Clinical pharmacology and development of Xanamem, a tissue specific inhibitor of 11β-HSD1

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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. 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, 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 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.

PET and quantitative cognitive testing guide dose selection

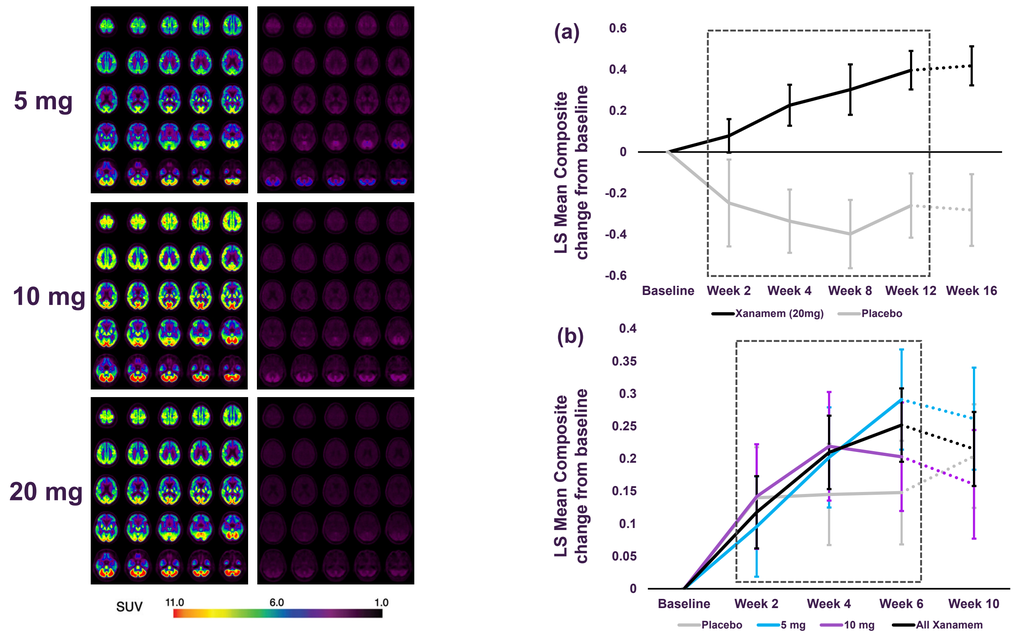

Fig 3: Left: Composite 11C-TARACT images at baseline (left) and with increasing Xanamem dosage (right). **Right:** Least squares (LS) mean change from baseline in scores in the attention composite of a cognitive test battery in healthy older participants in studies (a) XanaHES and (b) XanaMIA-DR. Error bars represent ± SE.

Population PK

Table 1: Population PK parameter estimates for the final population PK model

Model Parameters (Units)	Estimate	%RSE	Lower 95% CI	Upper 95% CI	Between-Participant Variability (CV%)
Structural Parameters					
CL/F ($L.h^{-1}$)	4.76	9.73	3.85	5.67	50.2
V/F (L)	64.3	4.70	58.4	70.2	33.0
k_a (h^{-1})	1.74	92.5	-1.42	4.90	51.5
ALAG (h)	0.900	38.1	0.228	1.57	75.8
Covariates					
WT on V/F	1.00	-	-	-	

Abbreviations: ALAG = absorption lag time; CI = confidence interval; CL/F = apparent clearance; CV = coefficient of variation; F = bioavailability; ka = absorption rate; RSE = relative standard error; V/F = apparent volume of distribution; WT = weight.

HPA axis peripheral PD

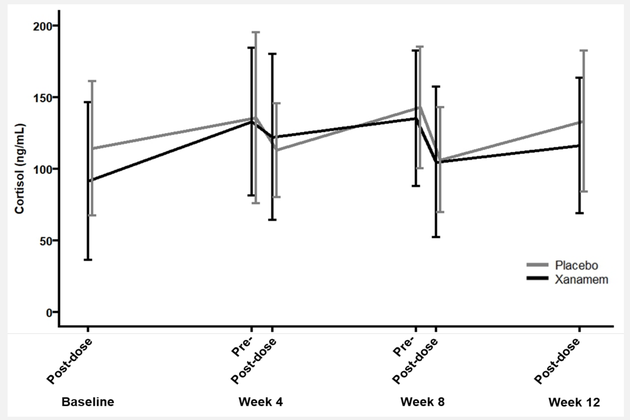

Fig 1: Mean cortisol level (ng/mL) and 95% confidence interval over time, pre- and 3 to 5 hours post-dose, for 10 mg Xanamem (blue line) and placebo (red line) in the XanADu study.

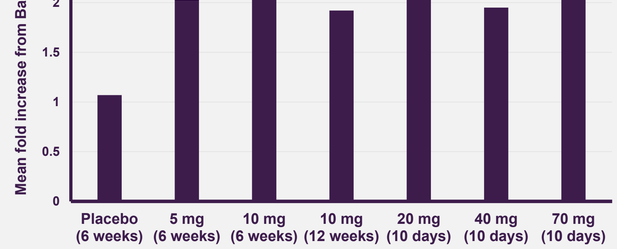

Fig 2: Mean fold increase from baseline in ACTH levels at end of treatment across multiple dose studies. ACTH levels were measured at end of treatment in trials for 10 days (20 mg, 40 mg, and 70 mg), 12 weeks (10 mg), and 6 weeks (placebo, 5 mg, and 10 mg).

Conclusions

- **A series of clinical trials demonstrates the utility of quantitative cognitive testing and PET imaging to support conventional methods for optimal dose selection.**
- **There is a high degree of confidence that ≤ 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.**

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