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Study No: GHP:89:17				
Title: A study to evaluate the effects of GR68755 on memory and information processing when co-administered with scopolamine in young healthy volunteers				
Rationale: Scopolamine has been shown to disrupt information processing performance, verbal memory and vigilance in humans. Alosetron (GR68755), is a selective antagonist at the 5-hydroxytryptamine type 3 (5-HT ₃) receptor. This study was undertaken to investigate the effect of a single intravenous (IV) dose of alosetron with a single intramuscular (IM) dose of scopolamine on memory and information processing.				
Phase: I				
Study Period: 22 January 1989 – 13 February 1989.				
Study Design: A randomised, double-blind, four-way crossover study.				
Centres: One centre in, UK.				
Indication: None.				
Treatment: Subjects received a single IM injection of scopolamine 400 µg or placebo followed immediately by an IV infusion of placebo, or alosetron 10 µg, or alosetron 250 µg, over 1 minute. Four treatment regimens were administered, each separated by a 7-day washout period: Treatment A: placebo + placebo Treatment B: scopolamine 400 µg + placebo Treatment C: scopolamine 400 µg + alosetron 10 µg Treatment D: scopolamine 400 µg + alosetron 250 µg.				
Objectives: To evaluate the effect of alosetron on a 'model' of cognitive dysfunction produced by administration of scopolamine.				
Statistical Methods: A battery of tests was used to investigate verbal and non-verbal memory, rapid visual information processing and logic. Tests were carried out at 1 and 3 h post-dose. All variables except the delayed recall of words and the data from the delayed spatial memory task were subjected to an analysis of variance allowing for effects due to subjects, periods and treatments. A test for carry-over effects was also conducted.				
Study Population: Healthy male subjects, aged 18-30 years, weighing between 60-90Kg and non-smokers.				
Number of Subjects:				
Planned N				20
Dosed N				20
Completed n (%)				20 (100)
Total Number Subjects Withdrawn N (%)				0
Withdrawn due to Adverse Events n (%)				0
Withdrawn due to Lack of Efficacy n (%)				0
Withdrawn for Other Reasons n (%)				0
Demographics				
N (ITT)				20
Females : Males				All male
Mean Age in Years [range]				26.4 [18 – 37]
Mean Weight in kg [range]				75 [60 – 90]
White n (%)				Not stated
Pharmacodynamics: Key data (difference from baseline) from the test battery of cognitive tests are presented below. All values represent the difference between scopolamine-placebo and alosetron-scopolamine.				
Parameter Difference (95%CI)	Hours post-dose	Scopolamine (400 µg)	Alosetron 10 µg + scopolamine	Alosetron 250 µg + scopolamine
Verbal memory – immediate recall (number correct out of 30)	1	-5.4 (-7.3, -3.4)	1.3 (-0.7, 3.2)	1.1 (-0.8, 3.0)
	3	-4.8 (-6.7, -2.9)	-0.5 (-2.4, 1.3)	-0.3 (-2.1, 1.6)
Spatial memory (number correct out of 20)	1	-2.4 (-4.2, -0.6)*	1.4 (-0.3, 3.1)*	0.8 (-0.9, 2.5)*
	3	-3.0 (-4.7, -1.3)*	1.8 (0.1, 3.5)*	0.9 (-0.8, 2.7)*
Rapid Visual Information	1	-6.5 (-11.9, -1.1)*	0.3 (-5.2, 5.8)*	-5.2 (-10.4, 0.0)*

Processing task (number correct out of 80)	3	-7.7 (-12.7, -2.7)*	(-4.1, 6.1)*	-3.0 (-8.0, 2.0)*
Baddeley logic test (number correct out of 64)	1	-1.4 (-4.1, 1.3)	-1.1 (-3.9, 1.6)	-1.9 (-4.7, 0.8)
	3	-1.5 (-4.4, 1.3)	1.1 (-1.8, 4.0)	-0.3 (-3.1, 2.6)
Visual Analogue Scales (summary alertness score)	1	-25.6 (-35.4, -15.8)*	-5.1 (-14.8, 4.5)*	-9.1 (-18.7, 0.5)*
	3	-19.3 (-30.9, -7.7)*	-11.5 (-23.2, 0.2)*	-7.3 (-18.7, 4.2)*
Visual Analogue Scales (alert/drowsy scale mm)	1	-24.7 (-38.6, -10.9) *	-8.1 (-21.4, 5.2) *	-7.8 (-21.1, 5.4) *
	3	-22.1 (-38.9, -5.3) *	-14.3 (-30.7, 2.2) *	-4.7 (-20.7, 11.4) *
Visual Analogue Scales (Summary calmness score mm)	1	-6.1 (-13.5, 1.3) *	0.5 (-6.7, 7.8) *	-3.8 (-11.0, 3.5) *
	3	-4.0 (-13.2, 5.3) *	-1.7 (-11.0, 7.6*)	-3.9 (-13.0, 5.2) *
Visual Analogue Scales (Summary happiness/sociability score mm)	1	-9.4 (-15.9, -3.0) *	-4.7 (-10.9, 1.6)*	-1.6 (-7.8, 4.7) *
	3	-4.8 (-11.8, 2.2) *	0.7 (-6.2, 7.7) *	-2.6 (-9.5, 4.2) *

* = Adjusted for design imbalance.

Parameter Difference from baseline	Hours post-dose	Placebo	Scopolamine (400 µg)	Alosetron 10 µg + scopolamine	Alosetron 250 µg + scopolamine
Verbal memory – Median delayed recall (number correct out of 30)	1	-2.0	-4.0 p=0.001* ¹	-3.5 p=0.424* ²	-3.0 p=0.319* ²
	3	-1.0	-4.0 p=0.001* ¹	-3.0 p=0.493* ²	-2.5 p=0.404* ²
Visuospatial memory task – Easy (trials to success)	1	0.0	5.0 p<0.001* ¹	4.0 p=0.628* ²	4.0 p=0.742* ²
	3	0.0	3.0 p=0.273* ¹	3.5 p=0.234* ²	1.0 p=0.539* ²
Visuospatial memory task – Medium (trials to success)	1	3.0	4.5 p=0.123* ¹	10.0 p=0.200* ²	9.5 p=0.314* ²
	3	2.0	11.0 p<0.001* ¹	6.0 p=0.206* ²	9.5 p=0.465* ²
Visuospatial memory task – Difficult (trials to success)	1	2.0	3.0 p=0.164* ¹	5.5 p=0.503* ²	4.0 p=0.366* ²
	3	0.5	6.0 p=0.056* ¹	4.5 p=0.958* ²	5.0 p=0.292* ²

*¹ compared to placebo

*² compared to scopolamine

Safety results:

Adverse Events:	Placebo	Scopolamine (400 µg)	Alosetron 10 µg + scopolamine	Alosetron 250 µg + scopolamine
N (ITT)	20	20	20	20
No. subjects with AEs n (%)	7 (35)	11 (55)	10 (50)	8 (40)
Most frequent AEs				
Headache	4 (20)	2 (10)	3 (15)	2 (10)
Red hands	2 (10)	6 (30)	5 (25)	4 (20)

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

No. subjects with SAEs n (%) -includes fatal and non-fatal events	0	0	0	0
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Publications:

No publication

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