Conflict of Interest

Inge De Lepeleire is an employee of MSD (Europe) Inc.

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IMPACT OF CHOLINERGIC TONE ON THE BINDING OF PET TRACER [^{11}C]MK-6884, A POSITIVE ALLOSTERIC MODULATOR OF M4 ACETYLCHOLINE RECEPTOR IN MONKEYS AND HEALTHY ELDERLY VOLUNTEERS

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Study outline

- [^{11}C]MK-6884 PET study in Rhesus Monkeys
- Human PK/PD model of plasma Donepezil (DPZ) concentrations vs Striatal Binding Potential (BP_{ND})
- [^{11}C]MK-6884 PET study in Healthy Elderly Volunteers (HVs)

⬇

To assess indirect, allosteric modulatory effects of Donepezil on binding of [^{11}C]MK-6884 to striatal M4 PAM sites

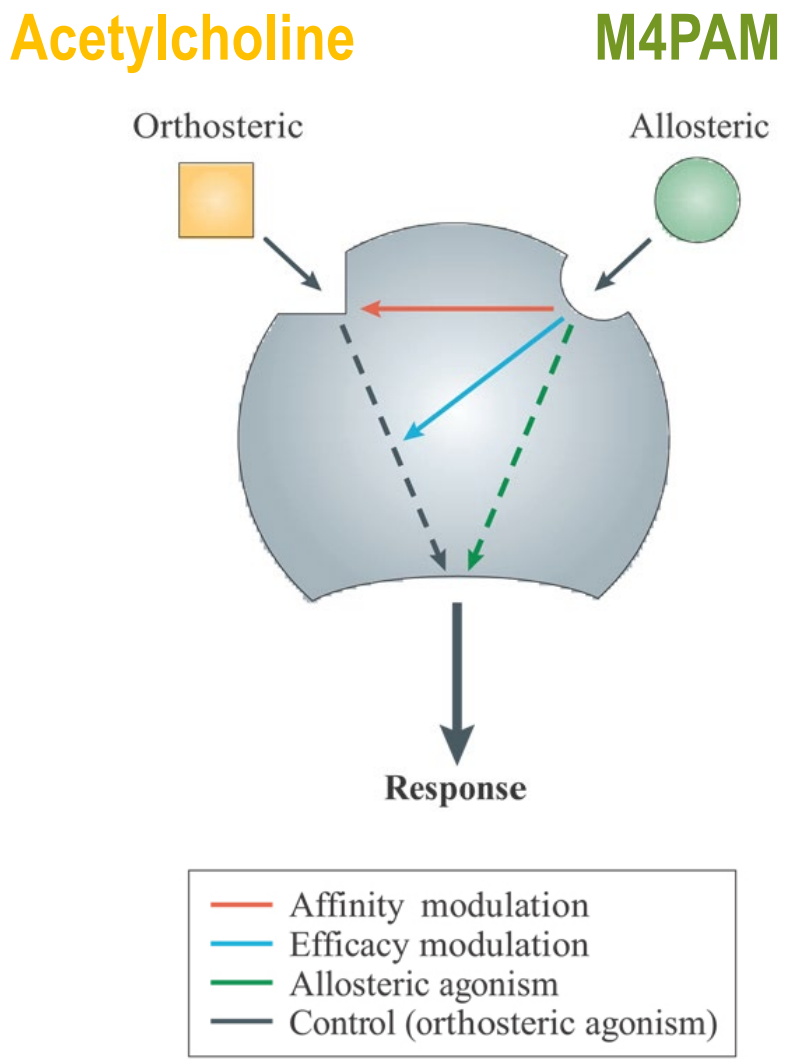
Background

[^{11}C]MK-6884 :

- Positive Allosteric Modulator of Muscarinic M4 Acetylcholine (ACh) receptors (M4 PAM)
- Novel PET tracer to inform on altered binding of M4PAM drugs in function of central cholinergic tone

Donepezil (DPZ) :

- Acetylcholinesterase (AChE) inhibitor for treatment of cognitive deficits in AD
- Increases brain ACh concentrations



P.J. Conn et al., Nature Rev. Drug Discov. (2009) 8, 41

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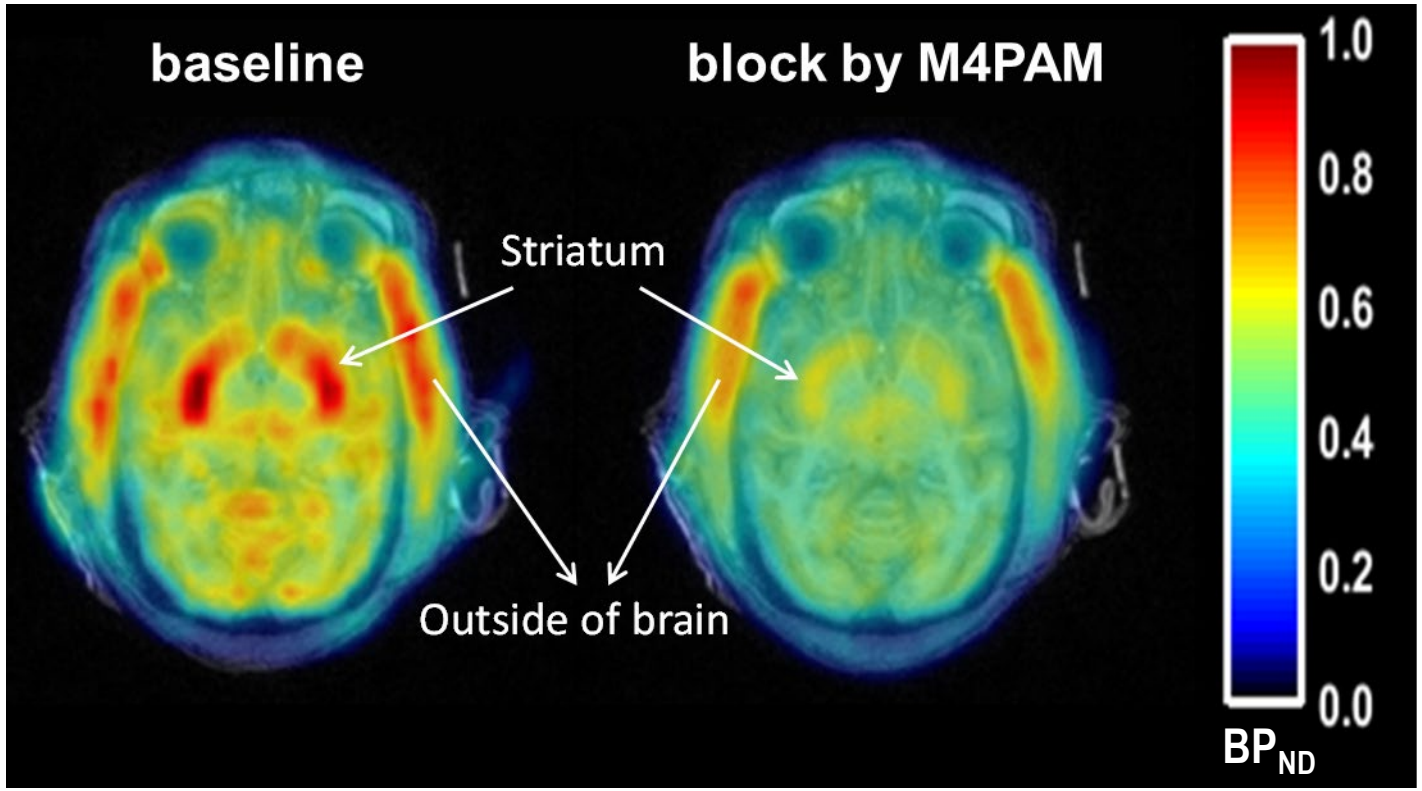
[^{11}C]MK-6884 In Vivo Characterization in Rhesus Monkeys



Specific binding signal of [^{11}C]MK-6884 in monkey striatal region

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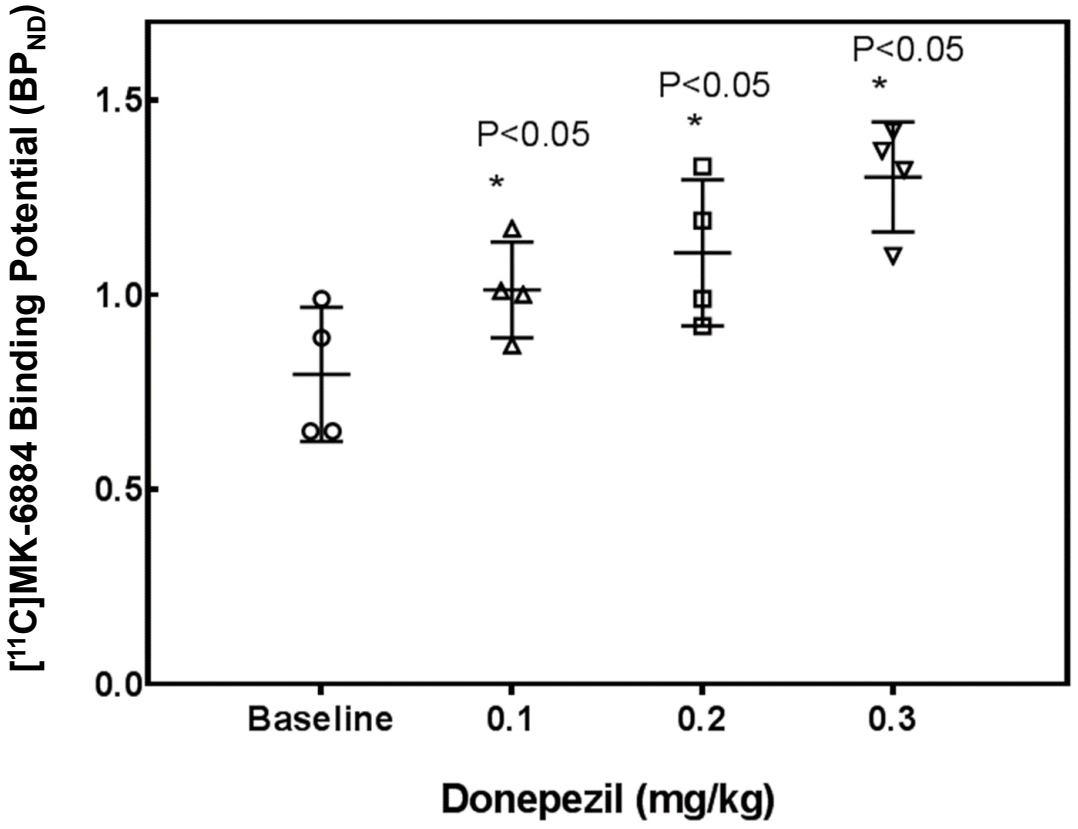
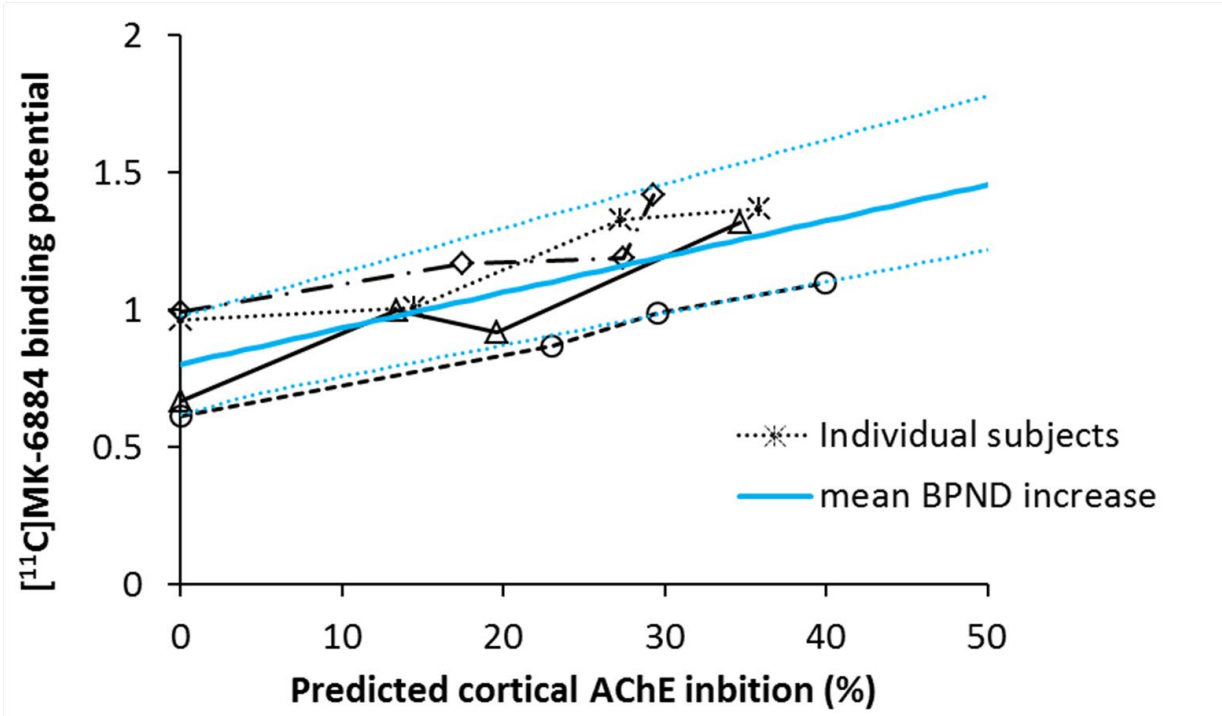
Cholinergic Tone Impacts Binding of [^{11}C]MK-6884 in Rhesus Monkeys

Striatal BP_{ND} vs DPZ Dose



Striatal BP_{ND} vs % inhibition of Brain AChE Activity



Shiraishi *et al.*, Neuropsychopharmacology (2005) 30, 2154

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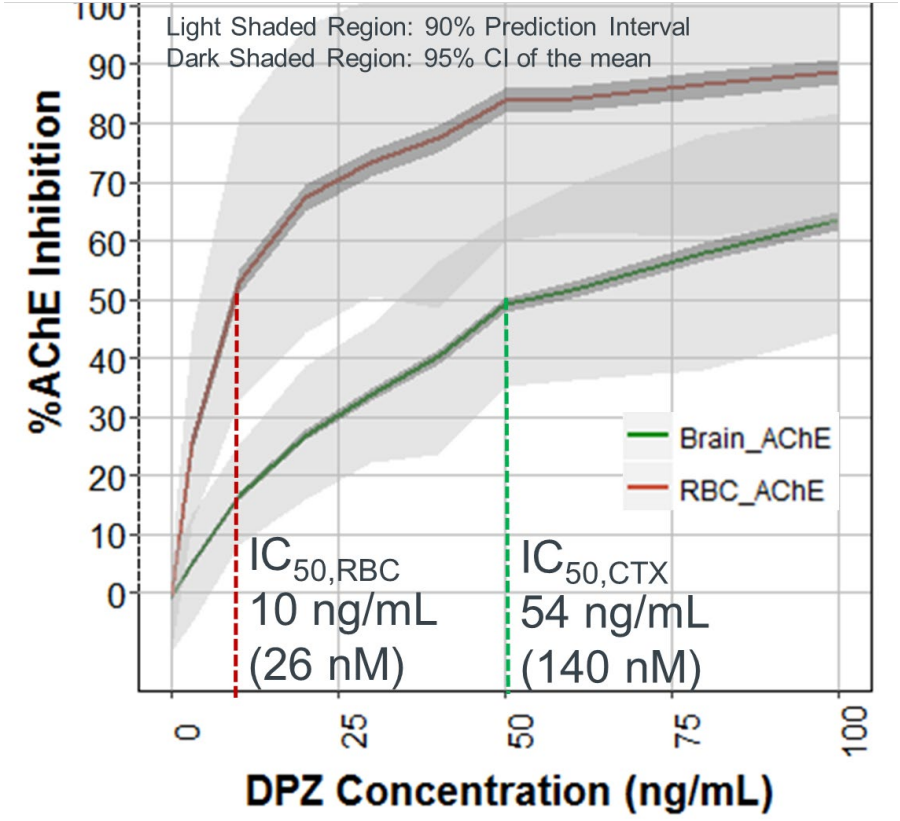
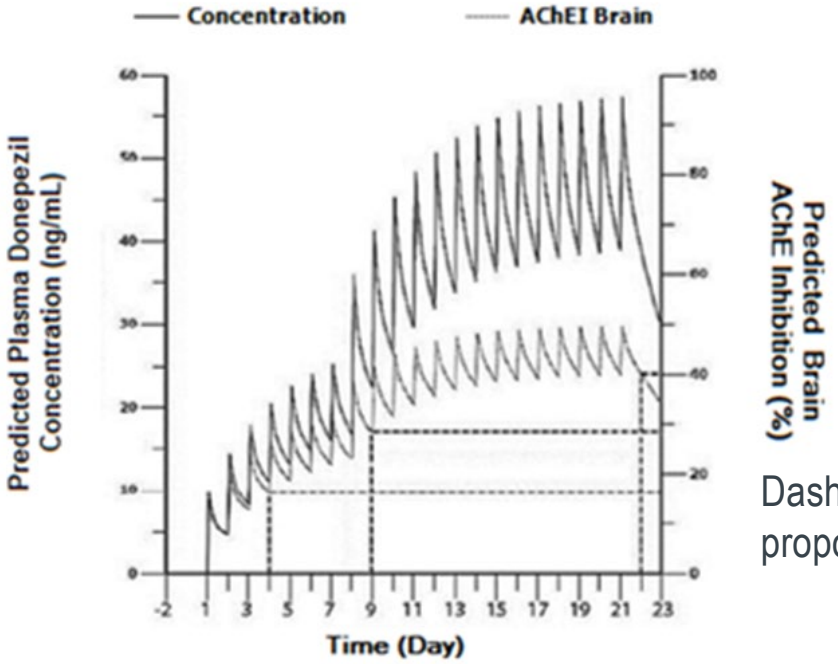
PK/PD modeling to Inform Human PET study

Inhibition of AChE activity in RBCs and cortex vs DPZ Cp



Simulations of DPZ Cp and brain AChE inhibition



Dashed lines = proposed PET scans

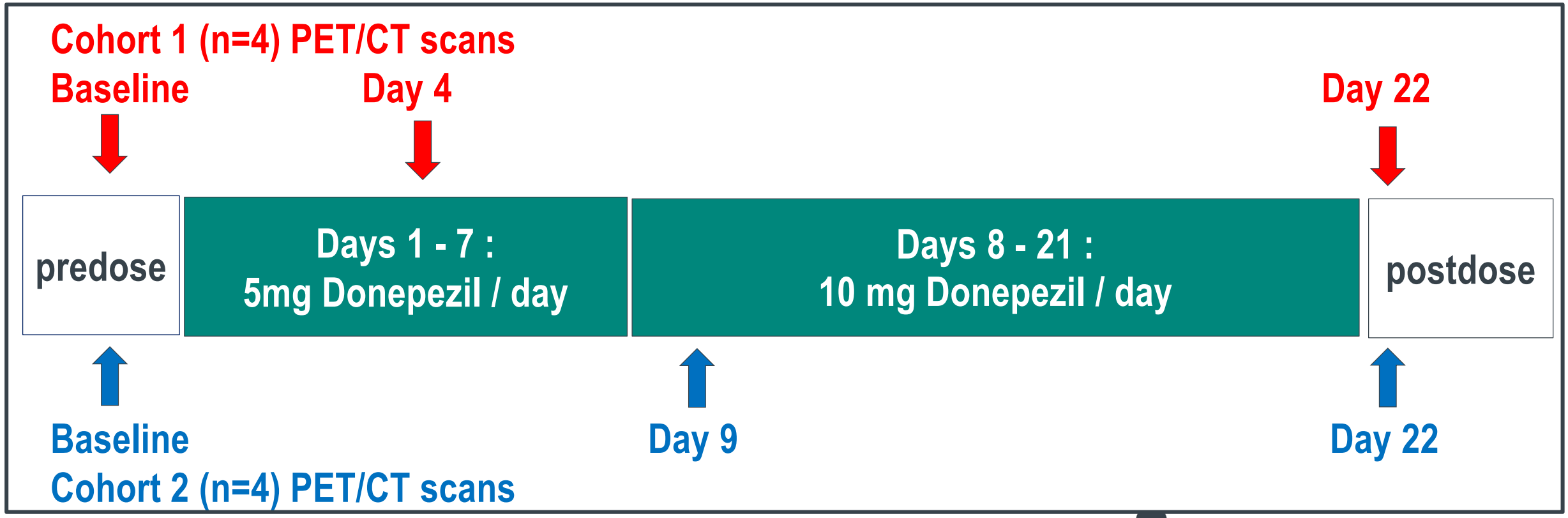
Predicted Increase in [^{11}C]MK-6884 Striatal BP_{ND}

- 7 days DPZ 5 mg qd : ~1.5 fold
- 21 days DPZ 10 mg qd : ~1.8 fold

Tiseo *et al.*, Br. J. Clin. Pharmacol. (1998) 46 (Suppl 1) 13
Tiseo *et al.*, Br. J. Clin. Pharmacol. (1998) 46 (Suppl 1) 40

Phase 1 Study Outline

2 cohorts of n= 4 HVs each (age 57-64 yrs)
3 PET/CT scans ([^{11}C]MK-6884 : ~300MBq, mass ≤ 4.9 µg per scan)
PK (DPZ Cp) and PD (RBC-AChE activity) at each scan



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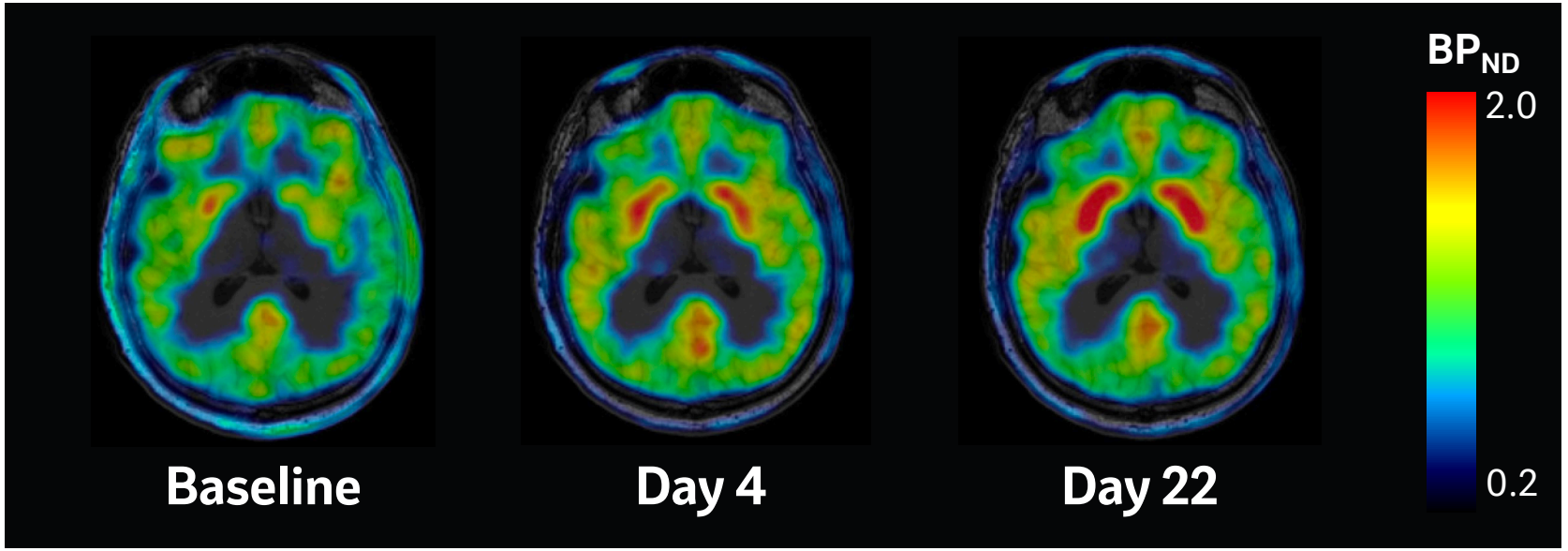
Effects of Donepezil on the Striatal BP_{ND} of [^{11}C]MK-6884 in HVs

PET-MR Fusion Parametric Images



Observed DPZ C_{trough}

	C_{trough} ng/mL (%CV)
Day 4	6.4 (31)
Day 9	19 (39)
Day 22	30 (58)

Donepezil Treatment 5mg QD x 7 days

Donepezil Treatment 10mg QD x 14 days

normal ACh tone

increased ACh tone

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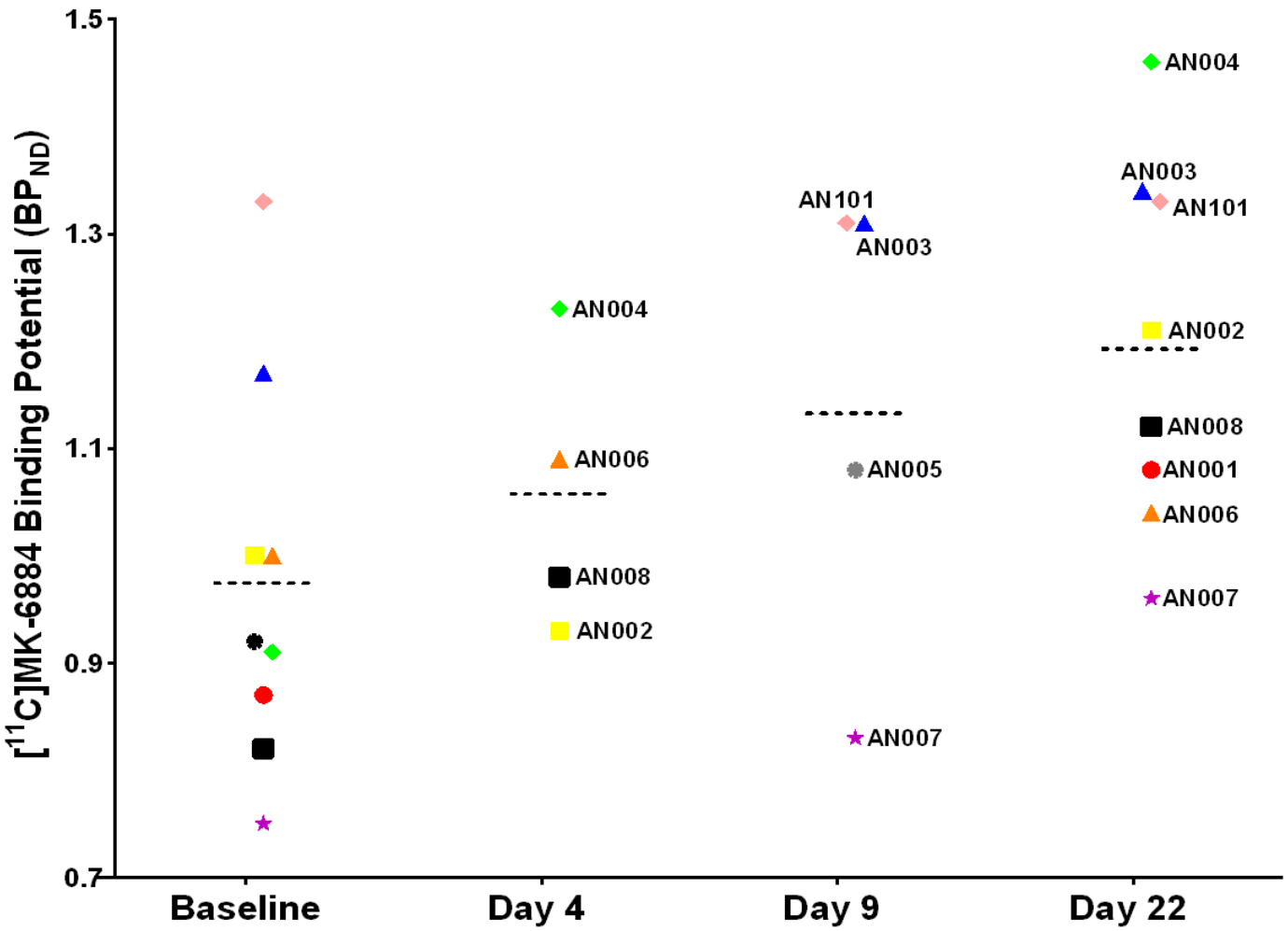
Donepezil dose-dependently enhances the Striatal BP_{ND} of [^{11}C]MK-6884 in HVs



1.2 fold (p=0.0076)
Increase in striatal BP_{ND}
at Day 22

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Conclusions

- BP_{ND} of [^{11}C]MK-6884 in monkey and HV increased by DPZ
  - Concentration-dependent => consistent with influence of cholinergic tone on M4PAM binding.
- Increase in striatal BP_{ND} more pronounced in monkey vs human.
- Minimal number of PET scans for optimal characterization of effect of altered ACh tone on [^{11}C]MK-6884 binding in human.
- Evidence of potential utility of [^{11}C]MK-6884 for assessment of receptor occupancy of M4PAMs

Data could aid in development of a model that would inform dose adjustments of M4PAM compounds in AD patients who are taking AChEI, thereby avoiding the development of adverse events while providing maximal efficacy.

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