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Study No: C92-058				
Title: An investigation of the gender differences in the pharmacokinetics of GR68755C.				
Rationale: GR68755C/ alosetron is a potent, highly selective 5-hydroxytryptamine-3 antagonist under development for gastrointestinal indications. A previous study in elderly healthy subjects indicated a gender difference in the pharmacokinetics of oral alosetron. This study investigated the pharmacokinetics of alosetron 2 mg in both young and elderly subjects of both genders, following single intravenous (IV) and oral doses, to establish the nature and magnitude of any gender differences.				
Phase: I.				
Study Period: January to March 1993.				
Study Design: This was an open, two-way, randomised crossover, balanced for treatment study in four parallel groups comprised of the following: Young males aged 18 – 40 years. Young females aged 18 – 40 years. Elderly males aged 65 years or greater. Elderly females aged 65 years or greater.				
Centres: One centre in Germany.				
Indication: None.				
Treatment: Each subject received, in random order, alosetron 2 mg as an IV infusion (15 mL over 15 minutes) and as an oral 2 mg tablet. Treatment periods were separated by at least 7 days.				
Objectives: To determine the effect of gender on the pharmacokinetics of alosetron.				
Statistical Methods: The pharmacokinetic parameter values AUC from time zero to infinity (AUC_{∞}), maximum plasma concentration (C_{max}), terminal elimination constant (λ_z), clearance (CLs) and volume of distribution (V_{dss}) were analysed for the IV and oral formulations (not CLs and V_{dss}) separately. The analysis was conducted using analysis of variance (ANOVA) allowing for the effects owing to weight, sequences and subject groups, where the data were log-transformed before analysis. The values of time to C_{max} (t_{max}) for the oral formulation were compared on a pairwise basis using the Wilcoxon Rank Sum test. Analysis of bioavailability (F) was by ANOVA of log-transformed AUC_{∞} allowing for the effects owing to subject groups, sequences, subjects within subject groups and sequences, periods, treatments and the interaction between treatments and subject groups. The primary comparison was of young males with young females, and elderly males with elderly females. Additional comparisons were made of young males with elderly males, and young females with elderly females. For each comparison, estimates of the ratio of subject groups, together with the 90% confidence interval were calculated.				
Study Population: Twelve subjects per group (total 48) for each of the four groups defined by age and gender. All subjects were healthy, and in the elderly groups at least four of each gender were to be older than 70 years.				
Number of Subjects:				
	Young males	Elderly males	Young females	Elderly females
Planned N	12	12	12	12
Dosed N	12	12	12	13
Completed n (%)	12 (100)	12 (100)	12 (100)	12 (92)
Total Number Subjects Withdrawn N (%)	0	0	0	1 (8)
Withdrawn due to Adverse Events n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0	0
Withdrawn for Other Reasons n (%)	0	0	0	1 (8)
Demographics				
N (ITT)	12	12	12	13
Females: Males	0 : 12	0 : 12	12 : 0	13 : 0
Mean Age in Years [range]	27.4 [19 – 39]	69.8 [66 – 78]	29.7 [19 – 39]	70.3 [66 – 75]
Mean Weight in kg [range]	74.1 [61.1 – 86.5]	76.9 [61.2 – 90.8]	61.1 [53.3 – 70.3]	66.4 [57.9 – 76.8]
Race n (%)	Not recorded	Not recorded	Not recorded	Not recorded

Pharmacokinetic Endpoints: Mean (SD) pharmacokinetic findings are summarised in the table below.										
		AUC _∞ (ng. h/mL)	Cmax (ng/mL)	tmax (h) * median [range]	t _{1/2} (h)	CLs (mL/min)	λ _z (1/h)	Vd _{ss} (L)	F	
Y M	IV	49.4 (11.25)	40.2 (12.76)	0.25 [0.25 – 0.33]	1.5 (0.25)	675 (166.9)	0.4571 (0.08)	82 (17.52)	0.50	
	PO	24.8 (10.12)	9.4 (3.54)	1.00 [0.75 – 2.00]	1.4 (0.24)		0.4814 (0.09)			
Y F	IV	61.3 (38.20)	44.6 (14.02)	0.25 [0.25 – 0.42]	1.6 (0.40)	544 (260.8)	0.4309 (0.09)	65 (20.32)	0.49	
	PO	30.5 (32.84)	12.0 (7.72)	1.00 [0.50 – 2.00]	1.4 (0.41)		0.4918 (0.13)			
E M	IV	52.2 (12.26)	49.8 (8.13)	0.25 [0.25 – 0.25]	1.7 (0.20)	639 (171.9)	0.4095 (0.05)	83 (14.82)	0.51	
	PO	26.5 (11.60)	9.8 (4.41)	0.75 [0.50 – 2.00]	1.6 (0.21)		0.4315 (0.06)			
E F	IV	74.1 (23.98)	62.9 (16.97)	0.25 [0.25 – 0.25]	1.8 (0.31)	450 (123.2)	0.3852 (0.06)	62 (13.03)	0.63	
	PO	47.1 (27.68)	17.2 (8.88)	0.75 [0.50 – 1.50]	1.7 (0.36)		0.4118 (0.09)			
F = Absolute Bioavailability, YM = Young Males, YF = Young Females, EM = Elderly Males, EF =Elderly Females PO=oral										
PK Statistical comparison of treatments Estimate (90% CI)										
Comparison	Route	YF/YM		EF/EM		EM/YM		EF/YF		
AUC _∞ (ng.h/mL)	IV	124% (94, 164)		142% (109, 185)		106% (84, 133)		121% (95, 154)		
	PO	123% (73, 206)		178% (109, 289)		107% (70, 163)		155% (100, 239)		
C max (ng/mL)	IV	111% (89, 139)		126% (102, 156)		124% (103, 149)		141% (117, 171)		
	PO	127% (79, 207)		176% (112, 278)		104% (70, 155)		144% (95, 216)		
Cl s (ml/min)	IV	81% (61, 107)		70% (54, 92)		95% (75, 119)		83% (65, 105)		
Vd _{ss} (L)	IV	79% (66, 94)		74% (63, 88)		101% (87, 117)		95% (82, 111)		
λ _z (1/h)	IV	94% (81, 110)		94% (82, 108)		90% (79, 101)		89% (79, 102)		
	PO	102% (86, 122)		95% (81, 112)		90% (78, 103)		84% (72, 97)		
t _{1/2} (h)	IV	106% (91, 123)		106% (92, 122)		112% (99, 126)		112% (98, 127)		
	PO	98% (82, 117)		105% (98, 123)		112% (97, 129)		119% (103, 138)		
F	-	98% (76, 127)		124% (96, 160)		101% (79, 131)		128% (99, 165)		
T _{max} (h)*	PO	(-0.25, 0.25)		0.0 (-0.25, 0.00)		-0.13 (-0.25, 0.00)		-0.25 (-0.25, 0.00)		
* non-parametric analysis, Wilcoxon Rank Sum test used F = Absolute Bioavailability, YM = Young Males, YF = Young Females, EM = Elderly Males, EF =Elderly Females PO=oral										
Safety results:										
Adverse Events:			GR68755 2 mg IV				GR68755 2 mg PO			
N (ITT)			49				48			
No. subjects with AEs n %			11 (22)				15 (31)			
Group (M/F, age range y)			M 18-40	F 18-40	M ≥65	F ≥65	M 18-40	F 18-40	M ≥65	F ≥65
N per group			12	12	12	13	12	12	12	12
No. subjects with AEs n %			2 (17)	6 (50)	2 (17)	1 (8)	5 (42)	7 (58)	1 (8)	2 (17)
Most Frequent AEs: episodes (number of subjects)										
Headache n, (%)			2 (17)	6 (50)	1 (8)	1 (8)	3 (25)	6 (50)	0	1 (8)
Tiredness n, (%)			0	0	3 (25)	1 (8)	0	1 (8)	1 (8)	1 (8)

Serious Adverse Events, n (%)								
No. subjects with SAEs, n (%) None								
No. subjects with SAEs, n (%) – Includes fatal and non-fatal events	0	0	0	0	0	0	0	0

Conclusion: See publication below.
Publications: Sex and age differences in the pharmacokinetics of alosetron. Koch KM, Palmer, JL, Noordin N, Tomlinson JJ, Baidoo C Brit J Clin Pharm 2002 Mar;53(3):238-42

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