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Study No.: S3B10935			
Title: An open-label, non-randomized, two-way cross-over trial to evaluate the effect of multiple-dose alosetron administration (1 mg PO BID for 14 days) on the pharmacokinetics of single-dose fluoxetine (PROZAC) administration in healthy subjects.			
Rationale: As fluoxetine is a frequently prescribed medication in the female target therapeutic population for alosetron, the potential for interaction with alosetron is of interest. <i>In vitro</i> data indicate that alosetron has no effect on cytochrome P450 (CYP) 2C9 or CYP2D6 metabolism, this study was conducted to investigate the potential for interaction <i>in vivo</i> .			
Phase: I			
Study Period: 23 September 1999 – 01 March 2000.			
Study Design: An open-label, non-randomized, two-period crossover study.			
Centers: One center in the United States.			
Indication: None.			
Treatment: Subjects received a single oral (PO) dose of fluoxetine 20 mg on Day 1 of Period 1. On Day 1 of Period 2, each subject received a single PO dose of fluoxetine 20 mg together with one oral tablet of alosetron 1 mg. Alosetron administration was continued twice daily (BID) for 14 days (total of 28 alosetron doses). Treatment periods were separated by a 4-week washout (6 weeks between fluoxetine doses).			
Objectives: To determine the effect of concomitant administration of multiple-dose alosetron (1 mg PO BID for 14 days) on the pharmacokinetics of single-dose (QD) fluoxetine 20 mg PO in healthy subjects.			
Statistical Methods: Blood samples for estimation of plasma S- and R-fluoxetine and S- and R-norfluoxetine were taken at intervals over each 15 day Period. The following pharmacokinetic parameters were derived: area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{∞}), maximal observed plasma concentration (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$) and terminal elimination phase constant (λ_z) for S- and R-fluoxetine (parent) and S- and R-norfluoxetine (metabolite). The sample size provided 80% power to detect a difference in AUC of 30% between treatments. All pharmacokinetic parameters except t_{max} were \log_e -transformed and analysed using analysis of variance (ANOVA) allowing for subject and treatment effects. Using the Wilcoxon signed-rank test for paired data, t_{max} was also analysed. The safety population was all subjects dosed and the PK population was those who received both treatments and provided evaluable pharmacokinetic data for both Periods.			
Study Population: Healthy male and female subjects, aged 18 to 50 years, non-smoking, who were not slow or ultra-rapid metabolisers of CYP2D6. Subjects with a history of constipation were excluded. Subjects had to refrain from the consumption of xanthine-containing foods and beverages, charbroiled foods, cruciferous vegetables, and grapefruit from prior to Period 1 until the end of the study.			
		Fluoxetine 20 mg	Fluoxetine 20 mg + alosetron 1 mg BID 14 days
Number of Subjects:			
Planned, N (to complete study)		12	12
Dosed, N		15	12
Completed, n (%)		12 (80)	11 (92)
Total Number Subjects Withdrawn, N (%)		3 (20)	1 (8)
Withdrawn due to Adverse Events n (%)		0	1 (8)
Withdrawn due to Lack of Efficacy n (%)		0	0
Withdrawn for other reasons n (%)		3 (20)	0
Demographics		Total	
N (Safety)		15	
Females: Males		9 : 6	
Mean Age, years (SD)		35.6 (10.1)	
Mean weight, kg (SD)		77.72 (13.07)	
White, n (%)		14 (93)	
Pharmacokinetic Endpoints: Geometric means (95% confidence intervals) for the pharmacokinetic parameters of both enantiomers of fluoxetine and norfluoxetine are presented in the following table.			
Enantiomer	Pharmacokinetic Parameter	Fluoxetine 20 mg	Fluoxetine 20 mg QD + alosetron 1 mg BID 14 days

S-fluoxetine	AUC _∞ (ng.h/mL)	150.88	(118.40, 192.25)	166.24	(128.17, 215.63)
	AUC _{clast} (ng.h/mL)	87.52	(57.63, 139.92)	89.50	(56.08, 142.83)
	C _{max} (ng/mL)	4.19	(3.42, 5.13)	4.54	(3.72, 5.54)
	t _{1/2} (h)	22.3	(17.1, 29.0)	20.9	(14.2, 30.8)
	λ _z (1/h)	0.03	(0.02, 0.041)	0.03	(0.02, 0.05)
	t _{max} (h) ^a	6.00	[3.00, 10.00]	11.92	[6.00, 11.95]
R-fluoxetine	AUC _∞ (ng.h/mL)	126.34	(107.12, 149.01)	138.16	(117.80, 162.03)
	AUC _{clast} (ng.h/mL)	69.04	(54.83, 86.93)	75.60	(59.91, 95.39)
	C _{max} (ng/mL)	2.72	(2.32, 3.20)	3.15	(2.71, 3.65)
	t _{1/2} (h)	28.5	(21.7, 37.6)	31.3	(24.0, 40.9)
	λ _z (1/h)	0.02	(0.02, 0.03)	0.02	(0.02, 0.03)
	t _{max} (h) ^a	9.00	[6.00, 12.00]	11.92	[9.00, 11.95]
S-norfluoxetine	AUC _∞ (ng.h/mL)	1511.74	(1199.84, 1904.72)	1509.07	(1227.94, 1854.57)
	AUC _{clast} (ng.h/mL)	1243.66	(999.88, 1546.89)	1244.35	(982.71, 1575.66)
	AUC _∞ ratio ^b	9.80	(6.39, 15.03)	9.01	(5.89, 13.79)
	C _{max} (ng/mL)	6.88	(5.67, 8.35)	7.01	(5.83, 8.42)
	λ _z (1/h)	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)
	t _{1/2} (h)	116.5	(97.4, 139.3)	107.8	(97.2, 119.5)
t _{max} (h) ^a	36.00	[24.00, 72.00]	36.00	[9.00, 96.00]	
R-norfluoxetine	AUC _∞ (ng.h/mL)	635.85	(515.64, 784.07)	627.36	(523.20, 752.27)
	AUC _{clast} (ng.h/mL)	382.14	(294.36, 496.10)	385.56	(302.78, 490.98)
	AUC _∞ ratio ^b	5.54	(4.61, 6.65)	4.86	(3.46, 6.84)
	C _{max} (ng/mL)	2.79	(2.47, 3.14)	2.83	(2.50, 3.21)
	λ _z (1/h)	0.01	(0.00, 0.01)	0.01	(0.01, 0.01)
	t _{1/2} (h)	135.5	(110.5, 166.2)	122.3	(100.2, 149.3)
t _{max} (h) ^a	36.00	[6.00, 72.00]	36.00	[6.00, 72.00]	

t_{max} was analyzed by non-parametric methods with median and [range] presented.

AUC_∞ ratio of S- and R-norfluoxetine/S- and R-fluoxetine.

A summary of the log_e-transformed pharmacokinetic analysis for assessment of drug interaction is presented below.

Pharmacokinetic Parameter	S-Fluoxetine		R-Fluoxetine	
	TRT Ratio ^a	90%CI	TRT Ratio ^a	90%CI
AUC _∞ (ng.h/mL)	1.10	(1.00, 1.21)	1.09	(0.91, 1.31)
AUC _{clast} (ng.h/mL)	1.02	(0.83, 1.26)	1.10	(0.91, 1.31)
C _{max} (ng/mL)	1.08	(0.97, 1.20)	1.16	(1.03, 1.30)
t _{1/2} (h)	0.94	(0.73, 1.20)	1.10	(0.87, 1.38)
λ _z (1/h)	1.06	(0.83, 1.36)	0.91	(0.73, 1.14)
t _{max} (h) ^c	2.98	(1.46, 4.48)	2.94	(1.45, 4.44)
	S-Norfluoxetine		R-Norfluoxetine	
AUC _∞ (ng.h/mL)	0.99	(0.95, 1.04)	0.99	(0.93, 1.05)
AUC _∞ ratio ^b	0.92	(0.82, 1.03)	0.88	(0.75, 1.03)
AUC _{clast} (ng.h/mL)	1.00	(0.94, 1.07)	1.10	(0.91, 1.12)
C _{max} (ng/mL)	1.02	(0.96, 1.08)	1.02	(0.96, 1.07)
t _{1/2} (h)	0.93	(0.85, 1.00)	0.90	(0.82, 0.99)
λ _z (1/h)	1.08	(1.00, 1.17)	1.11	(1.01, 1.22)
t _{max} (h) ^c	-11.93	(-21.00, 10.50)	0.00	(-12.00, 18.00)

TRT Ratio: treatment ratio of fluoxetine plus alosetron/fluoxetine.

AUC_∞ Ratio of S- and R-norfluoxetine/S- and R-fluoxetine.

The analysis of t_{max} was based on non-parametric methods

Safety Results: Adverse events were monitored from the time consent was signed until final discharge. Only drug-related SAEs were to be collected between screening and first dose. All AEs irrespective of causality occurring after the first dose of study medication were documented.

	Fluoxetine 20 mg	Fluoxetine 20 mg QD + alosetron 1 mg BID 14 days
Most Frequent Adverse Events		
Number of subjects, N.	15	12

Subjects with any AE(s), n(%)	7 (47)	6 (50)
Headaches	3 (20)	1 (8)
Gastrointestinal discomfort and pain	0	2 (17)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:		
Subjects with non-fatal SAEs, n (%)	0	1 (8) [0]
Injuries	0	1 (8) [0]
Subjects with fatal SAEs, n (%)	0	0

Publications:

D'Souza DL, Dimmitt DC, Robbins DK, Nezamis J, Simms L, Koch KM. Effect of alosetron on the pharmacokinetics of fluoxetine. *J Clin Pharmacol.* 2001;41:455-8.

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