



## ASX ANNOUNCEMENT

### Actinogen CEO presents at JP Morgan Annual HealthCare Conference Week

**Sydney, 10 January 2022. Actinogen Medical ASX: ACW (“ACW” or “the Company”)** CEO Dr Steven Gourlay will present at the Biopartnering @JPM associated with the 40<sup>th</sup> annual JP Morgan HealthCare Conference in San Francisco from 10 to 13 January 2022. While in San Francisco, Dr Gourlay will also present at the H.C. Wainwright BioConnect Virtual Conference that runs concurrently with the JP Morgan conference.

Dr Gourlay will conduct multiple business development and other stakeholder meetings during the conference week as well. The information used for all presentations and meetings is attached to this announcement.

The focus of Dr Gourlay’s presentations and meetings is to update the industry on recent developments in the Company’s clinical development pipeline, including:

- **Progress in the Alzheimer’s Disease (AD) XanaMIA Part A trial in older volunteers, with top line cognition data expected in Q2 CY2022**
- **Retrospective analysis of the effects of Xanamem® on “disease modifying” biomarkers using stored samples from the prior Phase 2 study in mild Alzheimer’s Disease, with results expected in H2 CY2022**
- **Expansion of the Phase 2 XanaFX clinical trial for patients with Fragile X Syndrome (FXS) to include sites in North America and a new 5mg dose group, with planned enrolment increased from 50 to 75. The trial is commencing following receipt of US FDA IND approval in November 2021, and results are expected in 2023**
- **Selection of Major Depressive Disorder (MDD) as the third indication for Xanamem trials, based on a strong scientific rationale, with a randomised phase 2 clinical trial scheduled to commence in 2022. Results are expected in 2023.**

**Dr Steven Gourlay, Actinogen CEO and MD, commented:**

*“We are delighted to update potential pharmaceutical industry partners on our expanded clinical development pipeline and its multiple near and medium-term milestones.*

*“Despite the worldwide COVID-19 situation it is pleasing to see strong ongoing interest and activity at the JP Morgan conference. This is especially true of the Alzheimer’s Disease field that was boosted by the 2021 approval of Aduhelm based largely on the surrogate of amyloid protein as a biomarker.*

*“Actinogen is actively exploring the effects of its lead molecule, Xanamem, on a range of biomarkers that could indicate modification of underlying disease.*

*“Actinogen’s clinical development pipeline is designed to fulfil our vision of making a material difference to the quality of life for people and their families living with serious neurological conditions like Alzheimer’s Disease, Fragile X Syndrome, and Depression.”*

® Xanamem is a registered trademark of Actinogen Medical Limited

## ENDS

### Investors

**Dr. Steven Gourlay**  
CEO & Managing Director  
P: +61 2 8964 7401  
E. [steven.gourlay@actinogen.com.au](mailto:steven.gourlay@actinogen.com.au)

**Michael Roberts**  
Investor Relations  
P: +61 2 8964 7401  
E. [michael.roberts@actinogen.com.au](mailto:michael.roberts@actinogen.com.au)

### Media

**Randal Killip**  
Profile for Media  
M: +61 425 714 159  
E. [randal@profileformedia.com.au](mailto:randal@profileformedia.com.au)

### ***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 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, reasoning, awareness and decision-making, and to a large extent, influence our personality.

We are currently developing our lead compound, Xanamem®, as a promising new therapy for Alzheimer's Disease, Fragile X Syndrome, Depression and other neurological diseases where reducing cortisol inside brain cells could have a positive impact. 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 works by blocking the production of intracellular cortisol through the inhibition of the 11β-HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing the drug capsule.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease, potentially linked to cognitive impairment and anxiety in Fragile X Syndrome, and cognitive impairment and underlying disease in Depression and other diseases.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 250 volunteers and patients, so far finding a statistically significant improvement in cognition over placebo in healthy, older volunteers. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterise 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.

#### **Disclaimer**

This announcement and attachments may contain certain forward-looking statements that are based on subjective estimates and assumptions and relate to circumstances and events that have not taken place and may not take place. Such forward looking statements involve known and unknown risks, uncertainties, and other factors (such as significant business, economic and competitive uncertainties and contingencies, and regulatory and clinical development risks and uncertainties) which may cause the actual results or the performance of Actinogen Medical to be materially different from the results or performance expressed or implied by such forward looking statements. Past performance is not a reliable indicator of future performance. There can be no assurance that any forward-looking statements will be realised. Actinogen Medical does not make any representation or give any warranty as to the likelihood of achievement or reasonableness of any forward-looking statements.

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



# JP Morgan Update Presentation

**Dr. Steven Gourlay MBBS PhD MBA: CEO & MD, CMO**

January 10, 2022

**NON-CONFIDENTIAL**





**H.C. Wainwright BioConnect Conference**

**January 10-13, 2022**

**Update presented by Steven Gourlay MBBS PhD, CEO**

**NON-CONFIDENTIAL**

# Disclaimer

This presentation has been prepared by Actinogen Medical Limited. ("Actinogen" or the "Company") based on information available to it as at the date of this presentation. The information in this presentation is provided in summary form and does not contain all information necessary to make an investment decision.

This presentation does not constitute an offer, invitation, solicitation or recommendation with respect to the purchase or sale of any security in Actinogen, nor does it constitute financial product advice or take into account any individual's investment objectives, taxation situation, financial situation or needs. An investor must not act on the basis of any matter contained in this presentation but must make its own assessment of Actinogen and conduct its own investigations. Before making an investment decision, investors should consider the appropriateness of the information having regard to their own objectives, financial situation and needs, and seek legal, taxation and financial advice appropriate to their jurisdiction and circumstances. Actinogen is not licensed to provide financial product advice in respect of its securities or any other financial products. Cooling off rights do not apply to the acquisition of Actinogen securities.

Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, no representation or warranty, express or implied, is made as to the fairness, accuracy, completeness or correctness of the information, opinions and conclusions contained in this presentation. To the maximum extent permitted by law, none of Actinogen its officers, directors, employees and agents, nor any other person, accepts any responsibility and liability for the content of this presentation including, without limitation, any liability arising from fault or negligence, for any loss arising from the use of or reliance on any of the information contained in this presentation or otherwise arising in connection with it.

The information presented in this presentation is subject to change without notice and Actinogen does not have any responsibility or obligation to inform you of any matter arising or coming to their notice, after the date of this presentation, which may affect any matter referred to in this presentation.

This presentation is not for general distribution or third party reliance or use.

This presentation contains certain budget information, forecasts and forward looking statements that are based on the Company's management's beliefs, assumptions and expectations and on information currently available to management in respect of which there is **NO guarantee of future performance**. Such budget information, forecasts and forward looking statements involve known and unknown risks, uncertainties, and other factors which may cause the actual results or performance of Actinogen to be materially different from the results or performance expressed or implied by such forward looking statements. These risks and uncertainties include, but are not limited to the performance of Actinogen in its clinical trials including whether its technology proves to be a safe and effective treatment, market penetration, competition from any other similar products, intellectual property risks (including securing rights in technology and patents) and global economic conditions. Furthermore, Actinogen's research, product development, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. There is no guarantee that Actinogen will obtain the required approvals, licences and registrations from the relevant authorities in jurisdictions in which it operates. Actinogen or others could identify product and efficacy issues relating to the safety of our technology. Accordingly, all forward looking statements are based on numerous assumptions regarding the Company's present and future business strategies and the political and economic environment in which Actinogen will operate in the future, which are subject to change without notice. Past performance is not necessarily a guide to future performance and no representation or warranty is made as to the likelihood of achievement or reasonableness of any forward looking statements or other forecast. There is no guarantee that Actinogen will achieve its stated objectives/milestones, that any of its forecasts will be met or that forward looking statements will be realised. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

Neither Actinogen nor any other entity or person in or associated with Actinogen guarantee any return (whether capital or income) or generally the performance of Actinogen or the price at which its securities may trade. Any investment in Actinogen is subject to investment risks including the possibility of loss of capital invested and no return of income or payment of any dividends.

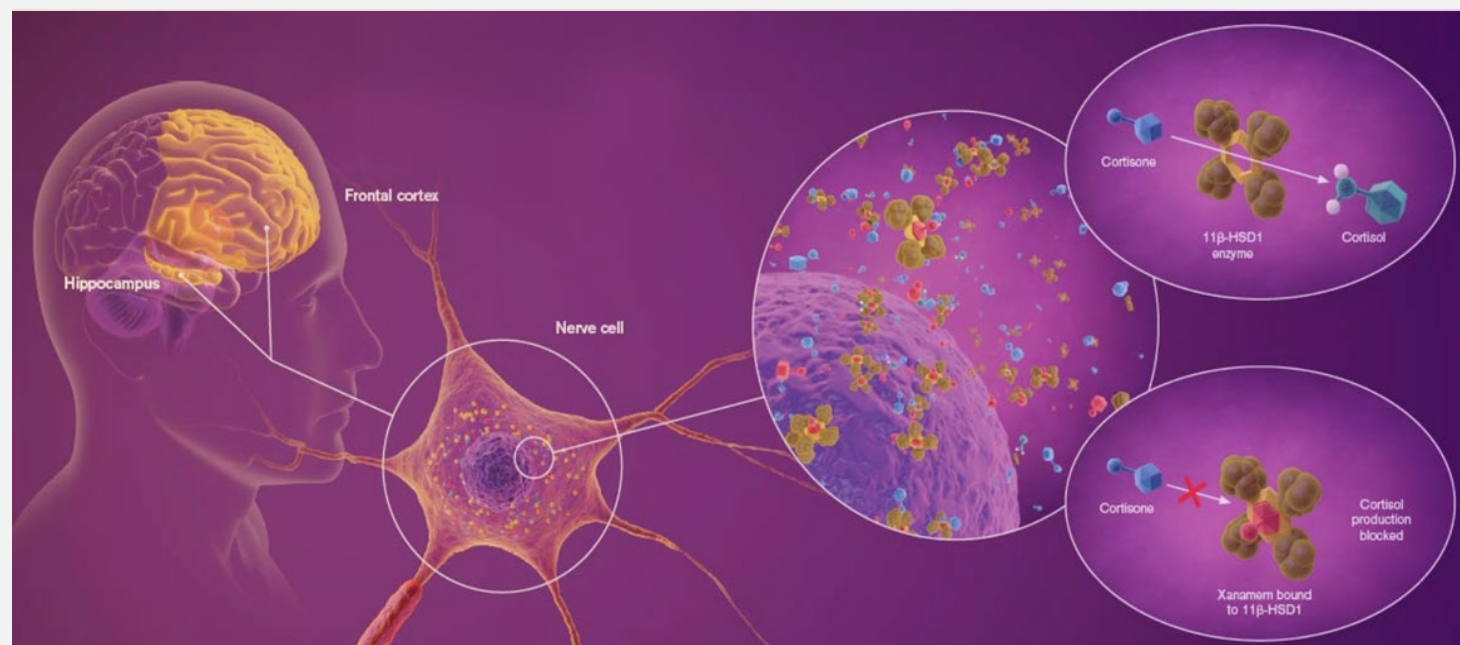
To the maximum extent permitted at law, Actinogen and all of its representatives, directors, officers, partners, employees or professional advisers (**Parties**) exclude all direct and indirect liability arising out of or in connection with any use or reliance of the information contained or described within this presentation. Other than to the extent required by law (and only to that extent), the Parties do not make any representation or give any assurance, guarantee or warranty (express or implied) as to, nor assume any responsibility or liability for, the authenticity, origin, validity, accuracy, suitability or completeness of, or any errors in or omissions from, any information, statement or opinion contained in this presentation or any accompanying, previous or subsequent material or presentation.



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

# 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

- ✓ >300 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 multiple CNS diseases: early stages of Alzheimer's Disease; Fragile X Syndrome; and depression/related cognitive impairment



## Protected and funded

- ✓ Molecule in-licensed from U Edinburgh in 2014
- ✓ Comprehensive patents in place<sup>1</sup>
- ✓ Pro-forma cash A\$26M<sup>2</sup> at 30 Sep 2021

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

2. Including \$13m capital raising in December and 1.4M R&D 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

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



**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 Tooли**

Head of Business Development

PhD; GAICD

# Established Scientific Advisory Boards

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

## Alzheimer's Disease Clinical Advisory Board



**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

Note: All logos and brands are registered trademarks of their respective owners.

# New Clinical Advisory Boards

Renowned global thought leaders in clinical trials for Fragile X Syndrome, Depression and assessment of Cognition

## Fragile X Syndrome Clinical Advisory Board



**Dr Elizabeth Berry-Kravis**



- Established Fragile X Clinic and Research Program at Rush University Medical Center, Chicago
- A leader in translational research in FXS and has over 250 publications on genetic neurological diseases
- Professor of Pediatrics, Neurological Sciences, and Biochemistry at Rush University Medical Center and on several Advisory/Review Boards



**Dr Pam Ventola**



- 20+ years experience conducting evaluations of children and adults with developmental disabilities
- Extensive clinical and research experience with paediatric neuropsychological and developmental assessments
- Associate Professor at the Yale Child Study Center and leads Cogstate's Rare Disease and Paediatric Center of Excellence

## Depression and Cognition Clinical Advisory Board



**Prof. John Harrison**



- Expert psychologist with a special interest in cognition
- 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



**Dr Dana C. Hilt**



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



**Christina Kurre Olsen**

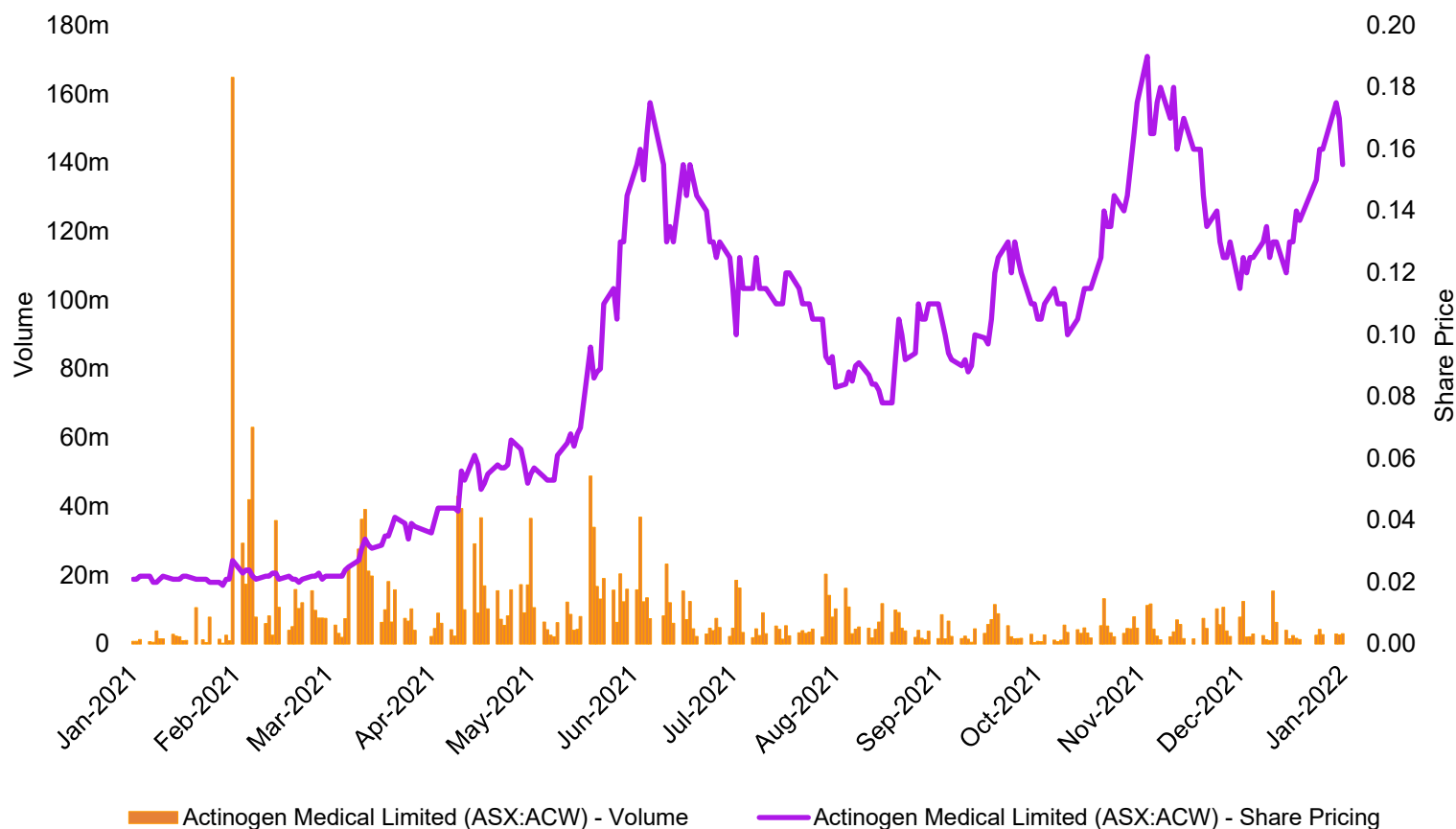


- 20+ years research expertise in neuroscience, neuropsychopharmacology, CNS therapeutics and monoclonal antibody immunotherapy
- Strong hands-on knowledge across drug development value chain and a passion for cognition
- Medical Director at Orphazyme A/S



# ACW stock performance 12 months

## Share price chart at 06 Jan 2022

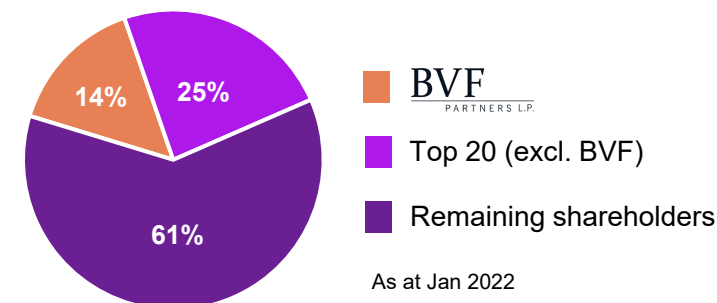


## Trading Information

52 week high	A\$0.20
52 week low	A\$0.02
Number of issued shares	1,775M
Market capitalisation (6 Jan 2022)	A\$275M
Pro-forma cash at 30 Sep <sup>1</sup>	A\$26M

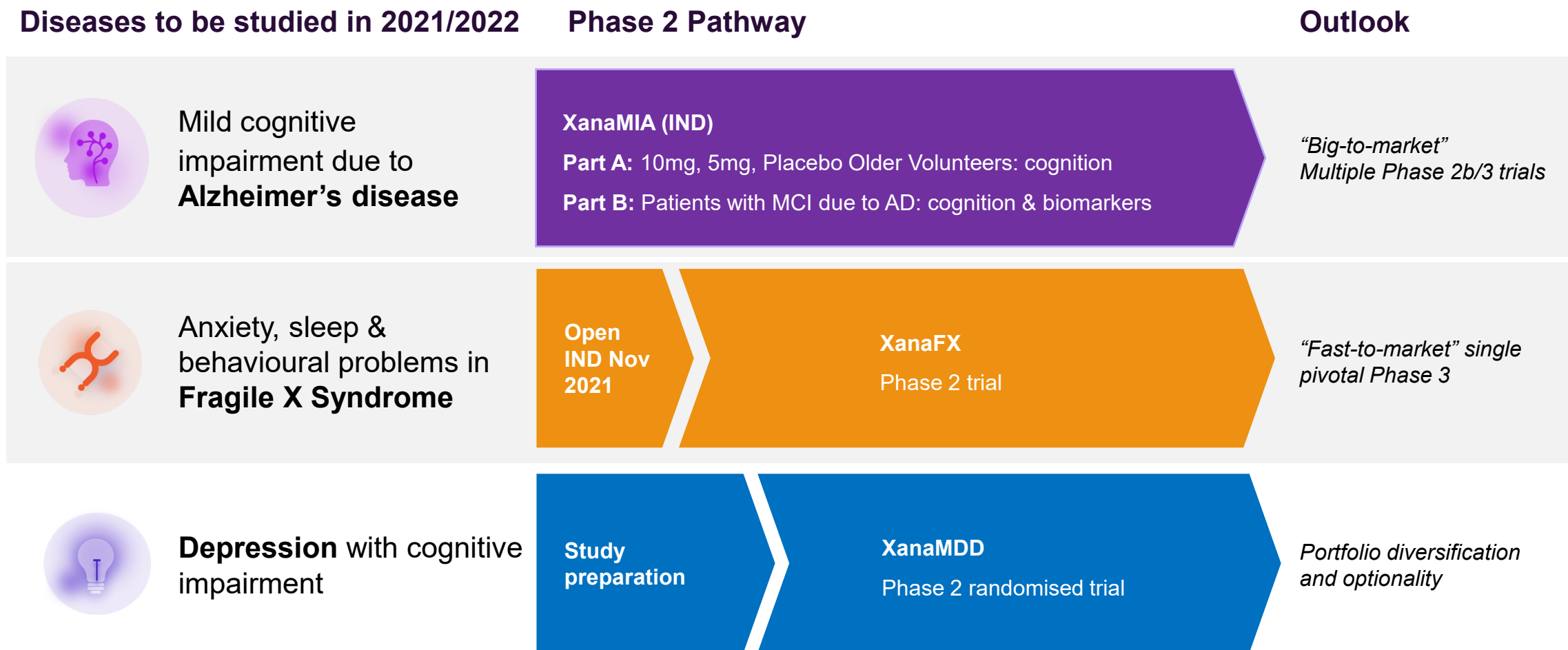
## Major Shareholders

BVF Partners	13.9%
Steven Gourlay	3.6%
Edinburgh Technology Fund	2.7%



1. Including A\$1.4M R&D tax incentive received, A\$13.3M capital raising in December 2021

# Xanamem Clinical Development Pipeline





Status: Analysis

# Alzheimer's Disease

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

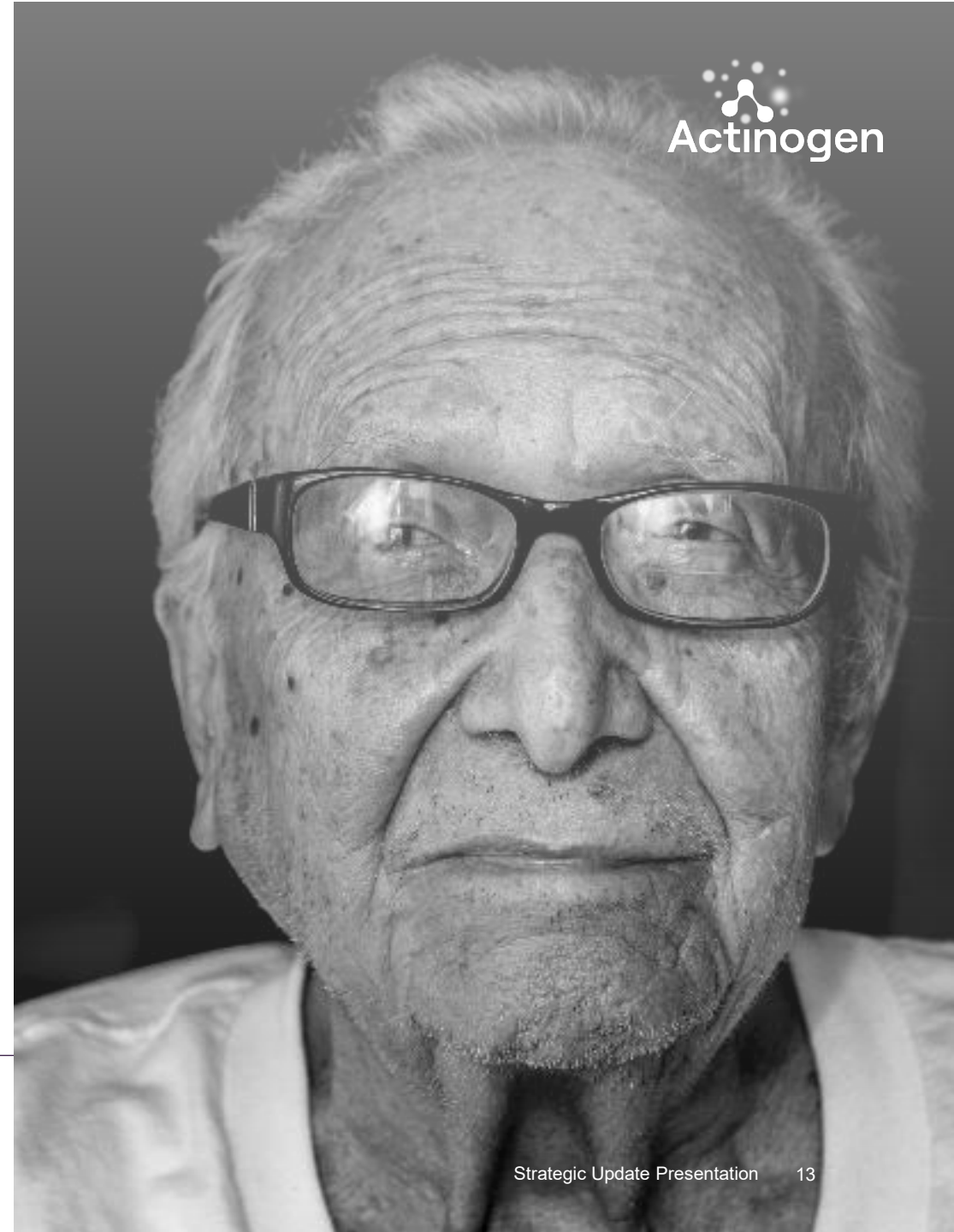
MRI



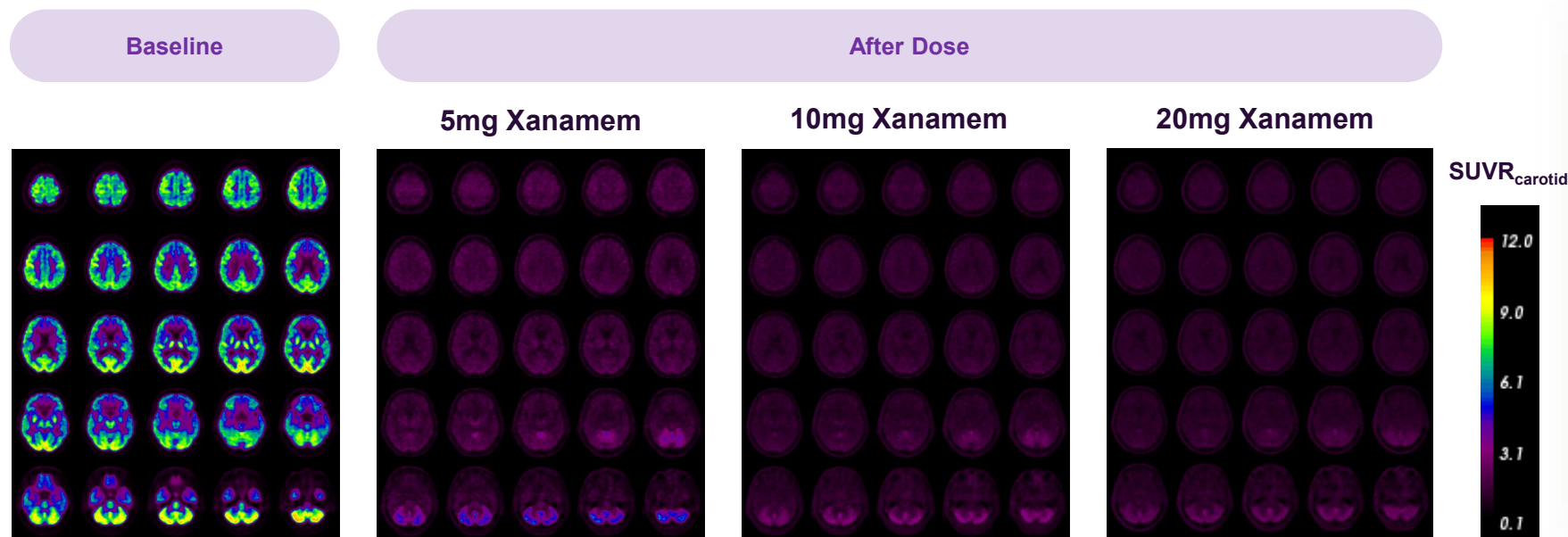
# Science Behind the Xanamem AD Program

- ✓ 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)



# PET data supports a low Xanamem dose $\leq 10\text{mg}$ daily



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

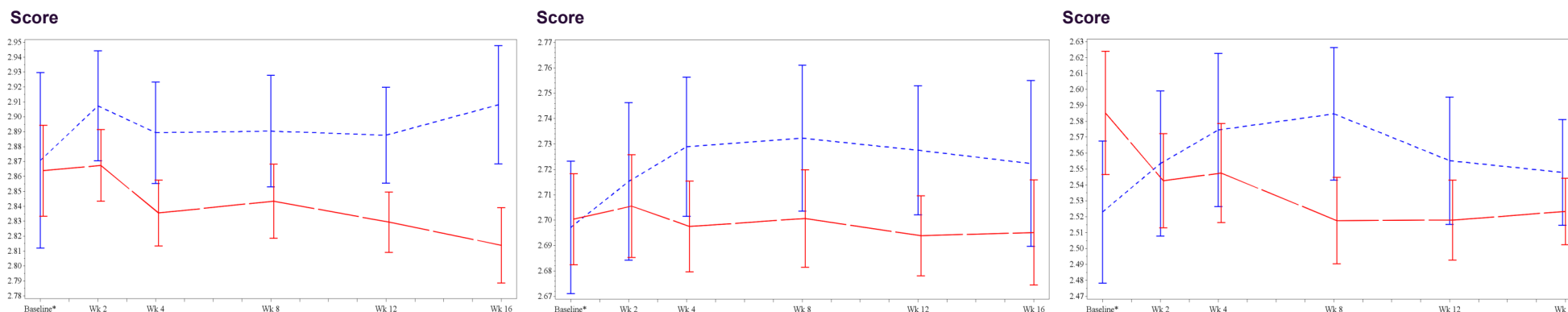
This is consistent with full hormonal pharmacodynamic activity seen with 10mg in clinical trials.

Note: Study population consisted of ~50% healthy subjects (cognitively normal) and ~50% with Alzheimer's disease. Subjects dosed for seven days.  
Baseline: Mean of baseline scans of patients in that dose group; After dose: Mean of post-dosing (7 days) scans in that dose group.

# 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

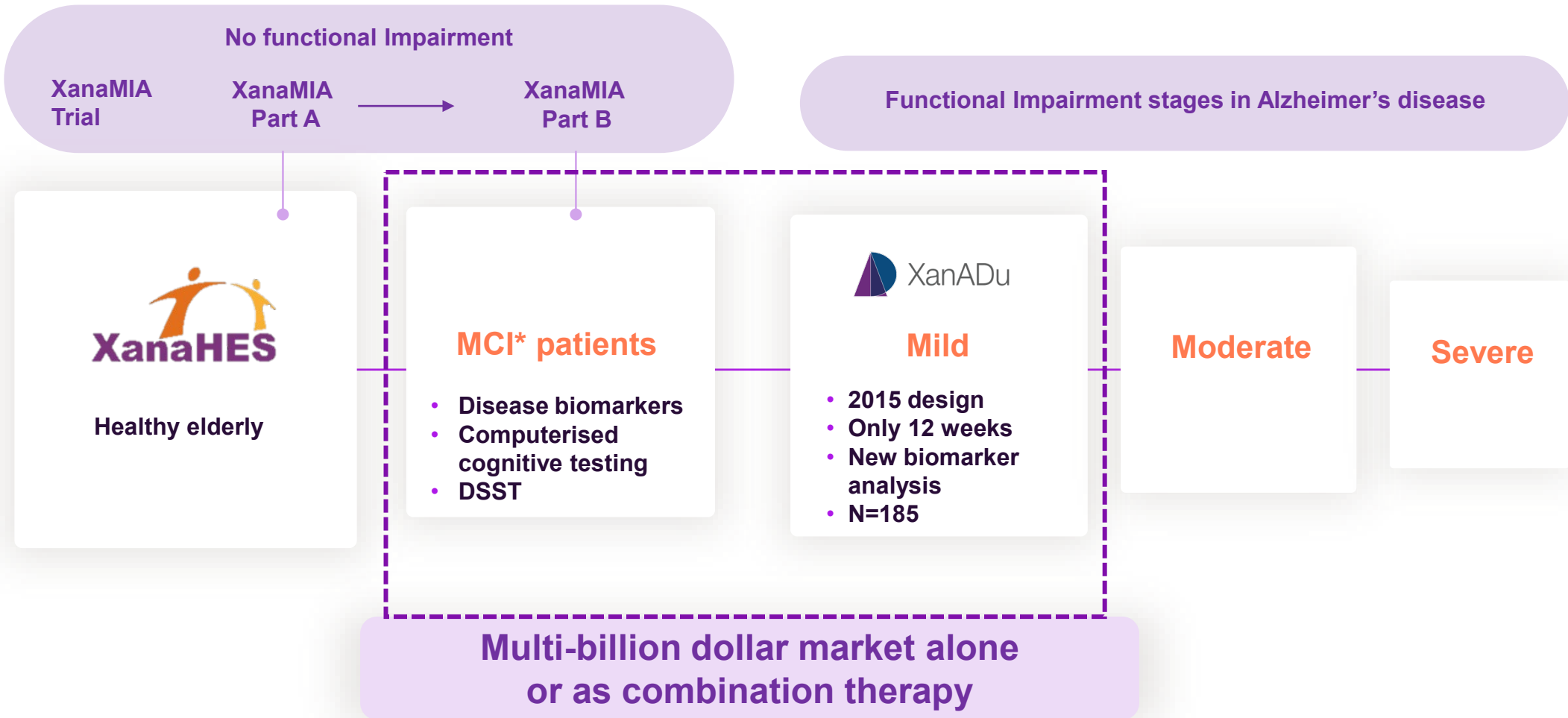
Large effect sizes seen in working memory and attention, trends in other domains

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



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

Bringing disease biomarker data readout forward into 2022

## XanADu Phase 2 trial

- ☐ 185 patients (n=91 active, n=94 placebo)
- ☐ 10mg daily
- ☐ Mild Alzheimer's Disease without biomarker or imaging confirmation

## Preliminary feasibility completed for biomarker analysis extension study

- ☐ Upwards of 50 patients/guardians sought to be reconsented
- ☐ Most sites willing to participate
- ☐ Established relationship with analytical laboratory
- ☐ Biomarkers assessed will include A $\beta$ 1-40, A $\beta$ 1-42, T-tau, Tau 181, NfL, and GFAP



# 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 (confirmed using positive serum biomarkers)
- **Cognitive endpoints** - highly sensitive cognition tests (Cogstate, iDSST)
- Prospectively measuring disease-modifying potential with change in **Alzheimer's Disease biomarkers** over 12 weeks treatment
- **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



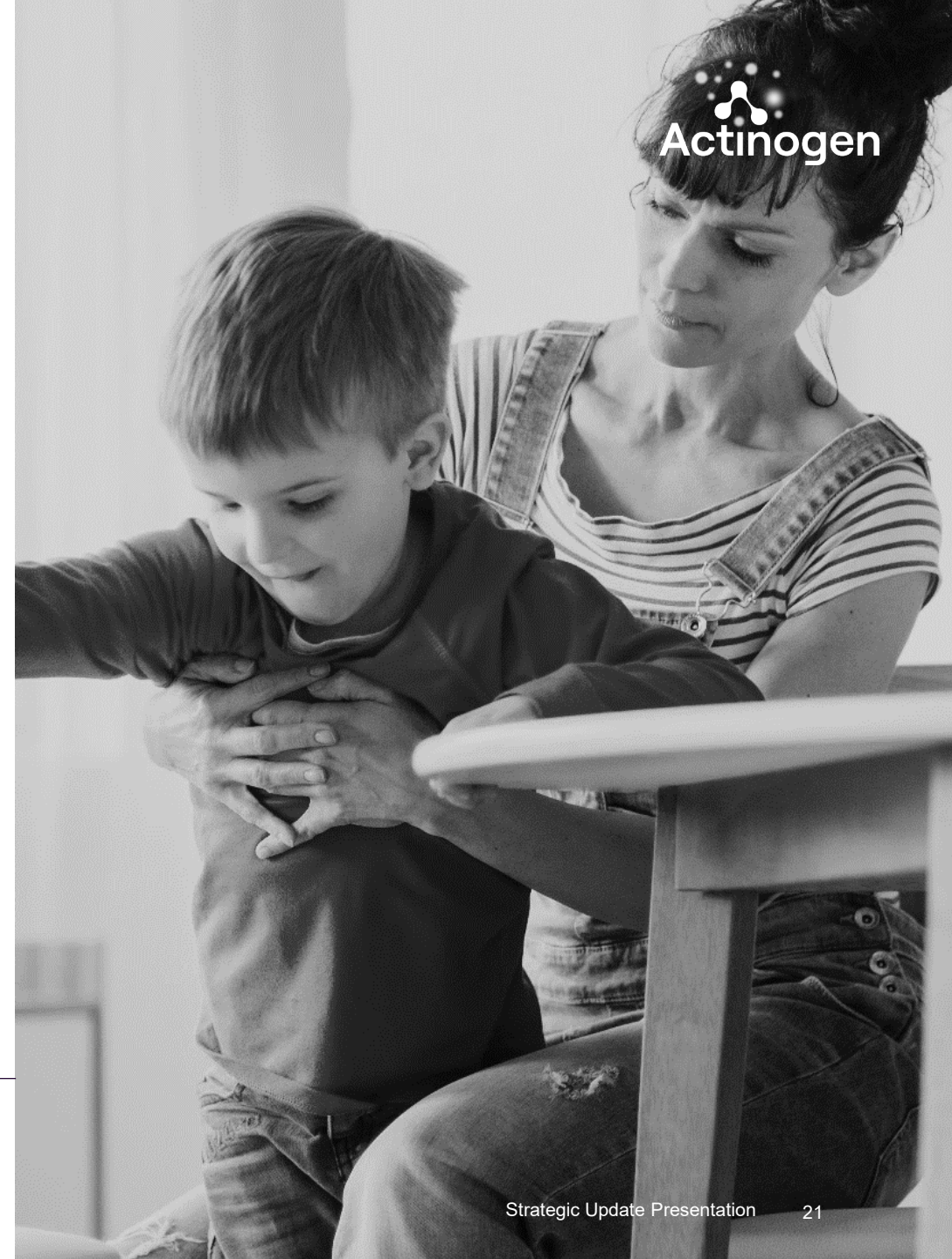
## Valuable commercial opportunity<sup>1</sup>

- 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. Hessel et al. 2002; Wisbeck et al. 2000  
2. Elevated cortisol correlates with symptoms, Hessel et al. 2002; Hardiman & Bratt 2016  
3. Mouse FMR1 mutation model of Fragile X & glutamate, cortisol mechanism Ghillean 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

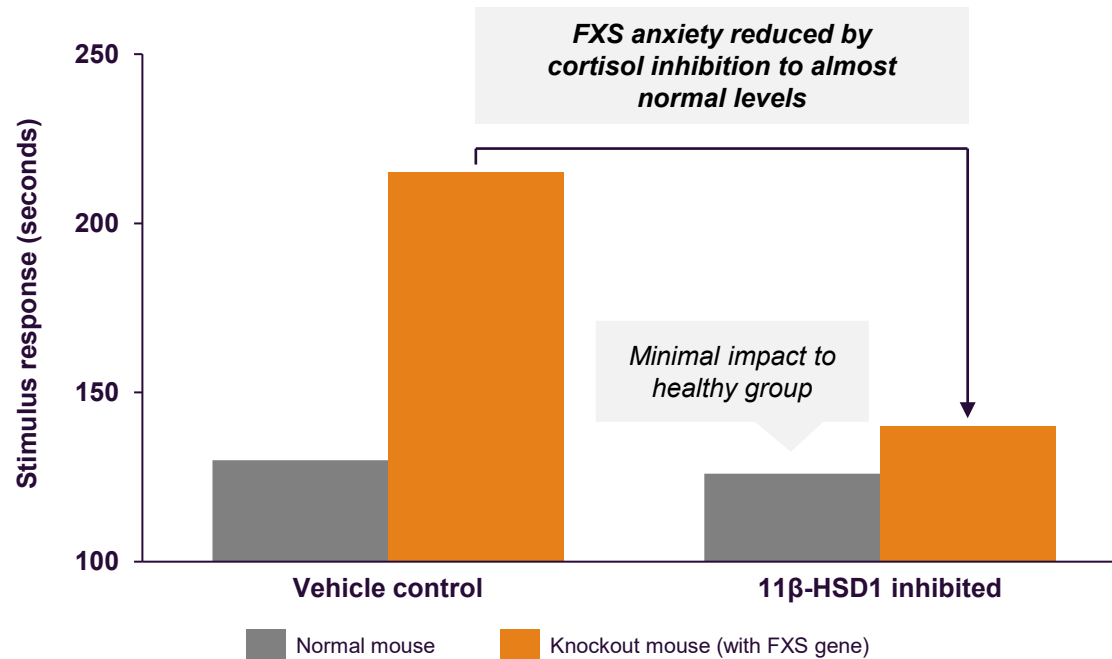






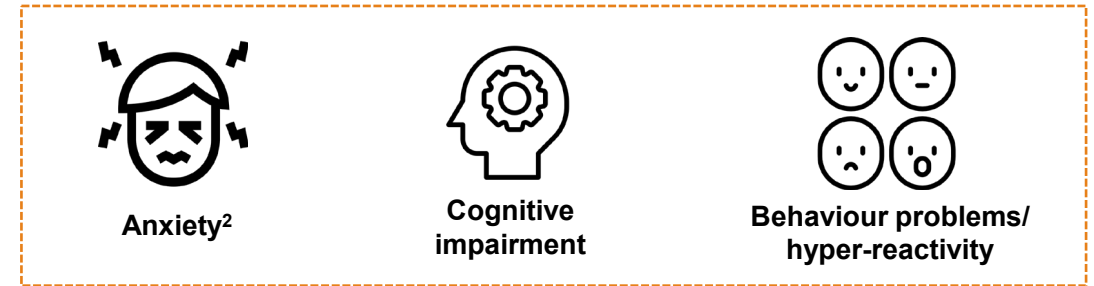
# Xanamem may treat multiple symptom domains in FXS

## 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

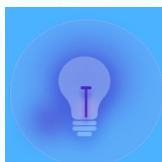


### Other FXS symptoms potentially amenable to Xanamem therapy



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



# Major Depressive Disorder associated with Cognitive Impairment

Targeting dual cognitive enhancement and anti-depressant activity





# Market 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 cognitive benefit claim**

**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

# Science Behind the Xanamem Depression Program

- ✓ 80-90% report neurocognitive symptoms<sup>1</sup>
- ✓ Cognitive symptoms often persist during remission<sup>1</sup>
- ✓ Elevated cortisol associated with severe, melancholic depression<sup>2</sup>
- ✓ Cortisol associated with treatment outcomes, relapse, & cognition<sup>3</sup>
- ✓ Positive effects with GR receptor antagonism with mifepristone<sup>4</sup>
- ✓ Xanamem & improved human cognition<sup>5</sup>

---

1. 3-year prospective study and review, Conradi et al. 2011  
2. Quantitative summary of four decades of research, Stetler & Miller 2011  
3. Depression literature review, Malhi & Mann 2018; HPA axis in major depression, Keller et al. 2016  
4. GR, **glucocorticoid receptor**; Combined analysis of mifepristone for psychotic depression, Block et al. 2018; mifepristone effects on depression in bipolar disorder, Young et al. 2004; Evidence from clinical studies with CRH<sub>1</sub> receptor antagonists, Holsboer & Ising 2008  
5. Xanamem placebo-controlled trial working memory & attention (Actinogen data on file)



# Clinical/Regulatory – established endpoints & regulatory path

Initial trial will be placebo-controlled Phase 2 of 6-weeks treatment

- MDD endpoints used by other programs
  - Trintellix endpoints: MADRS<sup>1</sup> and HAM-D<sup>2</sup> scores
  - Spravato (esketamine) endpoints: MADRS score
  - Zulresso endpoints: HAM-D score
- Cognitive endpoints used by other programs
  - Trintellix label claim for cognition largely based on DSST<sup>3</sup> score
  - Xanamem XanaHES study showed response in working memory & attention with Cogstate
  - Spravato also included cognition tests as safety endpoints in both short-term and long-term study, as ketamine is known to result in cognitive dysfunction
    - Used Cogstate Battery and HVLT-R<sup>4</sup>

<sup>1</sup> Montgomery-Asberg Depression Rating Scale

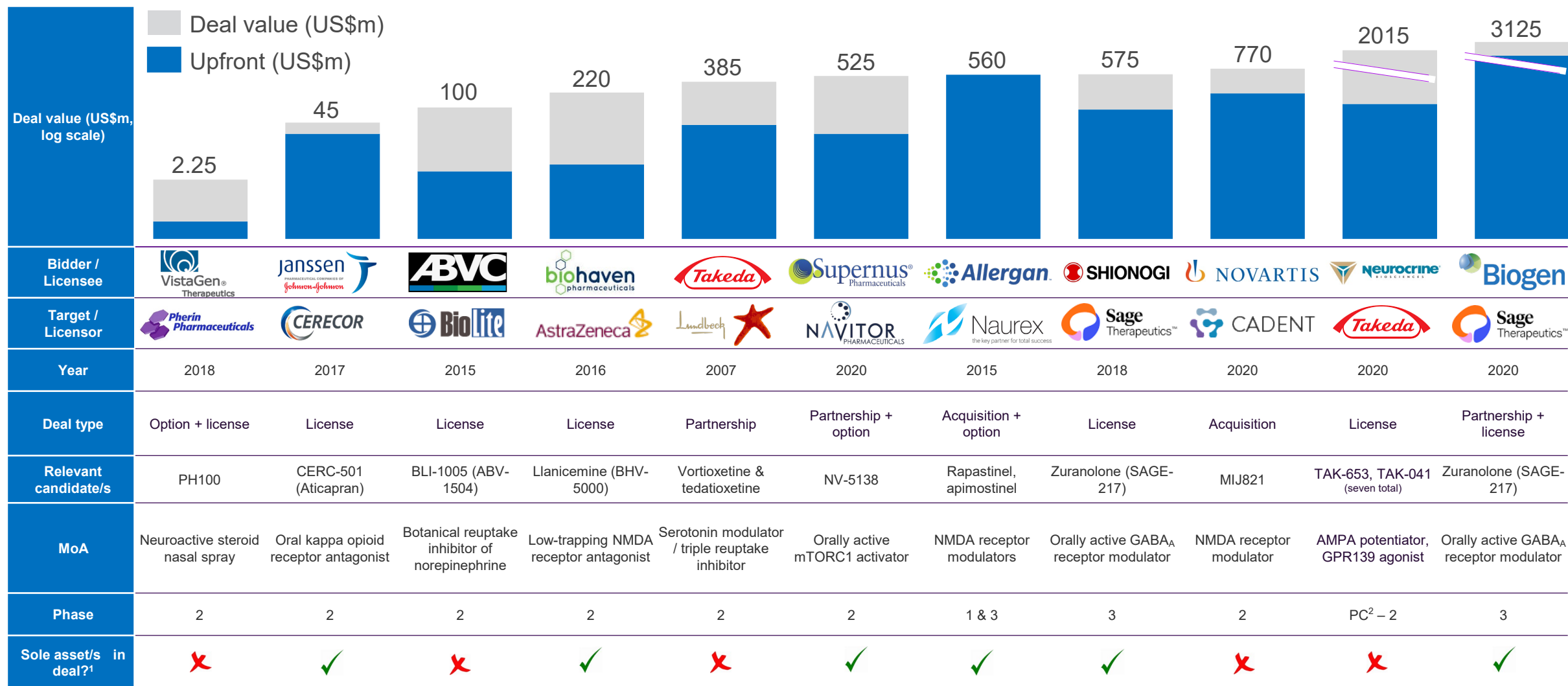
<sup>2</sup> Hamilton Depression Rating Scale

<sup>3</sup> Digit Symbol Substitution Test

<sup>4</sup> Hopkins Verbal Learning Test - Revised

# Commercial opportunity is large, even at Phase 2

Global Big Pharma strong M&A interest in acquiring or partnering and licensing assets with novel mechanisms of action where depression is the lead/key indication



1. Indicates whether listed assets were the sole target of the deal, or if additional assets for other indications were also included in deal terms; does not include agreements where an option to license future assets was secured.

2. Pre-clinical



# 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 depression 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



### 2 open INDs, FXS Priority Review

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



### Peer AD company valuations reflect growth potential

- Peer companies in phase 2 or 3 for AD: valuations ~US\$136M-\$1.9B<sup>1</sup>

1. Vivoryon Therapeutics, phase 2a/b AD lead asset (EURONEXT Amsterdam: 374m euro); Athira Pharma, phase 2 AD lead asset (NASDAQ GS:~US\$537m); Cortexyme, negative topline data in phase 2b/3 AD for lead asset (NASDAQ GS:~US\$353m) and same drug in phase II for periodontal disease and Parkinson's disease; Cassava Sciences, AD lead asset phase 2 asset with positive biomarker and cognition data (NASDAQ GS:~US1.9B); Annovis Bio, very early phase 2 data AD, PD (NASDAQ US\$136m). All companies' value primarily attributed to their lead AD asset. Market capitalisations as of January 8 2022.

# Next steps and key catalysts

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

### Alzheimer's Disease

- XanaMIA Part A cognition results Q2 CY2022
- XanADu retrospective biomarker results H2 CY2022
- XanaMIA Part B patient biomarker/cognition data 2023

### Fragile X Syndrome

- Commenced in 2021
- XanaFX trial results 2023

### Depression

- Commence program immediately, results 2023

## ❑ Publications and collaborations

- Focus on PET study and other key peer-review publications
- Leverage academic collaborations including Mild Autonomous Cortisol Secretion (MACS) Trial with Oxford University researchers

