## ASX ANNOUNCEMENT

# Actinogen CEO presents latest clinical data at Sachs Annual Neuroscience Innovation Forum and other meetings during the JP Morgan Healthcare Conference week

**Sydney, 08 January 2023. Actinogen Medical Ltd ASX: ACW ("ACW" or "the Company")** announces that CEO Dr Steven Gourlay will present at the Sachs Associates 6th Annual Neuroscience Innovation Forum in San Francisco on 8 January 2023. While in San Francisco, Dr Gourlay will also participate in meetings at BIO Partnering @JPM associated with the 41st Annual J.P. Morgan Healthcare Conference from 9 to 12 January as well as at the annual H.C. Wainwright Bioconnect Virtual Conference that runs concurrently with the J.P. Morgan conference.

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

The presentation summarizes the recent Phase 2a clinical biomarker study findings of a large clinical effect size on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) and new exploratory analyses showing clinically significant benefits on two composite endpoints (slides 14 & 15). These exploratory analyses supplement and extend the CDR-SB finding (patient function) by showing similar trends toward benefit in several cognitive measures (ability to think and remember things).

In the patient subgroup with high pTau 181 (a blood measure indicating Alzheimer's pathology in the brain that predicts progression) Xanamem® showed a protective effect against decline in the CDR-SB and two cognitive composites. In the group that did not have elevated pTau Xanamem showed a trend towards improved cognition, consistent with prior findings in healthy, older volunteers.

**Dr Steven Gourlay, Actinogen's CEO and MD, said:**

*"We are delighted to brief pharmaceutical industry stakeholders on our recent clinical developments and key product development milestones. The focus on neuroscience for a whole day in San Francisco points to the resurgent interest in this area from investors and biopharmaceutical companies.*

*"Actinogen now has a substantial safety database of more than 300 people treated and positive clinical efficacy results from three separate trials for our lead small molecule drug Xanamem.®*

*"We look forward to commencing enrolment in the XanaMIA Phase 2b Alzheimer's Disease trial in the first half of 2023 and continuing with the XanaCIDD Phase 2 Depression trial which commenced last month. Regional and global partnering deals continue to be the focus for our business development activities."*

® Xanamem is a registered trademark of Actinogen Medical Limited

**ENDS**


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***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 11β-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 11β-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 and clinically significant improvements in patients with biomarker-positive mild AD. 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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**ACTINOGEN MEDICAL ENCOURAGES ALL CURRENT INVESTORS TO GO PAPERLESS BY REGISTERING THEIR DETAILS WITH THE DESIGNATED REGISTRY SERVICE PROVIDER, AUTOMIC GROUP.**

# Third trial validates Xanamem® cognitive activity & Alzheimer's Disease program

## Positive Phase 2a data with large CDR-SB effect size

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

**Sachs 6th Annual Neuroscience Forum and JP Morgan Healthcare Conference week, 8-12 January 2023**

**Authorised by the Board of Directors of Actinogen Medical Limited**

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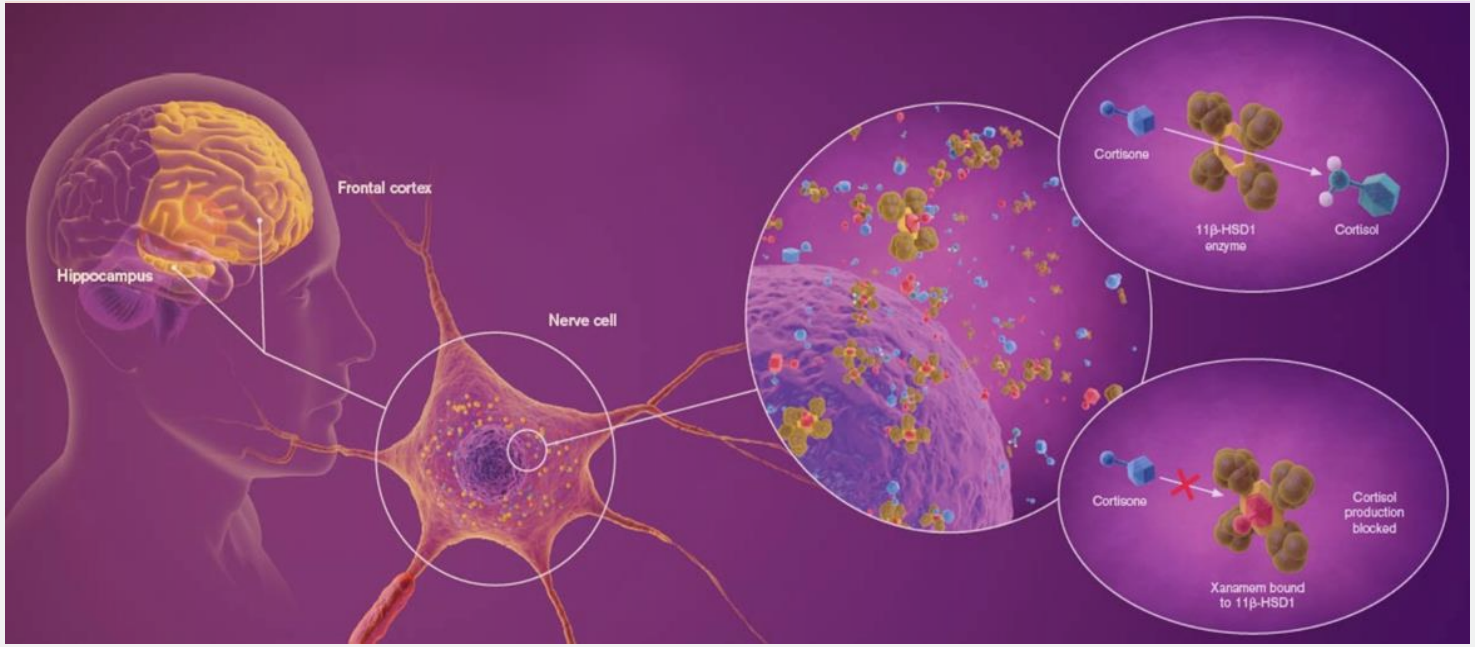
# Xanamem: Oral, low dose, once-a-day treatment with a unique non-amyloid/tau mechanism

Brain penetrant 11β-HSD1 small molecule enzyme inhibitor reduces cortisol inside brain cells - modulating signaling pathways and underlying disease processes[1,2]

Potential to be:

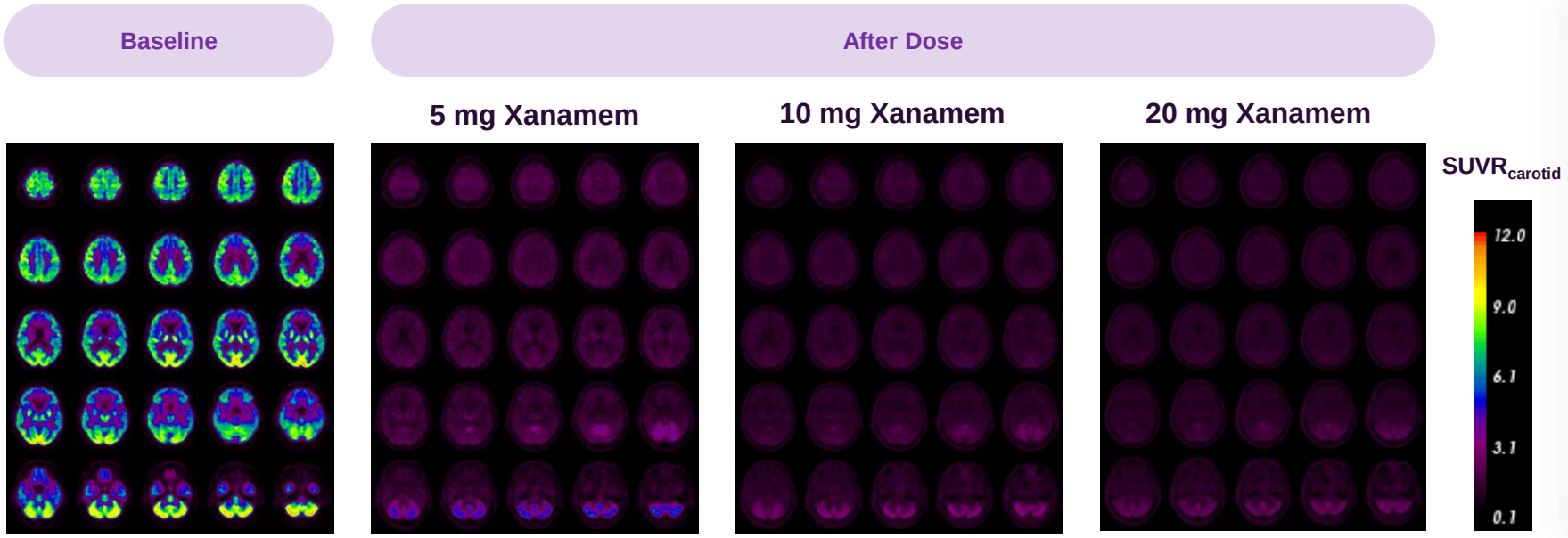
- Rapidly cognitive enhancing
- Disease-modifying (slow or halt progression) in AD
- Anti-depressant




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

# PET data shows full target engagement in the brain at well tolerated doses of 5-10 mg

## Previous molecules to this target have not achieved adequate brain concentrations



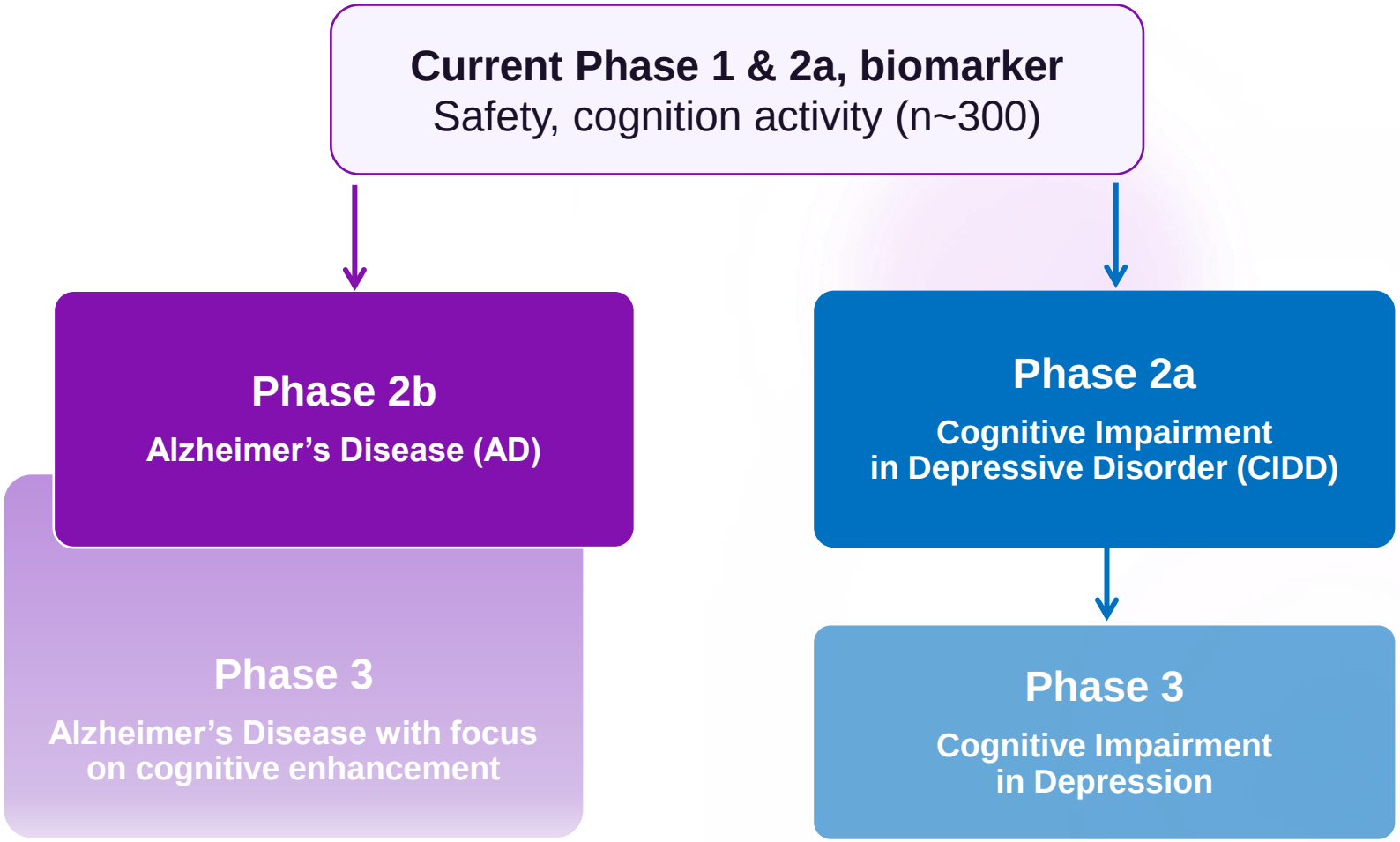

**PET data demonstrates that Xanamem extensively binds to the 11β-HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.**

**This is consistent with full hormonal pharmacodynamic activity seen with 10 mg in clinical trials. 5 and 10 mg show excellent clinical tolerability and safety.**

Note: Study population consisted of ~50% healthy older subjects who were 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.

# Xanamem Phase 2 & 3 program

## Building on four independent Phase 1 and 2 studies showing activity



# Previously: evidence of Xanamem activity on cognition from multiple sources

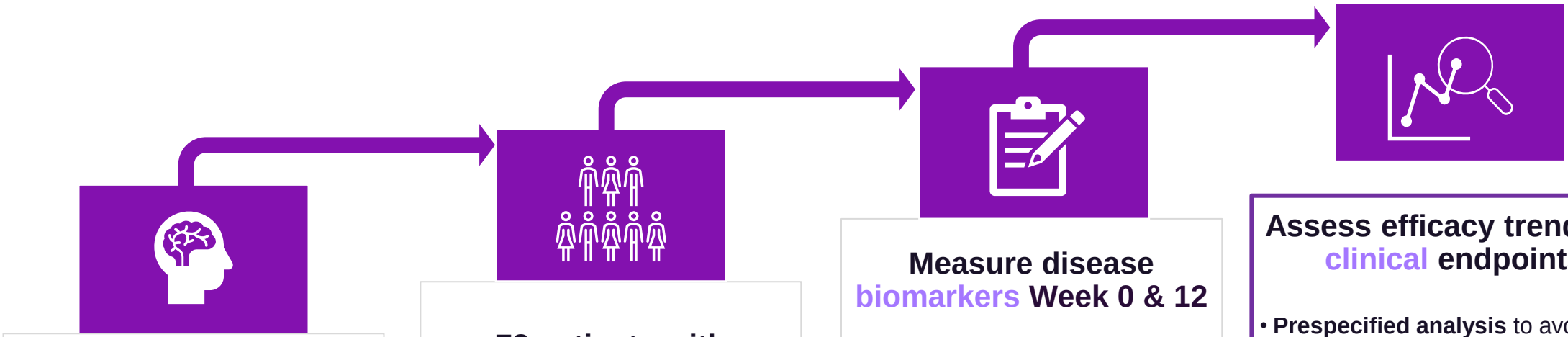
- ✓ **In animals**
  - ✓ **Protection against cognitive decline in animal model of AD using a Xanamem analogue independent of amyloid plaque[1]**
- ✓ **In humans**
  - ✓ **Consistent target engagement measured by PET & ACTH response**
  - ✓ **XanaHES trial in cognitively normal older volunteers – Positive effects on Cogstate attention & working memory**
  - ✓ **XanaMIA trial in cognitively normal older volunteers – Positive effects on Cogstate attention & working memory**
  - ✓ **New data shows activity in patients with mild AD**

**Human and animal data support Xanamem activity at doses of 5 to 10 mg daily**

1. Sooy et al. 2015

# Phase 2 blood biomarker study design & methods

## Uses a pre-specified protocol and analysis plan to avoid bias



### Phase 2a trial (XanADu)

- **185 people with mild AD** (MMSE 20-26)
- Clinical diagnosis: no amyloid imaging or biomarkers
- Placebo-controlled
- 12 weeks
- 10 mg Xanamem vs. placebo

### 72 patients with stored blood samples

- Available plasma stored at -80°C
- Evaluated by expert biomarker laboratory blinded to treatment assignment

### Measure disease biomarkers Week 0 & 12

- **pTau181**
- **Amyloid 42/40 ratio**
- **GFAP**
- **tTau (insufficient volume)**
- **NfL (insufficient volume)**

### Assess efficacy trends on clinical endpoints

- **Prespecified analysis** to avoid bias
- Select by **baseline pTau181, MMSE and amyloid ratio levels to reassess** efficacy
- Focus on **endpoints most sensitive to change** in a MCI/mild AD population (**CDR-SB)**
- Cohen's d to measure clinical effect size with no correction of p values for multiple comparisons

# Clinical Dementia Rating – Sum of Boxes (CDR-SB) functional endpoint to assess dementia in early-stage AD

| Test domain | Impairment | | | | |
|---|---|---|---|---|---|
| | None | Questionable | Mild | Moderate | Severe |
| | 0 | 0.5 | 1 | 2 | 3 |
| Memory | | | | | |
| Orientation | | | | | |
| Judgment & Problem Solving | | | | | |
| Community Affairs | | | | | |
| Home & Hobbies | | | | | |
| Personal Care | | | | | |

**Score is sum of each line i.e. score between 0 and 18 (0 = normal)**

# Xanamem doubled rate of disease stabilization on FDA-approved CDR-SB endpoint

## Response analysis in pTau-positive[1] AD patients (most likely to progress)

***Twice as many patients in the Xanamem group had stable or improved disease compared with placebo[2]***

***… meaning 56% of patients treated with Xanamem were stable or improved vs. 28% in placebo***

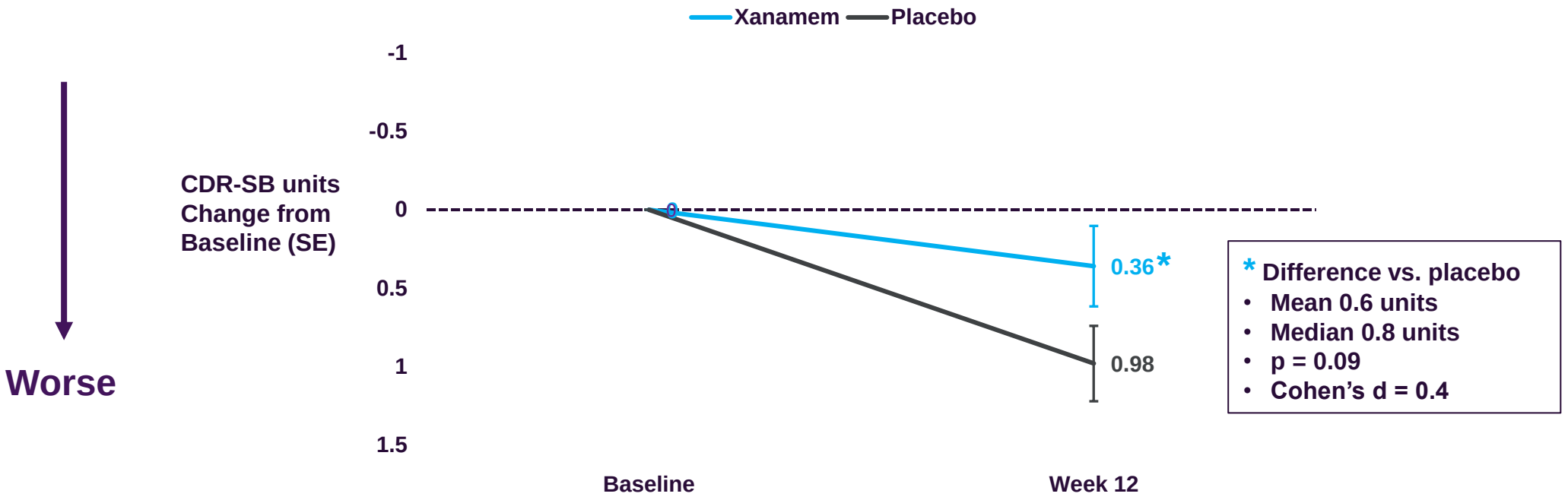
***Large effect size vs. placebo of 0.6 – 0.8 units over 12 weeks***

**Xanamem 10 mg protected the majority of patients from progression**

1. Pre-specified level of pTau181 above the median in plasma at baseline
2. Where CDR-SB decreased or was unchanged - Xanamem 9 of 16 (56%) vs. Placebo 5 of 18 (28%)

# Topline result from pre-specified analysis in AD patients with plasma pTau181 > median of 6.74 pg/mL

## Using pre-specified protocol, statistical analysis plan and blinded biomarker analysis




**Oral Xanamem 10 mg largely prevented progression over 12 weeks**

# Effect on CDR-SB in other three pre-specified groups

## Groups defined by biomarker median value, MMSE by 20-23 vs. 24-26

| | N | CDR-SB | | | | |
|---|---|---|---|---|---|---|
| **Group** | | **Desired change** | **Xanamem** | **Placebo** | **Cohen's d** | **p value** |
| **pTau >10.2 pg/mL[1] (mean)** | **9** | **Down** | **0.1** | **0.8** | **0.6** | **0.33** |
| Aβ42/40 ratio < 0.19 (mean) | 29 | Down | 0.5 | 0.4 | 0.1 | 0.91 |
| MMSE 20-23 | 46 | Down | 0.5 | 0.5 | 0.0 | 0.82 |

**Clinically significant effect size of CDR-SB 0.7 units in very high pTau group, with no apparent utility of low amyloid ratio or lower MMSE**

1. Published cutoff of 10.2 pg/mL[2] cutoff by Cullen et al. 2022 for progression to clinical AD. 6.74 pg/mL represents the median value of the dataset

# Exploring the high pTau group: baseline characteristics

| | Xanamem (n=16) | Placebo (n=18) |
|---|---|---|
| Age (mean, SD) | 71 (8) | 71 (8) |
| % female | 50% | 56% |
| % donepezil therapy[1] | 44% | 61% |
| ADASCog14 (mean, SD) | 34 (5) | 32 (8) |
| ADCOMS (mean, SD) | 0.56 (0.13) | 0.52 (0.19) |
| MMSE (mean, SD) | 22 (3) | 23 (2) |
| CDR-SB (mean, SD) | 4.1 (1.2) | 3.6 (1.6) |
| pTau pg/mL (mean, SD) | 9.3 (2.6) | 11.9 (11.6) |
| pTau pg/ml (median) | 8.6 | 8.8 |
| Aβ42/40 ratio (mean, SD) | 0.19 (0.03) | 0.19 (0.03) |
| GFAP pg/mL (mean, SD) | 132 (77) | 136 (95) |

**Groups were generally balanced in key characteristics**

1. [xxx]

# High pTau group: NTB and other endpoints

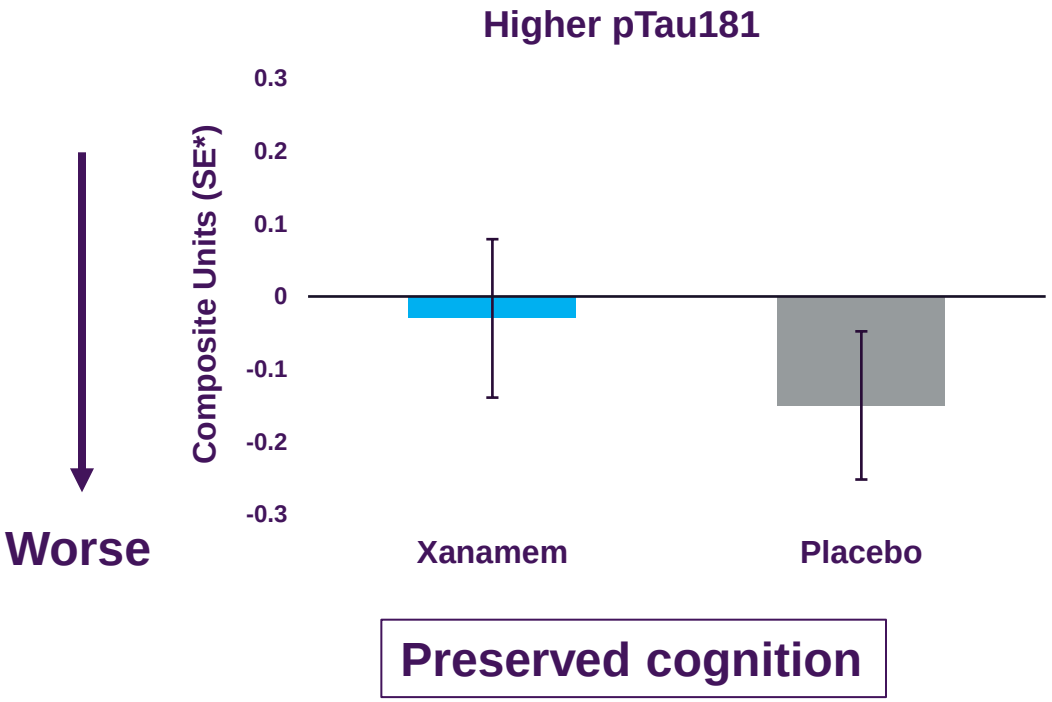
**NTB: a composite for executive function consisting of Controlled Oral Word Association (COWAT) and Category Fluency Test (CFT)**

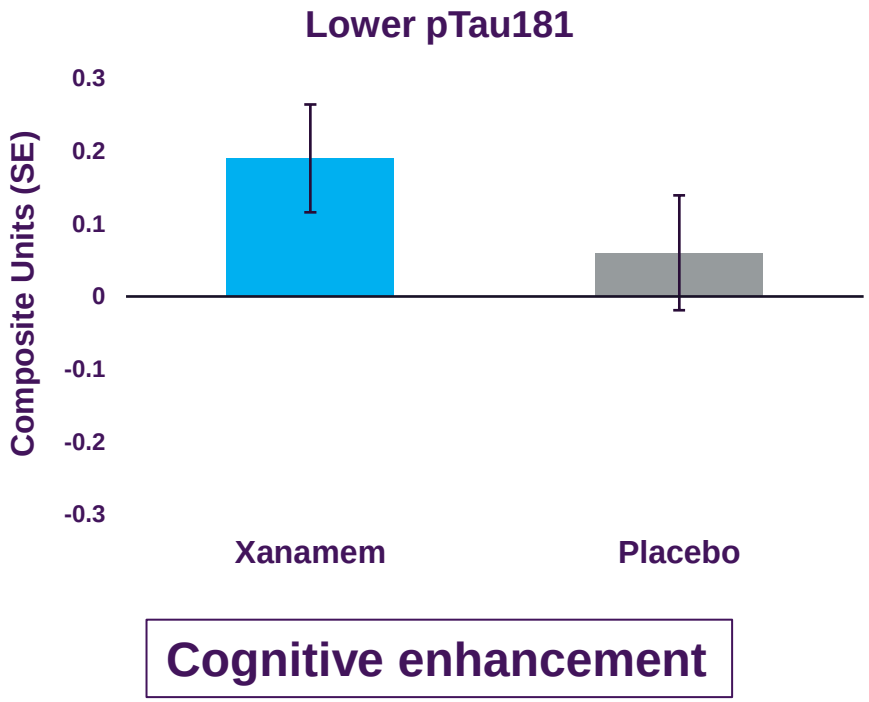
- **Improved NTB: Xanamem +0.5 vs. Placebo -2.3, Cohen's d = 0.3**
- **No effects on ADAS-Cog14, ADCOMS, MMSE, RAVLT, NPI (Cohen's d < 0.2)**

**Clinically significant effect size on NTB further explored in analysis of composite characteristics**

# Exploratory: Change from baseline in cognitive composite

## Trends in change of composite of word recall & recognition, CFT & COWAT (p=NS)




**Preserved cognition**

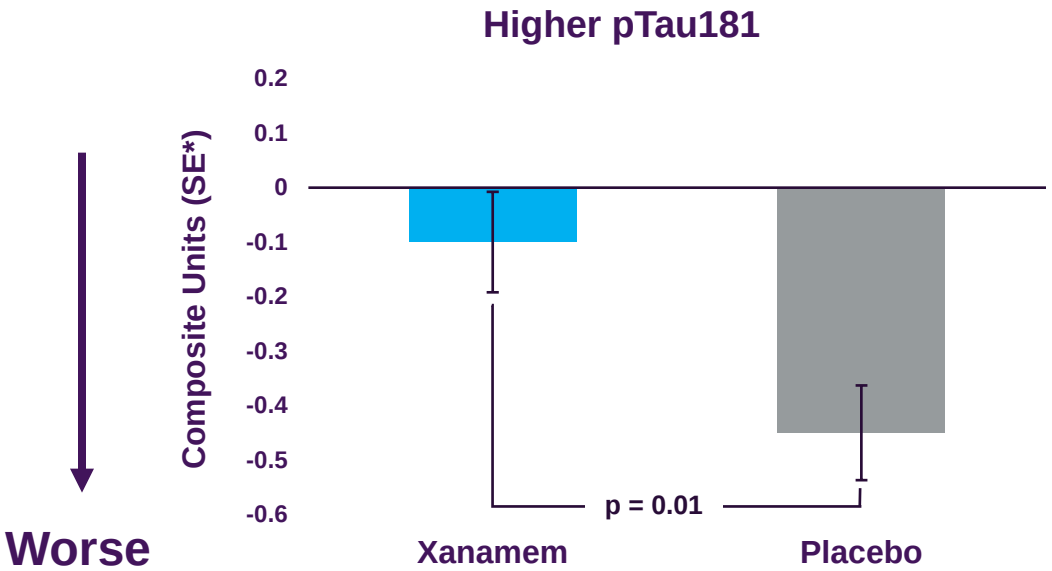
**Cognitive enhancement**

**Consistent with Xanamem activity as a cognitive enhancer & disease-modifier**

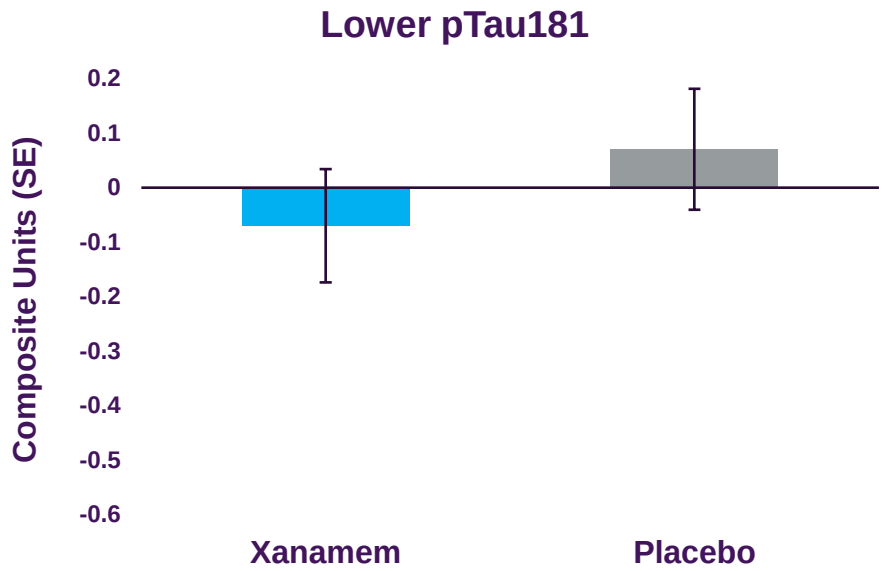
* Standard Error of the mean

# Exploratory: Change from baseline in cognitive-functional composite (with CDR-SB)

## Trends in change of composite of CDR-SB, word recall & recognition, CFT, COWAT




**Preserved cognition & function**




**No effect**

**Consistent with Xanamem activity as a cognitive & functional preserver**

* Standard Error of the mean

# The new analysis validates and de-risks the AD program

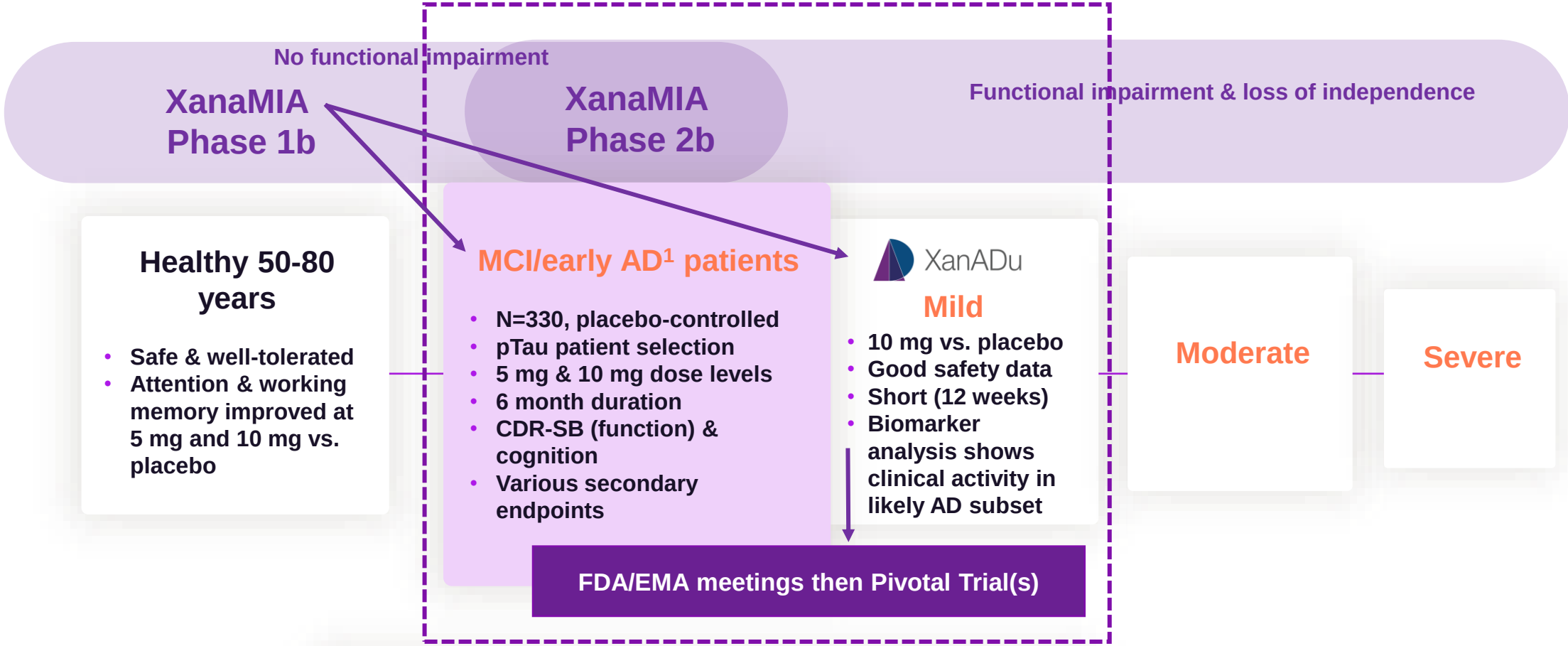
- ✓ **Confirming clinical activity of Xanamem in mild AD patients**
- ✓ **Large clinical effect size**
- ✓ **Utility of blood pTau levels to select suitable patients for next Phase 2b trial**
- ✓ **Utility of CDR-SB to measure the benefit of Xanamem in future trials**
- ✓ **Potential utility of other tests of cognition including executive function**

**Confirms the pro-cognitive & positive clinical effects of Xanamem at 10 mg daily**

# Moving forward rapidly in Cognitive Impairment in AD and Depression

## Biomarker data validate planned Phase 2b protocol in Mild Cognitive Impairment / mild AD with positive blood pTau

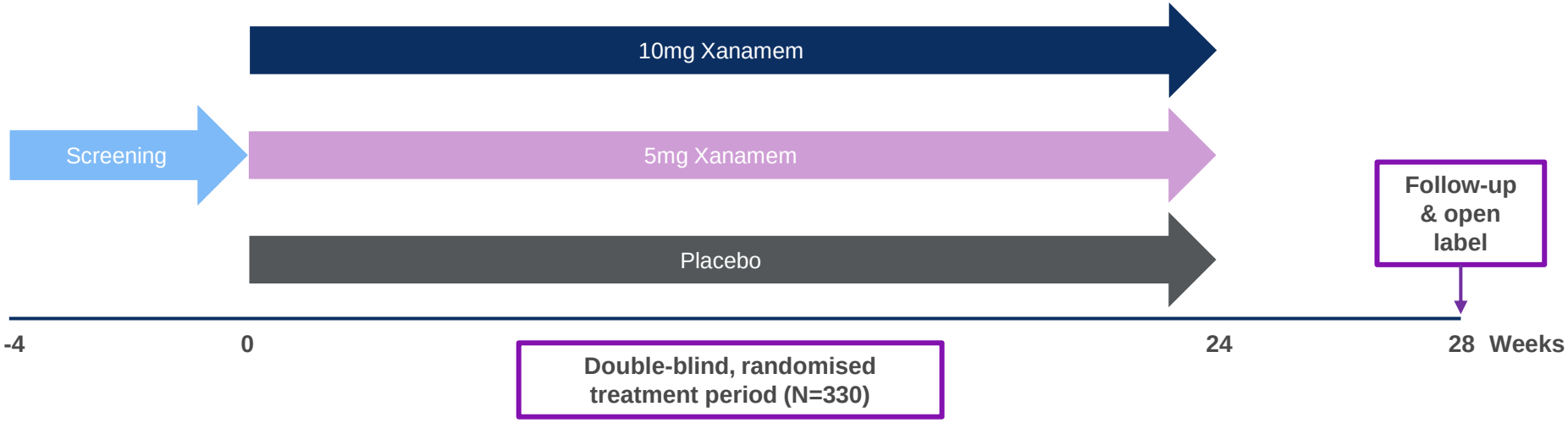
# Focus on speed to approval with 6 and 9-month trials




**Rapid path to patients as a standalone or combination therapy**

1. Mild Cognitive Impairment (MCI): memory, executive function deterioration with retained functional abilities; very mild AD with some functional impairment

# XanaMIA Phase 2b trial design & implementation model: selecting AD patients by blood pTau level




| Key inclusion/exclusion criteria | Primary Endpoints | Key Secondary Endpoints | Key Implementation Features |
|---|---|---|---|
| • Clinical diagnosis of **MCI or mild dementia** due to AD (NIA-AA)<br>• Elevated blood **p-tau181**<br>• Cognitive impairment relative to demographic norms<br>• Excluded vascular cause of dementia | • **CDR-SB**<br>• **Cogstate CTB attentional composite** (attention and working memory) | • **Amsterdam Activity of Daily Living** scale<br>• Cogstate **Executive Function & Episodic Memory** Function Composites<br>• Individual tests<br>• Carer questionnaire / Patient Global Improvement | • **Australian trial sites plus selected international locations**<br>• **Actinogen "hands-on" operational model**<br>• Optimized for scalable addition of international sites as required |

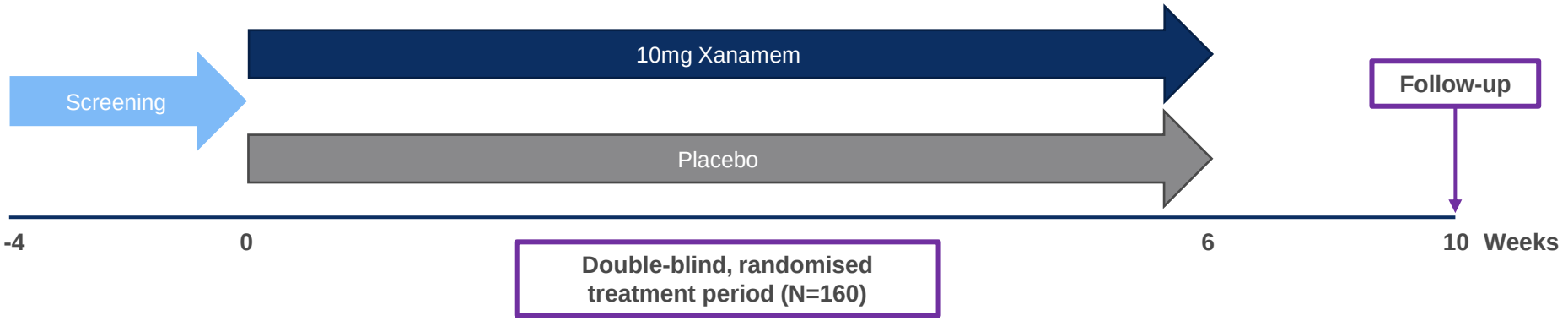
iDSST=international Digit Symbol Substitution Test - Symbols ; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; MCI=mild cognitive impairment; NIA-AA=National Institute of Aging - Alzheimer's Association; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status;

# Science Behind the Xanamem Depression Program

- ✓ 80-90% report neurocognitive symptoms[1]
- ✓ Cognitive symptoms often persist during remission[1]
- ✓ Elevated cortisol associated with severe, melancholic depression[2]
- ✓ Cortisol levels associated with treatment outcomes, relapse, & cognition[3]
- ✓ Positive effects with GR receptor antagonism with mifepristone[4]
- ✓ Meta-analysis of clinical cortisol approaches[5]
- ✓ Xanamem has improved human cognition in a number of studies[6]


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 biopolar disorder, Young et al. 2004; Evidence from clinical studies with $CRH_1$ receptor antagonists, Holsboer & Ising 2008
5. Meta-analysis of prior trials aimed at reducing cortisol, Ding et. al 2021
6. Xanamem placebo-controlled trial working memory & attention (Actinogen data on file)

# XanaCIDD trial design & implementation model




| Key inclusion/exclusion criteria | Primary Endpoints | Key Secondary Endpoints | Key Implementation Features |
|---|---|---|---|
| • Primary diagnosis of **MDD**<br>• **Persistent depressive symptoms despite existing therapy**<br>• **Cognitive impairment** relative to demographic norms | • **Cogstate CTB attentional composite** (attention and working memory) | • Montgomery-Åsberg Depression Rating Scale (**MADRS**)<br>• **Executive Function** Cognitive Composite<br>• **Memory Function** Cognitive Composite | • **Australian trial sites**<br>• **Actinogen "hands-on" operational model**<br>• **First patient enrollment planned for 2022** |

# Xanamem Development: Strategy & Timelines

# Actinogen strategy validated by new trial results

**Backed by strong balance sheet and intellectual property**

## Accelerate clinical development

- ***Focus on cognitive enhancement*:**
  - **Patients with early Alzheimer's Disease**
    - **Use pTau for patient selection**
    - **Phase 2b will use commercial tablets**
  - **Cognitive enhancement Depression** Phase 2
  - Trial **operations based in Australia** and selected other countries

## Forward planning

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

## Create value from partnerships

***Pharma/biotech engagement***

- **Actively engage large and mid-size potential partners with new results**
  - Seek value-add partnerships
  - Evaluate regional opportunities

***Regulatory engagement***

- Seek early **US FDA and EMA** interactions to agree endpoints for pivotal, approvable trials in AD

# Two major phase 2 trials of Xanamem in 2023-24

**2022**

- Two positive, independent clinical trials
- Commercial tablet manufacturing
- XanaCIDD trial started enrolling in Depression
- FDA “clear to proceed” with Phase 2b in AD

**2023**

- XanaMIA Phase 2b enrollment starts H1
- XanaCIDD enrollment ± depression results
- Presentations & publications

**2024**

- XanaMIA Phase 2b AD results
- Expand Cognitive/Depression program

# Appendix

# Selected glossary 1

**11β-HSD1** 11 beta HydroxySteroid Dehydrogenase-1 enzyme

**Aβ** Amyloid beta – a type of amyloid protein associated with Alzheimer's Disease, 42 and 40 are different forms

**ACTH** Adrenocorticotropic hormone that regulates blood levels of cortisol

**ADAS-Cog** Alzheimer's Disease Assessment Score - Cognition

**ApoE4** Apoprotein genotype associated with genetic risk of Alzheimer's Disease

**ATN** Amyloid, Tau, Neurodegeneration

**Clinical scales** Measure how a patient feels, performs and functions

**CDR-SB** Clinical Dementia Rating "Sum of Boxes" scale measuring cognition and function on an 18-point scale (high worse)

**CNS** Central nervous system

**CSF** Cerebrospinal fluid

**CTAD** Clinical Trials on Alzheimer's Disease (conference)

**CTB** Cognitive Test Battery of computerized tests

**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

**Filamen A** a protein believed to relate to amyloid toxicity

**GFAP** Glial Fibrilliary Acidic Protein – a marker of microglial cell activation in the brain

**IDSST** International Digit Symbol Substitution Test of cognition

# Selected glossary 2

**IQCODE** Informant Questionnaire on Cognitive Decline in the Elderly

**MCI** Mild Cognitive Impairment – memory, executive function deterioration with retained functional abilities

**MDD** Major Depressive Disorder

**MMSE** Mini Mental State Examination – a 30-point scale of simple questions to assess mental abilities

**NfL** Neurofilament Light – a nerve protein in the brain and rest of the body too

**NIA-AA** National Institutes of Aging and Alzheimer's Association

**NMDA** a type of receptor for glutamate in the brain

**NPI** Neuropsychiatric Inventory to assess psychiatric symptoms

**NTB** a Neurologic Test Battery, in this presentation one designed to measure executive function aspects of cognition

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

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

**p-Tau181 or 217** AD biomarker of phosphorylated Tau protein

**QPCT** Glutaminyl-peptide cyclotransferase is an enzyme proposed to create toxic amyloid species

**RAVLT** Rey Auditory Visual Learning Test

**RBANS** Repeatable Battery for the Assessment of Neuropsychological Status (a test of mental abilities)

**ROC AUC** Receiver Operating Curve Area Under the Curve (1.0 ideal) – a type of statistical test to compared two methods of measurement

**Tau** – a brain protein

**Ttau** – total tau levels including both phosphorylated and non-phosphorylated tau