



Xanamem:® A novel pro-cognitive and potentially disease modifying drug

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

Corporate Presentation February 5, 2024

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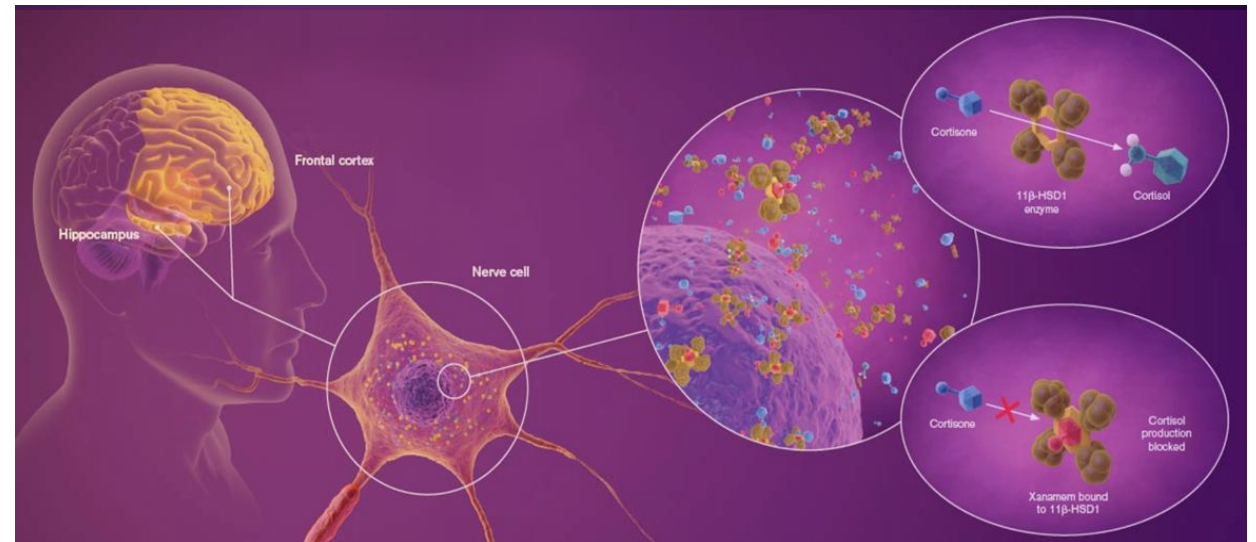
Xanamem: Oral, once-a-day treatment with a unique, non-amyloid/non-tau mechanism

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

Xanamem is a brain penetrant 11 β -HSD1 small molecule enzyme inhibitor which reduces brain cortisol^{3,4}

Potential to be:

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



Two large clinical opportunities: Depression and AD

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 not just MCI

Alzheimer's market ~\$14 billion in 2030

Actinogen Xanamem Phase 2 trials underway

De-risked by extensive existing clinical data from four previous trials of Xanamem 10mg

**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)**



**Interim results
H1 2025
n~100**

Targeting brain cortisol with Xanamem is a promising strategy in depression

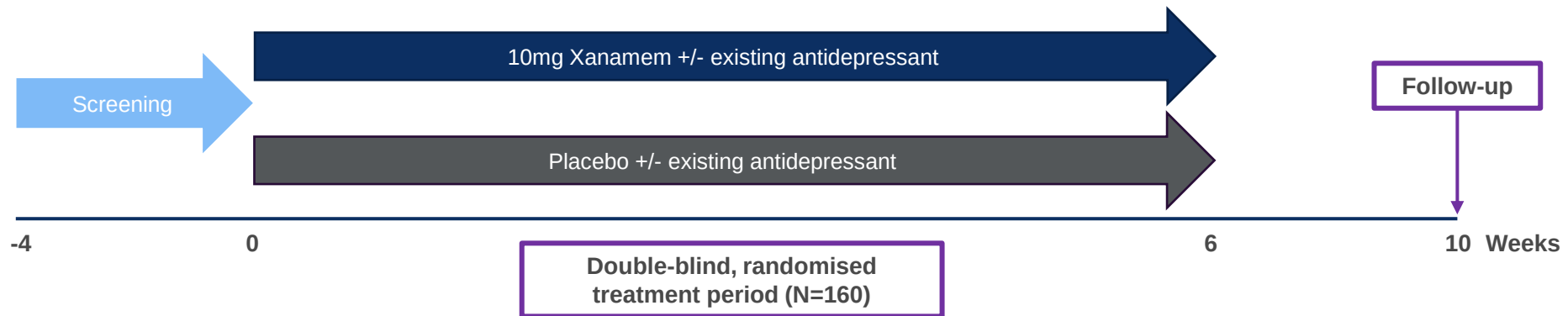
- ✓ 80-90% of MDD patients report neurocognitive symptoms¹
- ✓ Cognitive symptoms often persist during remission¹
- ✓ Elevated cortisol associated with severe, melancholic depression²
- ✓ Cortisol levels associated with treatment outcomes, relapse, & cognition³
- ✓ Positive effects with GR receptor antagonism with mifepristone⁴
- ✓ Meta-analysis of clinical cortisol approaches⁵

✓ **Xanamem has improved human cognition in 2 trials with same cognitive endpoint to be used⁶**

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. Two Xanamem placebo-controlled trials showing improved working memory & attention (Actinogen data on file)



XanaCIDD proof-of-concept Phase 2a trial in Depression and Cognitive Impairment



Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
- Primary diagnosis of MDD Persistent depressive symptoms/deficit despite existing therapy or no therapy Cognitive impairment relative to demographic norms (~ 0.5 SD)	Cogstate Cognitive Test Battery Attentional Composite (attention and working memory)*	- Montgomery-Åsberg Depression Rating Scale (MADRS) - Executive Function Cognitive Composite - Memory Function Cognitive Composite	Australia & UK trial sites Actinogen “hands-on” operational model > 110 enrolled Final Results Q2 CY24

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



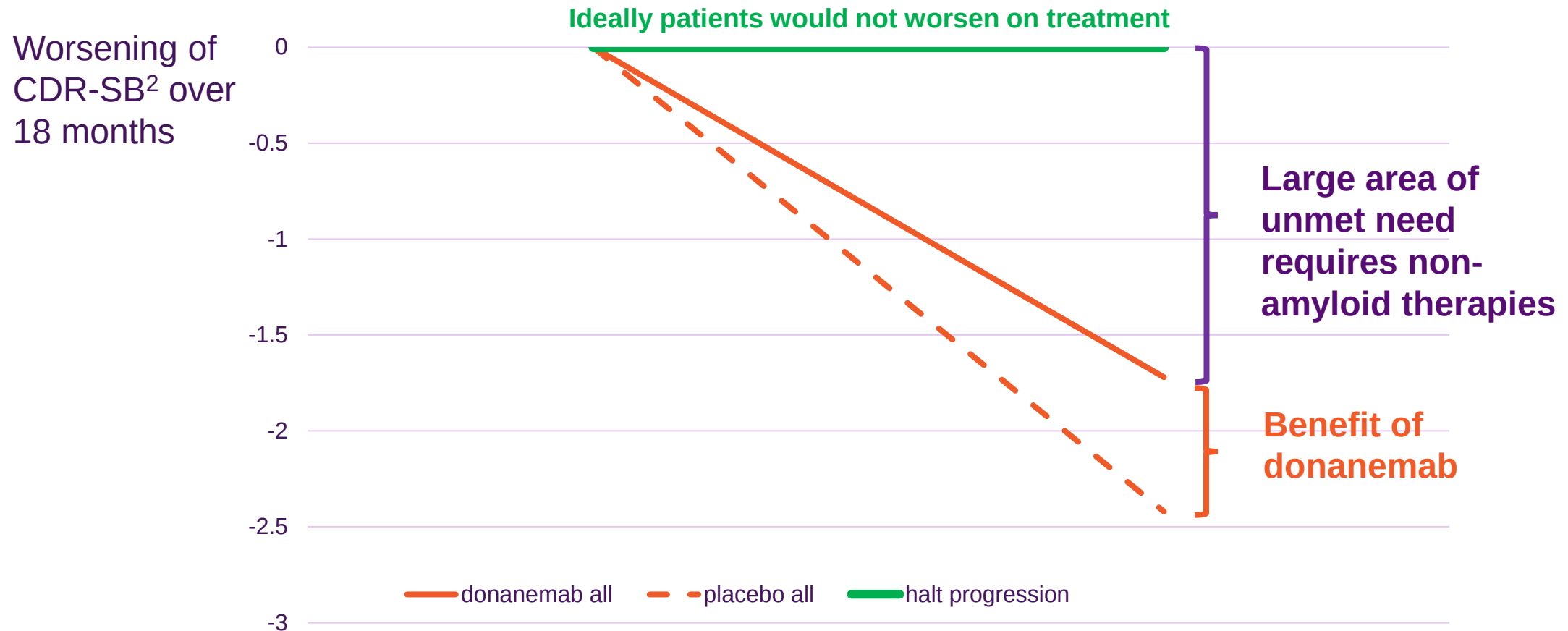
The answers to Alzheimer's Disease are starting to emerge in the clinic...

Alzheimer's proteins amyloid and tau are the pathology – not the cause...

Clearing amyloid produces a very modest benefit

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

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 at 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

Dr Howard Fillit, Founder Alzheimer's Drug Discovery Foundation¹

“Seventy-eight percent 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.”

1. <https://www.neurologylive.com/view/looking-ahead-development-alzheimer-disease-howard-fillit>; updated at recent October 2023 CTAD conference as 78% of programs

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



Multiple streams of data support the hypothesis

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

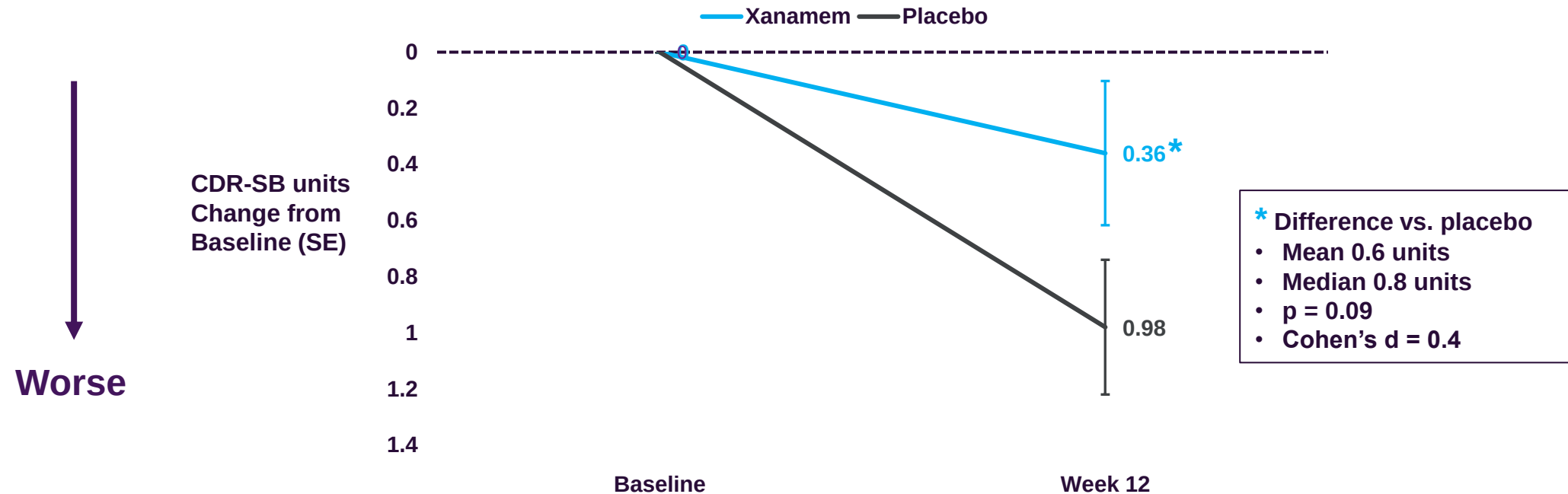
Clinical trials of Xanamem

- ✓ Inhibits brain 11 β -HSD1 target to a high degree in PET study at well tolerated doses⁸
- ✓ 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 ~350 people (5 trials)

Xanamem significantly 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)

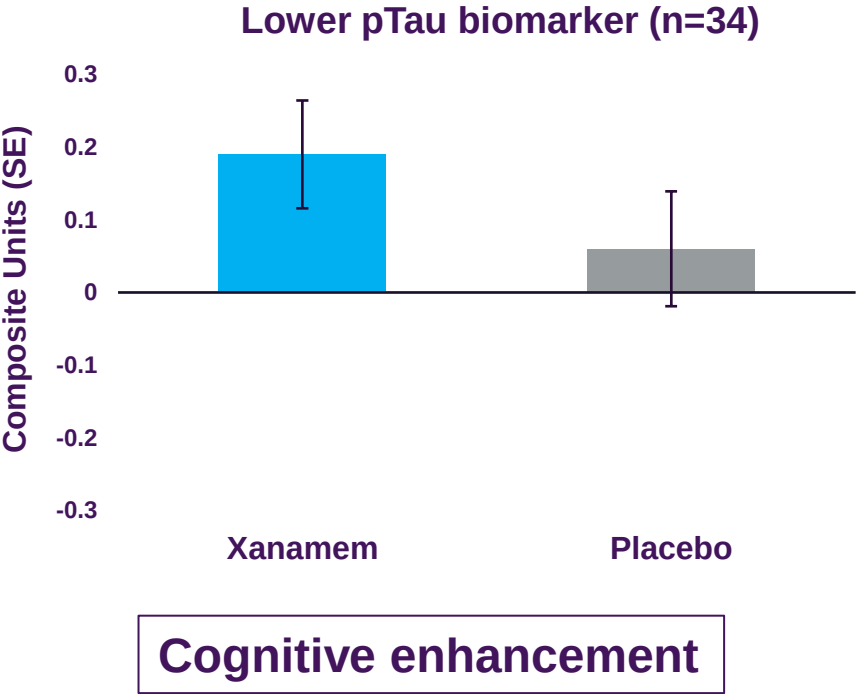
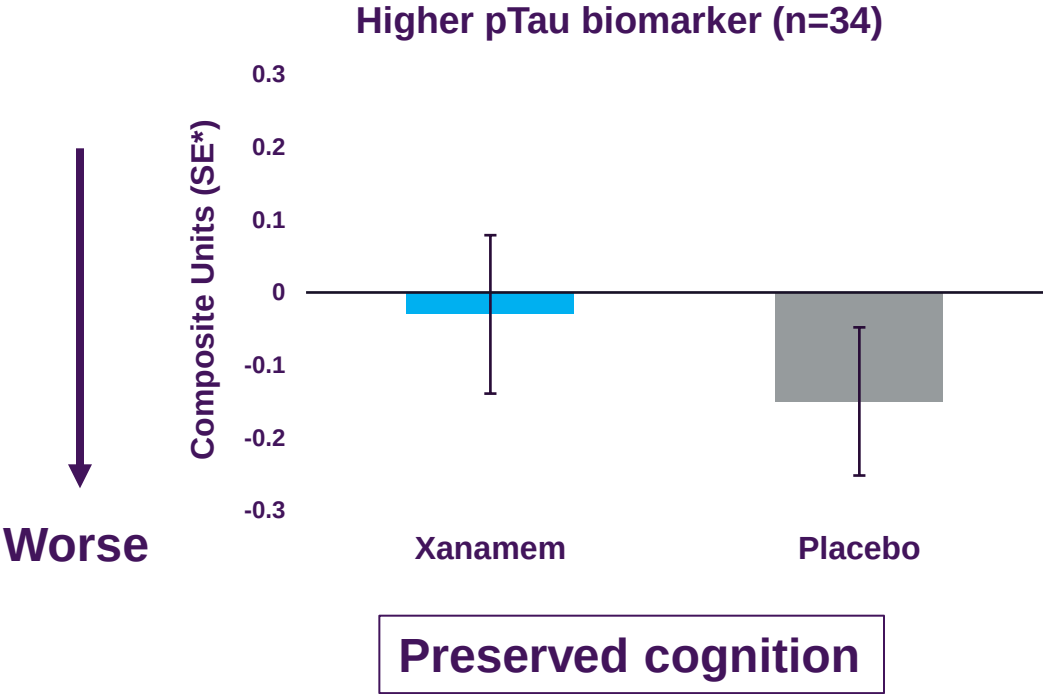


Xanamem benefits extrapolated to 18 months would produce a large effect size

Cognitive improvements suggest potential clinical benefits across dementia patient sub-types*



Positive trends in both high and low plasma pTau biomarker groups

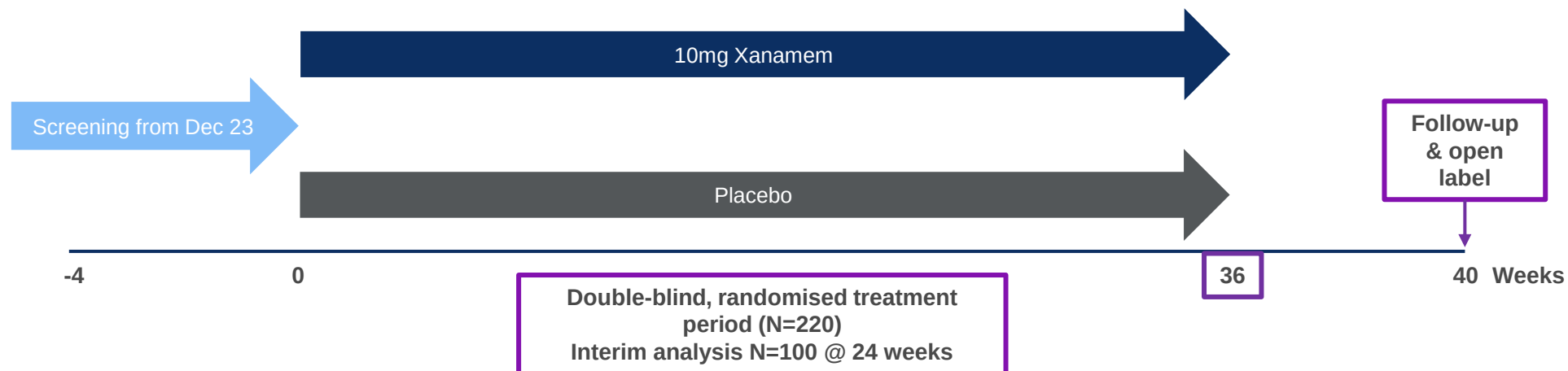


Consistent with Xanamem activity as a cognitive enhancer & disease-modifier

* 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 in Phase 2b as in the positive Ph 2a analysis

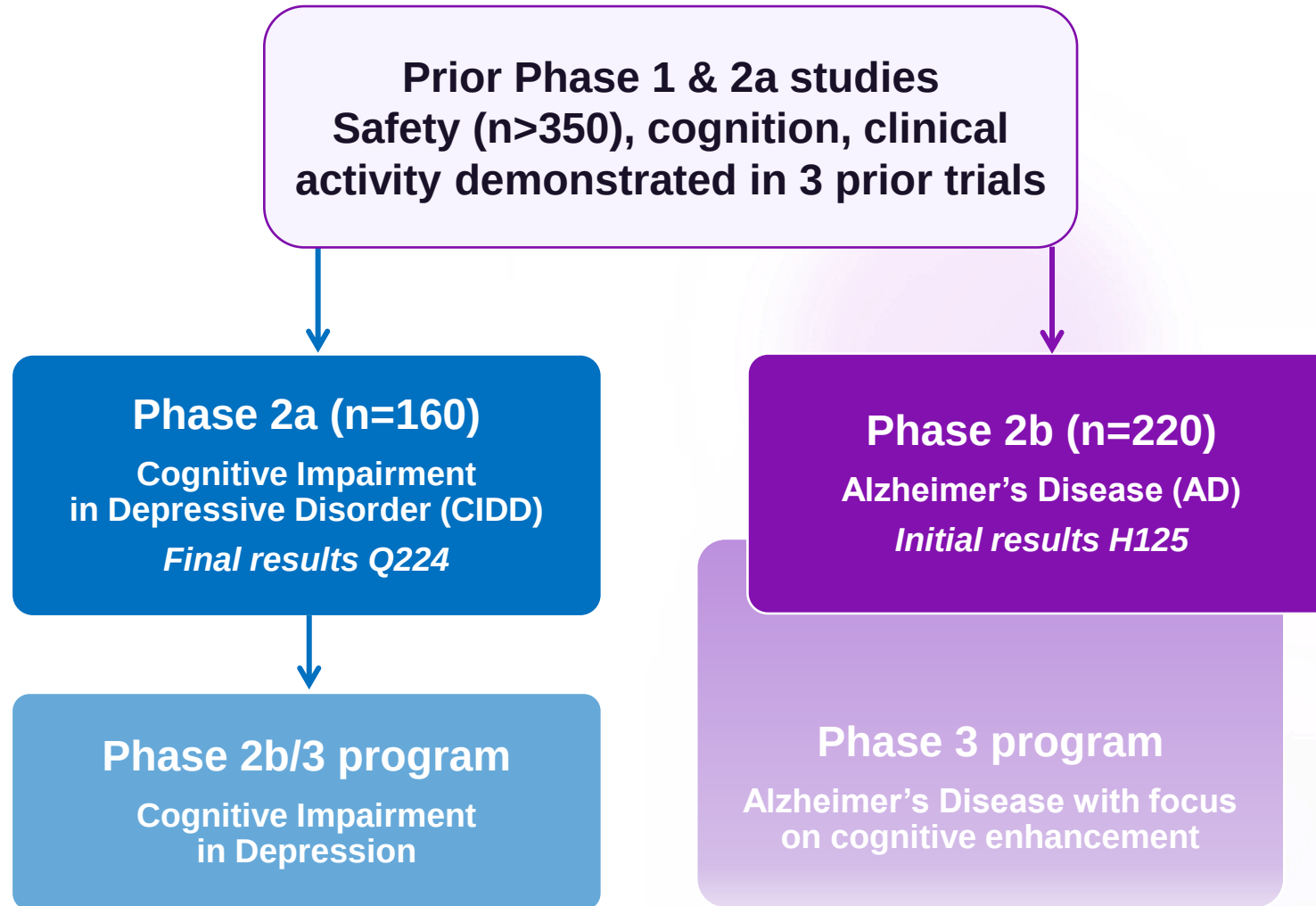


Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
- Clinical diagnosis of mild to moderate dementia due to AD (NIA-AA, MMSE 18-26) - Elevated blood p-tau181 to confirm progressive AD diagnosis - Cognitive impairment test deficit	Cognitive Test Battery (7 cognitive measures)	CDR-SB (functional measure) Amsterdam Activity of Daily Living scale - Executive Function & Episodic Memory Function Composites - Care Giver questionnaire / Patient Global Improvement	Initial 100 patients in Australia with Administrative IA in H1CY25 Expand to global trial sites including US, Asia, EU and other post IA Actinogen “hands-on” operational model assures high quality

Xanamem AD & Depression programs



Building on multiple Phase 1 and 2 studies showing safety and procognitive activity



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

- ✓ **~350 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\$11.5m (31 Dec 2023) & mkt cap. ~A\$70m (30 Jan 2024)**



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

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



Will Souter

Chief Financial Officer
BComm, LLB



Cheryl Townsend

VP Clinical Operations
RN, M Health Law



Dana Hilt

Chief Medical Officer
MD



Fujun Li

Head of Manufacturing
PhD



Michael Roberts

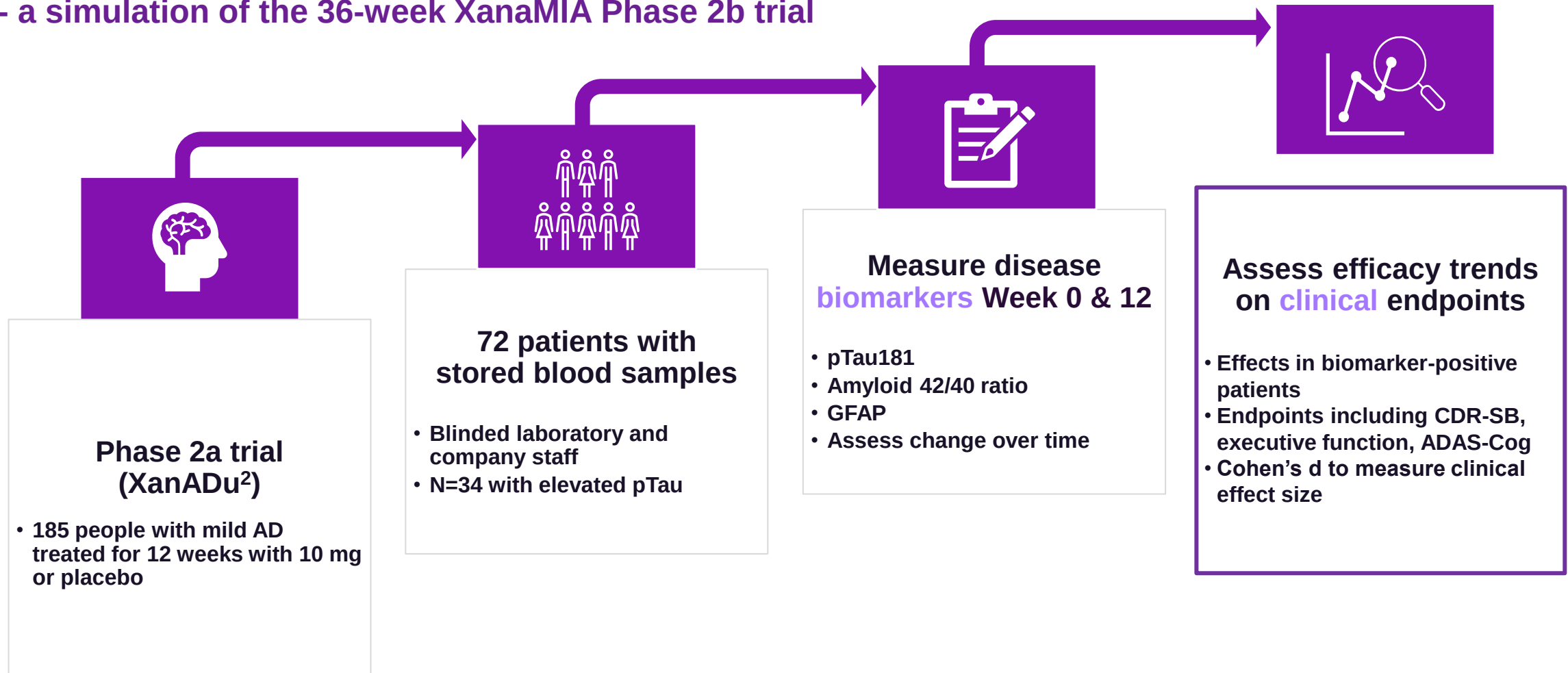
Head of Investor Relations and Communications
B.Ec (Hons), CPA, F FIN

Appendix



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

Re-examining the 12-week XanADu Phase 2a trial with biomarkers
- a simulation of the 36-week XanaMIA Phase 2b trial



1. Used a pre-specified protocol and statistical analysis plan, blinded laboratory and company personnel
2. Prior phase 2a trial completed in 2019 included participants with a clinical diagnosis but no PET or biomarker confirmation
<https://clinicaltrials.gov/ct2/show/results/NCT02727699?term=actinogen&draw=2&rank=3>

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



- 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

Selected glossary 1



11 β -HSD1 11 beta HydroxySteroid Dehydrogenase-1 enzyme. Selectively expressed in brain, liver, adipose.

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 Glutaminy-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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