

# Supplementary Material

## Brain 11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1 Occupancy by Xanamen<sup>TM</sup> Assessed by PET in Alzheimer's Disease and Cognitively Normal Individuals

**Supplementary Table 1.** Mean and coefficient of variation (CoV) of Baseline V<sub>T</sub> in the MCI/AD and CN groups.

	<b>MCI/AD (n=16) Mean V<sub>T</sub> (CoV)</b>	<b>CN (n=19) Mean V<sub>T</sub> (CoV)</b>
<b>Neocortex</b>	8.39 (0.19)	7.30 (0.28)
<b>Medial Temporal Lobe</b>	4.18 (0.25)	3.95 (0.29)
<b>Basal Ganglia</b>	7.47 (0.22)*	6.17 (0.27)
<b>Cerebellum</b>	14.94 (0.22)*	12.01 (0.33)

\*p<0.05

**Supplementary Table 2.** Incidence of treatment-emergent adverse events considered related to Xanamem treatment (including withdrawn participants)

System Organ Class Preferred term	Number (%) of subjects								
	5 mg		10 mg		20 mg		30 mg		Total (N=40)
	MCI/AD (N=4)	CN (N=5)	MCI/AD (N=4)	CN (N=8)	MCI/AD (N=4)	CN (N=5)	MCI/AD (N=5)	CN (N=5)	
<b>Cardiac disorders</b>								1 (20.0)	1 (2.5)
Chest pain								1 (20.0)	1 (2.5)
<b>Respiratory</b>								1 (20.0)	1 (2.5)
Hyperventilation								1 (20.0)	1 (2.5)
<b>Gastrointestinal disorders</b>			1 (25.0)					1 (20.0)	2 (5.0)
Abdominal pain/discomfort			1 (25.0)					1 (20.0)	2 (5.0)
Nausea			1 (25.0)						1 (2.5)
<b>General disorders and administration site conditions</b>						1 (20.0)	1 (20.0)	1 (20.0)	3 (7.5)
Fatigue						1 (20.0)	1 (20.0)	1 (20.0)	3 (7.5)
<b>Musculoskeletal and connective tissue disorders</b>								1 (20.0)	1 (2.5)
Muscle pain								1 (20.0)	1 (2.5)
<b>Nervous system disorders</b>		1 (20.0)				1 (20.0)	1 (20.0)	3 (60.0)	6 (15.0)
Dizziness							1 (20.0)	1 (20.0)	2 (5.0)
Loss of balance and coordination								1 (20.0)	1 (2.5)
Memory impairment						1 (20.0)			1 (2.5)
Tingling (arm)								1 (20.0)	1 (2.5)
Tremors		1 (20.0)							1 (2.5)
<b>Psychiatric disorders</b>						1 (20.0)	1 (20.0)		2 (5.0)
Depression						1 (20.0)			1 (2.5)
Hyperactivity								1 (20.0)	1 (2.5)

AD, Alzheimer's Disease group; CN, cognitively normal group; MCI, mild cognitive impairment; N, number of participants

**Supplementary Table 3.** Average estimates of occupancy based on change in SUV<sub>40-60</sub>.

Dose	10 mg NOCTE	5mg MANE	10 mg MANE	20 mg MANE	30 mg MANE
Neocortex	69.7%	71.5%	81.4%	84.0%	84.1%
Medial Temporal	64.2%	64.8%	71.7%	69.8%	70.5%
Basal Ganglia	67.3%	68.3%	81.2%	83.1%	83.5%
Cerebellum	42.3%	49%	73.2%	83.1%	85.4%

Average reduction in <sup>11</sup>C-Taract binding at increasing doses of Xanamem™ using the standardized uptake value (SUV) at 40-60 min post injection. Eight subjects were scanned at each dose. With mane dosing, the scan was performed approximately 4-6 h post dose and nocte dosing was scanned approximately 16 h post dose.

**Supplementary Figure 1.** Baseline and Post Treatment population based venous blood metabolite curves for  $^{11}\text{C}$ -TARACT. The curve was fitted to the average time point values from individual baseline (n=8) and post treatment (10 mg daily) (n=7) metabolite measures.

