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Study No: S3B-201		
Title: A randomized, double-blind, placebo-controlled, crossover evaluation of the effects of GR68755C on plasma levels of haloperidol in patients with a diagnosis of schizophrenia.		
Rationale: GR68755C/alosetron was targeted for investigation for treatment of schizophrenia. This study was conducted to examine the effects of oral alosetron on the pharmacokinetics of haloperidol in subjects with schizophrenia or schizoaffective disorder.		
Phase: II		
Study Period: 11May - 18 November 1992		
Study Design: Randomized, double-blind, placebo-controlled, two-period crossover, multi-center study.		
Centers: Three centers in the US.		
Indication: Schizophrenia.		
Treatment: Subjects received a maintenance dose of haloperidol once-daily for the 8-week study period. Subjects were dosed with placebo once-daily for a 1-week run-in period after which they randomised to one of two treatments: Treatment A: alosetron 1 mg once-daily for 2 weeks. Treatment B: placebo once-daily for 2 weeks. After a 2-week washout period subjects received the alternate dosing regimen.		
Objectives: To evaluate the effects of oral alosetron on the pharmacokinetics of haloperidol.		
Statistical Methods: Pharmacokinetic parameters were analyzed on untransformed and log transformed data using analysis of variance, allowing for subject, period and treatment. For each parameter, geometric and arithmetic means and 95% confidence intervals (CIs) and median and harmonic mean for half-life ($t_{1/2}$) and elimination rate constant were estimated. Estimates for treatment difference and 90% CIs were calculated and tested for significance. Time to maximum plasma concentration (t_{max}) values were summarized by the treatment medians and compared between treatments using the Koch procedure. Corresponding 90% CIs for estimates of differences between treatment medians were derived, and 95% CIs of treatment medians were constructed using Wilcoxon signed rank statistics. All subjects who completed the study were included in the pharmacokinetic analyses. The safety analyses included all subjects who received at least one dose of study drug.		
Study Population: Males and female inpatient or outpatient subjects, aged 18 – 64 years, with a diagnosis of schizophrenia or schizoaffective disorder who had been receiving oral haloperidol (≥ 5 mg) for at least 4 weeks prior to study entry. Subjects with a history of seizures, abnormal bleeding tendencies or thrombophlebitis, impaired renal function or impaired hepatic function were excluded. Female subjects had to be post-menopausal or surgically sterilized.		
Number of Subjects:		
Planned N	36	
Dosed N	13	
Completed n (%)	11 (85)	
Total Number Subjects Withdrawn N (%)	2 (15)	
Withdrawn due to Adverse Events n (%)	0	
Withdrawn due to Lack of Efficacy n (%)	0	
Withdrawn for Other Reasons n (%)	2 (15)	
Demographics		
N (ITT)	13	
Females: Males	2:11	
Mean Age in Years (SD)	38.31 (10.64)	
Mean Weight in kg (SD)	86 (12.5)	
White n (%)	11 (85)	
Pharmacokinetic Endpoints: Results of the analysis of variance for the comparison of pharmacokinetic parameters of haloperidol with both treatments and assessment of dose proportionality are presented in the table below (mean \pm standard deviation). None of the results was statistically significant (at the 5% level).		
Parameters	Alosetron Mean (sd)	Placebo Mean (sd)
Cmax (ng/mL)	10.13 (5.72)	8.69 (5.58)

Cmin (ng/mL)	3.02 (1.68)	2.78 (1.58)
tmax (h)	2.50 (0.94)	5.10 (3.81)
t½ (h)	15.03 (4.52)	17.88 (12.91)
AUC (ng.h/mL)	123.6 (64.7)	104.3 (70.02)
Cavg (ng/mL)	5.15 (2.70)	4.35 (2.92)
Fluctuation (%)	154.5 (71.62)	148.7 (74.5)
Clearance/F (L/h)	78.23 (45.1)	104.7 (69.0)
Dose-normalized Cmax (ng/mL)	6.40 (2.13)	5.75 (2.81)
Dose-normalized Cmin (ng/mL)	2.00 (1.07)	1.90 (1.07)
Dose-normalized Cavg (ng/mL)	3.58 (2.17)	2.85 (1.66)
Dose-normalized AUC (ng.h/mL)	86.0 (52.2)	68.5 (39.9)

Cmax = maximum plasma concentration; Cmin = minimum plasma concentration; AUC = area under the curve; Cavg = average plasma concentration; tmax = time to Cmax; t½ = half-life; Fluctuation = % change from minimum to maximum concentration; Clearance = concentration-normalized elimination rate. F = systemic availability

Safety results:

Adverse Events:

N (ITT)	13	
	Placebo	Alosetron
No. of subjects	13	11
No. subjects with AEs n (%)	9 (69)	10 (91)
Most Frequent AEs n (%)		
Headache	4 (31)	3 (27)
Musculoskeletal pain	2 (15)	3 (27)
Dizziness	2 (15)	2 (18)
Xerostomia	1 (8)	2 (18)
Constipation	2 (15)	1 (9)
Malaise/fatigue	2 (15)	0
Nausea/vomiting	2 (15)	0
Sleep disturbance	2 (15)	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
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Publications:

No Publication.

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