



## ASX ANNOUNCEMENT

### Actinogen CMO presents positive depression trial data at the American Psychiatric Association 2025 annual meeting

**Sydney, 19 May 2025. Actinogen Medical ASX: ACW (“ACW” or “the Company”)** is pleased to announce that its Chief Medical Officer, Dr Dana Hilt MD, PhD jointly presented an academic poster at the *American Psychiatric Association (APA) 2025 Annual Meeting* in Los Angeles, USA on Saturday 17 May, 2025 with poster co-author and renowned psychiatrist Professor Michael Berk PhD from Deakin University in Melbourne.

A copy of the poster is attached to this announcement and is titled *Xanamem<sup>®</sup>, a selective 11 $\beta$ -HSD1 inhibitor, has positive effects on depression in a Phase 2 trial of moderate Major Depressive Disorder*.

The poster details the promising benefits of Xanamem treatment on symptoms of depression reflected in a variety of measurements. Maximal benefits on depression were seen during the double-blind period of the trial four weeks after the end of Xanamem or placebo treatment, indicating a durable therapeutic effect resulting from effective control of brain cortisol levels.

The consistent benefits observed support the conclusion that a 10 mg Xanamem dose is clinically active in the brain with significant benefits in major depressive disorder. The benefits seen in depression symptoms also validate the 10mg dose used in the current XanaMIA trial in patients with mild to moderate Alzheimer’s disease.

#### Dr Hilt commented:

*“Actinogen is delighted to present a summary of the positive data from the phase 2a trial in major depressive disorder which showed that Xanamem’s mechanism of cortisol control in the brain has major clinical impact.*

*“The trial confirmed our conclusion that a 10 mg daily dose of Xanamem is clinically active in the brain and has the potential to be an effective anti-depressant with a novel mechanism. While the anti-depressant market is competitive, Xanamem’s promising safety profile and unique mechanism of action stand it apart from the competitors and the durability of benefit seen is intriguing.*

*“Anti-depressant activity would also be a beneficial feature of Xanamem treatment for Alzheimer’s disease, where depressive symptoms often occur alongside cognitive and functional impairment.”*

**ENDS**

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## ***Announcement authorised by the Board of Directors of Actinogen Medical***

### **About Actinogen Medical**

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

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

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

### **Clinical Trials**

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

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

### **About Xanamem (emestedastat)**

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

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

The Company has studied 11 $\beta$ -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<sup>®</sup> 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.**



# Xanamem®, a selective 11β-HSD1 inhibitor, has positive effects on depression in a phase 2 trial of moderate Major Depressive Disorder

Jack Taylor<sup>1</sup>, Paul Rolan<sup>1,2</sup>, XanaCIDD Investigator Group, John Harrison<sup>3,4</sup>, Mark Jaros<sup>5</sup>, Michael Berk<sup>6</sup>, Dana Hilt<sup>1</sup>



## Background

Brain cortisol is elevated in Major Depressive Disorder (MDD) and may contribute to the pathogenesis of depression and other CNS conditions. However, current treatments do not address this potential role and are poorly tolerated in some patients. Xanamem is a selective 11β-HSD1 inhibitor that decreases CNS tissue cortisol synthesis has been shown to improve cognition in 2 independent controlled trials in healthy older adults as well as improving function in AD patients. Therefore, a trial in patients with MDD was conducted to determine if Xanamem improves depression and/or cognition in MDD.

## Methods

MDD patients (n=165) either on stable SSRI/SNRI therapy (n=134) or not presently but previously treated (n=31) with persistent depression (Hamilton Depression Scale >17) and a cognitive deficit (Boxfiller cognition deficit > 0.5 SD below normal for age and education) were enrolled and treated with placebo or Xanamem (10mg qd) for 6 weeks with follow up to 10 weeks. Cognition was assessed with a variety of cognition tests including a customized Cogstate test battery. Depression was assessed by the MADRS and Participant Global Impression of Severity (PGI-S) changes over 10 weeks.

Table 1: Demographic and Baseline characteristics

	Xanamem 10mg (n=82)	Placebo (n=83)	All (n=165)
Age, mean (SD)	49.0 (12.6)	49.2 (14.6)	49.1 (13.6)
Sex (female), No. (%)	52 (63.4)	51 (61.4)	103 (62.4)
Race (white), No. (%)	76 (92.7)	75 (90.4)	151 (91.5)
Hispanic ethnicity, No. (%)	2 (2.4)	2 (2.4)	4 (2.4)
Concomitant Antidepressant use, No. (%)	63 (76.8)	71 (85.5)	134 (81.2)
BASIC Boxfiller, mean (SD)	21.5 (4.94)	21.2 (5.62)	21.4 (5.28)
MINI, No. (%)			
Major Depressive Episode	80 (97.6)	79 (95.2)	159 (96.4)
Major Depressive Disorder	80 (97.6)	73 (88.0)	153 (92.7)
Ham-D score, mean (SD)	21.3 (3.4)	21.3 (3.2)	21.3 (3.3)
MADRS score, mean (SD)	24.4 (6.2)	25.6 (6.6)	
PGI-S, mean (SD)	4.4 (1.0)	4.6 (0.9)	

## Xanamem displays clinically significant improvements in depression

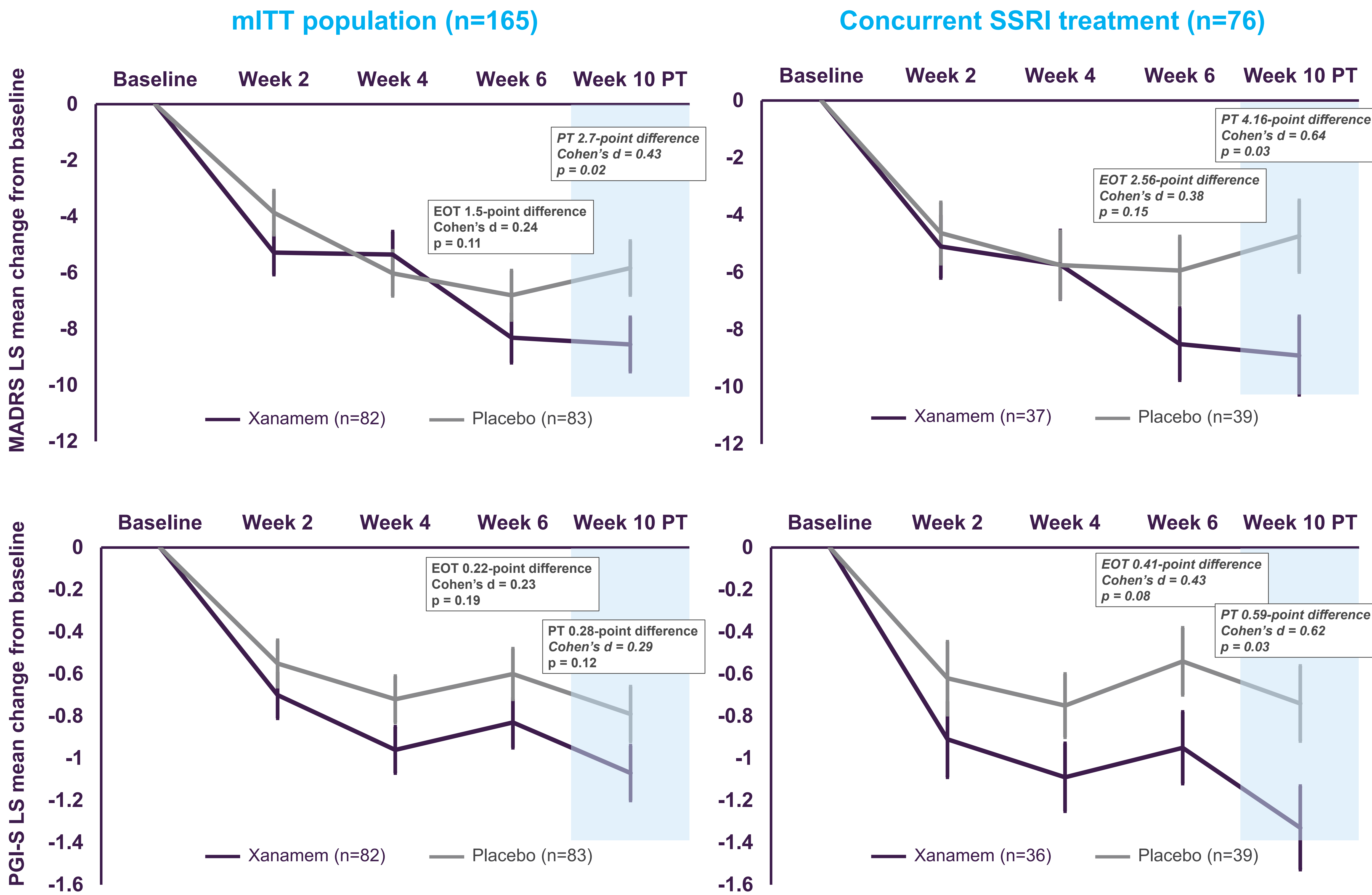


Fig 1: Change from baseline in MADRS (top panels) and PGI-S (bottom panels) scores in the mITT population (left panels) and in the subgroup of participants taking concurrent SSRI therapy (right panels). Blue shaded boxes indicate 4-week blinded post-treatment period. Error bars represent ± SE.

## Improvements in cognition in both treatment groups

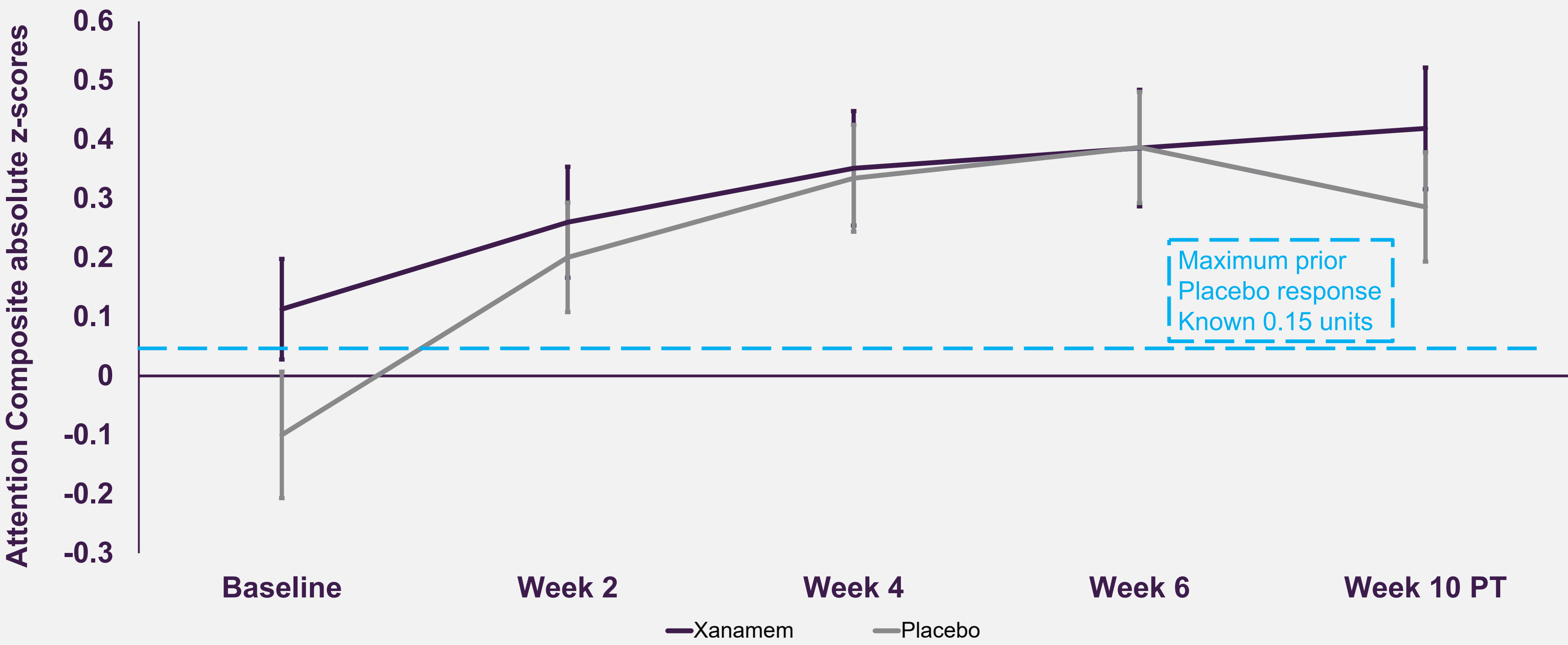
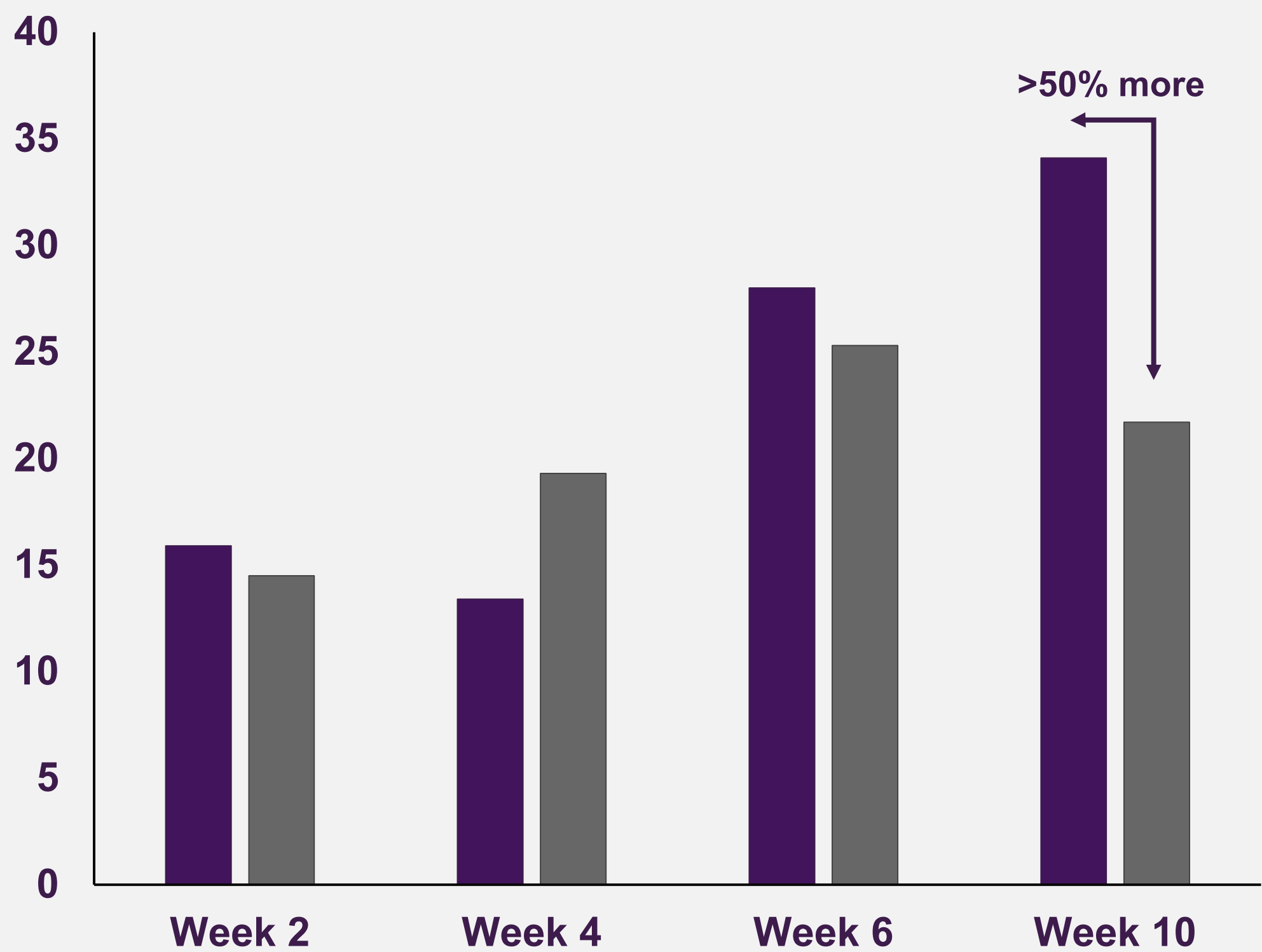


Fig 2: Performance on the Attention Composite in the Xanamem and placebo groups over 6 weeks treatment and 4 weeks follow up. The Attention Composite comprises the Detection, Identification, and One Back tests of the Cogstate battery. Individual tests were combined into z-scores with equal weighting. Higher z-scores in the Attention Composite indicate better performance. Error bars represent ± SE.

## Conclusions

- ✓ Xanamem displays a clinically meaningful MADRS benefit, and improvements in PGI-S compared to placebo
- ✓ Cognition improved markedly in both Xanamem and placebo groups
- ✓ Xanamem was safe and well tolerated
- ✓ Data support the hypothesis that decreasing CNS cortisol may be beneficial to patients with MDD. Xanamem represents a novel pharmacological approach to the treatment of depression and merits further study

## % with ≥ 50% reduction in MADRS



## % with < 10 points on MADRS

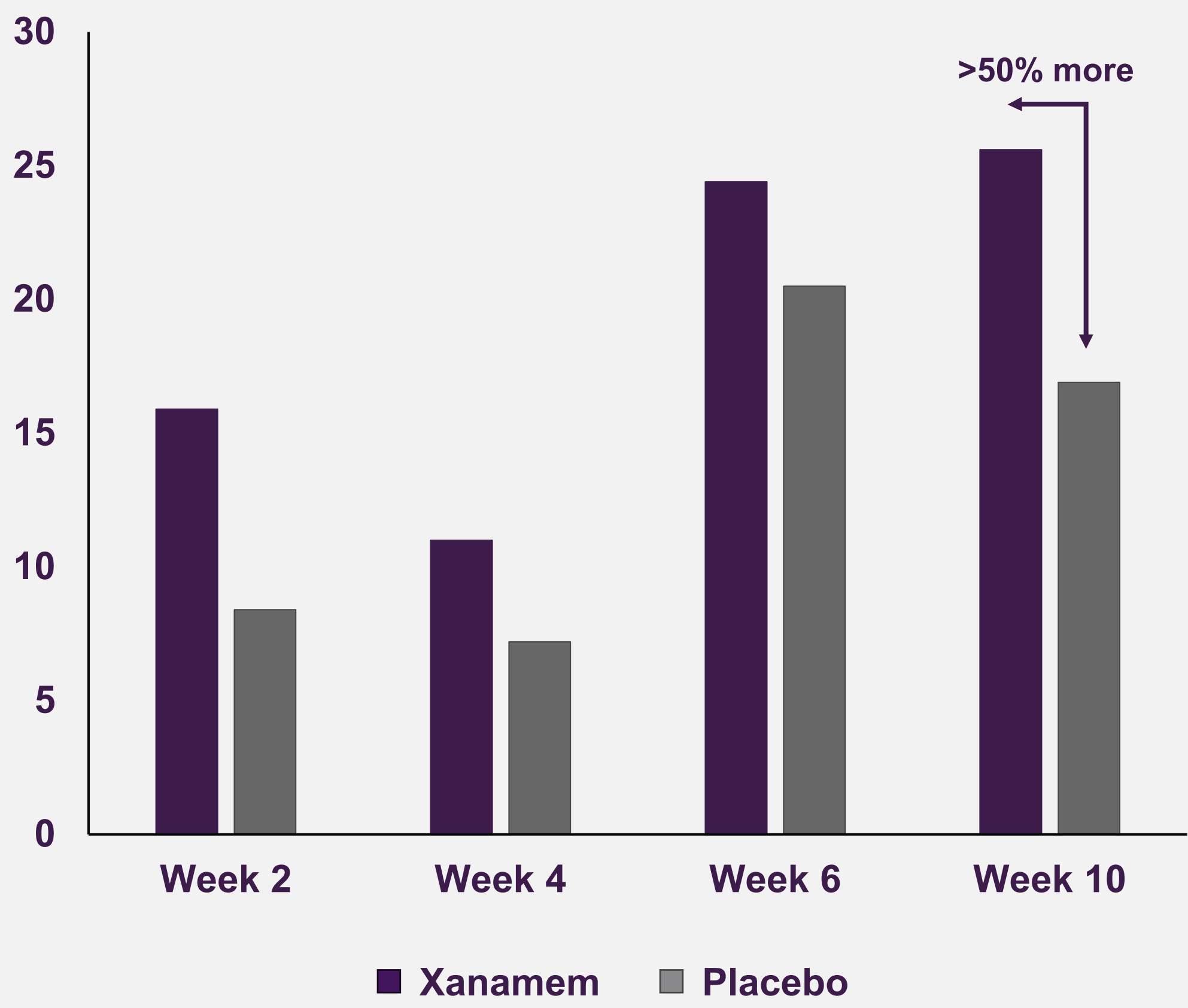


Fig 3: Increased rates of large improvements in depressive symptoms (upper panel) and remission (lower panel) observed in the Xanamem treatment group.

Table 2: Summary of Treatment-Emergent Adverse Effects

	Xanamem N = 82	Placebo N = 83
Any TEAE	70 (85.4%)	67 (80.7%)
TEAE related to trial drug	27 (32.9%)	24 (28.9%)
Serious adverse event	0	1 (1.2%)
Related TEAE discontinuation or interruption of drug	3 (3.7%)	1 (1.2%)
<b>TEAEs with incidence ≥ 5% overall</b>		
Headache	11 (13.4%)	16 (19.3%)
Fatigue	6 (7.3%)	5 (6.0%)
Nasopharyngitis	4 (4.9%)	6 (7.2%)
Upper respiratory tract infection	5 (6.1%)	5 (6.0%)

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