

### INTRODUCTION

Scopolamine is a non-selective, muscarinic receptor antagonist used in clinical research as a cholinergic challenge test resulting in cognitive impairment. The test induces temporary memory deficits similar to that seen in dementia or psychiatric diseases. Enhanced sensitivity to scopolamine in elderly has been attributed to a subclinical neuronal cholinergic reduction [1] which has led to a dose reduction for this population [2].

The objective of this study was to describe the pharmacokinetics (PK) and pharmacodynamic (PD) effects of scopolamine in subjects in a broad age-range to determine the age-related sensitivity to the drug.

### METHODS

- Data from 4 different studies with 139 healthy subjects were obtained (3 studies were placebo controlled), where adults (18 – 65 years) received 0.5 mg and elderly (> 65 years) 0.3 mg scopolamine, during a 15 minute IV infusion.
- Two neuro-cognitive PD marker were selected from the NeuroCart test battery: adaptive tracker performance test (ATT, 2142 data points) and saccadic peak velocity (SPV, 2067 data points).
- A sequential, population approach, non-linear mixed effect PK-PD analysis was performed (NONMEM 7.2).

### RESULTS

- A two-compartment PK model with age and bodyweight as covariates (Eq. 1 and 2) accurately described the PK (Table 1).
- An indirect maximum effect model with an effect compartment best described the ATT and SPV data (Fig. 1 & 2).
- No relationship between ATT and  $EC_{50}$  versus age could be identified (Fig. 3)
- Although a slight trend in the  $EC_{50}$  of SPV versus age can be observed at high age, no relationship could be quantitated (Fig. 4).

$$Eq. 1 \quad CL = e^{\left\{[\log(\theta_1)] + [\theta_5 \cdot \log(\frac{AGE}{28})] + [\theta_6 \cdot \log(\frac{WGT}{78.5})] + [\eta]\right\}}$$

$$Eq. 2 \quad V_2 = e^{\left\{[\log(\theta_4)] + [\theta_7 \cdot \log(\frac{WGT}{78.5})] + [\eta]\right\}}$$

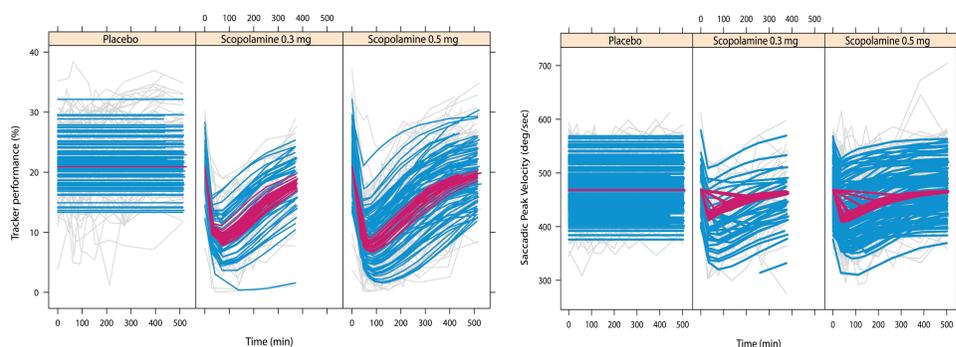


Fig. 1: Performance vs. time for ATT (left) and SPV (right) per dose group. Grey lines: lines through the observations, magenta lines: population predictions, blue lines: individual predictions.

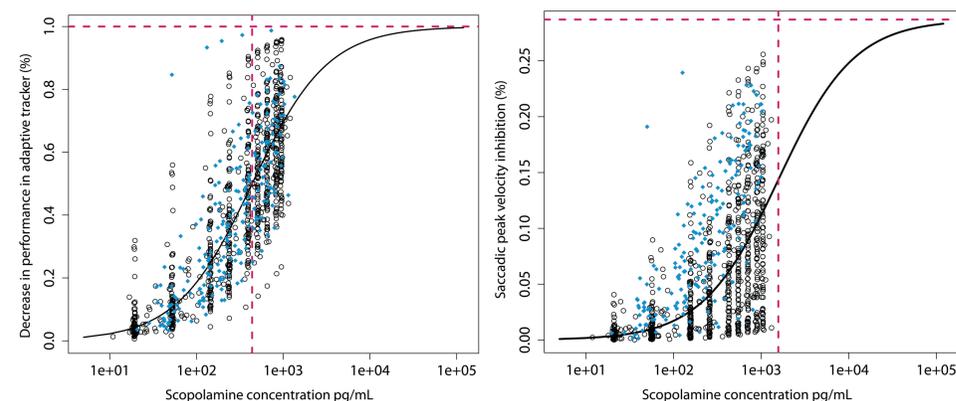


Fig. 2: Scopolamine concentration vs. effect in the ATT (left) and SPV (right) tests. Black line: population concentration-effect relationship, blue dots: observations in adults, black circles: observations in elderly, vertical dashed line: population  $EC_{50}$ , horizontal dashed line: population  $E_{max}$ .

### CONCLUSIONS

Neuro-cognitive effects of scopolamine on ATT and SPV in healthy subjects could be solely contributed to age-dependent differences in exposure and not age-related hypersensitivity to the drug.

	Parameter	Estimate	S.E.	IIV ( $\eta$ )	S.E.
PK	CL ( $\theta_1$ )	1.09 L · min <sup>-1</sup>	0.096	0.011	0.0017
	V <sub>1</sub>	2.66 L	1.050	0.438	0.1390
	Q	1.01 min <sup>-1</sup>	0.247	-	-
	V <sub>2</sub> ( $\theta_4$ )	62.10 L	10.100	0.009	0.0024
	$\theta_5$	-0.12	0.019	-	-
	$\theta_6$	0.56	0.097	-	-
	$\theta_7$	0.38	0.120	-	-
	$\sigma$ (prop)	0.045	-	-	-
Adaptive Tracker Test	$EC_{50}$	437.90	35.868	0.778	0.178
	K <sub>in</sub>	0.715	0.0544	0.041	0.006
	K <sub>out</sub>	0.034	0.0026	-	-
	E <sub>max</sub>	1	-	-	-
	$\sigma$ (prop)	0.066	-	-	-
Saccadic Peak Velocity	$EC_{50}$	1567.40	99.958	2.56	0.587
	K <sub>in</sub>	16.61	1.711	0.01	0.001
	K <sub>out</sub>	0.03	0.003	-	-
	E <sub>max</sub>	0.29	0.001	-	-
	$\sigma$ (prop)	0.003	-	-	-

Table 1: Parameters estimates. S.E.: standard error, IIV: Inter Individual Variability. prop: proportional error.

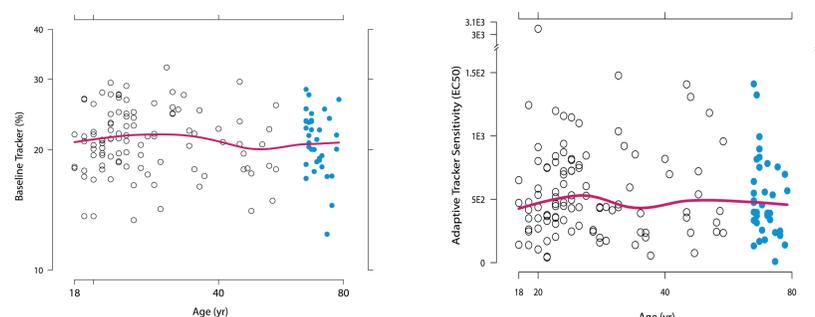


Fig. 3: Individual baseline estimates vs. age (left) and individual  $EC_{50}$  estimates (right) for ATT. Blue dots: adults, blue circles: elderly, magenta line: local polynomial regression.

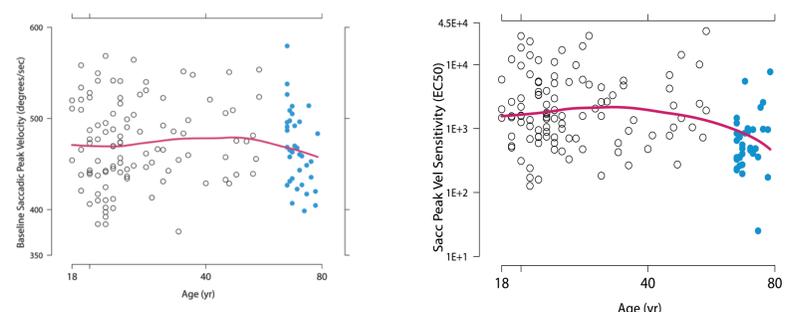


Fig. 4: Individual parameter estimates vs. age for baseline (left) and  $EC_{50}$  (right) for SPV. Blue dots: adults, blue circles: elderly, magenta line: local polynomial regression.

### REFERENCES

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- Flicker C, Ferris SH & Serby M. Hypersensitivity to scopolamine in the elderly. Psychopharmacology (Berl). 1992;107(2-3):437-41.

