XanaMIA-DR: A Double-Blind, Placebo-Controlled, Dose Ranging Study to Assess the Efficacy, Pharmacodynamics and Safety of Xanamem® in Healthy Elderly Volunteers

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Background

Xanamem® is a potent and selective inhibitor of 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol. In the brain, 11β-HSD1 is highly expressed in regions such as the hippocampus, frontal cortex, and cerebellum. There is evidence from studies in animals and in humans linking elevated cortisol with cognitive dysfunction and neurotoxicity. Thus, 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.

Methods

The main features of the XanaMIA Phase 1b trial were:

- Double-blind, placebo-controlled, dose-ranging
- Healthy older volunteers 50-80 years
- 5 mg Xanamem (n=36), 10 mg Xanamem (n=34), or matching placebo (n=37) orally for 6 weeks
- Primary objectives were safety, pharmacodynamics of ACTH and effects on cognition measured by the 6-domain Brief Cogstate Cognitive Test Battery (CTB)
- Main objective was estimation of the magnitude and consistency of clinical effect sizes in attention and memory composites
- Effect sizes were estimated from modeled data as Z scores and raw data as Standardized Mean Response (SMR) - a version of the Cohen's d statistic
- The a priori criterion for effect detection was SMR (d) ≥ 0.3 in one or more tests.

Adverse Events

Xanamem was safe and well-tolerated over the 6-week treatment period in this cognitively normal population aged 50-80 years (mean age 64 years, 65% female). There were no treatment-related serious adverse events, and other predominantly mild adverse events were generally equally distributed across the 3 groups (Table 1).

Table 1: Number (%) of Subjects with common TEAEs

	Placebo (N = 37)	5 mg Xanamem (N = 36)	10 mg Xanamem (N = 34)	All Subjects (N = 107)
All TEAEs	32 (86.5)	26 (72.2)	23 (67.6)	81 (75.7)
IP-related TEAEs	13 (35.1)	16 (44.4)	15 (44.1)	44 (41.1)
Headache	11 (29.7)	10 (27.7)	10 (29.4)	31 (28.9)
Nausea	1 (2.7)	4 (11.1)	3 (9)	8 (7.4)
Arthralgia	5 (13.5)	3 (8.3)	-	8 (7.4)

Cogstate "attention composite" benefit in working memory & attention replicate prior trial findings

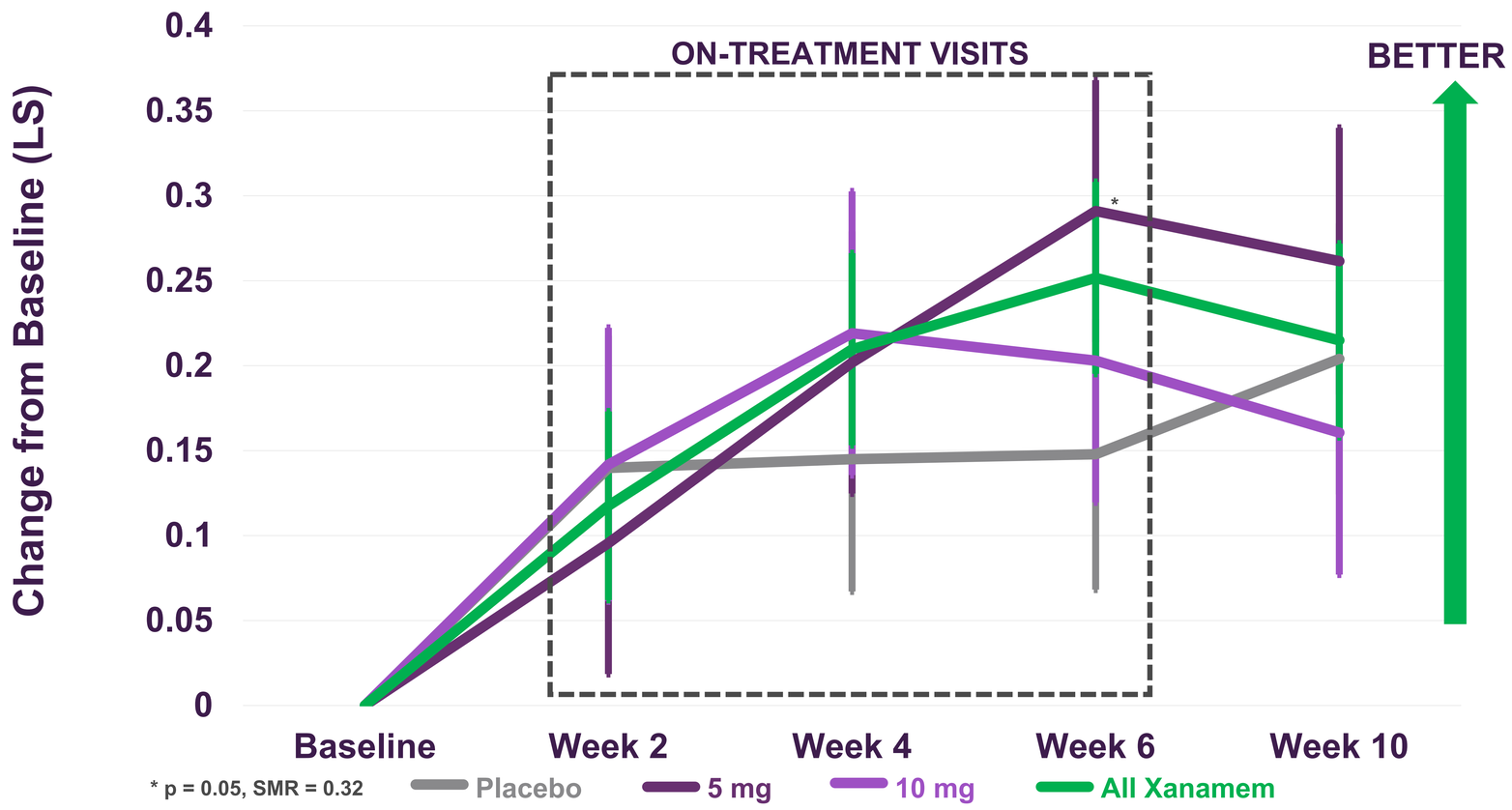

Fig 1: Mean (LS) change from baseline in scores in the Attention Composite of the CTB. Error bars represent ± SE.

Pharmacodynamics

Increases in plasma ACTH were similar to those observed previously and confirmed biologic activity of both doses (Fig 2).

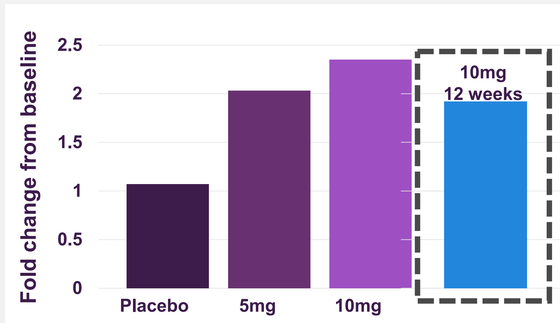

Fig 2: Mean fold increase in plasma ACTH concentration at end of treatment. Box represents fold change in previous 12 week trial XanaHES

Cognitive Results

Practice or placebo effects

Not unexpectedly for a cognitively normal population, practice or placebo effects were seen to Week 2 in the attention composite and to Week 10 in the memory composite.

Attention domain

Clinically significant improvements greater than placebo were seen beyond Week 2 for both dose levels in the attention composite, and for its three tests, including working memory. Performance declined after treatment cessation, consistent with removal of drug effect.

Memory domain and IDSST

Improvements in performance were seen during treatment in all groups including placebo in those test making up a memory domain composite (Fig 3). Performance did not decline after treatment cessation. For the IDSST active and placebo groups both had a mean improvement to Week 6 of ~3.5 units without reduction upon treatment cessation.

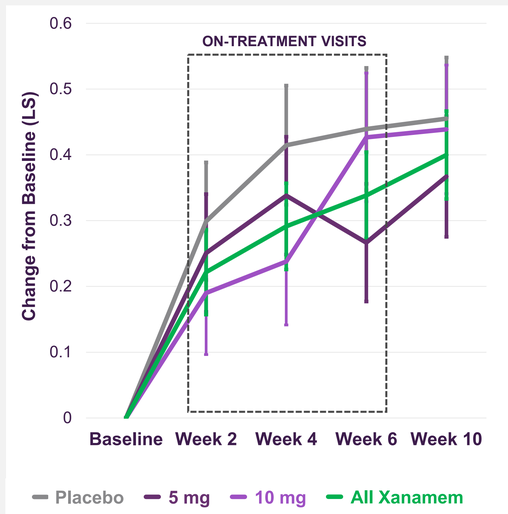

Fig 3: Mean (LS) change from baseline in scores in the Memory Composite of the CTB. Error bars represent ± SE.

Conclusions

- **In cognitively unimpaired older adults six weeks treatment with Xanamem 5 and 10 mg was associated with clinically important improvement in attention.**
- **Xanamem related improvement in attention was qualitatively and quantitatively consistent with that observed in a previous study using a 20 mg dose.**
- **Xanamem was safe and well tolerated.**
- **A larger Phase 2b trial in patients with MCI / mild Alzheimer's Disease is planned for commencement in 2023.**