



# Strategic Update & Investor Presentation

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November 10, 2021

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Actinogen is a neurotherapeutics developer realising a revolutionary therapy **so neurology patients can live their best lives**

CTscan

Sc 11  
FFEM  
SI 19  
Diffuse axonal injury

MRI



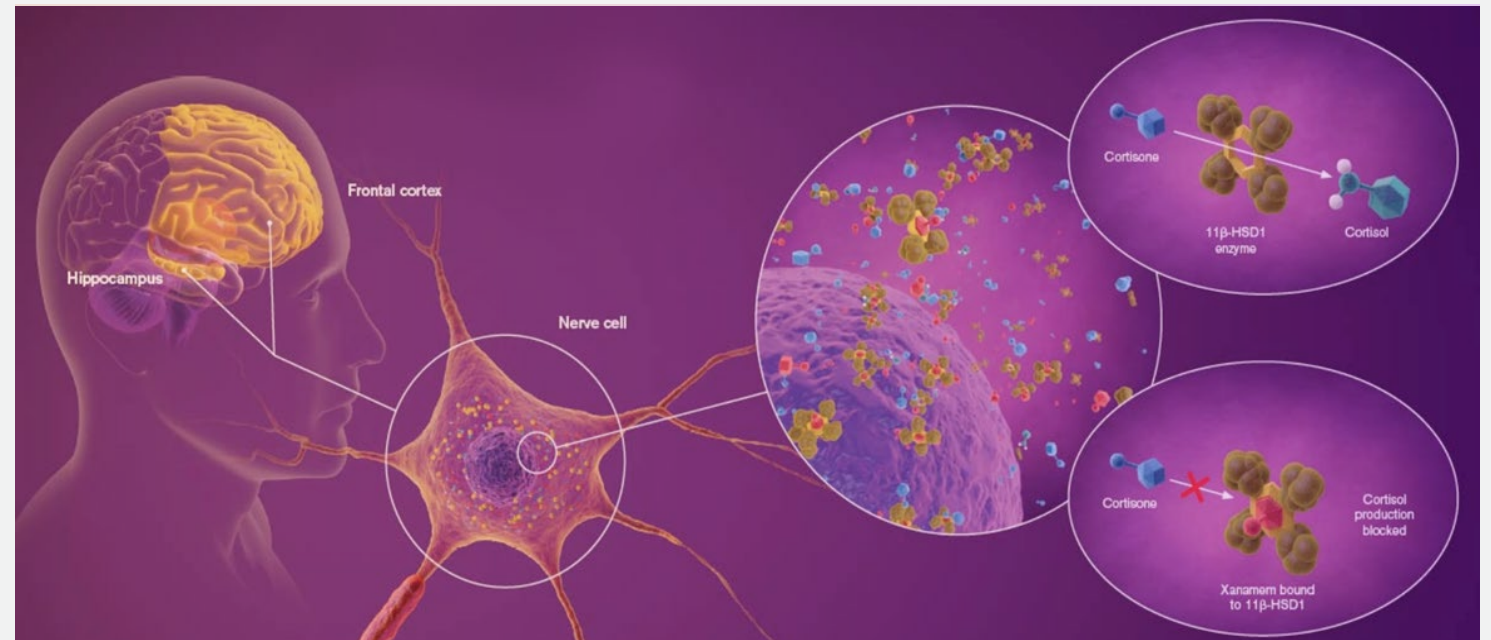
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T1  
T2  
FLAIR  
T1 contrast



# Xanamem: oral treatment and novel mechanism

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



1. Xanamem® is a CNS (Central Nervous System) penetrant small molecule based on human PET evidence and 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

# Actinogen snapshot

Actinogen Medical (ASX:ACW) is developing a novel oral treatment with rapid onset of clinical activity to address a range of central nervous system (CNS) diseases



**Favourable pharmaceutical properties**

- ✓ Demonstrated target engagement in brain and HPA axis in human trials
- ✓ Low dose,  $\leq 10\text{mg}$
- ✓ Low drug-drug interaction potential



**Substantial clinical data**

- ✓ >250 subjects or patients safely treated
- ✓ Large Phase 2 safety database with 12 weeks therapy (N=185)
- ✓ Cognitive enhancement activity shown in healthy older volunteers



**Attractive first target indications and rationale**

- ✓ Strong cortisol rationale for treatment of early stages of Alzheimer's Disease
- ✓ Strong cortisol rationale for multiple symptom domains of Fragile X syndrome
- ✓ Strong cortisol rationale for multiple other indications



**Protected and funded**

- ✓ Molecule in-licensed from U Edinburgh in 2014
- ✓ Comprehensive patents in place<sup>1</sup>
- ✓ Cash A\$13.3M at 30 September 2021 including tax credit received

# Strong Leadership and Management

Extensive drug development and commercial experience

## Experienced 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 Ventures, Chairman of Cynata Therapeutics, Board Member of Acrux



**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



**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

## ...with a talented management team in place



**Dr. Steven Gourlay**  
CEO & MD  
MBBS; FRACP; PhD; MBA



- 30+ years experience in development of novel therapeutics
- Former founding CMO at US-based Principia Biopharma Inc



**Jeff Carter**  
Chief Financial Officer  
B. Fin Admin;  
M. App. Fin; CA



**Tamara Miller**  
Vice President Drug Development & Strategy  
M.Med Sci; BSc; MSc;  
PMP; CPPM



**Therese Russell**  
Head of People & Infrastructure



**Dr. Christian Touli**  
Head of Business Development  
PhD; GAICD

See full team and bios at:  
<https://actinogen.com.au/our-company/#about-us>

# Esteemed Advisory Boards

World-leading, premier academics involved in the development of Xanamem

## Xanamem Clinical Advisory Board

Deeply experienced in Alzheimer's Disease drug development



**Prof. Craig Ritchie**

Chair



- World-leading authority on dementia; senior investigator on 30+ drug trials
- Chair of the Scottish Dementia Research Consortium; Professor of the Psychiatry of Ageing' Director of the Centre for Dementia Prevention (University of Edinburgh)



**Prof. Colin Masters**  
AO



- 35+ years research on Alzheimer's Disease and other neurodegenerative diseases
- Laureate Professor of Dementia Research and Head, Neurodegeneration Division at The Florey Institute (UniMelb)



**Prof. Jeffrey Cummings**



- World-renowned Alzheimer's researcher and leader of clinical trials
- MD, ScD; Founding Director of the Cleveland Clinic Lou Ruvo Center for Brain Health
- Recognised for his work through various awards



**Prof. Jonathan Seckl**



- Undertaken extensive research in endocrinology
- Senior VP at the university of Edinburgh; Chaired Panels for MRC, Innovate UK and Wellcome Trust
- MBBS UCL, PhD (London)



**Prof. Brian Walker**



- 20+ years research in the area of disease
- Extensive experience advising for pharmaceutical R&D
- Pro Vice Chancellor for Research Strategy & Resources at Newcastle University, UK



**Prof. Scott Webster**



- Chair of Medicines at the Centre of Cardiovascular Science, University of Edinburgh
- Former positions across both biotech and academia
- Founder and Chief Scientific Officer at Kynos Therapeutics

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# ACW stock performance 12 months

## Share price chart at 4 Nov 2021

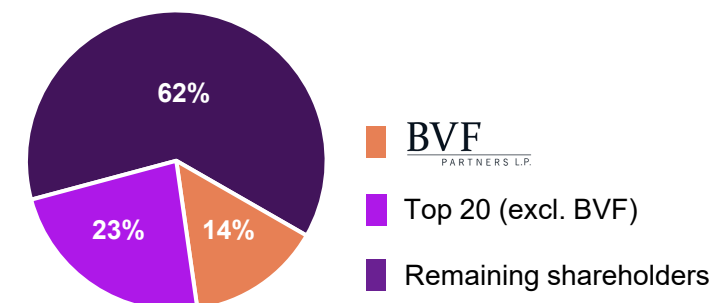


## Trading Information

52 week high	A\$0.195
52 week low	A\$0.019
Number of shares	1,660.6M
Market capitalisation (26 Oct 2021)	A\$270M
Net cash at 30 Sep	A\$13.3M

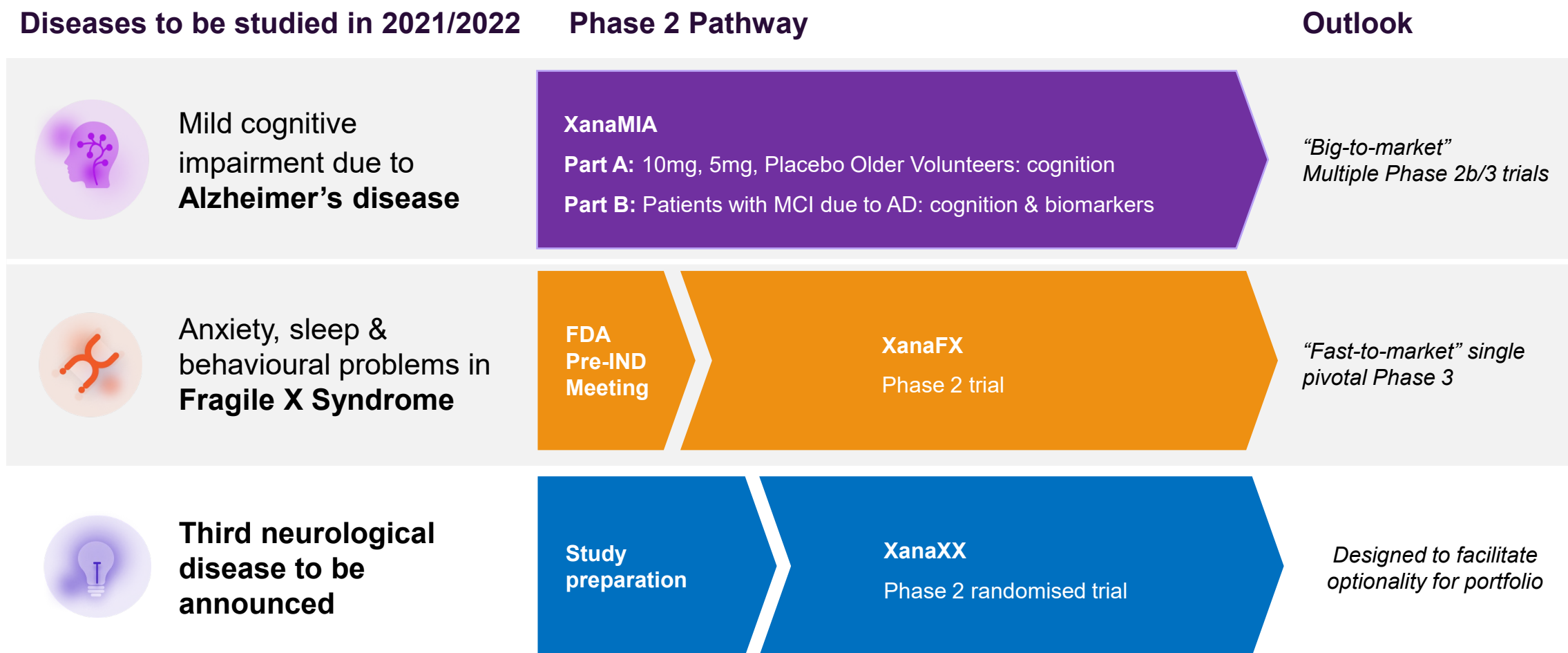
## Major Shareholders

BVF Partners	14.4%
Steven Gourlay	3.8%
Edinburgh Technology Fund	2.9%





# Xanamem Clinical Development Pipeline





Status: Analysis

# Alzheimer's Disease

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

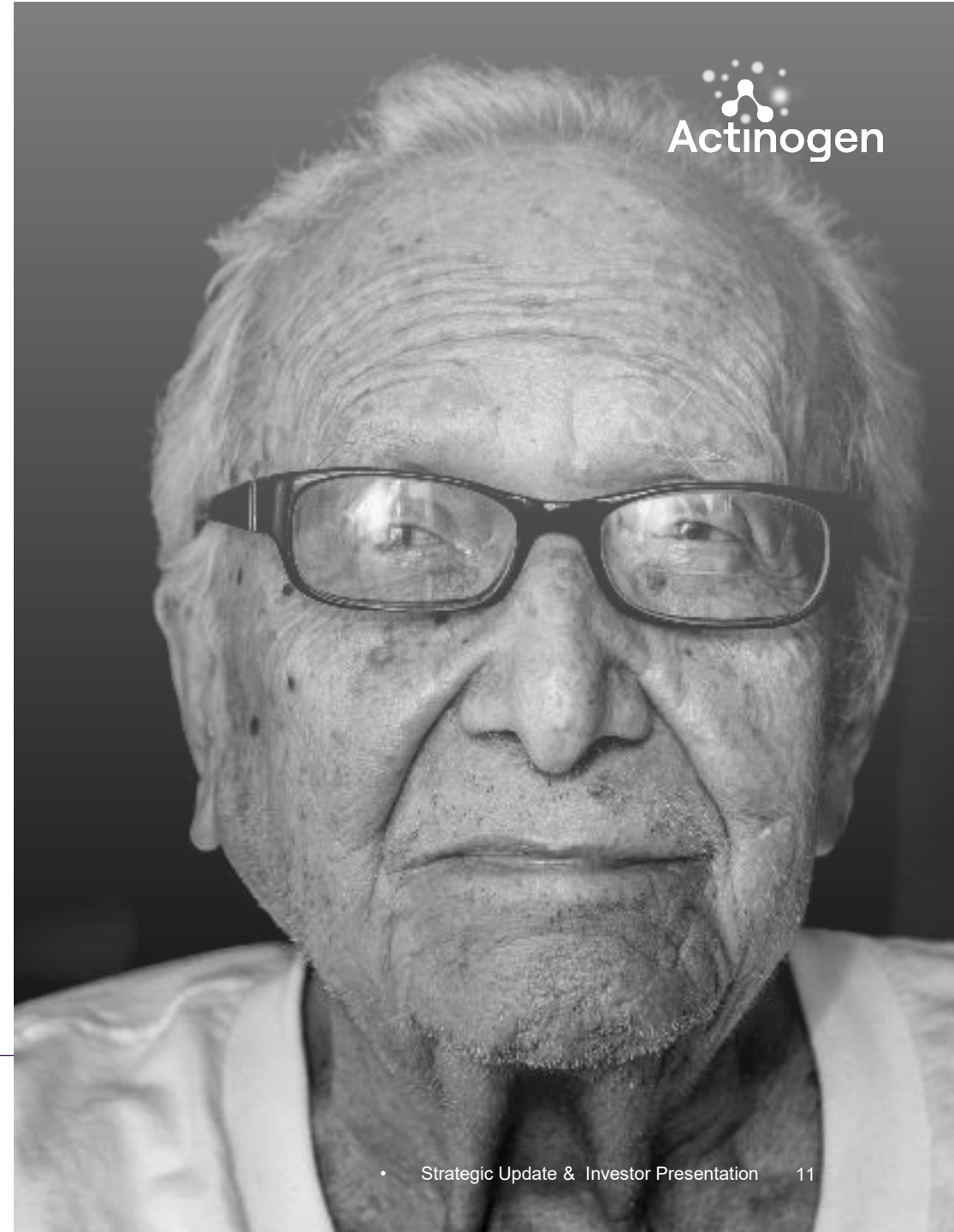


MRI

# Science Behind the Xanamem AD Program

- ✓ Cortisol is toxic to monkey brain cells<sup>1</sup>
- ✓ Cortisol impairs animal cognition<sup>2</sup>
- ✓ Cortisol & hippocampal volume/memory<sup>3</sup>
- ✓ Higher blood cortisol & cognitive decline<sup>4</sup>
- ✓ Higher CSF cortisol & cognitive decline<sup>5</sup>
- ✓ 11 $\beta$ -HSD1 Alzheimer's mouse model<sup>6</sup>
- ✓ Xanamem & improved human cognition<sup>7</sup>

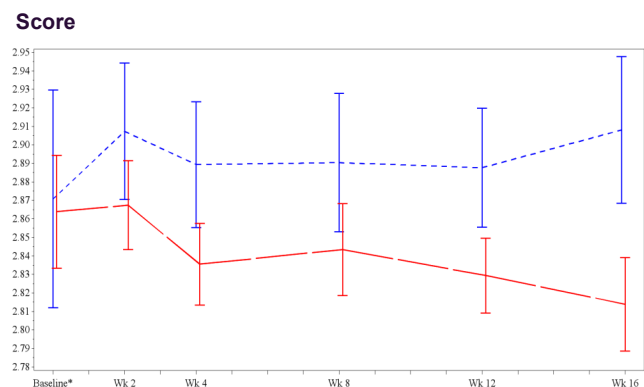
1. Implant in hippocampus, Sapolsky et al. 1990; increased amyloid proteins, Green et al. 2006
2. Literature review, Ouanes et al. 2019
3. Human study with MRI and cognitive assessment, Lupien et al. 1998
4. Morning cortisol & cognitive decline, Cernansky et al. 2006; Pietrzak et al. 2017
5. Longitudinal human study with multivariate modelling, Popp et al. 2015
6. 11 $\beta$ -HSD1 inhibition reduced amyloid and cognitive decline, Sooy et al. 2015
7. Xanamem placebo-controlled trial working memory & attention (Actinogen data on file)



# Cognitive improvement demonstrated

Phase 1 XanaHES study demonstrated statistically significant cognitive efficacy signal in multiple cognition domains based on Cogstate Cognitive Test Battery as early as 2 weeks<sup>1</sup>

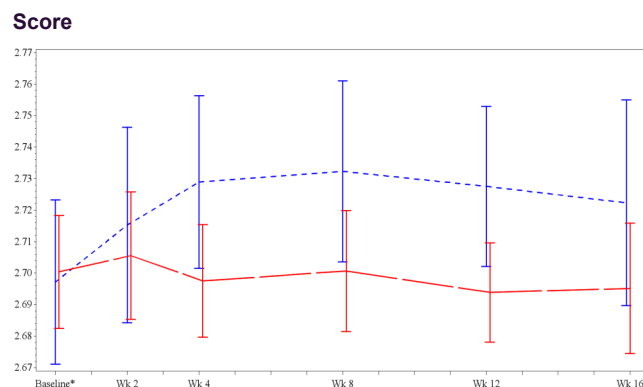
Treatment Group — Xanamem 30pts — Placebo 12 pts



P<0.01

**Working memory (One Back Test)**

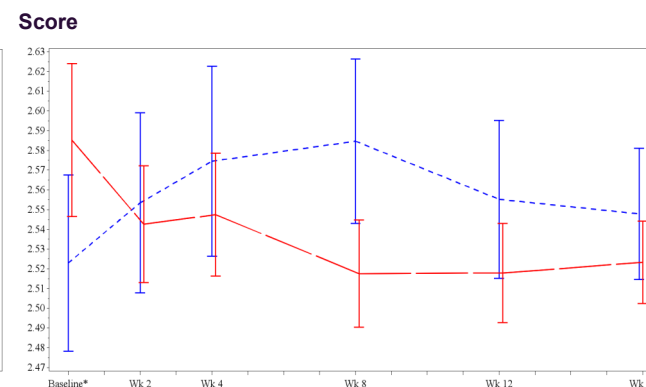
Strongly statistically significant result



P=0.05

**Visual attention (Identification Test)**

Statistically significant result



P=0.09

**Psychomotor function (Detection Test)**

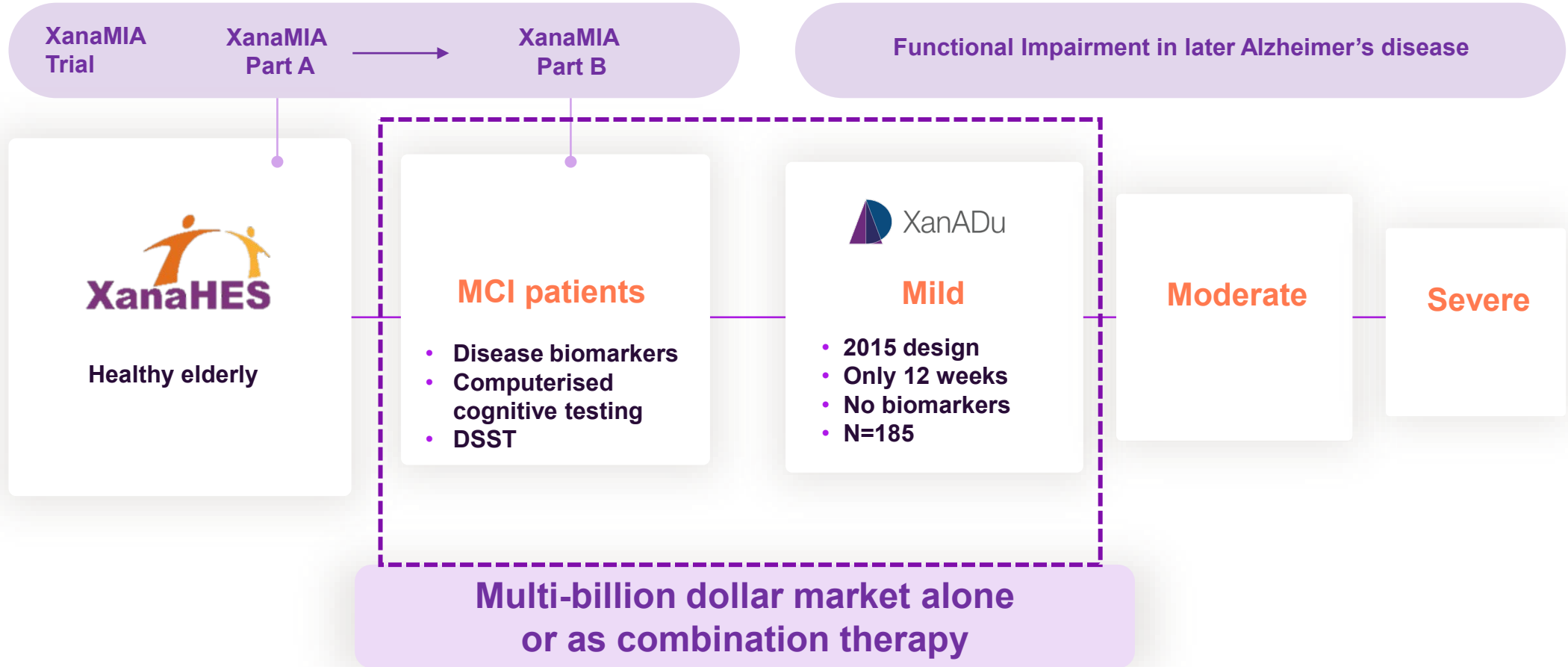
Good trend to a positive result

Large effect sizes seen in working memory and attention, trends in other domains

1. XanaHES Phase 1 clinical trial treated healthy elderly patients with 20mg Xanamem daily (n=30 active, n=12 placebo). All values are the means of observed data. p values were calculated with an ANCOVA (analysis of covariance) model using Baseline values as a covariate.



# Bridging Phase 1 cognition data to patients





# XanaMIA Phase 1b/2 trial data in 2022 & 2023

Targeting the first stages of Alzheimer's Disease

## XanaMIA - Part A

**H12022: minimum effective dose on cognition**

- **Healthy older subjects** - with normal cognition, ≥50 years of age (same as XanaHES trial)
- **Sensitive endpoints and testing criteria** - highly sensitive cognition tests (Cogstate, iDSST)
- DSST used for vortioxetine **regulatory cognitive** claim
- **Dose ranging** - 5mg, 10mg vs. placebo

## XanaMIA - Part B

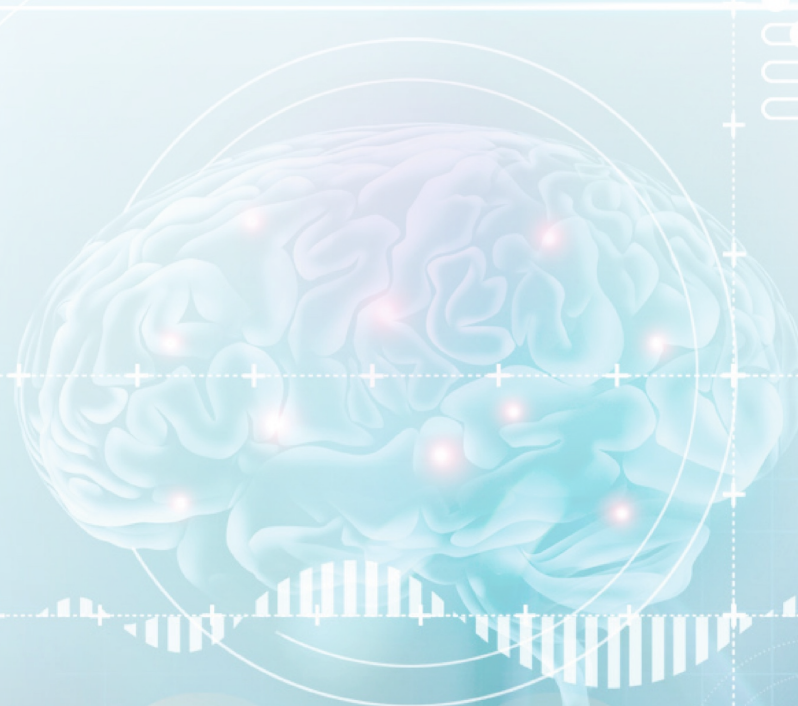
**2023: disease-modifying potential on biomarkers**

- Targeting subjects with **mild cognitive impairment** due to Alzheimer's disease (using positive serum biomarkers)
- Measuring disease-modifying potential with change in **Alzheimer's Disease biomarkers**
- **One or more** doses depending on Part A



# Fragile X syndrome

An inherited disorder caused by the FMR1 mutation on the X chromosome with no approved treatments



# Fragile X Syndrome has high unmet medical need



## Unmet medical need

- Commonest genetic cause of intellectual disability, predominantly males
- Management of FXS is often complex, with **life-long treatment** required for patients



## Strategic benefits

- Xanamem in FXS has been awarded **Rare Paediatric Disease Designation**, and eligible for **Orphan Drug** Designation
- **Broadens range of partners** in orphan space



## Fast-to-market path

- Moderate sized, **comprehensive proof-of-concept** Phase 2
- Anticipate **single Phase 3** for approval



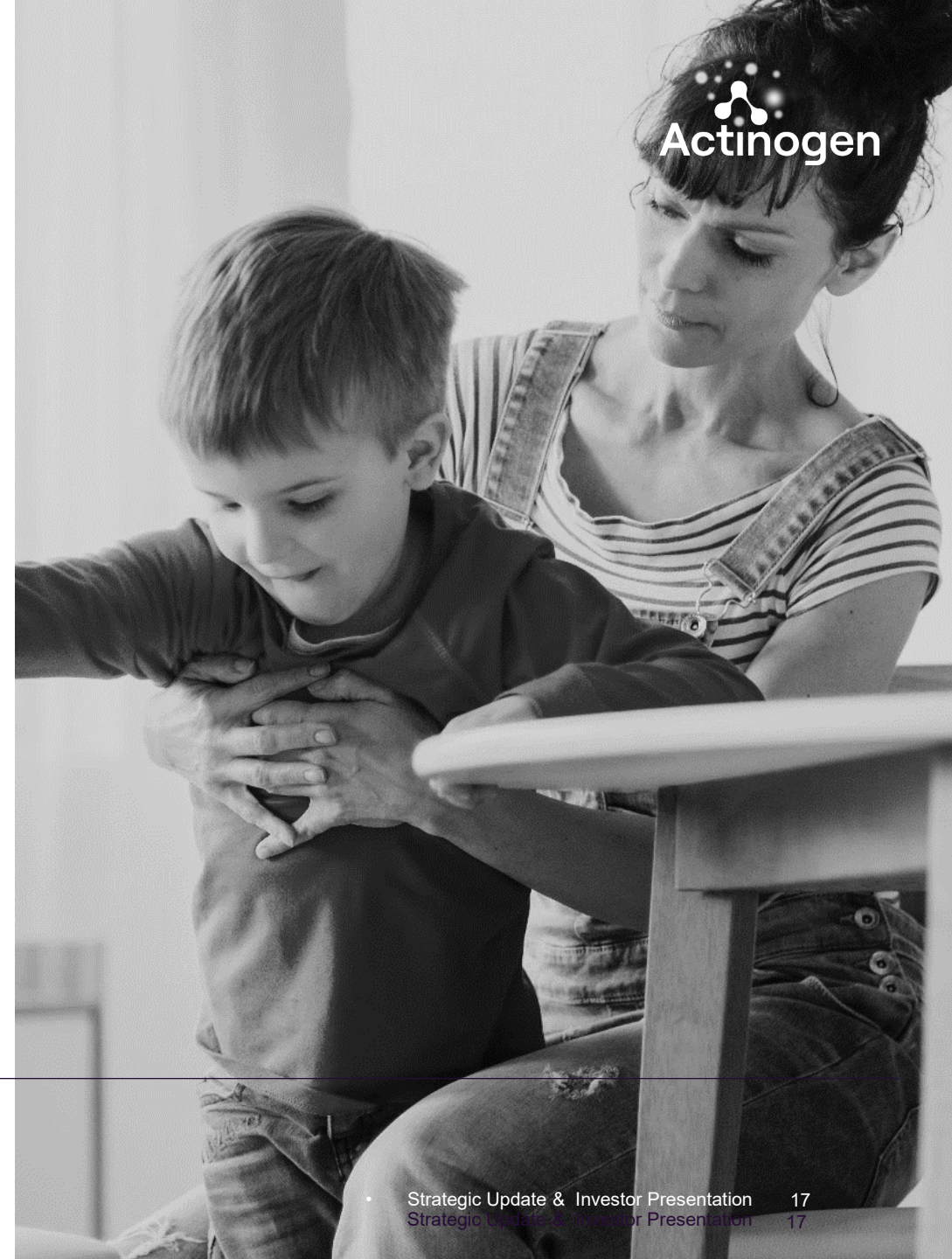
## Valuable commercial opportunity<sup>1</sup>

- Estimated **global market size of ~US\$250M**
- Related indications such as Autism Spectrum Disorder
- **Priority Review Voucher value ~US\$100-125M**



# Science Behind the Xanamem FXS Program

- ✓ Elevated blood cortisol in patients<sup>1</sup>
- ✓ Elevated cortisol & human symptoms<sup>2</sup>
- ✓ Glutamate linked to cortisol response<sup>3</sup>
- ✓ FMR1 KO mice show raised cortisol<sup>4</sup>
- ✓ Elevated 11 $\beta$ -HSD1 in FXS mouse<sup>5</sup>
- ✓ 11 $\beta$ -HSD1 Fragile X mouse model<sup>6</sup>

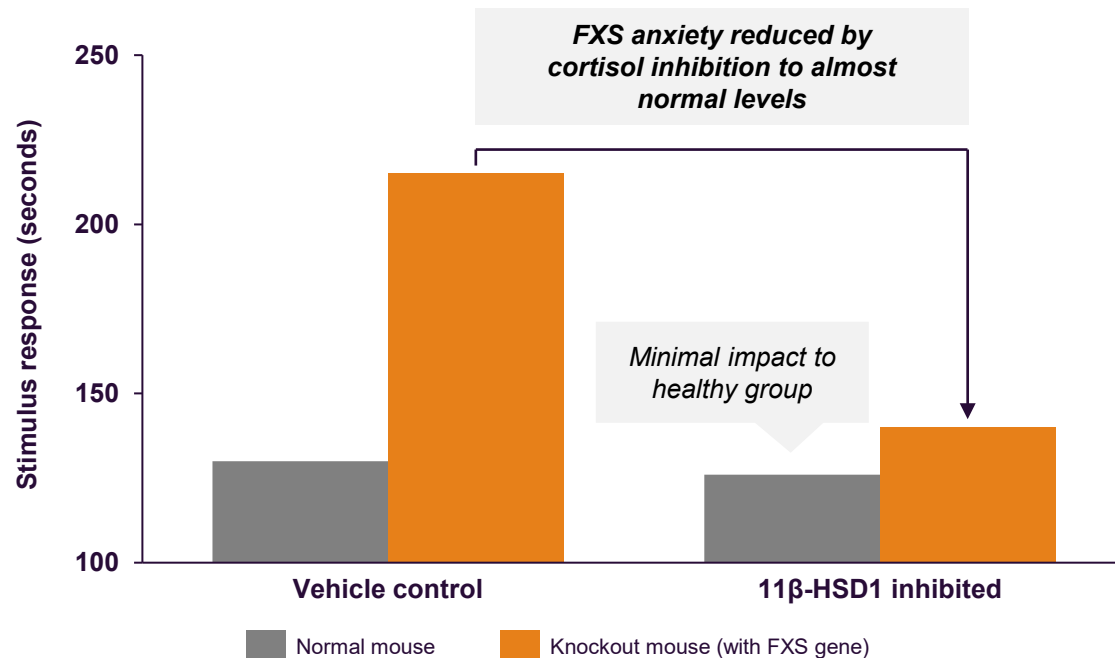


1. Hessler et al. 2002; Wisbeck et al. 2000  
2. Elevated cortisol correlates with symptoms, Hessler et al. 2002; Hardiman & Bratt 2016  
3. Mouse FMR1 mutation model of Fragile X & glutamate, cortisol mechanism Ghiliani et al. 2015  
4. Mouse cortisol (corticosterone), Lauterborn et al. 2004  
5. FMR1 deficiency promotes age-dependent alterations in the cortical synaptic proteome, Tang et al., 2015  
6. Normalisation of anxiety with 11 $\beta$ -HSD1 inhibition, Vanderklisch & Francesconi 2019



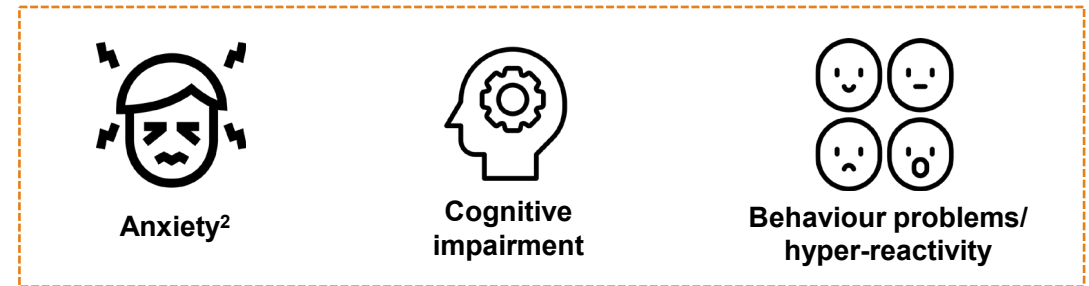
# Xanamem may treat multiple symptom domains in FXS

## Normalisation of anxiety in the FXS KO mouse<sup>1</sup>



## Symptoms of Fragile X syndrome are all potentially amenable to Xanamem therapy

### XanaFX trial target symptoms



Three icons are shown within a dashed orange box, representing target symptoms for the XanaFX trial:

- Anxiety<sup>2</sup>**: Icon of a person's head with lightning bolts and a sad expression.
- Cognitive impairment**: Icon of a head with a gear inside.
- Behaviour problems/hyper-reactivity**: Icon of four faces showing different expressions (happy, neutral, sad, surprised).

### Other FXS symptoms potentially amenable to Xanamem therapy



Three icons are shown below the dashed box, representing other symptoms potentially amenable to Xanamem therapy:

- Sleep problems**: Icon of a person in bed.
- Learning disabilities**: Icon of a person reading a book.
- Speech and language deficits**: Icon of a person's head with a speech bubble and sound waves.

1. Pre-clinical FMR1 knock-out mouse model using BVT 2733 as the 11β-HSD1 inhibitor showed highly significant results (\*\*p<0.0001). Normal mouse is a wild-type mouse. (Source: Vanderklish PW. 2019. Compounds for treatment of emotional/psychological symptoms in fragile x syndrome, WO 2019/075394 A1.)  
 2. ~90% of FXS patients suffer symptoms of anxiety

# Summary and Outlook



MEDICAL REPORT  
02-08-38 : MALE



02 : 43 : 080  
: 586 : 89 : 403  
: 253 : 684 : 01  
: 99 : RP\_809

# Significant value upside for Actinogen

## Accelerate clinical development

- Commence Fragile X Syndrome trial
- Expand pipeline with third Phase 2 program
- Create optionality for development and partnerships

## Forward planning

- Scale up and optimise manufacturing to prepare for commercially viable, large scale production
- Ancillary clinical and nonclinical studies

## Value from partnerships, peer companies



### Pharma/biotech engagement

- Actively engaging with large and mid-size potential partners



### Priority review and PR voucher

- Priority review granted by FDA
- PRVs recently traded for US\$100M- US\$125M



### High peer AD company valuations suggest near term growth potential

- Peer companies in phase 2 or 3 for AD: valuations ~US\$250M-\$3.4B<sup>1</sup>

1. Vivoryon Therapeutics, phase 2a/b AD lead asset (EURONEXT Amsterdam: 408 euro / ~US\$500m); Athira Pharma, phase 2 AD lead asset (NASDAQ GS:~US\$583m); Cortexyme, phase 2b/3 AD lead asset (NASDAQ GS:~US\$490m) and same drug in phase II for periodontal disease and Parkinson's disease; Cassava Sciences, AD lead asset phase 2 asset (NASDAQ GS:~US3.4B); Annovis Bio, early phase 2 data AD, PD (NASDAQ US\$249m). All companies' value primarily attributed to their lead AD asset. Market capitalisations as of November 5 2021.

# Next steps and key catalysts

## ❑ Clinical trials to read out in 2022 and 2023

### XanaMIA

- Part A cognition data H1 2022
- First disease biomarker data possible H2 2022
- Part B patient biomarker/cognition data 2023

### XanaFX

- Commencing in 2021, results 2023

## ❑ Pursue other high priority indications

- Announce **third disease Phase 2** program 2021, results 2023
- Leverage academic, grant collaborations

## ❑ Publications and scientific presentations

- Focus on PET and other peer-review publications