



Two near-term major Phase 2 readouts in Alzheimer's Disease & Depression in 2024 and 2025

Xanamem[®] is a low-dose oral therapy targeting reduced tissue cortisol in the brain

Bell Potter Healthcare conference 15 November 2023

Non-confidential

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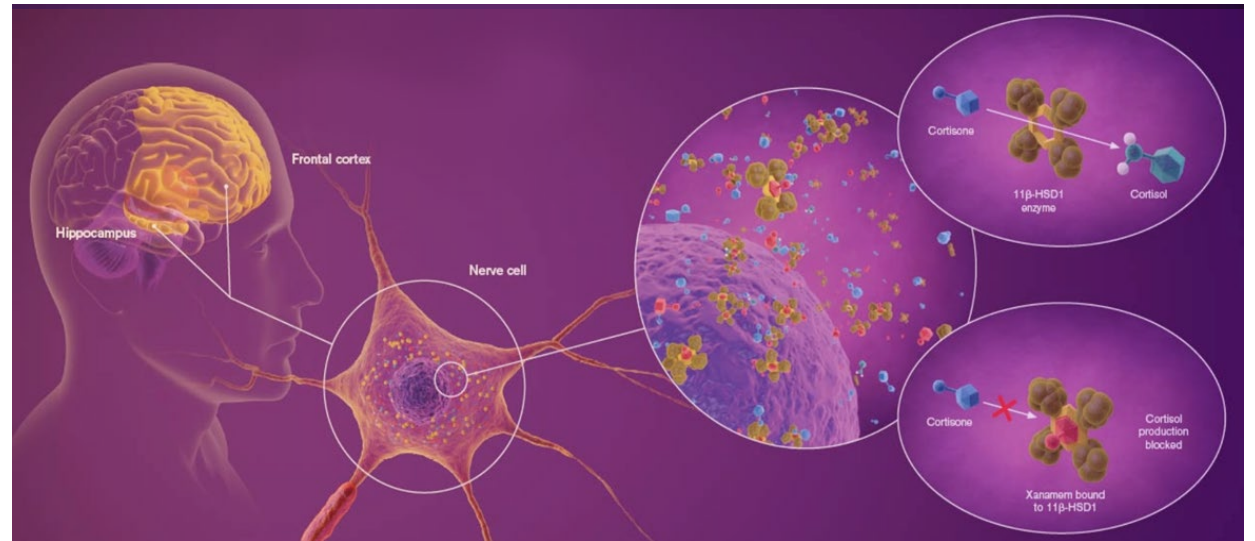
Xanamem: oral, once-a-day treatment with a unique, non-amyloid/non-tau mechanism

Mouse experimental studies & clinical trials validate cortisol as a target for the treatment of AD¹⁻⁴
Inflammation and glucose/lipid dysregulation emerging as causal mechanisms in AD⁵

Brain penetrant 11 β -HSD1 small molecule enzyme inhibitor reduces cortisol inside brain cells^{3,4}

Potential to be:

- **Anti-inflammatory**
- **Insulin sensitizing**
- **Rapidly cognitive enhancing**
- **Disease-modifying** (slowing progression)^{1,3}
- **Anti-depressant**



1. 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 – at 13 month cognitive protection was independent of continued amyloid deposition; 2. Popoli et al. 2011 microglial cell modulation in rats, effects on glutamate, cannabinoid and other signalling pathways; 3. Hilt, D. Oral symposium AD/PD International Conference 2023; Actinogen website: [Actinogen – News](#); 4. based on human PET scan evidence (data on file), Webster et al. 2017 Selection and early clinical evaluation of the brain-penetrant 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor UE2343 (Xanamem™); 5. CTAD conference Oct 2023

Two large clinical opportunities

Rapidly acting oral therapy with dual action on cognitive impairment / depression

Depression market size ~\$17 billion in 2032

Cognitively enhancing and disease modifying oral therapy for all stages of Alzheimer's disease

Alzheimer's market ~\$14 billion in 2030

Actinogen Phase 2 trials underway

**Phase 2a proof-of-concept trial in
Depression/Cognitive Impairment (n=160)**



**Results
Q2 2024**

**Phase 2b confirmatory trial in mild-moderate
Alzheimer's disease (n=220)**



**Initial results
H1 2025**

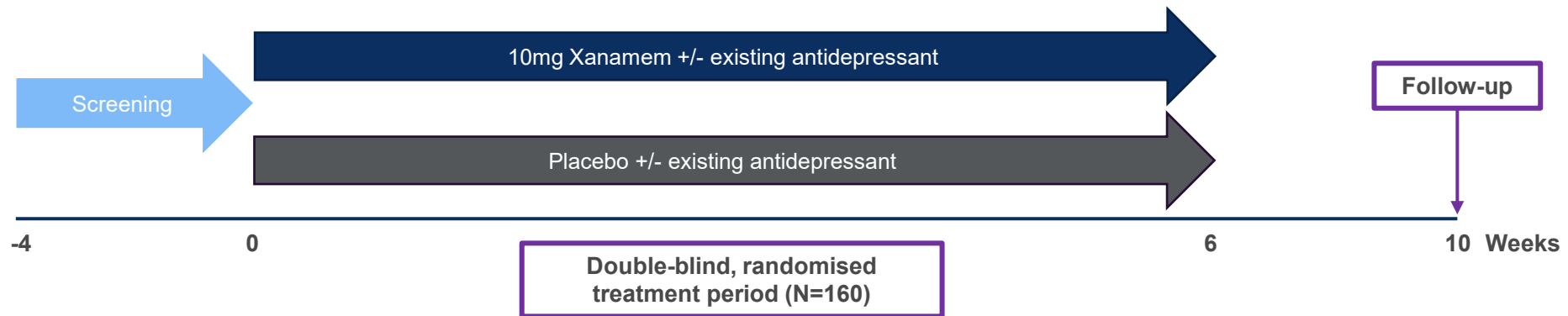
Why targeting brain cortisol with Xanamem is a promising strategy in depression

- ✓ 80-90% of patients report neurocognitive symptoms¹
- ✓ Cognitive symptoms often persist during remission¹
- ✓ Elevated cortisol associated with severe, melancholic depression²
- ✓ Cortisol levels associated with treatment outcomes, relapse, & cognition³
- ✓ Positive effects with GR receptor antagonism with mifepristone⁴
- ✓ Meta-analysis of clinical cortisol approaches⁵
- ✓ **Xanamem has improved human cognition in a number of trials⁶**

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 CRH₁ 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 proof-of-concept Phase 2a trial in Depression



Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
<ul style="list-style-type: none"> Primary diagnosis of MDD Persistent depressive symptoms despite existing therapy or no therapy Cognitive impairment relative to demographic norms 	<ul style="list-style-type: none"> Cogstate Cognitive Test Battery Attentional Composite (attention and working memory)* 	<ul style="list-style-type: none"> Montgomery-Åsberg Depression Rating Scale (MADRS) Executive Function Cognitive Composite Memory Function Cognitive Composite 	<ul style="list-style-type: none"> Australia, UK & US trial sites Actinogen “hands-on” operational model ~40% enrolled at Oct 16, 2023 Final Results Q2 CY24

* Same attention and working memory tests shown to demonstrate Xanmem effect in the XanaHES and XanaMIA Part A trials (see Slide 7)



The answers to Alzheimer's Disease are starting to emerge in the clinic...

Alzheimer's proteins are the pathology – not the cause...

Other causal processes are involved like inflammation, lipids and glucose handling...

Why targeting brain cortisol with Xanamem is a promising strategy in Alzheimer's disease



Many parts of the program have been de-risked

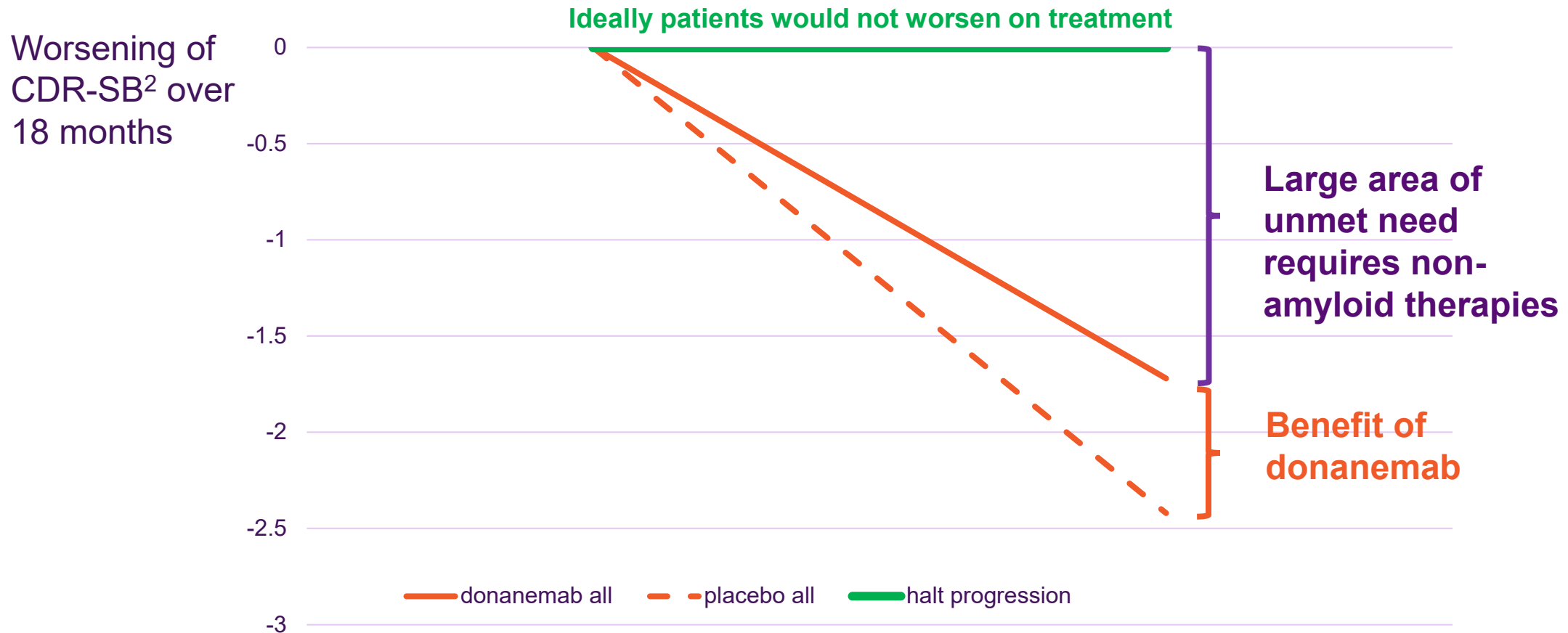
Epidemiology, cortisol and animal experiments

- ✓ Cortisol levels are elevated in brain fluid in early Alzheimer's^{1,2}
- ✓ Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment³
- ✓ Elevated cortisol levels are associated with clinical progression⁴⁻⁷
- ✓ Animal models of 11 β -HSD1 inhibition show neuroprotection independent of amyloid

Clinical trials of Xanamem

- ✓ Inhibits brain 11 β -HSD1 target to a high degree in PET study⁸
- ✓ Improves attention & working memory (2 trials)⁹
- ✓ Slows progression in CDR-SB and cognition in biomarker-positive patients with mild AD (1 trial)¹⁰
- ✓ Safety demonstrated in > 300 people (5 trials)

Newer anti-amyloid “immunotherapy” antibodies shown to slow but not halt progression of AD¹



Drugs targeting other mechanisms like Xanamem are needed

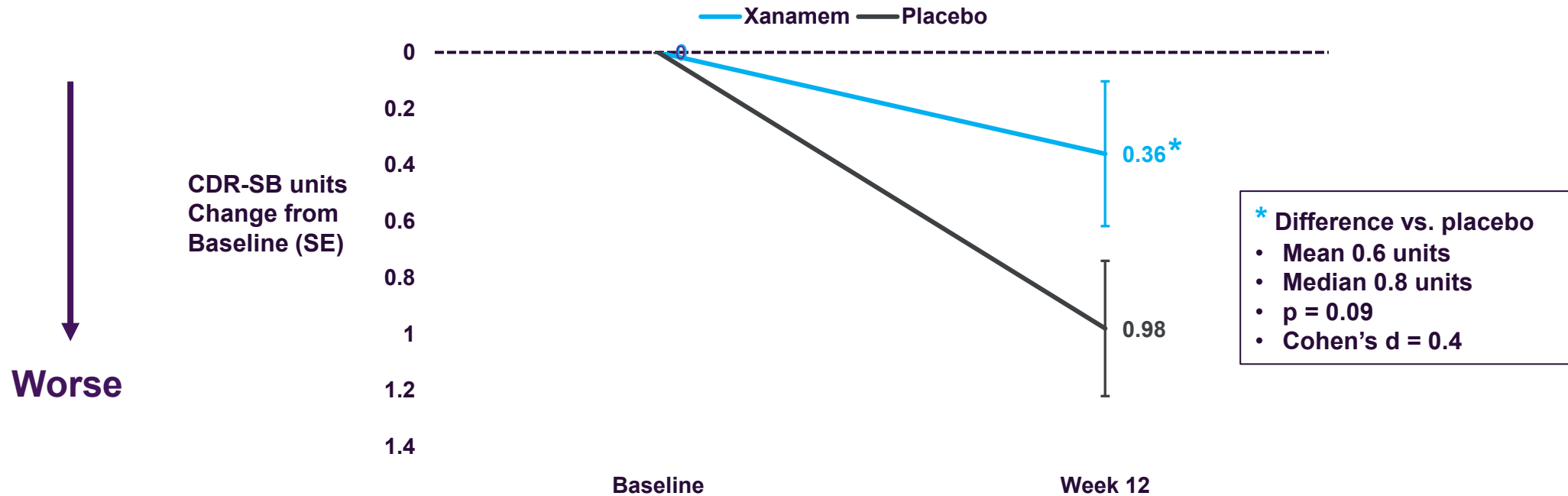
1. Donanemab is an anti-amyloid antibody given as an intravenous infusion every 4 weeks until amyloid clearance (Sims JR et al. *JAMA*. Published online July 17, 2023. doi:10.1001/jama.2023.13239 Data shown are for whole population studied with absolute difference to placebo of 0.7 points, intermediate tau population difference also 0.7 points

2. CDR-SB is an 18-point scale measuring functional status on an 18 point scale, patients in the donanemab trial had an average baseline score of 4 ± 2 points

Xanamem dramatically slows the rate of functional decline (CDR-SB) in patients with mild AD*



Patients with elevated plasma pTau181 indicating progressive, amyloid-positive disease (n=34)



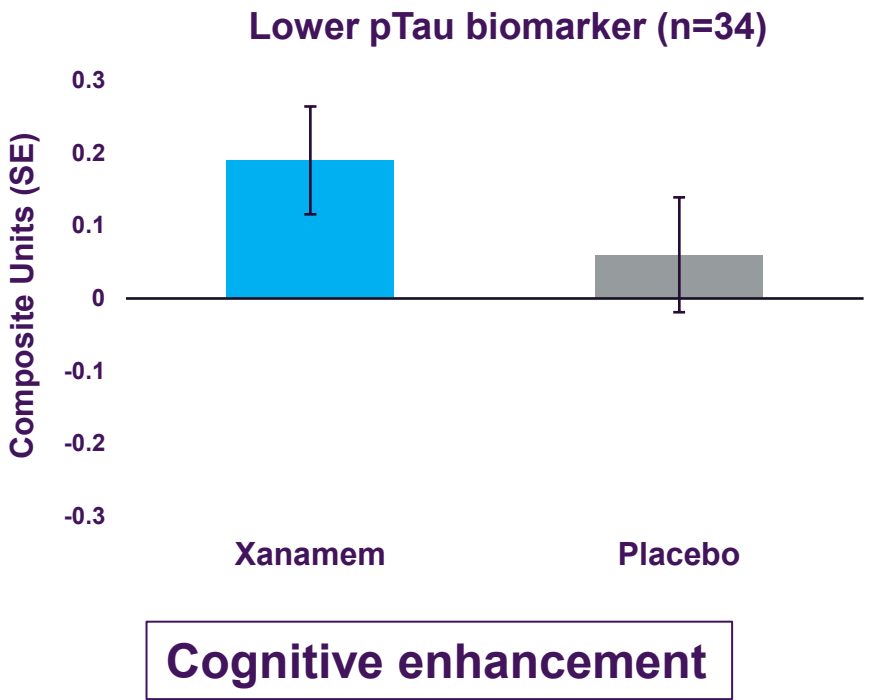
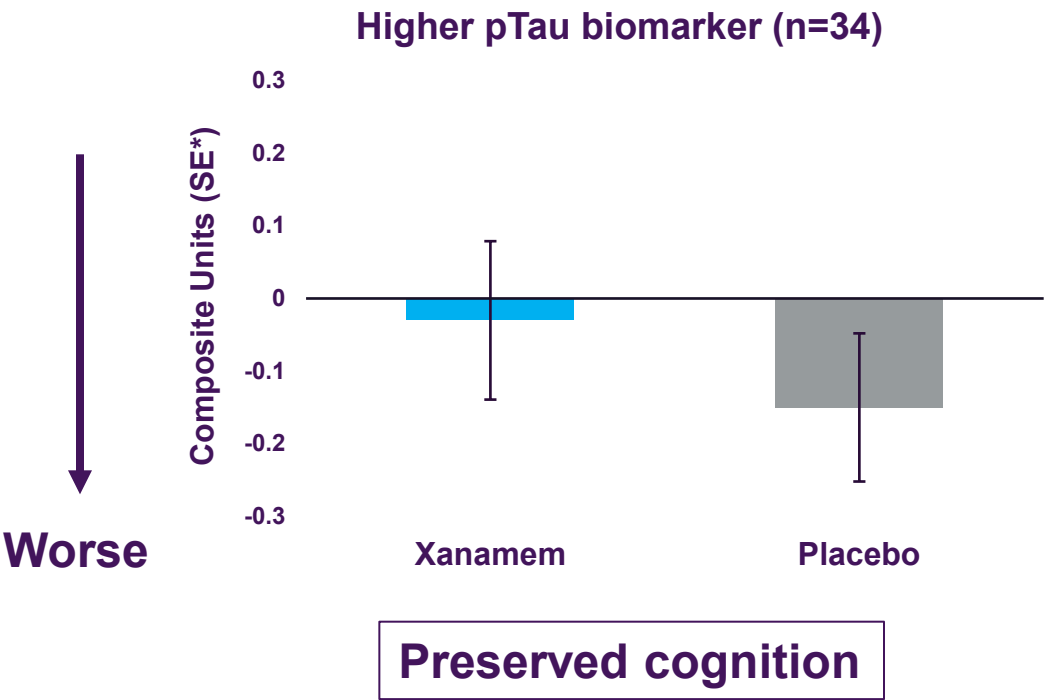
Extrapolated to 18 months effect size would be very large

* CDR-SB Clinical Demetia Rating Scale – Sum of Boxes is a measure of patient function and is an endpoint used by the FDA; Patients with a pre-treatment plasma pTau181 level greater than the pre-specified median of 6.74 pg/mL to indicate AD pathology and likelihood of progressive disease; similar effect size for pTau >10.2 pg/mL cutoff; extrapolated effect size 8-10 times greater than 0.4-0.45 reported for lecanemab (USPI Leqembi 2023 & van Dyck et al. 2022; DOI: 10.1056/NEJMoa2212948) if extrapolated to 18 months; no treatment effect detected in ADASCog-14 or ADCOMS

Cognitive scores suggest potential clinical benefit across dementia patient sub-types*



Positive trends in both high and low plasma pTau biomarker groups

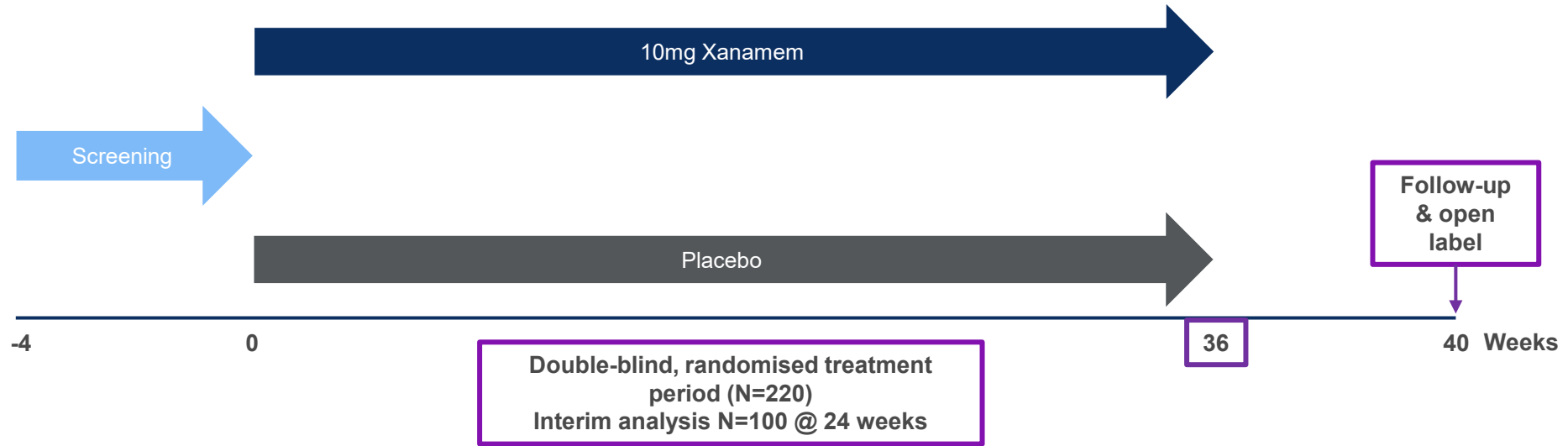


Consistent with Xanamem activity as a cognitive enhancer & disease-modifier

* Post hoc analysis of composite of word recall & recognition, CFT & COWAT tests (p=NS), error bars show Standard Error of the Mean; low pTau patients less likely to have amyloid-positive disease, results consistent with volunteer data shown in Slide 7

XanaMIA Phase 2b trial in Alzheimer's Disease

Matching patients and endpoints used in the positive Ph 2a analysis



Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
<ul style="list-style-type: none"> Clinical diagnosis of mild to moderate dementia due to AD (NIA-AA, MMSE 18-26) Blood p-tau181 to confirm progressive AD diagnosis Cognitive impairment test 	<ul style="list-style-type: none"> Cognitive Test Battery (cognitive measures) 	<ul style="list-style-type: none"> CDR-SB (functional measure) Amsterdam Activity of Daily Living scale Executive Function & Episodic Memory Function Composites Care Giver questionnaire / Patient Global Improvement 	<ul style="list-style-type: none"> Initial 100 patients in Australia Expand to global trial sites including US, Asia, EU and other Actinogen “hands-on” operational model Administrative interim analysis H1CY25

**Dr Howard Fillit,
Founder Alzheimer's Drug Discovery Foundation in 2022¹**

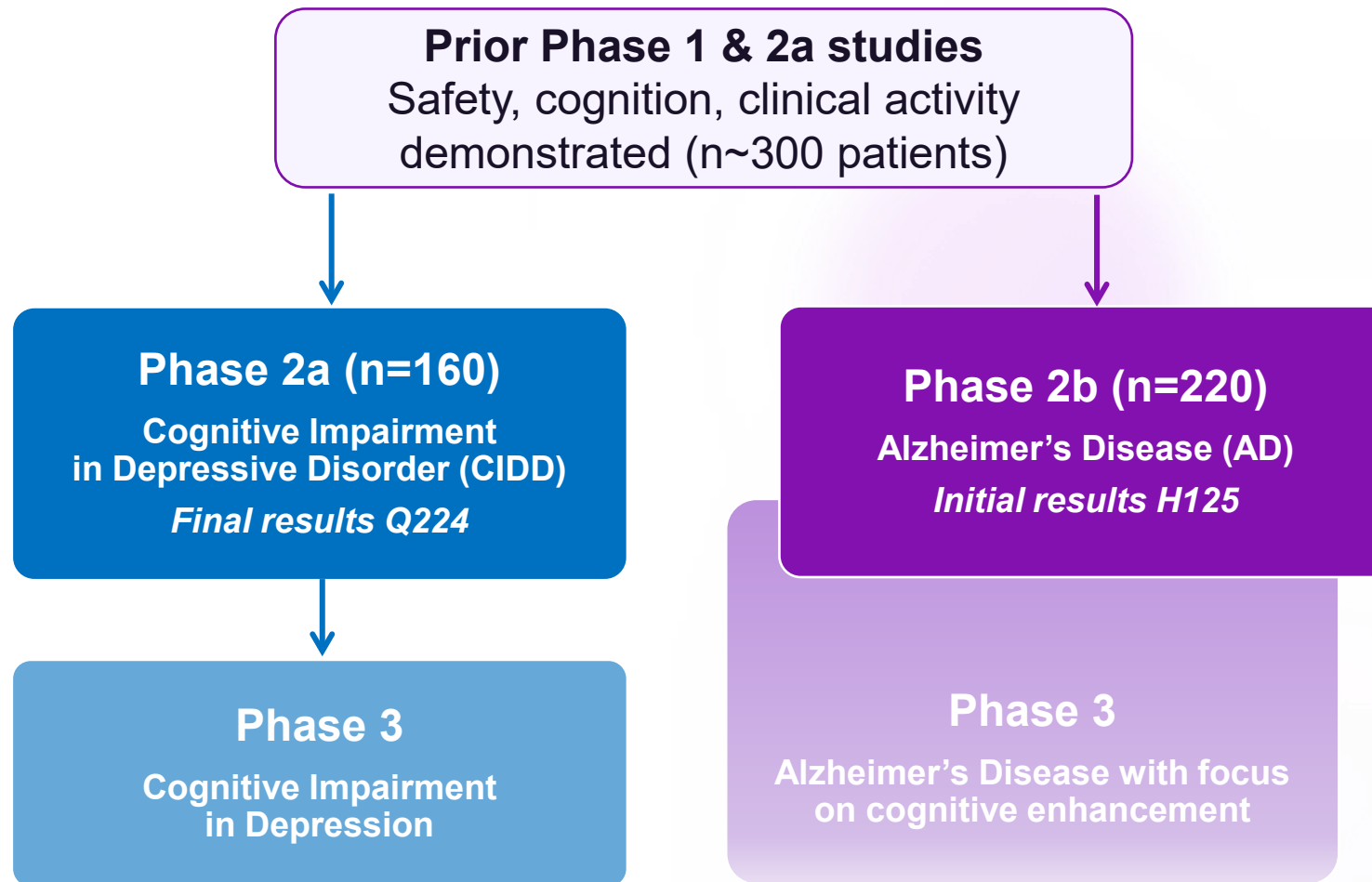
“Seventy-five percent, I think it is now, of all drugs in clinical development are non-amyloid, non-tau drugs.

Multiple targets are being addressed now, which is great for the field because I think the way we're going to have to go is combination therapy, addressing all the multiple pathways that are involved in Alzheimer's.”

Xanamem AD & Depression programs



Building on three independent Phase 1 and 2 studies showing safety and procognitive activity



Experienced 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



Dr. Nicki Vasquez
Non-Executive Director
PhD



- 25+ years experience in biopharmaceutical discovery research and development
- Chief Portfolio Strategy & Alliance Officer at Sutro Biopharma



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

...with a talented management team in place



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



Cheryl Townsend
VP Clinical Operations
RN, M Health Law



Dana Hilt
Chief Medical Officer
MD



Fujun Li
Head of Manufacturing
PhD



Michael Roberts
Head of Investor Relations and Communications
B.Ec (Hons), CPA, F FIN

Actinogen summary

Actinogen Medical (ASX:ACW) is conducting Phase 2 trials of oral Xanamem in patients with cognitive impairment associated with depression and Alzheimer's disease. Results due in 2024 and 2025.



Attractive disease indications and rationale

- ✓ **Strong cortisol rationale for treatment of multiple diseases:** Alzheimer's disease & other dementias, depression & related cognitive impairment; cognitive impairment in schizophrenia; many others



Favourable pharmaceutical properties

- ✓ Demonstrated target engagement in brain and HPA axis¹ in human trials
- ✓ **Low dose and cost of goods, ≤10mg**
- ✓ **Low drug-drug interaction potential** suitable for combination therapy



Substantial clinical data

- ✓ **>300 subjects or patients safely treated**
- ✓ Cognitive enhancement **activity in three placebo-controlled trials**
- ✓ **Clinical benefit** in biomarker-positive AD patients (Phase 2a data)



Protected and funded

- ✓ Molecule in-licensed from U Edinburgh in 2014 to ASX-listed shell company
- ✓ Key patents in place² ~A\$110m funding for Xanamem program to date
- ✓ **Cash ~A\$13.1m & mkt cap. ~A\$45m (30 Sept 2023)**



High functioning semi-virtual company model

- ✓ Core team of 15 highly skilled employees based in Australia & US
- ✓ Leveraging senior consultants in various fields in Australia, Asia, UK and USA
- ✓ **Our Australian-based projects gain 48% as R&D cash rebate**

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

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

Appendix



International Cognition Clinical Advisory Board

Preeminent global thought-leaders in clinical trials for assessment of cognition



Prof. John Harrison

Metis Cognition Ltd

- 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 (CMO)



- 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



Dr Christina Kurre Olsen

ORPHA Z YME

- 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



Prof. Paul Maruff



- Chief Innovation Officer at Cogstate Ltd
- Professor in Neuroscience at the Florey Institute of Neuroscience and in Psychology Monash University, Melbourne Australia
- Senior management committee of the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of Alzheimer's Disease
- Involved in the development and approval of 13 new drugs that affect cognition including most recently esketamine for treatment resistant depression



A/Prof Christopher Chen



- Senior Clinician-Scientist, Associate Professor at the Departments of Pharmacology and Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, and Director of the Memory Aging and Cognition Centre, National University Healthcare System.
- Major research and clinical interests are in neuroimaging, molecular biology and treatment of stroke and dementia.
- President of the Asian Society Against Dementia, Secretary-Treasurer of the Asian & Oceanian Association of Neurology.

International Scientific Advisory Boards

Preeminent thought-leader 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



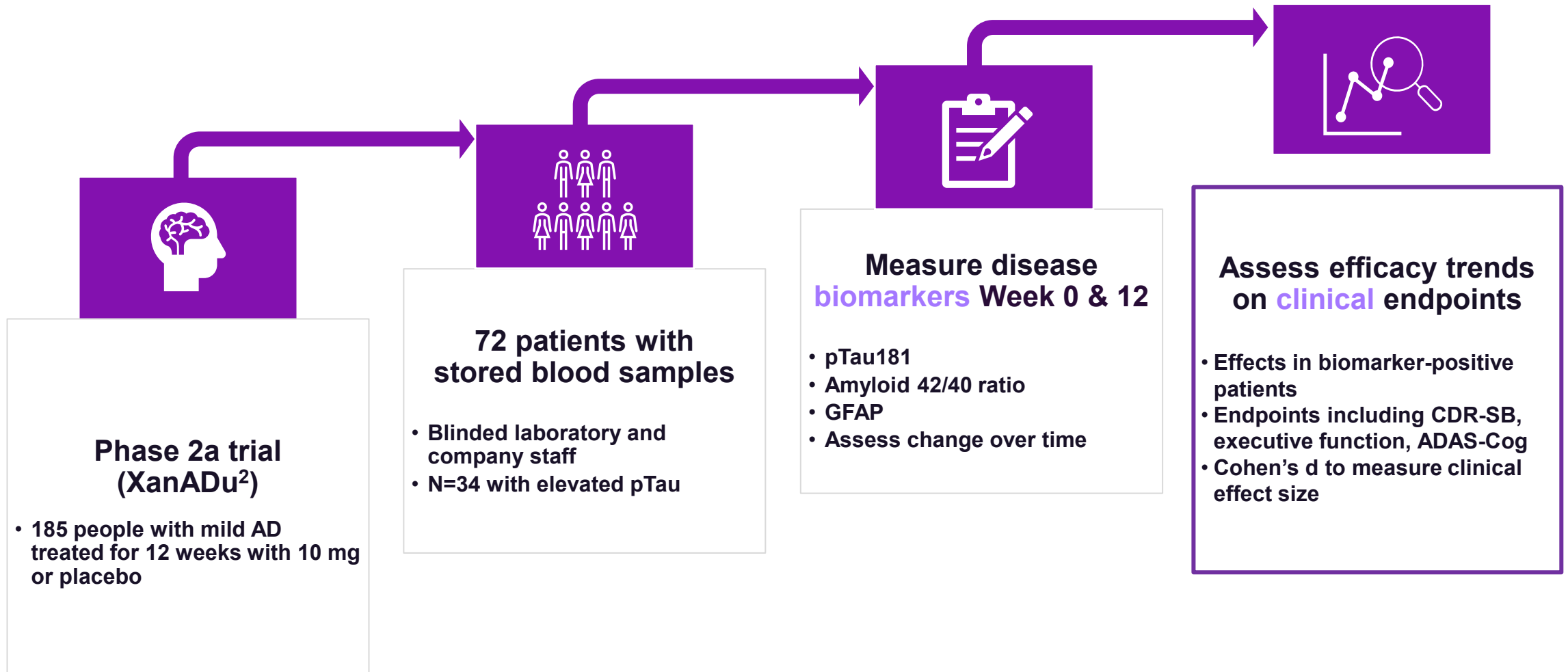
Prof. Scott Webster



- 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

Methods for double-blind, prospective assessment of biomarker-positive mild AD patients in Phase 2a¹

A simulation of the Phase 2b XanaMIA trial



1. Used a pre-specified protocol and statistical analysis plan, blinded laboratory and company personnel
2. Prior phase 2a trial completed in 2019 <https://clinicaltrials.gov/ct2/show/results/NCT02727699?term=actinogen&draw=2&rank=3>

Clinical Dementia Rating – Sum of Boxes (CDR-SB) functional endpoint to assess dementia in MCI/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)

Selected glossary 1



11 β -HSD1 11 beta HydroxySteroid Dehydrogenase-1 enzyme

A β Amyloid beta – a type of amyloid protein associated with Alzheimer’s Disease, 42 and 40 are different forms

ACTH Adrenocorticotrophic 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 Fibrillary 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

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