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Study No: GHP:89:38	
Title: Initial safety and tolerability study with oral doses of GR68755 in human volunteers.	
Rationale: Alosetron (GR68755) is a serotonin (5-hydroxytryptamine, 5-HT) type 3 receptor antagonist with activity in several animal models of central nervous system disorders. An earlier safety and tolerance study in healthy subjects found no significant changes in biochemical or cardiovascular parameters with alosetron administered IV at doses up to 10 mg. This study further investigated the safety and tolerance of alosetron at oral doses up to 16 mg.	
Phase: I	
Study Period: 11 September 1989 – 16 November 1989.	
Study Design: A double-blind, placebo-controlled, three-period crossover study, in which placebo was randomised with two ascending doses of study drug.	
Centres: One centre in the UK.	
Indication: None.	
Treatment: Subjects were divided into five groups and received single doses of alosetron or placebo according to the following schedule. Group I: alosetron 500 µg, alosetron 1000 µg, placebo Group II: alosetron 1 mg, alosetron 2 mg, placebo Group III: alosetron 2 mg, alosetron 4 mg, placebo Group IV: alosetron 4 mg, alosetron 8 mg, placebo Group V: alosetron 8 mg, alosetron 16 mg, placebo. All treatments were administered orally as solutions in grapefruit juice. Subjects were randomised to treatment group, and the position of the placebo dose in the treatment series was randomised. There was an interval of at least 48 hours between successive doses.	
Objectives: To assess the safety and tolerance of increasing oral doses of alosetron 500 µg to 16 mg in healthy male subjects.	
Statistical Methods: No formal statistical analysis was performed on the pharmacodynamic /safety data. Pulse rate and blood pressure were summarised over time for each individual by calculating weighted means for the interval from 30 min to 6 h post-dose. ECG parameters were summarised by weighted means for the time interval 30 min to 2 h post-dose. Cognitive performance tests were administered 60min before dose and at 100 and 200min after the dose; data were assessed using differences from baseline or placebo, except for Bond-Lader scores where undifferenced data was analysed. . The following pharmacokinetic parameters were derived: the maximum measured concentration of alosetron in plasma (C _{max}); the time of the sample in which the C _{max} was measured (t _{max}); the terminal rate constant for alosetron in plasma; the terminal half-life (t _{1/2}) for alosetron in plasma; the area under the curve of plasma alosetron concentration versus time, extrapolated to infinity (AUC _∞). No formal statistical analysis was planned in this study. Group means with standard deviation for pharmacokinetic parameters were calculated.	
Study Population: Healthy male subjects aged 18 to 45 years, not weighing greater than 99Kg or less than 60Kg	
Number of Subjects:	
Planned N	15
Dosed N	15
Completed n (%)	14 (93)
Total Number Subjects Withdrawn N (%)	1 (7)
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	1 (7)
Demographics	
N (ITT)	15
Males	15
Mean Age in Years [range]	28 [20 – 42]
Mean Weight in kg [range]	77.2 [65.8 – 85.6]
Race, n (%)	[not reported]
Pharmacodynamic Endpoints: For pulse rate, blood pressure and ECG data, weighted means were calculated for	

each individual, and then summarised for the group.

The following table summarises pulse rate (beats/min)

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	55.9	0.7	55.4	3.0	56.4	3.0	55.3	4.6
1.0 mg	54.5	2.8	56.9	4.5	58.9	6.5	59.1	9.5
2.0 mg	53.6	2.9	58.6	3.6	54.1	5.6	57.9	5.7
4.0 mg	57.4	7.0	61.9	6.6	56.0	6.3	60.3	3.1
8.0 mg	59.4	6.2	61.0	7.8	57.4	6.4	58.8	7.2
16.0 mg	57.2	4.3	56.6	5.6	53.9	2.7	54.9	3.5

The following table summarises systolic blood pressure (mmHg)

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	110.3	3.1	111.0	4.1	115.9	6.9	107.4	1.9
1.0 mg	112.3	3.3	117.2	8.1	114.3	6.4	115.5	7.9
2.0 mg	109.3	6.3	117.2	8.2	115.7	9.9	116.5	8.9
4.0 mg	113.1	10.9	118.6	10.4	114.6	6.8	120.7	7.8
8.0 mg	114.4	9.5	119.8	9.5	117.2	7.8	119.0	9.9
16.0 mg	106.9	3.4	113.9	8.2	110.6	9.4	113.9	11.7

The following table summarises diastolic blood pressure (mmHg)

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	60.8	1.3	64.5	1.7	66.6	7.5	61.0	1.1
1.0 mg	64.5	4.4	69.9	5.9	68.1	4.8	68.9	3.5
2.0 mg	64.6	3.9	71.1	4.9	68.5	6.0	67.6	7.9
4.0 mg	67.2	7.3	72.2	6.9	69.1	6.8	74.3	5.6
8.0 mg	66.3	7.9	70.4	7.5	70.7	5.2	73.1	6.6
16.0 mg	60.2	0.5	64.7	0.9	63.3	6.9	65.9	8.9

ECG – Heart rate (beats/min)

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	54.8	2.0	54.1	3.3	56.3	4.5	51.6	3.5
1.0 mg	53.2	1.4	53.5	2.2	58.5	8.7	57.0	6.8
2.0 mg	53.8	2.5	55.5	2.2	57.5	5.3	57.7	7.9
4.0 mg	58.6	7.0	60.1	4.0	55.7	5.2	57.7	5.3
8.0 mg	60.1	6.2	58.1	6.6	58.9	6.5	58.1	7.7
16.0 mg	57.8	3.2	52.9	4.1	55.7	4.2	54.3	4.5

ECG – Pulse rate interval (msec)

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	164.0	11.1	164.5	13.1	156.0	11.1	152.8	9.8
1.0 mg	154.8	9.2	154.0	14.3	150.0	13.2	148.5	15.4
2.0 mg	159.3	10.5	159.8	15.5	157.3	20.7	157.2	16.1
4.0 mg	159.3	10.6	161.9	11.3	159.3	10.1	159.3	14.7
8.0 mg	162.3	17.8	163.1	19.7	164.3	19.3	158.8	17.0
16.0 mg	172.0	19.1	172.0	25.8	168.0	23.1	170.0	26.0

ECG – QRS interval (msec).

Dose	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD

Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	90.0	6.0	93.3	2.1	93.3	4.2	91.3	2.8
1.0 mg	100.4	11.5	100.8	11.0	100.0	10.7	98.0	10.4
2.0 mg	104.7	9.0	105.2	8.6	106.3	8.1	103.2	8.7
4.0 mg	100.7	14.0	99.9	15.1	99.3	14.5	99.7	13.0
8.0 mg	99.7	13.6	98.4	14.4	96.3	9.6	98.7	12.1
16.0 mg	102.0	5.3	101.3	6.0	99.3	6.4	98.0	8.2
ECG – QT interval (msec)								
	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	413.3	2.3	417.8	10.6	410.7	13.3	434.0	26.9
1.0 mg	416.8	3.3	418.8	10.0	413.6	18.2	410.7	19.5
2.0 mg	422.7	12.9	419.6	7.6	417.7	16.6	422.1	19.8
4.0 mg	414.7	23.3	409.8	18.9	424.0	26.9	413.9	18.8
8.0 mg	408.0	16.7	415.5	25.3	406.7	16.4	413.0	26.6
16.0 mg	413.3	6.4	432.8	15.4	416.0	13.1	431.8	18.1
ECG – QTc interval (msec)								
	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	391.0	7.3	392.1	7.8	391.5	9.7	397.5	14.4
1.0 mg	387.8	5.1	390.2	5.6	402.5	16.8	395.3	15.0
2.0 mg	395.8	10.5	399.2	9.6	403.8	10.4	408.1	16.9
4.0 mg	404.1	6.1	405.3	8.5	402.7	12.7	400.6	4.0
8.0 mg	402.4	5.6	402.9	8.2	397.5	8.9	399.0	13.3
16.0 mg	400.2	5.3	402.2	2.2	396.8	12.4	406.2	9.2
Iris diameter (×3 mm)								
	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	26.0	1.7	26.2	0.8	26.0	0.5	26.0	1.1
1.0 mg	24.5	1.8	24.6	1.6	24.5	1.8	24.5	1.4
2.0 mg	24.1	1.1	24.1	1.2	24.2	1.6	24.1	1.1
4.0 mg	24.8	0.8	24.8	0.8	24.4	1.1	24.6	0.8
8.0 mg	25.4	0.5	25.3	0.4	25.0	0.5	25.0	0.4
16.0 mg	25.5	0.5	25.3	0.5	25.3	0.3	25.2	0.8
Pupil diameter (×3 mm)								
	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	11.7	3.1	11.5	1.3	12.5	2.5	12.5	2.5
1.0 mg	11.0	2.1	11.0	1.3	11.9	1.6	11.5	1.2
2.0 mg	11.3	2.1	11.2	1.9	11.1	1.7	11.0	1.6
4.0 mg	11.8	1.8	12.1	2.0	11.8	2.4	12.4	2.0
8.0 mg	12.4	1.1	12.7	1.1	12.0	1.3	12.6	1.4
16.0 mg	12.2	1.3	12.4	1.1	11.2	1.8	11.4	1.4
Adjusted pupil/iris diameter ratio								
	Placebo				Alosetron			
	Baseline		Post-dose		Baseline		Post-dose	
Dose	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.5 mg	0.44	0.10	0.44	0.04	0.48	0.09	0.47	0.08
1.0 mg	0.44	0.07	0.44	0.04	0.48	0.04	0.47	0.04
2.0 mg	0.46	0.07	0.46	0.06	0.45	0.05	0.45	0.05
4.0 mg	0.47	0.07	0.49	0.07	0.47	0.08	0.50	0.07

8.0 mg	0.49	0.04	0.50	0.04	0.47	0.05	0.50	0.05
16.0 mg	0.47	0.04	0.49	0.04	0.44	0.07	0.45	0.05

The following tables present adjusted mean differences from baseline in cognitive performance test scores or, in the case of Bond-Lader factors, adjusted mean scores.

	CRT – mean reaction time (msec)		Bond-Lader Alertness Factor (mm)	
Dose	100 mins	200 mins	100 mins	200 mins
Placebo	3.8	-0.1	2230	2150
0.5 mg	-18.7	-22.5	2279	2254
1.0 mg	0.0	0.7	2294	2426
2.0 mg	26.4	-12.9	2207	2048
4.0 mg	2.7	13.8	2024	2041
8.0 mg	-31.4	-6.7	2202	2190
16.0 mg	-16.0	-30.0	2329	2087

N = Number of evaluable subjects.

CRT = Choice reaction test.

	Bond-Lader Factor 2 (mm)		Bond-Lader Factor 3 (mm)	
Dose	100 mins	200 mins	100 mins	200 mins
Placebo	1113	1126	479.4	480.8
0.5 mg	1132	1147	460.7	507.7
1.0 mg	1177	1177	462.2	505.2
2.0 mg	1135	1133	484.1	479.4
4.0 mg	1038	1125	479.6	487.1
8.0 mg	1156	1149	495.1	489.4
16.0 mg	1138	1086	485.9	481.3

N = Number of evaluable subjects.

	RVIP – mean reaction time (msec)		RVIP – no. of hits (10 mins)	
Dose	100 mins	200 mins	100 mins	200 mins
Placebo	-9.7	-14.2	1.5	1.1
0.5 mg	-2.2	6.0	-2.9	3.6
1.0 mg	24.2	35.1	2.5	2.1
2.0 mg	-10.5	-14.4	2.3	0.0
4.0 mg	-26.7	-10.3	3.5	5.9
8.0 mg	5.6	-29.7	5.1	1.3
16.0 mg	-38.7	-94.7	4.8	-1.0

N = Number of evaluable subjects.

RVIP = Rapid visual information processing.

	RVIP – no. of false alarms (10 min)	
Dose	100 mins	200 mins
Placebo	0.3	-0.4
0.5 mg	-0.9	-0.3
1.0 mg	-1.8	0.9
2.0 mg	1.9	0.2
4.0 mg	-2.1	-2.7
8.0 mg	-2.5	-2.9
16.0 mg	-1.3	-2.3

N = Number of evaluable subjects.

RVIP = Rapid visual information processing.

Pharmacokinetic Endpoints: Median [range]

Pharmacokinetic parameter	1 mg	2 mg	4 mg	8 mg	16 mg
C _{max} (ng/mL)	4.8 [2.4 – 5.0]	4.8 [2.1 – 14.8]	17.6 [11.7 – 31.0]	55.7 [27.5 – 83.0]	118.0 [50.7 – 152.0]
t _{max} (h)	1.0	1.0 [0.5 – 3.0]	2.0 [1.0 – 3.0]	1.5 [1.0 – 2.0]	0.98 [0.5 – 1.0]
t _{1/2} (h)	1.7	1.4	1.7	1.6	1.7

		[1.3 – 1.5]	[1.5 – 2.0]	[1.0 – 2.2]	[1.3 – 2.8]
AUC _∞ (ng.h/mL)	15.0	25.8 [22.6 – 29.0]	65.6 [36.5 – 110.9]	198.2 [52.7 – 326.5]	533.6 [107.2 – 562.0]
Safety results: Adverse events were collected throughout the study. A monocytosis was noted in association with placebo in one subject and after alosetron in two subjects. One subject had eosinophilia, which occurred after 8 mg and 16 mg doses of alosetron.					
Adverse Events:		Alosetron		Placebo	
N (ITT)		15		15	
No. subjects with AEs n (%)		4 (27)		0	
Most Frequent AEs					
Headache		3 (20)		0	
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	

Publications: No publication

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