

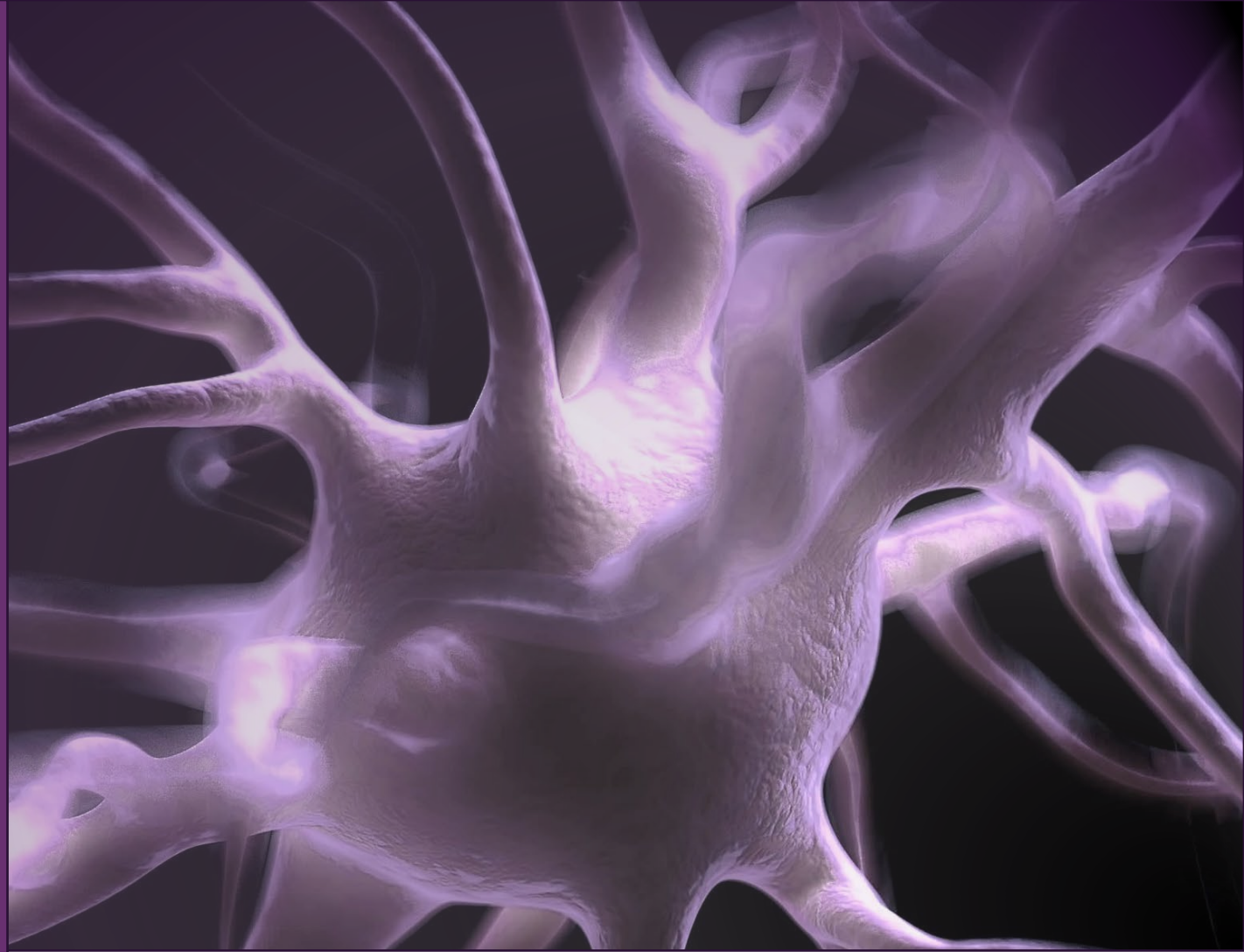
# BIO DIGITAL 2020

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

**June 2020**

*Developing innovative treatments for cognitive impairment associated with neurological and metabolic diseases due to raised cortisol, including Alzheimer's disease*



# Xanamem™ - lead compound

A novel Mechanism of Action (MoA) designed to inhibit cortisol production in the brain (through 11 $\beta$ -HSD1 inhibition), with proof of concept in animals and in humans, and a strong safety profile



**Novel MoA**  
(cortisol inhibition)



**PoC demonstrated in animal trials**



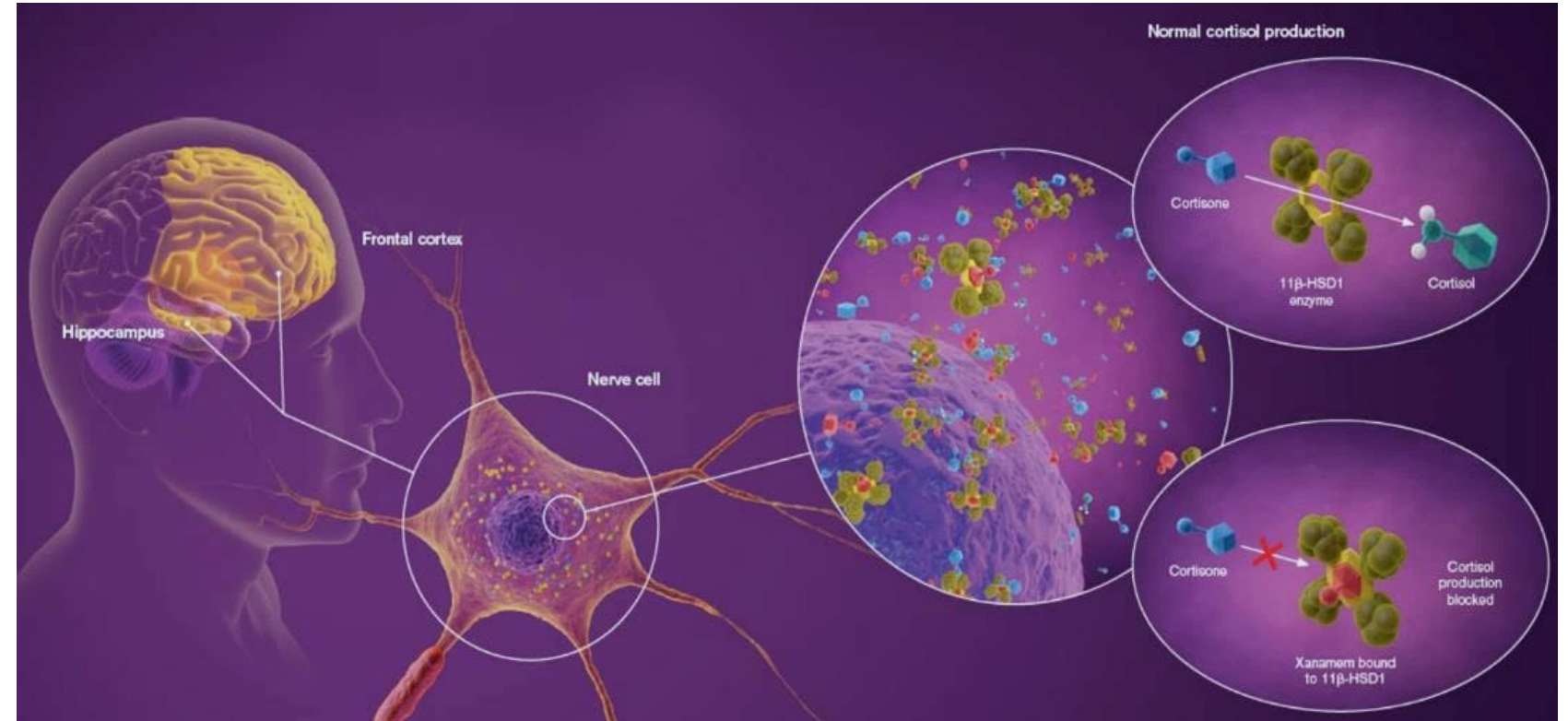
**PoC demonstrated in human trials**



**Strong safety profile**



**Excellent PK/PD profile**



**Xanamem - an efficacious, oral, brain penetrant, selective 11 $\beta$ -HSD1 inhibitor with a strong safety profile**

# Highlights: Demonstration of Xanamem's promising efficacy and safety

A significantly enhanced and growing dataset

|                                                                                                  |                                                                                    |                                                                                                                                                      |                                                                                                                            |
|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
|                 |  |  <b>Target Occupancy<br/>&amp; Homogenate<br/>Binding studies</b> |  <b>Comprehensive<br/>Data Analysis</b> |
| <i>Efficacy shown in Phase 1 clinical trial in healthy elderly patients (20mg Xanamem daily)</i> | <i>Phase 2 clinical trial in mild Alzheimer's disease (10mg Xanamem daily)</i>     | <i>Phase 1 Target Occupancy, &amp; Homogenate Binding Studies</i>                                                                                    | <i>QSP<sup>1</sup> and PK/PD<sup>2</sup> modelling incorporating all pre-clinical and clinical data</i>                    |
| ✓ <b>Completed</b>                                                                               | ✓ <b>Completed</b>                                                                 | ✓ <b>Progressing on schedule</b>                                                                                                                     | ✓ <b>Progressing on schedule</b>                                                                                           |

<sup>1</sup> Quantitative Systems Pharmacology  
<sup>2</sup> Pharmacokinetics/Pharmacodynamics

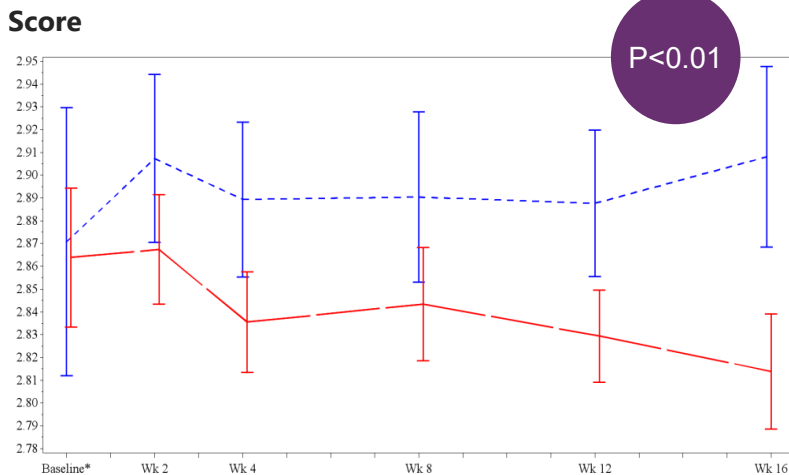
**Comprehensive review of Xanamem data near completion – updated clinical development plan well advanced**

# Significant cognitive efficacy signal achieved

Breakthrough XanaHES results demonstrate robust statistically significant cognitive efficacy improvement in multiple cognition domains - based on Cogstate Cognitive Test Battery

## Working memory (One Back Test)

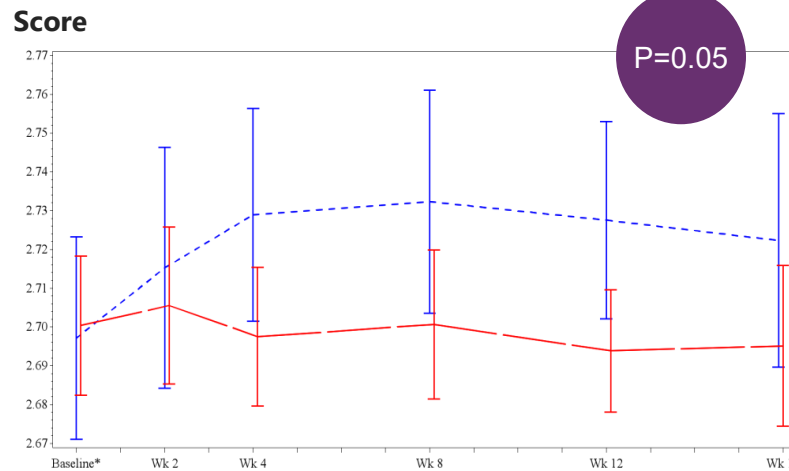
*Strongly statistically significant result*



**Rapid response, evident by week 4, and sustained response out to end of therapy (wk 12)**

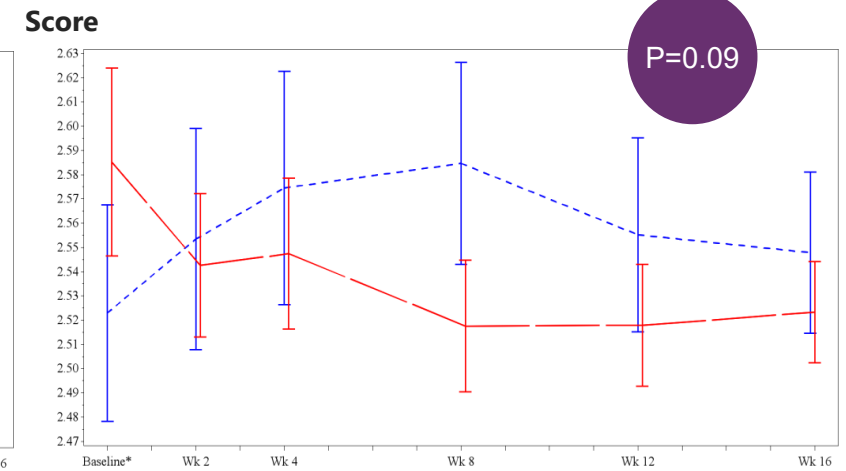
## Visual attention (Identification Test)

*Statistically significant result*



## Psychomotor function (Detection Test)

*Good trend to a positive result*



### Treatment Group

— Xanamem 30pts — Placebo 12 pts

**Efficacy results reflect high quality and consistent data in a small study population**

# Significant cognitive efficacy signal achieved

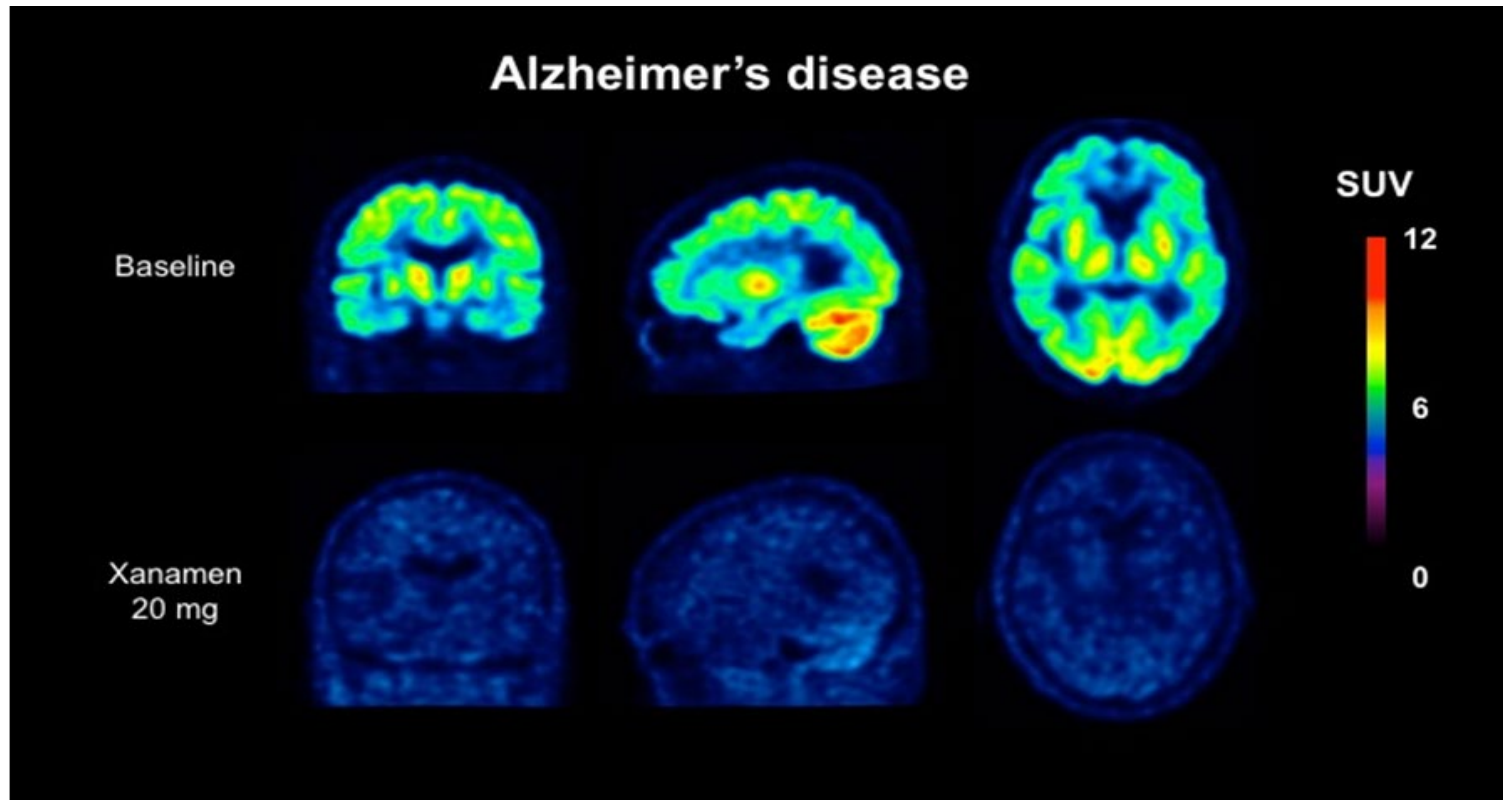
Cogstate Cognitive Test Battery evaluated six domains. Statistically significant cognitive improvement in three domains with significant effect size demonstrated. Rapid and sustained response achieved.

| Cognitive Evaluation (Test)                        | p value           |        |        | Treatment Effect Size: Cohen's d |                   |                   |                   |
|----------------------------------------------------|-------------------|--------|--------|----------------------------------|-------------------|-------------------|-------------------|
|                                                    | All               | Male   | Female | Week 2                           | Week 4            | Week 8            | Week 12           |
| Working Memory (One Back Test)                     | <0.01*            | <0.01* | 0.03*  | 0.64 <sup>#</sup>                | 0.78 <sup>#</sup> | 0.64 <sup>#</sup> | 0.83 <sup>Δ</sup> |
| Visual Attention (Identification Test)             | 0.05*             | 0.04*  | 0.60   | 0.19                             | 0.67 <sup>#</sup> | 0.62 <sup>#</sup> | 0.67 <sup>#</sup> |
| Psychomotor Function (Detection Test)              | 0.09 <sup>^</sup> | 0.94   | 0.13   | 0.47                             | 0.65 <sup>#</sup> | 1.12 <sup>Δ</sup> | 0.76 <sup>#</sup> |
| Paired Associate Learning (CPAL <sup>1</sup> Test) | 0.21              | 0.34   | 0.49   | 0.87 <sup>Δ</sup>                | 0.01              | 0.66 <sup>#</sup> | 0.08              |
| Memory (CPAL <sup>1</sup> – Delayed Test)          | 0.50              | 0.55   | 0.21   | 0.34                             | 0.23              | 0.06              | 0.48              |
| Visual Learning (One Card Learning Test)           | 0.92              | 0.41   | 0.64   | 0.11                             | 0.12              | 0.60 <sup>#</sup> | 0.19              |



## Target Occupancy study: positive confirmatory data

Phase I target occupancy study demonstrates that 5mg to 30mg Xanamen dosed for seven days significantly occupies the neuronal 11 $\beta$ -HSD1 enzyme throughout the brain (31 of 36 patients completed)



**50% to 85% occupancy,  
dependent upon brain  
region, dosage and study  
subject<sup>1</sup>**

**Additional ongoing cohorts at 10mg  
Xanamen with delayed PET imaging  
to confirm CNS half life**

**Phase I Target Occupancy supports Xanamen as a potent, orally bioavailable and brain-penetrant 11 $\beta$ -HSD1 inhibitor**

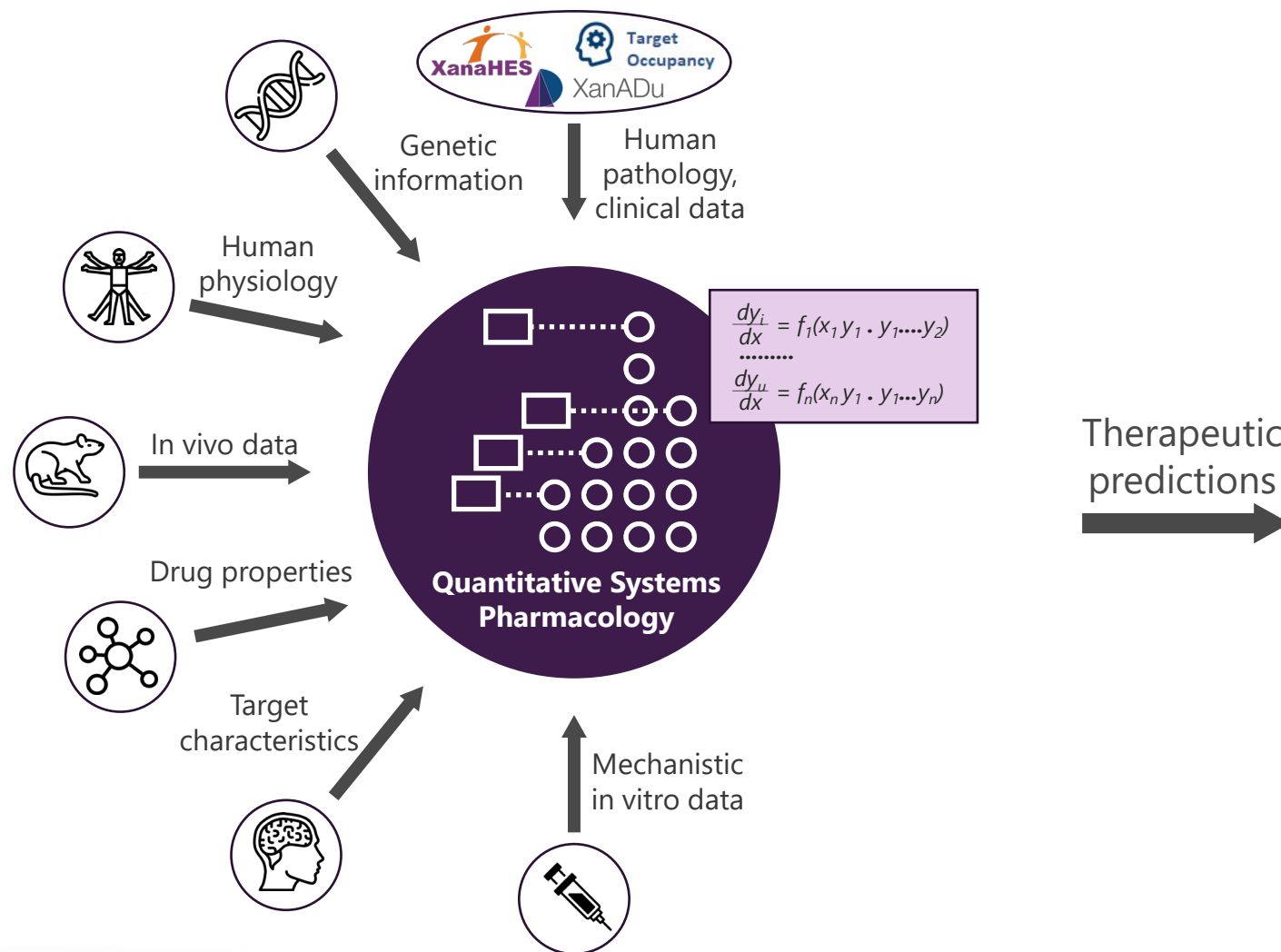
# Key outcomes from Xanamem studies

| <i>Xanamem dose</i>                                                                                          |                                                                                                                                             |             |
|--------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------|
|  <b>Cognitive Efficacy</b>   | Breakthrough results demonstrate a statistically significant clinical effect in improving cognition in healthy elderly patients             | 20mg        |
|  <b>Target Occupancy</b>    | Confirms Xanamem works as designed to penetrate the brain in concentrations that adequately inhibit the activity of 11 $\beta$ -HSD1 enzyme | 5mg - 30mg  |
|  <b>Cortisol inhibition</b> | Cortisol inhibition demonstrated in human trials                                                                                            | 10mg & 20mg |
|                                                                                                              | Statistically significant reduction in serum cortisol in human trial                                                                        | 20mg        |
|  <b>Safety</b>            | Strong safety profile demonstrated in human trials                                                                                          | 10mg & 20mg |



# Detailed data analysis in final stages

Quantitative Systems Pharmacology modelling and analysis underway



Analysis of entire dataset near completion

Conclusions will optimise dosing and patient characteristics for next series of clinical studies

# Strategic direction and next steps

Updated clinical development plan incorporating new Xanamem data supporting clinical development opportunities across multiple indications

## Enhanced clinical development strategy (in progress)

- **Comprehensive review** of all Xanamem data, new target indications, and potential funding options, to inform strategic direction
- **Clinical development plan** includes a study in:
  - Mild cognitive impairment due to Alzheimer's disease
- **Strategic development plan** includes ongoing evaluation into feasibility of studies in:
  - Cognitive impairment associated with schizophrenia, and
  - Cognitive impairment associated with diabetes.
- Proactive engagement with **key opinion leaders** and **relevant regulatory bodies**
- Potential **collaboration and partnership** discussions ongoing

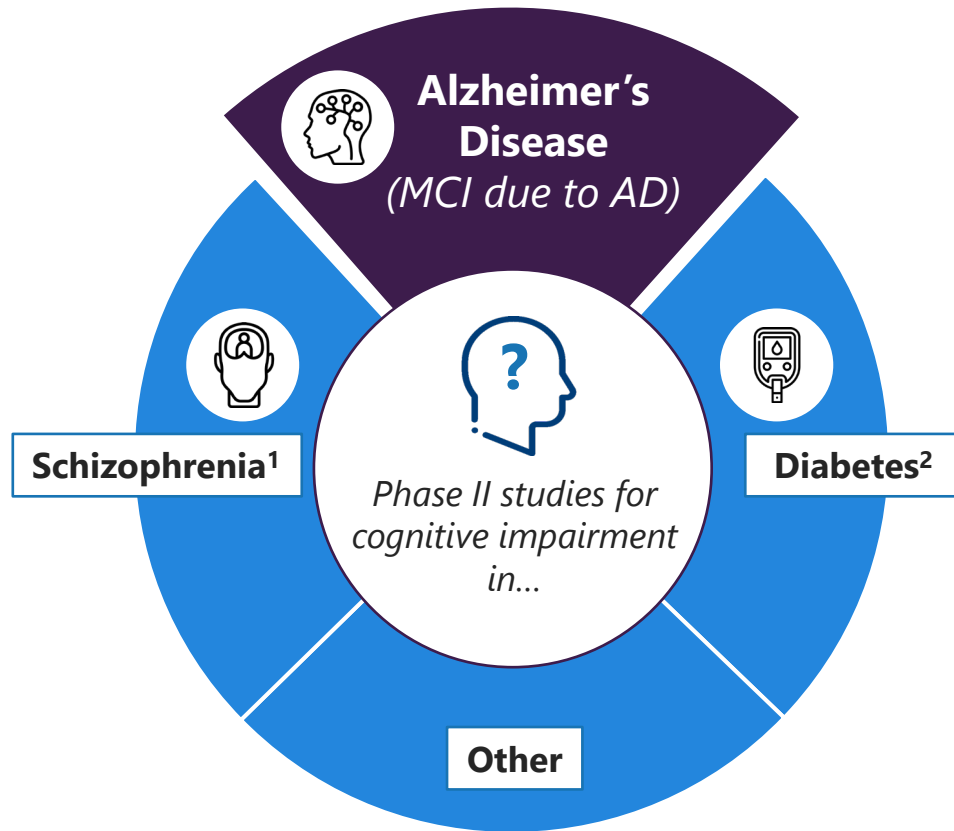
## Next steps (near future)

**Clinical studies  
expected to initiate  
in 2020/21**

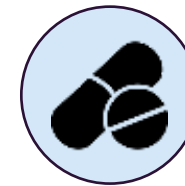
# Next series of Xanamem studies

Actinogen leveraging Xanamem development across multiple target indications

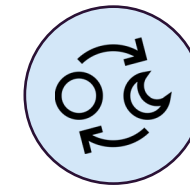
## A pipeline of potential opportunities



## Optimising study parameters



Dose



Dosing  
Regimen



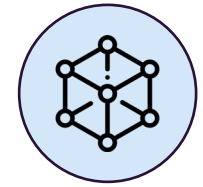
Treatment  
Duration



Patient  
Populations



Endpoints &  
Outcomes

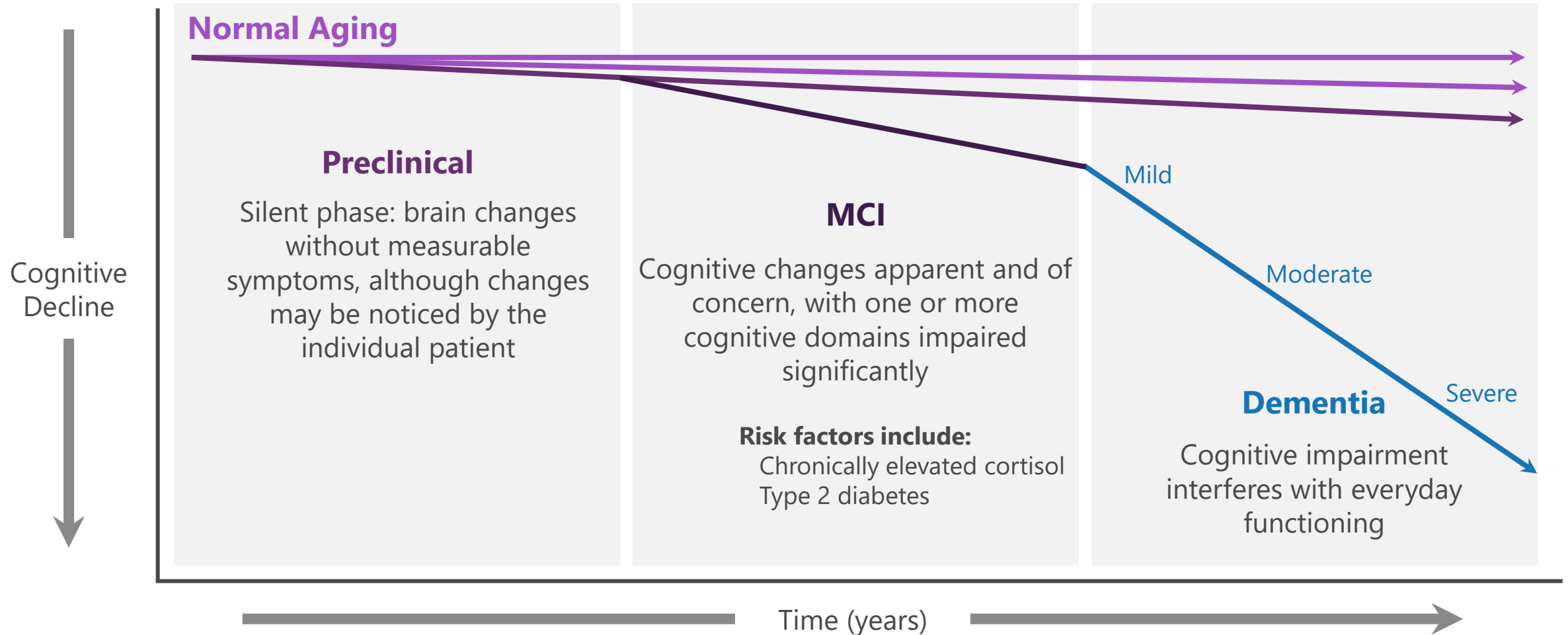


Stratification  
Factors



# Mild Cognitive Impairment (MCI) due to Alzheimer's disease

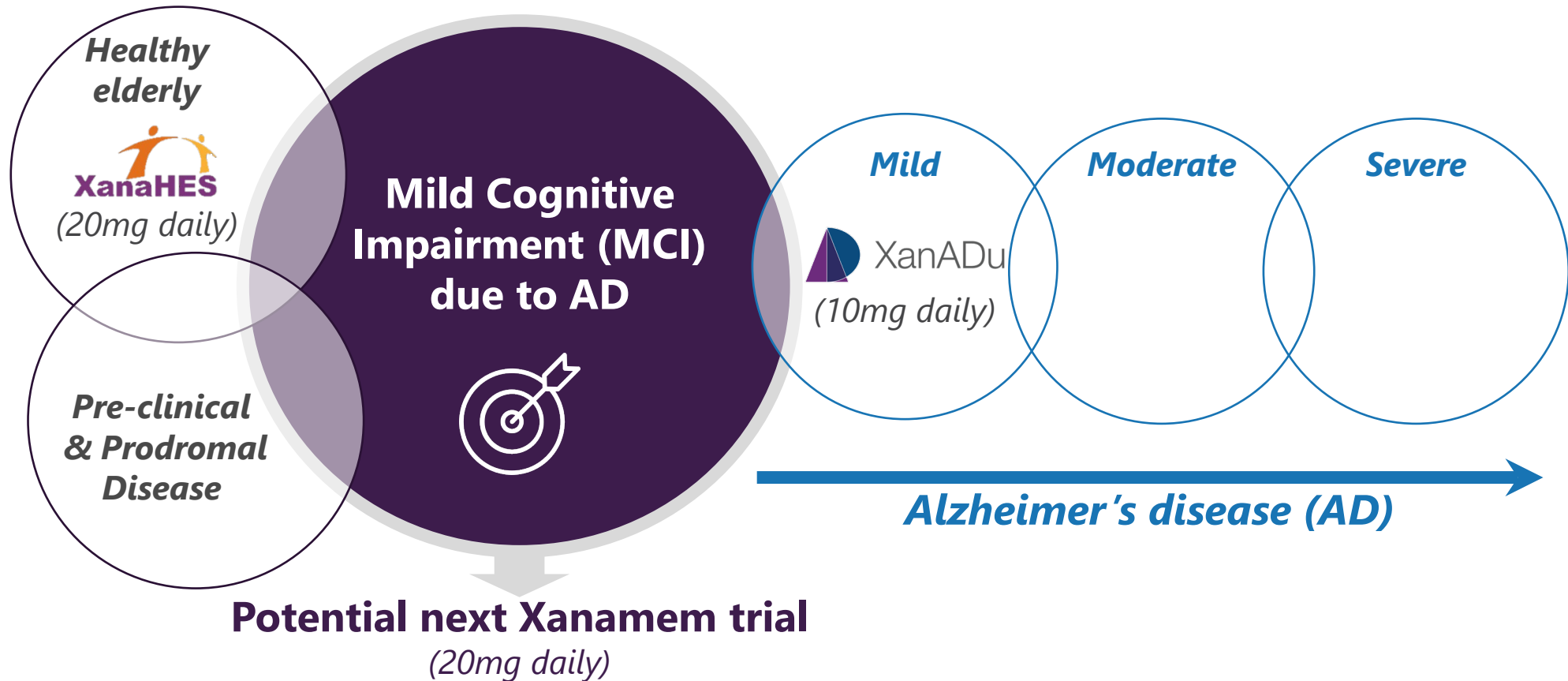
Everyone experiences slight cognitive changes during aging, with the progression to dementia becoming slowly apparent in everyday functionality and worsening over time as cognitive domains are impaired





# Alzheimer's disease - Mild Cognitive Impairment due to AD

Actinogen plans to target patients with Mild Cognitive Impairment due to AD (an early stage of the AD spectrum) as part of the next phase of studies, linking the XanaHES results with Alzheimer's disease



Study design to be confirmed and refined following discussions with the FDA and other regulators



# MCI due to Alzheimer's Disease

A large patient population significantly at risk of developing AD, with no approved therapy

|                             |                                                                                                                                                                                                                                    |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>MCI in AD</b>            | <ul style="list-style-type: none"><li>Patients with AD pathological changes, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and a mild but detectable functional impairment.</li></ul> |
| <b>Prevalence</b>           | <ul style="list-style-type: none"><li><b>~8% of &gt;65 years of age affected<sup>1</sup></b></li><li>~4.3m US patients, with a mild AD conversion rate of 10-15% p.a.</li></ul>                                                    |
| <b>Unmet need</b>           | <ul style="list-style-type: none"><li><b>No therapy currently available</b></li><li>MCI due to AD is a major drug development focus for pharma</li></ul>                                                                           |
| <b>Scientific rationale</b> | <ul style="list-style-type: none"><li>Chronically elevated cortisol levels are <b>a significant risk factor for developing AD</b> after presence of <math>\beta</math>-Amyloid plaques<sup>2</sup></li></ul>                       |
| <b>Synergistic study</b>    | <ul style="list-style-type: none"><li>Xanomem's differentiated mechanism of action indicates <b>potential synergy with other pipeline candidates</b></li></ul>                                                                     |
| <b>Outlook</b>              | <ul style="list-style-type: none"><li>Phase II trial in planning to demonstrate <b>Xanomem's pro-cognitive effects on a MCI due to AD patient population</b></li></ul>                                                             |





# Cognitive impairment due to diabetes

Diabetics are at increased risk of developing cognitive impairment and AD

|                      |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| At-risk population   | <ul style="list-style-type: none"><li>Elderly diabetics <b>have double the risk of developing cognitive impairment and dementia</b> over a non-diabetic population</li><li><b>Diabetics often present with chronically raised cortisol</b>, a risk factor for developing Alzheimer's disease</li></ul>                                                            |
| High prevalence      | <ul style="list-style-type: none"><li>The American Diabetes Association currently estimates <b>14.3 million diabetics &gt;65yrs (26.8% of the senior population) in the US<sup>1</sup></b></li></ul>                                                                                                                                                              |
| Scientific rationale | <ul style="list-style-type: none"><li><b>Clinical trial (Sandeep, 2004<sup>2</sup>; Edinburgh) in this population demonstrated a pro-cognitive effect of 11<math>\beta</math>-HSD1 inhibition</b></li><li><b>Pro-cognitive efficacy of Xanamem</b> 20mg daily demonstrated in healthy elderly volunteers in XanaHES, some of which had T2DM<sup>3</sup></li></ul> |
| Outlook              | <ul style="list-style-type: none"><li><b>Cognitive impairment associated with diabetes</b> is under evaluation by Actinogen into feasibility of new study</li><li><b>There is a strong likelihood of successfully demonstrating a similar pro-cognitive effect (seen in XanaHES) of Xanamem in an elderly diabetic population</b></li></ul>                       |





# Diversified Opportunity: Cognitive impairment due to schizophrenia

Significant unmet medical need with substantial pharma industry interest

|                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Cognitive impairment in schizophrenia</b> | <ul style="list-style-type: none"><li>• <b>Cognitive impairment is one of the most debilitating negative symptoms</b> in schizophrenia, affecting <b>~75% of patients<sup>1</sup></b></li><li>• Associated with poor treatment outcomes and patient reintegration into society - a major issue with ongoing patient management</li><li>• Potentially a <b>side-effect of current anti-psychotic therapy</b> (used to treat schizophrenia positive symptoms)</li></ul> |
| <b>Unmet medical need</b>                    | <ul style="list-style-type: none"><li>• <b>No therapy currently available</b> - huge unmet medical need with a <b>potential annual market of US\$3bn</b></li></ul>                                                                                                                                                                                                                                                                                                    |
| <b>Scientific rationale</b>                  | <ul style="list-style-type: none"><li>• <b>Good scientific rationale for cortisol</b> as a therapeutic target</li></ul>                                                                                                                                                                                                                                                                                                                                               |
| <b>Commercial interest</b>                   | <ul style="list-style-type: none"><li>• Significant biotech and pharma interest in developing drugs for schizophrenia and AD – 1/3 of large pharma companies have activities in both diseases</li></ul>                                                                                                                                                                                                                                                               |



# Investment summary

Actinogen is developing Xanamem for cognitive impairment associated with raised cortisol in neurological and metabolic diseases, with a primary focus on MCI due to Alzheimer's disease

- ✓ Xanamem – a **differentiated compound** (efficacious, oral, brain penetrant, selective 11 $\beta$ -HSD1 inhibitor) with a **validated novel mechanism of action** and **strong safety profile**
- ✓ XanaHES trial **achieved robust cognitive efficacy signal with Xanamem 20mg daily**. Results endorse the cortisol hypothesis and build on the positive pharmacodynamic (PD) and safety data from XanADu
- ✓ Next phase of Alzheimer's disease clinical development to **target patients with Mild Cognitive Impairment (MCI) due to AD** – building on the positive results from the recently completed XanaHES trial
- ✓ Investigate further Xanamem's mechanism of action across **multiple indications**, including cognitive impairment associated with schizophrenia, diabetes, and other conditions
- ✓ **Study parameters optimised, including dose**, following latest trial results and quantitative systems pharmacology analysis
- ✓ Exploring potential **partnership and collaboration funding** opportunities
- ✓ Xanamem development targeting **huge unmet medical needs** associated with **unsustainable healthcare costs**

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# APPENDIX: Background information



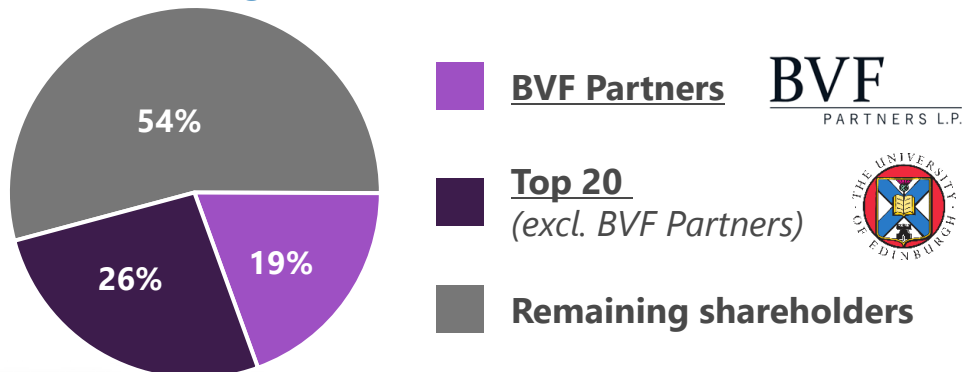
# Corporate overview ASX:ACW

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

## Share price performance



## Key shareholding metrics



## Board of Directors



**Dr. Geoff Brooke**

**Chairman**

MBBS; MBA

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



**Dr. Bill Ketelbey**

**CEO & MD**

MBBCh; FFPM; MBA; GAICD

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



**Dr. George Morstyn**

**Non-executive director**

MBBS; PhD; FRACP; MAICD

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



**Mr. Malcolm McComas**

**Non-executive director**

BEC, LLB; FAICD; SF Fin

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



# Advisory Boards

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

## Clinical Advisory Board (Alzheimer's disease)

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



**Prof. Craig  
Ritchie** *Chair*



THE UNIVERSITY  
of EDINBURGH



**Prof. Colin  
Masters** *AO*



THE UNIVERSITY OF  
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The Royal  
Melbourne Hospital

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FLOREY

INSTITUTE OF NEUROSCIENCE & MENTAL HEALTH



**Prof. Jeffrey  
Cummings**



Cleveland  
Clinic



**Prof. Jonathan  
Seckl**



THE UNIVERSITY  
of EDINBURGH



**Prof. Brian  
Walker**



Newcastle  
University



**Prof. Scott  
Webster**

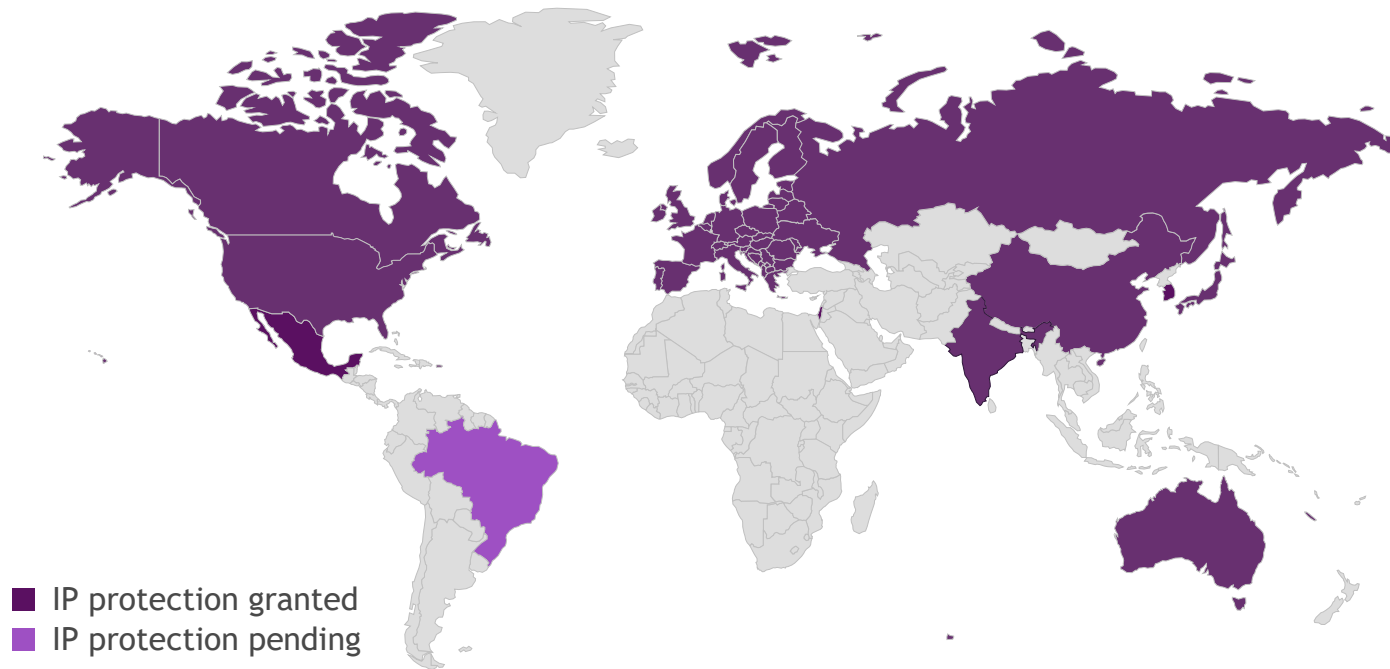


THE UNIVERSITY  
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# IP protection

Actinogen maintains a broad composition of matter patent estate, with key patents granted in all major target markets

## Patent overview



- Actinogen's patent portfolio **covers a broad range of neurological and metabolic diseases** including Alzheimer's disease
- Xanomem **patents granted in key markets** that account for over 90% of the global Alzheimer's market
- **Additional patents and patent extensions being actively prosecuted**

**>90%** of the global Alzheimer's disease market

# Xanamem

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



## Well researched

>15 years of R&D completed



## Well tolerated

Dosed >200 patients with strong clinical safety, toxicity & PK/PD<sup>1</sup> profile



## Well protected

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



## Validated in Alzheimer's model

Symptomatic and disease modifying effects (in vivo) and demonstrated effect of cortisol hypothesis (in humans)

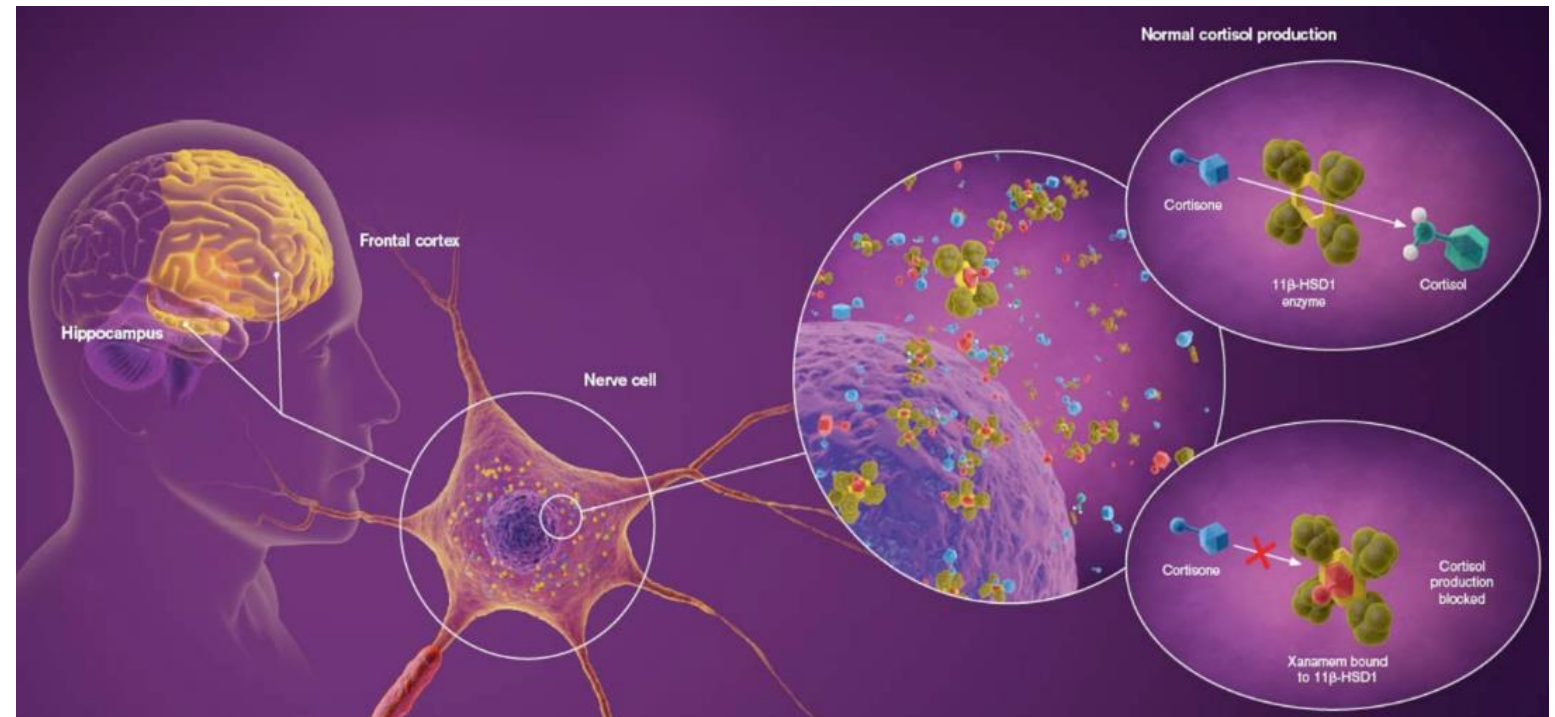


## Potential in other diseases

Cognitive impairment in schizophrenia and diabetes, and others with associated raised cortisol

## Differentiated mechanism of action:

Highly selective 11 $\beta$ HSD1 inhibitor, reducing excess cortisol production in the brain

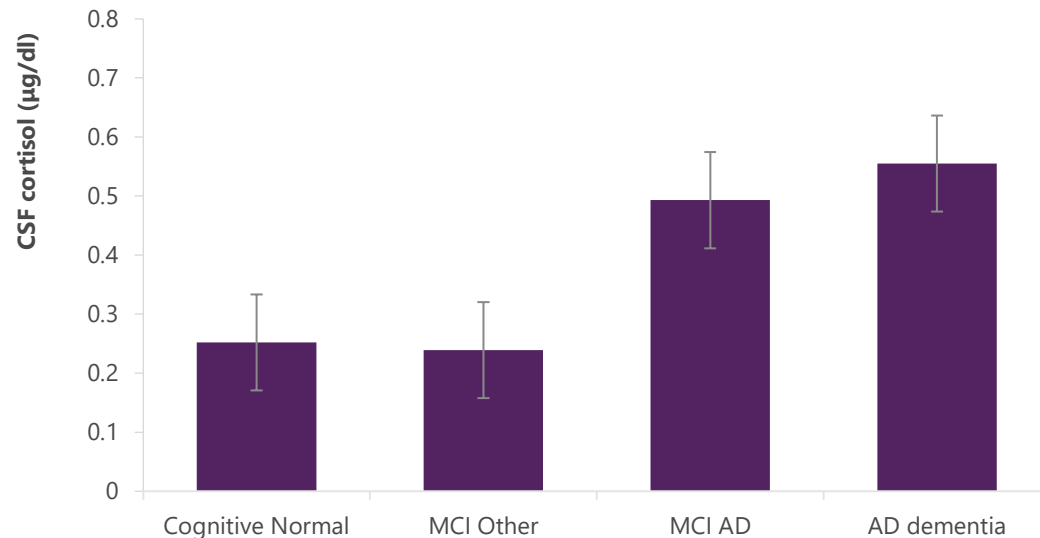


**Xanamem is a novel, first-in-class, potent, orally bioavailable and brain-penetrant 11 $\beta$ -HSD1 inhibitor**

# Alzheimer's strategic focus underpinned by medical research

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

## Raised cortisol associated with Alzheimer's disease<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>

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

AIBL study<sup>3</sup> demonstrates **that 50% of those aged 65+ have raised cortisol levels**

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

1. MCI: mild cognitive impairment; AD: Alzheimer's Disease

2. Recent studies also support the association between cortisol and cognitive impairment associated with neuroendocrine dysfunction

3. Plasma Cortisol, Brain Amyloid- $\beta$ , and Cognitive Decline in Preclinical Alzheimer's Disease: a 6-Year Prospective Cohort Study. Pietrzak et al., 2017. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2:45-52

# Market dynamics of Alzheimer’s disease

MCI due to AD and Mild AD present a compelling commercial opportunity for Actinogen to target

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

| Cognitively normal                     | Subjective memory decline | Cognitive and functional decline fulfilling dementia |             |           |
|----------------------------------------|---------------------------|------------------------------------------------------|-------------|-----------|
| At-risk                                | MCI due to AD             | Mild AD                                              | Moderate AD | Severe AD |
| 15.5m <sup>3</sup> -26.9m <sup>4</sup> | ~4.3m                     | ~1.7m                                                | ~2.3m       | ~1.7m     |

Upside potential for earlier use

Key focus

>US\$13.7bn

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

Source: Drugs.com, Biogen, Roche, Datamonitor, Alzheimer’s Association, Bio-Link  
MCI: Mild Cognitive Impairment; AD: Alzheimer’s disease  
1. Target market statistics expected in 2020, based on the current US treatment landscape. 2. Sales in 2036. Case assumes: (1) Launch: US 2027, EU5, JP and ROW 2028; (2) Penetration: 30% of mild AD and MCI markets in 5 years, sustained for 3 years with patent extension; (3) Pricing: US – US\$24/day gross (US\$19/day net), ROW: 50% of US price  
3. Biogen 2015 27% >65y/o Aβ+ 4. Raised cortisol in 50%>65y/o

## 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

# Significant upside potential, underpinned by recent deals

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

