Xanamem shows pro-cognitive activity with clinically meaningful effect sizes across 3 independent, placebo-controlled clinical trials

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Background

- Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1).
- 11β-HSD1 is highly expressed in regions such as the hippocampus, frontal cortex, and cerebellum.
- Elevated cortisol is associated with cognitive dysfunction and neurotoxicity in animals and in human studies.
- Reducing cortisol levels in the brain is considered an important therapeutic goal in the treatment of Alzheimer's Disease (AD) and other conditions where cognitive impairment and cortisol excess is a major component of the disease.
- Nonclinical and clinical studies to date indicate that Xanamem offers potential to be rapidly cognitive enhancing.

Phase 1 studies (older NHV)

XanaHES (n=42) and XanaMIA-DR (n=107):

- Phase 1 double-blind, placebo-controlled, dose-ranging trials
- Healthy older health normal volunteers (NHV) 50-80 years
- XanaHES: 20mg Xanamem or placebo orally for 12 weeks
- XanaMIA-DR: 5mg Xanamem, 10mg Xanamem, or placebo orally for 6 weeks
- Primary objectives were safety, and effects on cognition measured by the Brief Cogstate Cognitive Test Battery (CTB)
- Assessment of treatment effect sizes using Cohen's d and Standardized Mean Response (SMR)

Phase 2a XanADu Biomarker Ext.

- Phase 2 double-blind, placebo-controlled trial
- Probable mild AD (MMSE 20-26)
- 10mg Xanamem or placebo orally for 12 weeks (n=185)
- Biomarker extension prospectively analysed stored plasma samples (n=72) on the Quanterix SIMOA platform
- Plasma biomarkers included p-tau181, Amyloid 42/40, and GFAP
- A prespecified analysis explored clinical and cognitive outcomes in subgroups of above and below median p-tau181 conc.:
  - Higher (H; > 6.74pg/mL) or
  - Lower (L; ≤ 6.74pg/mL)

Xanamem improves cognition across multiple clinical trials

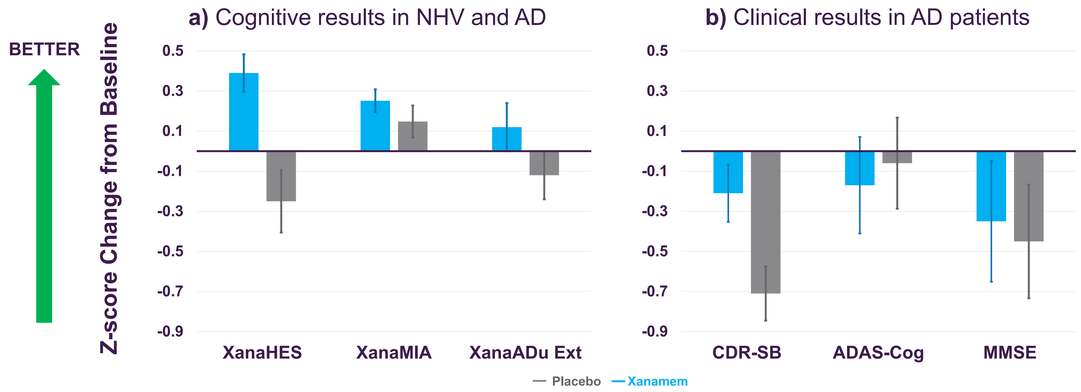

Fig 1: a) Z-score change from baseline in cognitive tests of attention, working memory in the XanaHES, XanaMIA-DR trial, and of executive function in XanADu Biomarker Ext trial. **b)** Z-score change from baseline on selected clinical outcomes measures in the prespecified high p-tau181 group from the XanADu biomarker Ext. trial. Error bars represent ± SE.

Administrations and clinical safety

- Easy, oral once-a-day administration
- Can be given with or without food
- Safe and well tolerated in >300 patients dosed
- No drug-related SAEs across all trials

Phase 1 trial results

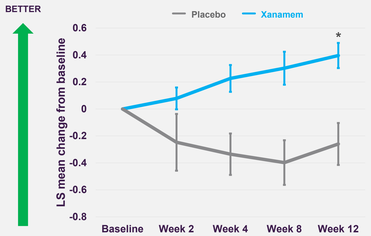

Fig 2: XanaHES: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE.
*** Cohen's d = 1.27.**

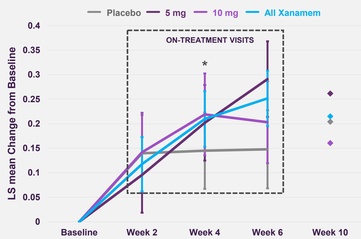

Fig 3: XanaMIA-DR: Least Squares (LS) mean change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE.
*** p = 0.05, SMR = 0.32**

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Phase 2 trial results

Activity consistent with Xanamem action as a cognitive enhancer & disease-modifier

Fig 4: XanADu phase 2 exploratory analysis. Least Squares (LS) mean change from baseline in cognitive composite scores. Trends in change of composite of word recall & recognition (ADAS-Cog), CFT & COWAT. Error bars represent ± SE.

Xanamem largely prevented clinical progression over 12 weeks

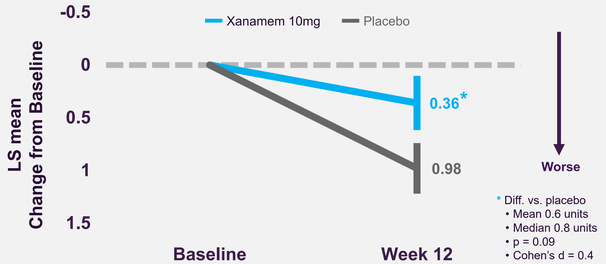

Fig 5: XanADu phase 2: Least Squares (LS) mean change from baseline in CDR-SB in high p-tau181 subgroup demonstrating large clinical effect size vs placebo. Error bars represent ± SE.

Conclusions

- **Xanamem displays positive activity in multiple domains of cognition including attention, working memory, and executive function, with clinically meaningful effect sizes**
- **Data from multiple clinical trials suggest Xanamem to be both a procognitive and disease-course modifying agent.**
- **A larger Phase 2b trial in patients with early AD is will begin in H2 2023 to confirm Xanamem's cognitive and clinical benefits.**