ASX ANNOUNCEMENT

Actinogen CEO & CMO present at Sachs Neuroscience Innovation Forum & JPM Week meetings

World Health Organization grants new and unique nonproprietary name 'emestedastat' for Xanamem®

Sydney, 13 January 2025. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that its Chief Medical Officer, Dr Dana Hilt, and CEO, Dr Steven Gourlay, will present today at the Sachs Associates 8th Annual Neuroscience Innovation Forum in San Francisco (12 January USA PST). Drs Hilt and Gourlay are joined in San Francisco by ACW Chief Financial Officer, Will Souter, and Chief Commercial Officer, Andrew Udell.

The Sachs Forum brings together large and small pharmaceutical companies, analysts and investors who are focused on neuroscience as a key component of their pipelines and portfolios. The audience includes - buy and sell side analysts from investment banks and funds, along with partnering executives from pharma, biotech, medtech, neurotech, and diagnostics companies.

While in San Francisco, the ACW team will participate in a significant number of partnering, analyst and investor meetings associated with the 43rd Annual J.P. Morgan Healthcare Conference from January 13 to 16, 2025 (JPM Week).

The information used for all Sachs Innovation Forum and JPM Week presentations and meetings is attached to this announcement or has been previously announced.

The attached presentation recaps the success of emestedastat (Xanamem), ACW's novel once daily oral treatment for Alzheimer's disease (AD) and major depressive disorder (MDD) and examines the near-term major phase 2b/3 readouts in the XanaMIA AD trial in 2025 and 2026.

New and unique nonproprietary name of 'emestedastat' granted for Xanamem

The Company is also pleased to announce that the World Health Organization (WHO) has granted the nonproprietary name 'emestedastat' to Actinogen for its Xanamem[1] once-a-day small molecule in accordance with the WHO's Procedure for the Selection of Recommended International Nonproprietary Names (INN) for Pharmaceutical Substances.

An INN is a unique, globally recognized name for a pharmaceutical drug or active ingredient. The WHO established an INN expert committee to select and assign a single, unique name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical, ensuring clear identification, safe

® Xanamem is a registered trademark of Actinogen Medical Limited

[1] Also known as UE2343 which is the original identifier used by the University of Edinburgh

prescription and dispensing of medicines to patients. Nonproprietary names are intended for wide use ranging from labelling and product information to drug regulation and scientific literature.

By granting this INN, the WHO has recognized emestedastat (Xanamem) as the first drug to be named for the class of enzyme inhibitors of 11β-HSD1 by assigning it the unique suffix of '-stedastat' pertaining to its mechanism of action on 11β-HSD1.

Emestedastat (Xanamem) is a unique orally administered molecule in its own class as a 'brain tissue cortisol synthesis inhibitor.' It is currently being developed as a promising new therapy for the treatment of Alzheimer's disease and depression. Its novel mechanism of action is to control the level of the 'stress hormone' cortisol in the brain through the inhibition of the cortisol synthesis enzyme, 11β-HSD1. The Company is currently conducting a phase 2b/3 trial of emestedastat in Alzheimer's disease and is planning for future depression trials.

Dr Steven Gourlay, Actinogen's CEO and Managing Director, said:

"It is pleasing to have emestedastat (Xanamem®) recognized as first-in-class with the award of an INN name with a new and unique suffix. The suffix used in the name highlights Actinogen's leading position in the field of 11β-HSD1 enzyme inhibition which is designed to control brain cortisol and result in clinically meaningful benefits for patients with Alzheimer's disease (AD) and major depressive disorder (MDD).

"Meanwhile, in San Francisco this week, we are focused on briefing potential pharmaceutical partners on the significant progress of our XanaMIA phase 2b/3 AD trial and the seminal proof-of-concept data obtained from the XanaCIDD phase 2a trial in patients with MDD.

"The clinical benefits seen in phase 2 trials with the 10mg daily dose of emestedastat in both AD and MDD give us confidence that the outcomes of current and future trials in these and other diseases will be positive."

ENDS

Dr. Steven Gourlay
CEO & Managing Director
P: +61 2 8964 7401
E. steven.gourlay@actinogen.com.au

Investors

Michael Roberts
Investor Relations
M: +61 423 866 231
E. michael.roberts@actinogen.com.au

Media

George Hazim
Media & Public Affairs Australia
M: +61 417 516 262
E: georgehazim@mediaaffairs.com.au

Announcement authorised by the Board of Directors of Actinogen Medical

About Actinogen Medical

Actinogen Medical (ACW) is an ASX-listed, biotechnology company developing a novel therapy for neurological 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.

Current Clinical Trials

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).

The **XanaMIA Phase 2b 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 of the first 100 participants are anticipated in Q3 2025 and final results H2 2026.

About Xanamem

Xanamem's novel mechanism of action is to control the level of cortisol in the brain through the inhibition of the cortisol synthesis enzyme, 11β-HSD1, without affecting production of cortisol by the adrenal glands. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing.

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 11β-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.

Disclaimer

This announcement and attachments may contain certain "forward-looking statements" that are not historical facts; are based on subjective estimates, assumptions and qualifications; and relate to circumstances and events that have not taken place and may not take place. Such forward looking statements should be considered "at-risk statements" - not to be relied upon as they are subject to known and unknown risks, uncertainties and other factors (such as significant business, economic and competitive uncertainties / contingencies and regulatory and clinical development risks, future outcomes and uncertainties) that may lead to actual results being materially different from any forward looking statement or the performance expressed or implied by such forward looking statements. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Actinogen Medical does not undertake any obligation to revise such statements to reflect events or any change in circumstances arising after the date hereof, or to reflect the occurrence of or non-occurrence of any future events. Past performance is not a reliable indicator of future performance. Actinogen Medical does not make any guarantee, representation or warranty as to the likelihood of achievement or reasonableness of any forward-looking statements and there can be no assurance or guarantee that any forward-looking statements will be realised.

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

Oral emestedastat[1] (Xanamem®/UE2343)

Controlling brain cortisol to slow progression in Alzheimer's disease and treat major depressive disorder

Sachs Neuroscience Innovation Forum & JP Morgan Healthcare week

January 2025

1. Emestedastat is the new nonproprietary or generic name for Xanamem allocated by the World Health Organization recognizing the "–stedastat" suffix as a unique, new identifier for 11β-HSD1 inhibitors

Disclaimer

- This presentation has been prepared by Actinogen Medical Limited. (“Actinogen” or the “Company”) based on information available to it as at the date of this presentation. The information in this presentation is provided in summary form and does not contain all information necessary to make an investment decision.
- This presentation does not constitute an offer, invitation, solicitation or recommendation with respect to the purchase or sale of any security in Actinogen, nor does it constitute financial product advice or take into account any individual’s investment objectives, taxation situation, financial situation or needs. An investor must not act on the basis of any matter contained in this presentation but must make its own assessment of Actinogen and conduct its own investigations. Before making an investment decision, investors should consider the appropriateness of the information having regard to their own objectives, financial situation and needs, and seek legal, taxation and financial advice appropriate to their jurisdiction and circumstances. Actinogen is not licensed to provide financial product advice in respect of its securities or any other financial products. Cooling off rights do not apply to the acquisition of Actinogen securities.
- Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, no representation or warranty, express or implied, is made as to the fairness, accuracy, completeness or correctness of the information, opinions and conclusions contained in this presentation. To the maximum extent permitted by law, none of Actinogen its officers, directors, employees and agents, nor any other person, accepts any responsibility and liability for the content of this presentation including, without limitation, any liability arising from fault or negligence, for any loss arising from the use of or reliance on any of the information contained in this presentation or otherwise arising in connection with it.
- The information presented in this presentation is subject to change without notice and Actinogen does not have any responsibility or obligation to inform you of any matter arising or coming to their notice, after the date of this presentation, which may affect any matter referred to in this presentation.
- This presentation is not for general distribution or third party reliance or use.
- This presentation contains certain budget information, forecasts and forward looking statements that are based on the Company’s management’s beliefs, assumptions and expectations and on information currently available to management in respect of which there is NO guarantee of future performance. Such budget information, forecasts and forward looking statements involve known and unknown risks, uncertainties, and other factors which may cause the actual results or performance of Actinogen to be materially different from the results or performance expressed or implied by such forward looking statements. These risks and uncertainties include, but are not limited to the performance of Actinogen in its clinical trials including whether it's technology proves to be a safe and effective treatment, market penetration, competition from any other similar products, intellectual property risks (including securing rights in technology and patents) and global economic conditions. Furthermore, Actinogen's research, product development, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. There is no guarantee that Actinogen will obtain the required approvals, licences and registrations from the relevant authorities in jurisdictions in which it operates. Actinogen or others could identify product and efficacy issues relating to the safety of our technology. Accordingly, all forward looking statements are based on numerous assumptions regarding the Company’s present and future business strategies and the political and economic environment in which Actinogen will operate in the future, which are subject to change without notice. Past performance is not necessarily a guide to future performance and no representation or warranty is made as to the likelihood of achievement or reasonableness of any forward looking statements or other forecast. There is no guarantee that Actinogen will achieve its stated objectives/milestones, that any of its forecasts will be met or that forward looking statements will be realised. You are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.
- Neither Actinogen nor any other entity or person in or associated with Actinogen guarantee any return (whether capital or income) or generally the performance of Actinogen or the price at which its securities may trade. Any investment in Actinogen is subject to investment risks including the possibility of loss of capital invested and no return of income or payment of any dividends.
- To the maximum extent permitted at law, Actinogen and all of its representatives, directors, officers, partners, employees or professional advisers (Parties) exclude all direct and indirect liability arising out of or in connection with any use or reliance of the information contained or described within this presentation. Other than to the extent required by law (and only to that extent), the Parties do not make any representation or give any assurance, guarantee or warranty (express or implied) as to, nor assume any responsibility or liability for, the authenticity, origin, validity, accuracy, suitability or completeness of, or any errors in or omissions from, any information, statement or opinion contained in this presentation or any accompanying, previous or subsequent material or presentation.

Overview

Emestedastat is now significantly de-risked

Novel 11β-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
- Approximately **400 people** treated to date with excellent safety profile and low drug interaction risk

Positive phase 2 clinical data in both indications

- **Phase 2a MDD trial showing clinically & statistically significant activity - benefits across multiple endpoints**
- Disease-modifying activity on CDR-SB in AD phase 2a trial in biomarker-positive AD patients 0.6 points over 12 weeks
- Positive data from both trials read through to other indications in psychiatry and the dementias

Patent & data exclusivity protection and manufacturing

- Composition of matter protection to 2031 – to 2036 with extensions in major markets, new chemical entity data protections
- **Additional recent patents protect further** against future competition e.g. use patent for MDD
- **Manufacturing process scaled up and patented**, contractors Asymchem (China) & Catalent (US)

Large clinical and commercial opportunities

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

Experienced board and management team

Board of Directors

Dr. Geoff Brooke
Chairman
MBBS; MBA

Dr. Steven Gourlay
CEO & MD
MBBS; FRACP; PhD; MBA

Mr. Malcolm McComas
Non-Executive Director
BEc, LLB; FAICD; SF Fin

Dr. George Morstyn
Non-Executive Director
MBBS; PhD; FRACP CD

Dr. Nicki Vasquez
Non-Executive Director
PhD

Management Team

Dr. Steven Gourlay
CEO & MD

Dr. Dana Hilt
Chief Medical Officer
MD

Will Souter
Chief Financial Officer
BComm, LLB

Andrew Udell
Chief Commercial Officer
MBA

Cheryl Townsend
VP Clinical Operations
RN, M Health Law

Fujun Li
Head of Manufacturing
PhD

Michael Roberts
Head of IR & Comms
B.Ec (Hons), CPA, FFIN

Phase 2 activity in AD and MDD validates cortisol MoA

Phase 2b/3 underway in AD, preparing phase 2b in MDD

Evidence of durable benefit on depression from control of brain cortisol validates the emestedastat program in terms of:

a. Clinical proof-of-concept for the “CNS cortisol control” MoA

b. Utility of the 10 mg once-daily dose used in Alzheimer’s phase 2b/3 trial

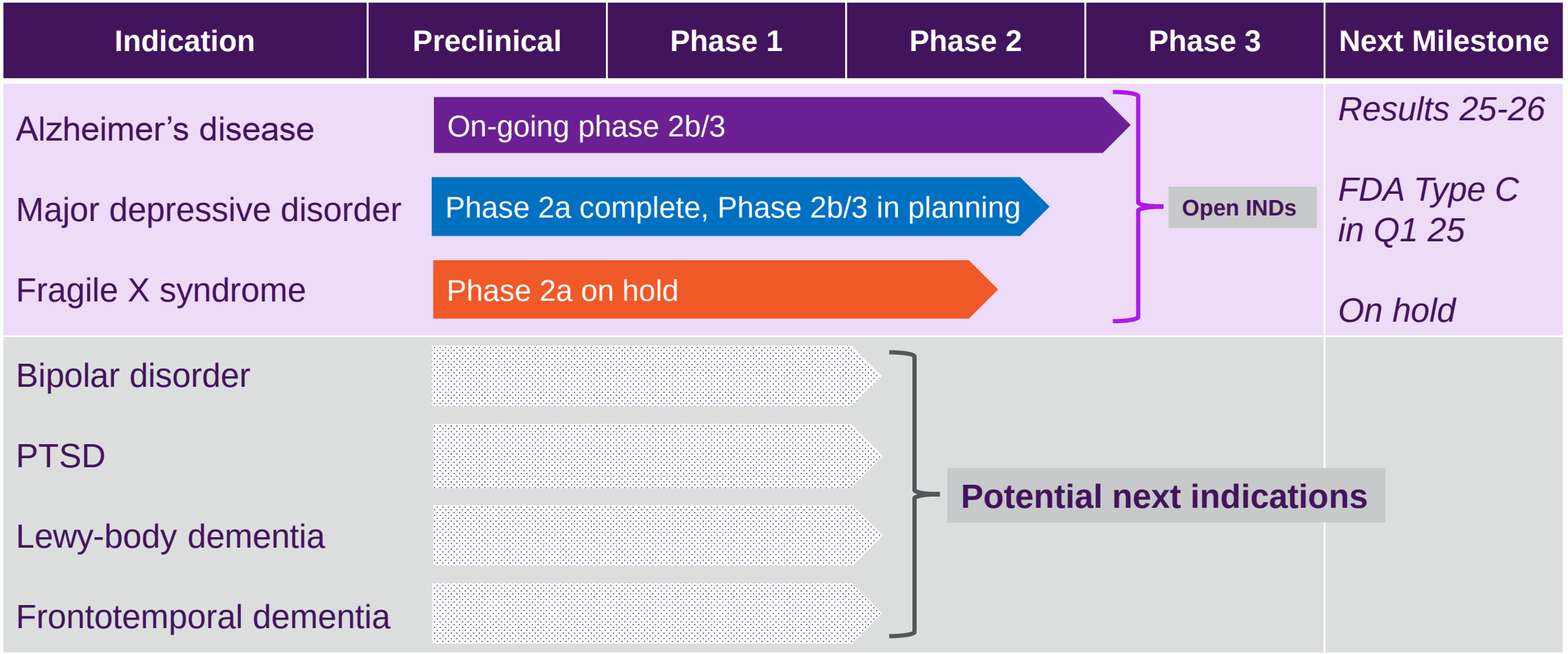
c. Utility of the 10 mg once-daily dose for the next MDD trial

Phase 2a MDD efficacy and safety data support further clinical development in MDD

Clinical activity on depression supports the likelihood of seeing a disease-modifying effect in Alzheimer’s disease over 36 weeks in current XanaMIA trial

MOA: mechanism of action

Emestedastat – Development Pipeline

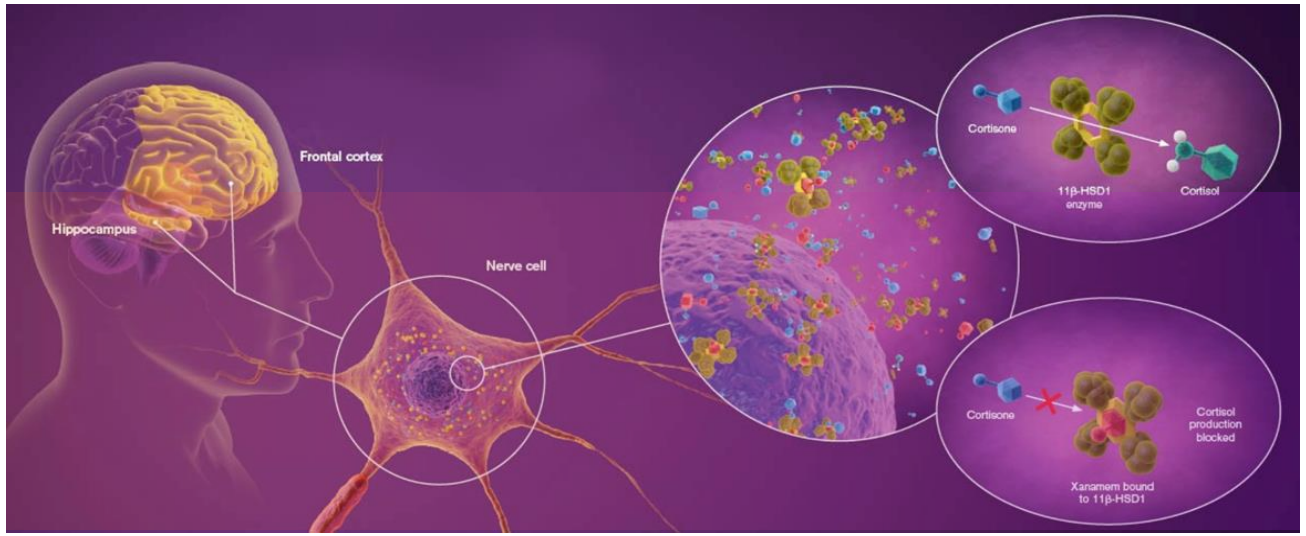


Emestedastat

Once-daily oral treatment with a unique mechanism

Small molecule tissue cortisol synthesis inhibitor (11β-HSD1 enzyme)

- Good safety profile in ~400 treated
- Brain-penetrant at low doses
- Potentially disease-modifying in AD
- Anti-depressant activity in phase 2
- Low drug interaction potential ideal for combination therapy



Mouse experimental studies, brain cortisol levels & human clinical trials validate cortisol as a target for the treatment of AD

Emestedastat and CNS 11β-HSD1 inhibition[1]

Controlling brain cortisol[2] has potential durable benefits

Reduction of the '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

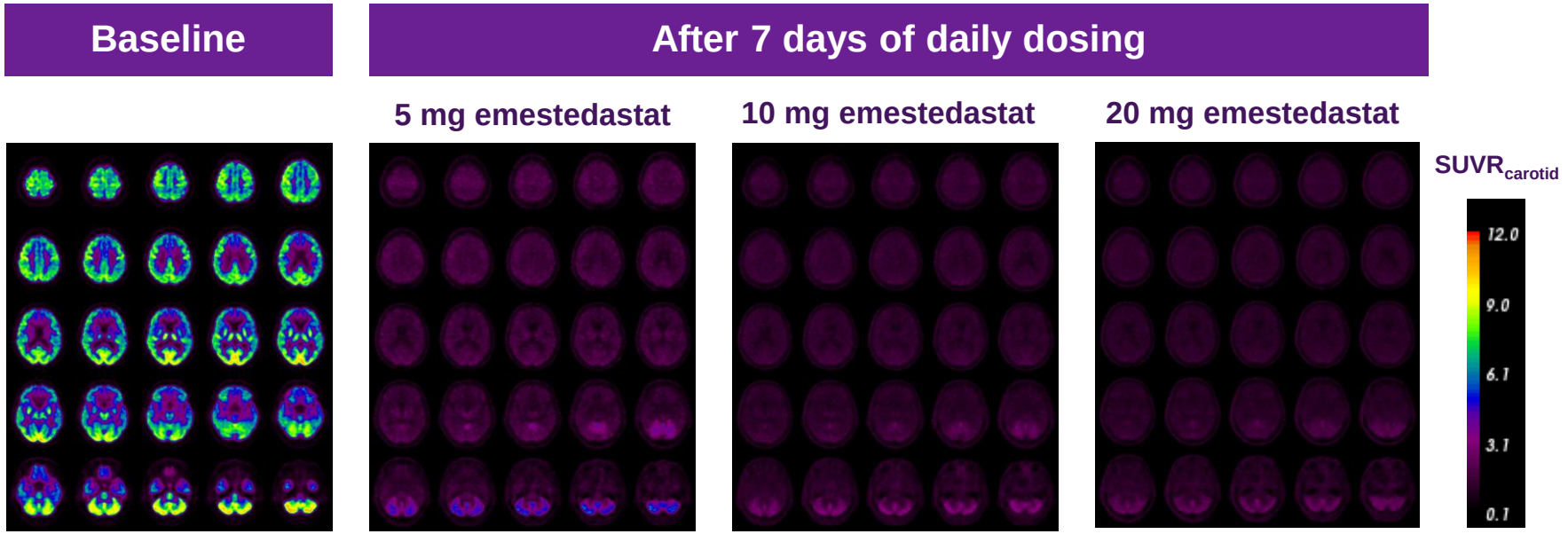
"Lower stress" longer term e.g.

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

1. For a comprehensive review of 11β-HSD1 see Seckl J. 2024 2. Ramamoorthy & Cidlowski 2016

Human PET study shows full target engagement

Other 11β-HSD1 enzyme inhibitors have not achieved adequate brain levels



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

This is consistent with full hormonal pharmacodynamic activity seen in clinical trials with doses as low as 5 mg.

Journal of Alzheimer's Disease 97 (2024) 1463–1475
Brain 11-Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamem™ Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals
Victor L. Villemagne, Vincent Dor, Lee Chong, Michael Kassiou, Rachel Mulligan, Azadeh Feizpour, Jack Taylor, Miriam Roesner, Tamara Miller and Christopher C. Rowe

Alzheimer’s disease program

Alzheimer's disease

Strong cortisol control scientific rationale to address huge unmet medical need

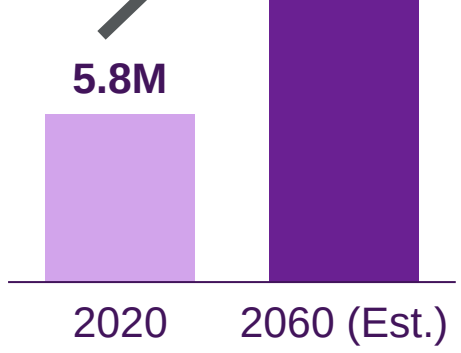
Rationale

- Cortisol levels are elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11β-HSD1 provides full neuroprotection
- AD Phase 2a trial shows slowed disease progression in biomarker-positive patients
- ***Safe & effective oral therapy is "holy grail"***

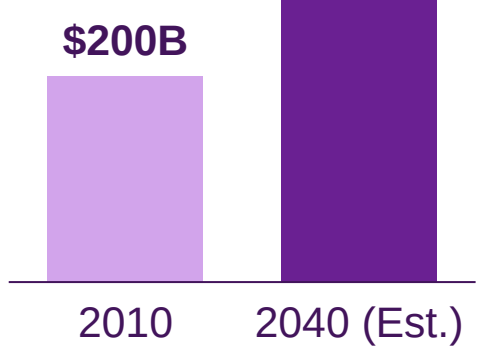
Growing Alzheimer's Disease market – U.S.

Large, unsatisfied and growing market

# of patients

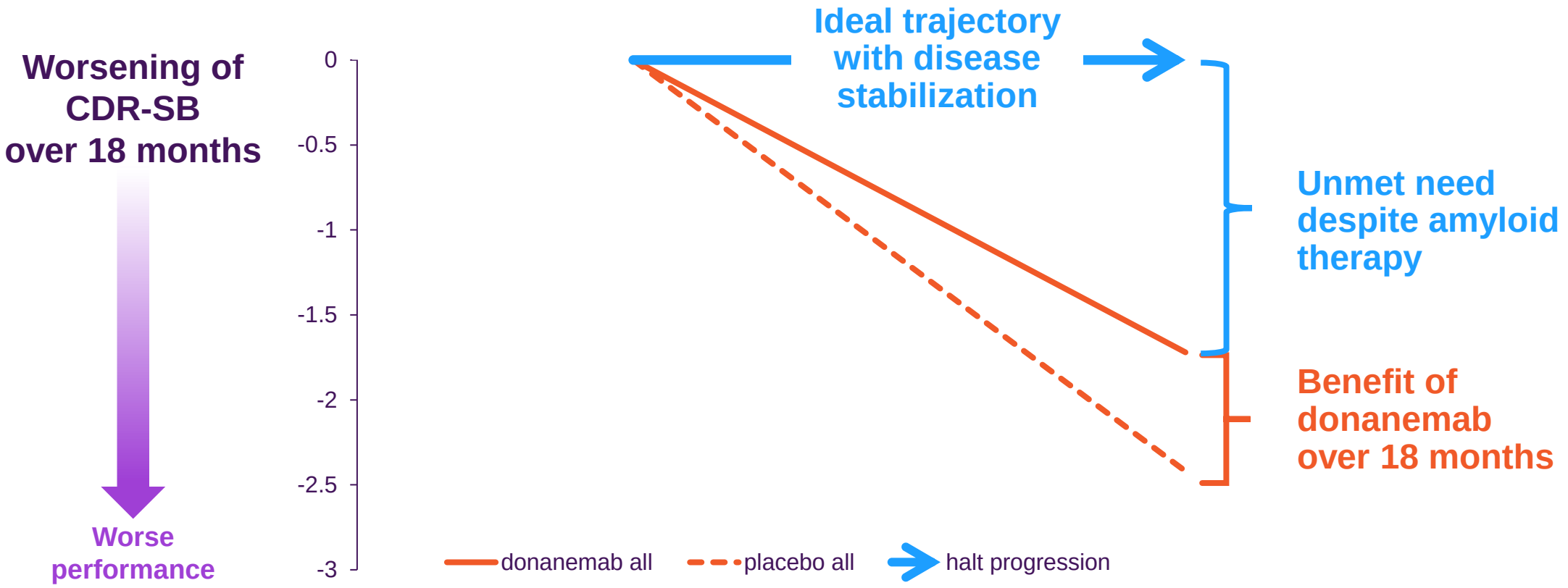


Cost to treat



Anti-amyloid therapy modestly slows AD progression

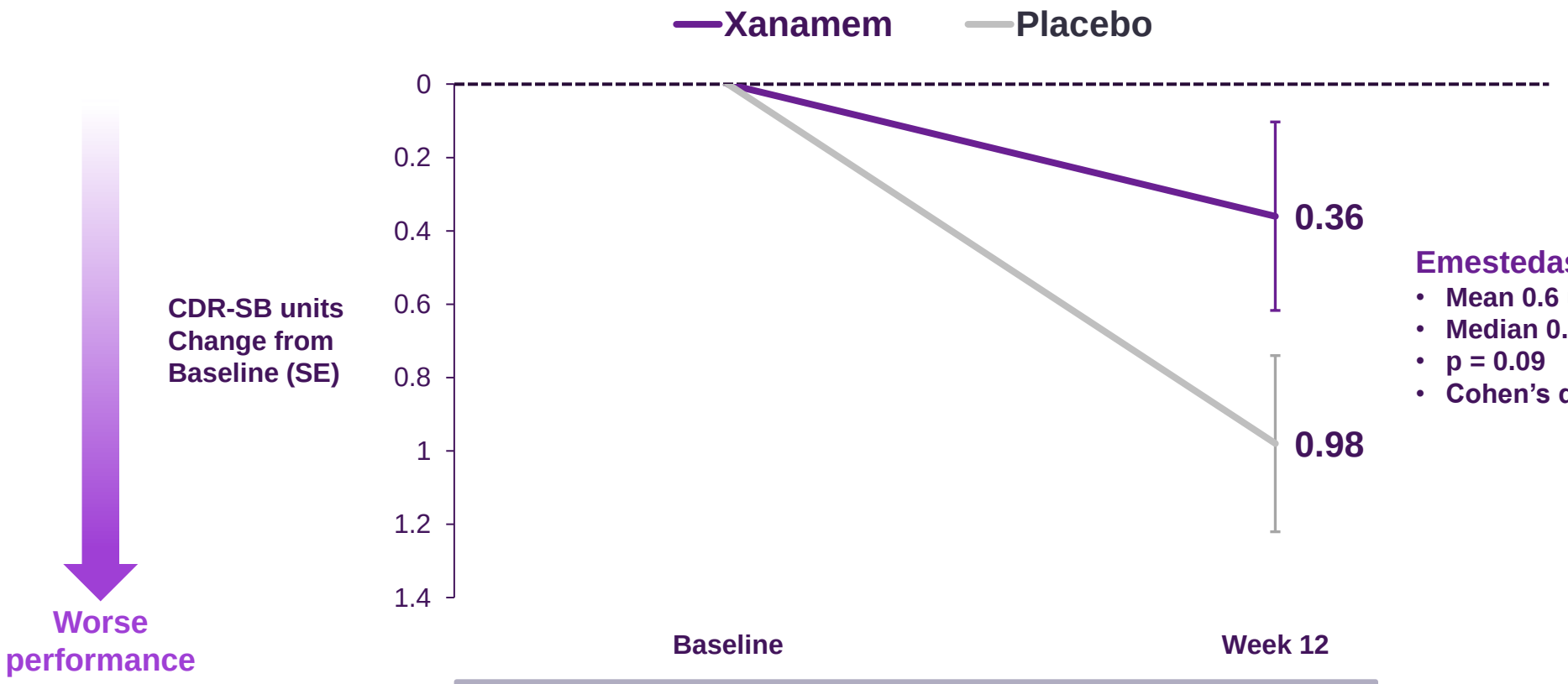
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like emestedastat are needed

Emestedastat benefit in pTau181-positive AD patients

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



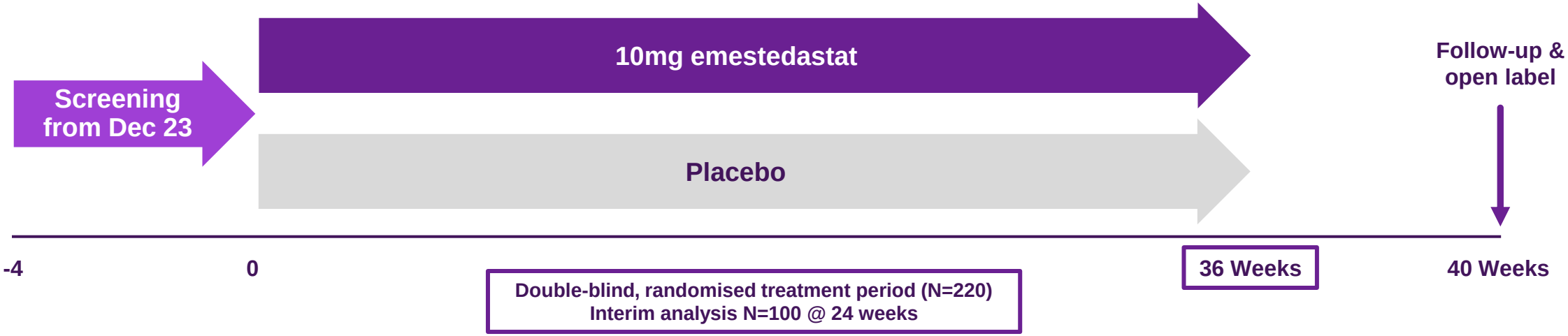
Emestedastat vs. Placebo

- **Mean 0.6 units**
- **Median 0.8 units**
- **p = 0.09**
- **Cohen's d = 0.4**

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 Q3 2025, final results H2 2026



Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
• Blood pTau biomarker positive • Mild-moderate Alzheimer's by NIA-AA criteria	• CDR-SB (functional and cognitive measure)	• Cognitive Test Battery (7 cognitive measures well-validated in the Alzheimer's field) • Amsterdam Activity of Daily Living (functional measure)	• Enrolment at 15 Australian & 10 US sites • Interim analysis planned when ~100 people complete 24 weeks

NIA-AA=National Institute of Aging - Alzheimer's Association; **CDR-SB** Clinical Dementia Rating Scale – Sum of Boxes

Phase 2b/3 AD trial in progress

XanaMIA Alzheimer's disease trial implemented as a pivotal, phase 2b/3 design

XanaMIA AD trial is established as one of two potential "pivotal" trials:

a. Independent Data Monitoring Committee
b. "Phase 3-standard" statistical methods
   - Full statistical power for primary endpoint at 36 weeks ($p < 0.05$)
   - Sequential examination of secondary endpoints after primary ($p < 0.05$)
c. High standard of quality oversight
d. Commercial tablet formulation

More than 270 screened, approximately 40 enrolled

Interim data expected Q3 2025, final results H2 2026

Depression program

There remains significant unmet need in depression

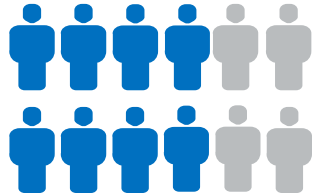
Emestedastat's unique mechanism and safety differentiate it from older drugs

Scientific rationale

- More than 50 years of research associates cortisol with depression
- Elevated CSF and plasma cortisol levels associated with diagnosis, treatment outcomes and relapse
- Positive effects of cortisol receptor antagonism reported with mifepristone[1]
- ***Now positive phase 2a data on depressive symptoms (MADRS, PGI-S)***

U.S. Depression market large unmet need

- 21M patients have had ≥ 1 MDD episode



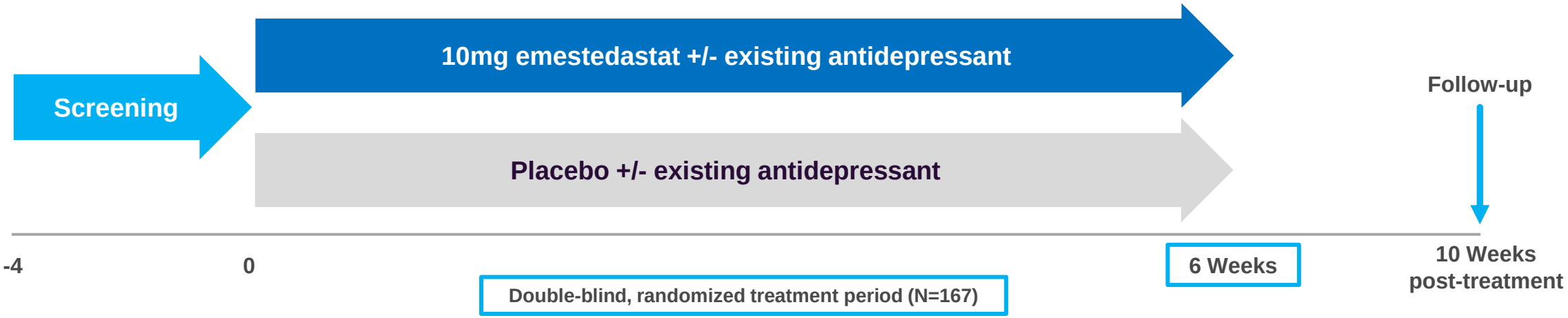
- Two-thirds with an episode **with severe impairment** in the past year
- 61% of all adults with MDD episodes receive treatment
- ≥365 M prescriptions per year

A safe, durably effective and combinable small molecule is a very attractive product profile for depression

1. Ding et al 2021

Completed Phase 2a XanaCIDD trial

Double-blind, proof-of-concept controlled trial to assess safety and efficacy



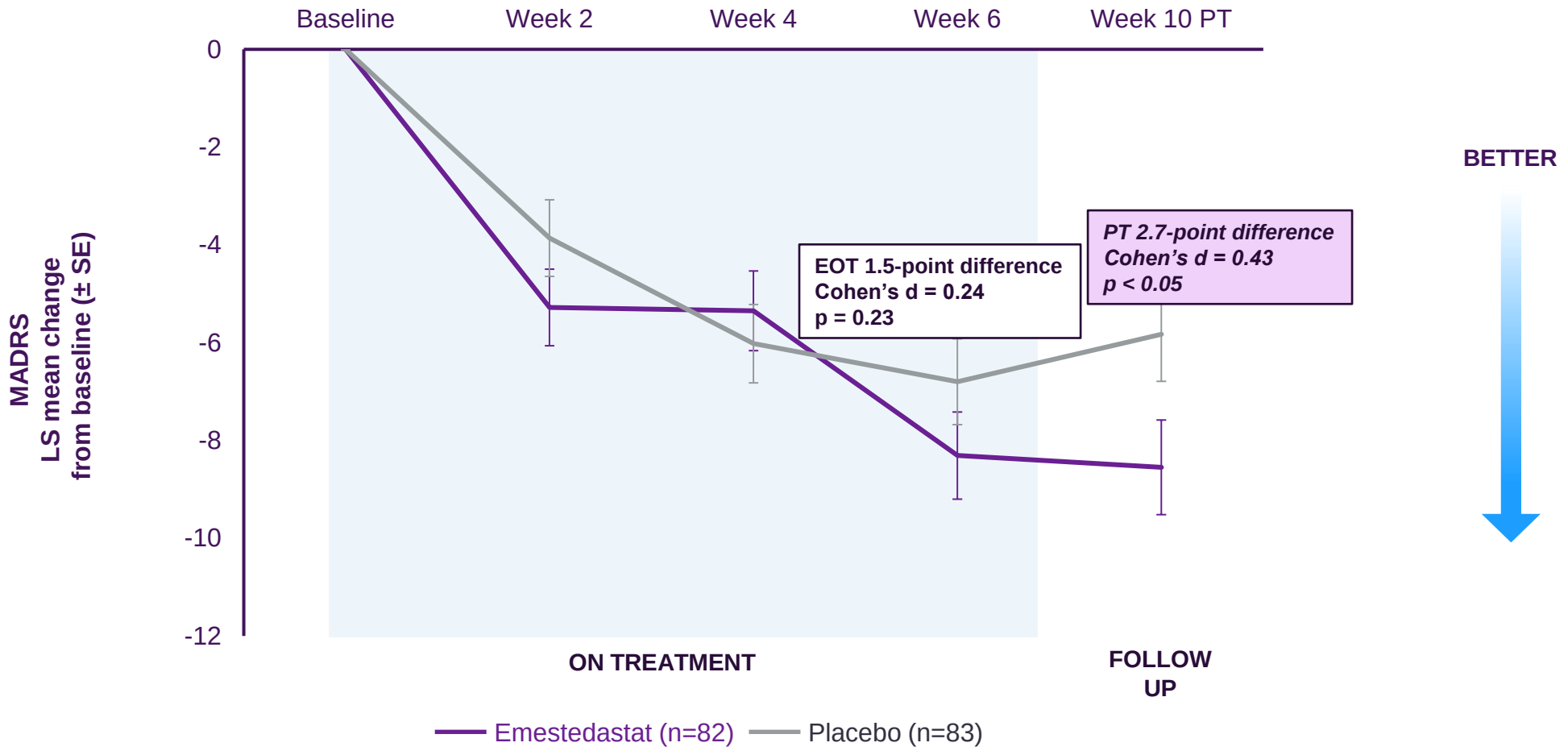
Primary Endpoint	Key Secondary Endpoints
• **Cogstate Cognitive Test Battery Attention Composite** (attention and working memory)	• Montgomery-Åsberg Depression Rating Scale (**MADRS**) • Patient Global Impression-Severity **(PGI-S)** • Other MDD and cognitive measures

Baseline characteristics were well-balanced

	Emestedastat (n = 82)	Placebo (n=83)
Mean (SD) age	49 (13)	49 (14)
% female	63	61
Mean (SD) HAM-D	21 (3)	21 (3)
Mean (SD) MADRS	24 (6)	26 (7)
Median number of prior MDD episodes	4	4
% on anti-depressant therapy	77%	86%
Mean (SD) Cognition – Boxfiller coding test	22 (5)	21 (6)

MADRS separation from Week 6 (n=165)

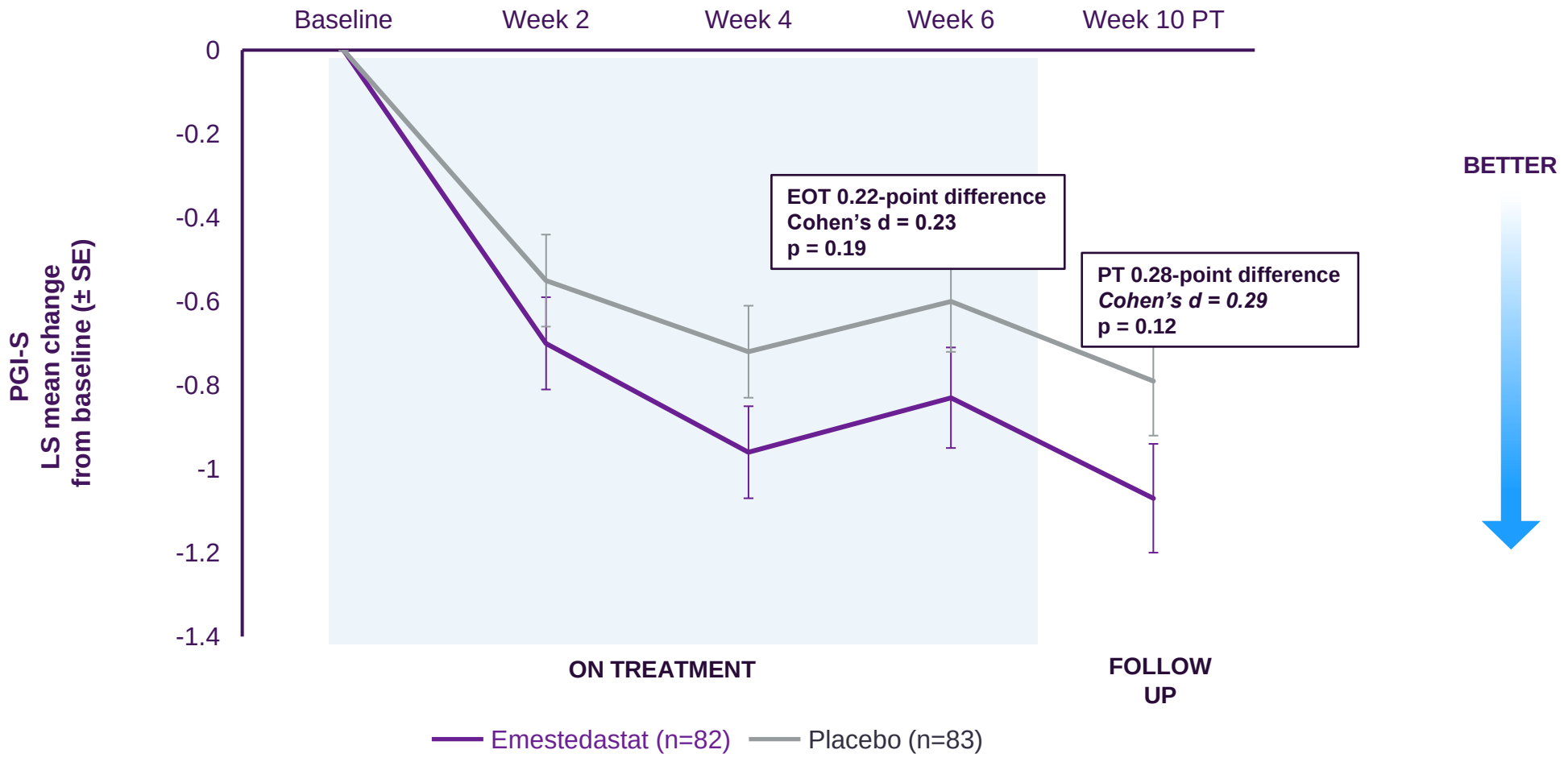
All randomized participants



Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

PGI-S separation from Week 2 (n=165)

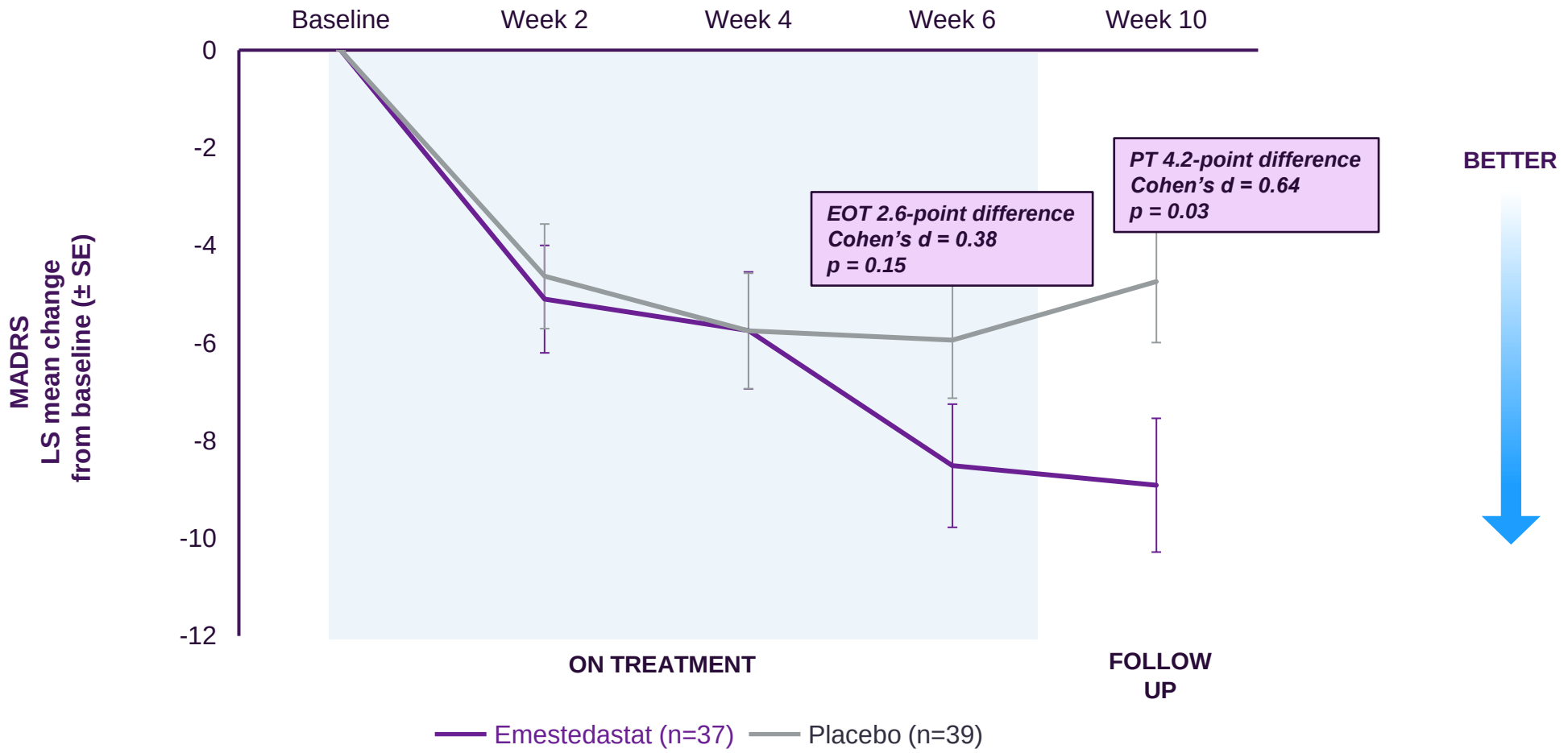
All randomized participants



Abbreviations: PGI-S = Patient Global Impression of Severity – a patient-reported outcome

MADRS in patients taking concurrent SSRI (n=76)

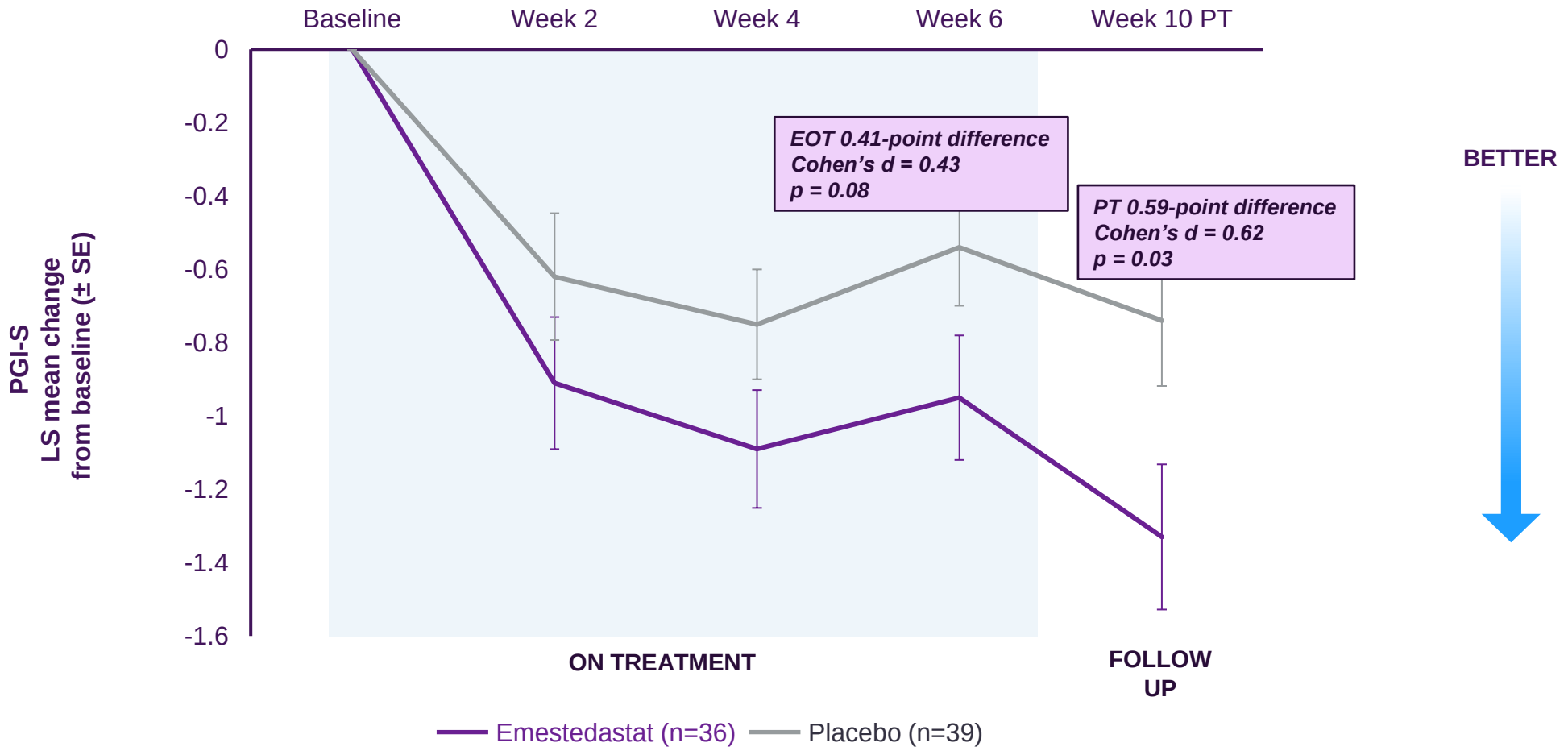
Largest co-treatment subgroup



Abbreviations: SSRI = selective serotonin reuptake inhibitor

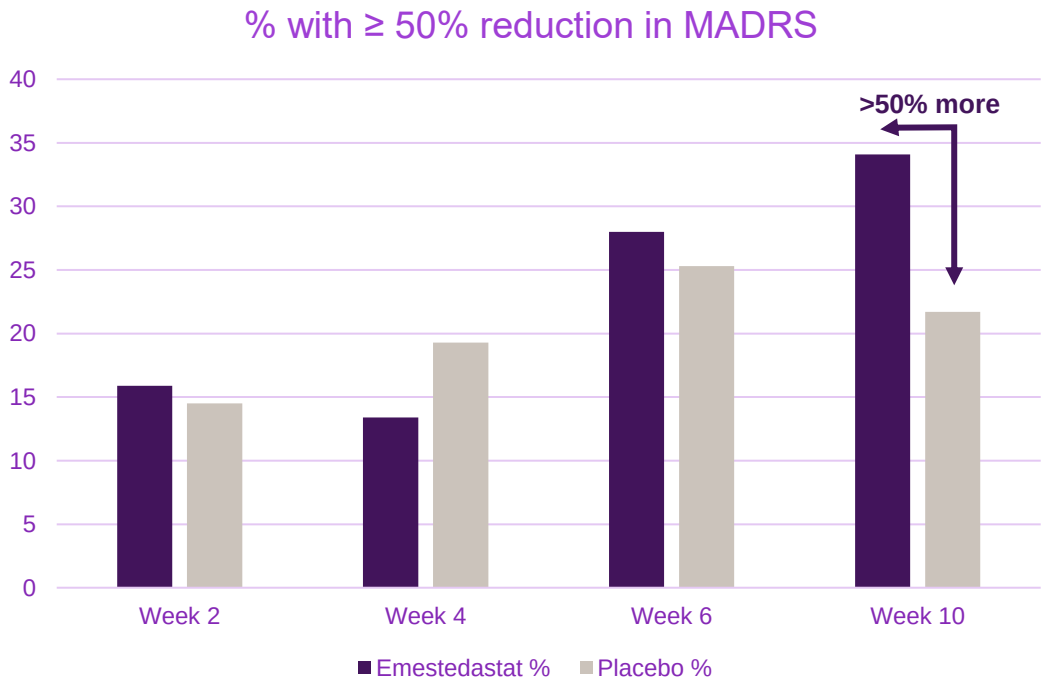
PGI-S benefit in patients taking SSRI (n=75)

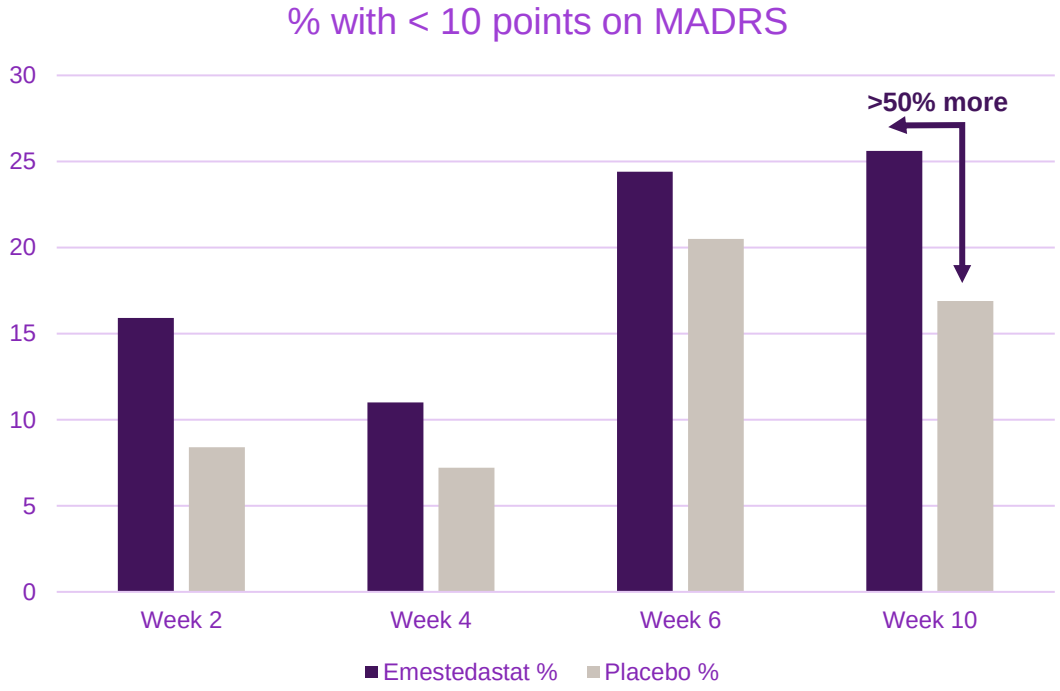
Largest co-treatment subgroup



Emestedastat improves MADRS response rates (n=165)

Increased rates of remission (MADRS < 10) and large (50%) improvements





Broad & durable subgroup effects - MADRS & PGI-S

Measured at Weeks 2, 4, 6 & 10 (green favors emestedastat, red placebo)

Response/variable	All (n=165)	*No anti-D (n=31)	Yes anti-D (n=134)	*MADRS < 26 (n=81)	MADRS ≥ 26 (n=83)	*Cog. < 0.07 (n=82)	Cog. ≥ 0.07 (n=82)
MADRS (Cd ≥ 0.3) (week)	10	2,6	10	2,6,10	(4),10	2,6,10	-
MADRS (p < 0.05) (week)	10	-	10	6	-	2,10	-
PGI-S (Cd ≥ 0.3) (week)	-	6,10	4,6,10	4,6,10	6,10	4,6,10	-
PGI-S (p < 0.05) (week)	-	-	10	-	-	10	-

Excellent safety profile consistent with prior trials

Summary of Treatment-Emergent Adverse Effects (TEAE)

	Emestedastat n = 82	Placebo n = 83	Overall n = 165
Any TEAE	70 (85.4%)	67 (80.7%)	137 (83.0%)
TEAE related to trial drug	27 (32.9%)	24 (28.9%)	51 (30.9%)
Serious adverse event	0	1 (1.2%)	1 (0.6%)
Related TEAE discontinuation or interruption of drug	3 (3.7%)	1 (1.2%)	4 (2.4%)
TEAEs with incidence ≥ 5% overall			
Headache	11 (13.4%)	16 (19.3%)	27 (16.4%)
Fatigue	6 (7.3%)	5 (6.0%)	11 (6.7%)
Nasopharyngitis	4 (4.9%)	6 (7.2%)	10 (6.1%)
Upper respiratory tract infection	5 (6.1%)	5 (6.0%)	10 (6.1%)

Depression phase 2a conclusions and next steps

- ***Clinically and statistically significant treatment benefits on depressive symptoms for MADRS and patient-reported outcome of severity***
- Heavily pre/co-treated population with moderate MDD
- Consistent depression efficacy across subgroups
- Strong placebo effect impaired ability to show expected pro-cognitive effect (primary endpoint, data not shown)
- Emestedastat was safe and well tolerated (n=165 treated) with no suggestion of suicide risk or withdrawal syndrome
- The trial was well-conducted, with excellent data quality, no major differences between Australia and the UK or at high enrolling clinical sites

Conclusion

Clinical 'Proof of Concept' established in two separate clinical indications: AD and MDD

Proof-of-concept

- **Strong scientific rationale for CNS cortisol control mechanism in MDD, AD, and other neurodegenerative and neuropsychiatric conditions**
- **Clinical activity established in AD with a strong CDR-SB effect in pTau-positive patients and in patients with moderate MDD who were heavily co/pre-treated**

AD program

- **AD Phase 2b/3 trial underway with interim analysis in 2025 and final read out in 2026 using CDR-SB as the primary endpoint**

MDD program

- **MDD preparations underway to confirm pivotal trials program design and registrational requirements with Regulatory Authorities**

Emestedastat has broad therapeutic potential in a variety of neurological and psychiatric conditions

Appendix

Key references

Other references see also https://actinogen.com.au/xanamem

11β-HSD1 inhibition

- Seckl J. 11β-Hydroxysteroid dehydrogenase and the brain: Not (yet) lost in translation. J Intern Med. 2024 Jan;295(1):20-37. doi: 10.1111/joim.13741. Epub 2023 Nov 8. PMID:37941106. https://onlinelibrary.wiley.com/doi/10.1111/joim.13741
- Cognitive and disease-modifying effects of 11β-hydroxysteroid dehydrogenase type 1 inhibition in male Tg2576 mice, a model of Alzheimer's Disease: Sooy, K., Noble, J., McBride, A., Binnie, M., Yau, J. L. W., Seckl, J. R., Walker, B. R., & Webster, S. P. 2015. *Endocrinology, 1-12.*
- Partial deficiency or short-term inhibition of 11β-hydroxysteroid dehydrogenase type 1 improves cognitive function in aging mice Sooy, K., Webster, S. P., Noble, J., Binnie, M., Walker, B. R., Seckl, J. R., & Yau, J. L. W. 2010. *Journal of Neuroscience, 30(41), 13867-13872.*

Xanamem clinical trials

- Plasma pTau181 Predicts Clinical Progression in a Phase 2 Randomized Controlled Trial of the 11β-HSD1 Inhibitor Xanamem® for Mild Alzheimer's Disease Taylor J, Jaros M, Chen C, Harrison J, Hilt D *J Alz Dis 2024; 100: 139-150*
- Brain 11-Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamem™ Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals Villemagne VL, Dore V, Chong L, Kassiouf M, Mulligan, R, Feizpoura A, Taylor J, Roesner M, Miller T, Rowe CC *J Alz Dis 2024: 97: 1463–1475*
- Selection and early clinical evaluation of the brain-penetrant 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor UE2343 (Xanamem™) Webster, S. P., Ward, P., Binnie, M., Craigie, E., McConnell, K. M., Sooy, K., Vinter, A., Seckl, J.R. & Walker, B. R. 2007. *Bioorganic & medicinal chemistry letters, 17(10), 2838-2843.*
- Various podium and poster presentations on website

Technical references

- CDR-SB Clinical Dementia Rating Scale – Sum of Boxes is an 18-point, 6-domain measure of patient cognition and function and is a common endpoint used by regulators. Patients in the Xanamem biomarker phase 2a analysis had a baseline of approximately 4 points, similar to that in the donanemab phase 3.
- Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*(1), 155–159. https://doi.org/10.1037/0033-2909.112.1.155
- Hengartner MP, Jakobsen JC, Sørensen A, Plöderl M (2020) Efficacy of new-generation antidepressants assessed with the Montgomery-Asberg Depression Rating Scale, the gold standard clinician rating scale: A meta-analysis of randomised placebo-controlled trials. PLOS ONE 15(2): e0229381. https://doi.org/10.1371/journal.pone.0229381

Alzheimer's disease and cortisol

- Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study Pietrzak RH, Laws SM, Lim YY et. al. for the Australian Imaging, Biomarkers and Lifestyle Research Group 2017. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 2017; 2(1):45-52
- Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease Starkman, M. N., Giordani, B., Gebarski, S. S., Berent, S., Schork, M. A., & Schteingart, D. E. 1999. *Biol psych*, *46(12), 1595-1602.*

Depression and cortisol

- Ding et. al. Front. Pharmacol 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8461240/
- Effect of glucocorticoid and 11β-hydroxysteroid-dehydrogenase type 1 (11β-HSD1) in neurological and psychiatric disorders Dodd S, Skvarc D R, Dean OM, Anderson A, Kotowicz M, Berk M *Int J Neuropsychopharmacol* 2022; 25(5):387-398
- Depression and Hypothalamic-Pituitary-Adrenal Activation: A Quantitative Summary of Four Decades of Research Stetler C, Miller GE *Psychosom Med* 2011; 73(2):114-26

Market & cost of treatment estimates

- Matthews, K. A., Xu, W., Gaglioti, A. H., Holt, J. B., Croft, J. B., Mack, D., & McGuire, L. C. (2018). Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged≥ 65 years. Alzheimer's & Dementia. https://doi.org/10.1016/j.jalz.2018.06.3063
- Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *NEJM*. 2013;368(14):1326-34.
- https://www.cdc.gov/aging/aginginfo/alzheimers.htm#treated
- https://www.nimh.nih.gov/health/statistics/major-depression
- Symphony Health and ICON plc Company, Metys® database full year 2023

Currencies

- Currencies are in Australian dollars unless otherwise stated

Selected Glossary 1

- **11β-HSD1 –** 11 beta HydroxySteroid Dehydrogenase-1 enzyme. Selectively expressed in brain, liver, adipose.
- **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
- **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 Fibrilliary Acidic Protein – a marker of microglial cell activation in the brain
- **IDSST –** International Digit Symbol Substitution Test of cognition
- **IQCODE –** Informant Questionnaire on Cognitive Decline in the Elderly

Selected Glossary 2

- **MADRS –** Montgomery-Åsberg Depression Rating Scale
- **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
- **PGI-S –** Patient Global Impression of Severity – a patient-reported outcome
- **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
- **SSRI –** Selective serotonin reuptake inhibitor
- **Tau –** A brain protein
- **Ttau –** Total tau levels including both phosphorylated and non-phosphorylated tau

Contacts

Michael Roberts
Investor Relations
P: +61 2 8964 7401
M: +61 423 866 231
E. michael.roberts@actinogen.com.au

Steven Gourlay
CEO & Managing Director
P: +61 2 8964 7401
E. steven.gourlay@actinogen.com.au