Alzheimer Treatment Needs a New Approach – Xanamem™

May/June 2018

Actinogen Medical

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Actinogen Medical (ASX:ACW)

- Developing Xanamem for the treatment of Alzheimer's disease (AD) and cortisol associated cognitive impairment
- Xanamem, a novel differentiated mechanism of action: prevents the production of excess brain cortisol
- Persistently raised cortisol in the brain is associated with the development and progression of AD
- First-in-class, brain penetrant, orally active, inhibitor of 11βHSD1 enzyme, reducing conversion of cortisone to cortisol
- Experienced board and management; expert clinical and scientific advisory board

STOCK METRICS*

Pending completion of the Placement of 300,000,000 shares (Tranche 1 and 2) and the Share Purchase Plan (SPP)

LARGEST HOLDERS

Pending completion of the Placement of 300,000,000 shares (Tranche 1 and 2) and the Share Purchase Plan (SPP)

- **Biotechnology Value Fund, L.P.**
- **Platinum Investment Management Limited**
- **Edinburgh Technology Fund Limited**
- **Australian Ethical Investment**
- JK Nominees
- Sunset Capital Management
- Warambi Sarl
- BNP Paribas Nominees

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Interim Analysis – recommendation to continue trial without modification*

- Interim Analysis undertaken by independent Data Safety Monitoring Board (DSMB)
- Safety and efficacy data reviewed
- Conducted on data from first 50 evaluable XanADu trial patients. Additional 37 patients' safety data also included in the analysis
- No treatment related serious adverse events
- Recommendation affirms the positive benefit-risk safety profile of Xanamem 10mg daily
- Supports progression of study as planned
- Underpins further development in other indications

*Announced 23 May 2018

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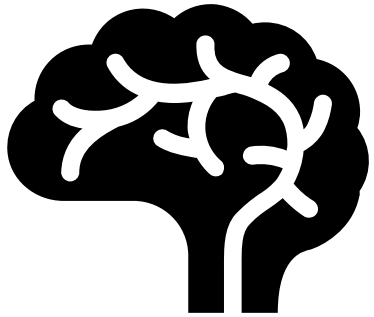
Substantial Institutional investment in Actinogen* Recognises potential and endorses strategy

- Positive interim analysis catalyses significant $15M investment through Placement
- Leading investors enter register:
  - USA specialist biotech investor **Biotechnology Value Fund L.P.**
  - Australian institutions **Platinum Investments Management** and **Australian Ethical Investments**
- Strong endorsement - Placement price represents an 13.4% premium to the 5-day VWAP
- BVF cornerstones Placement to become the largest shareholder with a 19.9% holding
- Funding to advance Company's development plan through additional Xanamem studies. Focus on enhancing the data-set for Xanamem, adding substantial value to ongoing partnering discussions

*Announced 23 May 2018

New Xanamem studies – funded through May ‘18 capital raising: Enhancing value, broadening scope, enhancing data-set

- New funding to advance Company's development plan
- Focus on enhancing the data-set for Xanamem, broadening scope of use and adding substantial value to asset
  - Target engagement study – will help define optimum dose
  - Safety studies with higher doses
  - Additional standard toxicology studies required by regulators (in all drug development)
  - New indications



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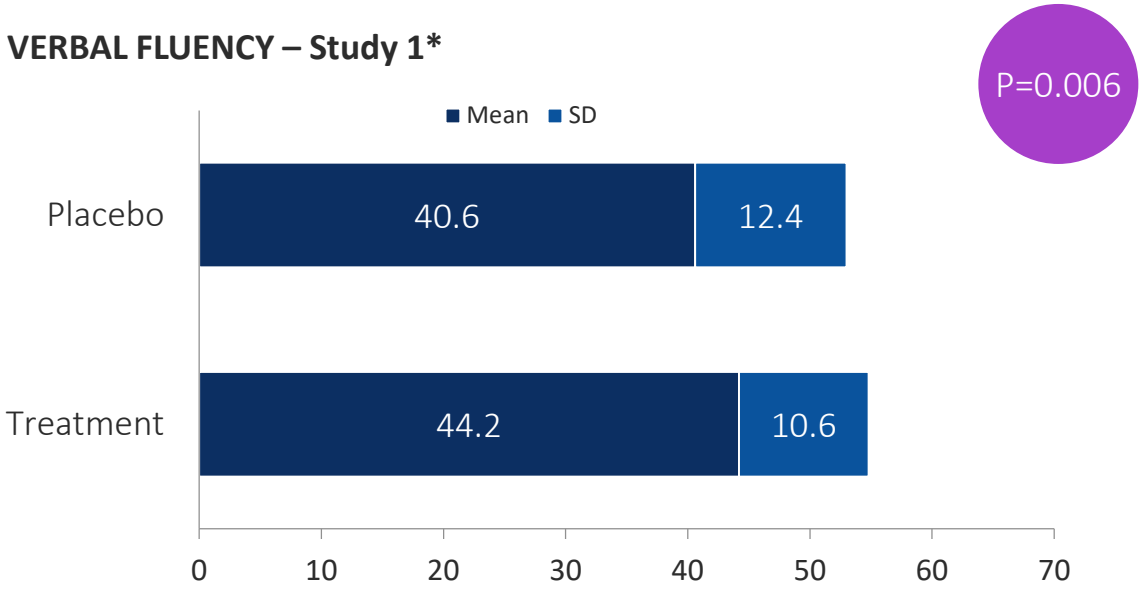
Cortisol inhibition improves cognition – Key Factor in 2014 Acquisition

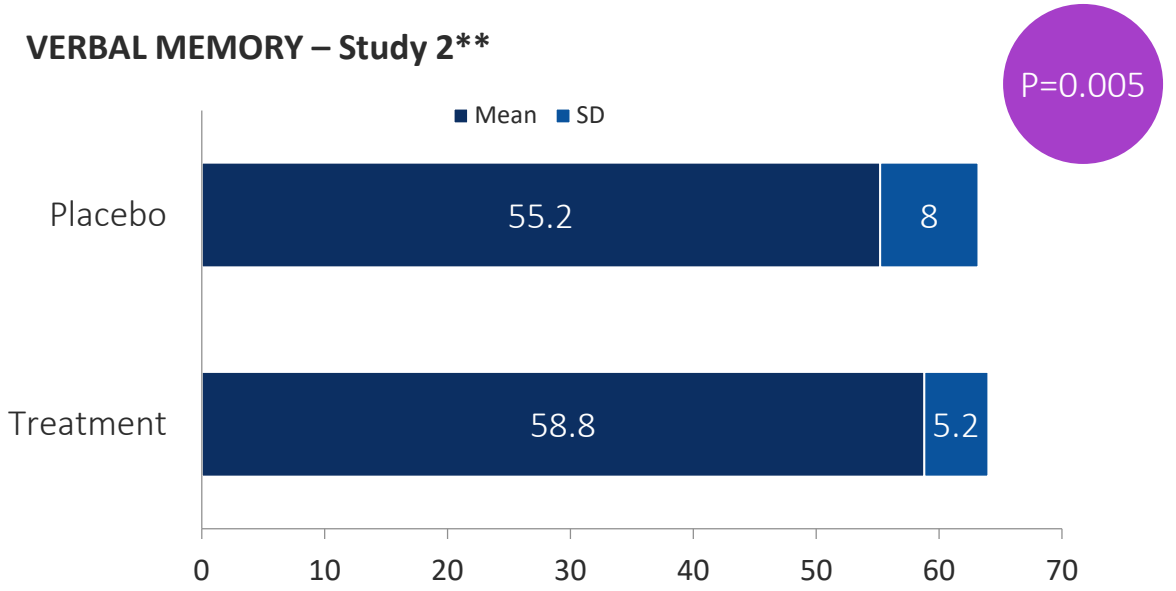
Two 2004 pilot studies concluded that inhibiting cortisol production in the brain with carbenoxolone improves cognitive function in healthy elderly men & type 2 diabetics – this established Edinburgh Uni hypothesis

VERBAL FLUENCY – Study 1*



* Study 1 = 10 healthy subjects Age 55-75 (Mean Age = 65.5 ± 5.5) receiving 100mg carbenoxolone 3 times daily compared to placebo for 4 weeks, in a double-blind randomised crossover study.

VERBAL MEMORY – Study 2**



**Study 2 = 12 type 2 diabetics (m=9; f=3) Age 52-70 (Mean Age = 60 ± 4.9) receiving 100mg carbenoxolone 3 times daily compared to placebo for 6 weeks, in a double-blind randomised crossover study.

Significant improvement in verbal fluency and verbal memory after only 4 and 6 weeks treatment

11β-Hydroxysteroid dehydrogenase inhibition improves cognition function in healthy elderly men and type 2 diabetics
Source: Sandeep et al., 2004 PNAS (vol. 101, no. 17) 6734-6739

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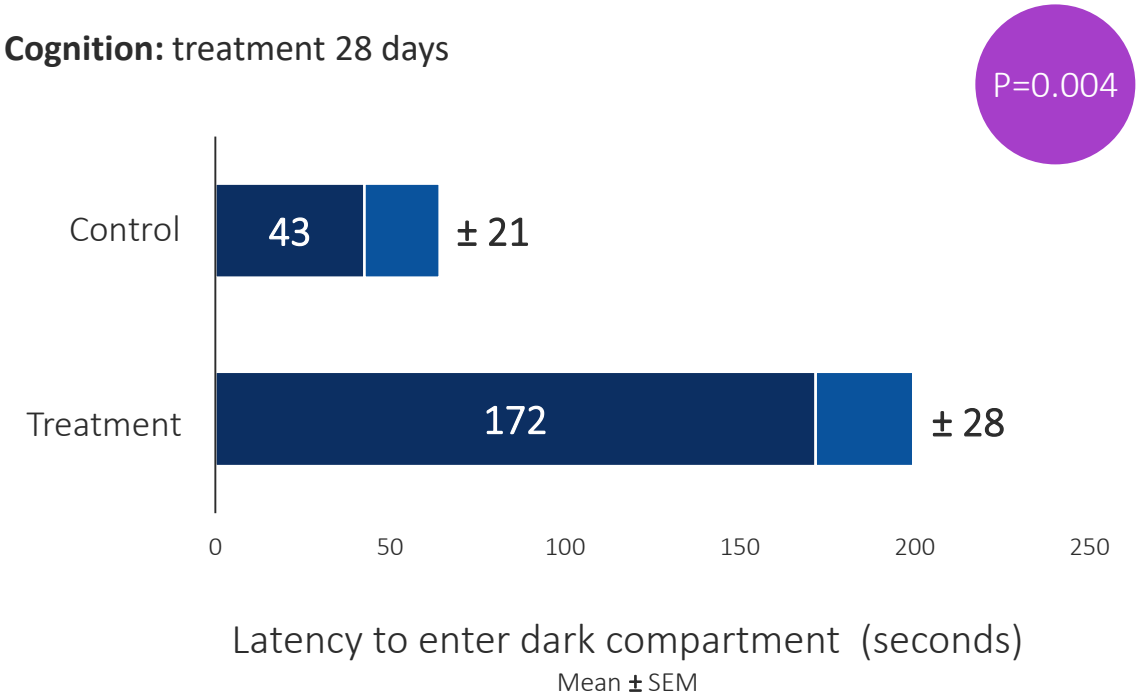
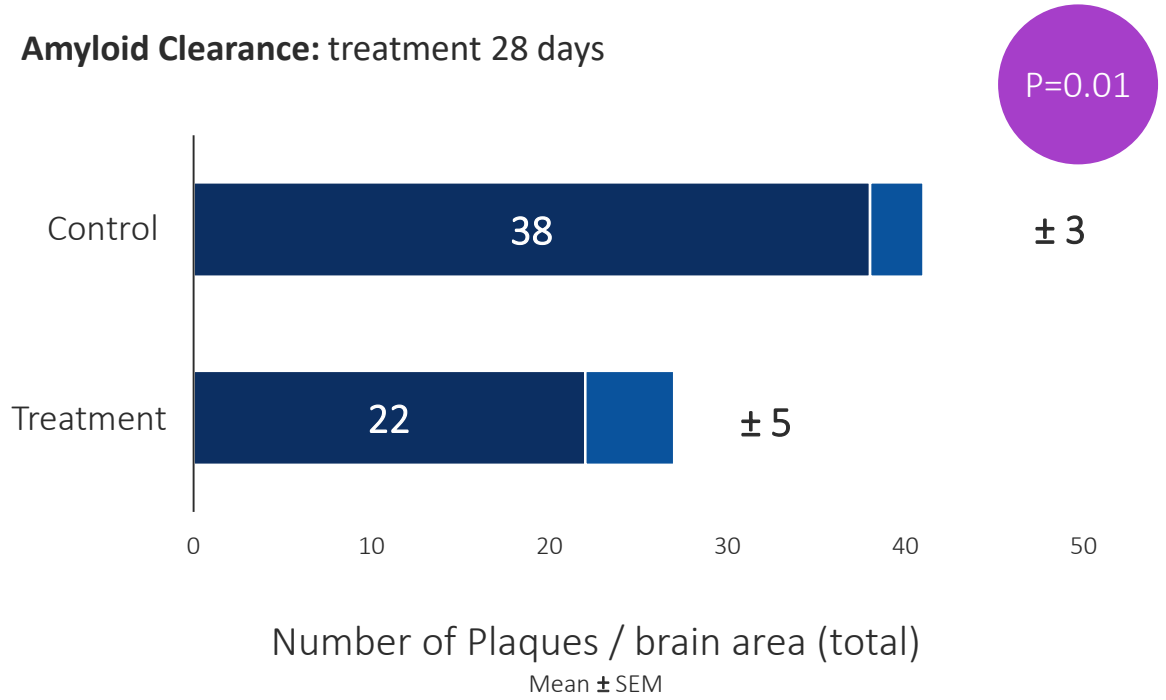
Robust Animal Data with new candidate - Key Factor in 2014 Acquisition

Symptomatic **and** disease modifying effects in mouse models – AUD $25 million invested pre acquisition

Cognition: treatment 28 days



Amyloid Clearance: treatment 28 days



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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Xanamem

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Xanamem

- A novel, first in class, potent, orally bioavailable, brain-penetrant, 11βHSD1 inhibitor[1]
- Differentiated mechanism of action: blocking cortisol production in the brain
- Symptomatic and disease modifying effects *in vivo*[1]
- Well-tolerated – dosed >100 patients/subjects: acceptable clinical safety, toxicity and PK/PD profile[1]
- Effective human brain concentrations demonstrated[1]
- 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 all major markets
- XanADu Alzheimer's trial fully funded following completion of ~A$5.3 million capital raise in November 2017
- A range of additional studies adequately funded following completion of ~$17 million capital raising in May 2018

1. Webster *et al.*, 2017, British J Pharmacol 174:396-408

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Cortisol: a validated biomarker and target for AD

Cortisol and Alzheimer's

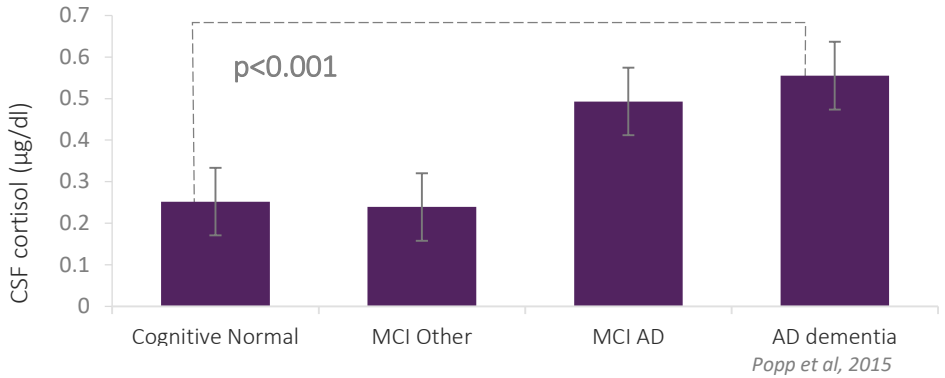
- Recent independent studies support the association between cortisol and AD development and progression[1-5]
- Cognitive impairment in patients with neuroendocrine dysfunction[6-9]
- Compelling evidence provided by the Australian Imaging, Biomarker & Lifestyle Study of Ageing (AIBL) study (2017)[5]
  - 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

MEAN CSF CORTISOL LEVELS



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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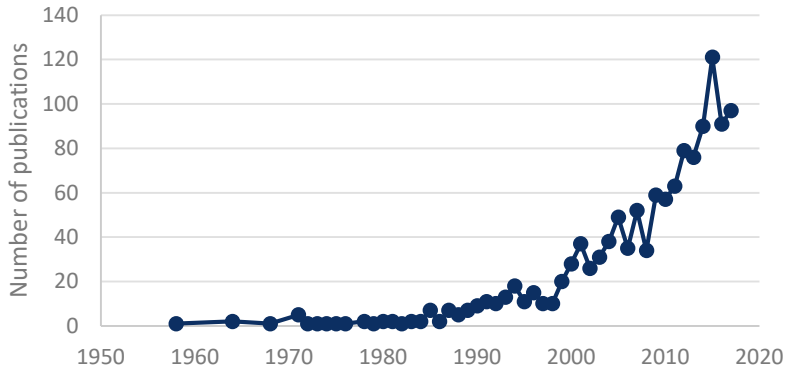
Cortisol, cognitive decline and AD: a growing body of literature

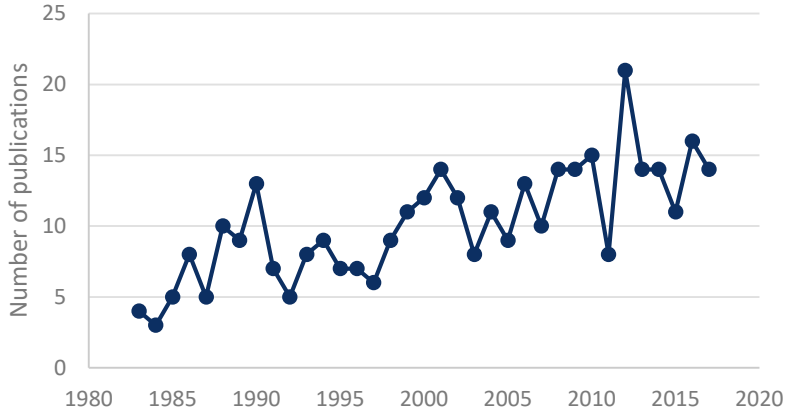
Recent relevant reviews:

- Cortisol: Mediator of association between Alzheimer's disease and diabetes mellitus? (Notarianni, 2017*, Psychoneuroendocrinology*)
- Unified theory of Alzheimer's disease (UTAD): implications for prevention and curative therapy. (Nehls 2016*, J Mol Psychiatry*)
- Is Dysregulation of the HPA-Axis a Core Pathophysiology Mediating Co-Morbid Depression in Neurodegenerative Diseases? (Du and Pang, 2015*; Front Psychiatry*)
- The impact of stress and glucocorticoids on memory. (Tatomir et al. 2014*; Clujul Med.*)
- Contribution of glucocorticoids and glucocorticoid receptors to the regulation of neurodegenerative processes. (Vyas and Maatouk, 2013*; CNS Neurol Disord Drug Targets*)
- Stress-induced cytokines and neuronal dysfunction in Alzheimer's disease. (Ricci et al., 2012; *J. Alzheimer's Dis.*)
- Local amplification of glucocorticoids in the aging brain and impaired spatial memory (Yau and Seckl, 2012; *Front. Aging Neuroscience*)

PUBMED:"CORTISOL AND COGNITION"



PUBMED: "CORTISOL AND ALZHEIMER'S"



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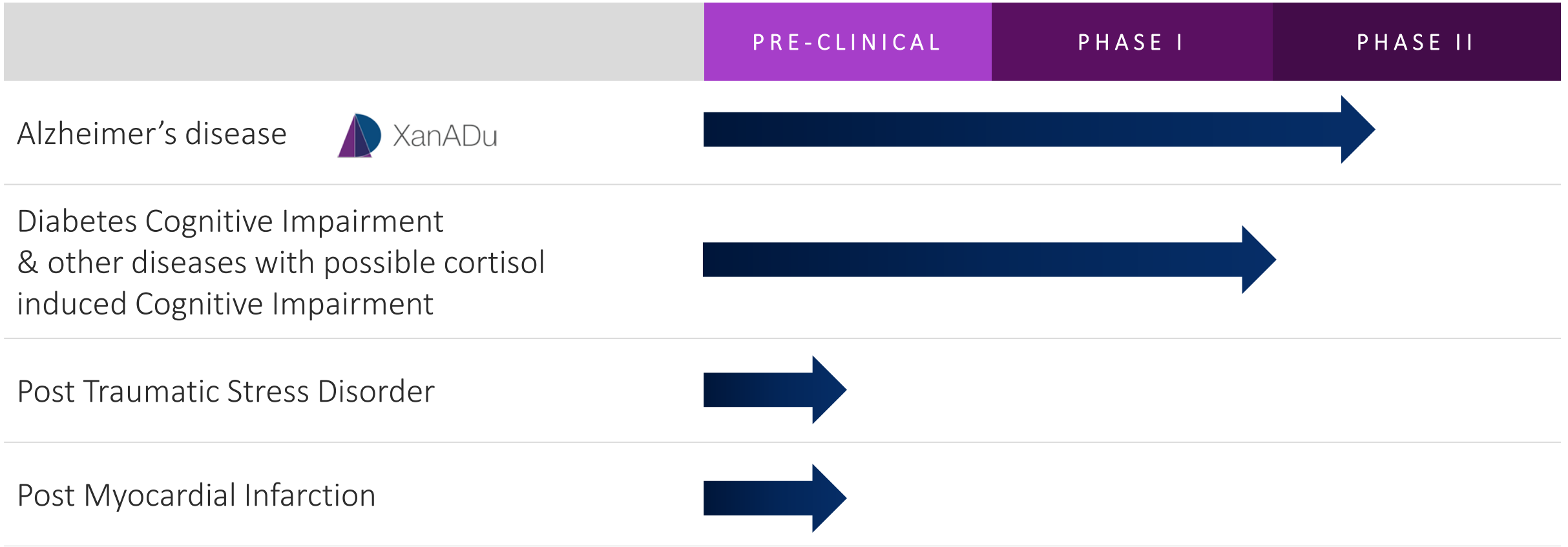
Xanamem pipeline of indications, back-up compounds*



* Back-up compounds to Xanamem, licenced from Edinburgh University

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XanADu – Phase II Trial

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XanADu – Xanamem in Alzheimer's disease

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

- 101 patients enrolled (58% of total study cohort) and more than 68 patients already completed study**
- On track for last patient enrolled in Q4 2018 and top line results in Q2 2019
- Interim Analysis on first 50 evaluable patients - DSMB recommends continuing XanADu without modification

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
**As at 25 May 2018

Investment potential

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Commercially experienced, globally recognised

Board of Directors

Dr. Geoff Brooke
Chairman

Dr. Bill Ketelbey
CEO & MD

Dr. Jason Loveridge
Non-Executive Director

Dr. George Morstyn
Non-Executive Director

GBS VENTURE PARTNERS

Pfizer

JAFCO

AMGEN

The Westmead Institute FOR MEDICAL RESEARCH

GENABLE

SymBio
SymBio Pharmaceuticals Limited

morphosys

Cancer Therapeutics CRC

Xanamem Clinical Advisory Board

Prof. Craig Ritchie
Chair

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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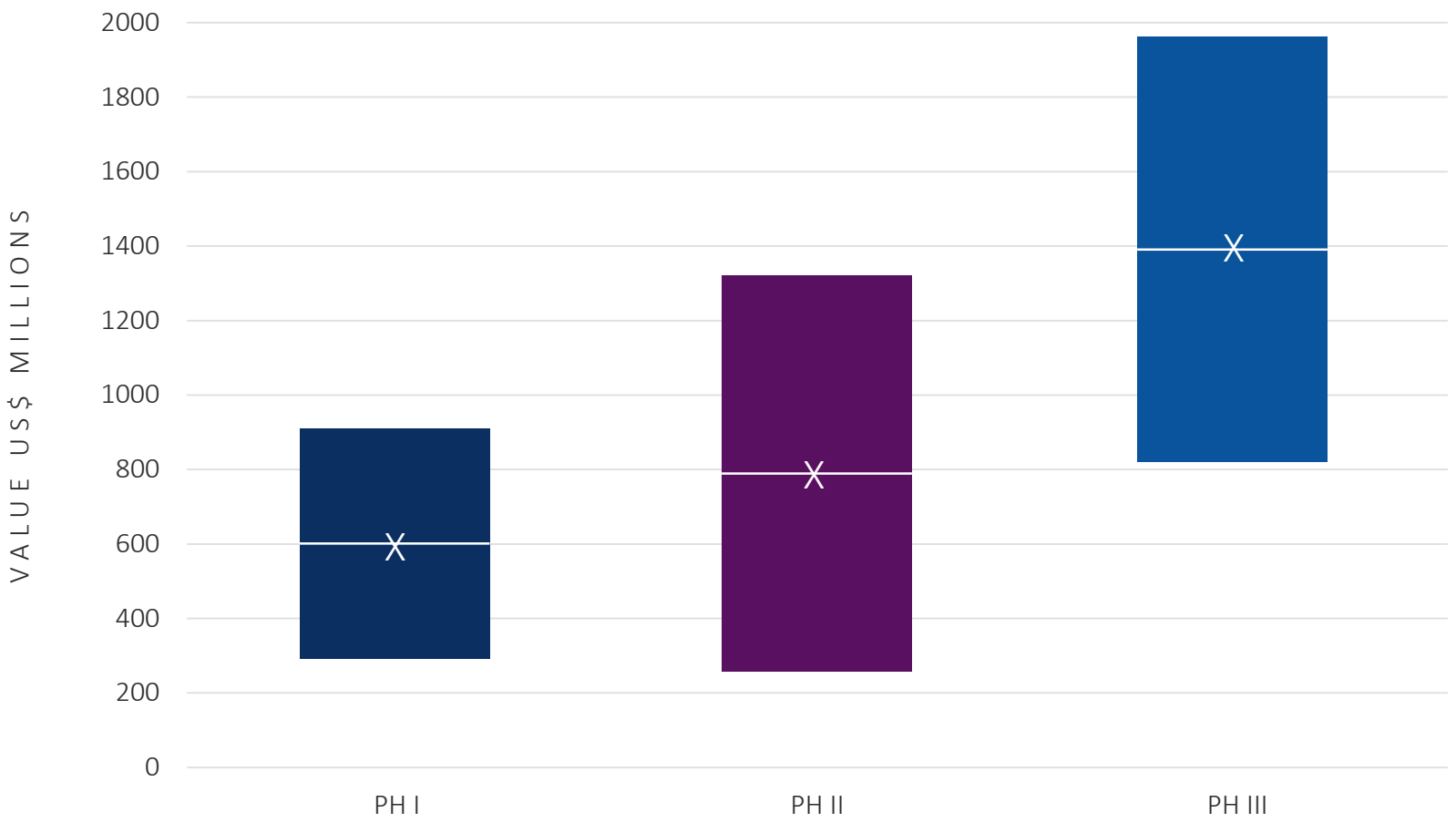
Peer comparison

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



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Xanamem™ in closing ……

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Summary

A huge market with a significant unmet medical need

Xanamem

- Differentiated, with a novel mechanism of action
- Small molecule - oral
- High quality development plan and regulatory review
- Solid IP out to at least 2031
- Potential utility in other neurological indications

XanADu

- Fully funded to completion of XanADu
- Additional studies funded with May 2018 capital raise
- Interim Analysis – continue study without modification
- On track for last patient enrolled before end 2018
- 101 patients enrolled (58% of total); 68 already completed

Substantial independent support for cortisol/Alzheimer's hypothesis

Highly experienced Board

Growing interest in Xanamem from pharma partners

A compelling investment opportunity

Actinogen Medical

Dr. Bill Ketelbey

CEO & Managing Director

☎ Main: +61 2 8964 7401

✉ Email: bill.ketelbey@actinogen.com.au

www.actinogen.com.au

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Appendix

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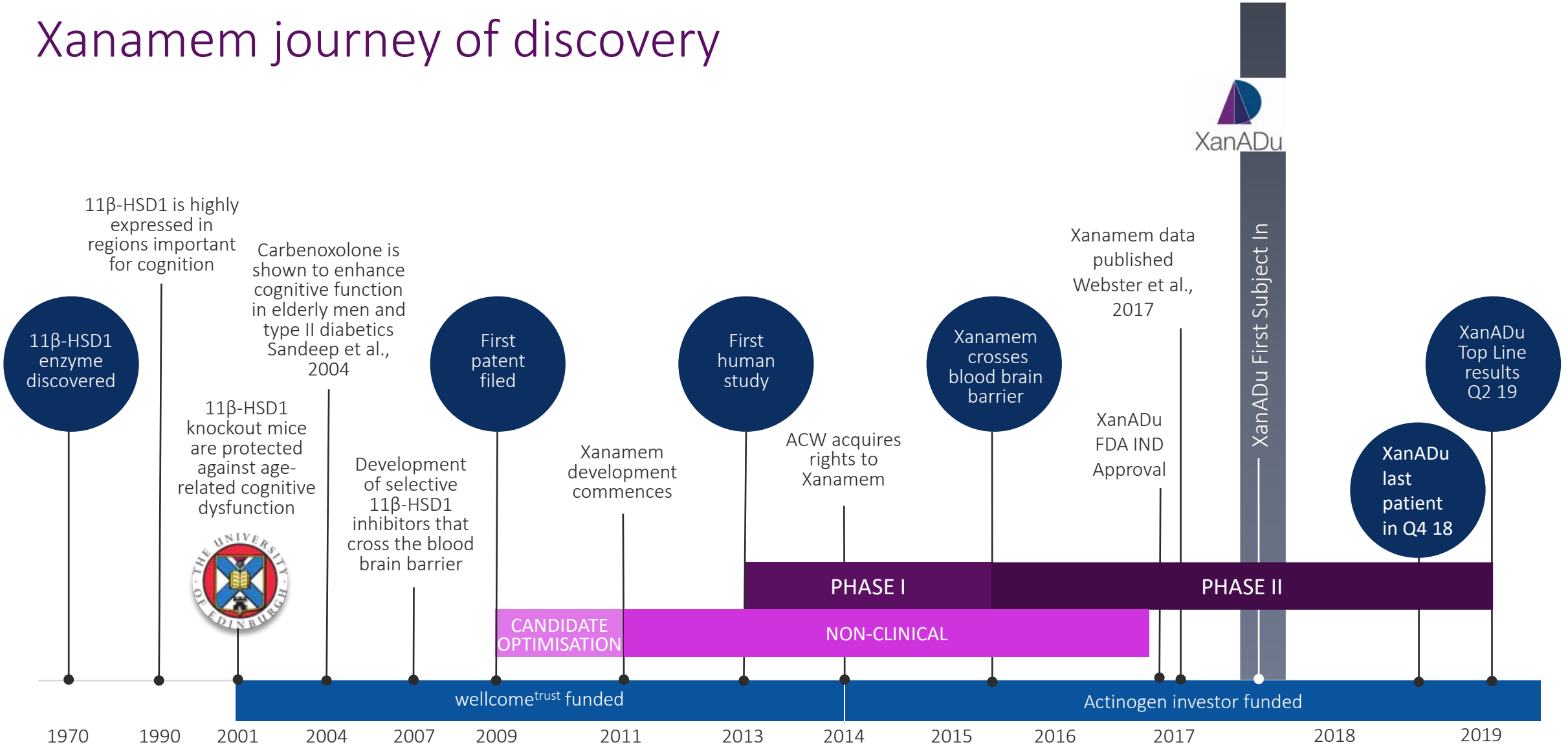
Xanamem journey of discovery



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Recent comparable deals

Assets with Alzheimer's disease as the lead indication or key indication

Licensee/acquirer	Licensor/acquired	Year	Candidate(s)	Phase	Deal Value (US$M)	Upfront (US$M)
Takeda	Denali	2018	ATV platform, three programs	Pre-clinical	~$1,000	$150
AbbVie	Voyager	2017	AAV anti-tau antibodies	Pre-clinical	$1,109	$69
Biogen	BMS	2017	BMS-986168	Ph 1	$710	$300
Allergan	Heptares	2016	Three M1/M4 agonists	Ph I	$3,340	$125
Janssen	AC immune	2015	ACI-35	Ph Ib	$509	Undisclosed
Merck	Bionomics	2014	BNC-375	pre-clinical	$526	$20
Eli Lilly	AstraZeneca	2014	AZD3293	Ph I	$500	$50
Iperian	BMS	2014	IPN007	pre-clinical	$725	$175
Otsuka	Lundbeck	2013	Idalopirdine	Ph II	$825	$150
Janssen	Orion	2013	ORM-12741	Ph IIa	Undisclosed	$31