Rationale and design of a Phase 2b trial to evaluate the efficacy of a specific inhibitor of 11β-HSD1, Xanamem®, in mild/moderate AD

Dana Hilt[1], Jack Taylor[1], Tamara Miller[1], John Harrison[2, 3, 4] , Christopher Chen[5], Craig Ritchie[2]

[1] Actinogen Medical, Sydney, Australia; [2] Scottish Brain Sciences, Edinburgh, United Kingdom; [3] King's College, London, United Kingdom; [4] Alzheimercentrum, AUmc, Amsterdam, The Netherlands; [5] Memory Aging and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Background

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), converts intracellular cortisone to cortisol and is highly expressed in brain regions such as the hippocampus. Elevated plasma and CSF cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD). Thus, reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of AD.

Effects of Xanamem on cognition have been assessed in 3 independent placebo-controlled, double-blind trials.

The XanaHES (n= 42, 20 mg) and XanaMIA (n=105, 5 & 10 mg) Phase 1b trials used the computerised Cogstate system to assess cognition in normal, older volunteers. A pattern of clinically significant improvements was observed in attention and working memory compared to placebo in the Xanamem groups, with Cohen's d up to 1.27 (Fig. 1 & 2).

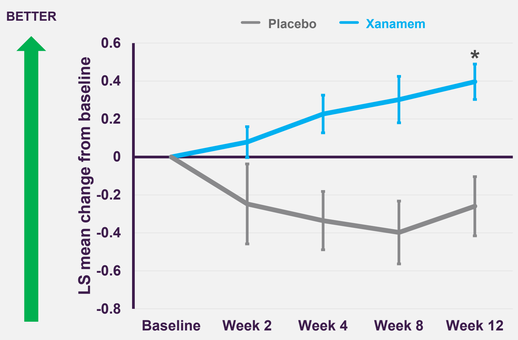


Fig 1: XanaHES: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE. * **Cohen's d = 1.27**.

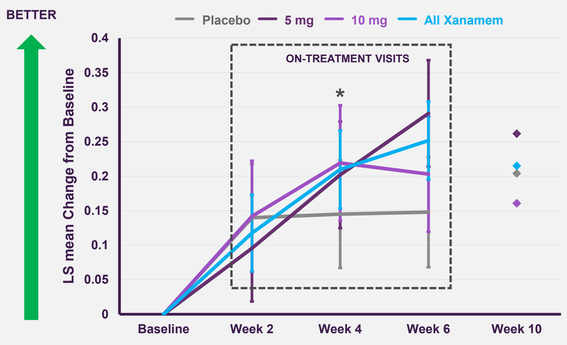
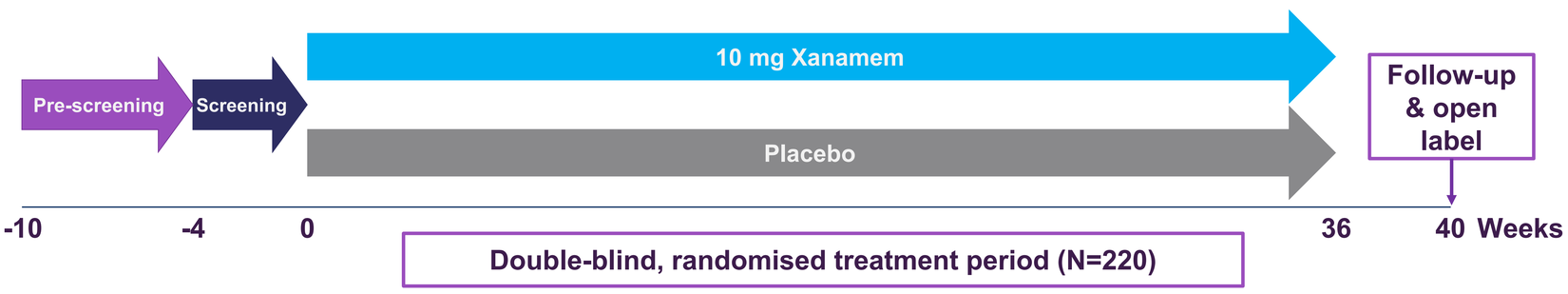


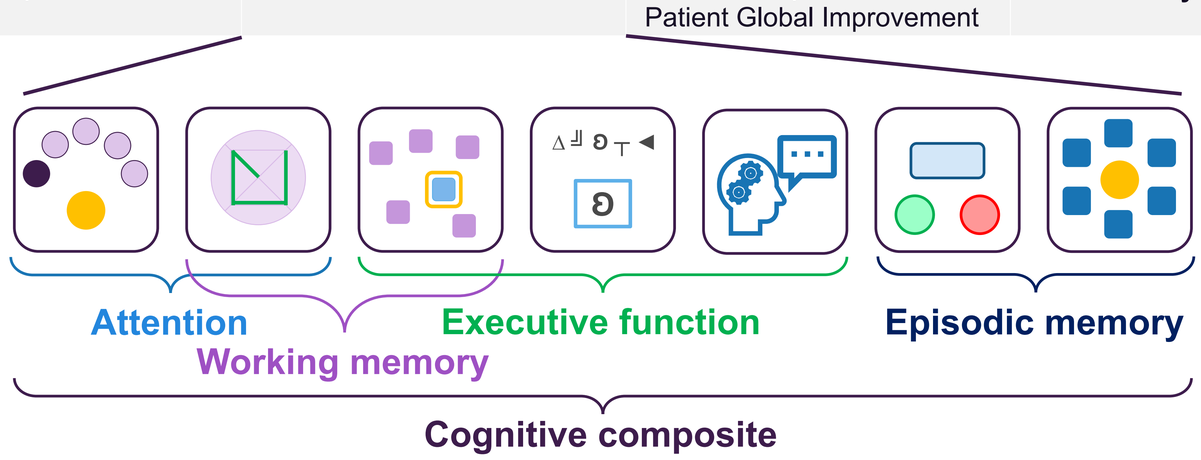
Fig 2: XanaMIA-DR: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE. * **p = 0.05, Cohen's d = 0.32**

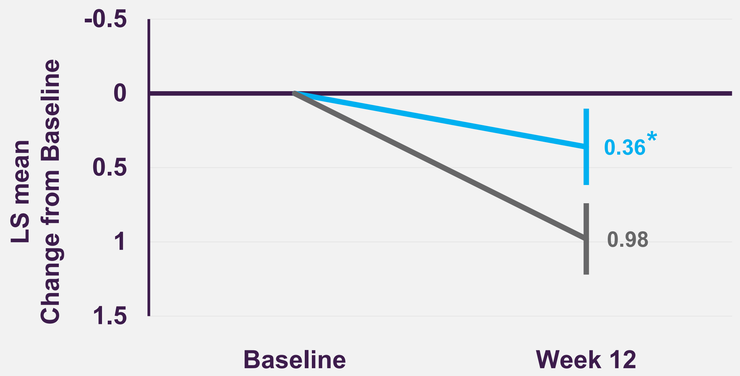
The XanADu-X biomarker extension study (n=72, 10 mg) explored clinical and cognitive outcomes in subgroups (n=34 each) of the XanADu Phase 2a AD trial with higher (H) or lower (L) plasma p-tau181 in a new prospective analysis. Xanamem largely prevented clinical progression over 12 weeks, displaying a clinically significant benefit (Cohen's d of 0.41) on the CDR-SB compared to placebo in the H group (Fig. 3). In H group, improvements were also seen favouring Xanamem in tests of executive function (Cohen's d=0.34 and 0.26, respectively) and the MMSE (Cohen's d=0.32 and 0.16, respectively).

XanaMIA Phase 2b trial design



Key inclusion/exclusion criteria	Primary Endpoints	Key Secondary Endpoints	Key Implementation Features
• Clinical diagnosis of **mild to moderate dementia** due to AD (NIA-AA, MMSE 18-26) • Blood **p-tau181** to confirm progressive AD diagnosis • Cognitive impairment test	• **Cognitive Test Battery** (Global cognition composite)	• **CDR-SB** • **Amsterdam Activity of Daily Living** scale • Executive Function & Episodic Memory Function Composites • Care Giver questionnaire / Patient Global Improvement	• **No PET, MRI, or CSF** • **Global** trial sites including US, AU, Asia, EU and other • Actinogen "hands-on" operational model • **Interim analysis H1 CY25**





* Diff. vs. placebo: Cohen's d = 0.4, Mean 0.6 units, Median 0.8

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. Error bars represent ± SE.

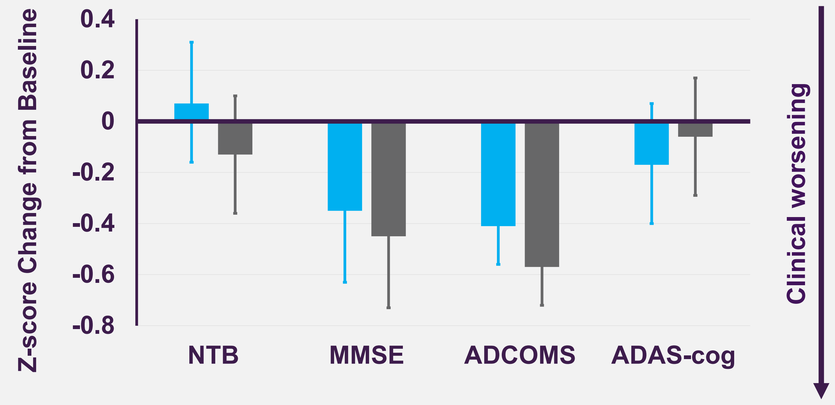


Fig 4: XanADu phase 2 biomarker trial: Z-score change from baseline on NTB, MMSE, ADCOMS, and ADAS-Cog in the prespecified high p-tau181 group. Error bars represent ± SE.

Conclusions

- **Xanamem displays activity in multiple domains of cognition including attention, working memory, and executive function with clinically meaningful effects in normal subjects and in patients with p-tau181-elevated mild AD.**
- **The XanaMIA Phase 2B trial is a robustly designed study using contemporary, treatment-sensitive endpoints, and patient enrichment strategies to demonstrate the procognitive and disease-course modifying benefits of Xanamem.**
- **The initial results of the XanaMIA Phase 2B trial are expected in H1 2025.**

Contact email: dana.hilt@actinogen.com.au; jack.taylor@actinogen.com.au
Website: actinogen.com.au