Xanamem™ for Alzheimer's disease

Actinogen Medical

Dr Bill Ketelbey CEO

October 2017

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Actinogen Medical

Actinogen Medical

- Headquartered in Sydney, Australia. ASX:ACW
- Developing Xanamem for the treatment of Alzheimer's disease (AD) and cognitive impairment in chronic neurodegenerative diseases.
- Xanamem, a novel first-in-class, brain penetrant, orally active, inhibitor of the 11βHSD1 enzyme – prevents the production of excess cortisol in the brain.
- Persistently raised cortisol in the brain is associated with the development and progression of Alzheimer's disease.
- Experienced board and management; expert clinical and scientific advisory board.

STOCK METRICS*

ASX CODE	ACW
Market Capitalisation	$35m
Enterprise Value	$32.0m
52-week High/Low	$0.04-$0.09
Top 20 Shareholdings	56%

TOP 10 HOLDERS

Rank	Name	A/C designation	%IC
1	EDINBURGH TECHNOLOGY FUND LIMITED		7.76
2	JK NOMINEES PTY LTD	<THE JK FUND A/C>	6.45
3	WEBINVEST PTY LTD	<OLSB UNIT A/C>	4.24
4	WARAMBI SARL		3.53
5	SUNSET CAPITAL MANAGEMENT PTY LTD	<SUNSET SUPERFUND A/C>	3.22
6	MR MARTIN ROGERS		3.22
7	MR BENJAMIN CRANSTOUN DARK	<THE BEN DARK HOLDINGS A/C>	2.54
8	DENLIN NOMINEES PTY LTD		2.46
9	OAKTONE NOMINEES PTY LTD		2.37
9	TISIA NOMINEES PTY LTD	<HENDERSON FAMILY A/C>	2.37
10	BNP PARIBAS NOMINEES PTY LTD HUB24 CUSTODIAL SERV LTD DRP		2.20

* Data as at 30 Sept 2017

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Commercially experienced, globally recognised

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Chairman

Dr. Bill Ketelbey
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Dr. Jason Loveridge
Non-Executive Director

GBS VENTURE PARTNERS

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Xanamem Clinical Advisory Board

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Prof. Colin Masters

Prof. Jeffrey Cummings

THE UNIVERSITY of EDINBURGH

THE UNIVERSITY OF MELBOURNE

Cleveland Clinic

THE FLOREY
INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH

The Royal Melbourne Hospital

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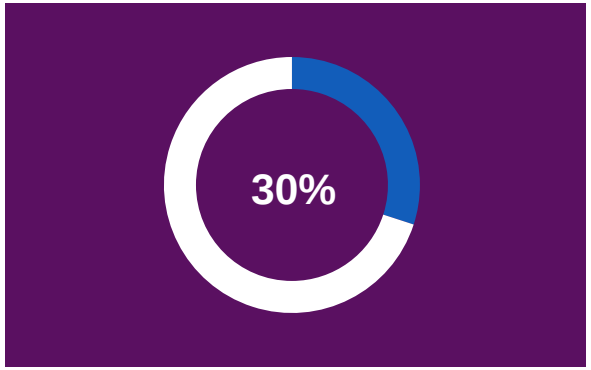
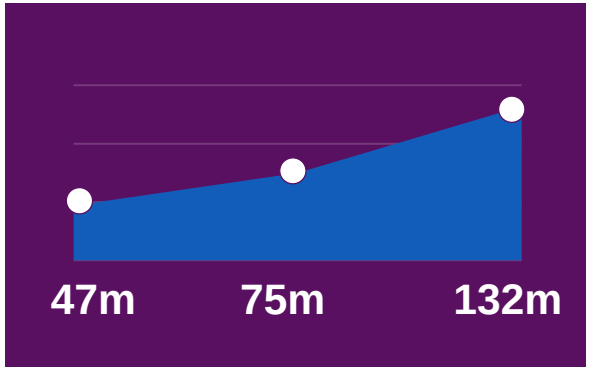
Alzheimer’s disease: a vast unmet medical need

- There are nearly 50 million Alzheimer's disease sufferers world-wide and the number is set to double every 20 years
- It’s the leading cause of death in Australian women and second only to heart disease in Australia, overall
- Of the top-ten leading fatal illnesses, Alzheimer's remains the only one that cannot be prevented, treated or cured
- There are only 4 drugs available to treat Alzheimer's disease (donepezil, rivastigmine, galantamine, memantine), however they all provide only limited symptomatic benefit – generally around 6 months. Once the patient fails on one of these, there are no alternatives



30% OF 85 YEAR OLDS HAVE ALZHEIMER’S DISEASE

1 in 3 seniors will die with Alzheimer’s disease or other dementia



NUMBERS WILL DOUBLE EVERY 20 YEARS

ONE PERSON EVERY 3 SECONDS

Globally there were ~10m new cases of dementia in 2015

TOTAL COST RISES TO US$2 TRILLION BY 2030

Dementia will become a trillion dollar disease by 2018

The Alzheimer’s Association Facts and Figures, 2014. The World Alzheimer’s Report. Australian Bureau od Statistics 2017

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Xanamem

- A novel, first in class, potent, orally bioavailable, brain-penetrant, 11βHSD1 inhibitor
- **Differentiated mechanism of action:** blocking cortisol production in the brain
- **Symptomatic and disease modifying effects *in vivo***
- **Well-tolerated**: acceptable clinical safety, toxicity and PK/PD profile
- **Efficacious human brain concentrations**
- **Compelling data package**: clinical safety, in vitro and in vivo mechanistic and efficacy data
- **XanADu – phase II clinical study underway**, dosing subjects with mild AD dementia in USA, UK, AU
- Planning ongoing for **additional clinical indications**
- **Composition of matter IP coverage ≥ 2031**, patents granted in most major markets

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Xanamem development indications

	PRE-CLINICAL	PHASE I	PHASE II
Alzheimer's disease (XanADu)	→	→	→
Diabetes cognitive impairment	→	→	
Post traumatic stress disorder	→		
Post myocardial infarction	→		

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Cortisol: a validated biomarker and target for AD

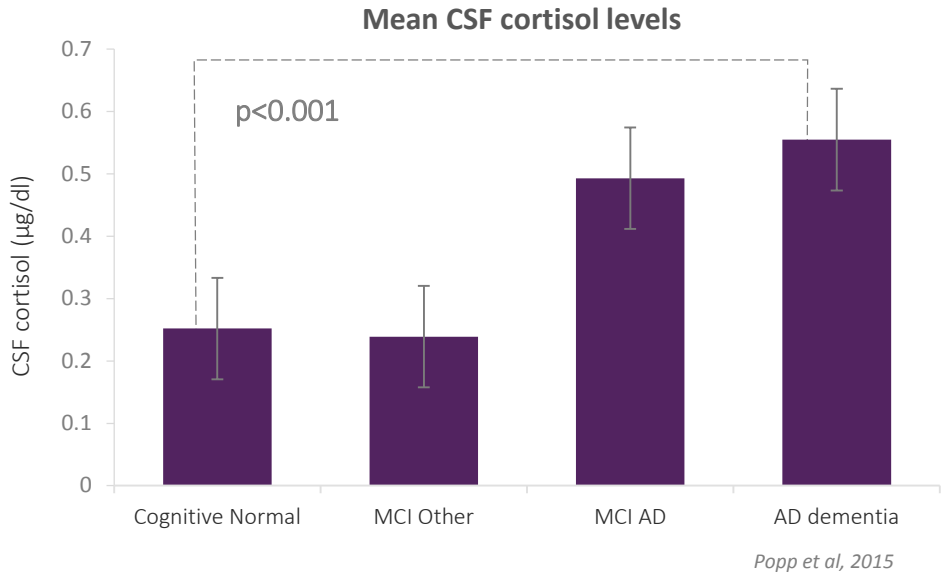
Cortisol and Alzheimer's

- Recent independent studies support the association between cortisol and development and progression of Alzheimer's disease [1-5]
- Cognitive impairment in patients with neuroendocrine dysfunction [6-9]
- Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017) [5]
    - subjects with higher plasma cortisol at much greater risk of developing AD
    - accelerated effect of Aβ+ on decline in global cognition, episodic memory, and attention

Xanamem

- Data presented at four major international medical congresses in 2016 – AAIC Toronto; CTAD San Diego; ICE Beijing; MMC Lisbon
- Pre-clinical and Phase I data published [10-11]

aibl
The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing



Popp et al, 2015

[1] Geerlings *et al.,* 2015, Neurology 85: 1-8; [2] Lehallier *et al.*, 2016, JAMA Neurology 73(2), 203-212; [3] Popp *et al.*, 2015, Neurobiol. Aging 36:601–607; [4] Ennis *et al.,* 2017, Neurology 88(4):371-378; [5] Pietrzak *et al.*, 2017, Biol Psychiatry: Cognitive Neuroscience and Neuroimagery, 2:45-52; [6] Lupien et al., 2009, Nat Rev Neurosci 10:434–445; [7] Starkman et al., 1999, Biol Psychiatry 46: 1595–1602; [8] Lupien et al., 1998, Nat Neurosci 1:69–73; [9] MacLullich et al., 2005, Psychoneuroendocrinology 30:505–515; [10] Sooy *et al.*, 2015. Endocrinology 156(12):4592-4603; [11] Webster *et al.*, 2017, British J Pharmacol 174:396-408.

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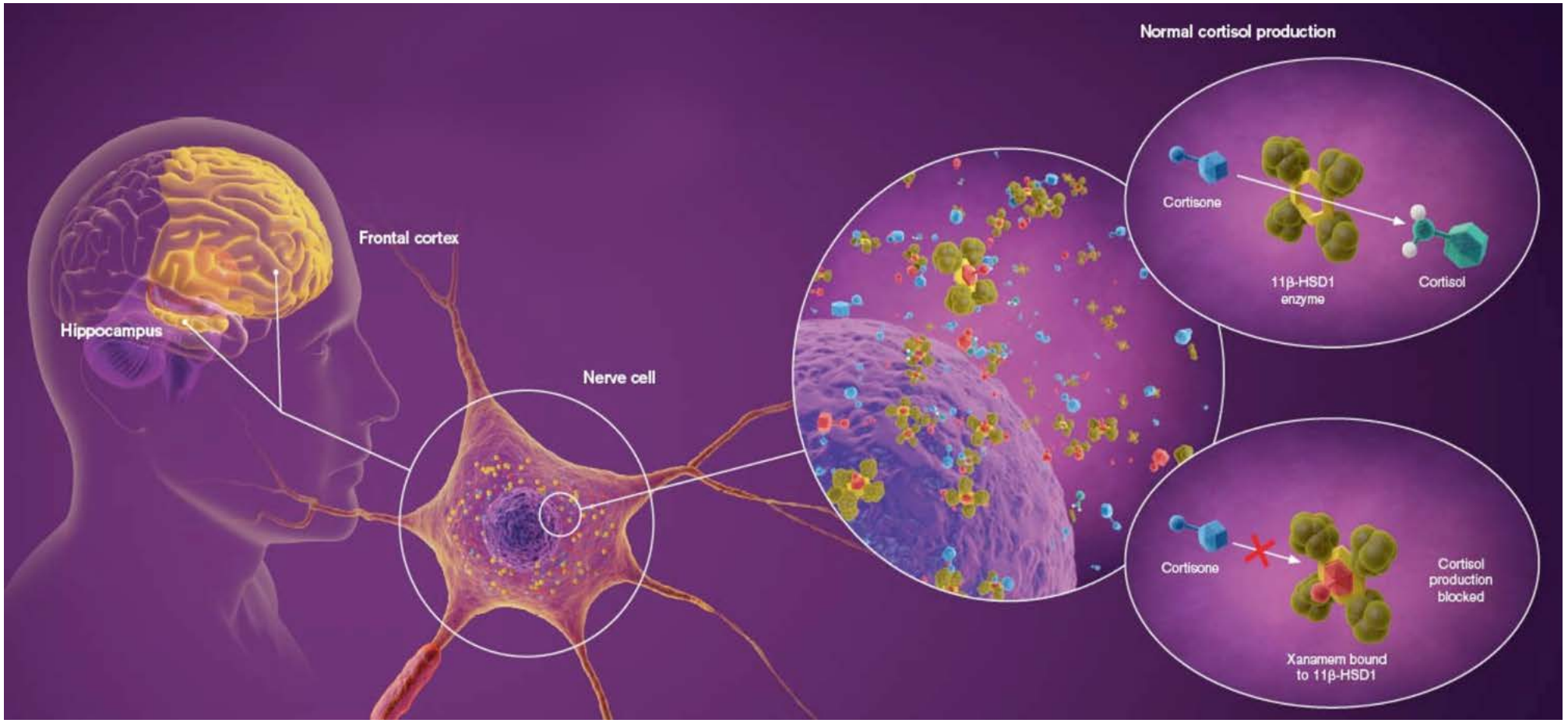
Mechanism of action

Xanamem binds to 11βHSD1, reducing brain cortisol production



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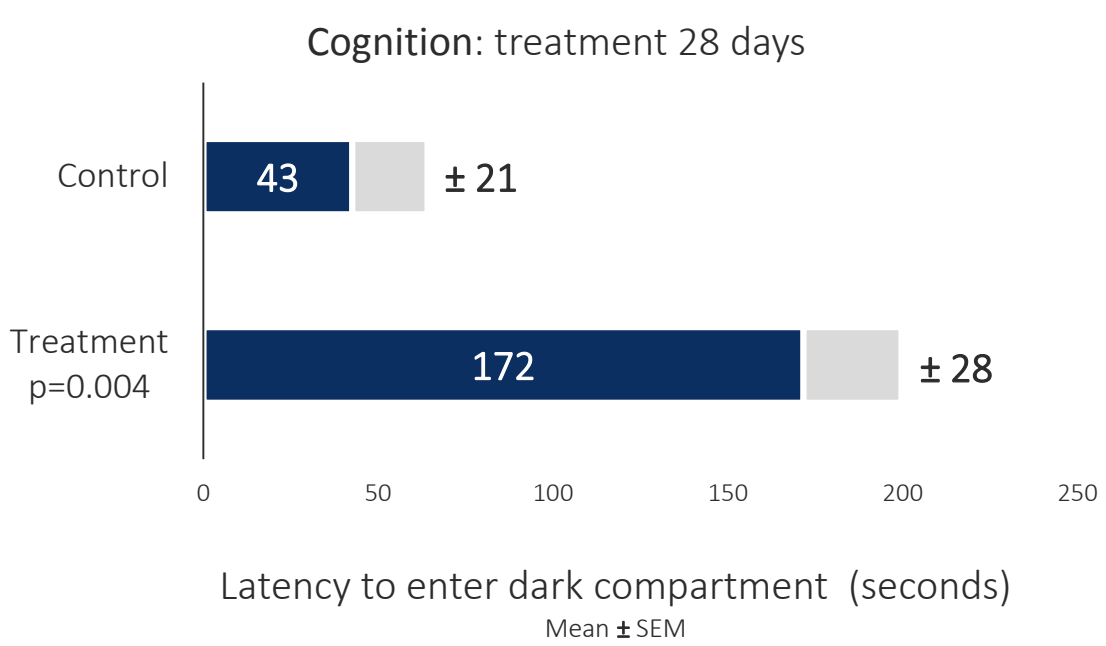
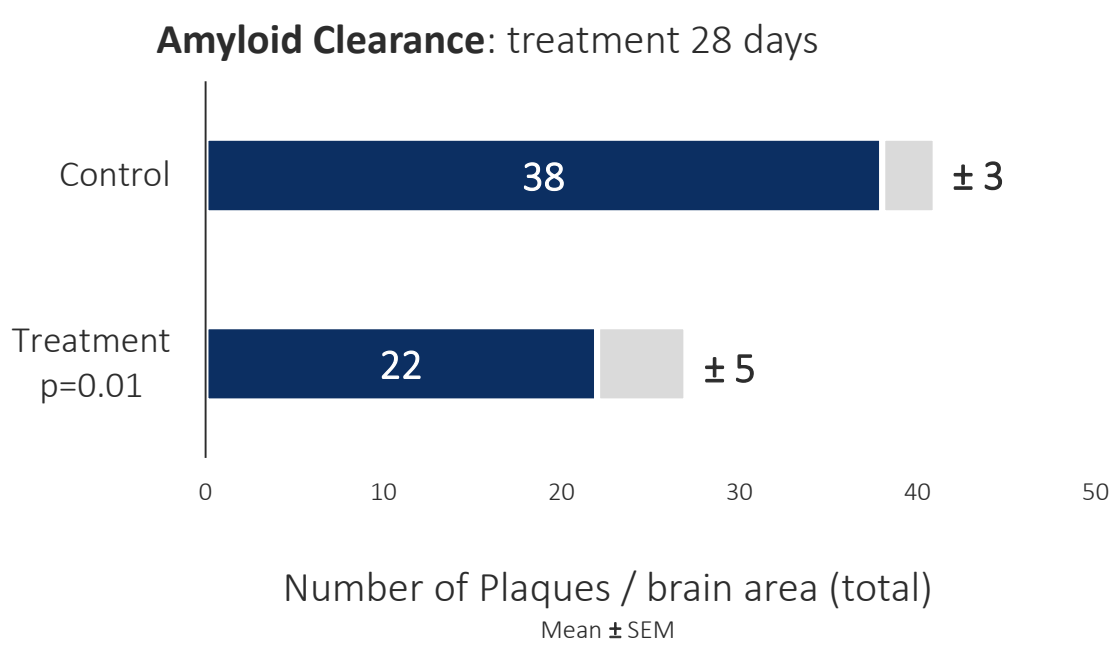
Xanamem

Symptomatic **and** disease modifying effects in mouse models





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

UE2316 in Tg2576 rodent model of Alzheimer's disease.
Source: Sooy, et al., 2015. Endocrinology 156 (12) 4592-4603

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Clinical Development

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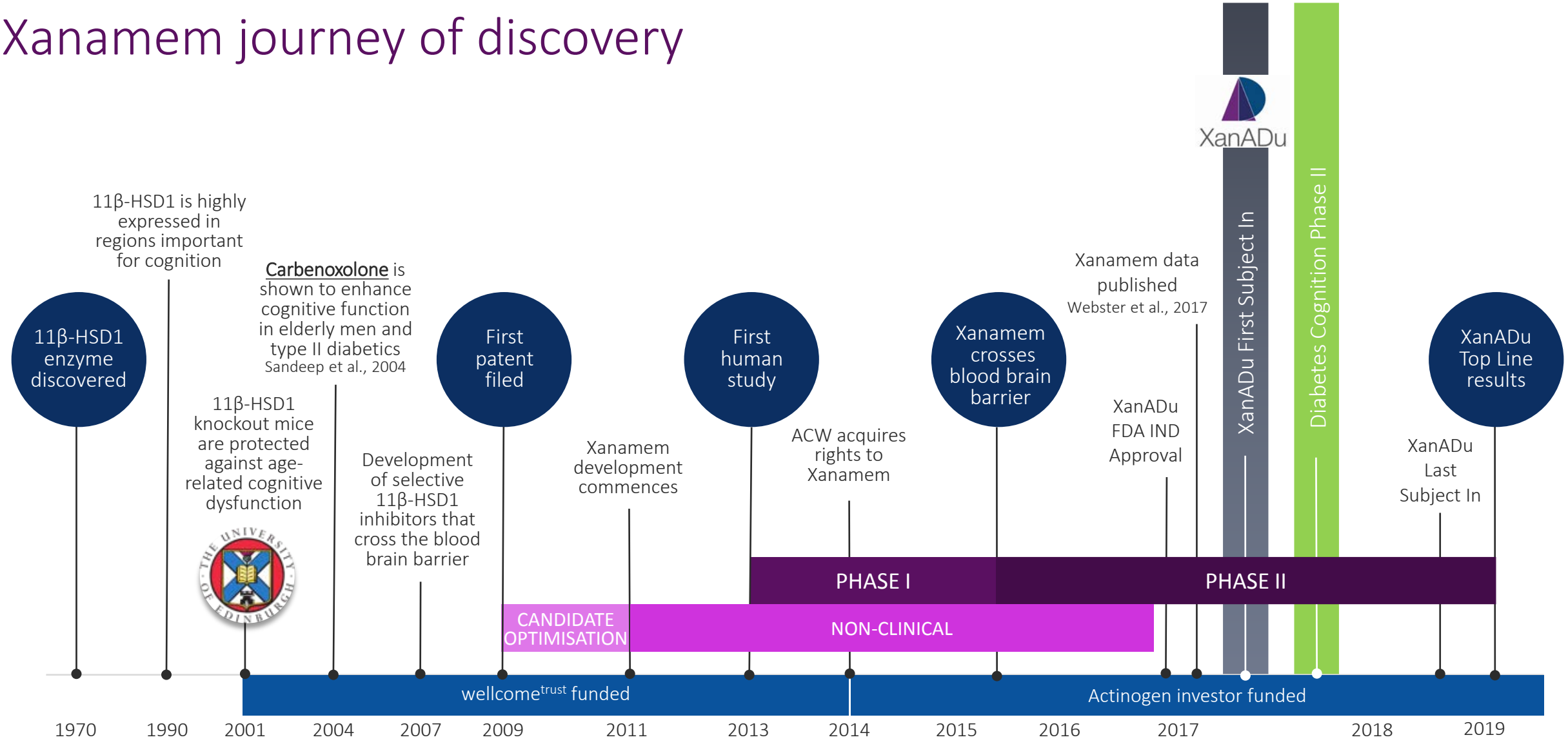
Xanamem journey of discovery



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Xanamem completed clinical studies

(Building on extensive historic 11βHSD1 class safety data from metabolic disease research)

A phase I **single ascending dose** (SAD) study[1]	A phase I **multiple ascending dose** (MAD) study[1]	A phase I **single-dose fed-fasted crossover** study	A phase I **CSF/ plasma pharmacokinetic** study[1]
• Surrogate peripheral pharmacodynamic markers support **potent target engagement** (48 healthy males and females) • Low number of clinically insignificant treatment-emergent adverse events (TEAEs)	• TEAEs mild to moderate in intensity (24 healthy males)	• TEAEs mild to moderate in intensity (12 healthy males)	• Xanamem **readily achieves CSF concentrations higher than its IC_{50}** (4 healthy males) • TEAEs mild to moderate in intensity

[1] Webster et al., 2017, British J Pharmacol 174:396-408;

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Xanadu Phase II trial

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

- 34 patients enrolled (end-Sept) and first patient has already completed study.
- All 20 study sites open and patients enrolled in USA, UK and Aus.

Xanamem treatment course
12 weeks

174
Mild Alzheimer's patients

Xanamem 10mg daily
for 12 weeks vs placebo

Trial conducted at 20 sites in
AUS, USA and UK

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

*Registered on Clinicaltrials.gov: NCT02727699

Xanamem secondary indication – DCI

Diabetes-related mild Cognitive Impairment

- Several potential secondary indications considered
- DCI selected due to a strategic mix of scientific, clinical, and commercial factors
  - Type 2 Diabetes Mellitus (T2DM) is a significant risk factor for cognitive impairment and dementia [1-4]
  - T2DM patients more likely to show abnormalities in hypothalamic-pituitary-adrenal (HPA) axis regulation [5]
  - Non-selective 11βHSD1 inhibitor carbenoxolone demonstrated cognitive improvements in cognitively normal patients with T2DM [6]
  - Large potential patient population, >15M diabetes patients with dementia
  - Expert clinical development partner (University of Edinburgh, UK)

[1] Saedi *et al.*, 2016, World J Diabetes 7(17):412-422; [2] Whitmer *et al.*, 2009, JAMA 301(15):1565-1572; [3] Saczynski *et al.*, 2008, Am J Epidemiology 168(10):1132–1139;
[4] Cukieman-Yaffe *et al.*, 2009, Diabetes Care 32(2):221-226; [5] Fienkohl *et al.*, 2015, Alzheimer's Research and Therapy 7:46; [6] Sandeep *et al.*, 2004, Proc Natl Acad Sci USA 101:6734–6739.

Commercial

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Value proposition

- Strong therapeutic rationale, differentiated mechanism of action
- Differentiated from, but complementary to anti-Aβ, anti-Tau and other AD therapeutic strategies
- Solid non-clinical and clinical data set
- First in class compound, designed for brain penetration
- 11βHSD1 class safety data
- Significant opportunities for additional clinical indications
- Composition of matter IP coverage ≥ 2031, patents granted in most major markets
- Deep commercial, scientific and clinical expertise
- Strong commercial and clinical interest

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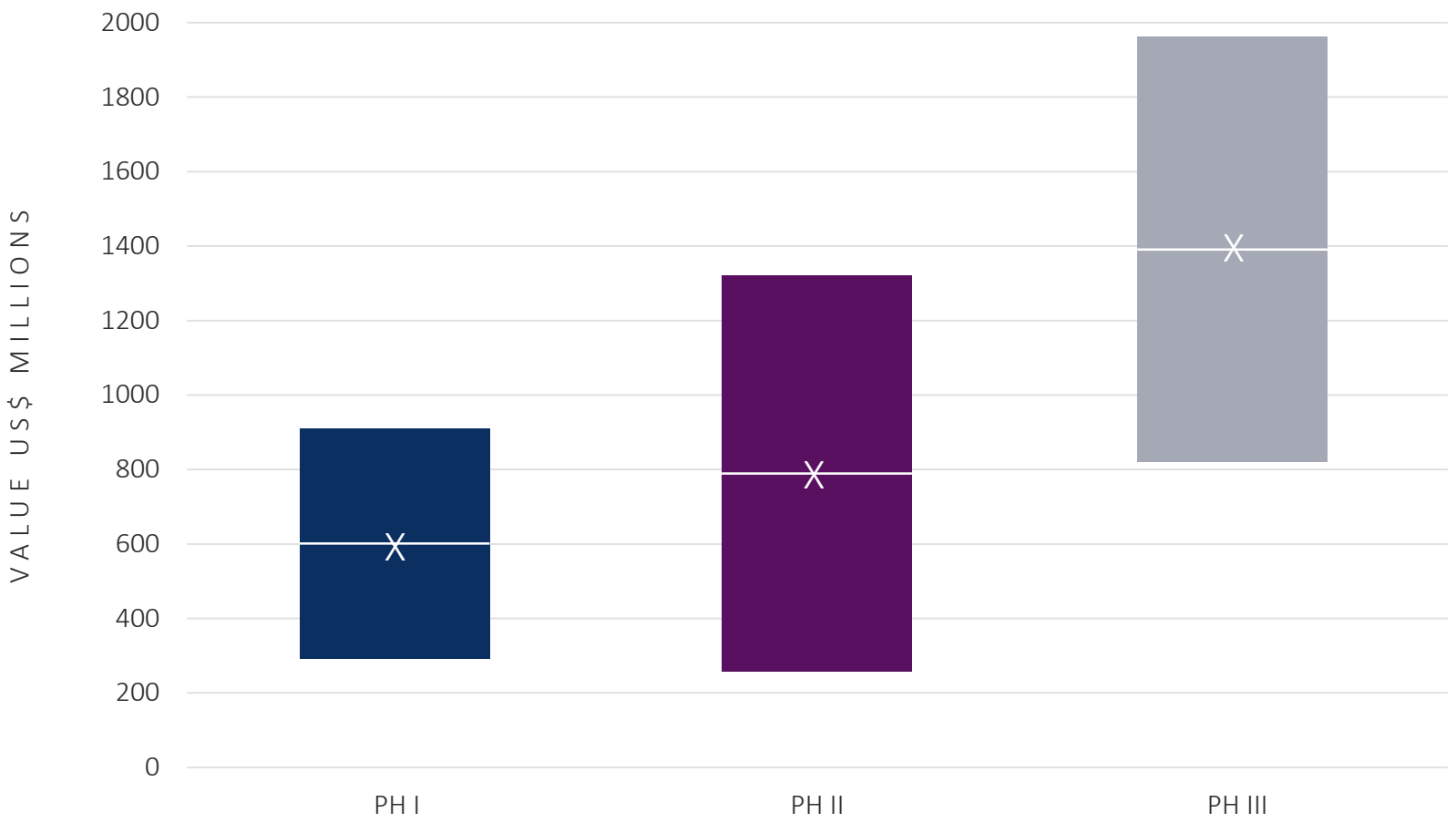
Peer comparison

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



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Summary

- A novel, first in class, potent, orally bioavailable, brain-penetrant, 11βHSD1 inhibitor
- Strong therapeutic rationale, differentiated mechanism of action: blocking cortisol production in the brain
- Symptomatic and disease modifying effects *in vivo*
- Well-tolerated: acceptable clinical safety, toxicity and PK/PD profile
- Efficacious human brain concentrations
- Compelling data package: clinical safety, in vitro and in vivo mechanistic and efficacy data
- XanADu – phase II clinical study underway, dosing subjects with mild AD dementia in USA, UK, AU
- Planning ongoing for additional clinical indications
- Differentiated from, but complementary to anti-Aβ, anti-Tau and other AD therapeutic strategies
- Significant investment upside potential on peer comparison
- Composition of matter IP coverage ≥ 2031, patents granted in most major markets
- Experienced board and management; expert scientific advisory board

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