



Oral Xanamem®

Controlling brain cortisol to treat depression and slow progression in Alzheimer's disease - a novel therapeutic mechanism

Corporate Presentation
September 2024

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 its 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



Novel mechanism and attractive oral profile

- Xanamem is a unique brain-penetrant tissue cortisol synthesis inhibitor (11 β -HSD1 enzyme)
- Once-daily oral therapy with potential efficacy, safety and ease of use greater than competitors
- More than 380 people treated with promising safety profile and low drug interaction risk



Large and growing market opportunities with significant unmet need

- Significant benefits on depression in recent phase 2a trial, phase 2b in planning
- Disease-modifying activity to slow Alzheimer's disease in phase 2a data, phase 2b on-going
- Trials potentially read through to schizophrenia, other dementias and Parkinson's disease



Patent protection

- Composition of matter protection to 2031 – to 2036 with extensions in major markets
- Additional recent patents protect against future competition



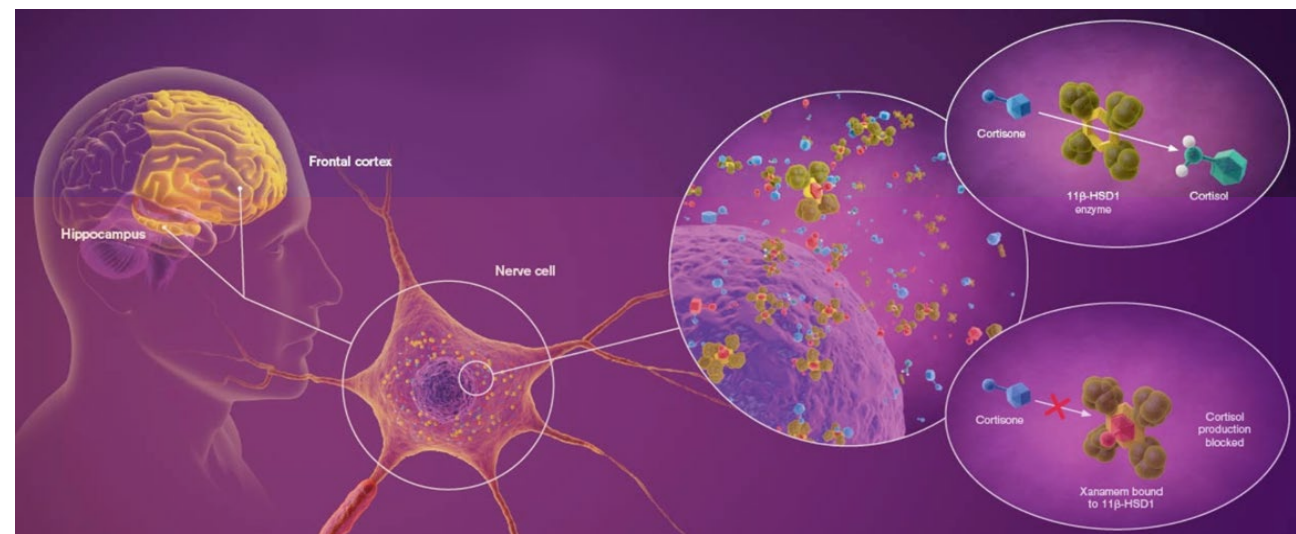
Near-term phase 2 milestones funded

- Cash runway through late 2025
- Positive phase 2a depression results on two major clinical endpoints
- Phase 2b Alzheimer's disease interim data mid 2025

Once-daily oral treatment with a unique mechanism

Xanamem is a small molecule tissue cortisol synthesis inhibitor (11 β -HSD1 enzyme)

- ✓ Good safety profile in >380 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

Controlling brain cortisol¹ has durable benefits



Xanamem inhibits local tissue production of cortisol in key regions of the brain via 11 β -HSD1²

“STRESS” in the brain becomes “CHILL”

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

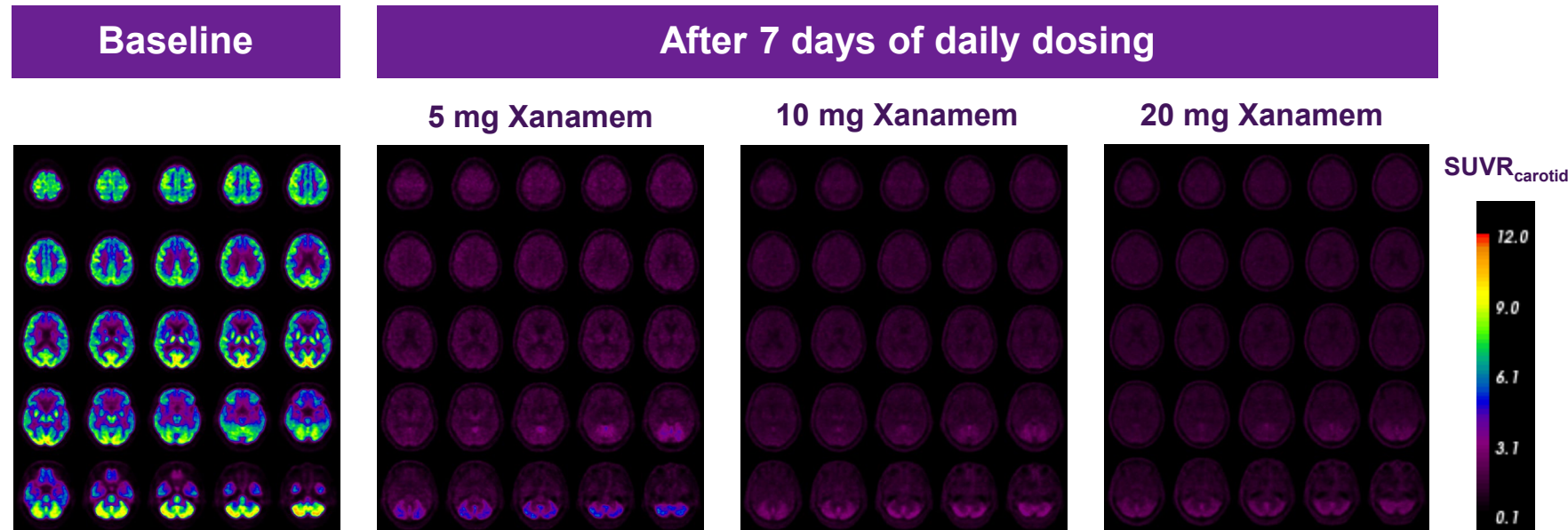


“Lower stress” longer term e.g.

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

Human PET study shows full target engagement

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

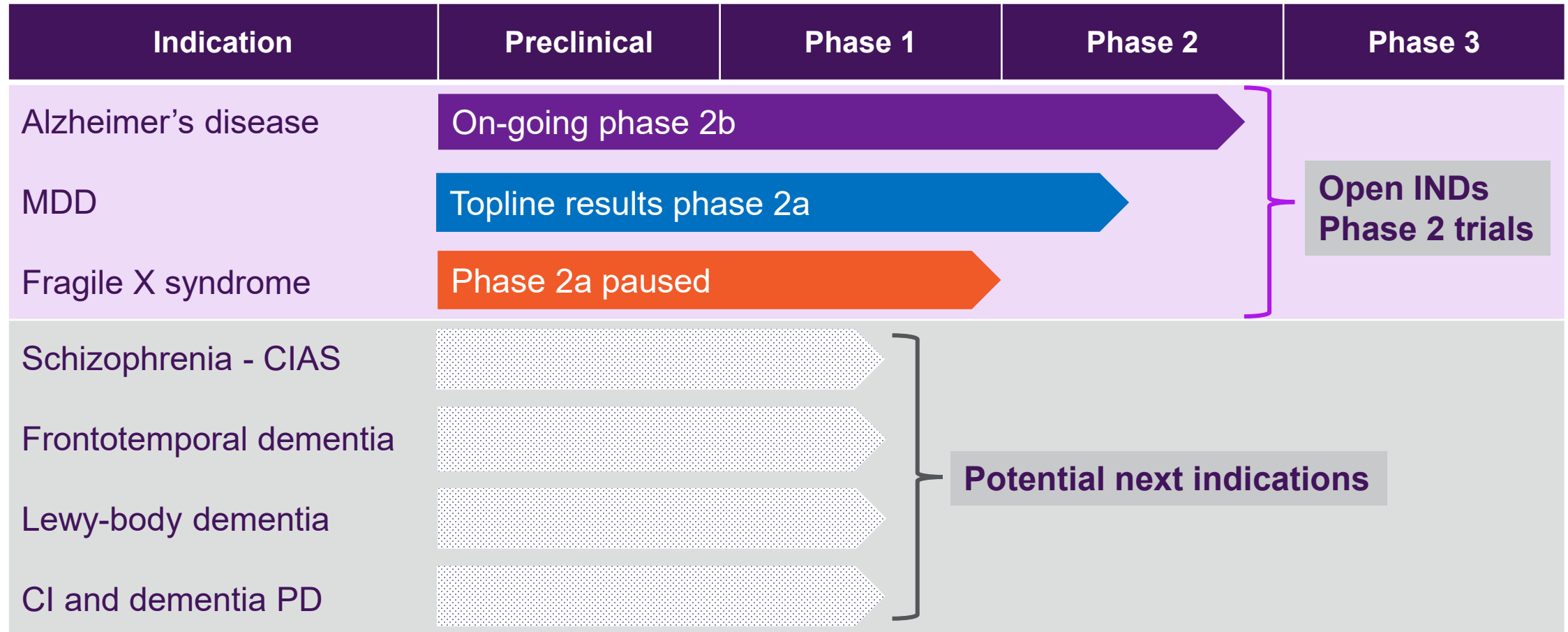


Xanamem extensively binds to the 11 β -HSD1 enzyme throughout the brain, with high post-treatment effects (absence of colour) after 7 days at all doses, slightly less at a 5 mg dose.

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

Validates 10mg dose in efficacy trials

Xanamem pipeline



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



Dana Hilt
Chief Medical Officer
MD



Will Souter
Chief Financial Officer
BComm, LLB



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



Stock price and key shareholders*



ASX: ACW – YTD CY24



Key Data

52 Week Range	\$0.015 – \$0.099
YTD CY24 change	103%
Shares on issue	2.7b
Unlisted options	367m
Closing price	\$0.044
Closing market cap*	\$119m
30 June cash balance	\$9.45m*

Key Shareholders

Biotech Value Fund	9.2%
CEO Steven Gourlay	3.6%
Top 20 (ex BVF/Management)	22.8%

Depression



There remains significant unmet need in depression

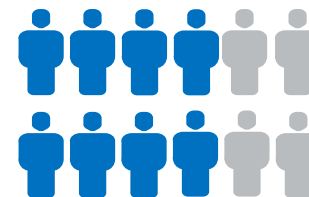
Xanmem's unique mechanism and safety differentiate it from older drugs

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 mifepristone³
- ***Now positive phase 2a data on depressive symptoms for Xanmem***

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 and Alzheimer's disease

AUVELITY MDD recent sales launch example

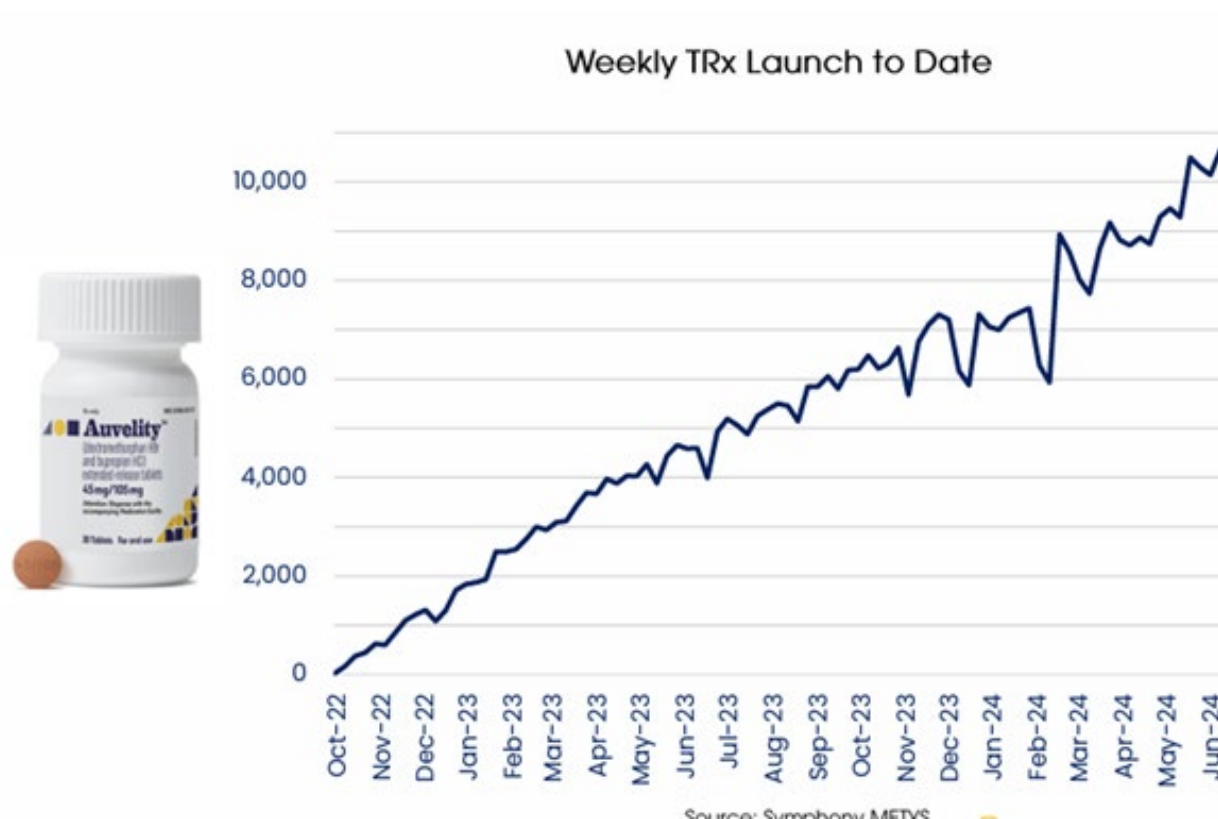
Axsome Therapeutics

- Combination product of dextromethorphan and bupropion – two generic drugs
- 3.8-point MADRS benefit vs. placebo⁶
- Indicated for the treatment of major depressive disorder (MDD) in adults
- Unique Selling Proposition:
 - “...started working for some people as early as 1 week”
 - “Symptom relief that’s fast & lasts”
 - “AUVELITY works differently”



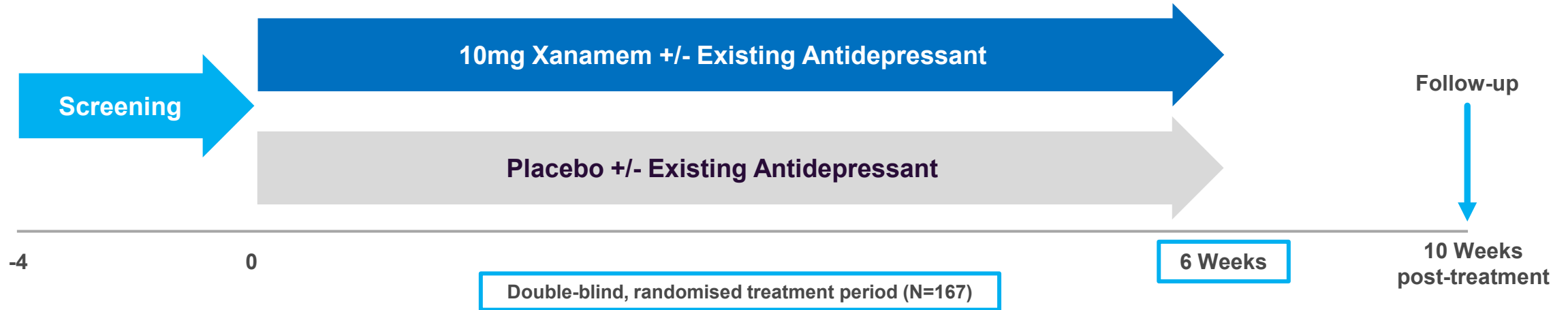
Axsome's successful AUVELITY launch

Last quarter net sales US\$65 million, estimated peak US sales US\$ 1 to 3 billion*



XanaCIDD trial design and methods

Phase 2, 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) • Executive Function Cognitive Composite (EFC) • Memory Function Cognitive Composite (MC)

XanaCIDD statistical methods

Statistical considerations reflect industry standard for proof-of-concept trials



- Primary & secondary endpoints analyzed using a standard Mixed Model for Repeated Measures (MMRM)
- Three pre-specified subgroups for efficacy: current anti-depressant therapy (yes/no), baseline depression severity (lower/higher) and degree of cognitive impairment (lower/higher)
- p values shown are 2-sided hypothesis tests unless stated otherwise
- Effect sizes were calculated using the Cohen's d (Cd) statistic representing the effect as a % of the baseline population variability or standard deviation. This metric is frequently used in the cognition field¹ and is useful in depression²:
 - > **0.2** = Potentially clinically meaningful effect size
 - ≥ **0.3** = Clinically meaningful effect size
 - ≥ **0.5** = Large and clinically meaningful effect size

Results summary



- The trial was well-conducted, with excellent data quality, no major differences between Australia and the UK or at high enrolling clinical sites
- Clinically and statistically significant treatment benefits were seen on depression
- No treatment benefit was observed for cognitive dysfunction – cognition improved markedly in both Xanamem and placebo groups
- Xanamem was safe and well tolerated (n=165 treated)

Typical, broad, moderate depression trial population



All patients on or previously treated with anti-depressants

	Xanomem (n=82)	Placebo (n=83)
Mean age (SD)	49 (13)	49 (15)
% female	63	61
Mean screening HAM-D depression score (SD)	21 (3)	21 (3)
Mean MADRS (SD)	24 (6)	26 (7)
% on anti-depressant therapy	77%	86%
Mean cognition – screening Boxfiller (SD)	22 (5)	21 (6)
Mean cognition – Attention Composite (SD)	0.11 (0.77)	-0.10 (0.98)

MADRS & PGI-S depression benefits

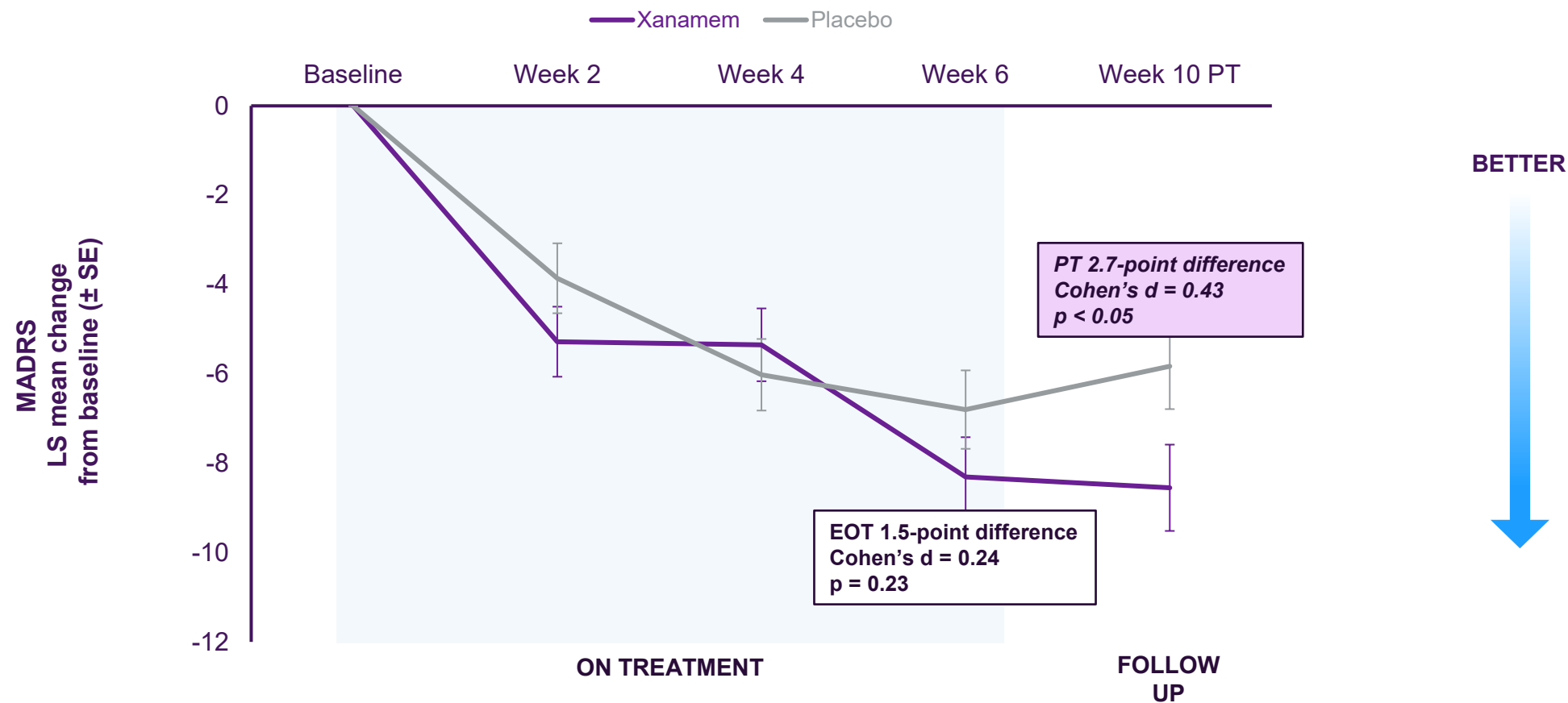
Montgomery-Åsberg Depression Rating Scale, Patient Global Impression-Severity



- Xanamem treatment performed better than placebo, to a clinically*, and in many cases, statistically significant extent:
 - ✓ In all patients (n=165) a clinically significant MADRS benefit was seen at the end of 6 weeks treatment and a clinically and statistically significant benefit four weeks post-treatment at Week 10 ($p < 0.05$)
 - ✓ Xanamem showed higher response rates e.g. achieving 50% MADRS reduction (34% vs. 22%) and 50% higher remission rates (26% vs. 17%)
 - ✓ PGI-S curves separated earlier than MADRS and favored Xanamem at all timepoints
 - ✓ Subgroup analysis showed consistent MADRS and PGI-S activity also with maximal effect at Week 10

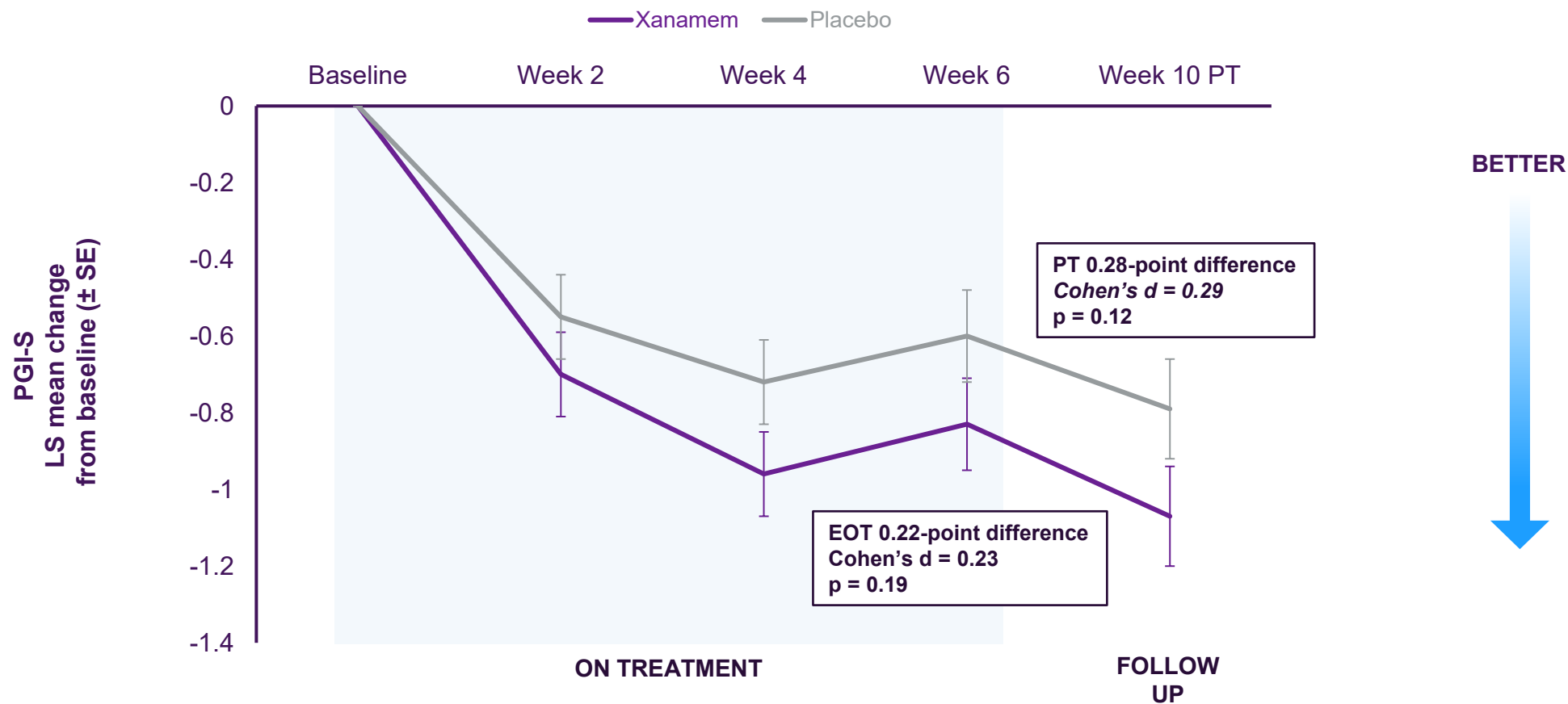
Xanamem MADRS separation from Week 6

All randomized participants (n = 165)



Xanamem PGI-S separation from Week 2

All randomized participants (n = 165)

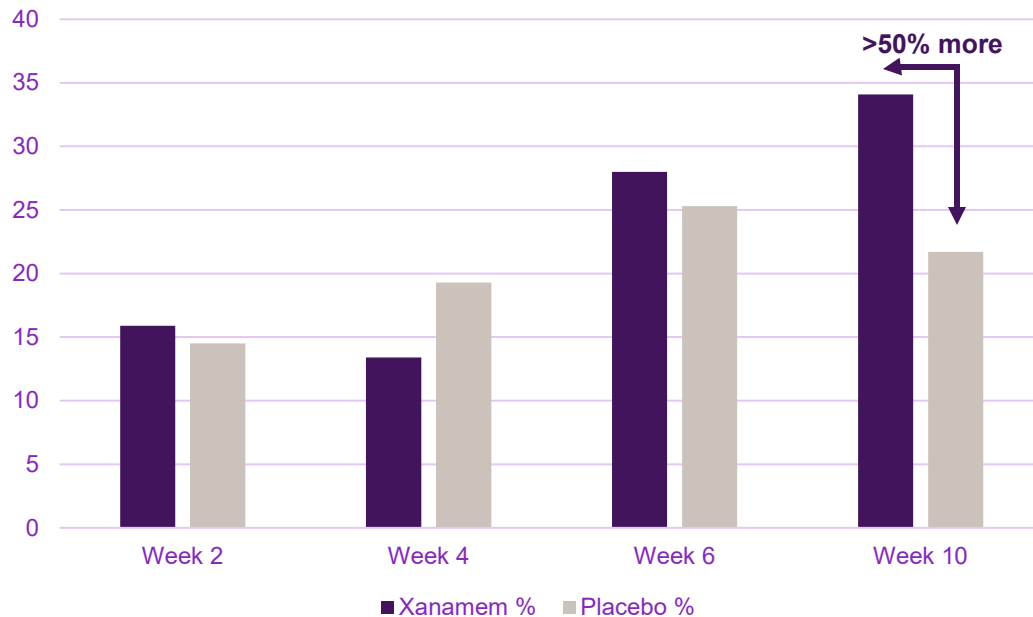


Xanamem major improvement in depression response

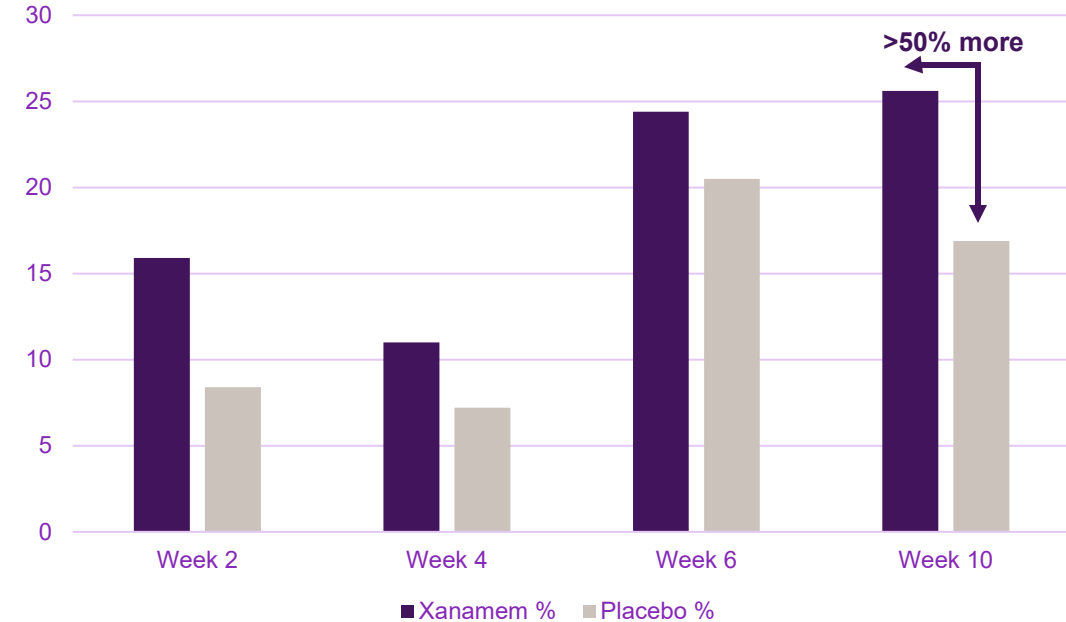


Increased rates of remission (MADRS < 10) and large (50%) improvements

% with $\geq 50\%$ reduction in MADRS



% with < 10 points on MADRS



Broad & durable subgroup effects - MADRS & PGI-S



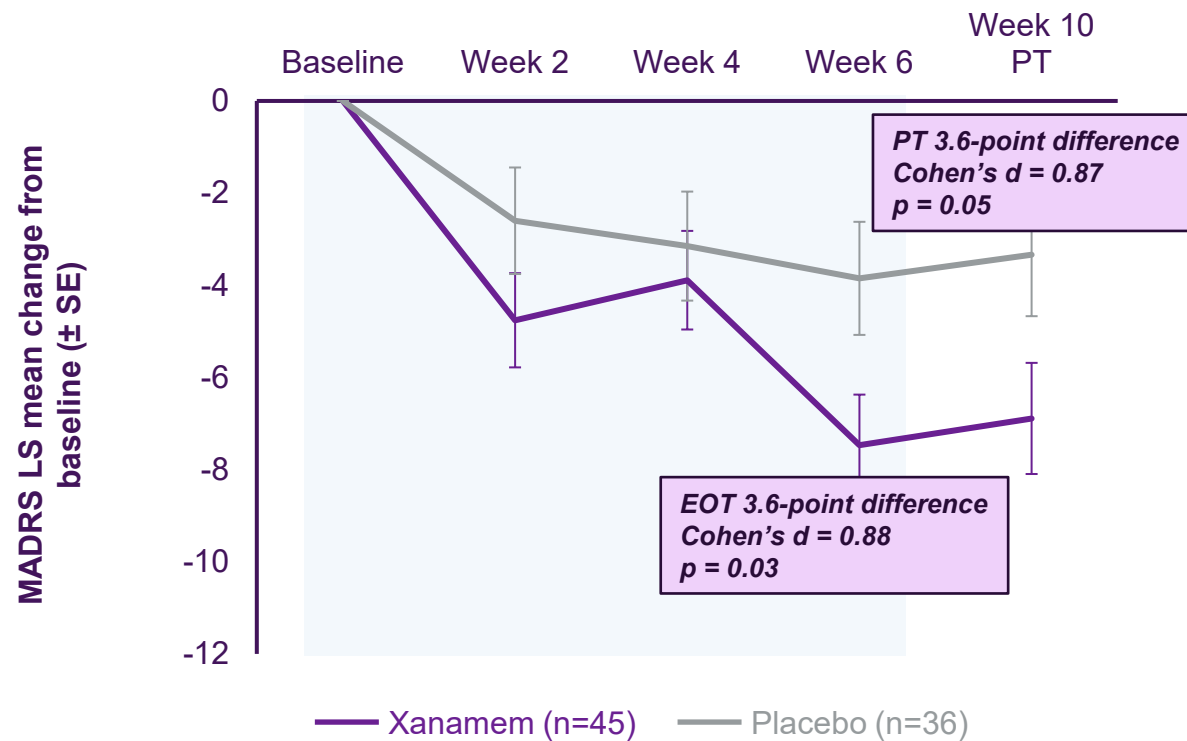
Measured at Weeks 2, 4, 6 & 10 (green favors Xanamem, red placebo)

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	-
Selected demographics:							
Mean age (SD)	49 (14)	50 (13)	49 (14)	49 (14)	50 (13)	53 (13)	45 (13)
% female	62%	45%	66%	62%	63%	66%	59%
Mean HAM-D (SD)	21 (3)	21 (4)	21 (3)	20 (3)	23 (3)	22 (3)	21 (3)
% on anti-D therapy	81%	0%	100%	79%	83%	79%	83%
Mean boxfiller (SD)	21 (5)	22 (6)	21 (5)	22 (5)	21 (6)	20 (5)	23 (5)

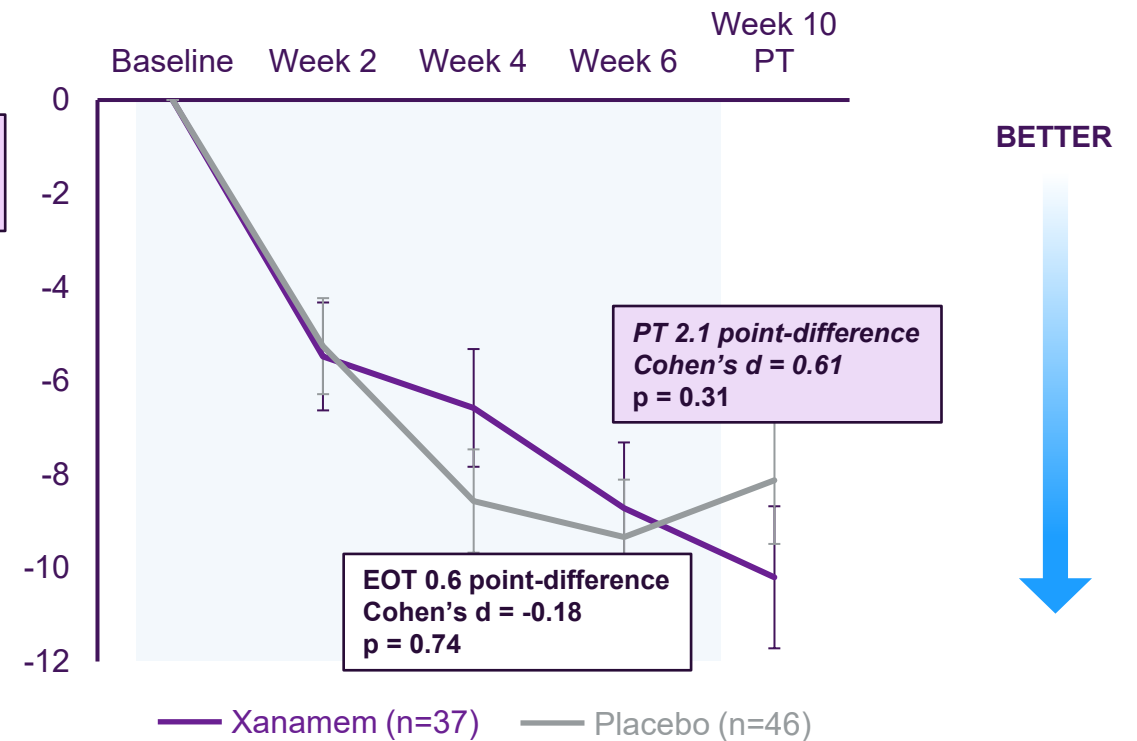
Stronger MADRS response in patients with milder MDD

Clinically significant in both subgroups at Week 10

MADRS < 26 at Baseline



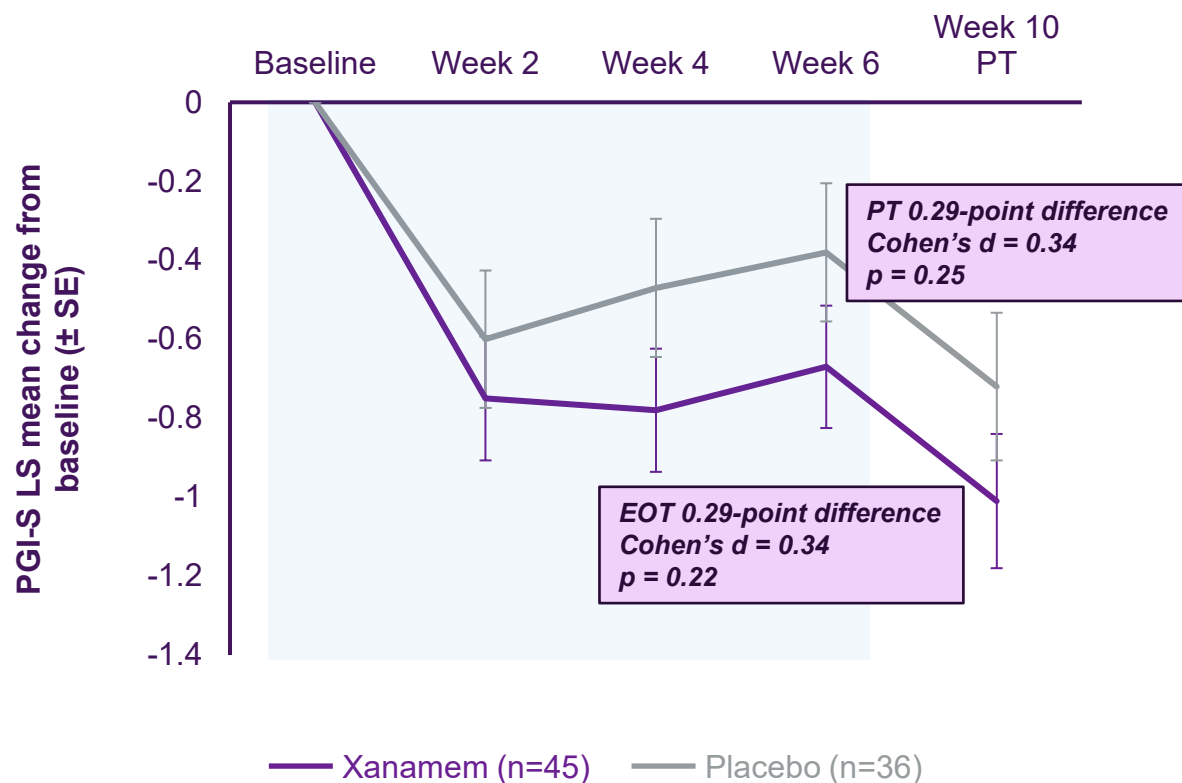
MADRS ≥ 26 at Baseline



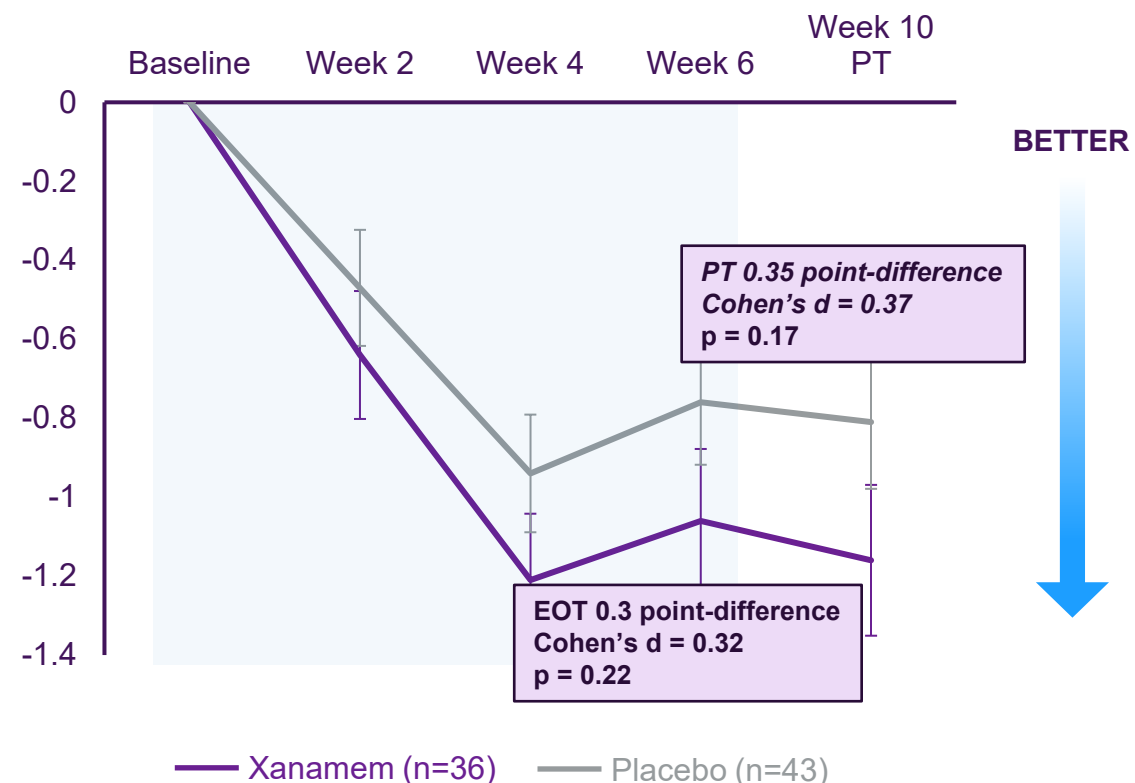
Positive PGI-S responses both MADRS groups

Clinically significant at Weeks 6 & 10

MADRS < 26 at Baseline



MADRS ≥ 26 at Baseline



Excellent safety profile consistent with prior trials

Summary of Treatment-Emergent Adverse Effects (TEAE)

	Xanamem N = 82	Placebo N = 83	Overall N = 165
Any TEAE	69 (84.1%)	67 (80.7%)	136 (82.4%)
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 $\geq$ 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%)

Controlling brain tissue cortisol really works!

Proof of 11 β -HSD1 as a therapeutic target is a major scientific and clinical advance



- Clinically, statistically significant and durable treatment benefits on depression
 - Key secondary endpoint, MADRS, at EOT and four weeks of post-treatment follow up
 - Broadly positive subgroup data for MADRS and PGI-S
 - Positive improvements in responder rates
- Xanamem was safe and well tolerated; no significant safety issues were observed
 - There was no clear pattern of treatment-related adverse effects related to Xanamem
 - Safety profile consistent with prior trials
- Durability of Xanamem benefits for four weeks after the end of treatment suggests underlying biological modification due to cortisol control has occurred

Positive implications for Alzheimer's

XanaMIA phase 2b – a 36-week trial in 220 biomarker-positive patients



- Evidence of durable benefit on depression from control of brain cortisol validates Xanamem's mechanism of action at a 10 mg daily dose
- Durable clinical activity on depression increases the likelihood of seeing a disease-modifying slowing of Alzheimer's disease on multiple endpoints over 36 weeks
- XanaCIDD cognitive findings of little relevance to assessments of long-term functional and cognitive decline used in Alzheimer's disease
 - XanaCIDD was an exploratory or proof-of-concept trial aimed at acute symptom improvement (6-weeks) in depressed patients with cognitive dysfunction
 - XanaMIA measures and describes Xanamem's ability to slow functional and cognitive decline in Alzheimer's over 36 weeks

Alzheimer's disease



Alzheimer's disease

Strong scientific rationale to address huge unmet medical need

Scientific rationale

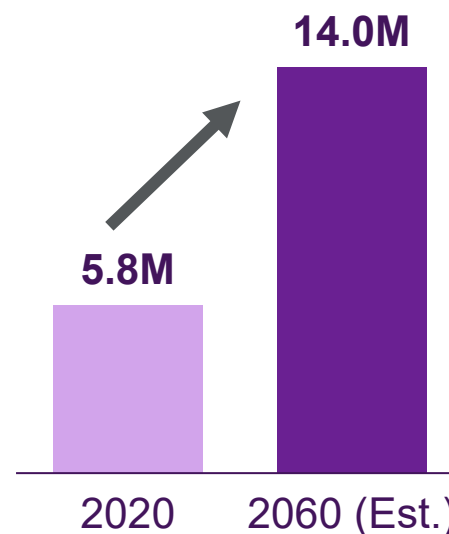
- Cortisol levels are elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11 β -HSD1 provides full neuroprotection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

Alzheimer's Disease market – U.S.

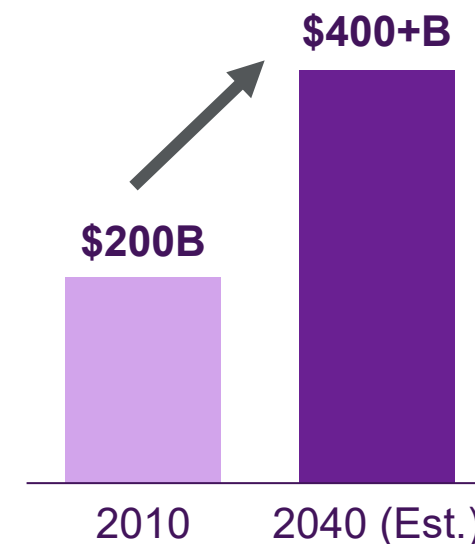
Large unsatisfied and growing market



of patients

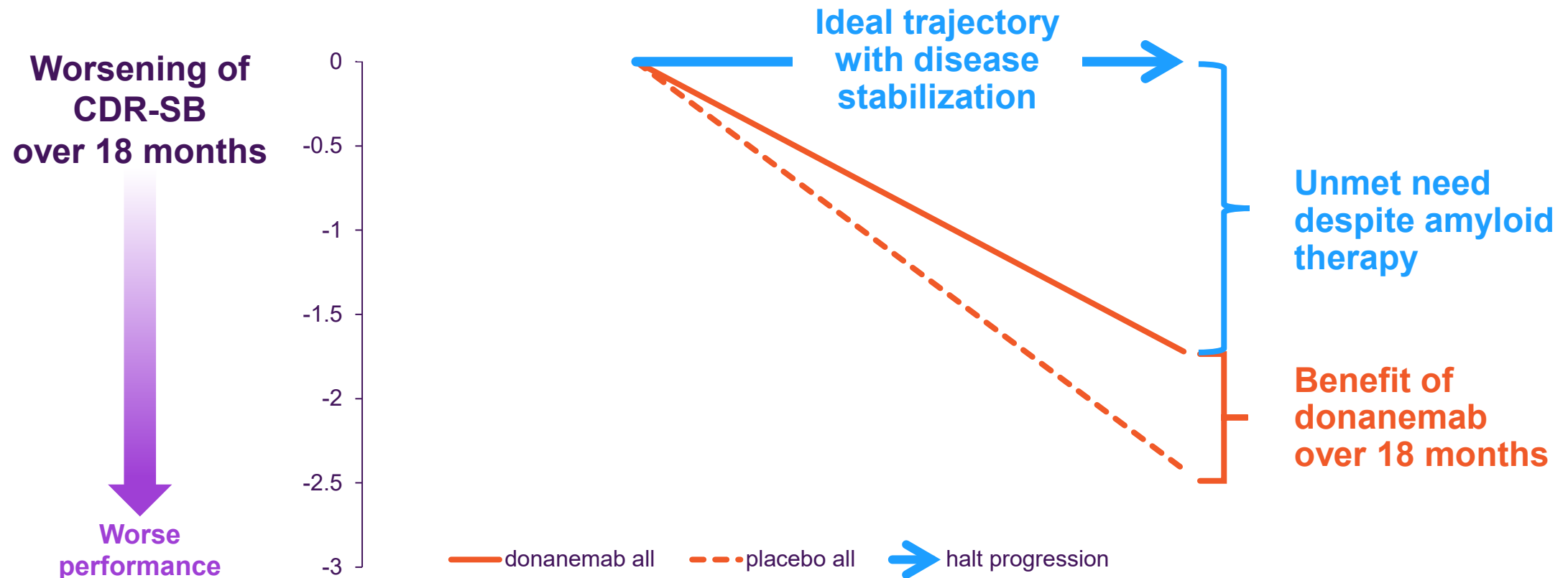


Cost to treat



Anti-amyloid therapy modestly slows AD progression

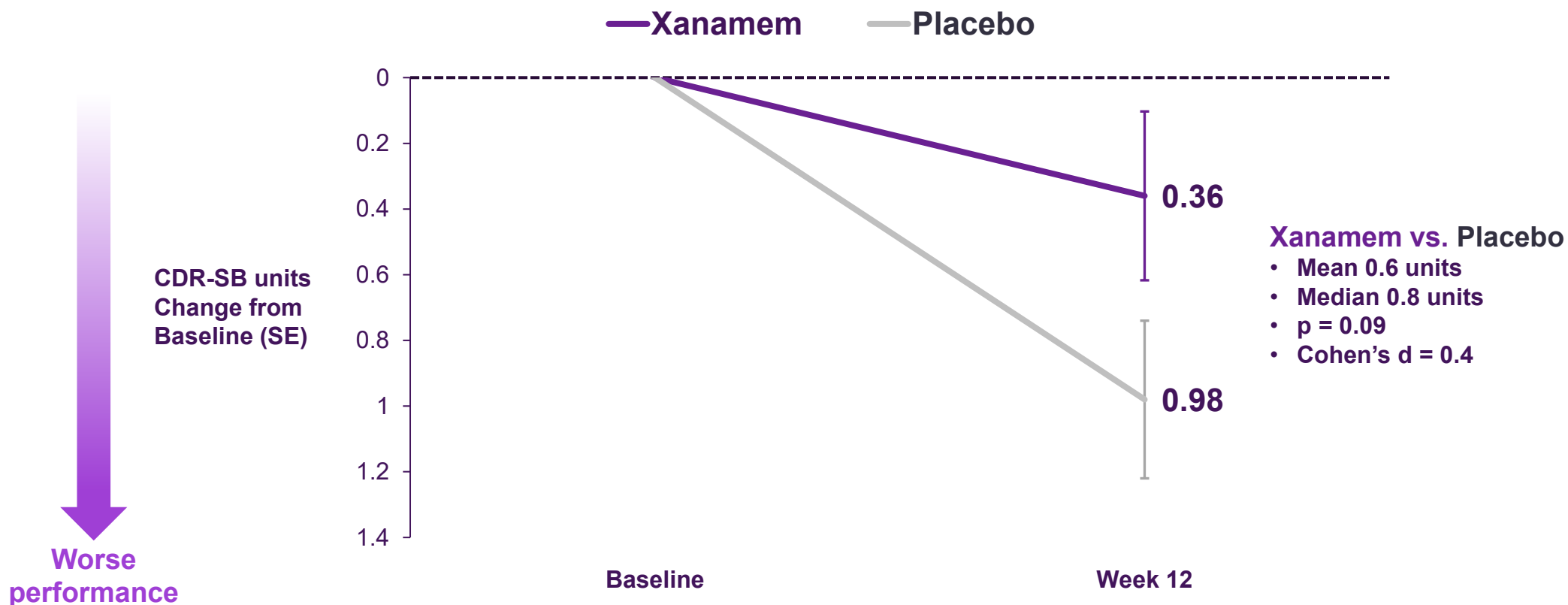
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanmem are needed

Xanamem in pTau181-positive patients with mild AD

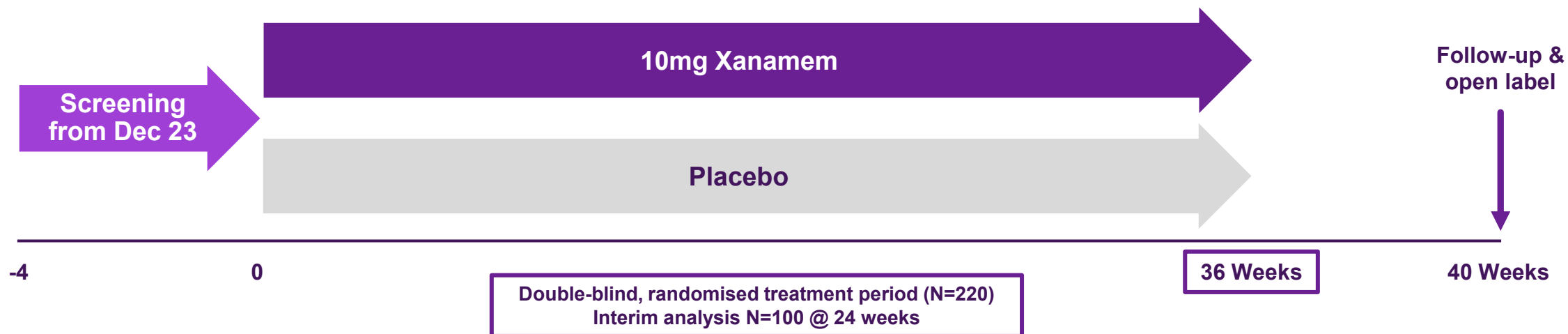
Phase 2a biomarker study: major slowing of CDR-SB decline (n=34)¹



Xanamem benefits extrapolated to 18 months would be ~8x anti-amyloid drugs

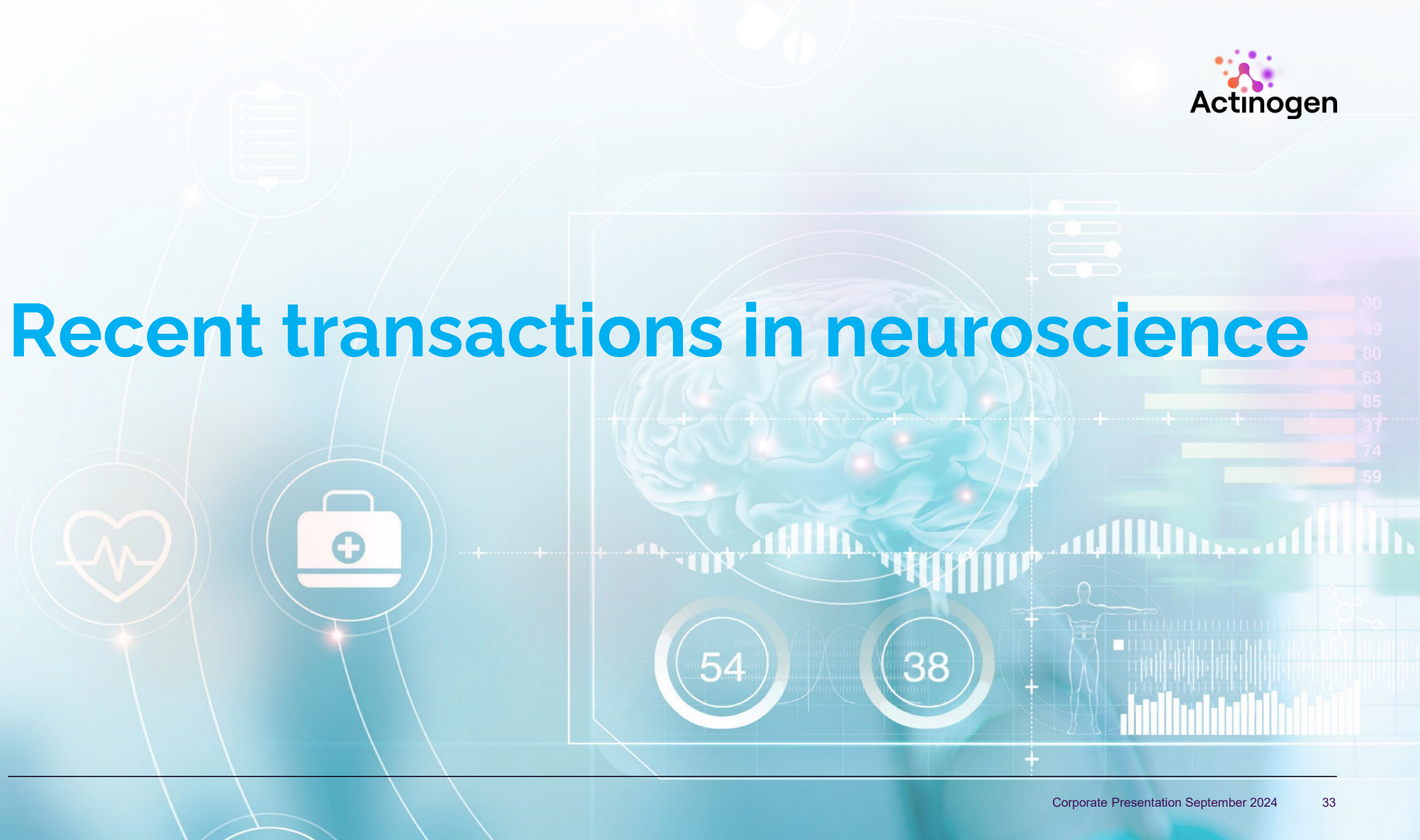
XanaMIA phase 2b trial in Alzheimer's disease

Initial, interim results in mid 2025, final results mid 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 sites - Currently expanding to US - Interim analysis when 100 people complete 24 weeks

Recent transactions in neuroscience



Recent neuroscience acquisitions and IPOs



Lead Drug(s)	TRPML1	KarXT	Emraclidine	ALTO-100	PIPE-307 PIPE-791	RAP-219
Phase	Preclinical	Phase 3	Phase 2	Phase 2	Phase 2	Phase 1
Lead asset	PD, other neuro	Schizophrenia	Schizophrenia	MDD	MS & MDD	Epilepsy, BPD, other neuro
Transaction	Acquisition	Acquisition	Acquisition	IPO	IPO	IPO
Amount	US\$610m*	US\$14.0b	US\$8.7b	US\$148m	US\$110m	US\$174m
Date	23-Nov	23-Dec	23-Dec	24-Feb	24-Apr	24-Jun

Active licensing for clinical neuroscience assets



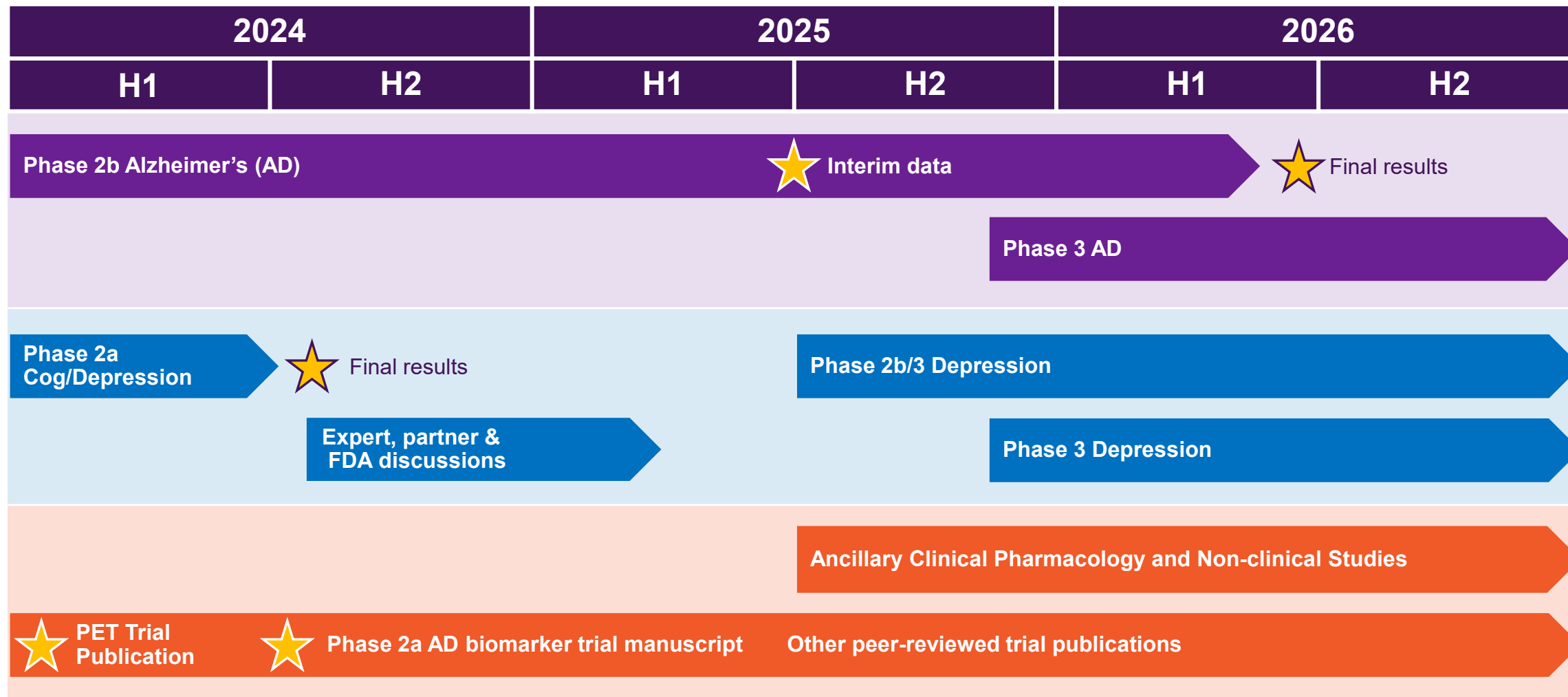
Drug	ACI – 24.060	PRX-005	NBI-1117567	ulotaront, SEP- 378614 and others	AL-001	BIIB-124	Bepranemab
Phase	Phase 1b/2	Phase 1	Phase 2	Phase 3	Phase 3	Phase 3	Phase 1
Indication	Alzheimer's (amyloid beta antibody)	Alzheimer's (tau antibody)	Schizophrenia	Schizophrenia/ Depression	Dementias (progranulin target)	Depression	Alzheimer's Disease (tau antibody)
Deal Type	Exclusive Option & License	Exclusive Option & License*	License	License	License	License	License
Upfront	US \$100m	US\$100m	US\$100m	US\$300m	US\$700m	US\$1.5b	US\$100m
Earnout	US \$2.1b	US\$2.1	US\$2.6b	US\$0.6b	US\$1.5b	US\$UNK	US\$2.0b
Total Consideration	US\$2.2b	US\$2.2b	US\$2.7b	US\$0.9b	US\$2.2b	>US\$1.5b	US\$2.1b
Date	May-24	Jun-21/Oct-23	21-Nov	21-Sep	21-Jul	20-Nov	20-Jun

* By exercise of previously negotiated option agreement during early development

Milestones & summary



Two promising phase 2 clinical programs



Next steps for Xanamem



- ✓ Enrol XanaMIA phase 2b in Alzheimer's as quickly as possible
- ✓ Implement product development plan for both Alzheimer's disease and depression with focus on speed to marketing approvals
- ✓ Finalize data analysis e.g. detail of MDD responder patient population
- ✓ Consultation on MDD:
 - Consult widely with local and global depression experts
 - Consult widely with potential pharmaceutical partners
 - Design phase 2b protocol for FDA consultation
 - Submit FDA briefing book and conduct meeting
- ✓ Commercial product definition for MDD “target product profile”
- ✓ Manufacture additional tablets
- ✓ Conduct pivotal (phase 2b/3) AD and MDD trials

Appendix



Key references

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



11 β -HSD1 inhibition

- Seckl J. 11 β -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 11 β -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 11 β -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 11 β -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, Kassiof 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 11 β -hydroxysteroid dehydrogenase type 1 (11 β -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 11 β -hydroxysteroid-dehydrogenase type 1 (11 β -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 $\geq$ 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

- **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** – 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

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