



## ASX ANNOUNCEMENT

### Actinogen Clinical Trials Science Forum presentation slides

**Sydney, 3 August 2022. Actinogen Medical ASX: ACW (“ACW” or “the Company”)** is pleased to release the presentation slides for this morning’s Clinical Trials Science Forum commencing at **11am AEST**.

**Event registration:** [https://us02web.zoom.us/webinar/register/WN\\_s0Qtndf3Tq-POeTdl1Xvnw](https://us02web.zoom.us/webinar/register/WN_s0Qtndf3Tq-POeTdl1Xvnw)

***Following the Science*** is fundamental to all Actinogen’s activities and the key theme of the presentation. Today’s webcast has been designed for a broad audience, including those from non-technical backgrounds, and will explore in more depth the science behind Xanamem® and ACW’s clinical trial program including:

- Xanamem’s pharmacology
- Measuring Xanamem’s effects on cognition and depression with suitable, sensitive endpoints
- Designing, conducting and analysing optimized clinical trials.

It will also summarize the clinical data gathered so far on more than 300 healthy volunteers and patients treated and outline in more detail the designs for the upcoming Phase 2 trials in patients with Alzheimer’s Disease and Major Depressive Disorder.

Presenters will include world-leading authorities on cognition trials and key senior members of the Actinogen management team.

A copy of the full presentation is attached. As soon as practicable after the conclusion of the webcast a full recording will be made available on the company’s website: [www.actinogen.com.au](http://www.actinogen.com.au).

**ENDS**

#### Investors

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® Xanamem is a registered trademark of Actinogen Medical Limited.

## ***Announcement authorised by the Board of Directors of Actinogen Medical***

### **About Actinogen Medical**

Actinogen Medical (ACW) is an ASX-listed, biotechnology company developing a novel therapy for neurological and neuropsychiatric diseases associated with dysregulated brain cortisol. There is a strong association between cortisol and detrimental changes in the brain, affecting cognitive function, harm to brain cells and long-term cognitive health.

Cognitive function means how a person understands, remembers and thinks clearly. Cognitive functions include memory, attention, reasoning, awareness and decision-making.

Actinogen is currently developing its lead compound, Xanamem, as a promising new therapy for Alzheimer's Disease and Depression and hopes to study Fragile X Syndrome and other neurological and psychiatric diseases in the future. Reducing cortisol inside brain cells could have a positive impact in these and many other diseases. The cognitive dysfunction, behavioural abnormalities, and neuropsychological burden associated with these conditions is debilitating for patients, and there is a substantial unmet medical need for new and improved treatments.

### **About Xanamem**

Xanamem's novel mechanism of action is to block the production of cortisol inside cells through the inhibition of the 11 $\beta$ -HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing its capsule.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease, and Xanamem has shown the ability to enhance cognition in healthy, older volunteers. Cognitive impairment is also a feature in Depression and many other diseases. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials.

The Company has studied 11 $\beta$ -HSD1 inhibition by Xanamem in more than 300 volunteers and patients, so far finding a statistically significant improvement in working memory and attention, compared with placebo, in healthy, older volunteers in two consecutive trials. Previously, high levels of target engagement in the brain with doses as low as 5 mg daily have been demonstrated in a human PET imaging study. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterize Xanamem's therapeutic potential.

Xanamem is an investigational product and is not approved for use outside of a clinical trial by the FDA or by any global regulatory authority. Xanamem® is a trademark of Actinogen Medical.

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This announcement and attachments may contain certain "forward-looking statements" that are not historical facts; are based on subjective estimates, assumptions and qualifications; and relate to circumstances and events that have not taken place and may not take place. Such forward looking statements should be considered "at-risk statements" - not to be relied upon as they are subject to known and unknown risks, uncertainties and other factors (such as significant business, economic and competitive uncertainties / contingencies and regulatory and clinical development risks, future outcomes and uncertainties) that may lead to actual results being materially different from any forward looking statement or the performance expressed or implied by such forward looking statements. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Actinogen Medical does not undertake any obligation to revise such statements to reflect events or any change in circumstances arising after the date hereof, or to reflect the occurrence of or non-occurrence of any future events. Past performance is not a reliable indicator of future performance. Actinogen Medical does not make any guarantee, representation or warranty as to the likelihood of achievement or reasonableness of any forward-looking statements and there can be no assurance or guarantee that any forward-looking statements will be realised.

**ACTINOGEN MEDICAL ENCOURAGES ALL CURRENT INVESTORS TO GO PAPERLESS BY REGISTERING THEIR DETAILS WITH THE DESIGNATED REGISTRY SERVICE PROVIDER, AUTOMIC GROUP.**



FOLLOWING THE SCIENCE

# Clinical Trials Science Forum

Wednesday 3 August 2022 | 11.00am to 1.00pm AEST

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# Introduction and welcome

**Michael Roberts** BEc Hons, CPA, Ffin

**Investor Relations**

- 25+ years' business experience
- Senior IR & comms professional in top-50 listed companies
- Corporate comms advisor for boutique agency

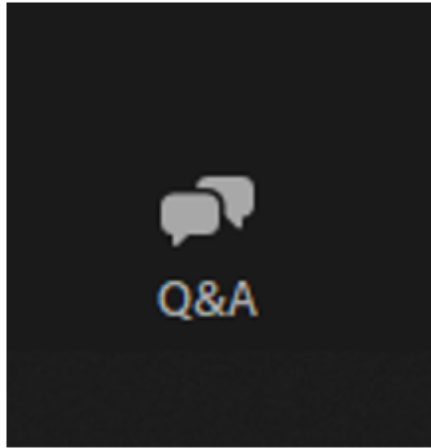
**Dr Steven Gourlay** MBBS FRACP PhD MBA

**Chief Executive Officer**

- Industry physician with more than 25 years experience
- Venture capital 8 years
- Recent successful startup exit with sale of Principia Biopharma to Sanofi for US\$3.7 billion

# Online Q&A

**1.** Click on the Q&A icon



**2.** Type your question in the new Q&A window

Type your question here...



**3.** Hit enter on your keyboard to submit your message

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## To contact support:

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# Agenda



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## Introduction and welcome



**Dr Steven Gourlay**  
Chief Executive Officer



**Michael Roberts**  
Investor Relations

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## The challenges and opportunities in drug development for neurology



**Dr Dana Hilt**  
Neurologist and  
International Neurology  
Trials Expert

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## How to measure cognition in clinical trials – state of the art



**Prof John Harrison**  
International Cognition  
Expert

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## Following the clinical science of Xanamem®



**Prof Paul Rolan**  
Chief Medical Officer

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## Integrated operational excellence



**Tamara Miller**  
Senior Vice President  
Product Development



**Cheryl Townsend**  
Vice President  
Clinical Operations

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## Questions and wrap-up

Moderator **Dr Steven Gourlay**

# Actinogen snapshot



Actinogen Medical (ASX:ACW) is developing a novel oral treatment with rapid onset of clinical activity to improve cognition and quality of life



**Favourable pharmaceutical properties**

- ✓ Demonstrated target engagement in brain and HPA axis<sup>1</sup> in human trials
- ✓ **Low dose,  $\leq 10\text{mg}$**
- ✓ Low drug-drug interaction potential suitable for combination therapy



**Substantial clinical data**

- ✓ **>300 subjects or patients safely treated**
- ✓ Cognitive enhancement activity (attention & working memory) confirmed in two consecutive well-controlled trials (5 mg, 10 mg & 20 mg dose levels vs. placebo)



**Attractive disease indications and rationale**

- ✓ Strong cortisol rationale for treatment of multiple diseases: early stages of Alzheimer's Disease; Depression & related cognitive impairment; Fragile X Syndrome; and many others



**Protected and funded**

- ✓ Molecule in-licensed from U Edinburgh in 2014
- ✓ Comprehensive patents in place<sup>2</sup>
- ✓ **Cash position A\$16.4M at 30 Jun 2022**



**High functioning semi-virtual company model**

- ✓ Core team of 10 fulltime employees based in Australia
- ✓ Leveraging senior consultants in various fields in Australia, Asia, UK and USA
- ✓ **Australian-based operations gains 43.5% as cash rebate**

1. Hypothalamic-Pituitary-Adrenal axis (body's system to regulate blood levels of cortisol)

2. Composition of matter to 2031 plus 5-year extension in most countries, new patents published and in process



# The challenges and opportunities in drug development for neurology

**Dr Dana Hilt** MD

**Neurologist and International Neurology Trials Expert**

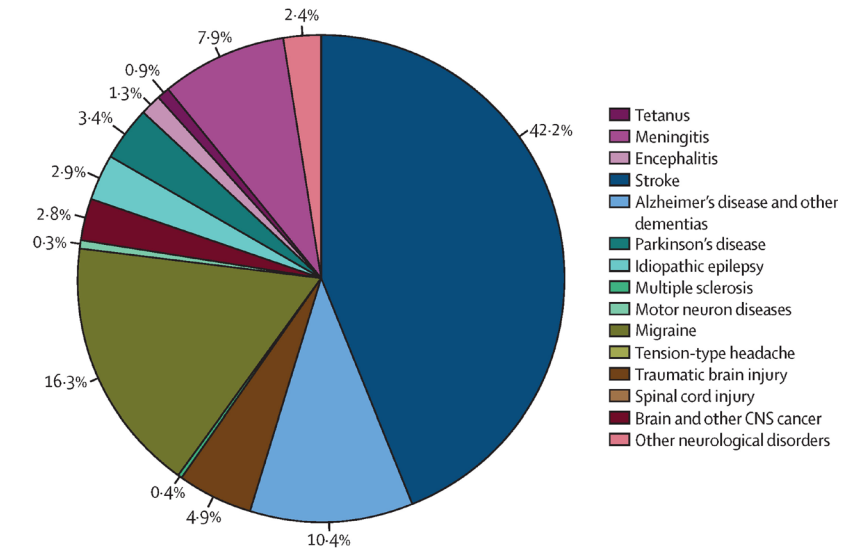
- 25+ years of drug development experience, primarily of Central Nervous System (CNS) drugs
- Phases 1 to 4 drug development
- CMO at Frequency Therapeutics and has held senior management positions as Chief Medical Officer at multiple pharmaceutical companies

# Neurologic diseases

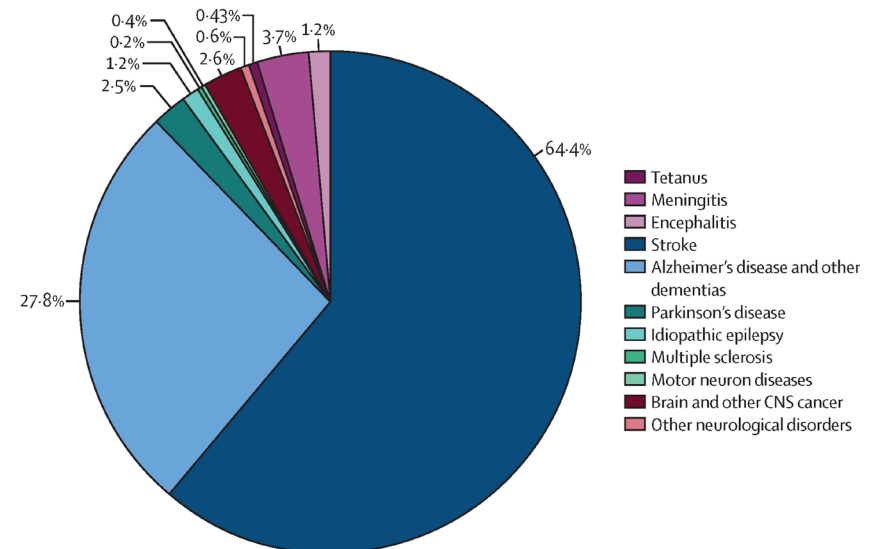
## The disease burden

- Globally, in 2016, The Global Burden of Disease Project analyzed the impact of neurological diseases
  - Leading cause of Disability-Adjusted Life-Years (DALYs) - 276 million
  - Second leading cause of death - 9 million
  - The only neurological disease for which mortality and DALY rates have decreased are ones with infectious etiologies (meningitis, encephalitis, tetanus, etc.)
  - Between 1990 and 2016 the absolute number of deaths increased by 39% and DALYs by 15% for neurological diseases
  - Risk factors such as obesity, hyperlipidemia, and advancing age of the population indicate that these trends will continue and potentially grow larger
- Degenerative diseases such as Alzheimer's and Parkinson's disease have significant and disproportionate disability and mortality impacts. Cognitive impairment contributes significantly to this burden**
- New pro-cognitive therapies can command high prices due to the significant disease burden and large gap in therapies**

**A DALY from neurological diseases**



**B Deaths from neurological diseases**

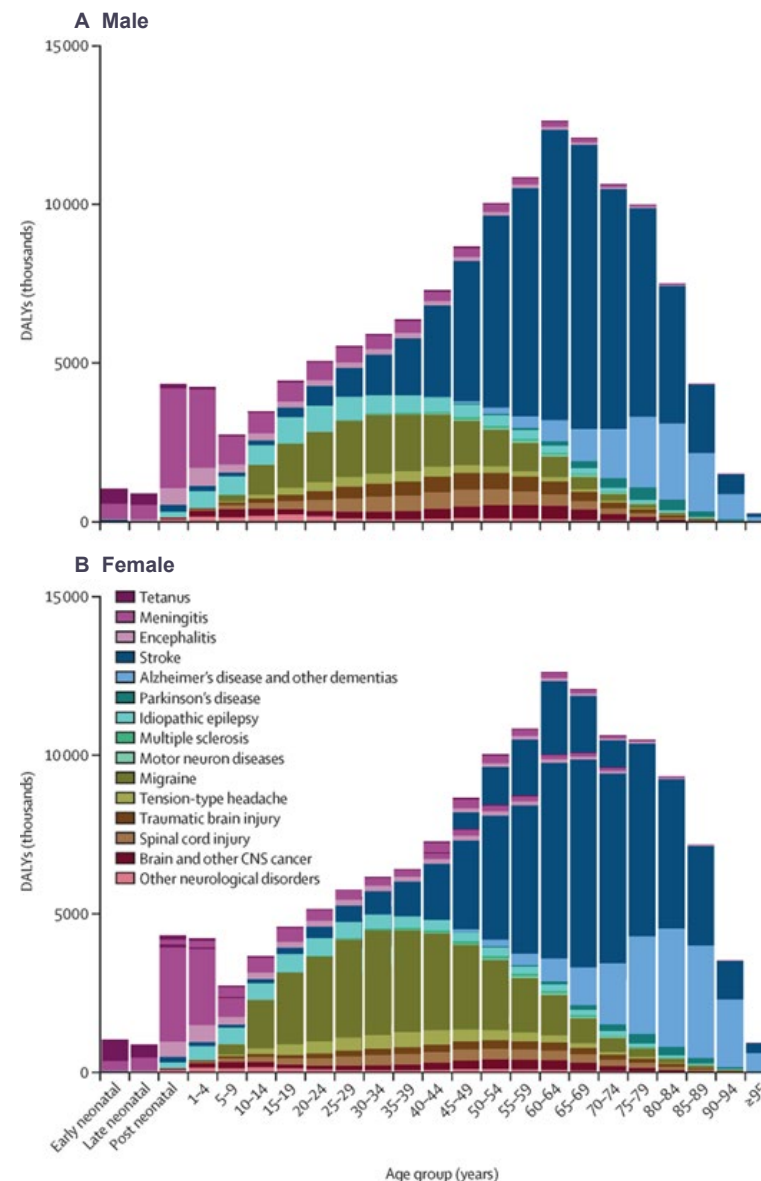


# Neurologic diseases

## The disease burden (cont.)

- As life expectancy increases - neurological disease burden increases
- After the age of 50 yo, the fractional burden of neurodegenerative diseases dramatically increases compared to other conditions
  - Protracted clinical course: average duration of AD clinical course is ~10 years, Parkinson's disease patients have near normal life expectancy
- Increased time with significant disease burden = high societal impact
- These trends emphasize the clinical need:
  - **Symptomatic medications to alleviate the disease burden of cognitive impairment independent of the underlying disease mechanism**

Global DALYs by age for neurological disorders

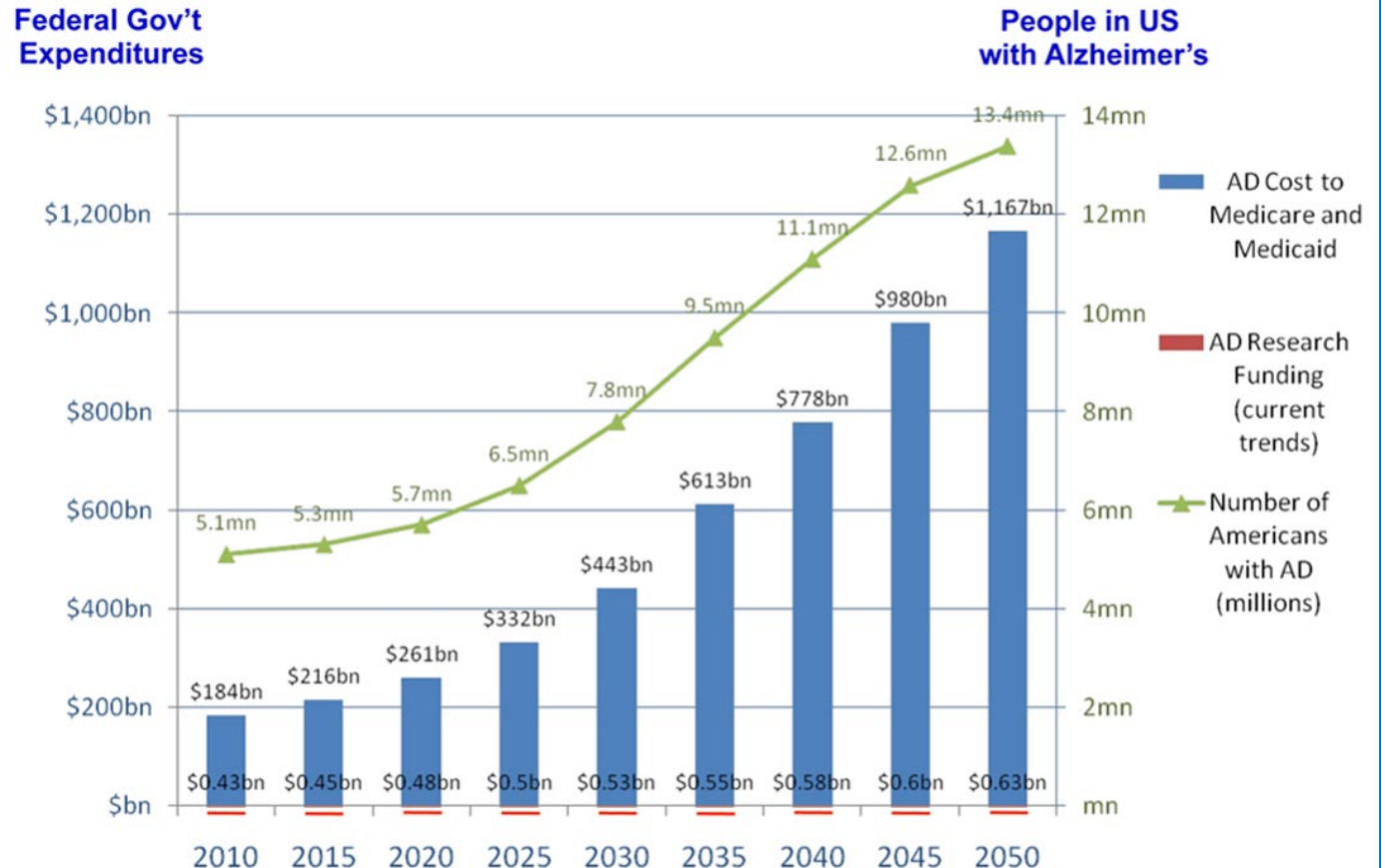


# Neurologic diseases

## The disease burden economic impact

- > One billion people worldwide suffer from Central Nervous System (CNS) diseases<sup>1</sup>
- The economic burden of all CNS diseases - including direct medical costs, non-medical costs, and family care costs was estimated to be > 2 trillion USD (2015)<sup>2</sup>. Of this the cost of neurological diseases was >800 billion (2017)
- These costs are expected to increase to >6 trillion USD by 2030
  - Dementia economic burden is 12x that of cancer
- In 2010 the CNS therapeutic drug market was estimated to be >80 billion USD making it the second largest after cardiovascular medicines<sup>3</sup>

## US Alzheimer's Disease: Economic Impact



Sources: Alzheimer's Study Group, A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group (March 2009); Alzheimer's Association, 2009 Alzheimer's Disease Facts and Figures (March 2009); National Institutes of Health Office of the Budget



# Neurologic drug development has been challenging



## Drug development phase transition success rates by disease area

Phase Success	Phase I to II (positive rate)	Phase II to III (positive rate)	Phase III to ND (positive rate)	NDA to App (positive rate)
Hematology	69.6%	48.1%	76.8%	93.1%
Metabolic	61.8%	45.0%	63.6%	87.5%
Infectious Dis	57.8%	38.4%	64.0%	92.9%
Ophthalmology	71.6%	35.5%	51.2%	91.1%
Autoimmune	55.2%	31.4%	65.3%	94.1%
Allergy	56.4%	28.3%	64.7%	100.0%
G.I.	46.7%	34.2%	57.1%	90.7%
<b>All Indications</b>	<b>52.0%</b>	<b>28.9%</b>	<b>57.8%</b>	<b>90.6%</b>
Respiratory	55.9%	21.0%	64.5%	95.6%
Psychiatry	52.7%	26.8%	56.3%	91.2%
Endocrine	43.3%	29.6%	66.2%	86.3%
<b>Neurology</b>	<b>47.7%</b>	<b>26.8%</b>	<b>53.1%</b>	<b>86.7%</b>
Oncology	48.8%	24.6%	47.7%	92.0%
Cardiovascular	50.0%	21.0%	55.2%	82.5%

### CNS drug development has been challenging

A number of large pharma scaled back their CNS drug development efforts due to the perceived challenge of CNS development

Biotech has filled in the discovery and early development gap

However, with the advance of biomarker technology, imaging, genetics, and other tools - **interest is again increasing in pharma**

**There is still a large clinical need for symptomatic relief and eventually disease modification**



# Neurologic diseases

## Why the gap and how to close it?

- **Psychiatric conditions - faulty 'activity' Neurological conditions - faulty 'wiring'**
  - **It may be easier to correct faulty 'activity' rather than correct faulty 'wiring'**
- Diagnosis by symptoms (eg depression, cognitive impairment, migraine etc) may have multiple underlying mechanisms
  - Genetic characterization of neurological conditions may help us target a drug to a mechanism rather than to a symptom
    - guided missile vs blunderbuss
  - Better characterization of potentially responsive patients and biomarkers of drug action
    - small, faster, cheaper trials with more robust effects
- Better drug design and CNS drug candidate selection
  - Greater selectivity, specificity, and potency
- The brain is 'inaccessible' .....but methods now exist to access information on drug effects
  - Use imaging and other biomarkers to prove brain penetration, drug target engagement, and biological effect in the CNS
  - Increasingly, some peripheral biomarkers (e.g. NfL) may provide an indication of what is going on 'behind the curtain' of the 'Blood Brain Barrier'

# Optimizing Xanamem development



**Xanamem now well positioned for larger clinical outcome studies in multiple indications**



## **Optimal target selection**

- ✓ Selective 11 $\beta$ -HSD1 Inhibitor



## **CNS penetration**

- ✓ Demonstrated CNS penetration at target oral doses (5-10 mg/d)



## **Target engagement**

- ✓ Positive PET Scanning evidence of optimal target engagement at safe and well tolerated doses



## **Initial indication safety, pro-cognitive, and clinical effects**

- ✓ Positive effects on cognition in two normal volunteer studies at safe and well tolerated doses



## **Clinical endpoint scales optimized to drug effect**

- ✓ Focus on optimized attention and cognitive measures to show positive pro-cognitive effects most impacted by Xanamem



## **Regulatory focus on Patient Reported Outcomes (PRO) and measures: How the patient 'feels, functions, and performs'**

- ✓ Use of sensitive PROs and functional scales optimally suited to measure clinical effects

# Neurologic diseases: The regulatory climate

## **Regulatory agencies have recognized the treatment gaps: *New focus to CNS drug development by regulators***

- Scott Gottlieb MD, former FDA Director, led an effort to streamline the team structure that reviews and guides Neurological Drug development.
  - Issued new guidance documents on 5 neurological conditions that give drug developers a clear development 'blueprint'
  - New focus on Patient Reported Outcomes as clinical endpoints.
- More flexibility on novel clinical trial methodology such as Adaptive Designs, Bayesian methods, remote measurements, etc.
  - more efficient, faster trials with larger effects
- Increasing use of Orphan Designation pathway to speed drug development and make it more efficient. Getting drugs to patients with significant unmet need more rapidly
- A rapidly growing recognition that early treatment may be key in impacting these diseases. Thus, showing flexibility on potential endpoints in early stage patients with minimal clinical deficits (e.g. MCI studies in very early AD)
  - Showing benefit on symptoms early in disease rather than disability, then follow patients over time.
- Other Regulatory Agencies (e.g. the European Medicines Agency) have made similar efforts

# A current summary of drug development in CNS diseases



- A growing clinical burden and treatment need exists worldwide in neurological conditions
  - As the world's population ages - this need will only grow
- Both more effective symptomatic treatments as well as drug that can impact, even modestly, the underlying disease process to modify the course of the disease are urgently needed
- Recent science has enhanced the ability to:
  - Categorize patients as to underlying mechanisms of disease
  - This has/will revolutionize our understanding of neurological conditions and development of drugs
  - Generate a better understanding of the dysfunctional biology in the disease condition
  - Measure CNS penetration and target engagement in the CNS by imaging and other biomarkers
- More sophisticated clinical trial methodology will improve efficiency of clinical drug testing

**These advances are indicating a new paradigm  
in drug development for neurological conditions  
Incorporated into the Xanamem Development Program**

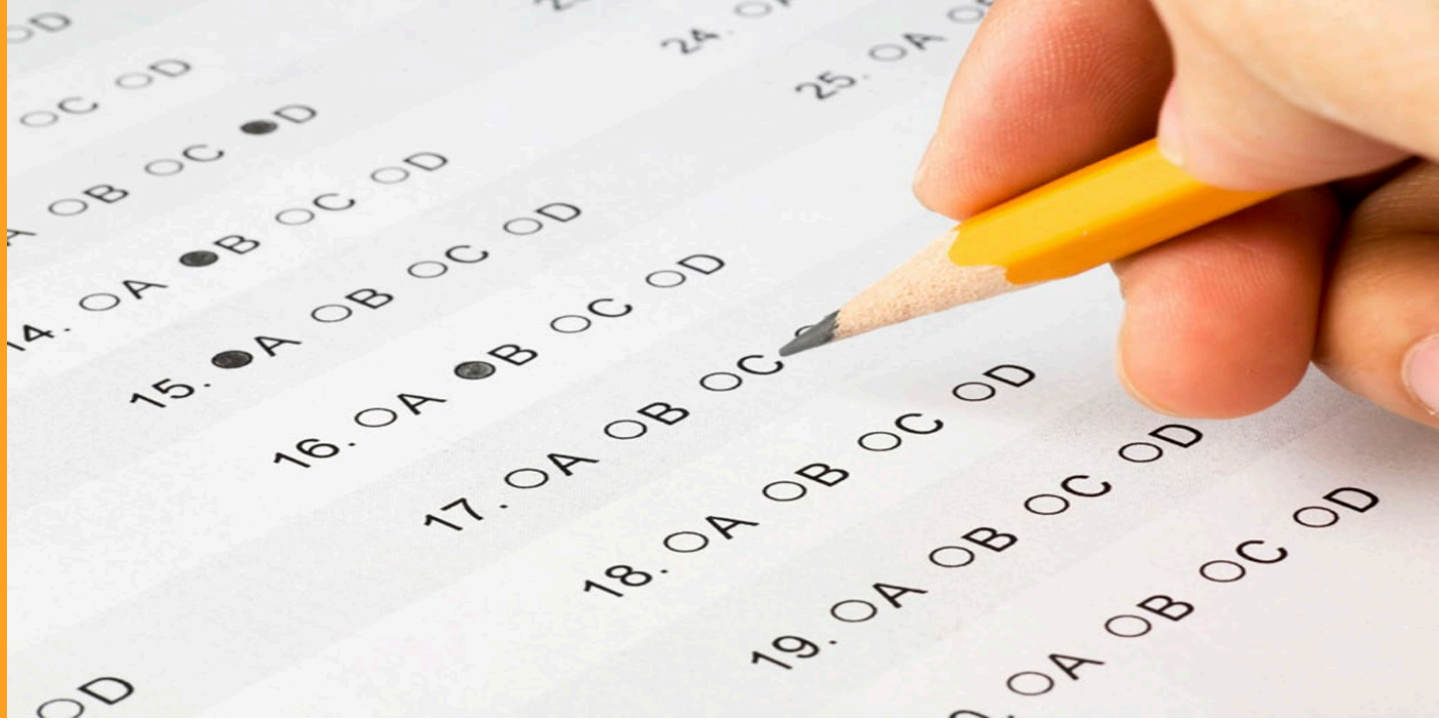
# How to measure cognition in clinical trials – state of the art

**Prof John Harrison** BSc (Hons), PhD, PhD, Dip CS, CSci, CPsychol, AFBPsS

**International Cognition Expert**

- Expert in cognitive assessment
- Chartered psychologist with two PhDs and author/co-author of more than 80 books and scientific articles
- Principal Consultant at Metis Cognition, which advises on selection and integration of cognitive testing into therapeutic development programs





# How to measure cognition in clinical trials – state of the art

John Harrison BSc (Hons), PhD, PhD, Dip CS, CSci, CPsychol, AFBPsS

*Associate Professor, Alzheimer Center, AUMc, Amsterdam*

*Visiting Professor IoPPN, King's College London*

*Consultant Psychologist, Metis Cognition Ltd., Kilmington, UK.*



# Content



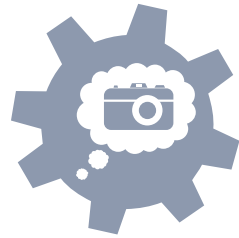
- About cognition
- The usual, suspect measures
- State of the art



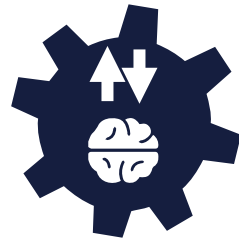
DOMAINS, DEFICIT DETECTION, AND DISEASES

# ABOUT COGNITION

# About cognition



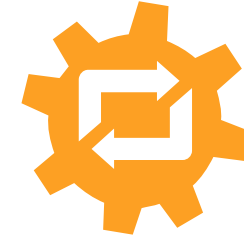
Episodic memory



Working memory



Attention



Executive function



Praxis



Language



The MMSE and the ADAS-cog

# THE USUAL SUSPECT, MEASURES




# Study participant selection using the MMSE



## MINI MENTAL STATE EXAMINATION (MMSE)

Name:  
DOB:  
Hospital Number:

One point for each answer

DATE:								
<b>ORIENTATION</b>								
Year	Season	Month	Date	Time		...../ 5	...../ 5	...../ 5
Country	Town	District	Hospital	Ward/Floor		...../ 5	...../ 5	...../ 5
<b>REGISTRATION</b>								
Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).						...../ 3	...../ 3	...../ 3
<b>ATTENTION AND CALCULATION</b>								
Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).						...../ 5	...../ 5	...../ 5
<b>RECALL</b>								
Ask for the names of the three objects learned earlier.						...../ 3	...../ 3	...../ 3
<b>LANGUAGE</b>								
Name two objects (e.g. pen, watch).						...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".						...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").						...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".						...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.						...../ 1	...../ 1	...../ 1
<b>COPYING:</b> Ask the patient to copy a pair of intersecting pentagons								
						...../ 1	...../ 1	...../ 1
<b>TOTAL:</b>						...../ 30	...../ 30	...../ 30

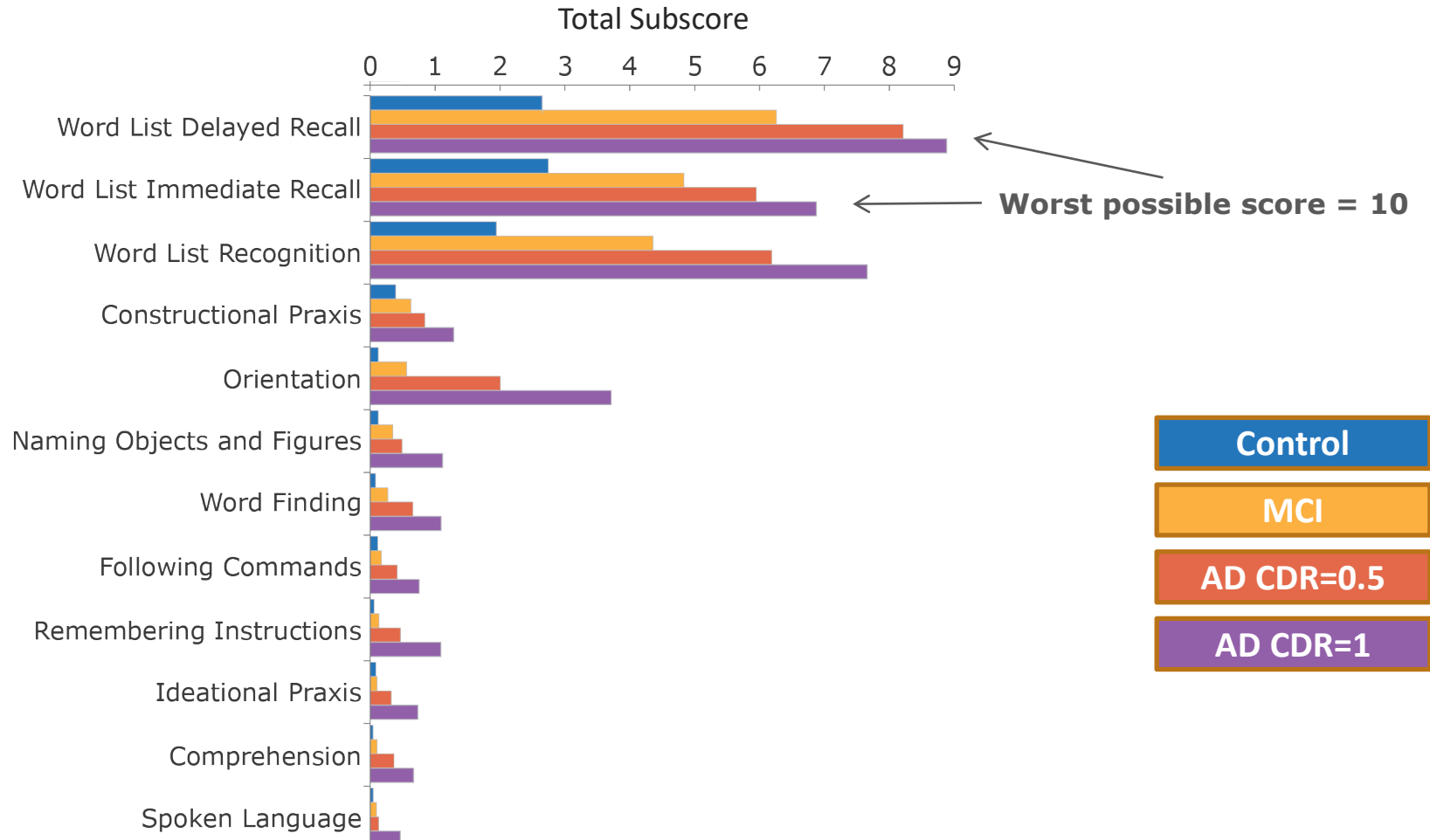
### MMSE scoring

24-30: no cognitive impairment  
18-23: mild cognitive impairment  
0-17: severe cognitive impairment



- Orientation to place 5
- Orientation to time 5
- Word registration 3
- Attention 5
- Word recall 3
- Language (naming objects) 2
- Repeating a phrase 1
- 3-step command 3
- Command 1
- Writing a sentence 1
- Figure copying 1

# ADAS-cog performance in early AD

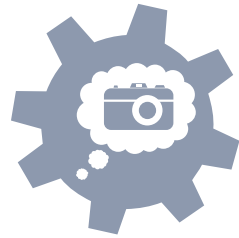




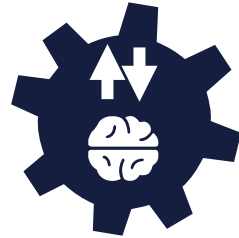
Focusing on reliability, validity and sensitivity

# STATE OF THE ART

# What should we measure?



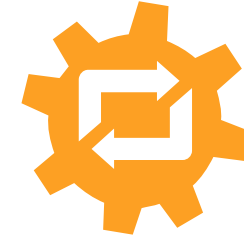
Episodic memory



Working memory



Attention



Executive function



Processing speed



Language & praxis

## Study population

The study's inclusion criteria are study participants, male or female, from  $\geq 50$  to  $\leq 80$  years with a diagnosis of MCI or mild dementia due to AD as per the 2018 NIAA research framework [20, 21], with a Mini Mental State Examination (MMSE) score of  $\geq 20$ , and a Wechsler Adult Intelligence Scale (WAIS) IV coding test score [22, 23]  $\leq 0.5$  standard deviations below the reference score adjusted for age. Our purpose in selecting the coding test requirement was to include only study participants likely to have a rescuable cognitive deficit. Also, the participants must be able to have a study partner accompany them at study visits, as well as be in a stable state regarding both AD and potential AD-medication.

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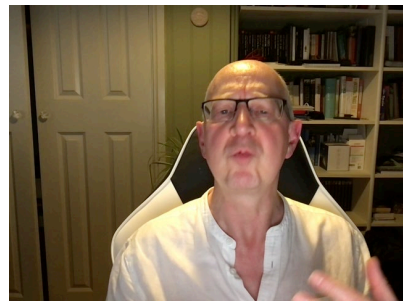
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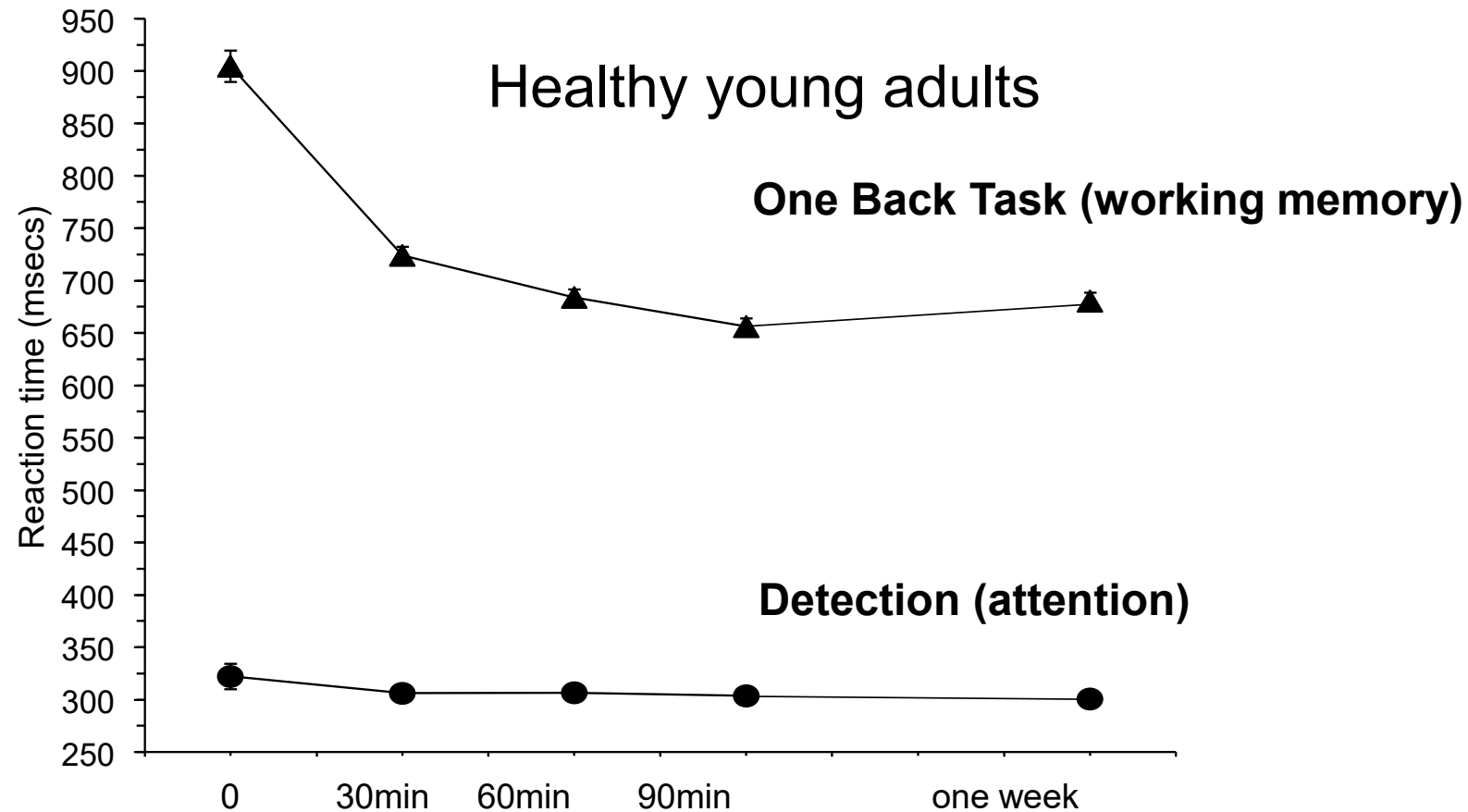


# Target engagement



- Phase 2a - Identify cognitive domains benefitted by treatment
- Phase 2b - Confirmatory evidence of target engagement
- Phase 3 – Replication

# Getting the study participants right

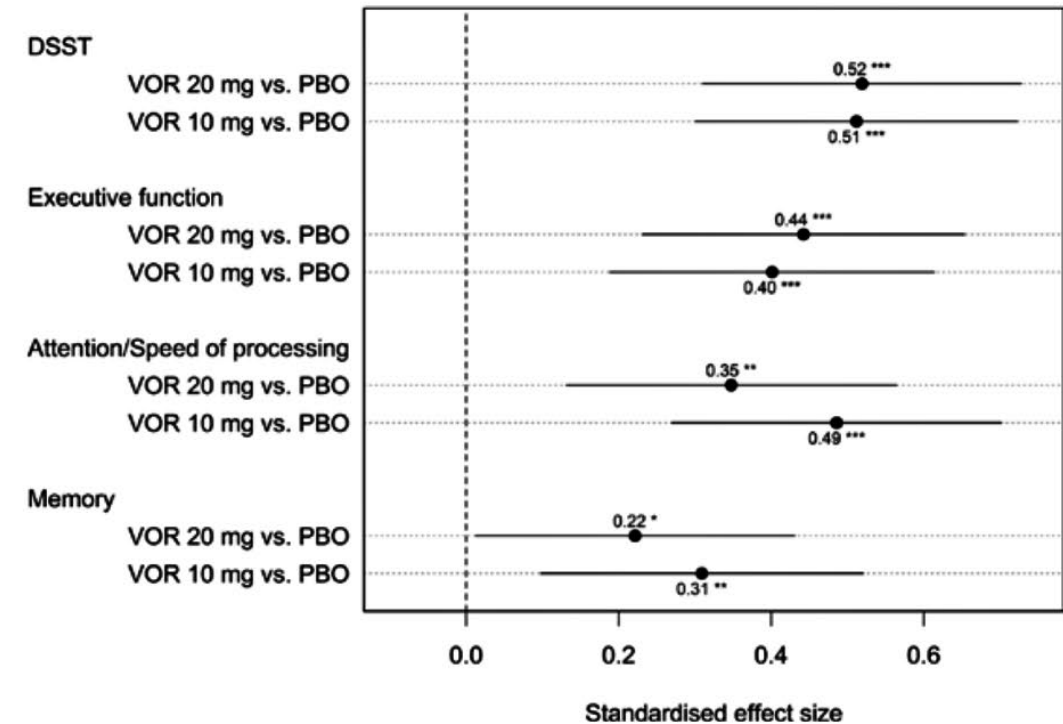
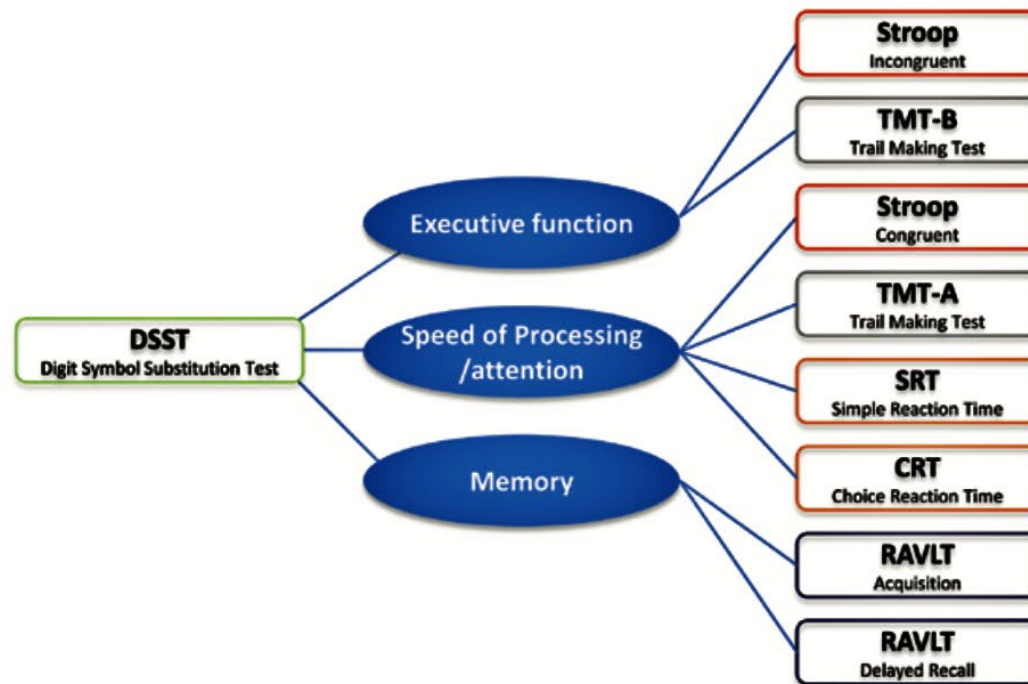


# Getting test selection right



- Brief, reliable, valid, and sensitive measures, especially:
  - *Temporal reliability*
  - *Content validity*
  - *Assay sensitivity*
- Ease of administration
- Often a blend of traditional ‘paper-and-pencil’ and digital tests

# Case study: Vortioxetine Lundbeck



# Summary



- Traditional instruments can lack content validity
- We must be sure to assess all relevant cognitive domains
- Enrich study cohorts for rescuable deficits in target domains
- Employ reliable, sensitive and valid measures

# Thanks for listening



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[open.academia.edu/JohnHarrison](https://open.academia.edu/JohnHarrison)



[@johncpc](https://twitter.com/johncpc)



# Following the clinical science of Xanamem

**Prof Paul Rolan** MBBS MD FRACP FFPM(UK) FFPMANZCA

**Chief Medical Officer**

- Clinical pharmacologist
- Pharmaceutical physician
- Principal investigator in over 750 clinical studies



**Scientific basis for our  
development pipeline**



**Benchmarking  
Xanamem**



**Planned  
clinical trials**

# Making a successful new medicine



## The “rights” of precision drug development for Alzheimer’s disease

Jeffrey Cummings<sup>1\*</sup>, Howard H. Feldman<sup>2</sup> and Philip Scheltens<sup>3</sup>

Cummings *et al. Alzheimer's Research & Therapy* (2019) 11:76  
<https://doi.org/10.1186/s13195-019-0529-5>

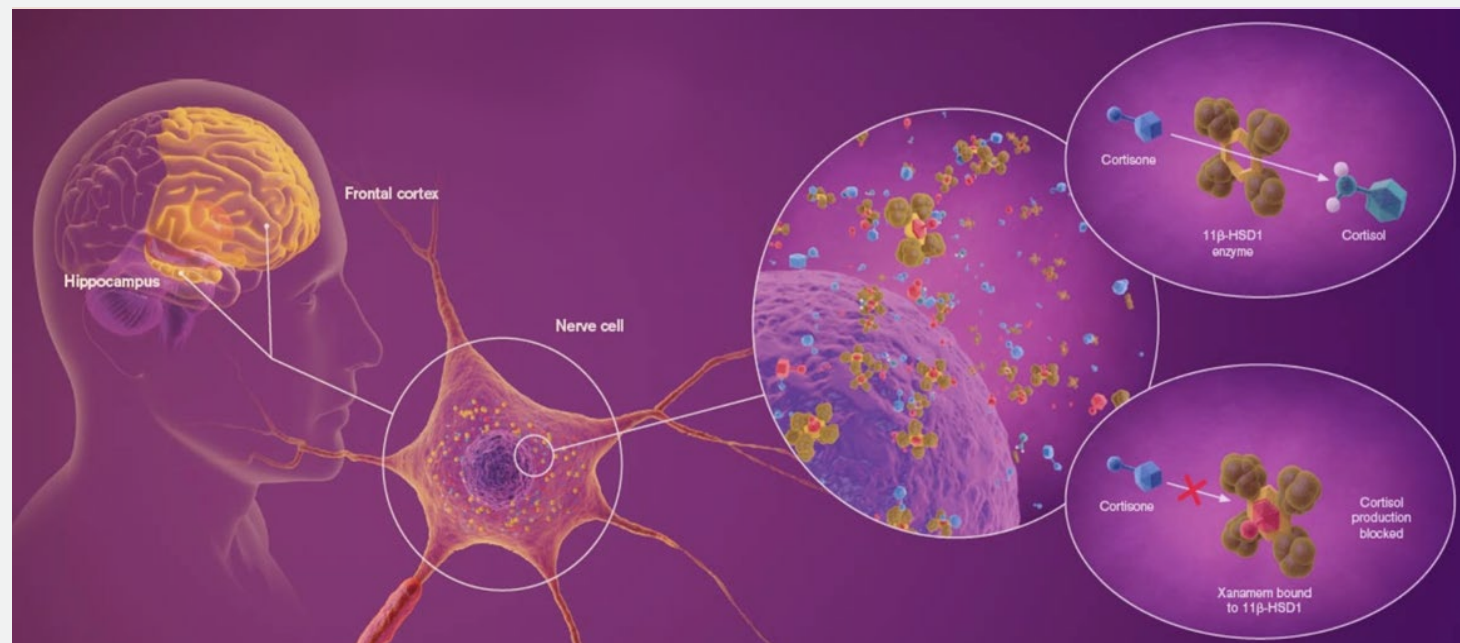
- Hits the right target
- The drug has the right properties
- The right biomarkers and assessments are used to guide development
- The right trial participants are selected
- The right trial design is used
- *The right dose*
- *The right safety profile*

# Xanamem®: Oral, low dose, once-a-day treatment with a unique mechanism – the right target

Brain penetrant 11 $\beta$ -HSD1 small molecule enzyme inhibitor reduces cortisol inside brain cells - modulating signaling pathways and underlying disease processes<sup>1,2</sup>

Potential to be:

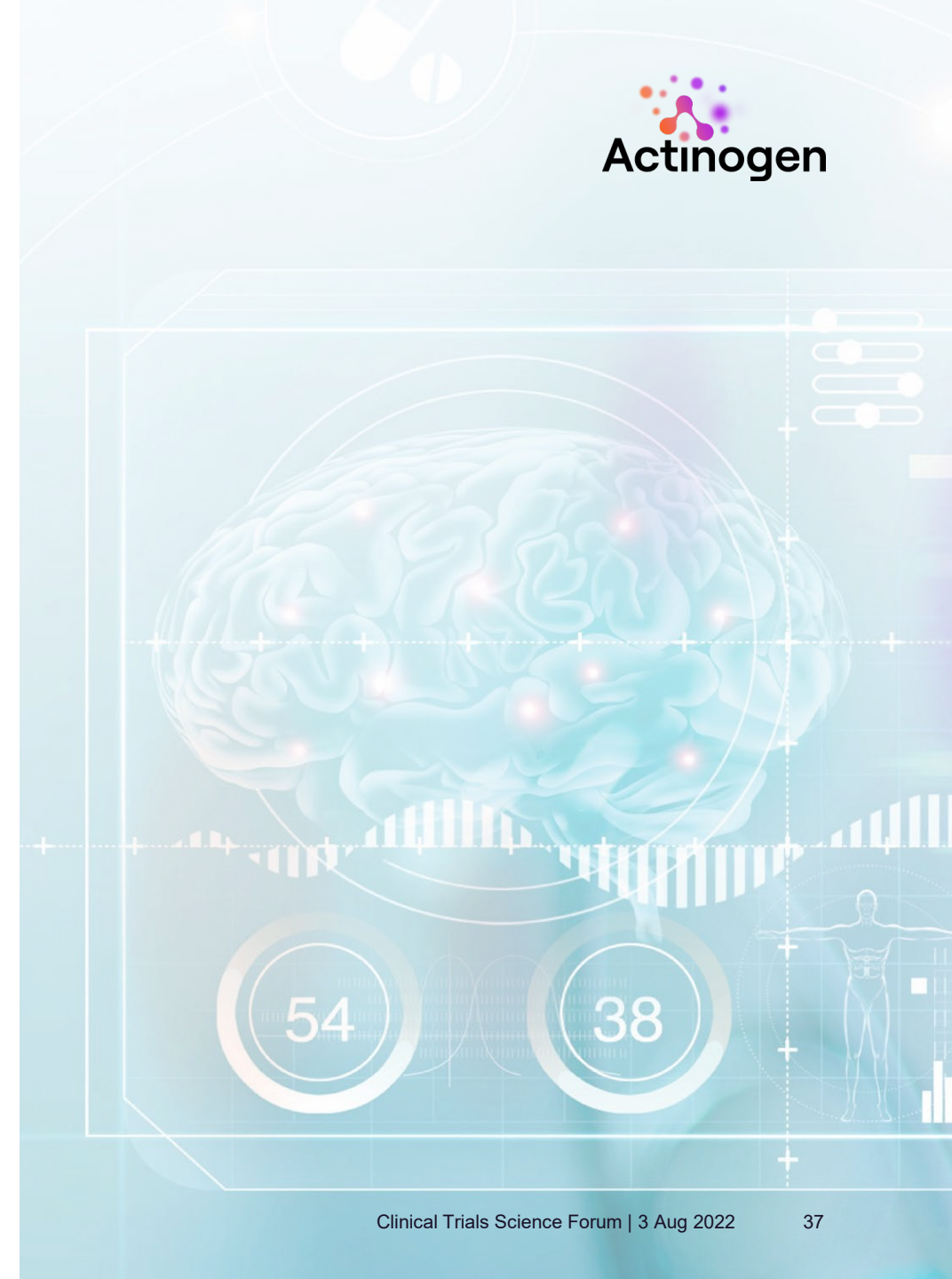
- Rapidly cognitive enhancing
- Disease-modifying (slow or halt progression) in AD



1. Xanamem® is a CNS (Central Nervous System) penetrant small molecule based on human PET scan evidence and cerebrospinal fluid (CSF) measurements  
 2. Sooy et al. 2015 showing effects on amyloid plaque reduction in an aged mouse model after 28 days associated with increases in insulin degrading enzyme; Popoli et al. 2011 microglial cell modulation in rats, effects on glutamate, cannabinoid and other signalling pathways

# The role of cortisol in health

- Cortisol is an essential hormone for health in humans
- Its key function is to modulate the response to stress:
  - physical stress such as infection
  - psychological stress
- Outside the brain, cortisol controls the amount of inflammation due to disease, infection
- Inside the brain, role is complex and modulates mood, attention, memory





# The role of elevated cortisol in brain disease

## Efficacy of Treatments Targeting Hypothalamic-Pituitary-Adrenal Systems for Major Depressive Disorder: A Meta-Analysis

Yudan Ding<sup>1</sup>, Zirou Wei<sup>2</sup>, Haohao Yan<sup>1</sup> and Wenbin Guo<sup>1\*</sup>

### SYSTEMATIC REVIEW

published: 10 September 2021

doi: [10.3389/fphar.2021.732157](https://doi.org/10.3389/fphar.2021.732157)

---

### High levels of brain cortisol are associated with:

- depressed mood (Major Depressive Disorder)
- shrinking parts of the brain needed for new memory formation (hippocampus)

### Cortisol synthesis inhibitors have been shown to improve depression in clinical trials

- validated target
- however, none reached regulatory approval as not adequately selective

### Depression and cognitive impairment are large market high unmet medical needs conditions

- our focus on these conditions

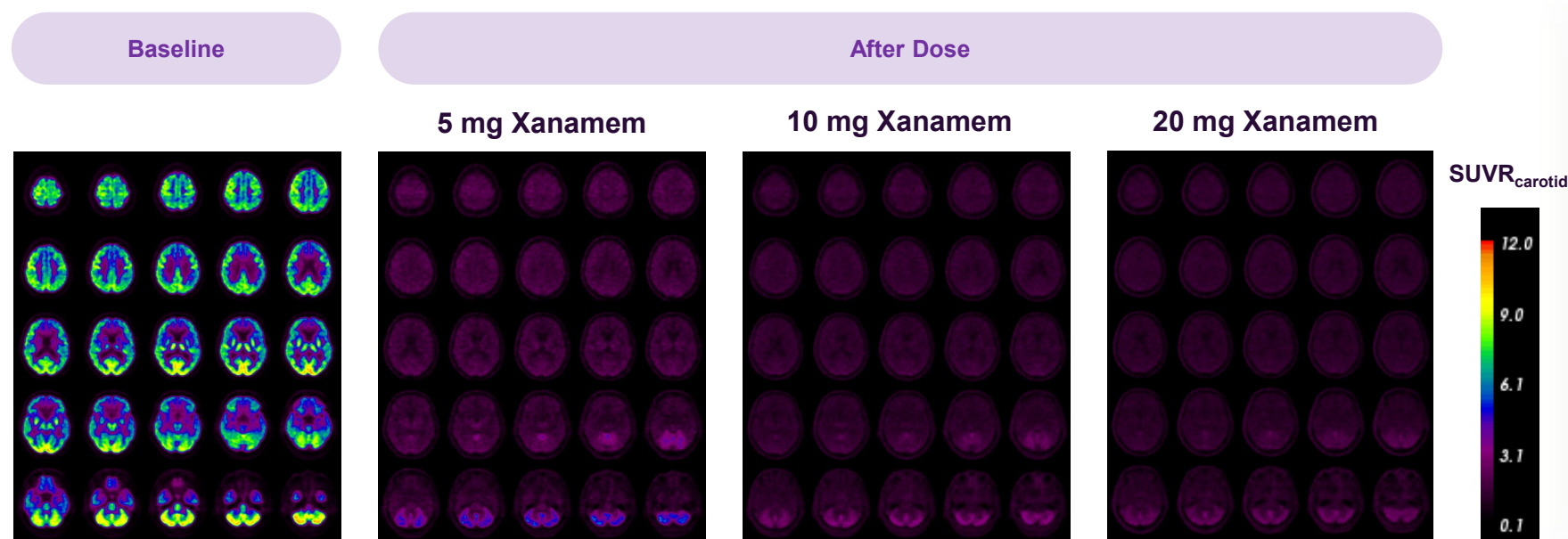


## The right properties

- Well absorbed, small dose (5-10 mg), once-a-day dosing, little affected by food
- Penetrates brain well
- High binding to target enzyme from 5mg (right biomarker)
- Safe and very well tolerated
- Good candidate for combination therapy due to low potential for drug interactions



# High target engagement confirms brain activity at Xanamem doses of $\leq 10\text{mg}$



PET brain scan data demonstrates that Xanamem extensively binds to the 11 $\beta$ -HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.

This is consistent with full hormonal pharmacodynamic activity seen with 10 mg in clinical trials.



Status: Analysis

# Alzheimer's Disease

Targeting cognitive enhancement and disease-modification in the early stages of disease

MRI

# Characteristics of early Alzheimer's Disease

## **AD is common<sup>1</sup>**

**~500,000 Australians have dementia, with AD the commonest type**

## **AD patients initially suffer memory loss**

**As AD progresses, memory worsens and other problems develop e.g. language, problem solving, ability to live independently**

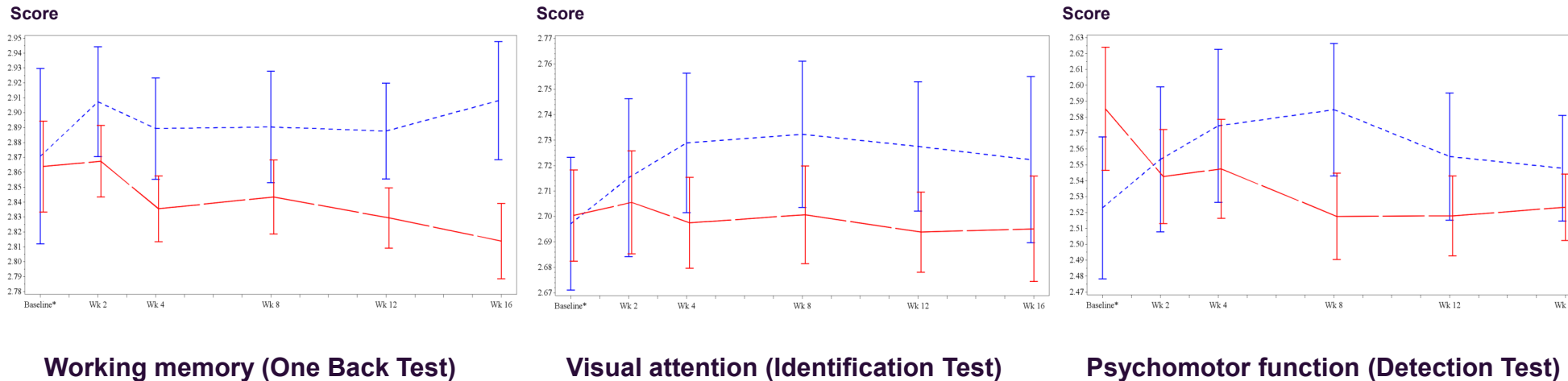
## **Existing treatments have minimal effectiveness and side effects**

**New treatments needed to improve memory and slow AD in its early stages**

# Previously: Cognitive improvement vs. placebo in healthy, older volunteers in XanaHES trial in 2019

- Cogstate Cognitive Test Battery (CTB) with 20 mg daily, 12-week treatment; effect size (ES) estimated with the same MMRM statistical model as the current trial<sup>1</sup>
- Clinically significant effects on “attention” domains of cognition (ES<sup>2</sup> attention composite = 1.2)

Treatment Group — Xanamem 30pts — Placebo 12 pts

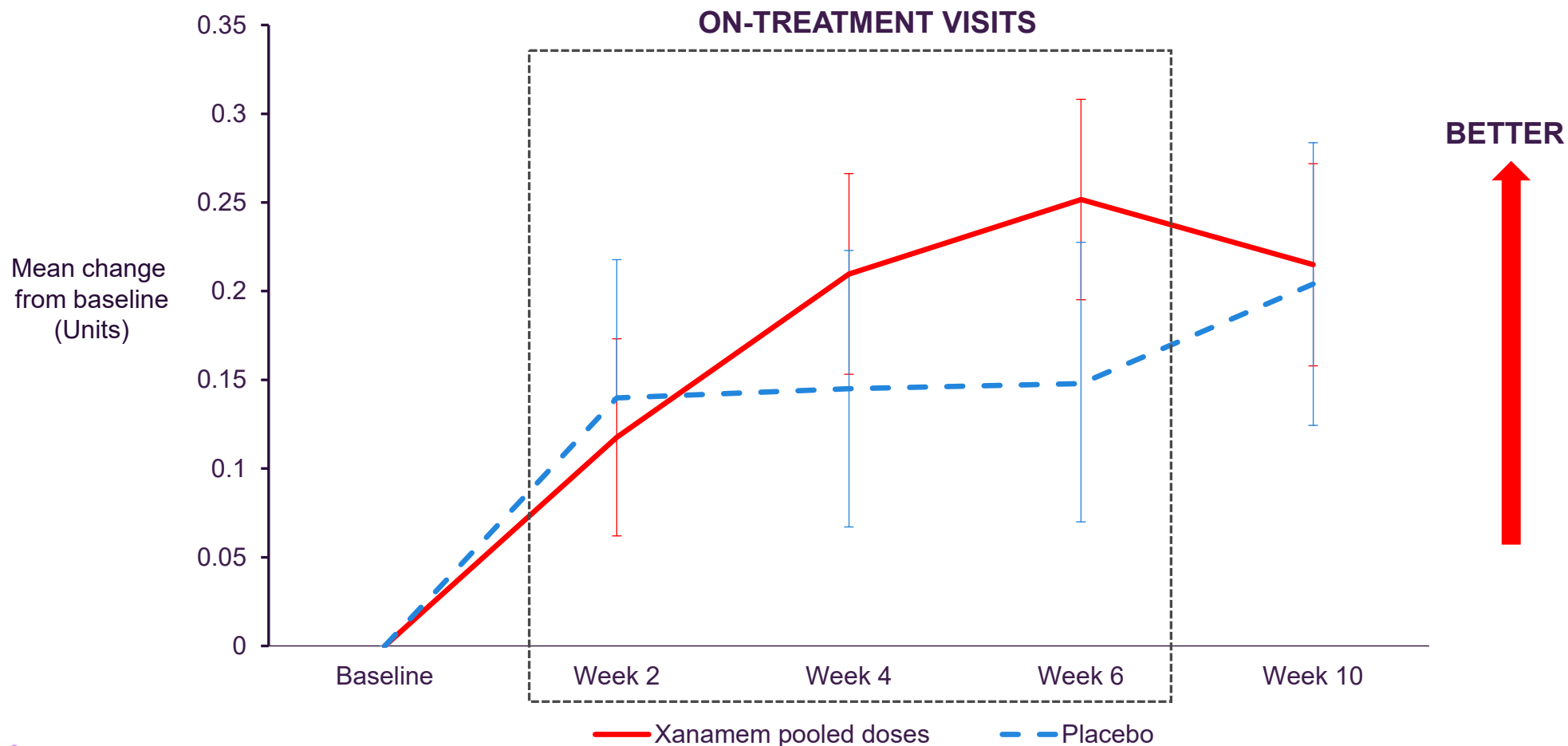


**Lower  
Xanamem  
scores in red  
are better**

1. XanaHES Phase 1 clinical trial treated healthy elderly patients with 20mg Xanamem daily (n=30 active, n=12 placebo). All plotted values are the means of observed data  
 2. Z-score of standardized treatment effect (mean difference in MMRM model change from baseline vs. placebo/standard error of change).

# Recently: Attention composite improved at weeks 4 and 6 vs. placebo – the right assessments

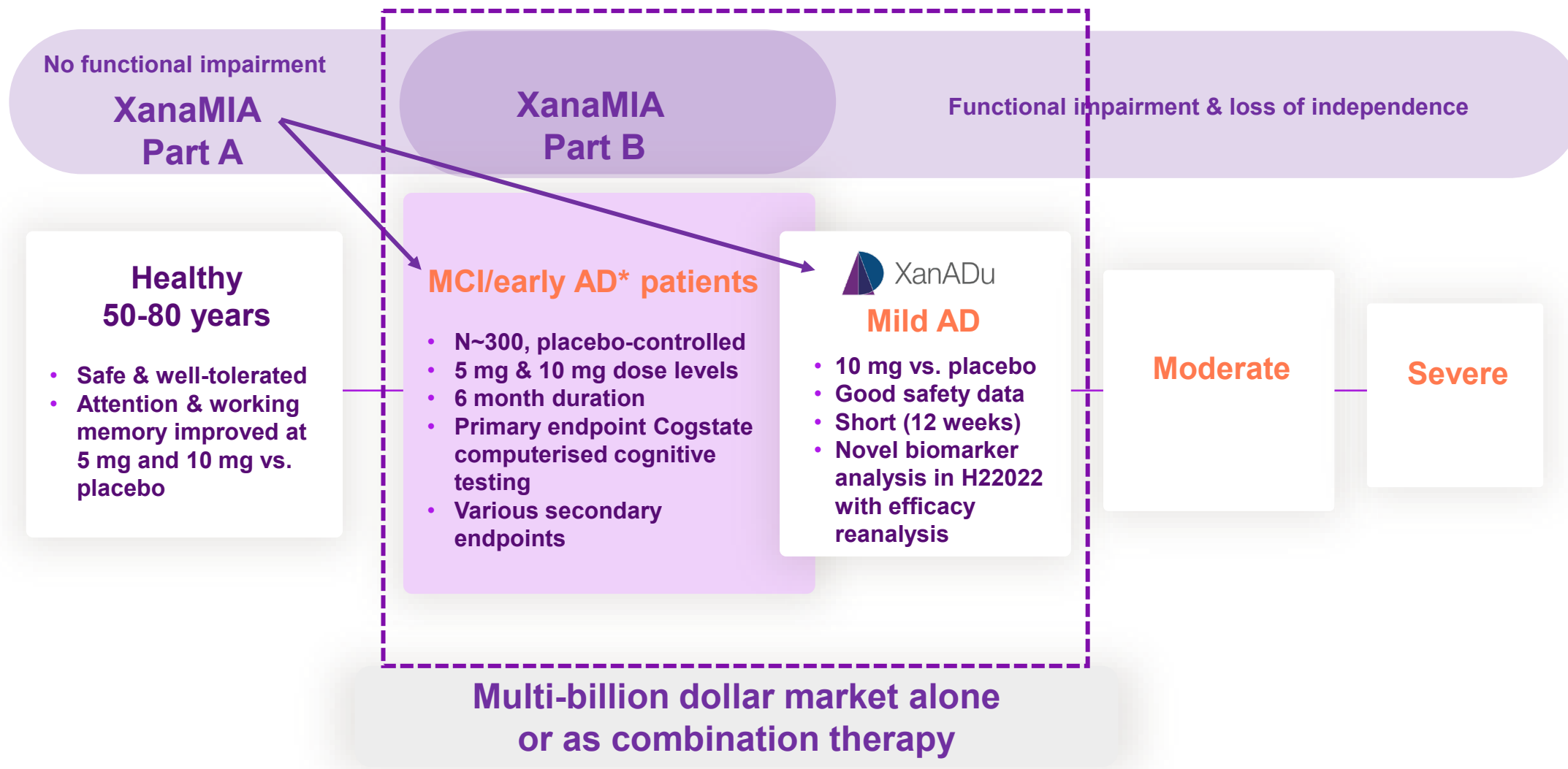
Pooled working memory / visual attention / psychomotor speed (mean, SE)







# Now: Moving Xanamem trials into AD patients with a focus on cognitive enhancement & biomarkers



# October: Planned analysis of Phase 2 plasma samples for Alzheimer's Disease biomarkers

Bringing disease biomarker data readout forward into 2022

## XanADu Phase 2 Trial



**~70/185 patients  
available for analysis**



**10mg daily**



**Mild Alzheimer's Disease without  
biomarker or imaging confirmation**



**We will now assess whether Xanomem  
improved AD blood biomarkers**



**We will also reassess efficacy trends in  
biomarker positive patients**

# XanaMIA Part B – Patients with early Alzheimer's Disease

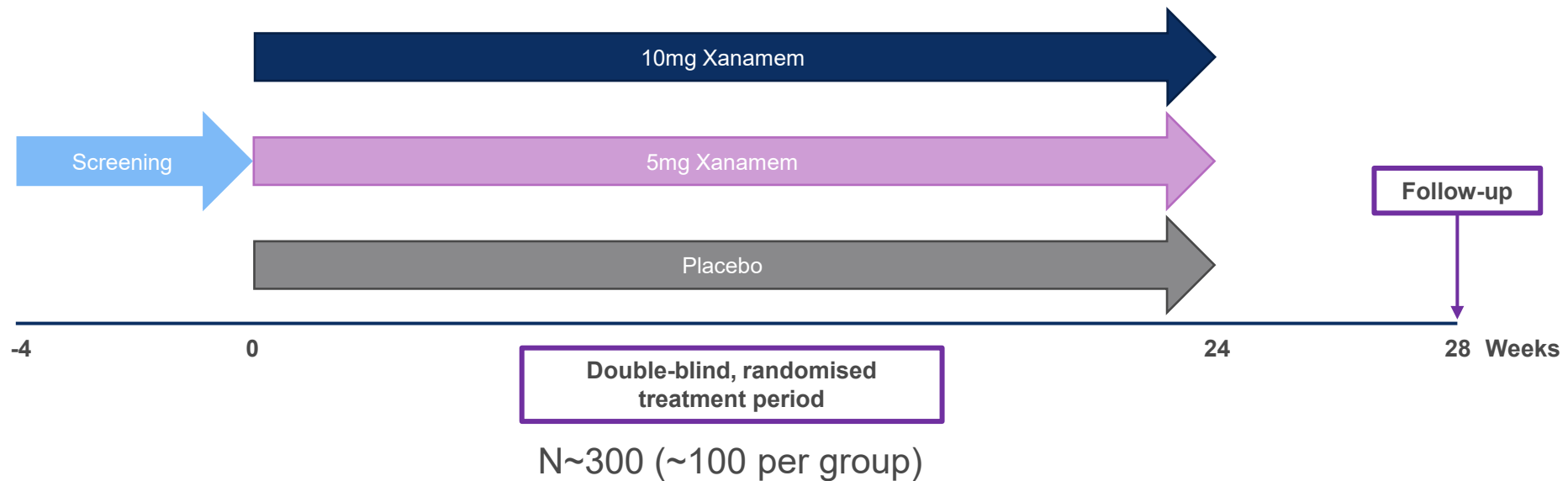
## Key design considerations

### Double-blind randomized parallel-groups design:

- Placebo, 5 and 10 mg Xanamem once daily
- Approx. 100 per group
- 24 weeks treatment

### Patients with:

- Clinical diagnosis of early-stage AD
- Demonstrated cognitive impairment by coding test
- Elevated p-Tau181 (AD biomarker signature)



# Key outcomes

## Primary outcome

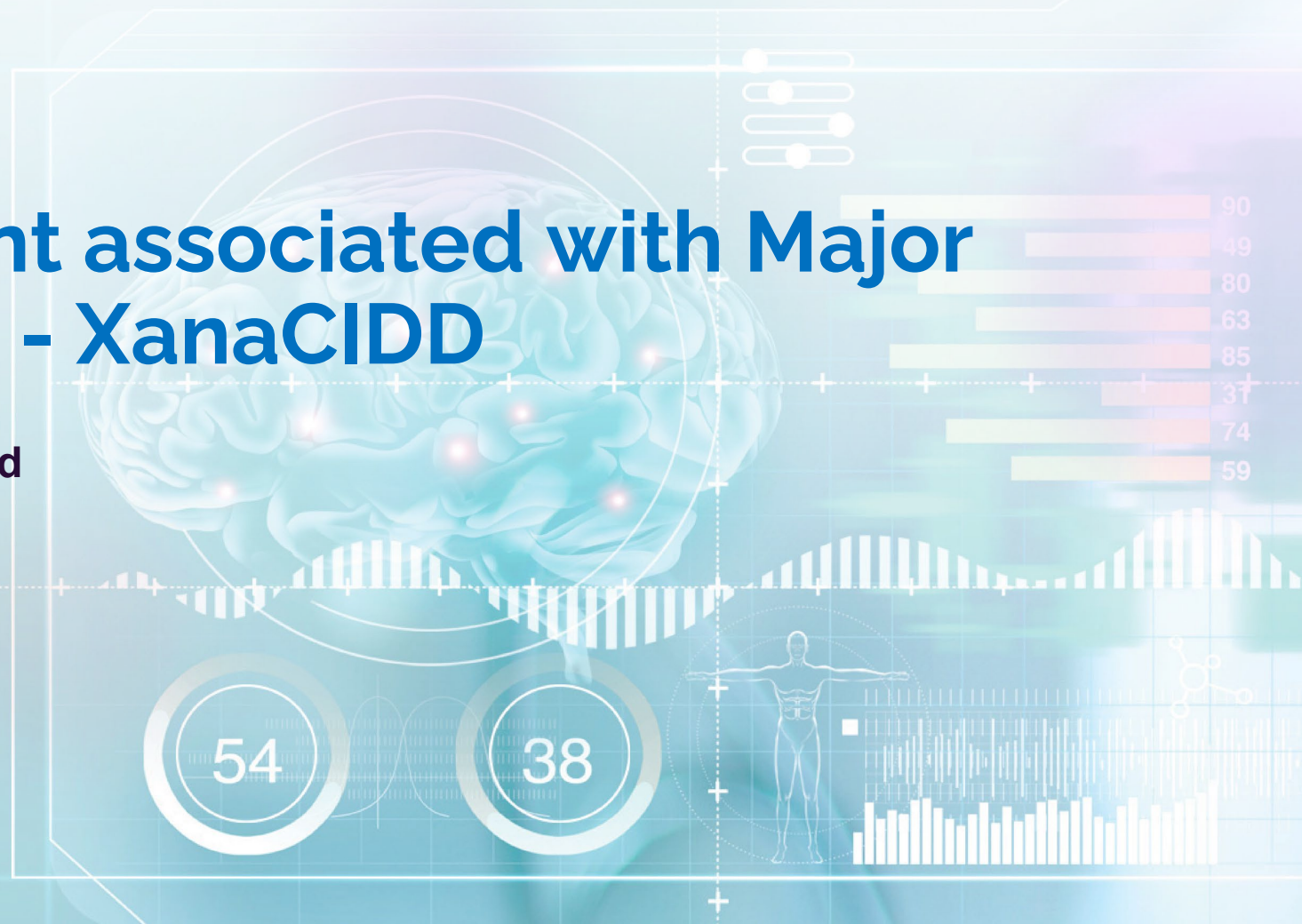
- Cogstate attention composite (same as XanaMIA Part A and XanaHES)

## Secondary outcomes

- Amsterdam Activity of Daily Living scale (more sensitive than ADAS-Cog)
- Cogstate
  - Executive Function Composite
  - Episodic Memory Function Composite
- Individual tests
- Carer questionnaire / Patient Global Improvement

# Cognitive Impairment associated with Major Depressive Disorder - XanaCIDD

Targeting dual cognitive enhancement and anti-depressant activity



# Characteristics of Major Depressive Disorder (MDD)



**MDD is common<sup>1,2</sup>**

**~5% prevalence globally, 1 in 7 lifetime risk**

**Neurocognitive symptoms are a typical feature (>80%)<sup>3</sup>**

**Difficulty thinking and concentrating, unable to make decisions**

**Only one anti-depressant has a statement re cognition**

**Vortioxetine sales US\$500m<sup>4</sup>**

1. World Health Organization, Depression. 2021.  
2. Kessler & Bromet 2013  
3. Conradi et al. 2011, *Psychol Med*, 41(6):1165-74.  
4. Lundbeck financial reports 2020



# The Xanamem opportunity in depression

## Current anti-depressants



work slowly (3 weeks) and  
initial suicide risk



do not target cognition



multiple adverse effects  
blood pressure, sexual function, appetite...



Xanamem improves cognition quickly

Xanamem may improve both depression and cognitive impairment

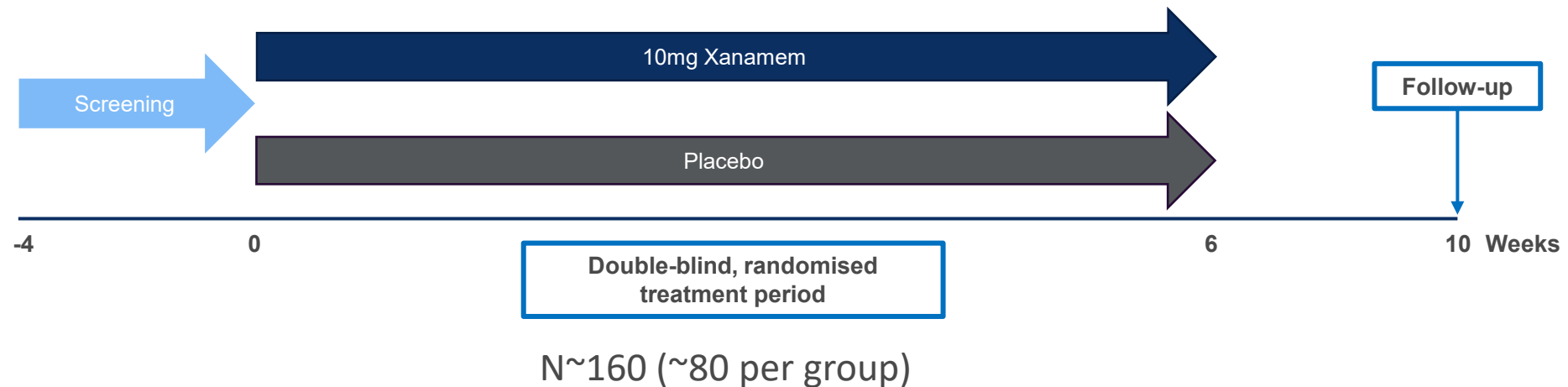
# XanaCIDD trial design & implementation model

## Double-blind randomized parallel-groups design:

- Placebo and 10 mg Xanagem once daily
- Approx. 80 per group
- 6 weeks treatment

## Patients with:

- Clinical diagnosis of MDD
- Demonstrated cognitive impairment by coding test
- Persistent depressive symptoms despite first line therapy (SSRI/SNRI)



# Key outcomes

## Primary outcome

- Cogstate CTB attentional composite (attention and working memory)

## Secondary outcomes

- Montgomery-Åsberg Depression Rating Scale (**MADRS**)
- Executive Function Cognitive Composite (**One-Back, COWAT, iDSST**)
- Episodic Memory Cognitive Composite (**OCL, HVLt-R**)

# Safety data Xanamem Phase 2 Mild Alzheimer's Disease trial



10mg daily over 12 weeks in patients with mild AD (MMSE\* 20-26)

TEAE** term	Xanamem (n=91)	Placebo (n=94)	Total (n=185)
Headache	5 (5.5%)	2 (2.1%)	7 (3.8%)
Dizziness	4 (4.4%)	3 (3.2%)	7 (3.8%)
Diarrhoea	1 (1.1%)	4 (4.3%)	5 (2.7%)
Fatigue	3 (3.3%)	1 (1.1%)	4 (2.2%)
Nerve conduction abnormal	1 (1.1%)	3 (3.2%)	4 (2.2%)
Somnolence	1 (1.1%)	3 (3.2%)	4 (2.2%)
Decreased appetite	2 (2.2%)	0 (0.0%)	2 (1.1%)

\* Mini Mental State Examination

\*\* Treatment Emergent Adverse Events possibly related to Xanamem reported by more than one patient in any group: all mild-moderate

✓ **No treatment-related Serious Adverse Events in whole program**

# Potential for Xanamem



**To be first-in-class  
in early stages of AD**



**To be first-in-class cognitive enhancer /  
dual label claim therapy in depression**

**Actinogen clinical trials have been designed to demonstrate these effects**



**Based on cognitive  
improvement seen so far**



**In collaboration with world's  
leading experts in cognition  
and neuroscience clinical trials**



**With execution focused  
on efficient delivery**

# Making a successful new medicine

## The “rights” of precision drug development for Alzheimer’s disease

Jeffrey Cummings<sup>1\*</sup>, Howard H. Feldman<sup>2</sup> and Philip Scheltens<sup>3</sup>

Cummings *et al. Alzheimer's Research & Therapy* (2019) 11:76  
<https://doi.org/10.1186/s13195-019-0529-5>

- ✓ Hits the right target
- ✓ The drug has the right properties
- ✓ The right biomarkers and assessments are used to guide development
- ✓ The right trial participants are selected
- ✓ The right trial design is used
- ✓ *The right dose*
- ✓ *The right safety profile*



# Integrated operational excellence

**Tamara Miller** MS, BSc, PMP, DipBus

**Senior Vice President  
Product Development**

- BSc, MSc, and project management certification
- 20 years of international product development and clinical operations experience in the UK, US, and Australia
- Managing all aspects of Actinogen product development plan for Xanamem

**Cheryl Townsend** RN, PG Clin Research, MLaw

**Vice President  
Clinical Operations**

- Registered nurse with post graduate degrees in Nursing and Clinical Research and Master's degree in Health Law.
- 30 years of international clinical research experience
- Responsible within Actinogen for the successful delivery of the Clinical Trial Program

- ✓ Right target
- ✓ Right drug
- ✓ Right biomarkers/assessments
- ✓ Right clinical trial
- ✓ Right participants
- ✓ Right dose
- ✓ Right safety profile

***Clinical Operations excellence is essential for success:***

Innovative implementation of the **right trial design**

Recruiting the **right participants**

# 'Hands-on' clinical operations team at Actinogen



**Administrative role, called a Clinical Trial Assistant (CTA), who supports the day-to-day activities for the trial**

**Field-based monitors, called Clinical Research Associates, who travel to different trial sites to ensure the trial is being conducted correctly in accordance with the Protocol and regulatory guidelines**

**Project managers, called Clinical Project Managers, who manage the internal cross-functional team and all the external vendors involved in the conduct of the trial**

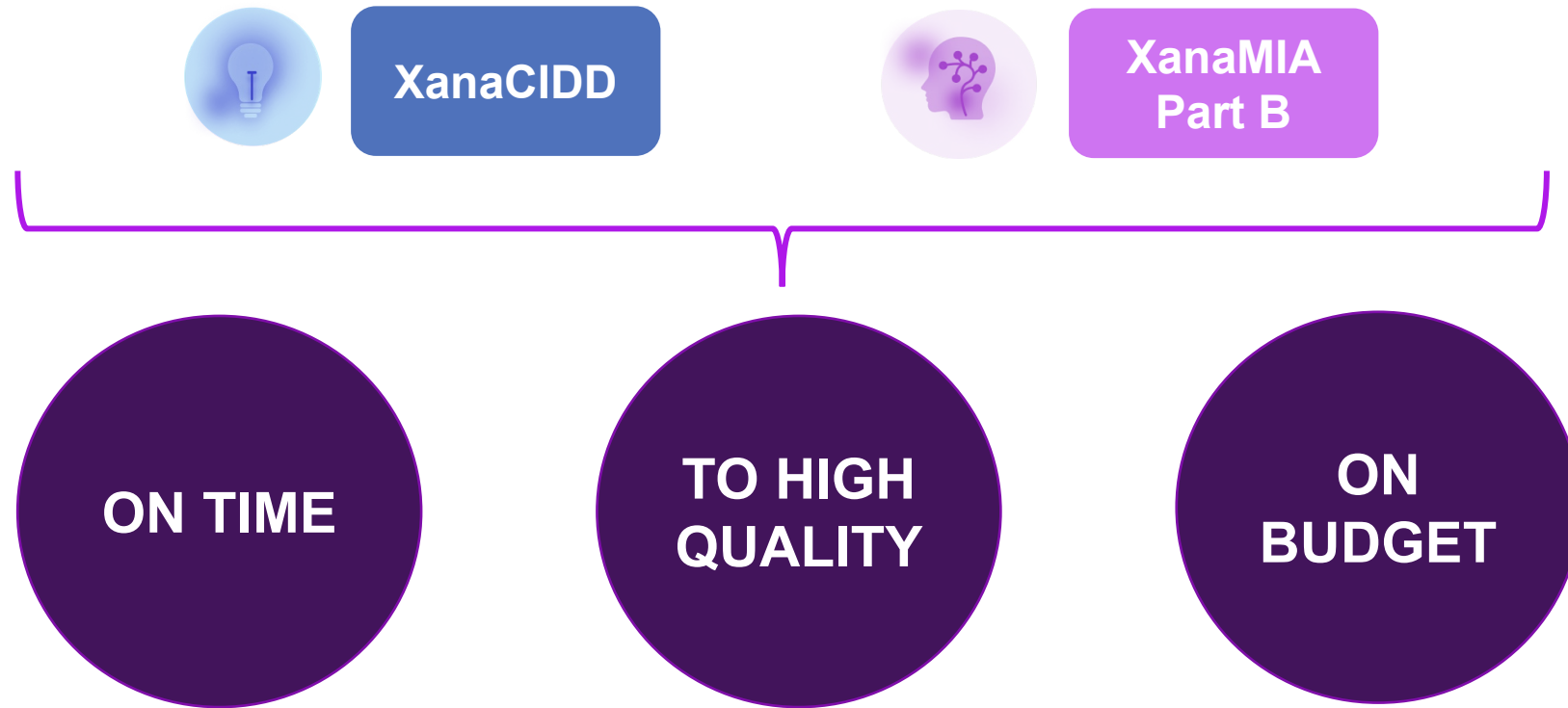
**Senior management oversight role, usually at Director or VP level, where the person has accountability for the delivery of the trial to cost, on time, and to quality standards**

# Leveraging strategic clinical operations partners



Biostatistics partner

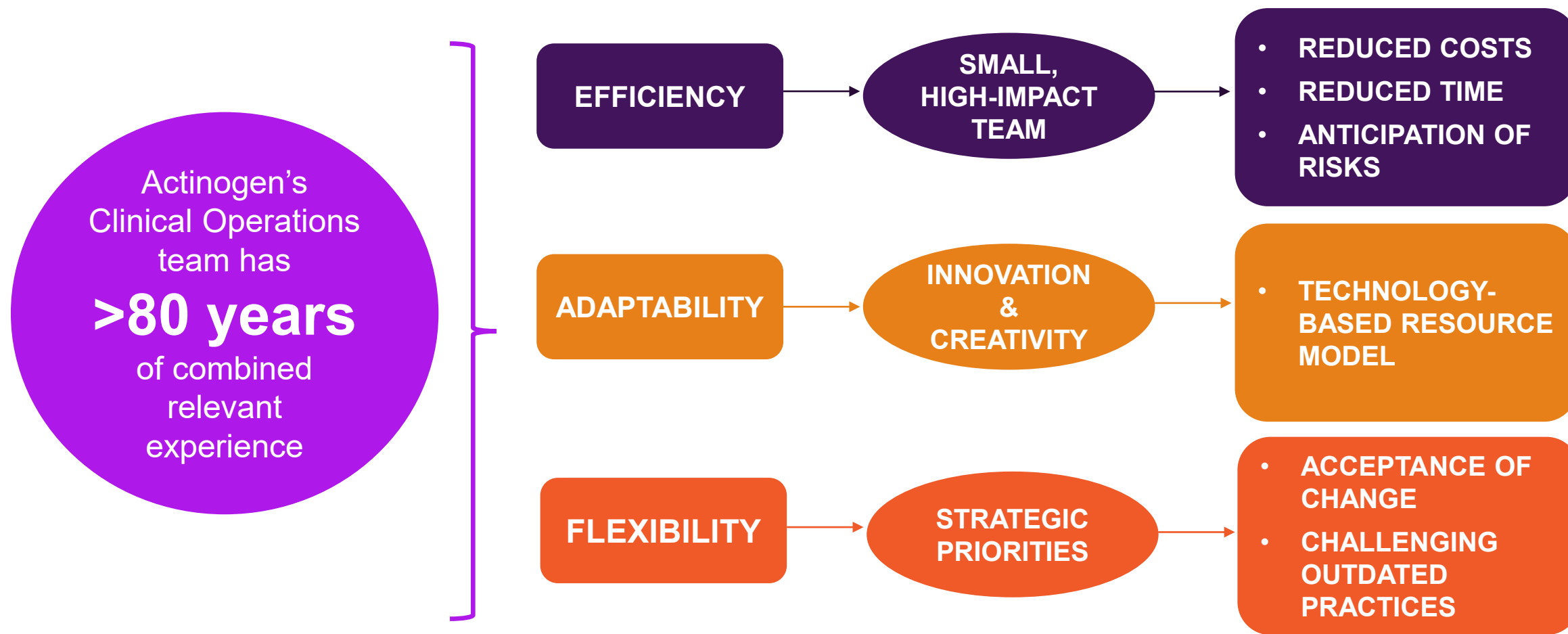
# Delivering operational excellence in Phase 2





# Implementing with efficiency, speed and quality

## The Actinogen difference





# The Actinogen difference



## OPERATIONAL EFFICIENCY

Healthy volunteer studies:

XanaHES: 42 participants *recruited in 4 months*

XanaMIA-DR: 106 participants *recruited in 6 months*

## OPERATIONAL FLEXIBILITY

In collaboration with Actinogen's Clinical Science team ensure the:

- trial design is as close to real-world / clinical practice as possible
- trial design is appealing to the patient
- trial utilizes start-of-the-art endpoints and measures to speed up development path, and provide Xanamem to patients in the shortest timeframe

# The Actinogen difference



## OPERATIONAL ADAPTABILITY

Leveraging the newest technology to reduce costs and increase quality:

- Electronic pre-screening & e-consent
- Centralised rating (diagnosis & endpoints)
- Remote monitoring
- GP / Psychologist / Psychiatrist Referral Networks & decentralized regional trial centres
- Targeted multichannel advertising



## The right science

- ✓ Target
- ✓ Drug
- ✓ Biomarkers/Assessments
- ✓ Clinical Trial
- ✓ Participants
- ✓ Dose
- ✓ Safety Profile

## The right implementation

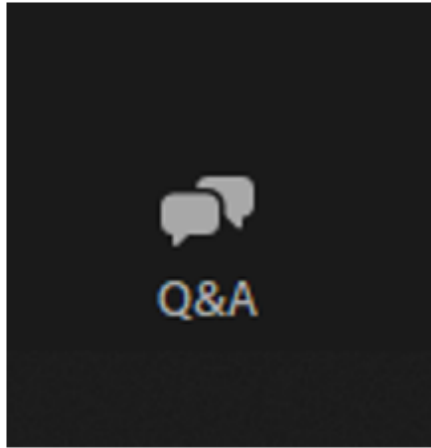
- ✓ Right team and partners
- ✓ Innovative clinical trials management
- ✓ Contemporary recruitment strategies

# Questions



# Online Q&A

**1.** Click on the Q&A icon



**2.** Type your question in the new Q&A window

Type your question here...



**3.** Hit enter on your keyboard to submit your message

Cancel

Send

## To contact support:

Please call 1300 816 159 (within Australia) or +61 2 8072 1479 (outside of Australia)





# Thank you

For any additional enquiries or questions contact us:

**Michael Roberts**

**Investor Relations**

**E: [michael.roberts@actinogen.com.au](mailto:michael.roberts@actinogen.com.au)**

**M: +61 423 866 231**



# Appendix



# Selected glossary

**11 $\beta$ -HSD1** 11 beta HydroxySteroid Dehydrogenase-1 enzyme

**CNS** Central nervous system

**CRO** Contract Research Organization - Clinical

**Double-blind** Investigators, participants and company do not know who has active vs placebo treatment during a trial

**EMA** European Medicines Agency

**FDA** US Food & Drug Administration

**Hyperlipidemia** Raised blood fats e.g. cholesterol

**Hypothalamic-Pituitary-Adrenal (HPA) axis** Body's system to regulate blood levels of cortisol

**mean, SE** Average, Standard Error of the mean

**PET** Positron Emission Tomography – a type of body scan

**Placebo controlled** Non-active treatment for double-blind design

**p-Tau181** AD biomarker of Tau protein



## **Dr Steven Gourlay** MBBS FRACP PhD MBA

### **Chief Executive Officer and Managing Director**

Dr Gourlay has more than 30 years of experience in the development of novel therapeutics and brings considerable skills and experience to Actinogen as the Company moves into further clinical development of its lead compound Xanamem. Formerly the founding Chief Medical Officer (CMO) at US-based Principia Biopharma Inc., Dr Gourlay was responsible for the supervision of multiple pre-clinical, first-in-human, Phase 2 and 3 clinical trial programs in orphan immunological diseases, multiple sclerosis and cancer. The data generated by these trials, and Dr Gourlay's roadshow presentations, supported a successful NASDAQ IPO of Principia Biopharma Inc. in 2018 – subsequently followed by an acquisition by Sanofi for US\$3.7 billion in 2020.

Prior to Principia Biopharma, Dr Gourlay was a Partner at GBS Venture Partners, the Australian specialist life sciences and healthcare venture capital firm, where he contributed to the success of multiple clinical stage therapeutic companies including Elastagen, Spinifex and Peplin. Before GBS, and after a post doctorate in clinical pharmacology at the University of California, San Francisco, he held positions of increasing responsibility at Genentech, Inc. in the areas of pharmacoepidemiology and early clinical development.

Dr Gourlay has significant drug regulatory experience with the US Food and Drug Administration (FDA), European Medicines Agency (EMA) at many levels, including filing more than 10 Investigational New Drug (IND) applications, achieving several orphan drug status approvals for his Company's product(s), and completing several biologics license applications.

Dr Gourlay is based in Sydney and holds a Bachelor of Medicine, Bachelor of Surgery (MBBS) from the University of Melbourne, a PhD in Medicine from Monash University, an MBA from Macquarie University and is a fellow of the Royal Australian College of Physicians (FRACP). He is also a specialist physician in general internal medicine.



**FREQUENCY**   
THERAPEUTICS

## Dr Dana Hilt MD

### Neurologist and International Neurology Trials Expert

Dr Dana C. Hilt MD has more than 25 years of drug development experience, primarily of Central Nervous System (CNS) drugs. Dr Hilt has deep experience in Phases 1 to 4 development of drugs for conditions including Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis, Schizophrenia, and other non-CNS conditions.

Dr Hilt is currently the Chief Medical Officer at Frequency Therapeutics and has held senior development and management positions as Chief Medical Officer at various pharmaceutical companies, including Guilford Pharmaceuticals, Ascend Pharmaceuticals, and Critical Therapeutics. Prior to that, Dr Hilt worked with Amgen, establishing a Clinical Neuroscience Group that focused on the potential therapeutic applications of neurotrophic factors in degenerative neurologic diseases such as Parkinson's disease.



metis

## **Prof John Harrison** BSc (Hons), PhD, PhD, Dip CS, CSci, CPsychol, AFBPsS

### **International Cognition Expert**

Prof John Harrison is an expert psychologist with a special interest in cognition whose principal professional interest is in helping people understand, maintain, and enhance their cognitive skills.

Professor Harrison is Principal Consultant at Metis Cognition, a psychology practice established to advise with the selection and successful integration of cognitive testing into therapeutic development programs. He is also an Associate Professor with the AUMc Alzheimer Center and Visiting Professor at King's College London.

Prof Harrison holds Chartered Psychologist status and has authored/co-authored more than 80 books and scientific articles, including a popular neuroscience book 'Synaesthesia: The Strangest Thing'.



## **Prof Paul Rolan** MBBS MD FRACP FFPM FFPMANZCA

### **Chief Medical Officer**

Professor Paul Rolan is a clinical pharmacologist and drug development consultant and one of Australia's most experienced clinical trial investigators and drug developers, having taken drugs from first human administration to market. His career has spanned academic medicine (Professor of Clinical Pharmacology and Director of Innovation at The University of Adelaide) and pharmaceutical medicine. He has extensive expertise in the development of medicines as principal investigator in more than 750 early phase proof-of-concept, clinical pharmacology, drug interaction and special patient groups studies.

Professor Rolan joined Actinogen in 2022 and his prior industry roles have included Medical Director of the U.K.'s largest phase 1 contract research organisation, Medeval, Chief Medical Officer for ASX listed biotech company, Bionomics Limited and Director of Drug Development for Singapore's first listed pharmaceutical company, iX Biopharma. Professor Rolan continues to advise on drug development for the international pharmaceutical industry, with a focus on the development of biomarkers, evaluation of novel therapies and mechanisms of disease, as well as conduct clinical practice in chronic pain management and headache.

Professor Rolan holds numerous academic and professional qualifications including a Bachelor of Medicine and Bachelor of Surgery (MBBS), and a Doctor of Medicine (MD). He also holds fellowships of the Royal Australian College of Physicians (FRACP), the Faculty of Pharmaceutical Medicine, Royal College of Physicians, (FFPM) and the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, (FFPMANZCA).



## **Tamara Miller** MS, BSc, PMP, DipBus

### **Senior Vice President Product Development**

Tamara Miller joined Actinogen in September 2017 and 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, managing all aspects of the drug development life cycle, and leading cross-functional teams.

As part of the Actinogen team, Tamara Miller oversees and manages the overall drug development process and strategy including pre-clinical, clinical development, clinical operations, CMC & manufacturing, regulatory operations, and R&D budget/finance operations.





## **Cheryl Townsend** RN, PG Clin Research, MLaw

### **Vice President Clinical Operations**

Cheryl Townsend joined Actinogen in March 2022 as Vice President of Clinical Operations and is responsible for Actinogen's clinical operations and the successful delivery of the company's clinical trial program.

Cheryl brings 30 years of international clinical research experience to Actinogen, including senior positions in clinical operations and medical affairs in pharmaceutical companies and clinical research organisations. She has worked across many therapeutic spheres ranging from Phase 1 through Phase 4 trials, including 10 years working in rare diseases.

Most recently Cheryl held increasingly senior positions in clinical operations at Alexion Pharmaceuticals Australasia.

Cheryl is a registered nurse with post graduate degrees in Nursing and Clinical Research as well as a Master's degree in Health Law.



## Michael Roberts BEC Hons, CPA, FFin

### Investor Relations

Michael Roberts heads the investor relations and corporate communications function at Actinogen Medical in Sydney. He is a corporate communications specialist with more than 25 years' experience working with prominent ASX 50 Australian companies including Brambles, Lion Nathan and Foster's Group. Michael also provides investor relations and corporate communications consulting services at Trinity Communications.

Michael built his early career in finance and treasury before moving into corporate communications, with specialist senior executive roles in investor relations and corporate affairs where he developed a deep understanding of and passion for best practice corporate communications. Prior to joining Actinogen in May 2021, Michael was the Investor Communications Director at Sydney design and branding agency Designate Group where he provided advisory and consulting services to clients from a broad range of ASX listed companies and industries.

Michael holds a Bachelor of Economics (Hons) from Monash University and a Graduate Diploma of Applied Finance & Investment from the Financial Services Institute of Australasia. He is a Certified Practising Accountant (CPA) and a Fellow of the Financial Services Institute of Australasia (FFin).