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Study No: GHP:90:27				
Title: A study to investigate the duration of effect of oral GR68755 on intradermal 5-HT induced flare response in volunteers				
Rationale: Alosetron (GR68755) is a 5-hydroxytryptamine receptor type 3 (5-HT ₃) antagonist. Intradermal injection of 5-HT into human skin produces a local erythema, followed by an axon-reflex flare response. The present study investigates the duration of effect of a single oral dose of alosetron on 5-HT ₃ receptor activity, over 12 h, using 5-HT-induced flare response as a model. Based on pharmacodynamic data from rat, mouse, primate and human models of central nervous system disorders and flare response, alosetron doses of 50, 250 and 1000 µg were evaluated.				
Phase: I				
Study Period: 5 November 1990 – 28 November 1990.				
Study Design: A double-blind, randomised, four-way, crossover study.				
Centres: One centre in the UK.				
Indication: None.				
Treatment: On each of four study days, each subject received either placebo (100 mL grapefruit juice) or one of three oral doses of alosetron (50, 250 and 1000 µg in 100 mL grapefruit juice) administered 2 h after a light breakfast. Subjects were divided into two groups of six and each group was studied on separate days. There was a washout period of 1 week between treatment periods. On each occasion following alosetron, duplicate intradermal injections of 5-HT (160 µM) were made in 0.05 mL volumes into the skin of the back pre-dose and at 1, 2, 4, 8, and 12 h after alosetron or placebo administration.				
Objectives: To investigate the duration of effect of single, oral doses of alosetron on the flare response induced by intradermal 5-HT at time intervals over a 12-h period.				
Statistical Methods: For each time, subject and period, the mean of the duplicate responses on the left- and right-hand side of the back was calculated. The pre-dose measurement was then subtracted from the post-dose measurement. For each time, subject and period, these differences were then summarised by the weighted mean response over 12 h. An estimate of the ratio of the flare size at each dose of alosetron to that of placebo was calculated. The duration of action was taken as the total time period over which the post-treatment flare size was decreased by at least 25% from the pre-treatment flare size. The estimated duration of action was analysed using a method adapted from Koch's method.				
Study Population: Healthy male subjects, aged 18-50y. Subjects with highly pigmented, hairy or blemished skin on their back were excluded				
Number of Subjects:				
Planned N		12		
Dosed N		12		
Completed n (%)		12 (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)		12		
Females : Males		All male		
Mean Age in Years [range]		31 [24 – 44]		
Mean Weight in kg [range]		79 [56 – 92]		
White n (%)		Not stated		
Pharmacodynamic Endpoints: A summary of results is presented below.				
Weighted Mean Response (0–12 h)	Alosetron			Placebo
	50 µg	250 µg	1000 µg	
Geometric Mean	0.87	0.68	0.46	1.00
Decrease compared with placebo	12%	32%	54%	
	p = 0.046	p<0.001	p<0.001	
Linear trend per quadrupling dose 25% (confidence interval = 21%–30%) p<0.001				

Duration of Action of alosetron on 5-HT induced Flare response (hours)	Alosetron			Placebo
	50 µg	250 µg	1000 µg	
No. of subjects	12	12	12	12
Median	1.6	5.7	8.9	0
Mean	1.0	6.1	9.8	0
Lower quartile	0	3.2	7.7	0
Upper quartile	2.2	8.0	11.3	0
Comparisons				
Placebo	p=0.045	p=0.005	p=0.005	
Alosetron 50 µg		p=0.015	p=0.005	
Alosetron 250 µg			p=0.015	
Safety results: Adverse events (AEs) were collected throughout the study.				
Adverse Events:				
	Alosetron			Placebo
	50 µg	250 µg	1000 µg	
N (ITT)	12	12	12	12
No. subjects with AEs n (%)	3 (25)	7 (58)	4 (33)	4 (33)
Headache n (%)	3 (25)	7 (58)	4 (33)	4 (33)
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 SAEs	0		0	

Publications: No publication
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