



Oral Xanamem®

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

Capital Raising – \$11.1 million to accelerate Alzheimer's phase 2b/3 trial

18 September 2024

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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 in major depressive disorder (MDD) in phase 2a trial, phase 2b/3 in planning
- Disease-modifying activity to slow Alzheimer's disease (AD) in phase 2a data, phase 2b/3 on-going
- Trials potentially read through to bipolar disease, other dementias including Parkinson's



Patent protection

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



Capital Raising of \$11.1m led by \$1 million investment from CEO, clinical milestones funded

- Undertaking a capital raising of \$11.1m via a \$8.1m Placement and \$3m SPP at \$0.03 per share. Placement and SPP shares will receive an attaching three for four option with an exercise price of \$0.05 and expiry date of 30 September 2027
- CEO, Dr Steven Gourlay, will be subscribing for \$1m in the Placement (subject to shareholder approval)
- Funds raised will be used for XanaMIA phase 2b/3 trial
- Post capital raising the company will have a cash runway through mid 2026
- Phase 2b/3 XanaMIA Alzheimer's Disease interim data mid 2025, final data mid 2026

Experienced board and management team



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



Alzheimer's disease phase 2b/3

Recent developments increase confidence in XanaMIA



XanaMIA Alzheimer's disease trial moving to full enrolment and full phase 2b/3 design

- Recently released data showing clinically and statistically significant improvement in depression symptoms validate Xanamem's mechanism of action and 10 mg dose to control brain cortisol
- Lack of superiority over placebo for cognitive enhancement in depressed patients prioritizes modification and functional endpoints as the primary evaluation tool in XanaMIA
- XanaMIA is established as one of two potential "pivotal" trials by:
 - Continuous enrolment of the full 220 participants in Australia and US to speed enrolment
 - CDR-SB as the primary endpoint (used for Eisai's Leqembi's FDA approval)
 - Independent Data Monitoring Committee to conduct interim analysis similar to market precedents
 - "Phase 3-standard" statistical methods
 - Full statistical power for primary endpoint ($p < 0.05$)
 - Sequential examination of secondary endpoints after primary ($p < 0.05$)
 - Additional quality oversight and auditing of trial sites, vendors and procedures
 - Use of commercial tablet formulation

Alzheimer's disease

Strong scientific rationale to address huge unmet medical need

Scientific rationale

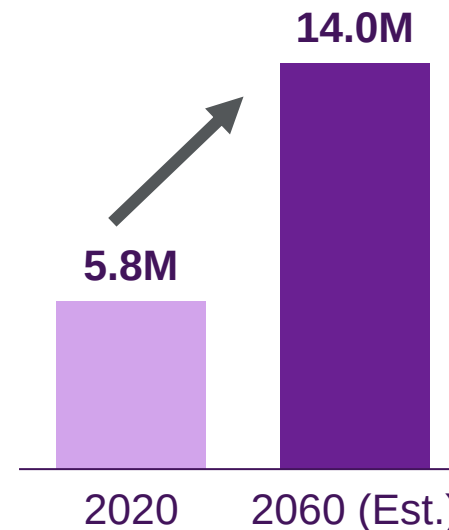
- Cortisol levels are elevated in brain fluid in early AD
- Chronic corticosteroid treatment leads to hippocampal atrophy and cognitive impairment
- Elevated cortisol levels are associated with clinical progression
- Alzheimer's disease mouse model: 30–60% inhibition of 11 β -HSD1 provides full neuroprotection
- 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.

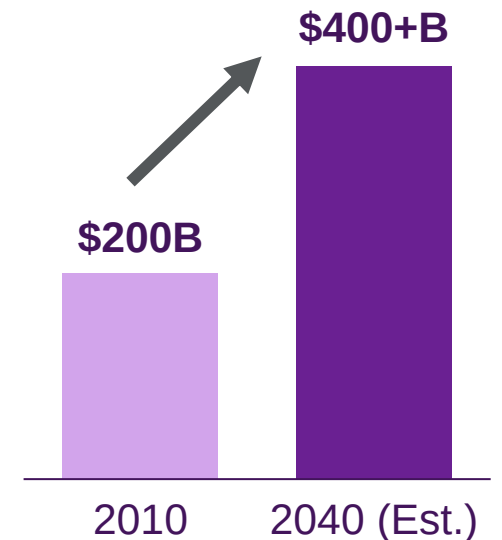
Large unsatisfied and growing market



of patients

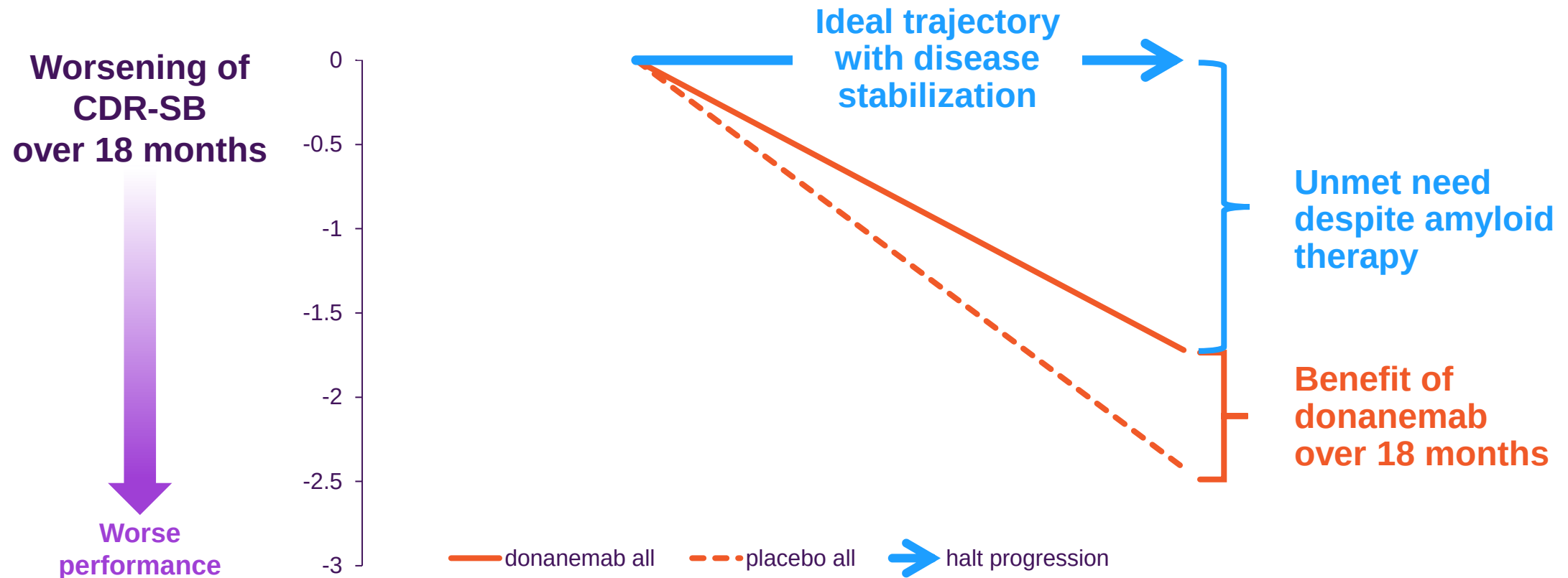


Cost to treat



Anti-amyloid therapy modestly slows AD progression

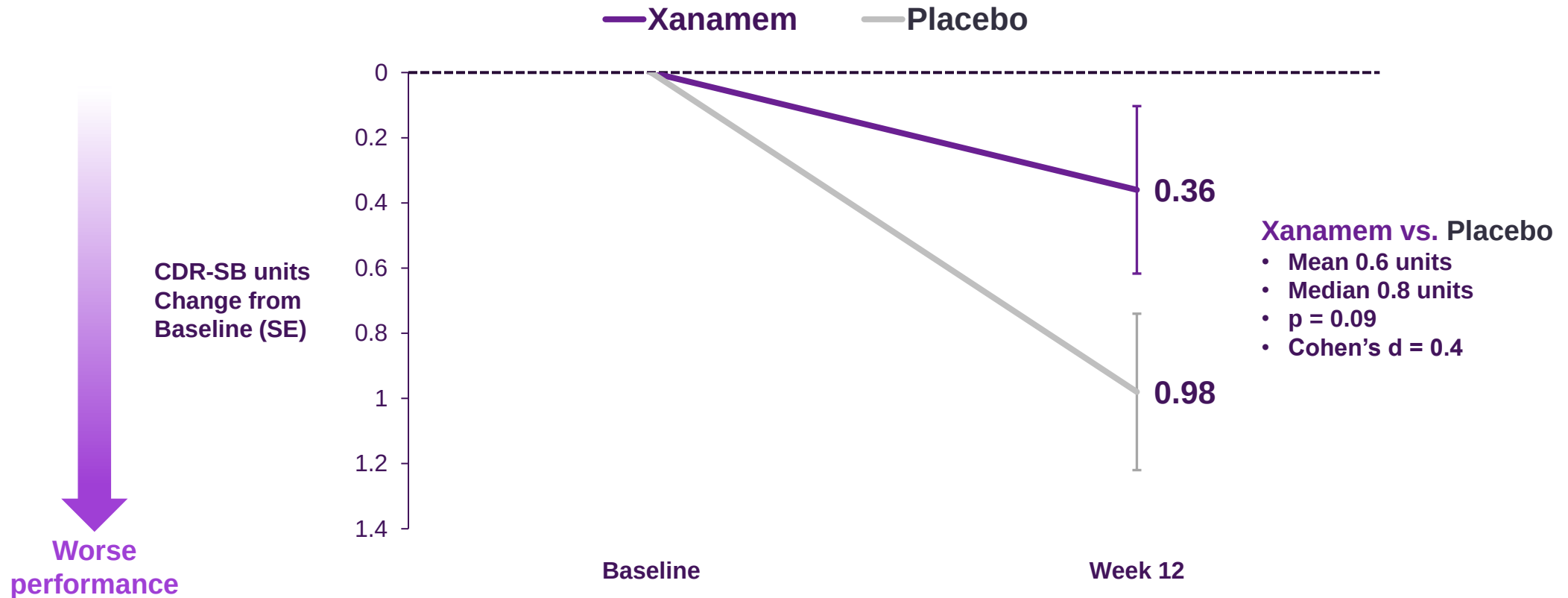
Ideally patients with AD would not worsen on treatment at all



Drugs targeting other mechanisms like Xanomem are needed

Xanamem slows AD progression markedly

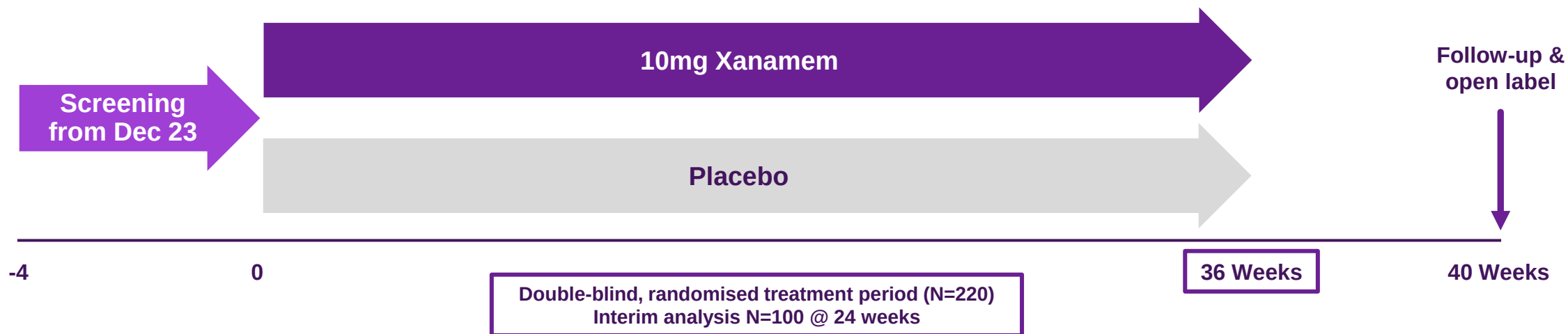
Phase 2a data in biomarker-positive patients with mild AD (n=34)¹



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

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

Interim results mid 2025, final results mid 2026



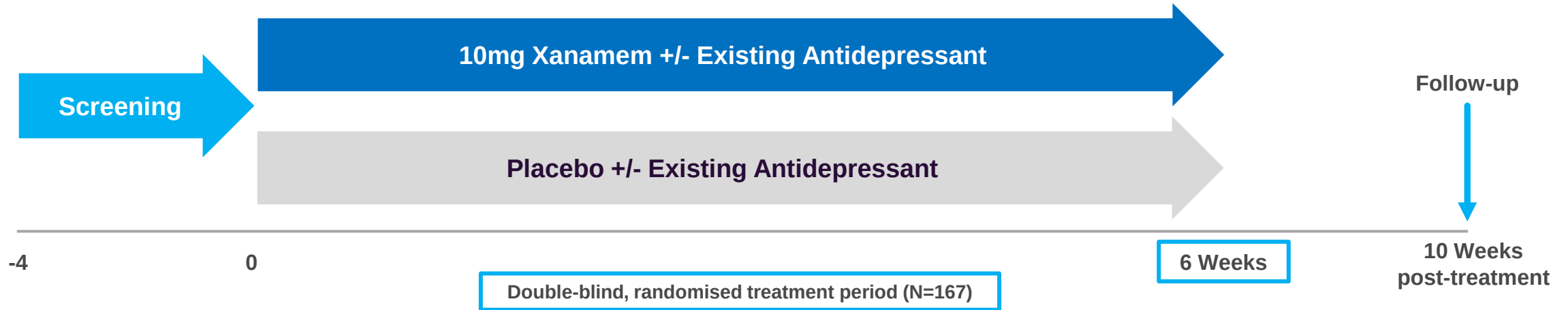
Key Inclusion Criteria	Primary Endpoint	Key Secondary Endpoints	Implementation
- Blood pTau biomarker positive - Mild-moderate Alzheimer's by NIA-AA criteria	CDR-SB (functional and cognitive measure)	- Amsterdam Activity of Daily Living (functional measure) - Cognitive Test Battery (7 cognitive measures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

Positive phase 2a depression data



XanaCIDD trial design

Phase 2a, 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)

Results summary



- ***Clinically and statistically significant treatment benefits on depression symptoms***
- Cognition improved markedly in both Xanamem and placebo groups without evidence of greater Xanamem benefit vs. placebo
- Xanamem was safe and well tolerated (n=165 treated)
- The trial was well-conducted, with excellent data quality, no major differences between Australia and the UK or at high enrolling clinical sites

MADRS & PGI-S depression benefits

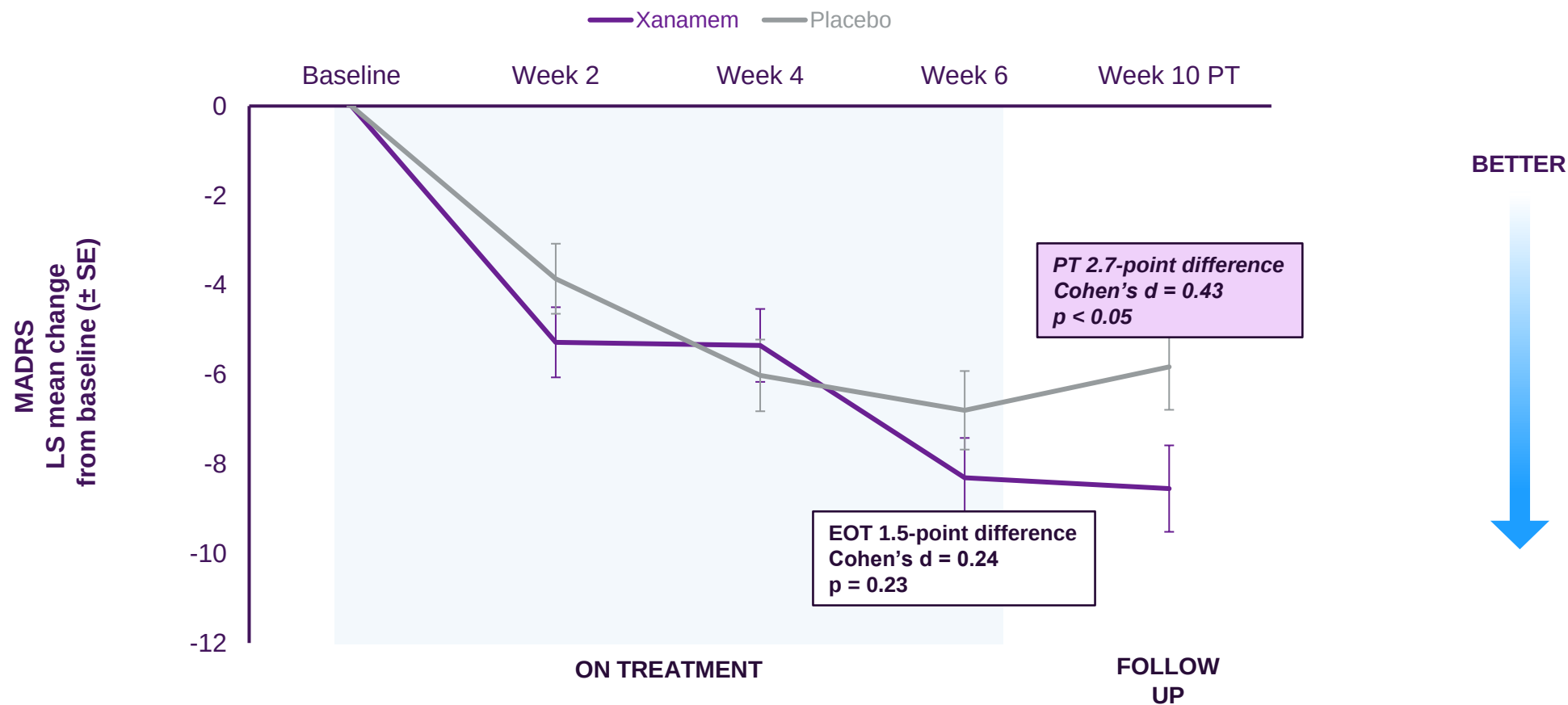
Montgomery-Åsberg Depression Rating Scale, Patient Global Impression-Severity



- 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 broadly consistent MADRS and PGI-S activity also with maximal effect at Week 10

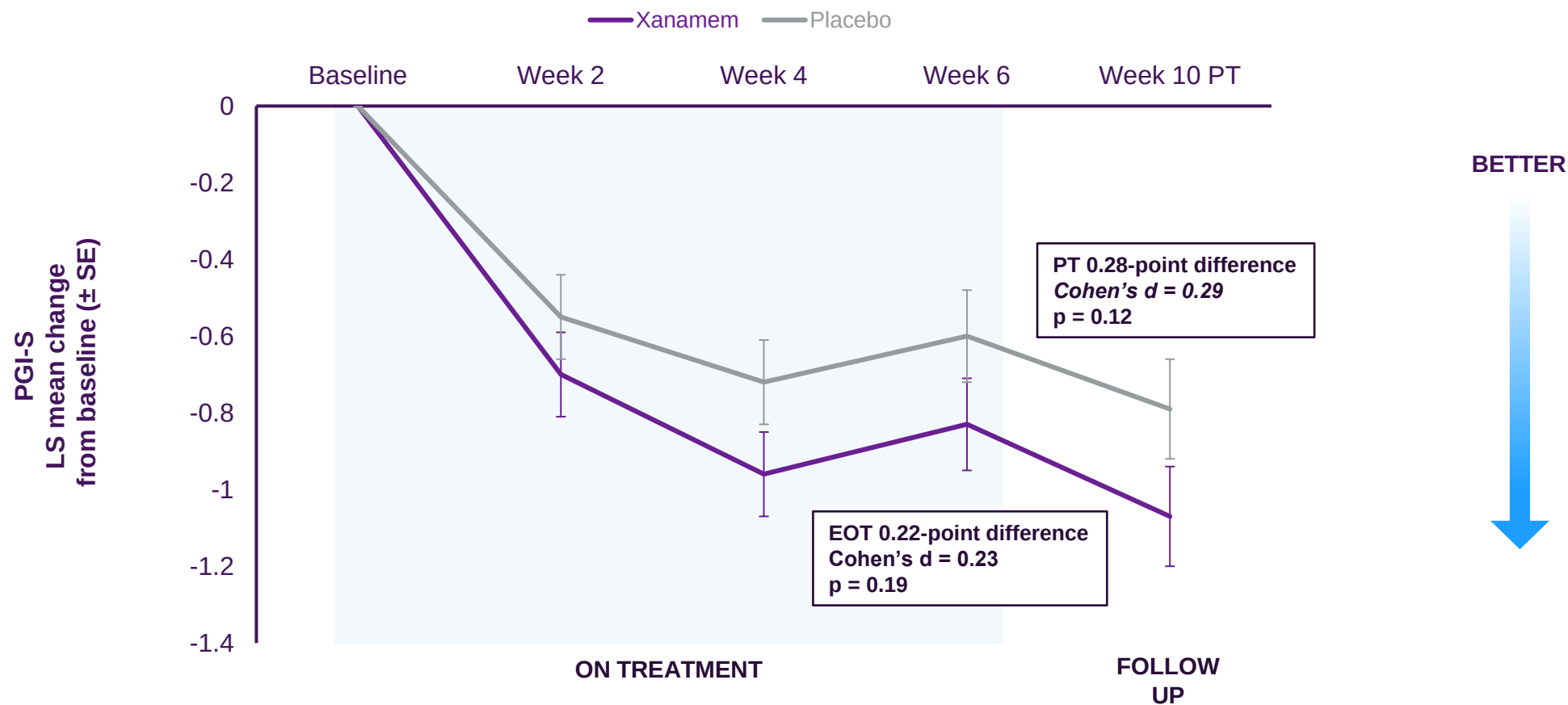
Xanamem MADRS separation from Week 6

All randomized participants (n = 165)



Xanamem PGI-S separation from Week 2

All randomized participants (n = 165)

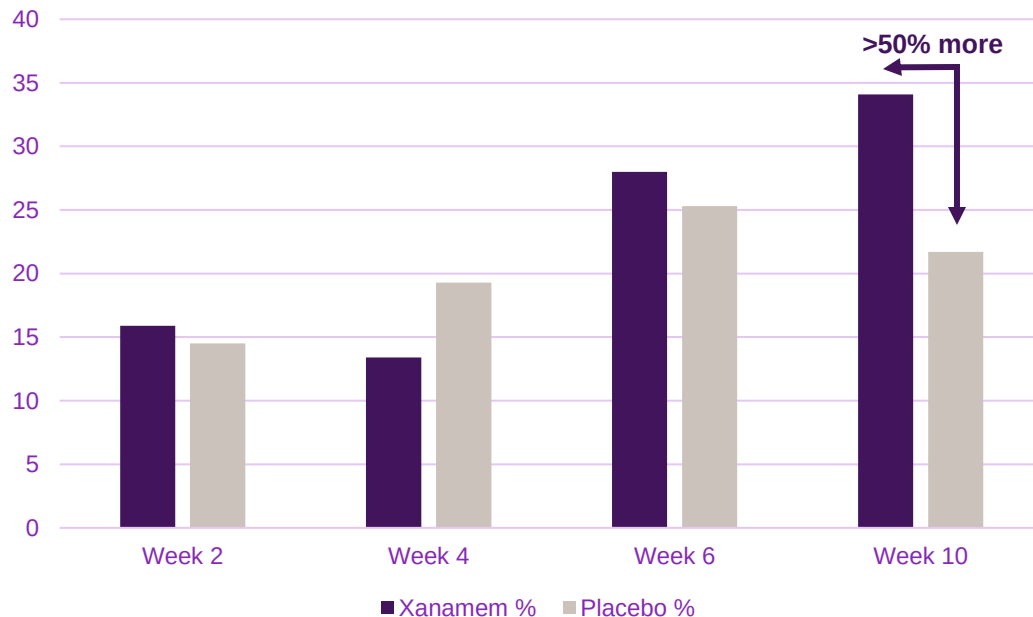


Xanamem major improvement in depression response

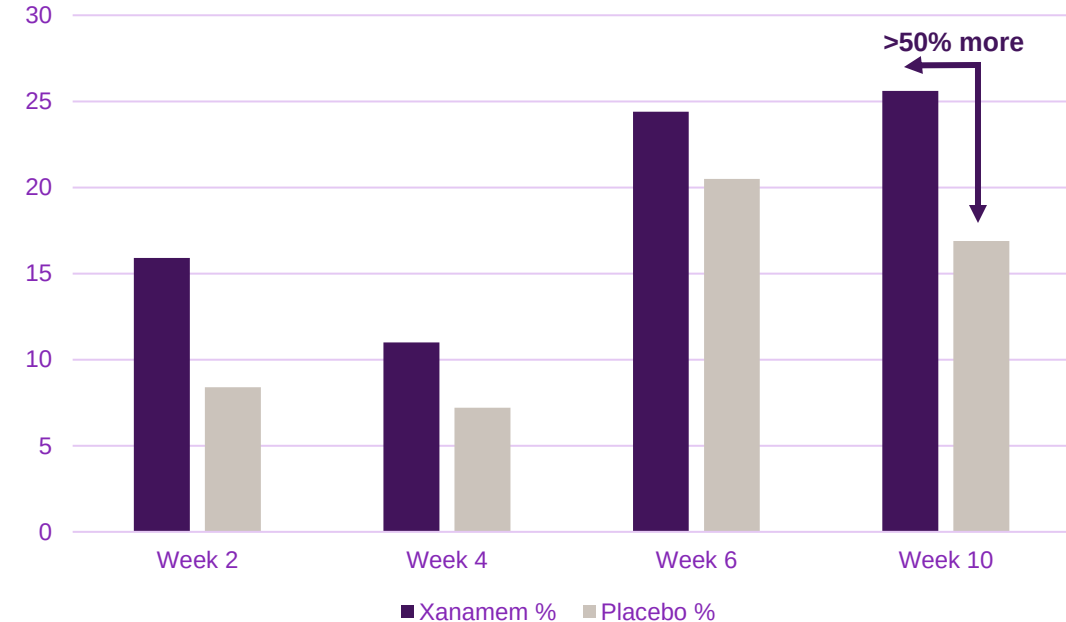


Increased rates of remission (MADRS < 10) and large (50%) improvements

% 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)

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%)

There remains significant unmet need in depression

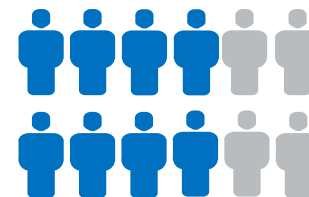
Xanmem's unique mechanism and safety differentiate it from older drugs

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 adults with MDD episodes receive treatment with existing drugs (that have many side effects)
- ≥ 365 M prescriptions per year

A safe, effective and combinable small molecule is an attractive product profile for depression

Offer Summary



Capital raising overview



Actinogen is seeking to raise up to approximately A\$11.1m via a Placement and SPP

Placement	▪ Institutional Placement to raise approximately A\$7.0m under Actinogen's existing L.R. 7.1 placement capacity (Institutional Placement) and; ▪ Placement to Directors of \$1.1m, including CEO, Dr Steven Gourlay for \$1.0m, subject to shareholder approval (Director Placement) (together, the Institutional Placement and Director Placement are the Placement) ▪ Approximately 270.2 million new fully paid ordinary shares in Actinogen (New Shares) to be issued under the Placement, representing approximately 10.0% of Actinogen's current shares on issue
Share Purchase Plan	▪ The Company intends to offer eligible shareholders the opportunity to participate in a Share Purchase Plan (SPP) and apply for up to \$30,000 of New Shares, to raise up to an additional \$3 million ▪ Record date for determining eligibility for the SPP is 7:00pm on Tuesday, 17 September 2024 ▪ The Company reserves the right to increase the size of the SPP or to scale back applications in its absolute discretion ▪ Further details in relation to the SPP including the timetable will be provided to eligible shareholders in an SPP booklet expected to be released following the Placement. The SPP is subject to shareholder approval and is not underwritten.
Offer Pricing	▪ New Shares issued under the Placement and SPP will be issued at an offer price of A\$0.03 per share (Offer Price), which represents: – A discount of 14.3% to the last close of A\$0.035 per share on 16 September 2024 – A discount of 18.2% to the 5-day VWAP of A\$0.0375 per share to 16 September 2024 – A discount of 30.6% to the 15-day VWAP of A\$0.0436 per share to 16 September 2024
Attaching Options	▪ New Shares will be offered under the Placement and SPP with three free attaching options (intended to be listed on the ASX) for every four New Shares issued (Options) subject to shareholder approval at the upcoming EGM ▪ The Options will have an exercise price of \$0.05 and will expire on 30 September 2027
Director participation	▪ Directors Steven Gourlay, Geoff Brooke, George Morstyn and Malcolm McComas will participate in the Placement for \$1.13m. This includes a subscription of \$1.0m by CEO Steven Gourlay. Director participation is subject to shareholder approval at an extraordinary general meeting.
Ranking	▪ New shares under the Placement and SPP will rank pari passu with existing ordinary shares in Actinogen
Joint Lead Managers	▪ Bell Potter Securities Limited and MA Moelis Australia Advisory Pty Ltd

Use of funds

XanaMIA phase 2b/3 trial and other activities

Details	A\$m
Full enrolment of phase 2b/3 XanaMIA trial for 220 participants	
▪ Additional site and patient costs	9.5
▪ Additional data management, data monitoring committee and statistical costs	0.5
▪ Additional quality activities	0.5
▪ Offer costs	0.6
Total	11.1

Offer timetable



Indicative capital raising timetable ¹	Date
Trading halt	Monday, 16 September 2024
Record Date for SPP	Tuesday, 17 September 2024
Placement and SPP announced, and trading halt lifted	Wednesday, 18 September 2024
Settlement of Placement Shares	Monday, 23 September 2024
Allotment of Placement Shares and SPP Opens	Tuesday, 24 September 2024
SPP Closes	Tuesday, 8 October 2024

Conclusions



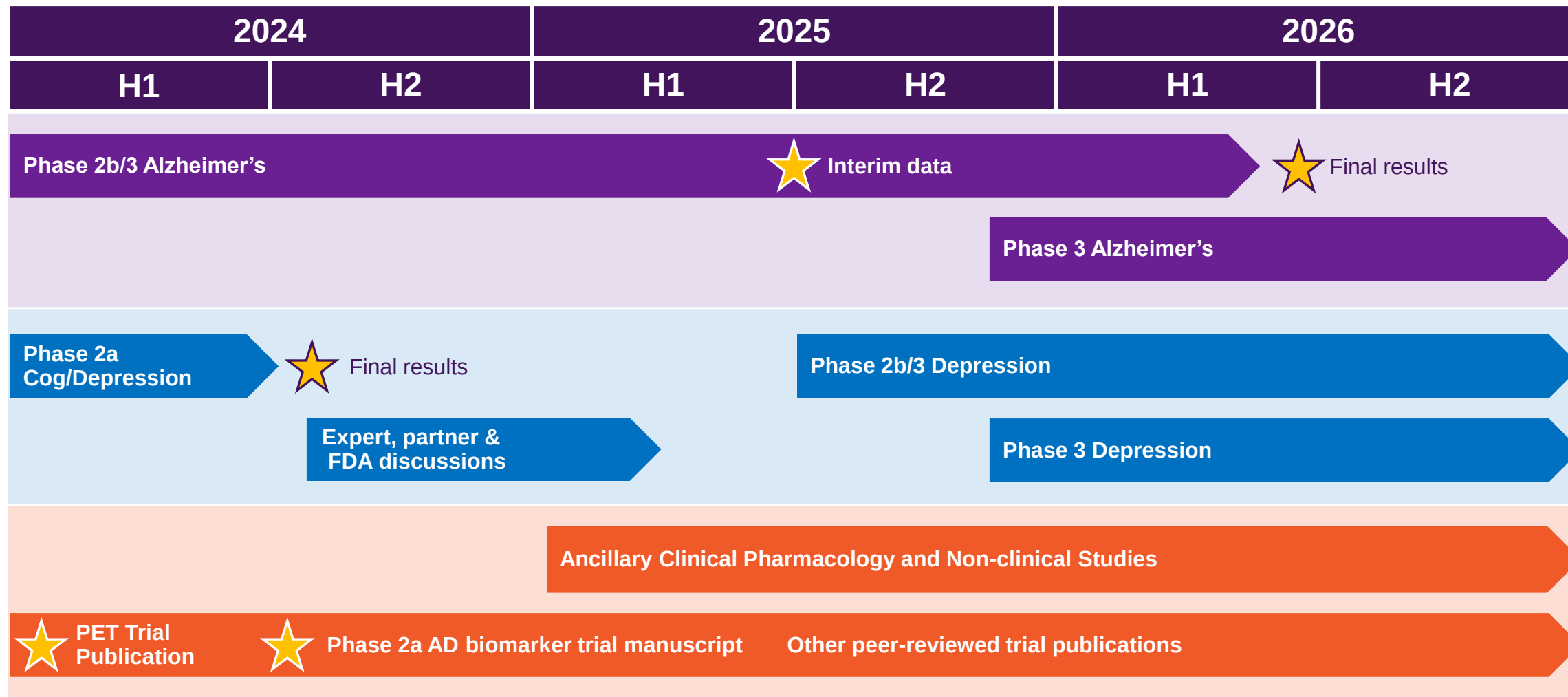
Controlling brain tissue cortisol really works!

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
- Xanamem was safe and well tolerated; no significant safety issues were observed
- Durability of Xanamem benefits for four weeks after the end of treatment suggests underlying biological modification due to cortisol control has occurred
- Depression data suggest higher probability of success for XanaMIA phase 2b/3 trial

Two promising late-phase clinical programs



Appendix – corporate

Stock price and key shareholders*

ASX: ACW – Last 12 months



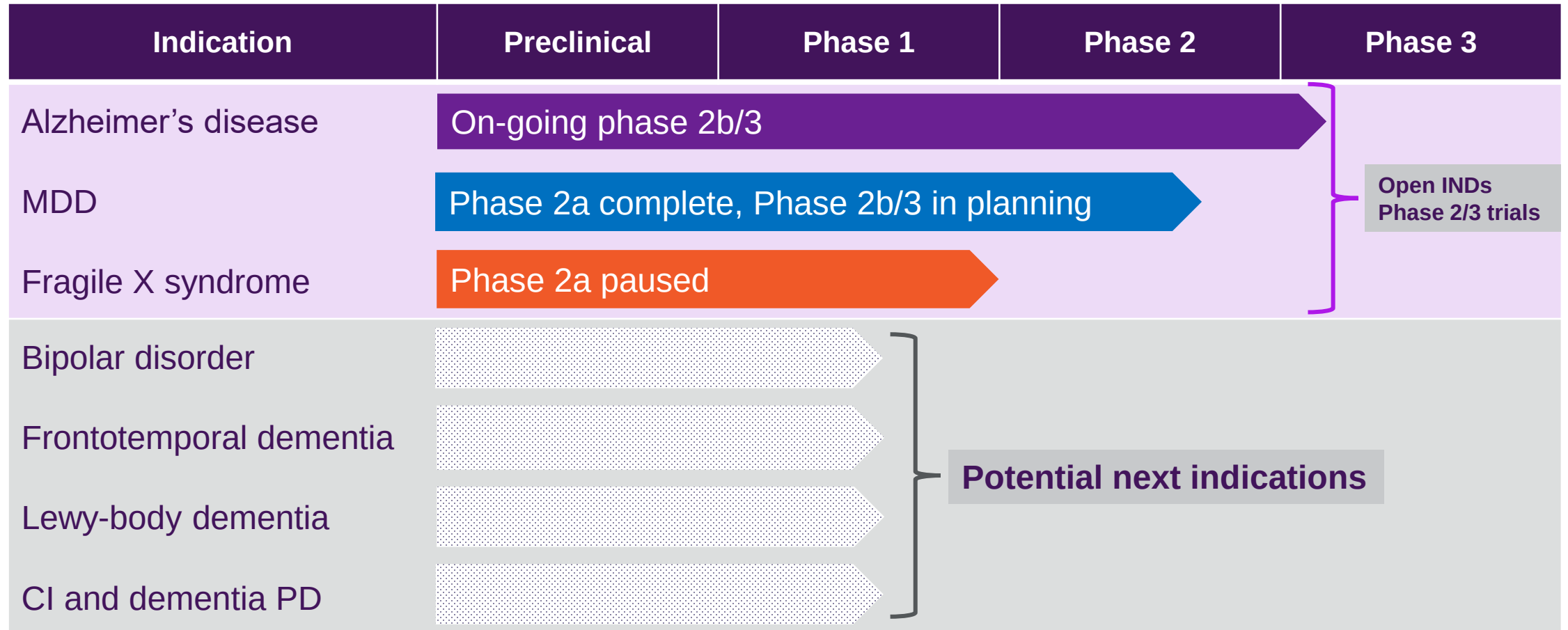
Key data

52 Week Range	\$0.015 - \$0.099
YTD CY24 change	+75%
Shares on issue	2.7Bn
Unlisted options	349m
Closing price	\$0.035
Closing market cap*	\$94.9m
30 June cash balance	\$9.45m

Key Shareholders

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

Xanamem pipeline



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

Appendix – other Xanamem

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”

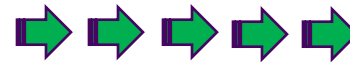
RAPID changes in kinases, cell function, neurotransmitters over hours to days lead to short-term “low stress” settings



“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

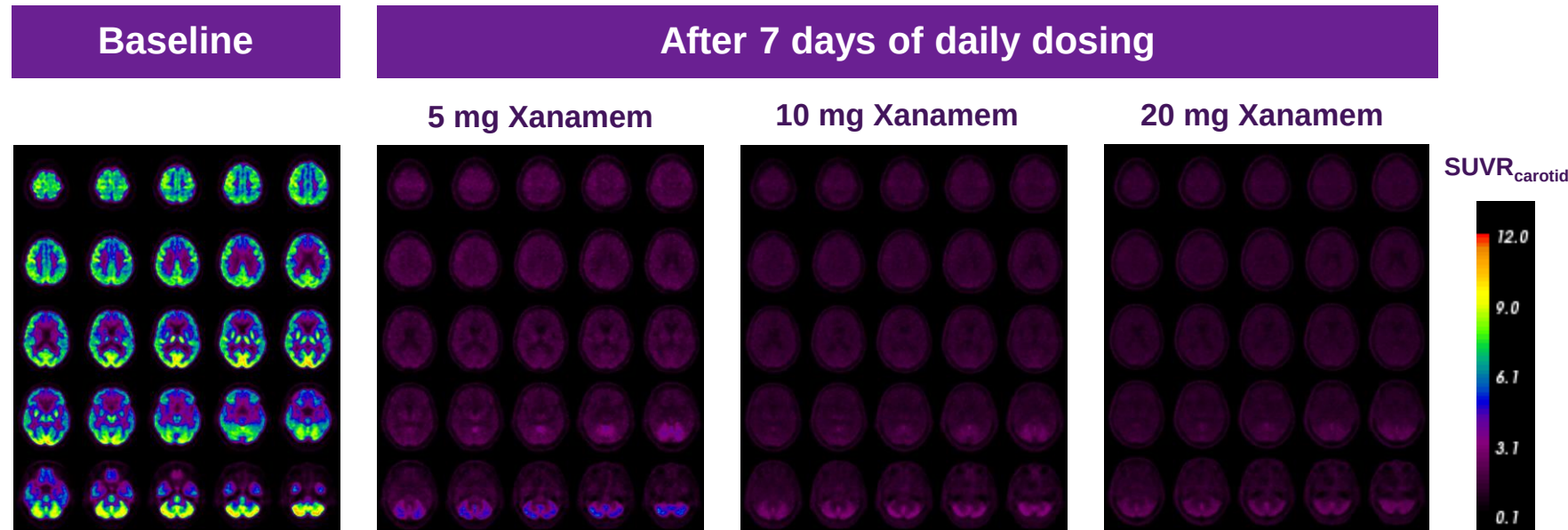


“Lower stress” longer term e.g.

- 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

Appendix – depression data

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

Typical, broad, moderate depression trial population

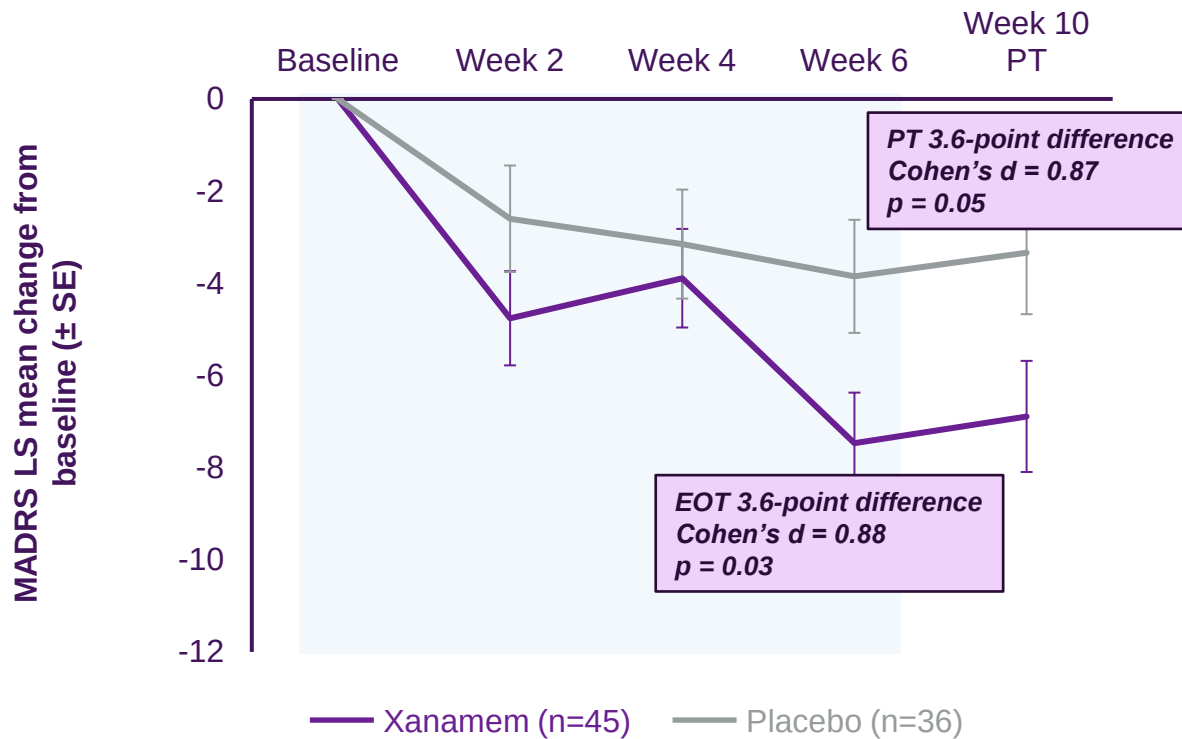
All XanaCIDD patients were either on, or previously treated with, anti-depressants

	Xanamem (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)

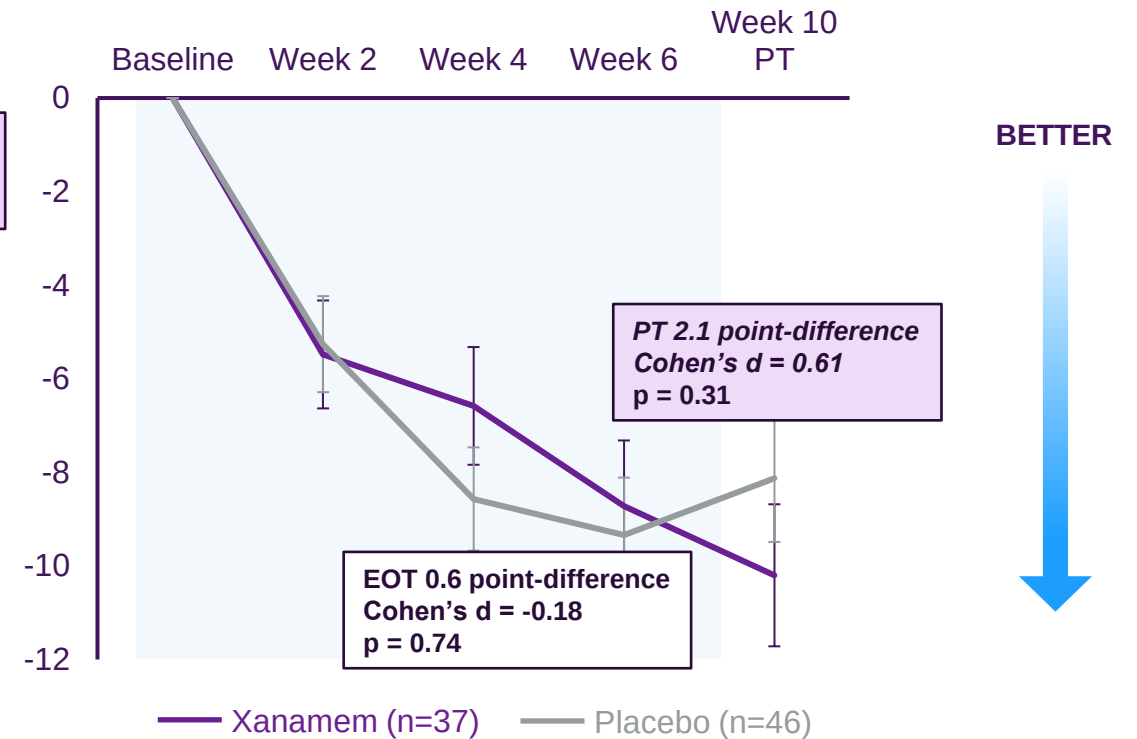
Stronger MADRS response in patients with milder MDD

Clinically significant in both XanaCIDD subgroups at Week 10

MADRS < 26 at Baseline



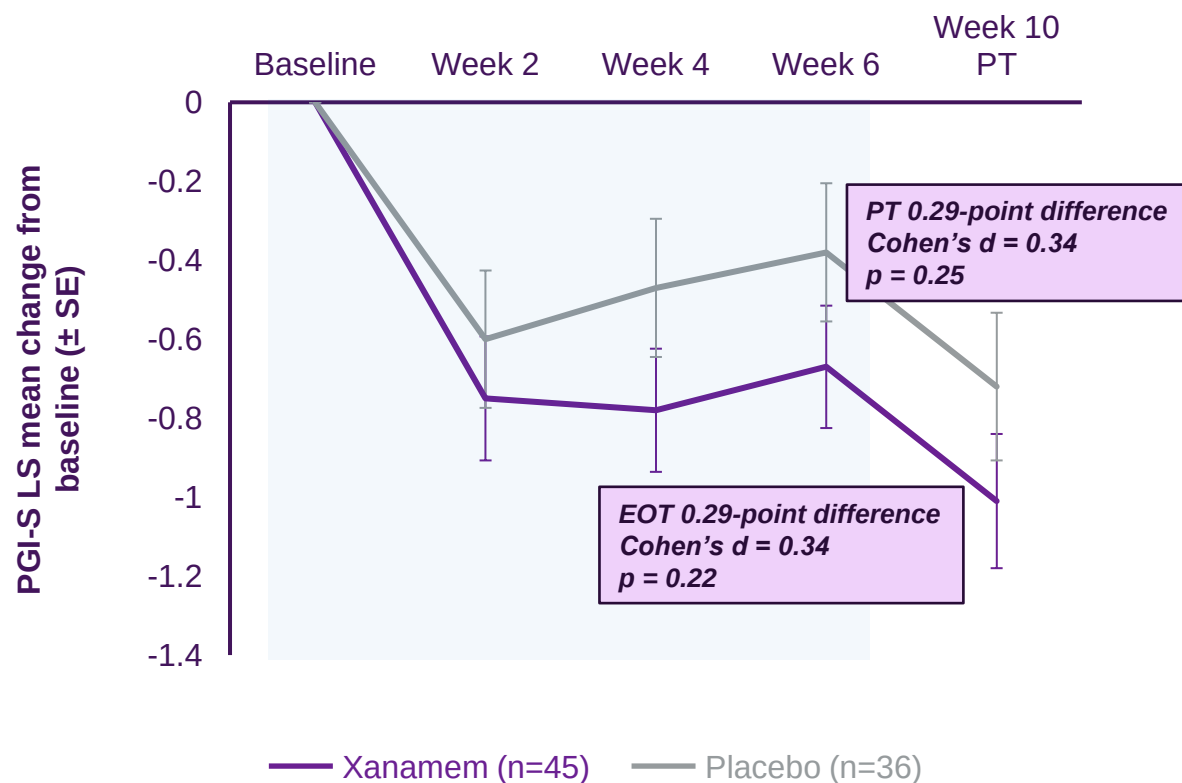
MADRS ≥ 26 at Baseline



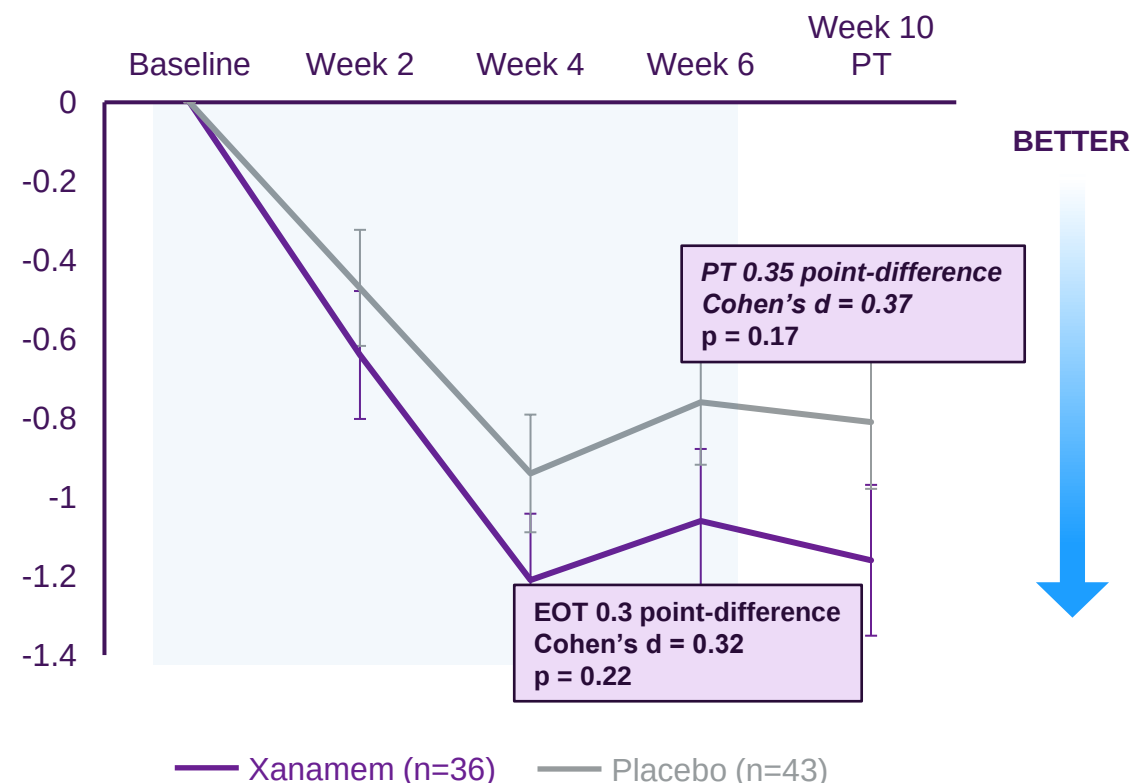
Positive PGI-S responses both MADRS groups

Clinically significant XanaCIDD findings at Weeks 6 & 10

MADRS < 26 at Baseline



MADRS ≥ 26 at Baseline



Appendix – references

Key references

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



11 β -HSD1 inhibition

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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

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