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Study No: S3B10936	
Title: An open-label, non-randomized, cross-over trial to evaluate the effect of alosetron (1 mg PO BID for 5 days) on the pharmacokinetics of single-dose amitriptyline (Elavil) administration in healthy subjects.	
Rationale: Amitriptyline is a tricyclic antidepressant that is often prescribed in the alosetron target female population. The principal metabolic pathway for amitriptyline involves the cytochrome P450 (CYP) 2D6 isoenzyme and drugs that have the potential to affect this system can impact on systemic exposure to amitriptyline. Although <i>in vitro</i> data indicate that alosetron has no effect on the activity of the CYP2D6 isoform, this study was undertaken to confirm in healthy subjects the absence of any interaction in terms of amitriptyline pharmacokinetics.	
Phase: I	
Study Period: 18 October 1999 – 09 December 1999	
Study Design: A single-center, open-label, single-dose, non-randomized, two-period crossover study.	
Center: One centre in the USA.	
Indication: None	
Treatment: In Period 1, subjects received a single oral dose of amitriptyline 50 mg on Day 1 and were studied for the next 6 days. After an 8-day washout between periods (14 days between amitriptyline doses), in Period 2 subjects received a further single oral dose of amitriptyline 50 mg in combination with one alosetron 1 mg tablet; subjects continued to receive alosetron 1 mg tablets twice daily (BID) for a total of 5 days (10 doses). Blood samples were collected for pharmacokinetic analysis of plasma amitriptyline and its metabolite nortriptyline pre-dose and for 6 days following the amitriptyline dose on each Day 1 (Period 1 and Period 2).	
Objectives: To determine the effect of concomitant administration of alosetron (1 mg BID) for 5 days on the pharmacokinetics of a single oral dose of amitriptyline 50 mg in healthy subjects.	
Statistical Methods: The study had 80% power to detect a difference of 30% in area under the plasma concentration-time curve (AUC) of amitriptyline and its active metabolite, nortriptyline. Comparisons for evaluation of a drug interaction were the amitriptyline and nortriptyline pharmacokinetic parameters AUC from time zero extrapolated to infinity (AUC _∞) and maximal observed plasma concentration (C _{max}) obtained with single dose amitriptyline compared with amitriptyline plus alosetron. Pharmacokinetic data were investigated using analysis of variance (ANOVA) models, allowing for subject and treatment effects. Both log _e -transformed and untransformed analyses were performed. For each treatment geometric mean, 95% confidence intervals (CI) were constructed. For the log _e -transformed analysis, the difference in least squares (LS) means (amitriptyline alone as the reference) and the corresponding 90% CI were back-transformed (exponentiated). For the untransformed analysis, the 90% CI for the difference in LS means were expressed as a proportion of the reference mean plus one. The analysis of t _{max} was based on untransformed data using non-parametric methods including the Wilcoxon Signed Rank test. The safety population, comprising subjects who received at least one dose of study drug, was used for demographic, baseline and safety data. The pharmacokinetic population consisted of all subjects who received study drug and provided evaluable results during each of the treatment periods.	
Study Population: Subjects were healthy, non-smoking male and female volunteers aged 18 – 50 years who were extensive CYP2D6 metabolizers. Subjects with a history of chronic constipation, any predisposing condition that might interfere with the absorption, distribution, metabolism or excretion of drugs, and those who had undergone any previous gastrointestinal surgery (except appendectomy or cholecystectomy more than 3 months prior to the study) were excluded from the study.	
Number of Subjects: All 12 subjects who entered the study completed as per the study protocol and were included in the safety and pharmacokinetic populations.	
Planned N	12
Dosed N	12
Completed n (%)	12 (100)
Total Number Subjects Withdrawn N (%)	0
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	Not applicable
Withdrawn for Other Reasons n (%)	0
Demographics	
N (Safety)	12

Females: Males	8: 4
Mean Age in Years (SD)	28.4 (9.8)
Mean Weight in kg (SD)	68.72 (13.35)
White n (%)	9 (75)

Pharmacokinetics (PK):

Pharmacokinetic Parameters: Geometric means and 95% CI

	PK Parameter	Amitriptyline 50mg	Amitriptyline 50mg + Alosetron 1mg
Amytrypyline	AUC _∞ (ng.h/mL)	564.2 (413.7, 769.5)	593.1 (456.4, 770.7)
	C _{max} (ng/mH)	33.5 (25.9, 43.4)	35.8 (26.8, 47.7)
	t _½ (h)	24.6 (19.7, 30.8)	25.6 (19.9, 32.9)
	λ _z (1/h)	0.03(0.02, 0.04)	0.03 (0.02, 0.03)
	t _{max} (h)*	3.0 (2.0, 4.0)	2.0 (2.0, 4.0)
Nortriptyline	AUC _∞ (ng.h/mL)	452.4, (347.1, 589.8)	427.4 (307.3, 594.5)
	Ratio ^(a)	0.8 (0.6, 1.1)	0.72 (0.47, 1.11)
	C _{max} (ng/mH)	7.7 (6.8, 8.6)	7.2 (5.9, 8.8)
	t _½ (h)	36.6 (30.3, 44.3)	38.9 (32.4, 46.8)
	λ _z (1/h)	0.02 (0.02, 0.02)	0.02 (0.01, 0.02)
	t _{max} (h)*	6.0 (3.0, 36.0)	6.0 (3.0, 47.9)

* t_{max} was analyzed by non-parametric methods (median and range presented)

(a) Ratio: nortriptyline AUC_∞/ amitriptyline AUC_∞

The statistical comparison of the PK parameter values in two treatment groups

Parameter	Amitriptyline			Nortriptyline		
	Ratio (B/A)	90% CI	P value	Ratio (B/A)	90% CI	P value
AUC _∞ (ng.h/mL)	1.05	(0.93, 1.19)	0.484	0.94	(0.87, 1.03)	0.268
Ratio ¹	NA	NA	NA	0.90	(0.76, 1.06)	0.271
C _{max} (ng/mL)	1.07	(0.92, 1.23)	0.441	0.94	(0.82, 1.07)	0.424
t _½ (h)	1.04	(0.92, 1.17)	0.572	1.06	(0.93, 1.22)	0.436
λ _z (1/h)	0.96	(0.85, 1.08)	0.561	0.94	(0.82, 1.08)	0.431
t _{max} (h)*	-0.01	(-0.53, 0.00)	0.688	-0.02	(-1.04, 1.96)	0.727

Treatments: A = amitriptyline 50 mg; B = amitriptyline 50 mg + alosetron 1 mg.

*The analysis of t_{max} was based on untransformed data using non-parametric methods; comparisons were based on median difference between treatments with an approximate 90% CI.

¹ Ratio: nortriptyline AUC_∞/ amitriptyline AUC_∞

Safety results:

Adverse events were monitored from signing the consent form to study discharge.

Adverse Events:	Amitriptyline 50 mg	Amitriptyline 50 mg + alosetron 1 mg
N (Safety)	12	12
No. subjects with AEs n (%)	11 (92)	11 (92)
Most Frequent AEs (more than one subject in any treatment period)		
Hypnagogic effects n (%)	8 (67)	11 (92)
Nausea n (%)	3 (25)	1 (8)
Nasal signs and symptoms n (%)	2 (17)	1 (8)

Serious Adverse Events:

No. subjects with SAEs -includes fatal and non-fatal events	0	0
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Publications:

No Publication

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