Plasma pTau181 predicts clinical progression in mild Alzheimer's Disease in a randomized controlled trial

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Background

Evidence suggests plasma pTau181 is a useful biomarker in the staging of AD. Prospective longitudinal studies can elucidate the relationship between plasma pTau181 and clinical progression.

Xanamem® is a brain-penetrant inhibitor of 11β-HSD1, which acts to reduce brain cortisol. Chronically elevated cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD).

The Phase 2a XanADu biomarker trial identified patients with elevated plasma pTau181 and explored their clinical progression and potential efficacy of Xanamem.

Methods

A prespecified, double-blind analysis was conducted using stored plasma samples of 72 participants from the "XanADu" trial with clinically diagnosed AD. The analysis prespecified plasma pTau181 > median to identify patients more likely to have progressive AD.

The objectives of the 12-week biomarker trial were to:

1) observe the natural history of disease progression in low (L; pTau181≤6.74 pg/mL) and high (H; pTau181 > 6.74 pg/mL) pTau181 groups over 12 weeks;
2) analyze the efficacy of Xanamem in the H pTau181 subgroup

Efficacy variables assessed included four clinical scales: ADAS-Cog v14, ADCOMS, CDR-SB, and MMSE. Endpoint scores were z-transformed to control for the varying scoring properties of each clinical scale. Other endpoints included NPI, NTB-Exec, and RAVLT. A potentially clinically meaningful improvement was defined by a Cohen's d (*d*) statistic ≥ 0.2

Elevated plasma pTau181 predicts progressive AD

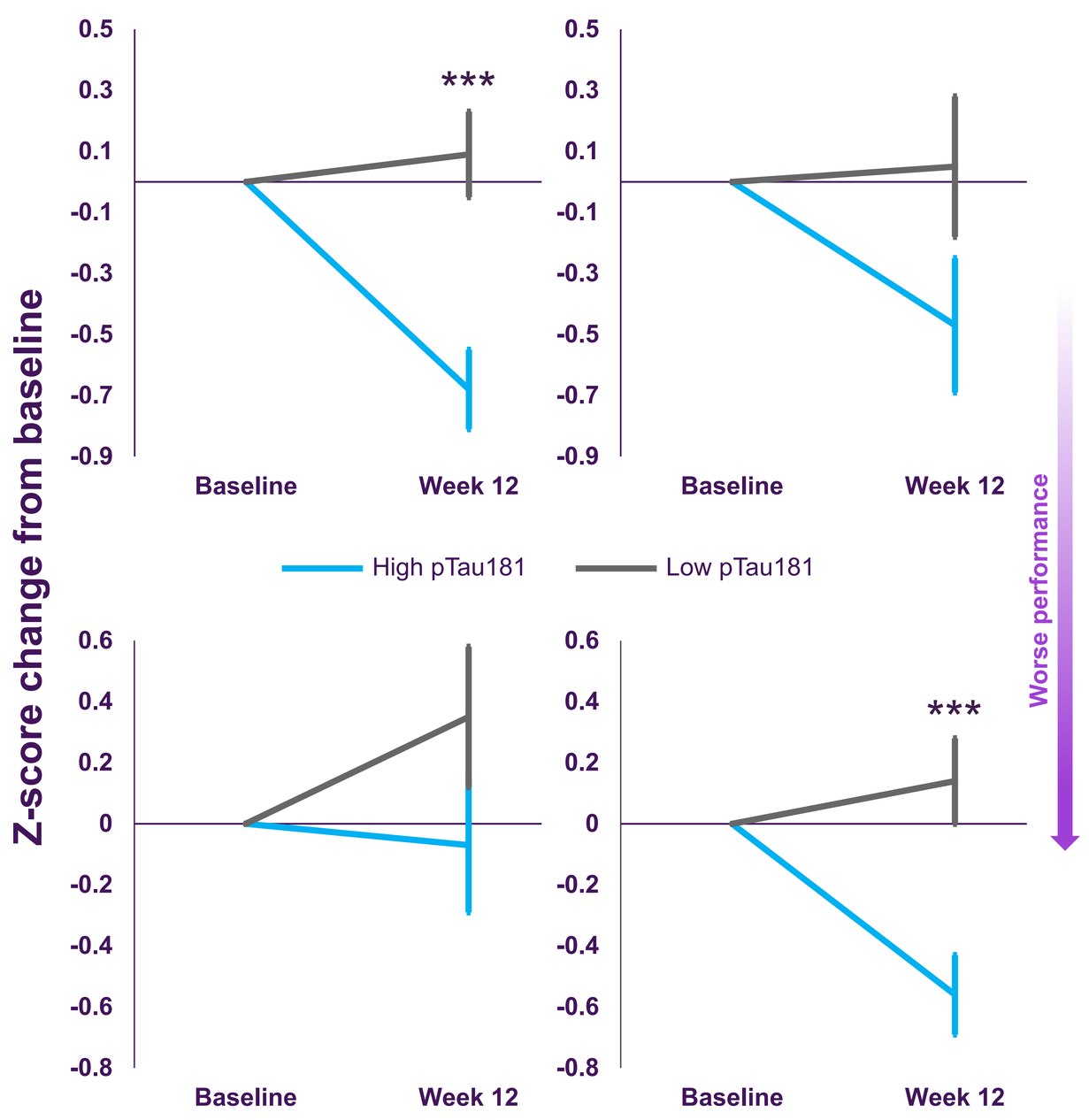

Fig 1: Elevated plasma pTau181 (> median of 6.7 pg/mL) predicts clinical progression over 12 weeks in the placebo group (n = 34). Z-score change from baseline scores (LS mean ± SE) were compared in the high pTau181 and the low pTau181 subgroup on the CDR-SB (*d* = 0.63, ***p < 0.001; Upper left), MMSE (*d* = 0.52, p = 0.12; Upper right), ADAS-Cog (*d* = 0.53, p = 0.19; lower left), and ADCOMS (*d* = 0.55, ***p < 0.001; lower right). The directionality of scores was reversed for the ADAS-Cog and the CDR-SB such that lower scores indicate worse clinical condition

Conclusions

- **Elevated plasma pTau181 may have utility for patient enrichment in AD trials of patients with mild AD.**
- **Enrichment in this way may reduce sample size, cost, and duration of clinical trials.**
- **Xanamem showed evidence of potentially clinically meaningful benefits in these patients with elevated plasma pTau181.**
- **The XanaMIA Phase 2b/3 randomized controlled trial is currently recruiting in Australia and USA to evaluate the benefits of 10mg Xanamem in mild and moderate AD patients with elevated plasma pTau181 (NCT06125951).**

Xanamem attenuates clinical progression

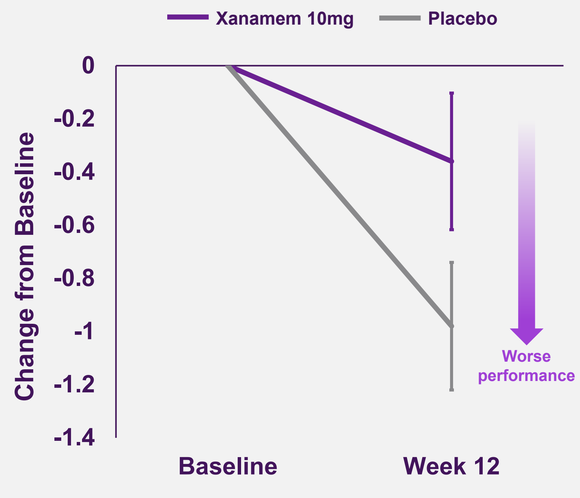

Fig 2: Least Squares (LS) mean change from baseline in CDR-SB in high plasma pTau181 subgroup demonstrating large clinical effect size vs placebo. Mean difference vs placebo 0.6 units (*d* = 0.41) Lower scores represent worse clinical condition. Error bars represent ± SE.

Xanamem has positive Executive function effects in AD

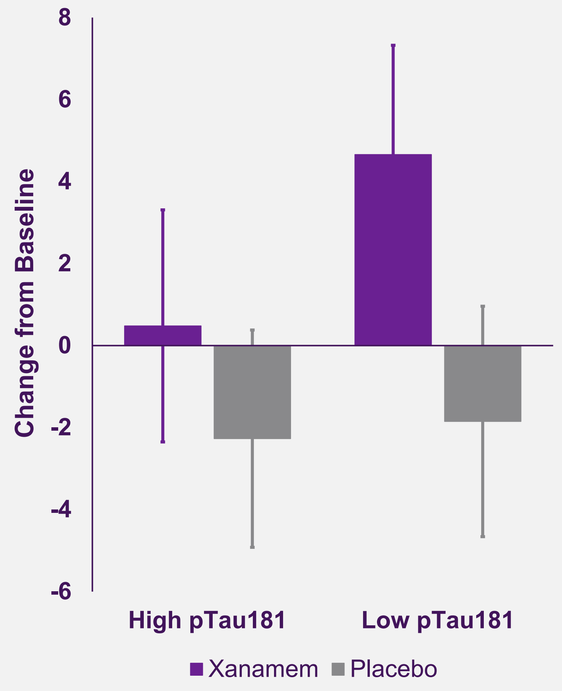

Fig 3: Xanamem vs placebo LS mean change from baseline score in both high and low pTau181 subgroups for a Neuropsychological test battery—Executive function. The NTB comprised the COWAT and CFT. In both High and Low pTau181 groups, improvements were seen favoring Xanamem (*d* = 0.26 and 0.34, respectively).

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