquarie University.	Tamara Miller has over 20 years of international clinical operations and product development experience. She holds a Masters and a Bachelor's Degree in Biomedical Sciences, as well as a Diploma of Business and Project Management Professional (PMP) certification. Tamara has lived and worked in Australia, the UK, and the US while holding senior positions in product development, clinical operations, and project management. Her background includes positions within pharmaceutical and biotechnology companies as well as for CROs, working across a multitude of therapeutic areas. Tamara oversees and manages the overall product development process and strategy including pre-clinical, clinical development, clinical operations, CMC & manufacturing, regulatory operations, commercial and R&D budget/finance operations.
CFO: Jeff Carter	**CMO: Professor Paul Rolan**
Mr Carter joined Actinogen in September 2020 and has more than 30 years' expertise in professional accounting, investment banking, corporate finance and commercial/strategic planning roles. He has international experience as VP of corporate development and served as a member of the board of a US-based company. Mr Carter holds a Bachelor of Financial Administration (UNE) and a Master of Applied Finance (Macquarie University), and is a qualified chartered accountant.	Professor Rolan joined Actinogen in 2022. He is an experienced clinical pharmacologist and drug development consultant. His career has spanned academic medicine (professor of clinical pharmacology and director of innovation at the University of Adelaide) and pharmaceutical medicine. Professor Rolan's prior industry roles have included medical director of the UK's largest Phase I contract research organisation Medeval, CMO for ASX-listed biotech company Bionomics and director of drug development for Singapore's first listed pharmaceutical company iX Biopharma. He holds numerous academic and professional qualifications, including a Bachelor of Medicine and Bachelor of Surgery (MBBS) and a Doctor of Medicine (MD).
VP clinical operations: Cheryl Townsend	
Cheryl Townsend joined Actinogen in March 2022 as vice president of clinical operations and is responsible for the company's clinical operations and delivery of its clinical trial programme. She brings 30 years of international clinical research experience, including senior positions in clinical operations and medical affairs in pharmaceutical companies and clinical research organisations. She is a registered nurse with post-graduate degrees in nursing and clinical research as well as a Master's degree in health law.	

Top shareholders	(%)
BVF Partners	13.5
Steven Gourlay	3.7
Edinburgh Technology Fund	2.71
JSC Wealth Management	2.51
State Street Corp	1.04

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