AC4R – Is cortisol still a valid target?

A novel approach to treating cognitive impairment and Alzheimer's disease

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Actinogen Medical

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XanADu Phase II clinical trial

Double-blind, randomised, placebo-controlled study to assess the efficacy and safety of Xanamem in subjects with mild Alzheimer's disease[1]

Xanamem treatment course
12 weeks

186 patients with mild Alzheimer's disease (enrolment complete)[2]

10mg daily
Xanamem for 12 weeks (vs. placebo)

Trial conducted at 25 sites in
AUS, USA and UK

Largest AD global clinical trial run by an Australian biotech

1. Study registered on Clinicaltrials.gov: NCT02727699
2. Fully enrolled 26 November 2018

Comprehensive Xanamem Clinical Development Program

The ongoing comprehensive review of the data and results from XanADu and the additional studies will inform the optimal clinical development path

XanADu

Multiple endpoints and sub analyses will allow insight into Xanamem's potential and where it is most effective

Totality of results assessed by Actinogen and expert Clinical Advisory Board

XanaHES

Assess safety and tolerability of higher doses (to allow higher doses in future trials), with an efficacy assessment included

Phase I Target Occupancy, & Homogenate Binding Studies

Measures effects of different Xanamem doses on inhibiting the 11β-HSD1 enzyme in the brain

Additional Toxicology Studies

Pre-clinical safety and toxicology studies to allow for longer treatment periods

The totality of results will inform further Xanamem development

Phase I clinical trial

Single blind placebo-controlled, dose escalation study to assess safety, tolerability and efficacy of Xanamem in healthy elderly subjects – full results expected in 4Q CY2019

12 weeks
Xanamem treatment course
Trial conducted at 1 site in Australia

42
Healthy elderly subjects
(no cognitive impairment)

20mg daily
Xanamem 30 subjects
Placebo 12 subjects

Cognition assessed
Through computerised efficacy tests
(Cogstate CTB[1])

Key objective to expand the Xanamem safety dataset and evaluate potential for higher dosage in future clinical trials

1.Cogstate Cognitive Test Battery

Cognitive Efficacy Signal Achieved

XanaHES included a cognition endpoint to evaluate the cognitive efficacy of Xanamem using the Cogstate Cognitive Test Battery which evaluated six domains. Cognitive improvement demonstrated in three domains

XanaHES 20mg Cogstate Cognitive Test Battery: p values and Cohen's d effect size

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

Additional details on slide 5

Notes: * statistical significance achieved; # effect size >0.5 (moderate treatment effect); Δ effect size >0.8 (large treatment effect)

1: CPAL – Continuous Paired Associate Learning

Cognitive Efficacy Signal Achieved (cont'd)

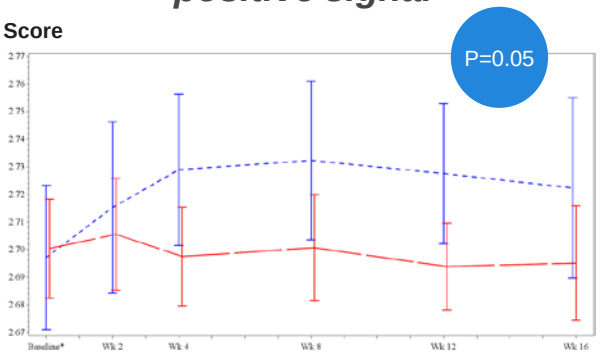
Breakthrough results demonstrated statistically significant cognitive efficacy signal in multiple cognition domains – based on Cogstate Cognitive Test Battery

Working memory (One Back Test)

Strongly statistically significant result

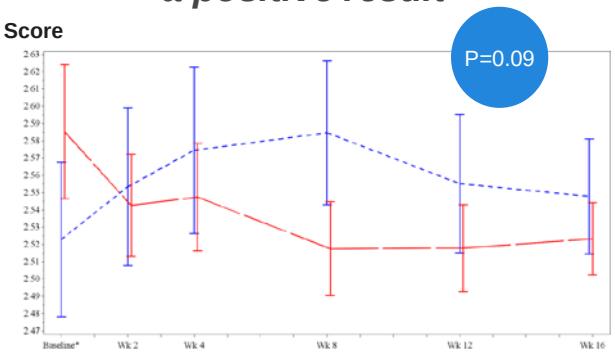
Visual attention (Identification Test)

Statistically positive signal



Psychomotor function (Detection Test)

Good trend to a positive result



Efficacy results of particular interest, reflecting high quality and consistent data in a small study population

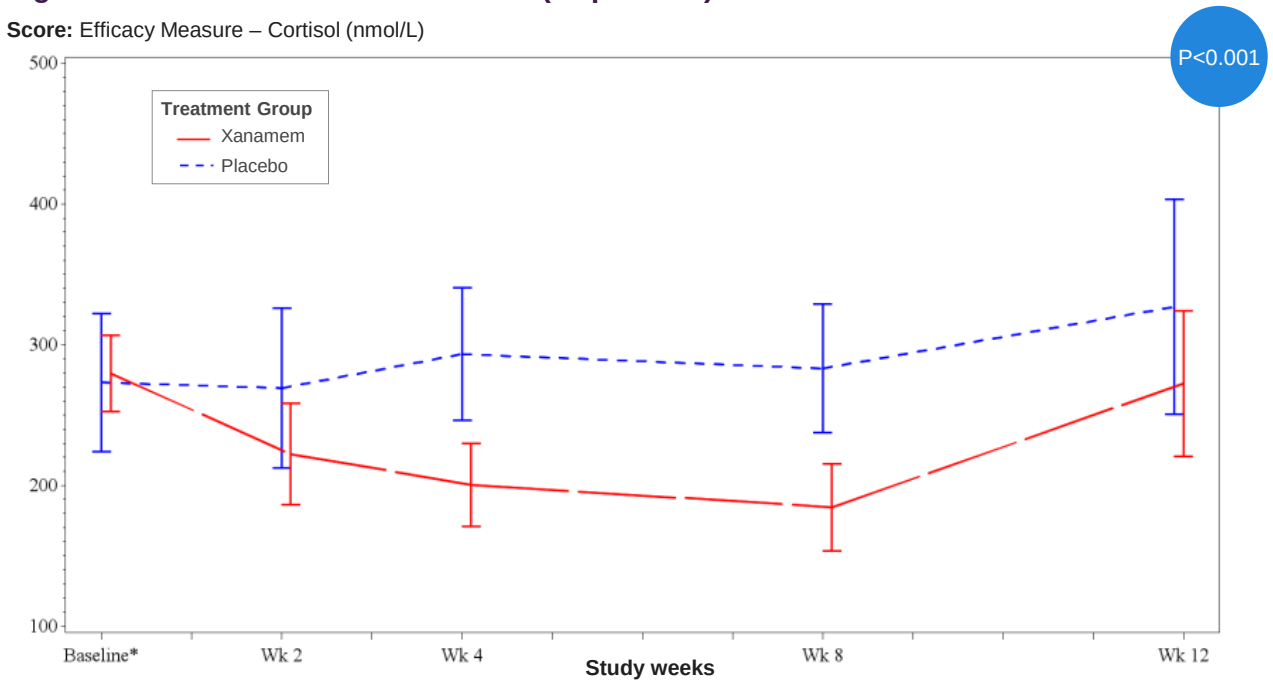
Baseline* Mean of Observed Data

Cortisol Levels Reduced with Acceptable Safety

Efficacy results complemented by the statistically significant reduction in serum cortisol observed in the trial

Significant reduction in cortisol levels (all patients)

Score: Efficacy Measure – Cortisol (nmol/L)



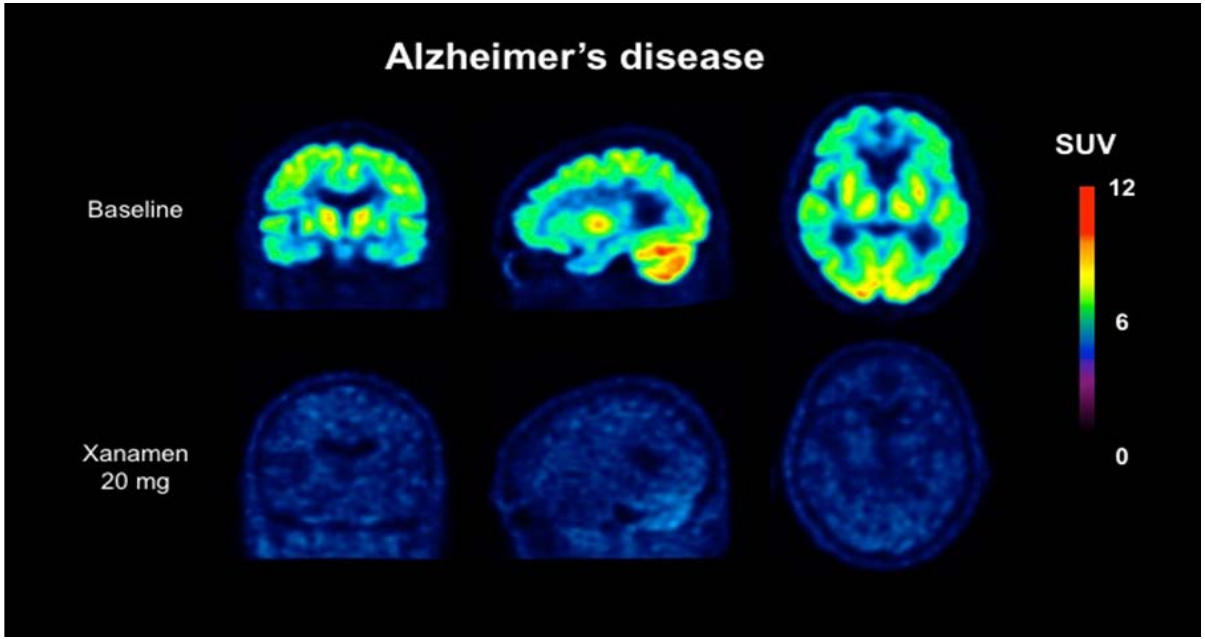
Baseline * Mean of Observed Data

Xanamem achieved an average decrease of 73.2 vs. placebo (p<0.001)

These breakthrough results support the cortisol hypothesis that lowering persistently raised cortisol levels in the brain is expected to positively enhance cognition

Target Occupancy Study: Preliminary Results

Phase I target occupancy study demonstrates that 10-30mg Xanamem dosed for seven days significantly occupies neuronal 11β-HSD1 throughout the brain



50% to 85% occupancy, dependent upon brain region, dosage and study subject

Further study data available in 4Q CY2019

Additional ongoing cohorts at 5mg Xanamem and 10mg with delayed PET imaging

Phase I Target Occupancy supports Xanamem as a potent, orally bioavailable and brain-penetrant 11β-HSD1 inhibitor

Summary

- Xanamem 10mg-30mg effectively achieves target occupancy (50-80%) of 11β-HSD1 enzyme in the brain
- Xanamem 10mg and 20mg inhibits cortisol production and Xanamem 20mg achieves statistically significant reduction in serum cortisol
- Xanamem 10mg and 20mg – no serious adverse events reported after 12 weeks therapy
- **Xanamem 20mg - statistically significant cognitive improvement in healthy volunteers after 12 weeks therapy. Effect apparent after only 4 weeks, and sustained**

Cortisol – most certainly a valid target!

Appendix:
Background information

Summary

Actinogen is developing innovative treatments for cognitive impairment associated with neurological and metabolic diseases with an initial focus on Alzheimer‘s disease

Xanamem - lead compound

Differentiated with a novel mechanism of action
First-in-class, brain penetrant, orally active, small molecule, inhibitor of 11β-HSD1 enzyme
Xanamem mechanism of action validated by independent research on the cortisol hypothesis

Targeted strategic market focus

Initially focused on developing a treatment for Alzheimer's disease
Addressable market worth >US$7.5bn with unmet needs and potential upside.
Target indication underpinned by efficacy results from animal model studies.
Mood disorders and schizophrenia identified as additional opportunities

Clinical stage asset

Advanced clinical stage program assessing Xanamem in Alzheimer’s disease and cognitive impairment in other neurological conditions. Complementary higher dose and target occupancy phase I studies will inform future development

Potential value upside

Totality of existing studies will inform further development and commercial potential of Xanamem

De-risked opportunity

Fully funded programs
Initial data from additional studies indicate brain penetration, good target occupancy and safety profile

Experienced leadership

Board and Management with significant drug development and corporate experience, supported by key opinion leaders and Xanamem discovery team

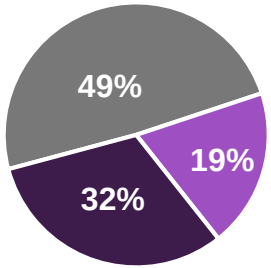
Corporate overview ASX:ACW

Actinogen is an ASX-listed biotech company focused on innovative approaches to treating cognitive impairment associated with neurological and metabolic diseases

Overview

- Actinogen is developing Xanamem, a novel therapy for Alzheimer's disease, mood disorders and schizophrenia, with significant market potential
- Xanamem - lead drug, designed to inhibit cortisol production in the brain, with the potential to treat cognitive impairment
- Actinogen has completed a Phase II double-blind, 12 week, randomised, placebo-controlled study of Xanamem in Alzheimer's disease (XanADu)

Key shareholding metrics



BVF Partners

Top 20 (excl. BVF Partners)

Remaining shareholders

Board of Directors

Dr. Geoff Brooke

Chairman

MBBS; MBA

- **30+ years experience** in the healthcare investment industry
- Founder and MD of Medvest Inc and GBS Venture Partners

Dr. Bill Ketelbey

CEO & MD

MBBCh; FFPM; MBA; GAICD

- **30+ years experience** in healthcare, biotech and pharmaceutical industries
- Formerly senior international roles at Pfizer and Director at Westmead Institute of Medical Research

Dr. George Morstyn

Non-executive director

MBBS; PhD; FRACP; MAICD

- **25+ years experience** in biotech investment and drug development
- Board member of Biomedvic, Cancer Therapeutics and Symbio; Former Senior VP and SMO at Amgen

Mr. Malcolm McComas

Non-executive director

BEc, LLB; FAICD; SF Fin

- **25+ years experience** in the financial services industry
- Chairman of Pharmaxis and Fitzroy River Corporation; formerly senior leadership roles in investment banking

Advisory Boards

World's premier academics involved in the development of Xanamem and as a novel treatment for Alzheimer's disease

Clinical Advisory Board (Alzheimer's disease)

Positions Xanamem at the forefront of Alzheimer's drug development

Prof. Craig Ritchie *Chair*

THE UNIVERSITY of EDINBURGH

Prof. Colin Masters *AO*

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

THE FLOREY INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH

Prof. Jeffrey Cummings

Cleveland Clinic

Scientific Advisory Board

Combining deep understanding of cortisol, 11β-HSD1 and drug discovery

Prof. Jonathan Seckl

THE UNIVERSITY of EDINBURGH

Prof. Brian Walker

Newcastle University

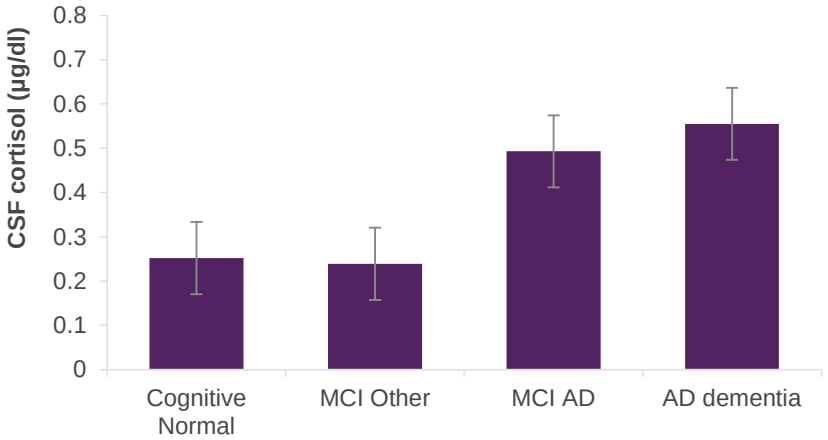
Prof. Scott Webster

THE UNIVERSITY of EDINBURGH

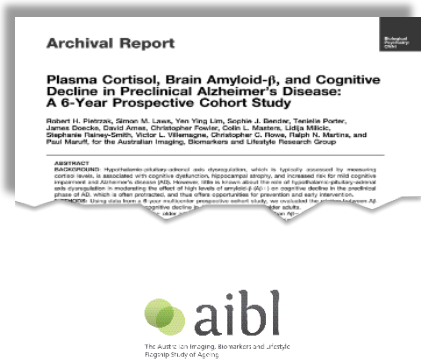
Alzheimer‘s strategic focus underpinned by medical research

A growing body of medical literature supports the association between cortisol and Alzheimer‘s disease

Raised cortisol associated with Alzheimer’s disease[1]



Supported by growing body of medical literature


Archival Report

Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study

Many studies support the association between **cortisol and Alzheimer’s disease development and progression**[2]

A recent AIBL[3] study provided compelling evidence that elderly subjects with **higher plasma cortisol levels are at much greater risk of developing Alzheimer‘s disease**

This study[3] also demonstrated **that 50% of those aged 65+ have raised cortisol levels**

Research suggests that lowering cortisol levels may prevent the development / progression of Alzheimer’s disease

1. MCI: mild cognitive impairment; AD: Alzheimer’s Disease
2. Recent studies also support the association between cortisol and cognitive impairment associated with neuroendocrine dysfunction
3. Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer’s Disease: a 6-Year Prospective Cohort Study. Pietrzak et al., 2017. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2:45-52

Xanamem

A novel drug designed to inhibit cortisol production in the brain, with the potential to treat cognitive impairment

Well researched
>15 years of R&D completed

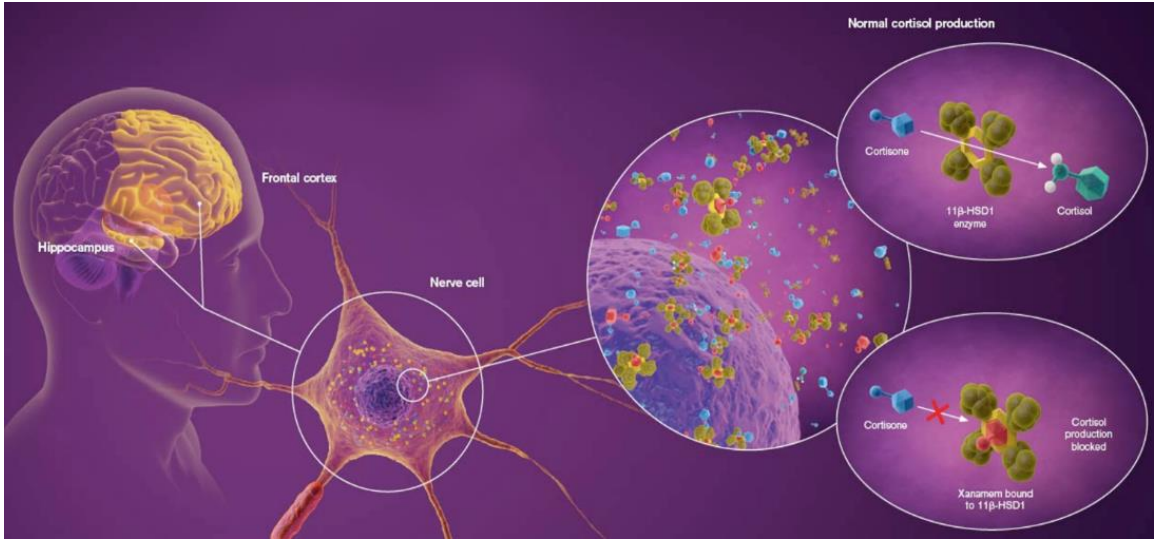
Well tolerated
Dosed >200 patients with acceptable clinical safety, toxicity & PK / PD[1] profile

Well protected
Composition of matter IP coverage, patents granted in all major markets

Validated in Alzheimer's disease
Symptomatic and disease modifying effects (in vivo) and demonstrated effect of cortisol hypothesis (in humans)

Potential in other diseases
Secondary focus on cognitive impairment in mood disorders and schizophrenia

Differentiated mechanism of action
Highly selective 11β-HSD1 inhibitor in the brain which reduces excess cortisol production

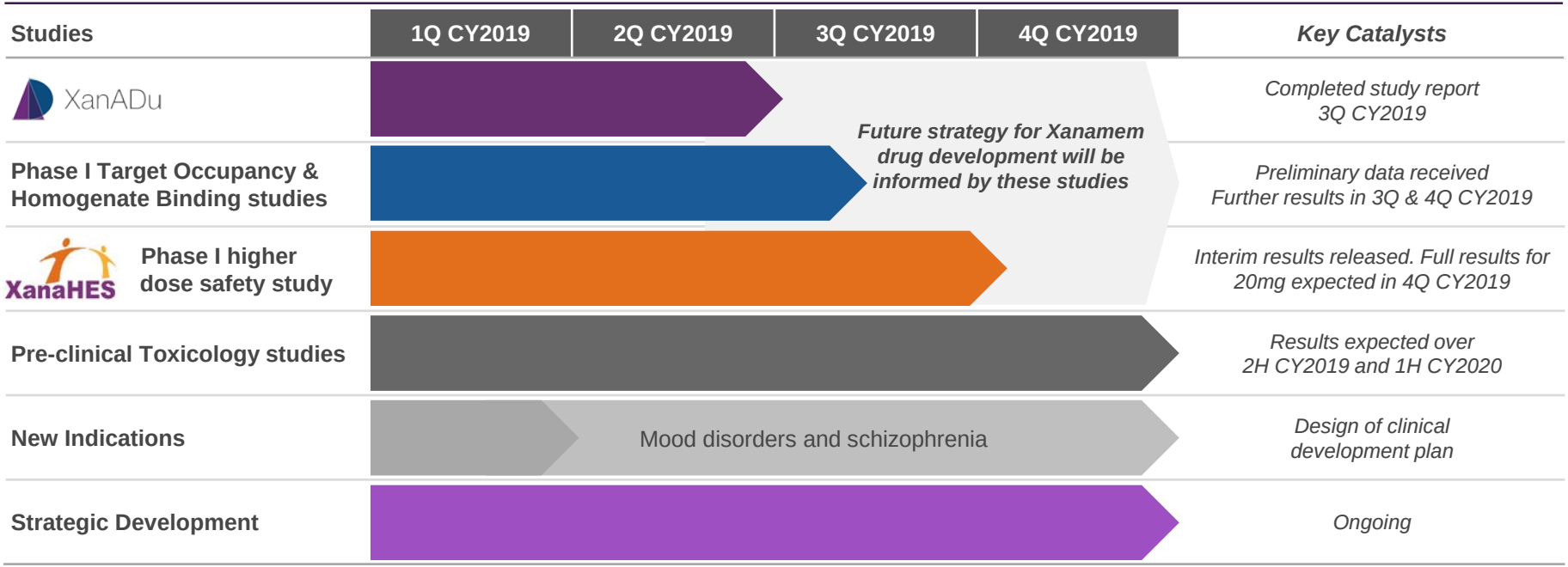


Xanamem is a novel, first-in-class, potent, orally bioavailable and brain-penetrant 11β-HSD1 inhibitor

1. PK / PD: pharmacokinetic / pharmacodynamic

Development Pipeline and Upcoming Catalysts

Multiple studies currently underway with significant upcoming milestones in the near term



Actinogen is fully funded to complete all current studies

XanADu: Phase II Clinical Trial Completed

Double-blind, randomised, placebo-controlled study to assess the efficacy and safety of Xanamem in subjects with mild Alzheimer's disease[1], with initial results announced 7th May 2019

XanADu initial results

- Efficacy end points were not achieved
- Potent pharmacodynamic modulation of cortisol-related hormones achieved
- Xanamem is well-tolerated with no safety concerns
- Sub-analyses of results currently underway

Possible reasons behind XanADu results

- Recurrent challenges seen in AD drug development
- Xanamem dose / study duration

Ongoing development

- Phase I **target occupancy** studies
- **XanaHES** dose escalation study
- Long-term animal **toxicology** studies
- New indications for future focus selected: mood disorders (such as **bipolar disorder**) and **schizophrenia**

1. ADAS-COG14: Alzheimer's Disease Assessment Scales – Cognitive Subscale Score (version 14); ADCOMs: AD COMposite Scores (composite data derived from ADAS-COG14, CDR-SOB and MMSE); CDR-SOB: Clinical Dementia Rating Scale – Sum of Boxes; RAVLT: Rey Auditory Verbal Learning Test; MMSE: Mini-Mental Status Examination; NTB: Neuropsychological Test Batteries; NPI: Neuropsychiatric Inventory

XanADu: Possible Reasons Behind XanADu results

Likely due to the recurrent challenges seen in Alzheimer's disease drug development

Conceptual model of the disease

- Causality unknown; cortisol as a target is a hypothesis
- Diagnoses largely based on highly subjective tools

Stage of disease

- Wrong patient population ("too early" or "too late")
- High heterogeneity as to the real biological drivers behind each individual's disease state

Outcome/endpoint measures

- Absence of valid biomarkers
- Subjectivity of outcome assessments flawed

Patient recruitment and retention

- Overall patient population may have been too heterogeneous to generalise results

Xanamem

- Dose: too low or too high?
- Dosing regimen: may need bi-daily dosing?
- Treatment duration: may need to treat for longer?

Xanamem: Phase I Target Occupancy Study & Homogenate Binding Studies

To assist with confirming and optimising Xanamem dosing

Aim

To accurately demonstrate the effects different doses of Xanamem have on inhibiting the 11β-HSD1 enzyme in the human brain.

Phase I Target Occupancy studies

- Competitive binding, radio-labelled tracer PET imaging assay
- Subject cohorts tested with Xanamem at 5mg, 10mg, 20mg, and 30mg doses.
- Data available from 10-30mg dosing cohorts

In vitro Homogenate Binding Studies

- Enzyme occupancy competition studies, saturation binding studies, and enzyme activity assays in rat and human brain sections (ongoing)
- To correlate enzyme occupancy and enzyme activity at incremental doses of Xanamem

Key studies to help interpret XanADu results and support future clinical development strategy

Long-Term Safety and Toxicology Studies

Aim

Evaluate safety and toxicology in rodent (six months) and dog (nine months) studies in preparation for longer term clinical studies

- Studies **required by all regulators - FDA**
- Will allow future **clinical studies beyond 12 weeks**
- Studies **ongoing**
- **No substantive safety issues** observed to date

Key study to support future clinical development strategy

Market dynamics of Alzheimer's disease

Presents a compelling commercial opportunity for Actinogen to target initially

Substantial target market with significant upside[1]

Cortisol-high, cognition normal	Subjective memory decline	Cognitive and functional decline fulfilling dementia		
At-risk	Prodromal	Mild	Moderate	Severe
~25.0m (50% over 65 yrs)	**~4.0m**	**~1.5m**	~1.7m	~2.5m

Upside potential for earlier use *Key focus*

>US$7.5bn

Target annual peak sales (mild AD)[2]

Underpinned by favourable market dynamics

- ✓ Targeting **large addressable** markets (US, EU5, JP)
- ✓ All **currently approved drugs are symptomatic treatments** (that do not affect disease progression) **providing limited benefit**
- ✓ Treatment **prices are robust** (despite generic competition) – with users paying for modest clinical efficacy

US branded products (gross price)

US$10/day

US$8/day

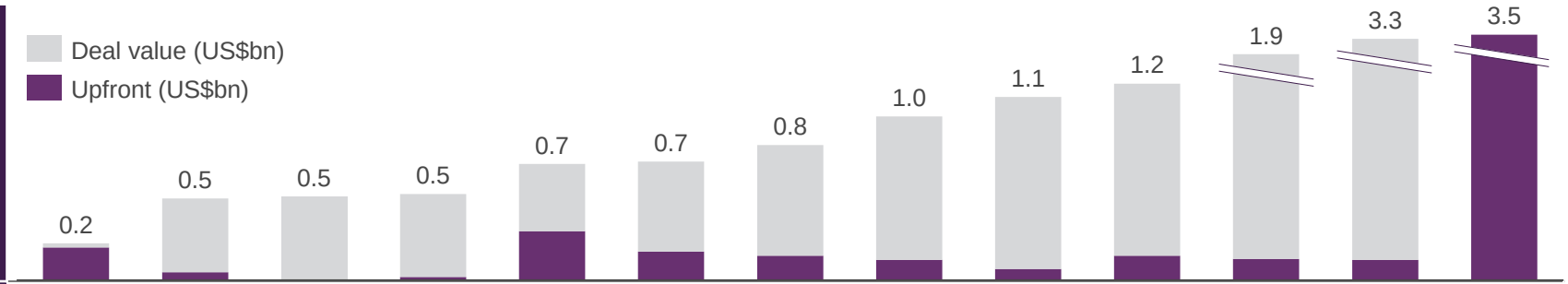
US$18/day

Source: Drugs.com, Biogen, Roche, Datamonitor, Alzheimer's Association

1. Target market statistics based on the current US treatment landscape
2. Base case annual peak sales assumes: (1) Launch: US 2024, EU5, JP and ROW 2025; (2) Penetration: 30% of mild AD market in 5 years (i.e. ~470,000 in the US); (3) Pricing: US – US$19/day gross (US$12/day net), ROW: 50% of US price

Big Pharma interest

Global Big Pharma demonstrating strong M&A interest in acquiring or partnering with companies and licensing novel mechanism of action assets with Alzheimer's disease as the lead/key indication



Deal value (US$bn)	0.2	0.5	0.5	0.5	0.7	0.7	0.8	1.0	1.1	1.2	1.9	3.3	3.5
Bidder / Licensee	abbvie	Lilly	janssen	MERCK	Biogen	PIERIAN	Otsuka	Allergan	abbvie	Takeda	Lilly	Allergan	Otsuka
Target / Licensor	ALECTOR	AstraZeneca	AC Immune	Bionomics	Bristol-Myers Squibb	Bristol-Myers Squibb	Lundbeck	CHASE Pharmaceuticals Corporation	Voyager THERAPEUTICS	DENALI	AC Immune	HEPTARES therapeutics	AVANIR
Year	2017	2014	2015	2014	2017	2014	2013	2016	2018	2018	2018	2016	2014
Deal type	Partnership	Partnership	Partnership	Partnership	Licence	Asset	Partnership	Acquisition	Partnership	Partnership	License	License	Acquisition
Candidate	Immuno-neurology platform	AZD3293	ACI-35	BNC-375	BMS-986168	IPN007	LU AE58054	CPC-201	Gene Therapy platform	Brain-penetrant ATV	ACI-3024	Three M1/M4 agonists	AVP-786
Phase	Pre-clinical	I	I	Pre-clinical	I	Pre-clinical	II	II	Pre-clinical	Pre-clinical	Pre-clinical	I	III
Novel MoA (not anti-amyloid)	✓	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓