ASX ANNOUNCEMENT

Actinogen updated positive depression results - webinar at 11am today

Sydney, 29 August 2024. Actinogen Medical ASX: ACW ("ACW" or "the Company") is pleased to announce that CEO, Dr Steven Gourlay, CMO Dr Dana Hilt and commercial leader Mr Andy Udell will present at a webinar this morning to discuss the positive and consistent XanaCIDD depression trial data announced on Monday 26 August, how the trial results teach about Xanamem's cortisol control mechanism, and the outlook for the depression trial program.

Click here to pre-register for the webinar, or simply register and attend at 11am (AEST) today.

A copy of the webinar slide presentation is attached to this announcement.

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

To re-cap, highlights of the updated trial results are:

- MADRS[1] depression score improvement confirmed ($p < 0.05$) and positive effects were observed in five of six pre-specified subgroups, indicating broad effect in the population studied
- Analysis of further data from a second, well-validated endpoint for clinical function in depression, called the Patient Global Impression of Severity (PGI-S)[2], reveals consistent Xanamem benefits that corroborate MADRS observations
- New MADRS responder analyses underscore MADRS benefit at Week 10 with a 50% higher rate of remission of depression[3]
- Maximal benefits on depression for all endpoints at Week 10, four weeks after the end of treatment, indicate a durable therapeutic effect resulting from controlling brain cortisol
- Xanamem's durable therapeutic effect is consistent with the known pharmacology of cortisol to modify gene expression and consequent protein synthesis and thus Xanamem may be controlling underlying "stress" biological processes for an extended period
- The XanaCIDD data indicate that Xanamem's novel mechanism has clinically significant activity for the treatment of major depressive disorder (MDD) and we are exploring the path forward in MDD with regulators, global thought leaders and potential strategic partners.

[1] MADRS (The Montgomery-Asberg Depression Rating Scale) is a structured psychiatric interview evaluating MDD symptoms
[2] Patient Global Impression of (depression) Severity(PGI-S) is a self-assessment of depression severity on a 7-point scale
[3] Remission of depressive symptoms defined as MADRS < 10 points

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Announcement authorised by the Board of Directors of Actinogen Medical

About Actinogen Medical

Actinogen Medical (ACW) is an ASX-listed, biotechnology company developing a novel therapy for neurological and neuropsychiatric diseases associated with dysregulated brain cortisol. There is a strong association between cortisol and detrimental changes in the brain, affecting cognitive function, harm to brain cells and long-term cognitive health.

Cognitive function means how a person understands, remembers and thinks clearly. Cognitive functions include memory, attention, reasoning, awareness and decision-making.

Actinogen is currently developing its lead compound, Xanamem, as a promising new therapy for Alzheimer's Disease and Depression and hopes to study Fragile X Syndrome and other neurological and psychiatric diseases in the future. Reducing cortisol inside brain cells could have a positive impact in these and many other diseases. The cognitive dysfunction, behavioural abnormalities, and neuropsychological burden associated with these conditions is debilitating for patients, and there is a substantial unmet medical need for new and improved treatments.

Current Clinical Trials

The **XanaCIDD Phase 2a cognition & depression trial** is a double-blind, six-week proof-of-concept, placebo-controlled, parallel group design trial in 167 patients. Participants are evenly randomized to receive Xanamem 10 mg once daily or placebo, in some cases in addition to their existing antidepressant therapy, and effects on cognition and depression are assessed. Positive topline results on depression were announced 12 August CY2024.

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 effects on cognition, function and progression of Alzheimer's disease are assessed. Thus, Xanamem is being assessed in this trial for its potential effects as a both a cognitive enhancer and a disease course modifier. Initial results from an interim analysis of the first 100 participants are anticipated in mid 2025.

About Xanamem

Xanamem's novel mechanism of action is to block the production of cortisol inside cells through the inhibition of the 11β-HSD1 enzyme in the brain. Xanamem is designed to get into the brain after it is absorbed in the intestines upon swallowing.

Chronically elevated cortisol is associated with cognitive decline in Alzheimer's Disease and excess cortisol is known to be toxic to brain cells. Cognitive impairment is also a feature in Depression and many other diseases. Cortisol itself is also associated with depressive symptoms and when targeted via other mechanisms has shown some promise in prior clinical trials.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 300 volunteers and patients, so far finding a statistically significant improvement in working memory and attention, compared with placebo, in healthy, older volunteers in two consecutive trials and clinically significant improvements in functional and cognitive ability in patients with biomarker-

positive mild AD. Previously, 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. A series of Phase 2 studies in multiple diseases is being conducted to further confirm and characterize Xanamem's therapeutic potential.

Xanamem is an investigational product and is not approved for use outside of a clinical trial by the FDA or by any global regulatory authority. Xanamem® is a trademark of Actinogen Medical.

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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.

Further positive depression results from XanaCIDD phase 2a trial

Clinically & statistically significant Xanamem® benefits on depression validate the biological activity of Xanamem 10 mg daily and the "cortisol hypothesis"

Dr Dana Hilt MD, Chief Medical Officer
Mr Andy Udell, Head of Commercial Development
Dr Steve Gourlay, MBBS PhD, CEO

29 August 2024 Nonconfidential

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Controlling brain cortisol[1] has durable benefits

Xanamem inhibits local tissue production of cortisol in key regions of the brain via 11β-HSD1

"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

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

Xanamem has a unique class name

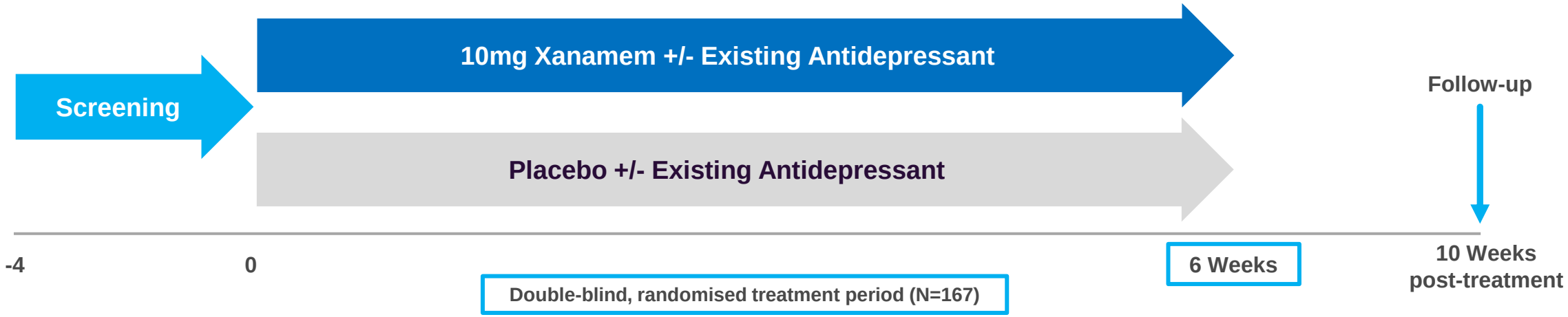
Reflecting the drug's unique tissue cortisol control mechanism

- The World Health Organization administers the procedure for selecting Nonproprietary or "generic" names for pharmaceutical substances
- This INN name (International Nonproprietary Name) is used worldwide in combination with one or more brand names, which are selected later, at the time of market approvals
- Xanamem has been assigned a unique suffix or ending recognizing it as a new class of tissue cortisol synthesis inhibitor (not yet disclosed)
- There are no other known 11β-HSD1 inhibitors with an INN name or in development for brain diseases
- Actinogen will use the INN name from 2025 onwards

XanaCIDD updated results

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)**

How do MADRS and PGI-S differ?

Two very different measurement systems for depressive symptoms

Endpoint	Domains	How assessed
MADRS 60-point scale	Apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts	Rater interview
PGI-S 7-point scale	1-not present, 2-very mild, 3-mild, 4-moderate, 5-moderately severe, 6-severe, 7-extremely severe	Self-assessment to standardized question

XanaCIDD statistical methods

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

- Primary endpoint of the Attention composite was analyzed using a standard Mixed Model for Repeated Measures (MMRM)
- Secondary endpoints (including depression by MADRS & PGI-S) analyzed in the same way
- 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 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 field[3] and is useful in depression[4]:
  - **> 0.2** = Potentially clinically meaningful effect size
  - **≥ 0.3** = Clinically meaningful effect size
  - **≥ 0.5** = Large and clinically meaningful effect size

3. Cohen et al. 1992 4. Hengartner et al. 2020

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

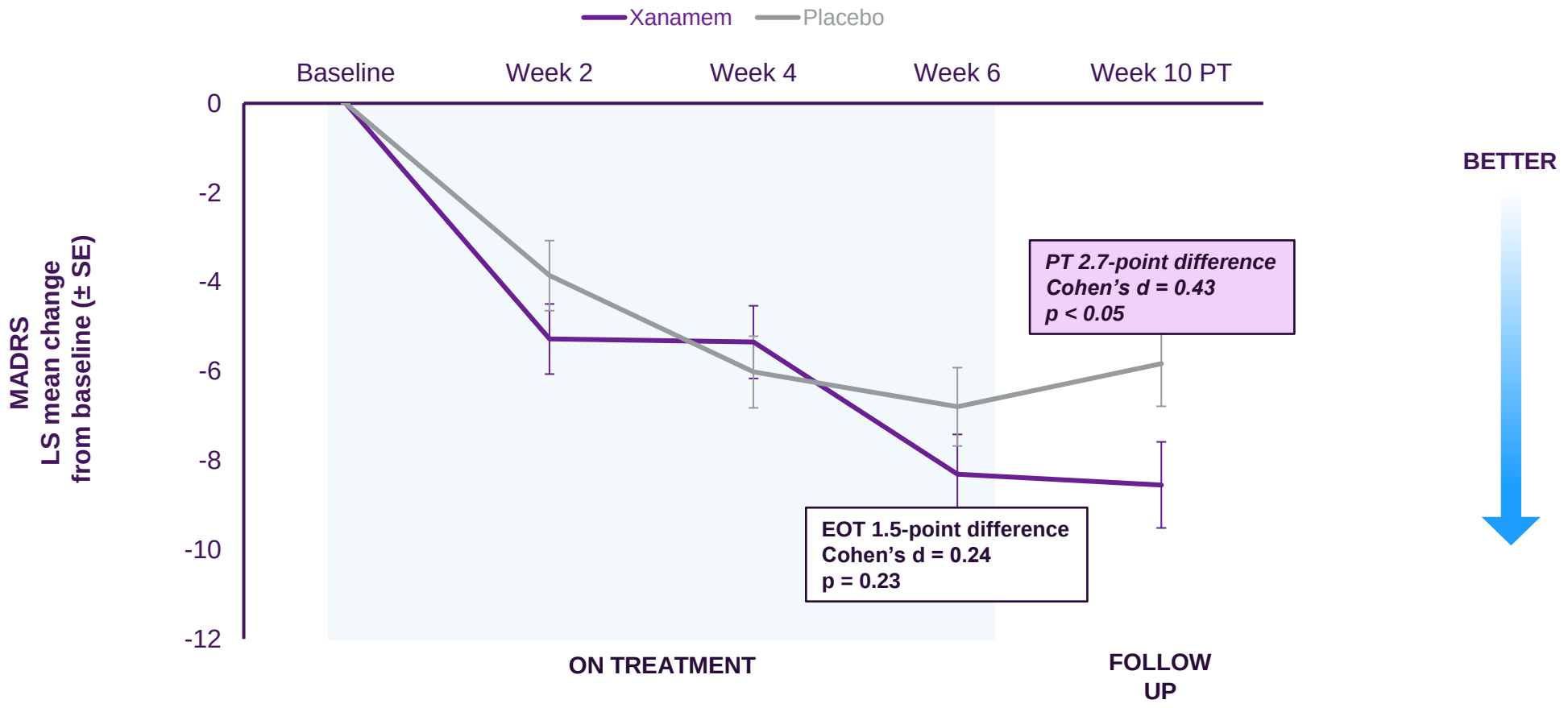
Typical, broad, moderate depression trial population

All patients 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)

Xanamem MADRS separation from Week 6

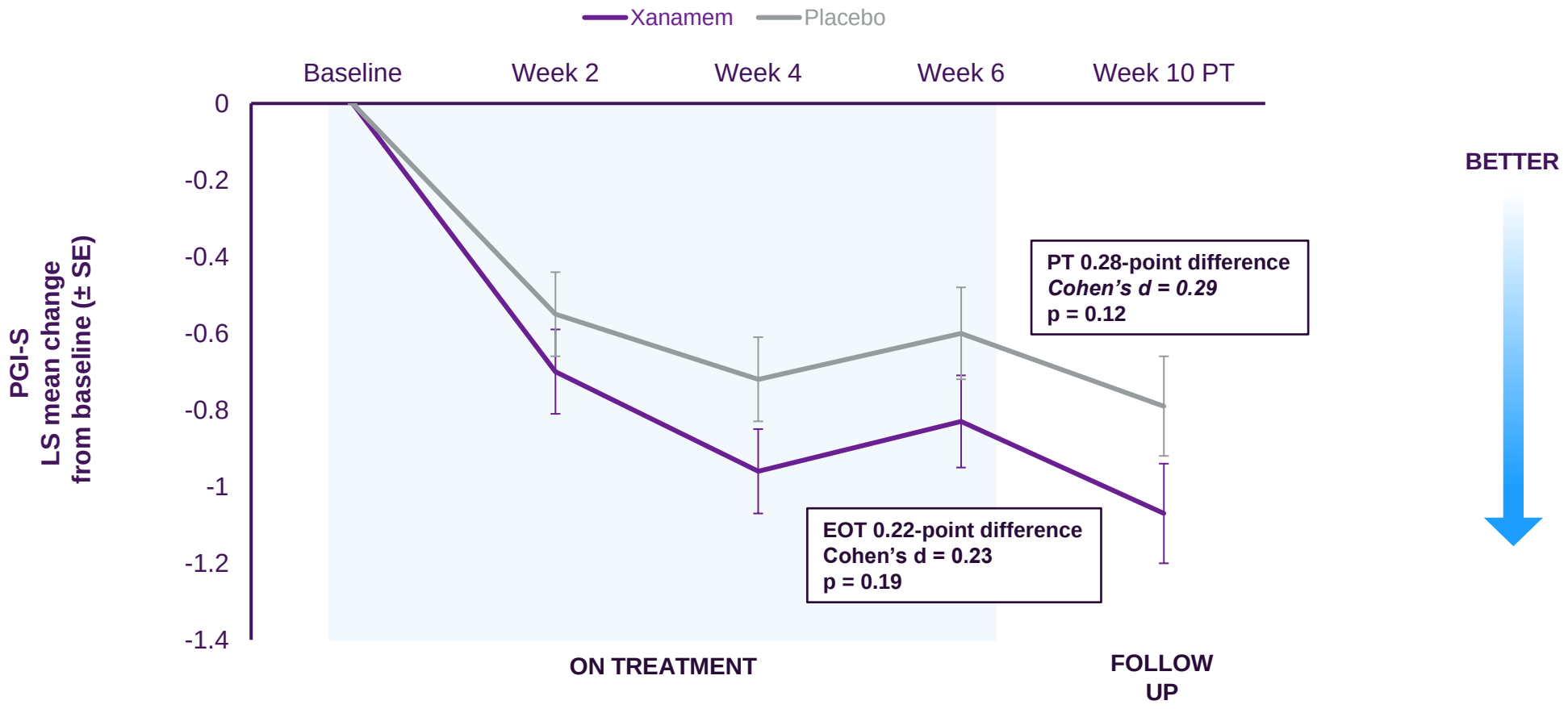
All randomized participants (n = 165)



Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

Xanamem PGI-S separation from Week 2

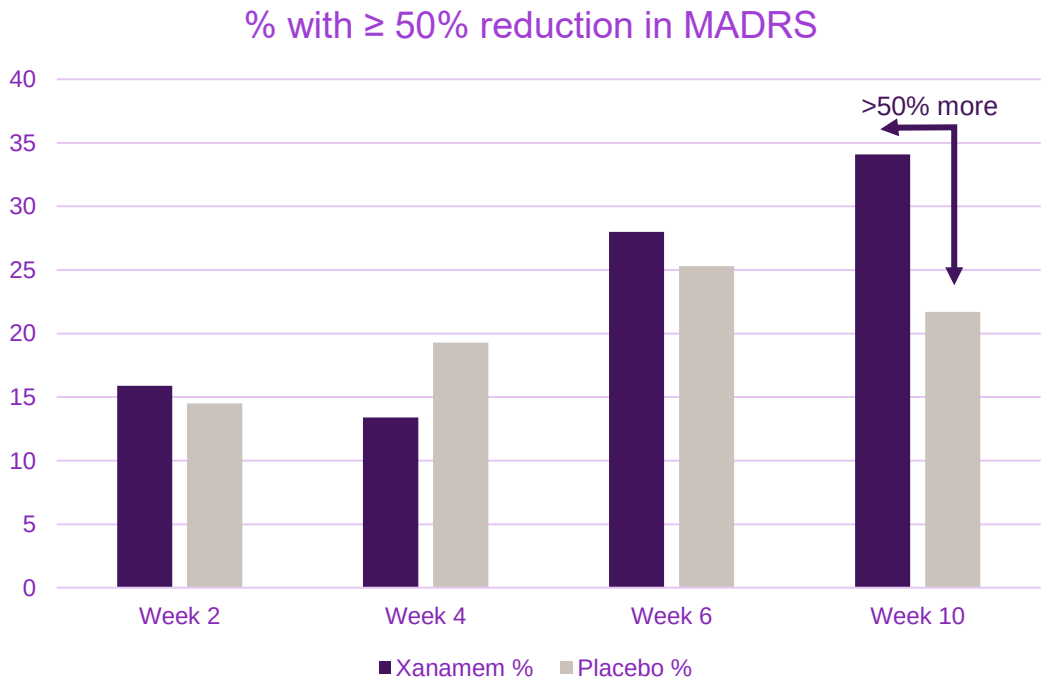
All randomized participants (n = 165)

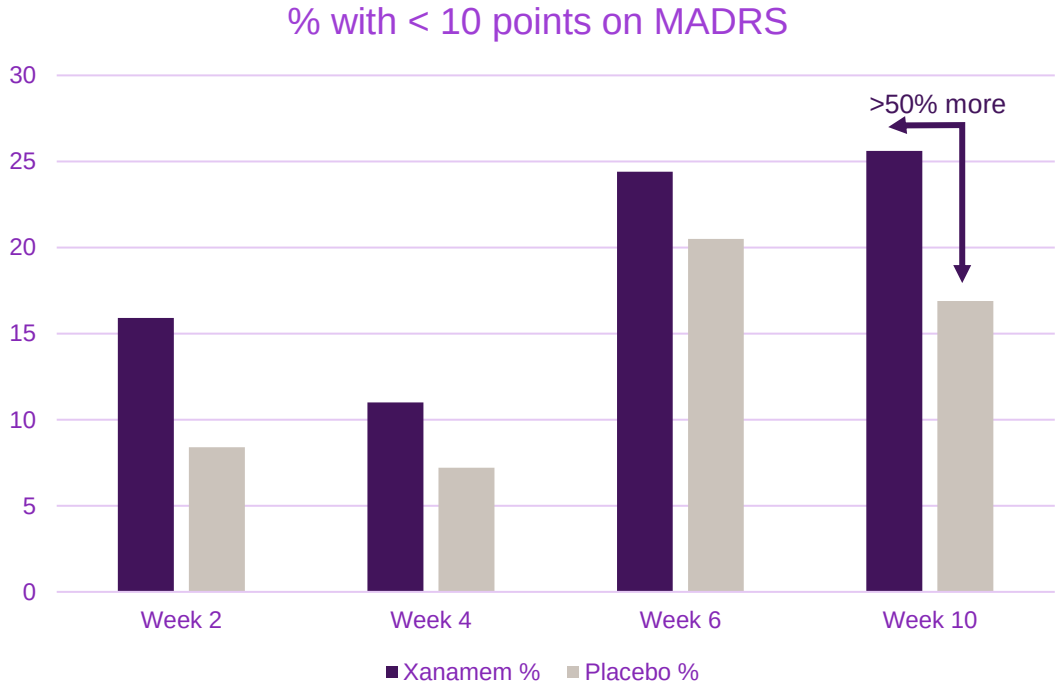


Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale

Xanamem major improvement in depression response

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





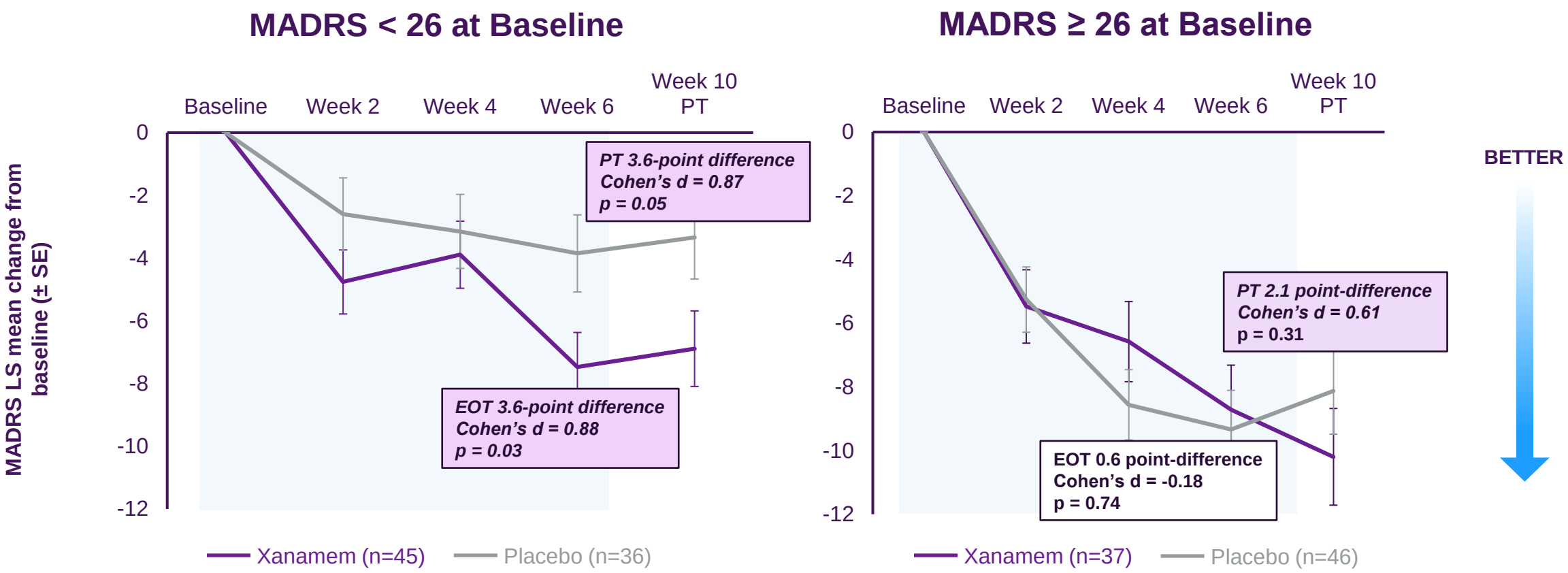
Broad & durable subgroup effects - MADRS & PGI-S

Measured at Weeks 2, 4, 6 & 10 (green favors 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

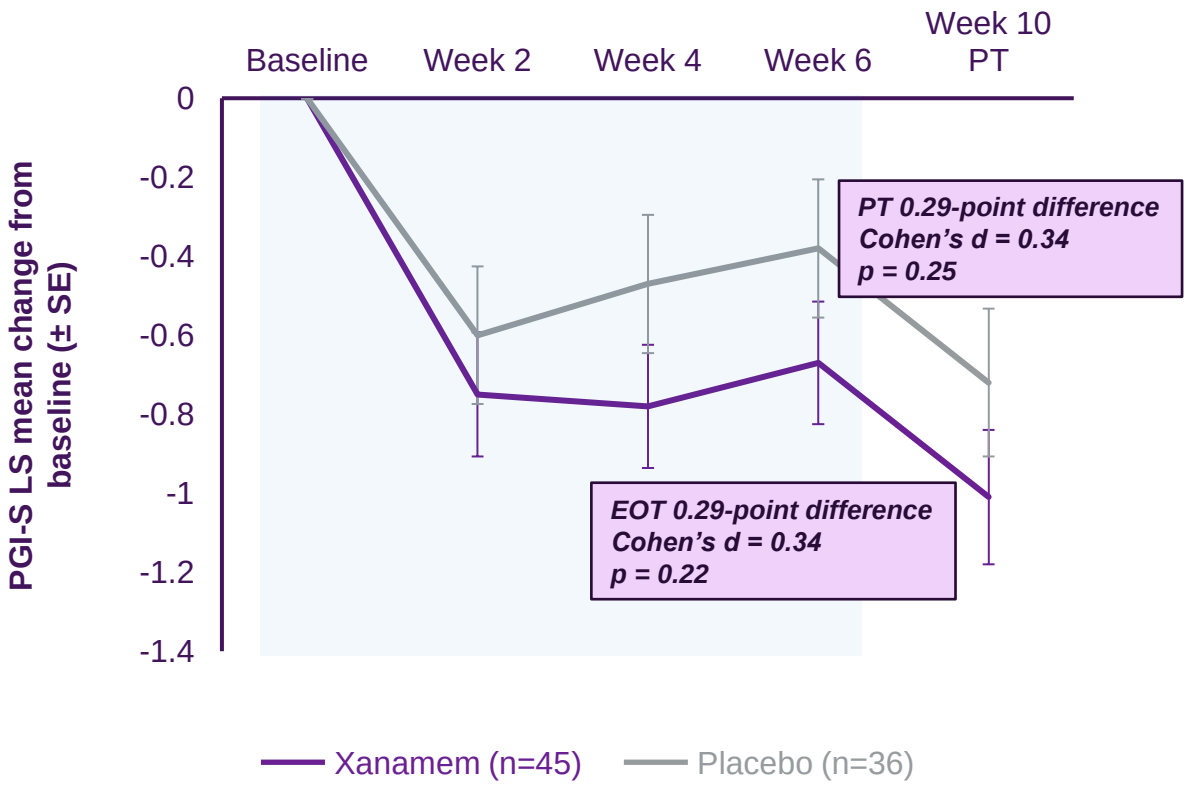
Clinically significant in both subgroups at Week 10



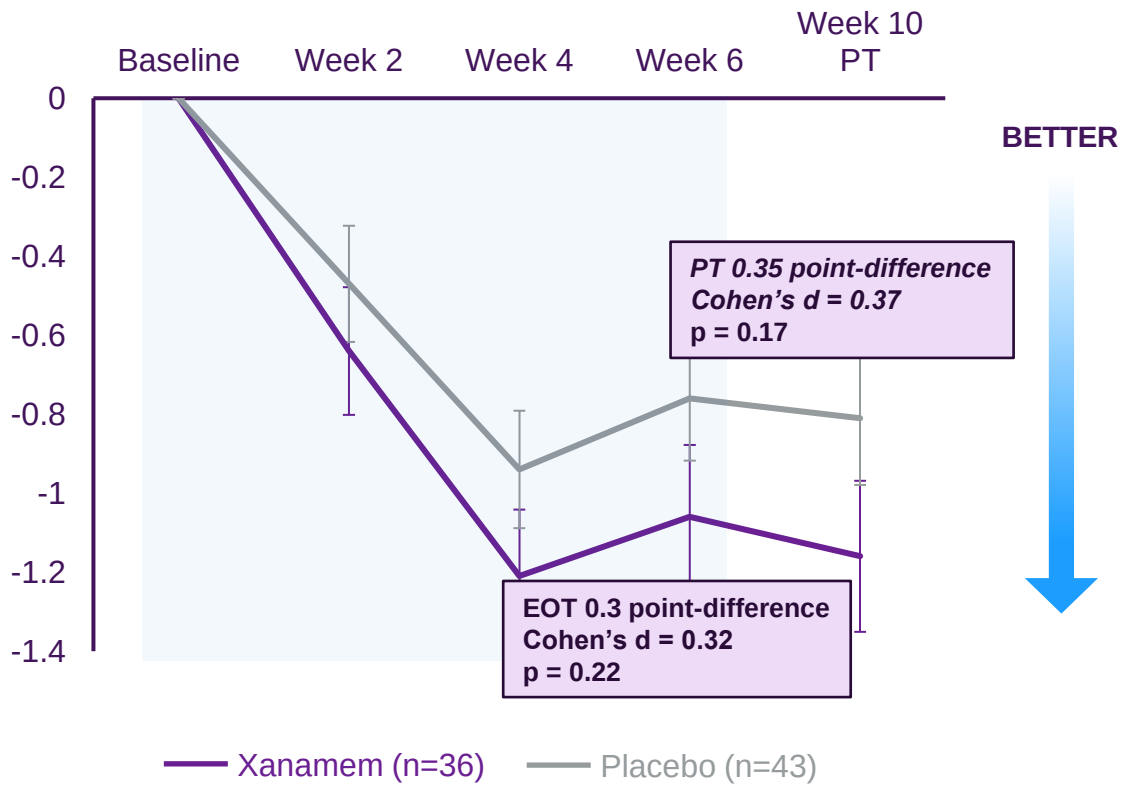
Positive PGI-S responses both MADRS groups

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 ≥ 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%)

Conclusions & next steps

Controlling brain tissue cortisol really works!

Proof of 11β-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

There remains significant unmet need in depression

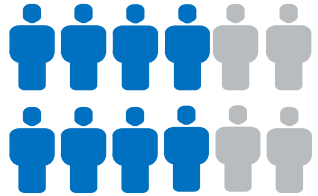
Xanamem's unique mechanism and safety differentiate it from older drugs

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[5]
- ***Now positive phase 2a data on depressive symptoms for Xanamem***

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

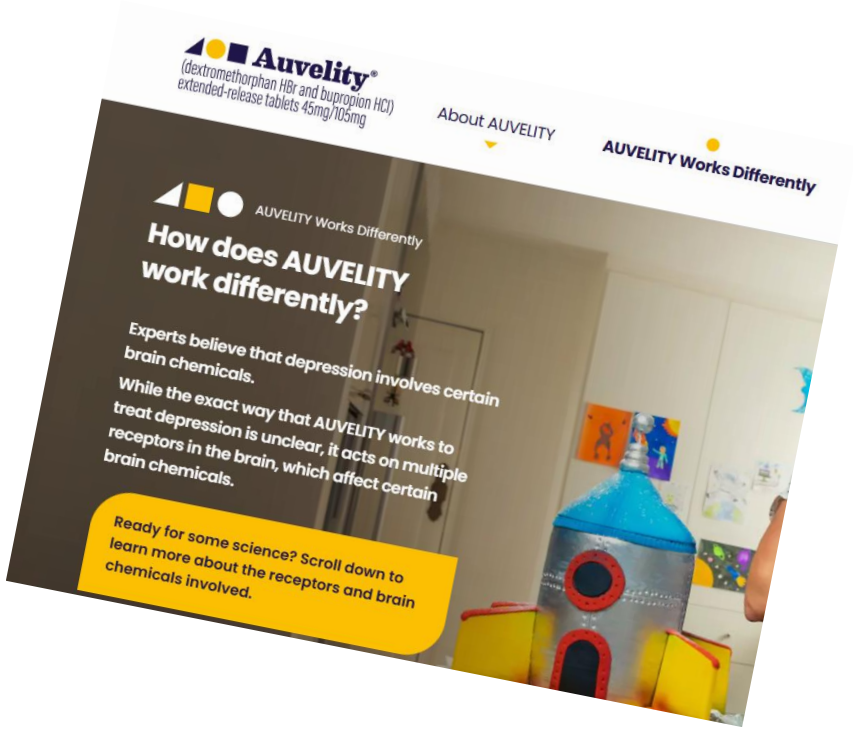
A safe, durably effective and combinable small molecule is a very attractive product profile for depression and Alzheimer's disease

5. Ding et al 2021

AUVELITY MDD recent sales launch example

Axsome Therapeutics

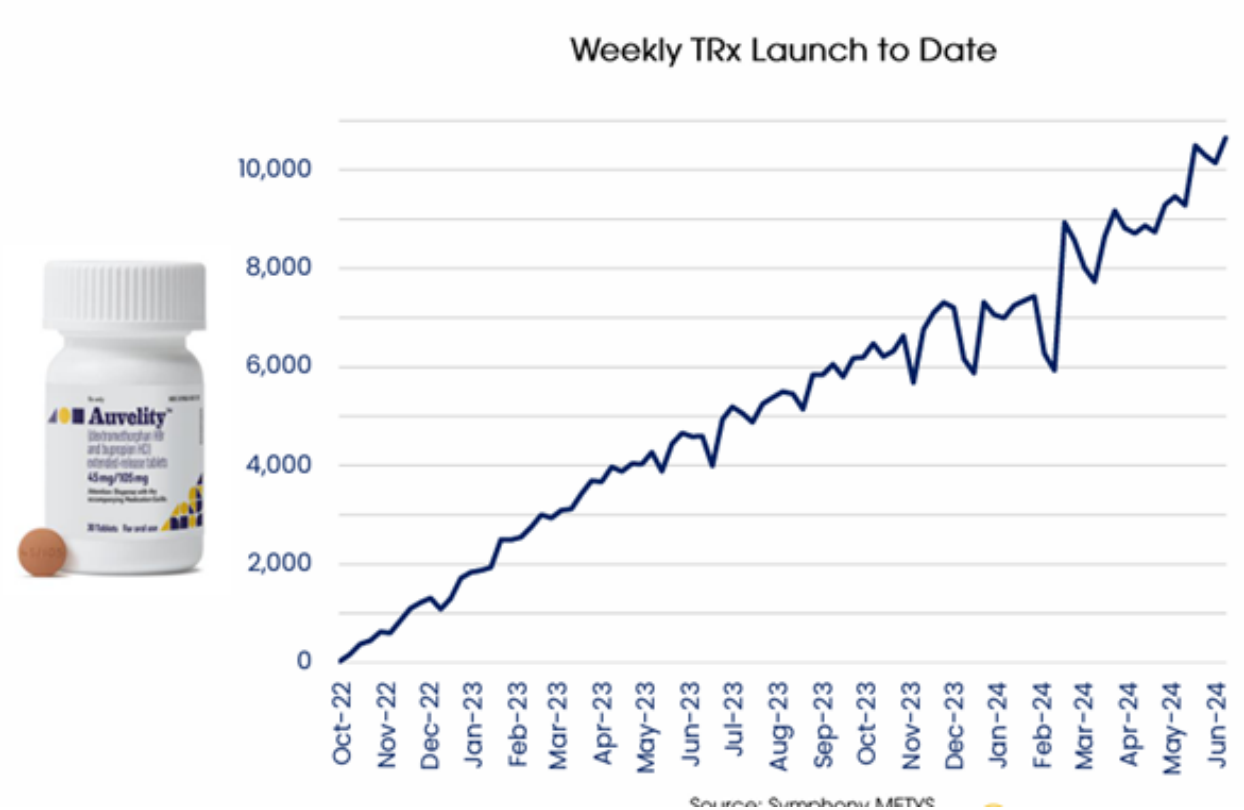
- Combination product of dextromethorphan and buproprion – two generic drugs
- 3.8-point MADRS benefit vs. placebo[6]
- Indicated for the treatment of major depressive disorder (MDD) in adults
- Unique Selling Proposition:
  - "…started working for some people as early as 1 week"
  - "Symptom relief that's fast & lasts"
  - "AUVELITY works differently"



6. AUVELITY US prescribing information

Axsome's successful AUVELITY launch

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

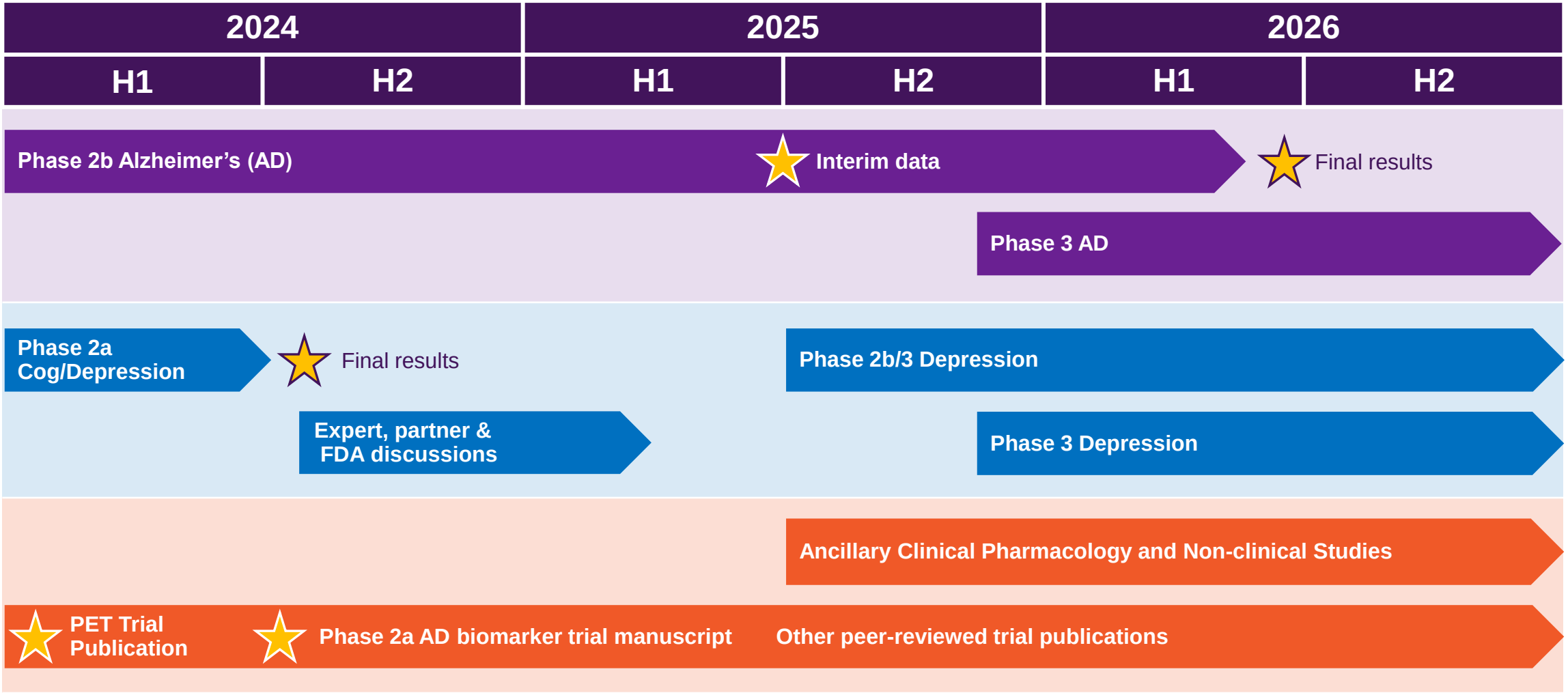


Source: https://axsometherapeuticsinc.gcs-web.com/static-files/5fdf5d50-57da-4655-872b-d8b302cc470d

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) MDD trials

Two promising phase 2 clinical programs



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6. AUVELITY US prescribing information: https://www.axsome.com/auvelity-prescribing-information.pdf

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