



ASX ANNOUNCEMENT

Actinogen Clinical Trials Science Forum today – The critical importance of preparing for commercialization

ACW Chief Medical Officer Dr Dana Hilt and panelists discuss the latest developments in the quest for effective Alzheimer's treatments and how Actinogen is preparing for the future commercialization of its novel once-a-day oral medication, Xanamem®

Pre-register now, or register and join at 11am AEST today:

https://actinogenmedical.zoom.us/webinar/register/WN_EmFwifoRTZSI25qwoBy92g

Sydney, 15 May 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that Actinogen's Chief Medical Officer, Dr Dana Hilt, Chief Commercial Officer, Andy Udell and guest A/Prof Michael Woodward from Austin Health will join in a highly informative 'plain English' panel discussion that will review the scope of leading current and potential treatments in development for Alzheimer's disease and the ongoing significant unmet medical need for effective therapies.

Then, relevant to the Xanamem program now in late-stage clinical development, Andy Udell will outline what commercialization planning means for a company like Actinogen. He will explain how the Company is actively engaging in an important range of initiatives that include 1) careful design of pivotal, phase 2b/3 and phase 3 trials with insurance and other payors in mind, 2) thought leader development in multiple geographies, and 3) refined messaging for doctors and patients. Furthermore, full value from any future partnership will depend upon these activities being successfully conducted.

A copy of the webinar presentation is attached to this announcement. At the conclusion of the presentation, there will be an opportunity for questions from webinar attendees. A recording of the forum will be made available as soon as possible after the conclusion of the event on the Company's YouTube channel and links to the recording will be provided on the Company's website <https://actinogen.com.au/> and social media platforms.

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.

Clinical Trials

The XanaMIA Phase 2b/3 Alzheimer's disease trial is a double-blind, 36-week treatment, placebo-controlled, parallel group design trial in 220 patients with mild to moderate AD and progressive disease, determined by clinical criteria and confirmed by an elevated level of the pTau181 protein biomarker in blood. Patients receive Xanamem 10 mg or placebo, once daily, and its ability to slow progression of Alzheimer's disease is assessed with a variety of endpoints. The primary endpoint of the trial is the internationally-recognized CDR-SB (Clinical Dementia Rating scale – Sum of Boxes). The trial is being conducted in Australia and the US. Initial results from an interim analysis triggered by the 100th participant reaching 24 weeks of treatment are anticipated in Q4 2025 and final results Q4 2026.

The XanaCIDD Phase 2a depression trial was a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 167 patients with moderate, treatment-resistant depression and a degree of baseline cognitive impairment. Participants were evenly randomized to receive Xanamem 10 mg once daily or placebo, in most cases in addition to their existing antidepressant therapy, and effects on cognition and depression were assessed. Trial results were reported in August 2024 and showed clinically and statistically significant benefits on depression symptoms with positive effects on the MADRS scale (a validated scale of depression symptom measurement) and the PGI-S (a valid patient reported assessment of depression severity). Cognition improved markedly and to a similar extent in both Xanamem and placebo groups.

About Xanamem (emestedastat)

Xanamem's novel mechanism of action is to control the level of cortisol in the brain through the inhibition of the cortisol synthesis enzyme, 11 β -HSD1, without affecting production of cortisol by the adrenal glands. Xanamem is a first-in-class, once-a-day pill designed to deliver high levels of cortisol control in the brain.

Chronically elevated cortisol is associated with progression in Alzheimer's Disease and excess cortisol is known to be toxic to brain cells. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials. The recent XanaCIDD trial demonstrated clinically and sometimes statistically significant benefits on depressive symptoms.

The Company has studied 11 β -HSD1 inhibition by Xanamem in approximately 400 volunteers and patients in eight clinical trials. Xanamem has a promising safety profile and has demonstrated clinical activity in patients with depression, patients with biomarker-positive Alzheimer's disease and cognitively normal volunteers. 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.

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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Clinical Trials Science Forum 2025

The critical importance of preparing for commercialization

Dr Dana Hilt, Chief Medical Officer

Andy Udell, Chief Commercial Officer

A/Prof Michael Woodward, Head of Dementia Research, Austin Health

15 May 2025

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Disclaimer



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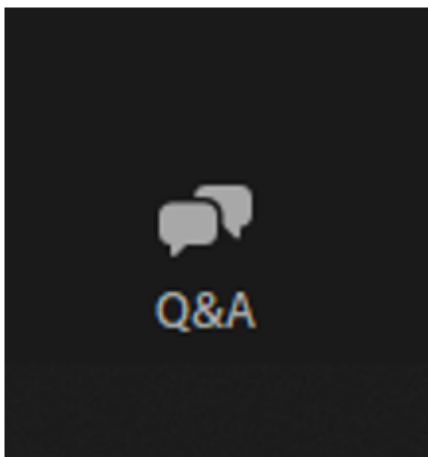
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Type your question here...



3. Hit enter on your keyboard to submit your message

Cancel

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Preparing for Xanamem's success

- Existing Alzheimer's treatments are clearly inadequate
- Newer "Next-Gen" Alzheimer's treatments are coming
- Oral Xanamem is one of the few late-stage and promising treatments with a novel mechanism

The time to prepare for Xanamem marketing and product launch is now

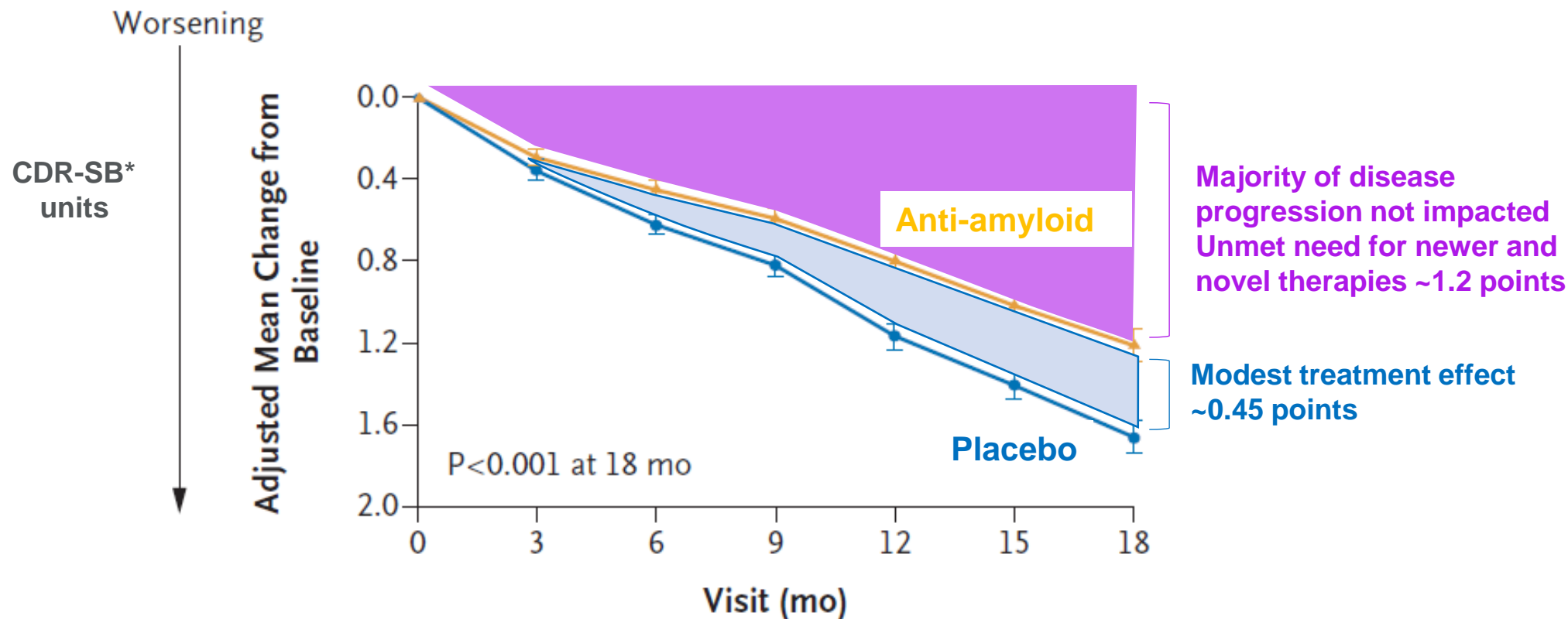
Alzheimer's disease treatment landscape

The treatment landscape is moving beyond amyloid therapy

Dr Dana C Hilt MD FAAN
ACW Chief Medical Officer

Modest effect of anti-amyloid antibodies

MCID of 1-2 points in CDR-SB not achieved plus cost, safety and monitoring issues*



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

* MCID: Minimally Clinically Important Difference to placebo; safety issues include brain swelling and bleeding, need for frequent brain scans to monitor
CDR –SB: Clinical Dementia Rating – Sum of Boxes

Physician concerns re anti-amyloid therapies (ATT)

Polling question (2025 AD/PD Congress):

Which of the following is the greatest barrier/challenge to implementing ATTs for early AD?

- | | |
|--|------------|
| 1. Interest/willingness of clinicians to treat patients | 3% |
| 2. Patient workup required to select the right patients for treatment | 2% |
| 3. Ability to guide patients about the risks/benefits based on medical and genetic profile | 5% |
| 4. Resources and workflows needed to deliver infusion therapy and monitor for ARIA | 15% |
| 5. Availability/reimbursement/regulatory status | 22% |
| 6. <i>All of the above are significant challenges/barriers to implementing ATTs</i> | 53% |

- ***Challenges to administration***
 - ***Very modest treatment effect***
 - ***Safety concerns***
- 
- Need for additional (non-amyloid) therapies***

Mechanisms upstream of amyloid are being explored

Virtually all chronic diseases require treatment of multiple mechanisms

Mechanism of Action (color)

- Amyloid
- ApoE, Lipids and Lipoprotein Receptors
- Epigenetic Regulators
- Growth Factors and Hormones
- Inflammation/Immunity
- Metabolism/Bioenergetics
- Neurogenesis
- Neurotransmitter Receptors
- Oxidative Stress
- Proteostasis/Proteinopathies
- Synaptic Plasticity/Neuroprotection
- Tau
- Vasculature
- Other

The initial focus of development has been both **anti-amyloid** and **anti-tau therapies**: Goal is to remove amyloid and tau

ApoE4 as a significant AD genetic risk factor has gained attention. But the exact mechanism by which ApoE4 increases AD risk is still not clear. It may facilitate amyloid deposition and promote inflammation.

The potential role of '**neuro-inflammation**' is increasingly receiving attention

Modulation of '**neurotransmitter tone**' is also being re-addressed. e.g. Combination drugs that can minimize peripheral side effects

Insights into the molecular pathogenesis and factors contributing to AD disease progression are now starting to inform the staging and identification of new treatments and new mechanisms

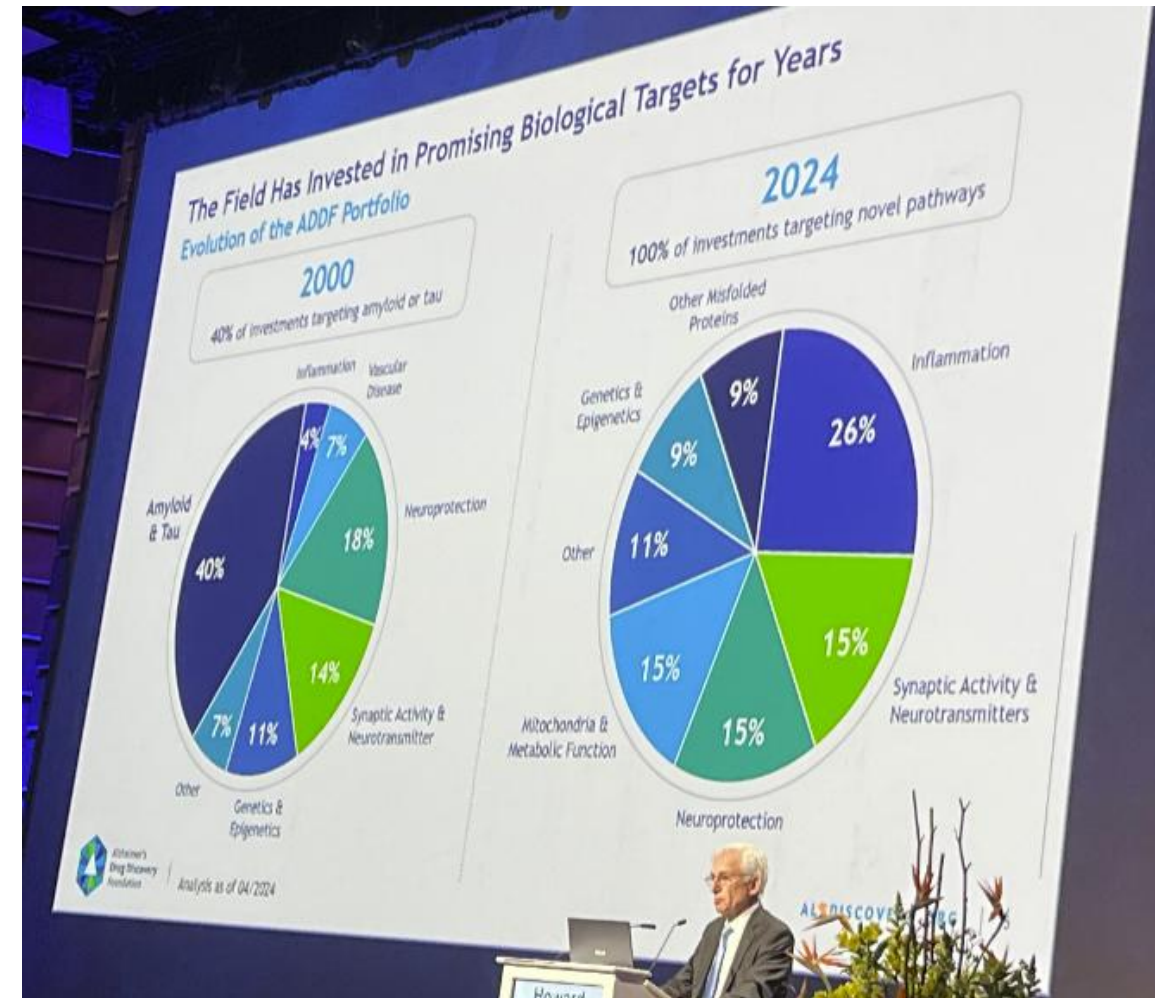
Chronic diseases are usually treated by drugs with different mechanisms at different stages

Alzheimer's Drug Discovery Foundation (ADDF)* view

Diversity of approaches now clearly necessary

Per Dr Howard Fillit, Founder and CSO:

- Anti-amyloid therapies have some benefit and slow disease process by up to ~25% but have **safety risks, iv administration issues, high costs**
- Significant remaining unmet need, field is moving towards a multi-targeted approach beyond amyloid and tau
- ADDF portfolio has shifted to greater target diversity: inflammation has had largest increase from 4% to 26%



* The ADDF is a leading US venture-charity focused solely on innovation in Alzheimer's disease

Xanamem is in advanced stages of development



Novel 11 β -HSD1 cortisol control mechanism, oral, attractive safety profile

- Brain cortisol has long been proposed as a pathogenic mechanism in Major Depressive Disorder (MDD) and Alzheimer's (AD)
- Unique brain-penetrant tissue cortisol synthesis inhibitor that leaves adrenal cortisol synthesis unaffected
- Over **400 people** treated with excellent safety and low drug interaction risk



Positive phase 2 clinical data de-risk Xanamem program

- **Disease-modifying activity on CDR-SB** in phase 2a trial in biomarker-positive Alzheimer's patients
- **Phase 2a MDD trial showing clinically & statistically significant activity - benefits across multiple endpoints**
- Positive data from both trials read through to other indications in psychiatry and the dementias



Large clinical and commercial opportunities

- **No other brain-penetrant cortisol control drugs in development, first to be awarded INN and USAN names¹**
- Alzheimer's market likely to be \$20 billion by 2030, with major opportunity for a safe & effective oral agent
- Anti-depressant market is currently ~\$20 billion, with major opportunities for novel mechanisms & better-tolerated drugs

1. Xanamem's International Nonproprietary Name (INN), emestedastat, was awarded by a naming committee of the World Health Organization: "stedastat" chosen for the first time for all 11 β -HSD1 inhibitors; USAN (United States Adopted Name)

Xanamem controls cortisol by inhibition of 11 β -HSD1¹

Controlling brain cortisol² has potential durable benefits

Reduction of “stress response” in brain

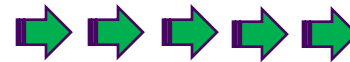
RAPID changes in kinases, cell function, neurotransmitters over hours to days lead to short-term “low stress” settings



“Lower stress” shorter term e.g.

- Reducing inflammation
- Improving neurotransmitter balance
- Decreasing cell death

SLOW changes in gene expression and protein synthesis over days to weeks lead to durable “low stress” settings

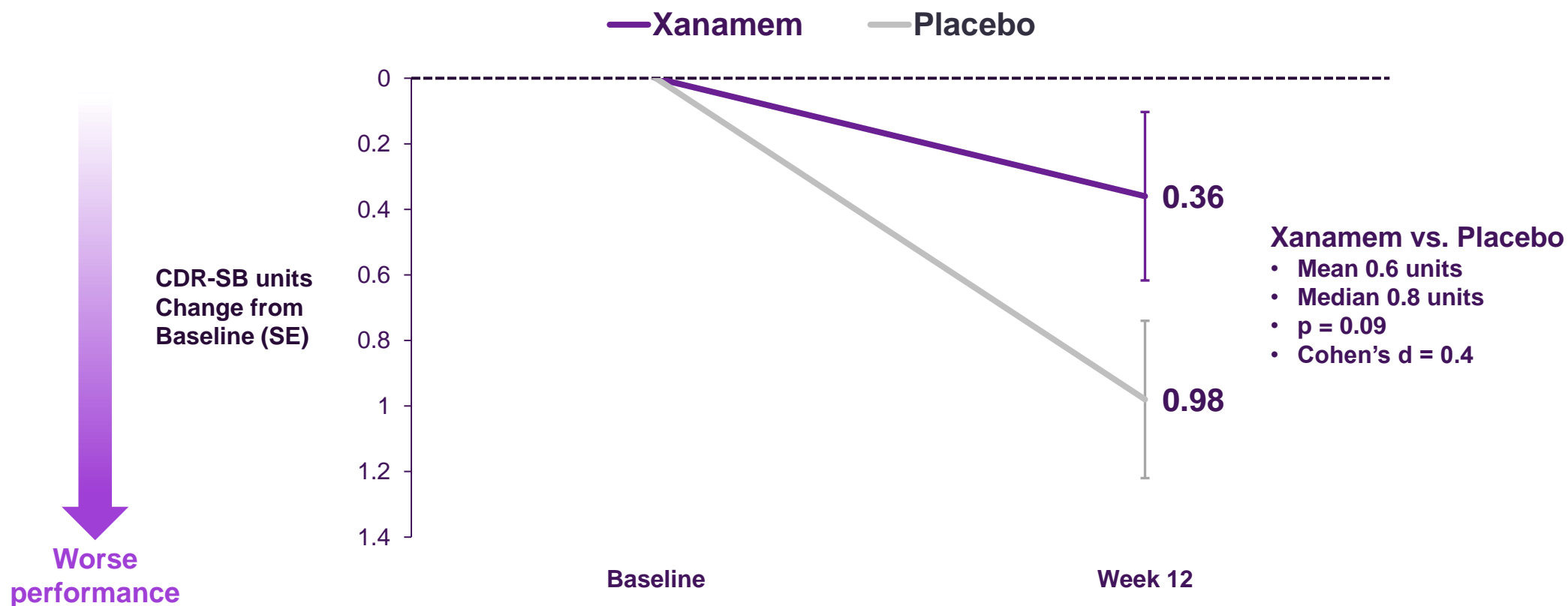


“Lower stress” longer term e.g.

- Improving neural circuitry
- Generating new brain cells
- Ideal receptor configurations

Large Xanamem benefit in high pTau181 patients

Phase 2a biomarker study: major slowing of CDR-SB decline over 12 weeks (n=34)

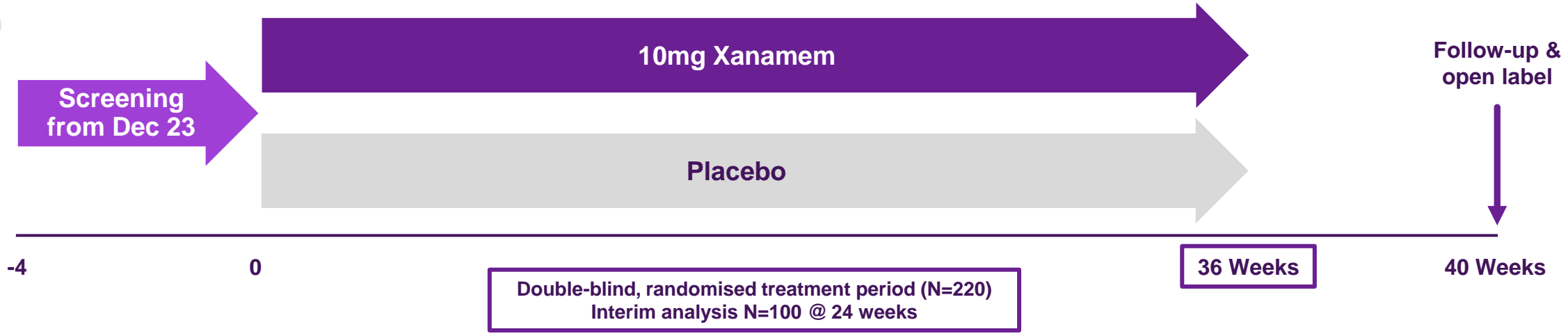


Journal of Alzheimer's Disease 100 (2024) 139–150
 Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11-HSD1 Inhibitor Xanamem® for Mild Alzheimer's Disease
 Jack Taylor, Mark Jaros, Christopher Chen, John Harrison and Dana Hilt

XanaMIA phase 2b/3 trial in Alzheimer's disease

Initial, interim results in Q4 2025, final results Q4 2026

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Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
<ul style="list-style-type: none">Blood pTau biomarker positiveMild-moderate Alzheimer's by NIA-AA criteria	<ul style="list-style-type: none">CDR-SB (functional and cognitive measure) @36 weeks	<ul style="list-style-type: none">Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field)Amsterdam Activity of Daily Living (functional measure)	<ul style="list-style-type: none">Enrolment at 15 Australian & 20 US sitesInterim analysis planned when ~100 people complete 24 weeks

Medical & Cognitive Research Unit (MCRU)

Clinical Trials in Alzheimer's Disease & Geriatric Medicine

Associate Professor Michael Woodward AM

MB BS MD FRACP FANZSGM FAAG FAWMA(FWA)

Head of Dementia Research, Austin Health

Austin MCRU

Who we are:

- Senior Geriatrician-led service with dedicated nurses, neuropsychologists and administration staff
- A centre of excellence for research into ageing and frailty, dementia and wound management
- One of the largest dementia clinical trials sites for Alzheimer's disease in the Southern Hemisphere.

Collaborations:

- Austin Health – Cognitive, Dementia and Memory Service (CDAMS)
- Australian Dementia Network (ADNet)
- The Florey Institute of Neuroscience and Mental Health
- National Ageing Research Institute (NARI)/Melbourne Ageing Research Collaboration (MARC)
- Australian Frailty Network (AFN)/University of Queensland.

Location:

Level 3 Centaur Building
Heidelberg Repatriation Hospital
300 Waterdale Road, Ivanhoe VIC 3079



Austin MCRU - history



- Established 1993
- Over 200 clinical trials in AD
 - Some 120 individual compounds
- Most are multicenter global trials
- Have conducted most of the early phase trials in emestedastat
 - I have been National Principal Investigator for these
- Recent successes
 - Lecanemab
 - Donanemab
 - Blarcamesine
- One of 20 clinical trial sites in Australia predominantly conducting AD research

The Clinician's Perspective

- Some 150 million will have dementia, mostly due to AD, within 25 years
- Likely another 300 million have Mild Cognitive Impairment
 - Also usually due to AD
 - Not really mild!
- Current therapies have limited effects
- Whilst it may be unrealistic to expect a moderately demented patient to “turn back the clock”, we should be able to arrest disease progression
 - And possibly prevent MCI, and progression from MCI to dementia, if treated early enough

We have done this before

- Cancer in 1970's was largely untreatable and cures were limited
 - There was a "conspiracy of silence"
 - Now, treatments and cures are the norm
 - And much better prevention
- Heart failure in 1980's had very few treatment options
 - PCI, ACEI's and numerous risk factor modifications have turned this around
- Rheumatoid arthritis
 - I recall most patients developing severe joint deformities and suffering pain
 - Very ineffective therapies to 1990's
 - Now I rarely see those "rheumatoid" hands
- And the brain too!
 - Multiple sclerosis is now a treatable disease, in most cases

We need a palette of treatment options

- Amyloid targeting therapies are not cutting the mustard
 - Unless used early, and even safer
- Just as in other now-curable conditions, we will need a range of treatment options
- Neuroinflammation is currently the “darling” of AD research
 - GLP1-RA drugs reduce dementia incidence in diabetics
 - Semaglutide etc
 - Clear role on inflammation in neurodegeneration
- If found successful, I see emestedastat used extensively in AD
 - As an important part of the palette
 - And as an oral small molecule it will be simple to use

Conclusion



- Austin MCRU is typical of many larger AD research sites around the world
- We are tirelessly trialing Investigational Products in AD
- Many potential targets in AD pathogenesis
- Amyloid-targeting therapies are becoming extensively used but are not the whole solution
- We need more safe, effective therapies

Panel discussion of Alzheimer's pipeline

Status: Analysis

CTscan

S411
ITEM
S119
Diffuse axonal injury

MRI

FOV 230

10/30/27
10/31/16
0033/11/24/16
T1:2309
Brain MRI T1, post
FOV:24x24
5.00x6.00,5sec
27/104/108
256x128x1.00 NEX
1437 FC09A11/TIF

T1

T2

FLAIR

T1 contrast

The critical importance of preparing for commercialization

Mr Andy Udell

ACW Chief Commercial Officer

Andrew Udell, Chief Commercial Officer

- 25+ years in the industry
- Majority with mid/late-stage biotech:
 - Several therapeutic areas in both large indications / markets and rare disease
 - Successful exits as well as building and launching a company and first product
 - More than “commercial”
- Biotech experience started - CLDA / PGx Health (anti-depressant market / vilazodone)
- Most recent experience - Calliditas Therapeutics

Commercial preparation needs to start in phase 2

Phase 3 needs to be designed for commercial success

- Commercial isn't just sales and marketing
- EVERY product is unique
- The earlier the input the better
- It takes time to do it optimally
- The good news: Actinogen and leadership team are ahead of the curve



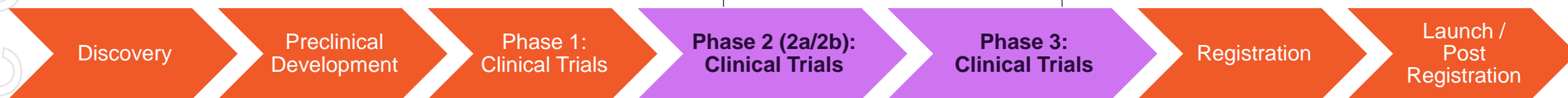
A word cloud of terms related to commercial preparation. The words are arranged in a cluster, with 'Commercial' being the largest and most central. Other prominent words include 'Marketing', 'Sales', 'Market Access', 'Patient Journey', 'Patient Services', 'Pricing', 'Trade and Distribution', 'Health', 'Economic', 'Promotion', 'Outcomes', 'Research', 'Medical education', 'mechanism of action', 'messages', and 'naming'.

marketing patient journey patient services pricing
SALES Market Access
Commercial Trade and Distribution
Health Economic Promotion messages
Medical education Outcomes Research
mechanism of action
naming MARKET RESEARCH

Xanamem is in late-stage development

Commercial preparation provides great impact

“Typical” partnering process



Xanamem (emestedastat)
current stage

Where biotech companies typically begin
to consider “commercial” preparedness

**Where do we begin?
What do we do first?**

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Understanding the markets...

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Alzheimer's Disease (AD) Market

Large market with a large unmet need

- AD prevalence:
 - Over 55 million people worldwide living with dementia
 - AD accounts for 60 – 70% (33-38.5M patients)
 - U.S. prevalence of AD estimated to be 6.9M
 - A.U. prevalence of AD estimated to be 300k
- AD has fluctuated between the 6th and 7th leading cause of death amongst older people in the US
- By 2050 healthcare costs related to AD in the U.S. alone are projected to exceed \$1 trillion
- Limited efficacy of the few available treatments – with none being truly disease modifying

Alzheimer's Disease Pipeline

- Busy pipeline, without too many unique approaches
- Amyloid hypothesis
 - Limited efficacy
 - Undifferentiated
- Anti-Tau: virtually all have already failed in the clinic
- GLP-1s results of clinical trials in Q4 2025 heavily anticipated – need to test and understand how this will impact the category and Xanamem
- No silver bullet in development – as is the case with many chronic diseases, it will likely take several different treatments used concomitantly

Major Depressive Disorder (MDD)

Large market

- Global prevalence and economic impact:
 - Estimated 280 million people
 - World Health Organization (WHO) reports that depression and anxiety disorders cost the global economy approximately \$1 trillion annually
- United States prevalence and economic impact:
 - ≈ 21.0 million U.S. adults experienced at least one major depressive episode annually
 - Prevalence higher among females compared to males and highest among individuals aged 18-25
 - Economic burden of MDD ≈ \$326 billion (in 2020 U.S. dollars)
 - Costs encompass direct healthcare expenses, suicide-related costs, and workplace costs

New antidepressants are still needed

The market is not satisfied and has room for new entrants and mechanisms

- Treatment resistant & inadequate response
 - 30 – 50% of patients do not achieve full remission with first-line antidepressants
 - Up to 30% of patients classified as having treatment-resistant depression
- Current treatment challenges:
 - Delayed onset of action – often 4 to 6 weeks
 - 30-40% of patients discontinue treatment within 3 months due to side effects including: sexual dysfunction, weight gain, emotional blunting
 - Patients commonly change and add on additional therapies
- Recent launches are still successful, even with *limited differentiation*
 - AUVELITY (dextromethorphan and bupropion): 2024 net sales \$291M+ (2nd full year on the market)
 - “Treatment Resistant” medications

Truly understand our product...

We must *truly* understand our product

- How does it work?
- How is it unique?
- What unmet need(s) does our product address?
- What are the stakeholder perceptions of our target product profile?
- Are we facing any preexisting beliefs?
- What is easily understood and what isn't?
- What do the stakeholders need to understand BEFORE they would decide:
 - If appropriate (safe and efficacious) to prescribe our product for their patients
 - To reimburse/pay for our product
 - To take our product

Additional challenges to prepare for

- Market access
 - Payers (insurance)
 - Distribution
 - Patient services, a price of entry
- Existing marketed products as well as those in development
- Treatment guidelines
- How to obtain or administer treatment – is it typical for this therapeutic area / specialty?

What have we learned?

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Research, conversations and findings

Understand our (*initial*) audience and their reaction to Xanamem through:

- Target product profile (TPP) - qualitative market research
- One-on-one meetings with key opinion leaders (KOLs) in AD
- MDD advisory board

Initial output / lessons learned

1. Focus on our novel mechanism – which piques the interest of our audience
2. PET data, clinical results in biomarker confirmed AD patients, and XanaCIDD's MDD results all support success and differentiation

Our unique mechanism of action is key

Xanamem[®]
(emestedastat)
Mechanism of Action

What's next?

Focus until XanaMIA clinical trial read out

- Continued mechanism of action education
- Market / competitive assessment and monitoring
- Expanded KOL reach (and frequency)
- Increased presence at key relevant congresses and conferences

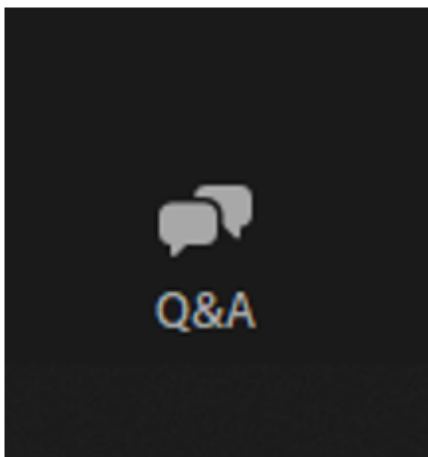
Preparing for Xanamem's success

- Know your market and all stakeholders
- Truly understand Xanamem and its benefits as a product
- Design the final stages of the clinical trial program to optimize the initial prescribing information and market access at launch

The time to prepare for Xanamem commercialization is now

Online Q&A

1. Click on the Q&A icon



2. Type your question in the new Q&A window

Type your question here...

3. Hit enter on your keyboard to submit your message

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Appendix

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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
- **AD** – Alzheimer's disease
- **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
- **SSRI** – selective serotonin reuptake inhibitor
- **Tau** – A brain protein
- **Ttau** – Total tau levels including both phosphorylated and non-phosphorylated tau

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