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<b>Study No:</b> S3B10938	
<b>Title:</b> An open-label, randomized, two-period, cross-over trial to evaluate the effect of alosetron (1 mg PO BID for 2 days) on the pharmacokinetics of single-dose alprazolam (1 mg PO) in healthy subjects.	
<b>Rationale:</b> Alprazolam is a short-acting benzodiazepine that is extensively metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme. As alprazolam may be prescribed for people with irritable bowel syndrome, the potential for interaction with alosetron is of interest. Although <i>in vitro</i> and <i>in vivo</i> data indicate that alosetron has no impact on the activity of the CYP3A4 isoenzyme, this study was undertaken to confirm the absence of any <i>in vivo</i> interaction between alosetron and alprazolam in terms of alprazolam pharmacokinetics in healthy subjects.	
<b>Phase:</b> I	
<b>Study Period:</b> 18 November 1999 – 18 January 2000.	
<b>Study Design:</b> This was an open-label, single-center, randomized, two-period, crossover trial in healthy subjects.	
<b>Centers:</b> One center in the USA.	
<b>Indication:</b> None.	
<b>Treatment:</b> After a screening period of no more than 14 days prior to Day 1 of Treatment Period 1, subjects were randomised to receive one of two treatments, Treatment A: alprazolam 1 mg single dose or Treatment B: alprazolam 1 mg single dose, plus alosetron 1 mg (administered twice-daily for 2 days). Following a between treatment washout period of 4 days (providing a 6-day interval between alprazolam doses), subjects received the alternate treatment. For each treatment period serial blood samples were collected pre-dosing with alprazolam on Day 1 and up to 12 hours post dose, with additional samples collected on Day 2 (24 h) and Day 3 (36 h) for determination of plasma alprazolam concentration. Adverse events were collected at Screening, during Treatment Period 1 and Treatment Period 2 and post-study.	
<b>Objectives:</b> To determine the effect of concomitant administration of multiple-dose alosetron 1 mg po bid for 2 days on the pharmacokinetics of single-dose alprazolam 1 mg po in healthy subjects.	
<b>Statistical Methods:</b> Alprazolam pharmacokinetic parameters area under the plasma concentration-time curve to $\infty$ ( $AUC_{\infty}$ ), area under the plasma concentration-time curve to last measurable concentration ( $AUC_{last}$ ), maximum plasma concentration ( $C_{max}$ ), time to $C_{max}$ ( $t_{max}$ ), terminal half-life ( $t_{1/2}$ ) and terminal plasma rate constant ( $\lambda_z$ ) were summarized using descriptive statistics. Comparisons for evaluation of a drug interaction were the alprazolam pharmacokinetic parameters $AUC_{\infty}$ and $C_{max}$ obtained on single-dose alprazolam compared with alprazolam plus alosetron. With the exception of $t_{max}$ , the pharmacokinetic parameters were analyzed using analysis of variance models allowing for subject, period, sequence and treatment effects. Both $\log_e$ -transformed and untransformed analyses were carried out. For each treatment geometric mean, 95% confidence intervals were constructed. $t_{max}$ was analyzed using the standard Koch procedure. Vital signs (blood pressure, heart rate and temperature), clinical laboratory tests and adverse events (AEs) were described using descriptive summary statistics or frequencies and proportions. No formal statistical analyses of safety endpoints were carried out. All subjects who received at least one dose of study medication were included in the safety population. Subjects who provided evaluable pharmacokinetics results during each of the treatment periods were included in the pharmacokinetic population.	
<b>Study Population:</b> Healthy, non-smoking male and female subjects aged 18 – 50 years with a body mass index within the range 19 – 29 kg/m <sup>2</sup> and weight of 50 – 90 kg for females and 55 – 95 kg for males. Subjects were excluded from the study if they had taken warfarin in the previous 2 months, dextrometorphan, sumatriptan, dopaminergic agents such as selegiline, a prescription monoamine oxidase inhibitor, antidepressants such as amoxapine, nortriptyline, desipramine, doxepin, trimipramine maleate, imipramine and protriptyline hydrochloride, or an antipsychotic agent such as thiorazine or lithium or had a history of hypersensitivity reaction to any component of the study treatment or any drug chemically-related to the study treatments. Subjects were also excluded if they had any predisposing condition that might interfere with the absorption, distribution, metabolism or excretion of drugs, any previous gastrointestinal surgery (except appendectomy or cholecystectomy more than 3 months prior to the study).	
<b>Number of Subjects:</b>	
Planned N	12
Dosed N	13
Completed n (%)	12 (92)

Total Number Subjects Withdrawn N (%)	1 (8)
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	1 (8)
<b>Demographics</b>	
N (ITT)	13
Females: Males	9: 4
Mean Age in Years (SD)	32.7 (9.8)
Mean Weight in kg (SD)	71.95 (8.93)
White n (%)	6 (46)

**Pharmacokinetic Endpoints:** The table below summarises the pharmacokinetic findings in terms of geometric mean and 95% confidence intervals (with the exception of tmax, for which data is provided as median [range]).

Parameters (unit)	Alprazolam 1 mg (A)	Alprazolam 1 mg + alosetron 1 mg (B)
AUC <sub>∞</sub> (ng.h/mL)	210.3 (175.4, 252.3)	202.5 (173.8, 235.8)
Cmax (ng/mL)	13.5 (11.4, 16.0)	12.5 (11.0, 14.1)
t <sub>1/2</sub> (h)	13.1 (11.0, 15.7)	13.9 (11.5, 16.8)
λ <sub>Z</sub> (h <sup>-1</sup> )	0.05 (0.04, 0.06)	0.05 (0.04, 0.06)
tmax (h) <sup>a</sup>	1.0 [0.5, 4.0]	1.0 [0.5, 4.0]

. A summary of the log<sub>e</sub>-transformed analysis for the assessment of drug interaction is presented in the table below.

Parameters	Ratio (B:A)	90% confidence interval	p-value
AUC <sub>∞</sub> (ng.h/mL)	0.96	0.91, 1.02	0.254
Cmax (ng/mL)	0.93	0.79, 1.08	0.385
t <sub>1/2</sub> (h)	1.06	0.96, 1.17	0.291
λ <sub>Z</sub> (h <sup>-1</sup> )	0.94	0.86, 1.04	0.294
tmax (h) <sup>a</sup>	0.00 (B – A)	-0.75, 0.29	0.655

A: alprazolam alone, B: alprazolam plus alosetron

a = The analysis of tmax was based on non-transformed data using the non-parametric methods and comparisons were based on median differences between treatments with an approximate 90% confidence interval.

**Safety results:**

Adverse Events:	Alprazolam 1 mg	Alprazolam 1 mg + alosetron 1 mg
N (ITT)	13	12
No. subjects with AEs n (%)	6 (46)	7 (58)
Most Frequent AEs		
Hypnagogic effects n (%)	4 (31)	7 (58)
Abdominal discomfort/pain n (%)	0	2 (17)
<b>Serious Adverse Events:</b>		
No. subjects with SAEs -includes fatal and non-fatal events	0	0

**Conclusion:**

See publication below

**Publications:**

D'Souza DL, Levasseur LM, Nezamis J, Robbins DK, Simms L, Koch KM Effect of alosetron on the pharmacokinetics of alprazolam J Clin Pharm 2001;41(4):452-454

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