

# Australian Microcap Investment Conference

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

Dr. Bill Ketelbey: CEO & Managing Director

October 2018



**Actinogen**  
Medical

# Key investment highlights

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



## Novel compound

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



## Targeted strategic market focus

Initially focused on developing a treatment for Alzheimer's disease  
Addressable market of >US\$5bn with unmet needs and potential upside  
Target indication underpinned by efficacy results from animal model studies



## Clinical stage asset

Fully funded advanced clinical stage program  
Reported positive interim analysis  
Enrolment >95% complete and top line results available by mid CY2019



## Potential value upside

Well positioned to unlock further value  
Significant big pharma interest



## De-risked opportunity

Additional Xanamem studies initiated  
Pipeline development opportunities under evaluation



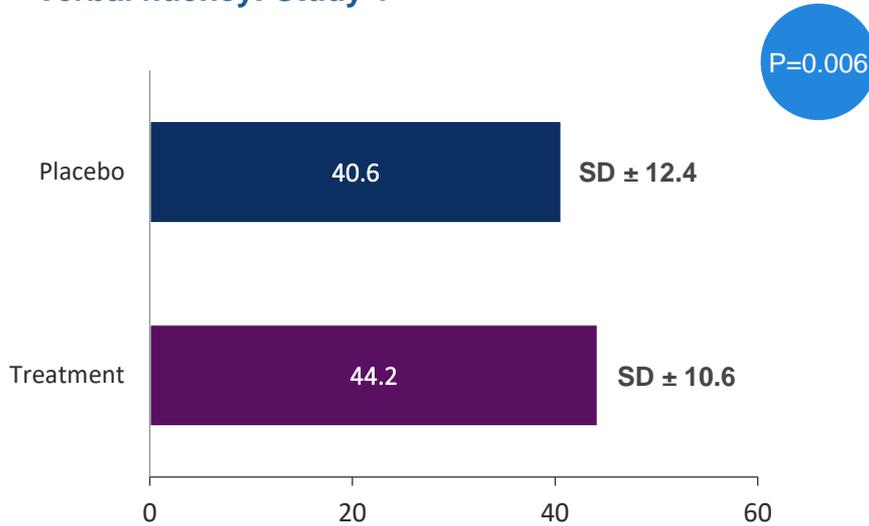
## Experienced leadership/advisors

Significant drug development and investment experience  
Leading AD clinicians and Xanamem discovery team

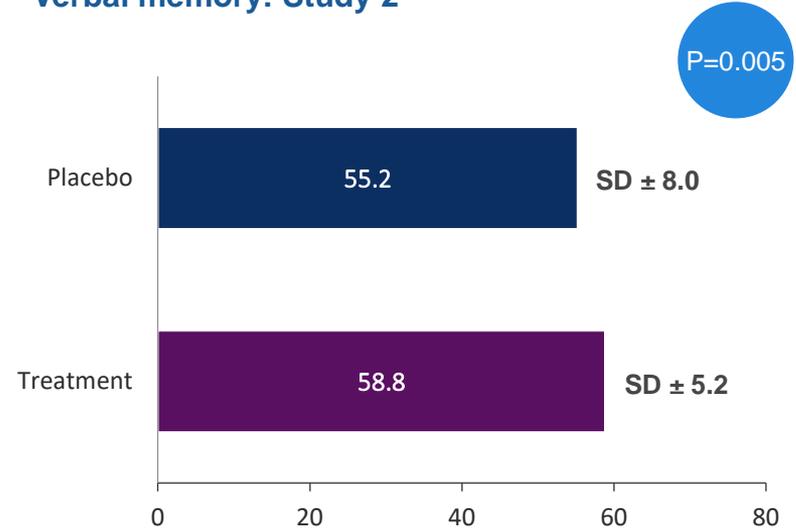
# Human pilot studies validate the cortisol hypothesis

Two completed pilot studies that indicated inhibiting cortisol production in the brain improves cognitive function in healthy elderly men and subjects with Type 2 diabetes

## Verbal fluency: Study 1<sup>1</sup>



## Verbal memory: Study 2<sup>2</sup>



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

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

1. Study 1: 10 healthy subjects Age 55-75 (Mean Age = 65.5  $\pm$  5.5) receiving 100mg carbenoxolone 3 times daily compared to placebo for 4 weeks, in a double-blind randomised crossover study
2. Study 2: 12 type 2 diabetics (m=9; f=3) Age 52-70 (Mean Age = 60  $\pm$  4.9) receiving 100mg carbenoxolone 3 times daily compared to placebo for 6 weeks, in a double-blind randomised crossover study.

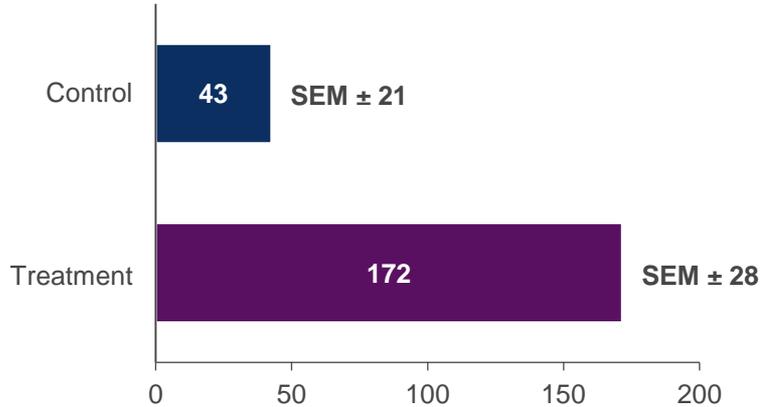
# Efficacy underpinned by animal model

Significant and rapid symptomatic and disease modifying effects demonstrated with significant improvement in cognition within one month, continuing out to 41 weeks

## Cognition: 28 days treatment

Latency to enter dark compartment (seconds)

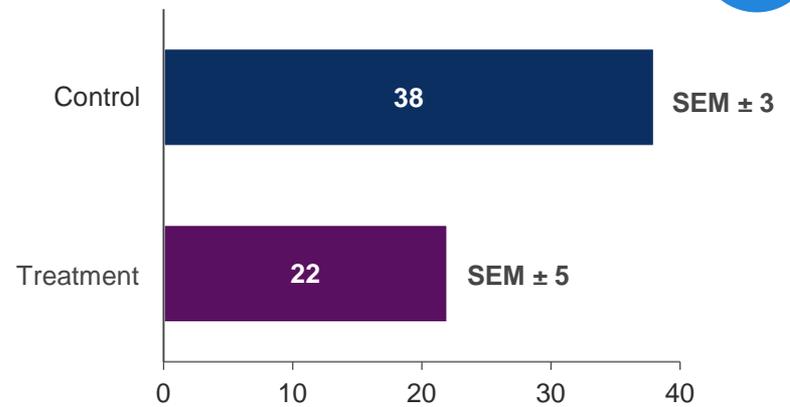
P=0.004



## Amyloid clearance: 28 days treatment

Number of Plaques / brain area (total)

P=0.01



**Results from the animal model study underpins the significant promise of the XanADu study**

# What is Xanamem

Actinogen's lead compound, Xanamem, is a novel drug designed to inhibit the production of cortisol in the brain, with the potential to treat cognitive impairment and Alzheimer's disease



## Well researched

Over 15 years of R&D completed, with A\$40m invested to date



## Well tolerated

Dosed >150 patients with acceptable clinical safety, toxicity and PK / PD<sup>1</sup> profile



## Differentiated mechanism of action

Highly selective inhibitor of the 11 $\beta$ HSD1 enzyme in the brain preventing excess cortisol production



## Validated

Symptomatic and disease modifying effects (in vivo) and effective demonstration of cortisol hypothesis (in humans)



## Well protected

Composition of matter IP coverage  $\geq$  2031, patents granted in all major markets



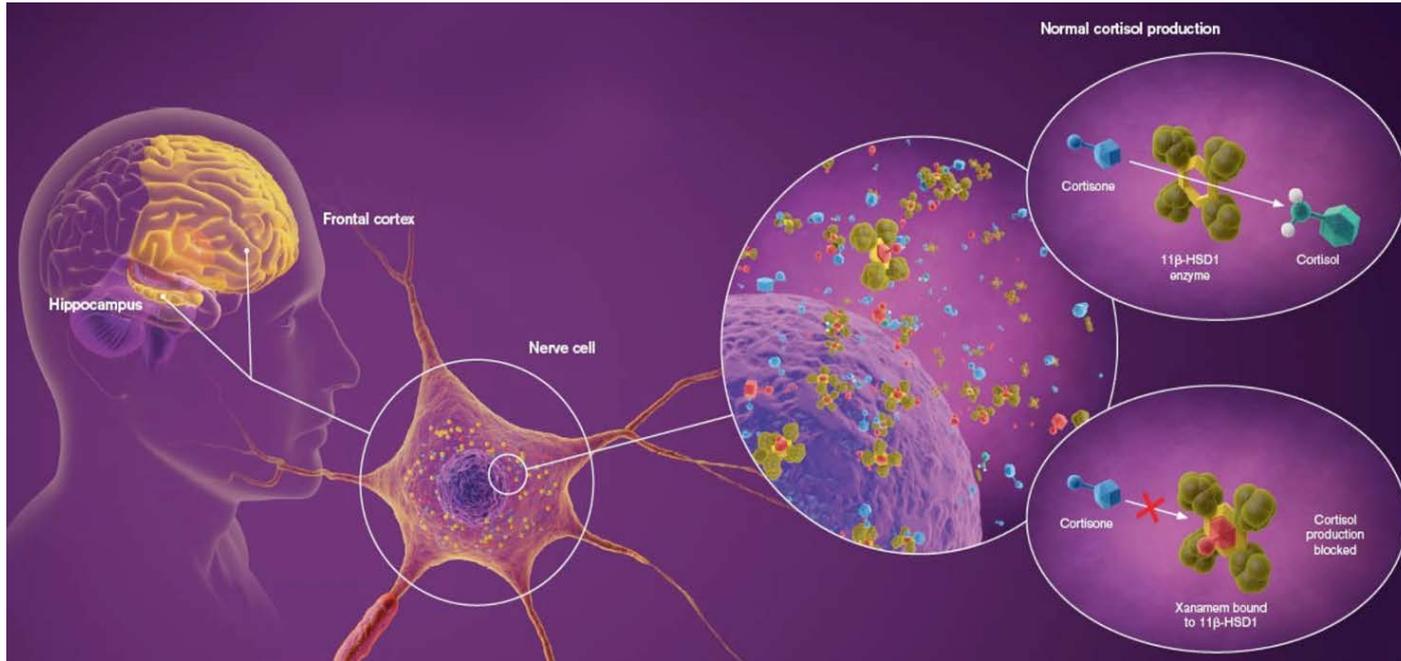
**Xanamem is a novel, first-in-class, potent, orally bioavailable and brain-penetrant 11 $\beta$ -HSD1 inhibitor**

1. PK / PD: pharmacokinetic / pharmacodynamic

# Mechanism of action

Xanamem inhibits the activity of the 11 $\beta$ -HSD1 enzyme, reducing the production of cortisol in the brain

## Overview



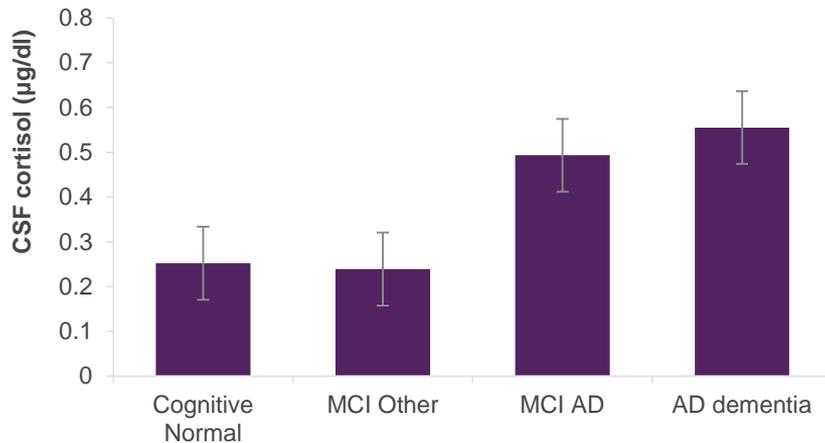
**Xanamem is targeting diseases with possible cortisol induced cognitive impairment**

- **Alzheimer's disease (key focus)**
- Diabetes
- Depression
- Parkinson's disease
- Schizophrenia
- and more....

# Initial 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<sup>1</sup>



## Supported by growing body of medical literature



Many studies support the association between **cortisol and Alzheimer's disease development and progression**<sup>2</sup>

A recent AIBL<sup>3</sup> study provided compelling evidence that elderly subjects with **higher plasma cortisol levels are at much greater risk of developing Alzheimer's disease**

This study<sup>3</sup> 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. AIBL (Australian Imaging, Biomarker & Lifestyle Study of Ageing) study published in 2017

# 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<sup>1</sup>



Xanamem treatment course  
**12 weeks**



**174** patients with mild Alzheimer's disease (**166 enrolled; >111 completed**)<sup>2</sup>



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



Trial conducted at 25 sites in  
**AUS, USA and UK**

**Fully funded study on track to complete enrolment in 4Q CY2018 with top line results in 2Q CY2019**

1. Study registered on Clinicaltrials.gov: NCT02727699  
2. As at 17<sup>th</sup> October 2018

# Interim analysis

Positive recommendations from the DSMB<sup>1</sup> reflect confidence in the safety of the drug and the design of the XanADu study. Supports the broader development of Xanamem



## First DSMB review (23 May 2018)

- Evaluation of 50 patients' safety and efficacy data reviewed by an independent DSMB<sup>2</sup>
- **Recommendation by DSMB to continue XanADu without modification**

## Second DSMB review (22 August 2018)

- Evaluation of 125 patients' safety data
- **Reaffirmed continuation of XanADu without modification**

## Third DSMB review

- Expected to be completed before the end of CY2018

 XanADu

**Positive DSMB recommendations underpin the XanADu study and further development of Xanamem in other indications**

1. DSMB: Data Safety Monitoring Board

2. Evaluable patients to have completed the study – note: an additional 37 patients' safety data was also included in the analysis (data was from patients still ongoing in the study)

# Additional Xanamem studies

Actinogen is focused on completing key additional studies to enhance the Xanamem data set



## Target occupancy study

Aims to accurately demonstrate the effect different doses of Xanamem has on the 11 $\beta$ -HSD1 enzyme in the human brain

Currently underway with **results expected in 2Q CY2019**



## Higher dose safety study

To expand the safety data-set for Xanamem and allow for higher doses of the drug to be used (including in non-Alzheimer's applications)

Study is expected to **initiate in 4Q CY2018**



## Further safety / toxicology studies

To allow for longer treatment periods, as normally required by global regulatory authorities in the development of any drug

Studies are expected to **initiate in 4Q CY2018**

**Actinogen is fully funded to complete these key Xanamem studies**

# Other potential indications

Secondary focus is on developing the use of Xanamem in other indications to optimise shareholder value

## Overview



Multiple potential target indications beyond Alzheimer's represent significant market expansion opportunities



Growing literature on cortisol-induced cognitive impairment associated with many conditions



Actinogen intends to follow a rapid development pathway to identify suitable target indications



Development program leverages existing data from earlier clinical programs

## Possible target indications

Diabetes

Depression

Parkinson's disease

Schizophrenia

Post-traumatic stress disorder

And more..

**Preliminary assessment currently underway to identify high priority indications for development**

# Market dynamics of Alzheimer's disease

Presents a compelling commercial opportunity for Actinogen to target initially

## Substantial target market with significant upside<sup>1</sup>

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\$5bn**

Target annual peak sales<sup>2</sup>

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 and JP 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), ROW: 50% of US price

## 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

# Big Pharma interest

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



# Board of Directors

Commercially experienced and globally recognised leadership team with decades of experience in drug development and biotech investment



**Dr. Geoff  
Brooke**  
*Chairman*

- **30+ years experience** in the healthcare investment industry
- Founder and MD of Medvest Inc and GBS Venture Partners
- MBBS (University of Melbourne); MBA (IMEDE, Switzerland)



**Dr. Bill  
Ketelbey**  
*CEO & MD*

- **30+ years experience** in the healthcare, biotech and pharmaceutical industries
- Formerly senior international roles at Pfizer; Director at the Westmead Institute of Medical Research
- MBBCH (University of the Witwatersrand); FFPM; MBA (Macquarie); GAICD



**Dr. Jason  
Loveridge**  
*Non-executive  
director*

- **20+ years experience** in biomedical technology industry
- Venture investor with JAFCO Nomura; Non-Executive Director of Resonance Health (ASX: RHT); CEO of 4SC AG
- B.Sc (UNSW), PhD (University of Adelaide) FRSM



**Dr. George  
Morstyn**  
*Non-executive  
director*

- **25+ years experience** in biotechnology investment
- Board member of Cancer Therapeutics, Symbio and Biomedvic; Former Senior VP and SMO at Amgen
- MBBS (Monash University); PhD (Walter and Eliza Hall Institute); FRACP; MAICD



# Advisory Boards

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

## Xanamem™ Clinical Advisory Board

*Positions Xanamem at the forefront of Alzheimer's drug development*



**Prof. Craig Ritchie**  
*Chair*



THE UNIVERSITY  
of EDINBURGH



**Prof. Colin Masters**  
*AO*



THE  
**FLOREY**  
INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH



**Prof. Jeffrey Cummings**



**Prof. Jonathan Seckl**



THE UNIVERSITY  
of EDINBURGH



**Prof. Brian Walker**



**Newcastle**  
University



**Prof. Scott Webster**



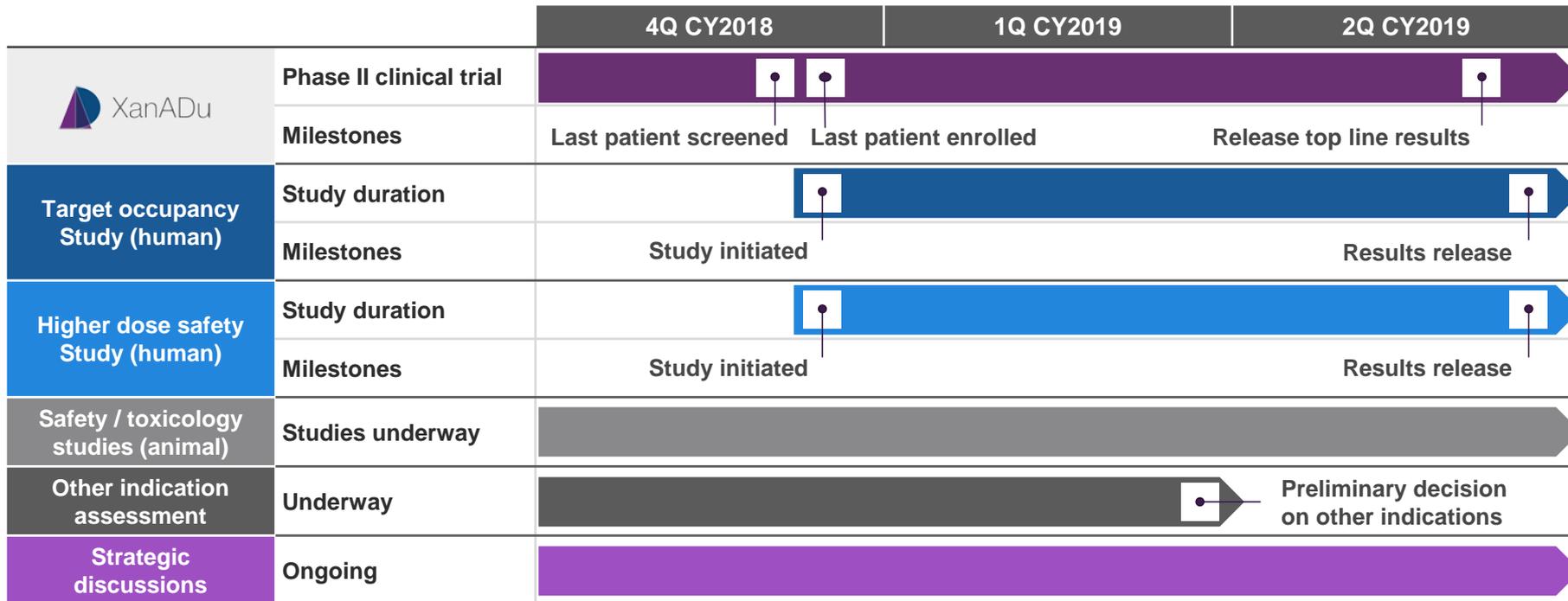
THE UNIVERSITY  
of EDINBURGH

## Scientific Advisory Board

*Combining deep understanding of cortisol, 11 $\beta$ -HSD1 and drug discovery*

# Upcoming catalysts

Significant upcoming milestones across 2018/19



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Leading AD clinicians and Xanamem discovery team

Dr. Bill Ketelbey: CEO & Managing Director

P: +61 2 8694 7401

E: [bill.ketelbey@actinogen.com.au](mailto:bill.ketelbey@actinogen.com.au)



**Actinogen**  
Medical

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