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Study No: C92-006	
Title: To assess the effects of GR68755C on psychological and psychomotor responses to amphetamine in healthy volunteers.	
Rationale: Alosetron (GR68755) is a selective antagonist at serotonin type 3 receptors (5-hydroxytryptamine, 5-HT ₃). The present study assessed the effects of alosetron in healthy subjects administered moderate doses of amphetamine in order to produce psychological and psychomotor responses similar to those observed in patients with schizophrenia and mania.	
Phase: I	
Study Period: September 2002 – April 2003	
Study Design: A randomised, double-blind, double-dummy, four-way crossover study.	
Centres: One centre in the, UK.	
Indication: None.	
Treatment: Subjects received a single oral dose of alosetron 2 mg or placebo followed 30 minutes later by a single oral dose of amphetamine 20 mg or placebo. Four treatment regimens were administered randomly on treatment days separated by a 7- to 14-day washout period: Treatment A: Alosetron placebo + Amphetamine placebo Treatment B: Alosetron 2 mg + Amphetamine placebo Treatment C: Alosetron placebo + Amphetamine 20 mg Treatment D: Alosetron 2 mg + Amphetamine 20 mg.	
Objectives: To assess the effects of alosetron on changes in visual analogue scales (VAS) of hunger, alertness, mind-racing and feeling bothered induced by amphetamine..	
Statistical Methods: Subjects completed VAS testing 60 and 50 minutes prior to dosing, and for 3 hours post-dose of amphetamine (or placebo) at 20 minute intervals. VAS categories were as follows: Mood/arousal (confident, cheerful, mind racing, alert, restless, lethargic), Hunger (hungry, strong wish to eat), Reinforcement (feeling good, getting a buzz) and Suspiciousness (feeling bothered, feeling of being treated fairly). Weighted mean VAS scores were analysed using analysis of covariance (ANCOVA), allowing for the effects subject, treatment and study period. Two psychomotor tests, a Simple Reaction Time (SRT) Test and Rapid Visual Information Processing (RVIP) Test, were completed 50 minutes prior to dosing and at 2 hours 20 minutes post-dose of amphetamine (or placebo). The SRT Test measured speed of response to computer generated visual stimulus. The RVIP Test measured speed and accuracy of response in spotting numerical sequences of 3 consecutive odd or even digits within computer-generated number sequences. Mean reaction time for both tests, and mean number correct per minute for the RVIP Test, were analysed using ANCOVA, allowing for effects due to subjects, treatment and study period. Time taken to eat the meal given to all subjects post-dosing was recorded, as was the weight of food consumed and the number of calories consumed was derived from this data, analysed using ANCOVA, allowing for the effects subject, treatment and study period. A VAS for satiety was completed 10 minutes prior to and post meal. Subjects completed a GRS of 0–4 (0 = normal) at the end of each study period to record how they had felt during the study, 95% CIs were calculated and treatments were analysed pair-wise.	
Study Population: Healthy male subjects aged 18-45years. Subjects who drank more than 8 cups of coffee or tea per day or who smoked >10 cigarettes (or equivalent) per day were excluded. Vegetarian subjects were also excluded	
Number of Subjects:	
Planned N	24
Dosed N	26
Completed n (%)	25 (96)
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 (%)	1 (4)
Demographics	
N (ITT)	26

Females : Males	All male		
Mean Age in Years [range]	28.4 [20 – 41]		
Mean Weight in kg [range]	78.0 [58.2 – 99.9]		
White n (%)	Not reported		
Pharmacodynamic Endpoints: A summary of statistically significant Visual Analogue Scale results are presented in the following table.			
VAS category	Treatment comparison	Estimate	95% CI
Hunger (mm)	Amphetamine – placebo	-9	-13, -5
	Alosetron – placebo	1	-2, 5
	Alosetron + amphetamine – amphetamine	3	-1, 7
	Alosetron + amphetamine – alosetron	-8	-12, -4
Alertness (mm)	Amphetamine – placebo	9	5, 13
	Alosetron – placebo	0	-3, 4
	Alosetron + amphetamine – amphetamine	1	-3, 5
	Alosetron + amphetamine – alosetron	9	5, 13
Mind racing (mm)	Amphetamine – placebo	7	3, 12
	Alosetron – placebo	0	-4, 5
	Alosetron + amphetamine – amphetamine	0	-4, 5
	Alosetron + amphetamine – alosetron	7	3, 11
Feeling bothered (mm)	Amphetamine – placebo	0	-1, 2
	Alosetron – placebo	-1	-3, 1
	Alosetron + amphetamine – amphetamine	0	-2, 2
	Alosetron + amphetamine – alosetron	1	-1, 3
Confidence (mm)	Amphetamine – placebo	4	2, 7
	Alosetron – placebo	0	-2, 2
	Alosetron + amphetamine – amphetamine	0	-2, 2
	Alosetron + amphetamine – alosetron	4	2, 7
Cheerfulness (mm)	Amphetamine – placebo	4	2, 7
	Alosetron – placebo	0	-3, 2
	Alosetron + amphetamine – amphetamine	0	-2, 3
	Alosetron + amphetamine – alosetron	5	3, 7
Restlessness (mm)	Amphetamine – placebo	2	-1, 6
	Alosetron – placebo	0	-3, 3
	Alosetron + amphetamine – amphetamine	2	-1, 5
	Alosetron + amphetamine – alosetron	5	2, 8
Lethargy (mm)	Amphetamine – placebo	-8	-12, -4
	Alosetron – placebo	-1	-5, 2
	Alosetron + amphetamine – amphetamine	0	-4, 4
	Alosetron + amphetamine – alosetron	-7	-11, -3
Desire to eat (mm)	Amphetamine – placebo	-11	-15, -6
	Alosetron – placebo	1	-3, 6
	Alosetron + amphetamine – amphetamine	1	-3, 6
	Alosetron + amphetamine – alosetron	-10	-15, -6
Feeling of being fairly treated (mm)	Amphetamine – placebo	1	-1, 2
	Alosetron – placebo	0	-1, 2
	Alosetron + amphetamine – amphetamine	1	0, 3
	Alosetron + amphetamine – alosetron	1	0, 3
Feeling good (mm)	Amphetamine – placebo	9	5, 14
	Alosetron – placebo	1	-4, 5
	Alosetron + amphetamine – amphetamine	0	-5, 4
	Alosetron + amphetamine – alosetron	8	4, 13
Getting a buzz (mm)	Amphetamine – placebo	7	3, 11
	Alosetron – placebo	0	-4, 4
	Alosetron + amphetamine – amphetamine	1	-3, 5
	Alosetron + amphetamine – alosetron	7	4, 11

A summary of Rapid Visual Information Processing data, number correct per minute (ms), is presented in the following table.				
Treatment comparison	Estimate	95% CI		
Amphetamine – placebo	0.6	0.3, 0.9		
Alosetron – placebo	0.3	0.0, 0.6		
Alosetron + amphetamine – amphetamine	0.1	-0.2, 0.4		
Alosetron + amphetamine – alosetron	0.4	0.2, 0.7		
The following table presents treatment comparisons for the choice reaction time (ms).				
Treatment comparison	Estimate	95% CI		
Amphetamine / placebo	0.98	0.95, 1.03		
Alosetron / placebo	0.99	0.95, 1.03		
Alosetron + amphetamine / amphetamine	0.98	0.94, 1.02		
Alosetron + amphetamine / alosetron	0.97	0.93, 1.01		
The following table presents treatment comparisons of total calorie intake during the study.				
Treatment comparison	Estimate	95% CI		
Amphetamine - placebo	-1846	-2648, -1045		
Alosetron – placebo	68	-716, 853		
Alosetron + amphetamine – amphetamine	-32	-834, 770		
Alosetron + amphetamine – alosetron	-1946	-2736, -1157		
Safety results: Adverse events (AEs) were collected throughout the study and were recorded using standard questioning techniques.				
Adverse Events:	Treatment regimen			
	Alosetron placebo + Amphetamine placebo	Alosetron 2 mg + Amphetamine placebo	Alosetron placebo + Amphetamine 20 mg	Alosetron 2 mg + Amphetamine 20 mg
N (ITT)	26	26	26	26
No. subjects with AEs n (%)	6 (23)	3 (12)	4 (15)	3 (12)
Most Frequent AEs				
Insomnia	1	0	3	5
Headache	1	3	2	2
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 (%) -include fatal and non-fatal events	0	0	0	0
Publications: No publication				

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