



Development of Xanamem, a specific inhibitor of 11- β HSD1, as a procognitive and disease modifying treatment for mild/moderate Alzheimer's disease. A pharmacodynamic and biomarker driven approach



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Background

Xanamem® is a potent and selective inhibitor of 11 β hydroxysteroid dehydrogenase type 1 (11 β -HSD1), which catalyzes the conversion of cortisone to cortisol. Elevation of CNS cortisol has been associated with impaired cognition, neuroinflammation and neuronal death.

Xanamem is under clinical development as a pro-cognitive and disease modifying drug for Alzheimer's. One of the biggest challenges for development of CNS-targeted drugs, like Xanamem, is the selection of optimal dosage.

We describe Xanamem's clinical pharmacology, including the approach to dose selection and proof-of-concept studies. By combining conventional PK, PD, and tolerability studies with CNS PET occupancy data, and quantitative cognitive testing, dosage for Phase 2 programs can be determined with sufficient confidence.

Methods

The clinical pharmacology analysis included plasma PK, endocrine measures, target occupancy PET imaging, and cognitive assessment evaluated over a daily dose range of 5 mg to 70 mg in 6 clinical trials.

- PK was summarized by a population PK model using data from 4 clinical trials.
- A PET imaging trial used the displacement of a 11C-TARACT tracer to measure target occupancy in the brain after 7 days of Xanamem therapy with doses of 5mg to 30mg daily in patients with AD and cognitively normal individuals.
- Detailed hormonal assessment of the hypothalamic-pituitary-adrenal axis (HPA) was conducted with doses of 10mg to 70mg daily.
- Computerized cognitive testing (Cogstate) with doses of 5mg to 20mg daily in healthy older participants for 6 and 12 weeks. The test battery included tests of attention, working memory, episodic memory, executive function.
- A prespecified, double-blind analysis was conducted using stored plasma. samples of 72 participants from the "XanADu" trial with clinically diagnosed AD. It explored clinical progression and potential efficacy of Xanamem in those with elevated levels of plasma pTau181.

PET and quantitative cognitive testing guide dose selection

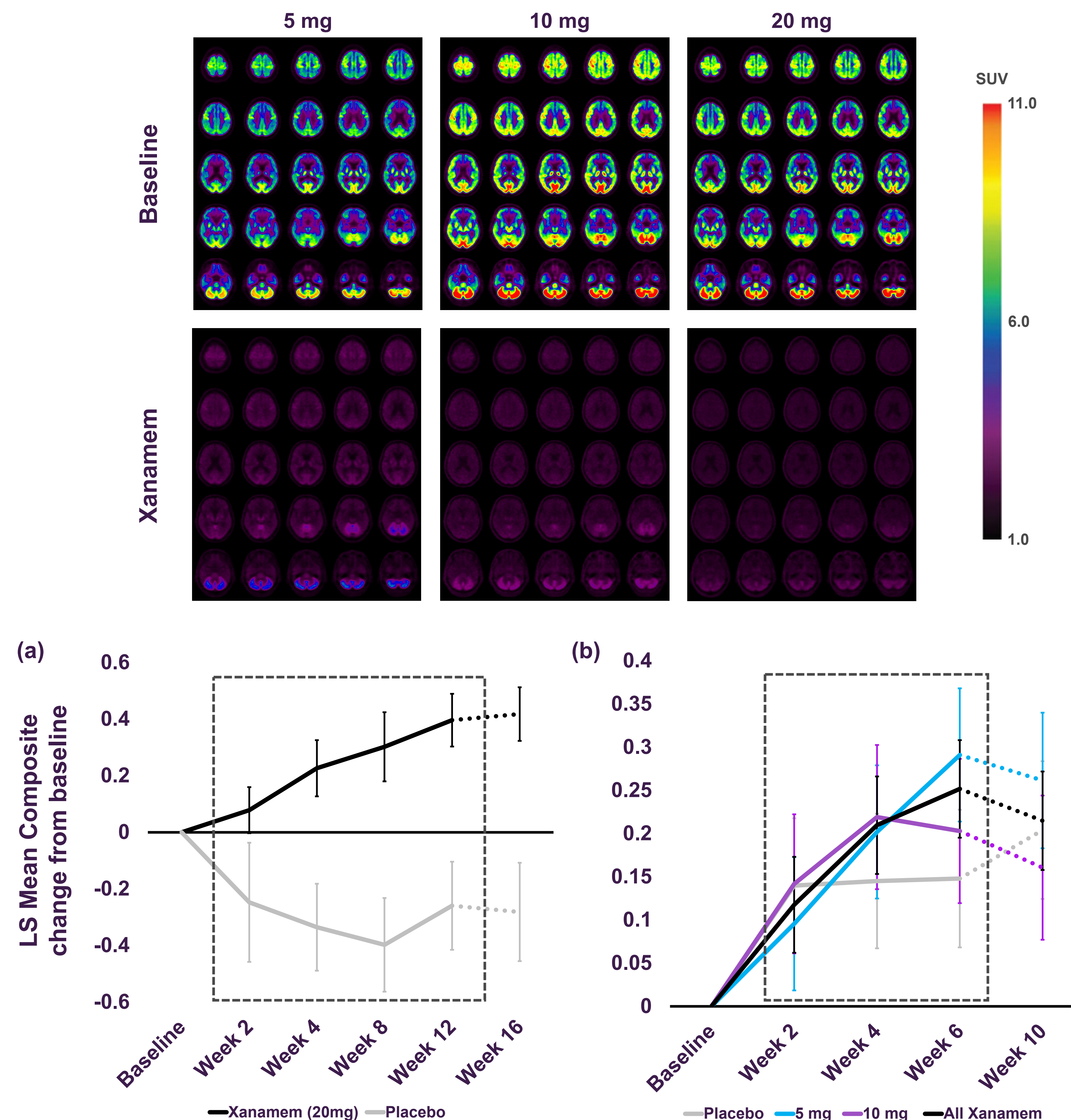


Fig 4: Upper: Composite 11C-TARACT images at baseline and with increasing Xanamem dosage. **Lower:** Least squares (LS) mean change from baseline in scores in the attention composite of a cognitive test battery in healthy older participants in trials (a) XanaHES and (b) XanaMIA-DR. Error bars represent $\pm$ SE. Boxes represent on-treatment visits.

HPA axis peripheral PD

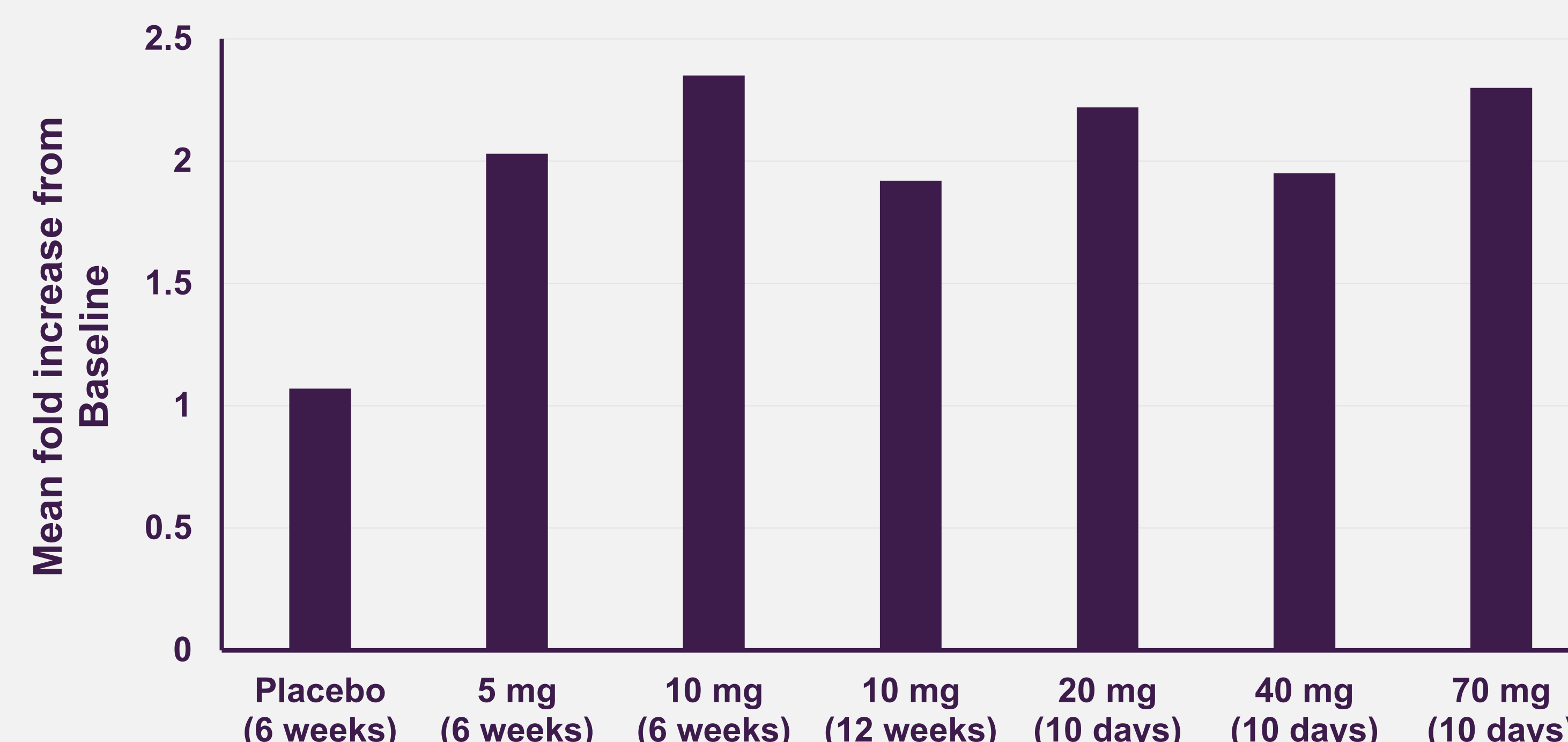


Fig 1: Mean fold increase from baseline in ACTH levels at end of treatment across multiple dose trials. ACTH levels were measured at end of treatment in trials for 10 days (20 mg, 40 mg, and 70 mg), 12 weeks (10 mg), and 6 weeks (placebo, 5 mg, and 10 mg).

Plasma pTau181 predicts clinical progression

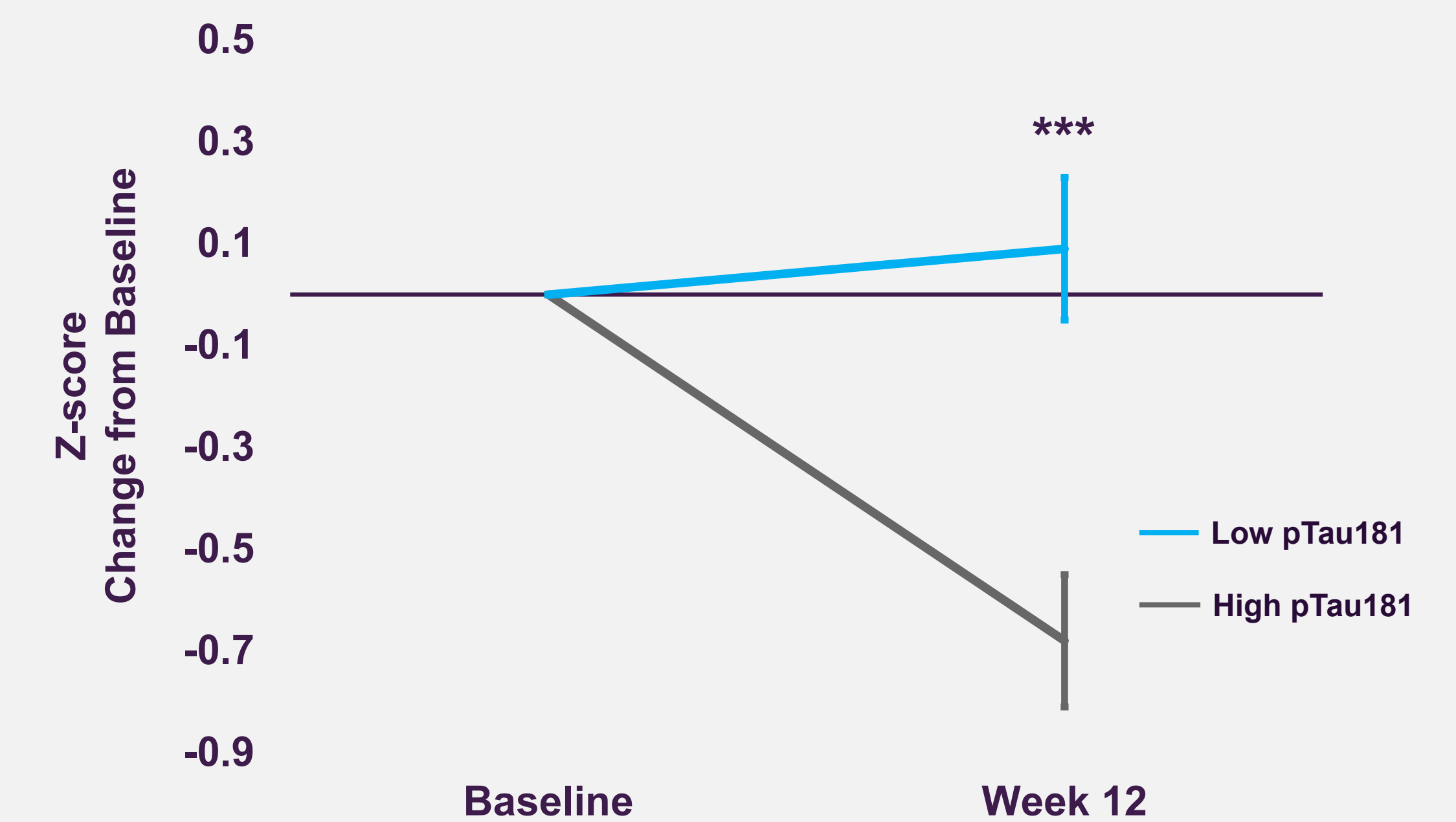


Fig 2: Elevated plasma pTau181 (> median of 6.7 pg/mL) predicts clinical progression over 12 weeks in the placebo group (n=34) on the CDR-SB (Cohen's d = 0.63, ***p < 0.001).

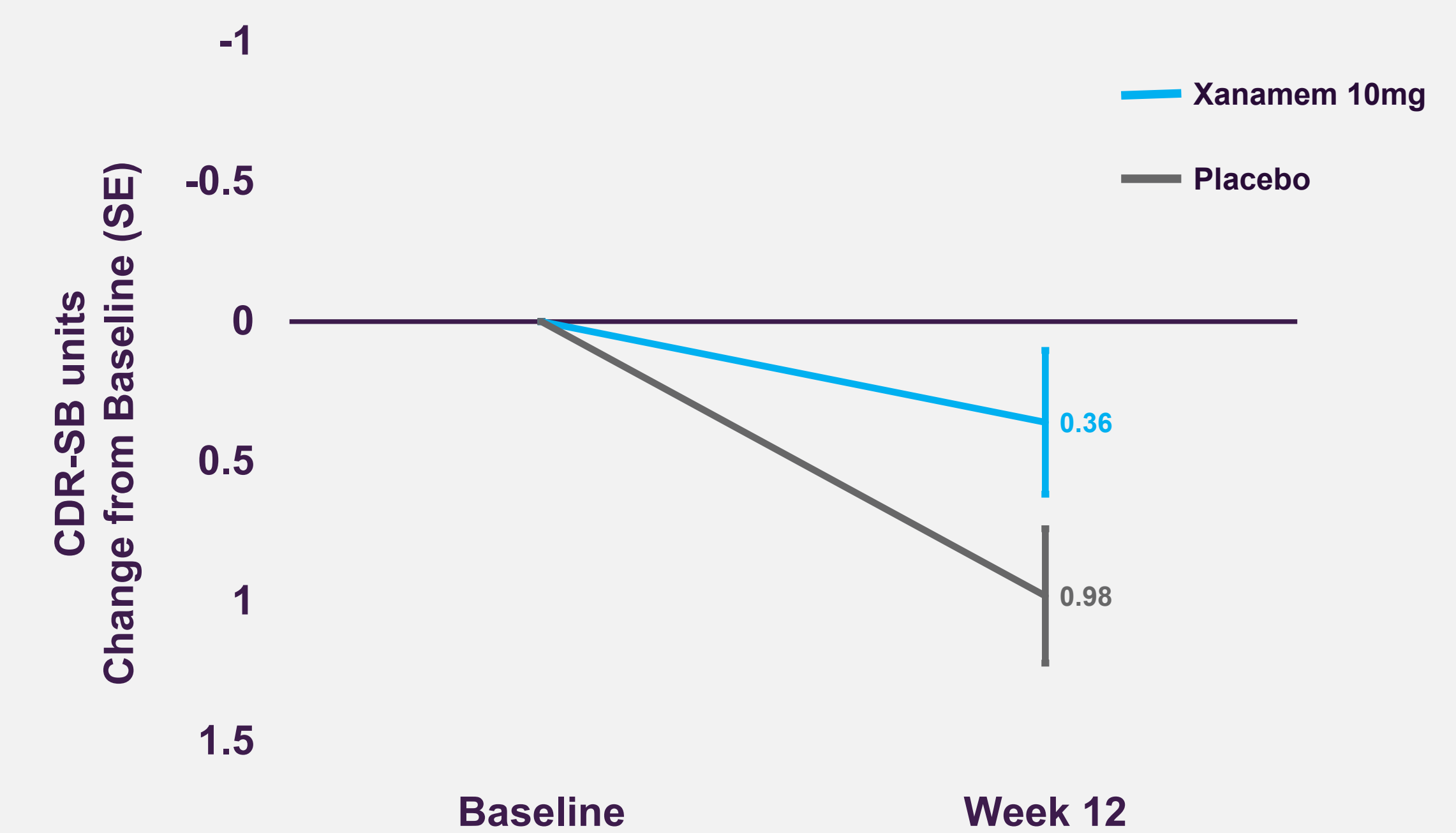


Fig 3: XanADu phase 2 biomarker trial: Least Squares (LS) mean change from baseline in CDR-SB in high p-tau181 subgroup demonstrating large clinical effect size vs placebo. Mean difference vs placebo 0.6 units (Cohen's d = 0.4) Error bars represent $\pm$ SE

Conclusions

- ✓ A series of clinical trials demonstrates the utility of quantitative cognitive testing and PET imaging to support conventional methods for optimal dose selection.
- ✓ Xanamem 10mg showed potential clinical and pro-cognitive treatment benefit in the high pTau181 group
- ✓ There is a high degree of confidence that $\leq$ 10mg daily will be pharmacologically active at the target in the CNS
- ✓ A larger Phase 2b trial in patients with early AD is now underway with a daily dose of 10 mg.