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<b>Study No:</b> GHP:89:23							
<b>Title:</b> Initial safety and tolerability study with intravenous GR68755 in human volunteers.							
<b>Rationale:</b> The study was conducted to assess the safety and tolerance of escalating doses of intravenous alosetron/GR68755 in healthy male volunteers over a dose range of 1 µg to 10 mg in a double-blind, placebo-controlled study. The dose range was selected to initiate human intravenous dosing at an exposure level equivalent to one-tenth of that which affected any observable pharmacodynamic effect in animal models.							
<b>Phase:</b> I							
<b>Study Period:</b> 20 June 1989 – 20 July 1989.							
<b>Study Design:</b> Double-blind, placebo-controlled, randomised, crossover study in healthy subjects.							
<b>Centres:</b> One centre in the UK.							
<b>Indication:</b> None.							
<b>Treatment:</b> Ascending incremental intravenous doses of alosetron, or placebo (normal saline), were given in a randomised crossover on 10 separate days to five groups of three subjects as follows: Dosing days 1 and 2: 1, 2, 4 and 8 µg. Total = 15 µg or placebo. Dosing days 3 and 4: 8, 16, 32 and 64 µg. Total = 120 µg or placebo. Dosing days 5 and 6: 64, 128, 256 and 512 µg. Total = 960 µg or placebo. Dosing days 7 and 8 = 0.25 mg, 0.5 mg, 1 mg and 2 mg. Total = 3.75 mg or placebo. Dosing days 9 and 10 = 1 mg, 2 mg, 3 mg and 4 mg. Total = 10 mg or placebo. In the incremental series, drug was infused for 15min, followed by a 15min observation period before the next dose was administered. Randomisation was such that on the first of each pair of dosing days, two subjects received placebo and only one subject received active drug.							
<b>Objectives:</b> To assess the safety and tolerance of incremental intravenous doses of alosetron, 1 µg to 10 mg in healthy male subjects.							
<b>Statistical Methods:</b> No formal statistical analysis was performed on the pharmacokinetic data from this safety and tolerance study, other than calculation of group means.							
<b>Study Population:</b> Healthy male subjects aged between 18 and 40 years.							
<b>Number of Subjects:</b>							
Planned N				14			
Dosed N				14			
Completed n (%)				14 (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Total Number Subjects Withdrawn N (%)				0			
Withdrawn due to Adverse Events n (%)				0			
Withdrawn due to Lack of Efficacy n (%)				0			
Withdrawn for Other Reasons n (%)				0			
<b>Demographics</b>							
N (ITT)				14			
Males				14			
Mean Age in Years [range]				32 [22 – 39]			
Mean Weight in kg [range]				78.1 [63.7 – 98.6]			
White n (%)				[not stated]			
<b>Pharmacokinetic Endpoints:</b> Pharmacokinetic analysis from the highest dose group (10 mg total infused in increments) is presented below.							
	<b>Observed values</b>			<b>Predicted values</b>			
<b>Subject</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>t<sub>1/2</sub> (h)</b>	<b>AUC<sub>∞</sub> (ng.h/mL)</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>AUC<sub>∞</sub> (ng.h/mL)</b>	<b>CL<sub>p</sub> (mL/min)</b>	<b>V<sub>d</sub> (L)</b>
13	121.0	1.6	223.4	70.3	89.2	747	103
14	125.0	1.7	217.9	87.8	111.2	600	91
15	107.0	2.7	349.0	65.4	171.1	390	92
<b>Median</b>	121.0	1.7	223.4	70.3	111.2	600	92
C <sub>max</sub> = maximum alosetron plasma concentration; t <sub>max</sub> = time at which C <sub>max</sub> was achieved; λ <sub>z</sub> = terminal rate							

constant for alosetron in plasma; $t_{1/2}$ = terminal half-life; $AUC_{\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; $CL_p$ = plasma clearance for alosetron; $V_d$ = apparent volume of distribution.		
<b>Safety results:</b> Adverse events (AEs) were collected throughout the study.		
<b>Adverse Events:</b>		
N (ITT)	14	
No. subjects with AEs n (%)	Placebo 2(14)	Alosetron 1(7)
Most Frequent AEs		
Headache	2(14)	1(7)
<b>Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:</b>		
No. subjects with SAEs, n (%) -includes fatal and non-fatal events	0 (0)	

<b>Publications:</b> No Publication
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