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Study No: S3B10932				
Title: A double-blind, randomized-step study of the effect of alosetron 1 mg, 2 mg, and 4 mg BID versus placebo on QT and QTc following 4 days of administration in healthy females.				
Rationale: Several studies have examined the effect of maximum alosetron concentration on electrocardiograms; no effect of alosetron on QTc was apparent. However, to supplement these studies, this study was conducted in accordance with current recommendations for the evaluation of the effect of new chemical entities on QTc interval.				
Phase: I				
Study Period: 19 July 1999 – 05 August 1999.				
Study Design: A double-blind, placebo-controlled, randomized step study in healthy female subjects.				
Centers: One center in the USA.				
Indication: None.				
Treatment: Subjects were randomized to receive alosetron 1 mg, 2 mg or 4 mg, or matching placebo, orally twice-daily for 3.5 days. The first dose in a subsequent treatment period was given 24h after the last dose in the previous period.				
Objectives: To determine the effects of alosetron 1 mg, 2 mg and 4 mg twice-daily, compared with placebo twice-daily, on the mean maximum and weighted mean QTcF (QT corrected using Fridericia's formula) on the fourth day of administration in healthy female subjects.				
Statistical Methods: On Day 4 of each treatment period machine and manually derived weighted means were calculated by estimating the area under the QTcF (QT interval corrected for heart rate using Fridericia's formula) and QTcB (QT interval corrected for heart rate using Bazett's formula) time curves using the trapezoidal method. Analysis of variance including terms for subject, treatment group, period and treatment sequence was used to compare mean maximums and weighted means of QTcF and QTcB. Maximum plasma concentration (C _{max}) was summarized. Plots of maximum observed alosetron concentration versus maximum and weighted mean QTcF were produced. The per protocol population consisted of 16 subjects to achieve sequence balance. All subjects were included in the safety population, pharmacodynamic categorical analyses and pharmacokinetic population.				
Study Population: Healthy, non-smoking female subjects aged 18 to 60 years. Subjects were excluded from the study if they had QT or QTc intervals greater than 450 milliseconds, or any clinically significant abnormality on the ECG at screening.				
Number of Subjects:				
Planned N		20		
Dosed N		20		
Completed n (%)		19 (95)		
Total Number Subjects Withdrawn N (%)		1 (5)		
Withdrawn due to Adverse Events n (%)		0		
Withdrawn due to Lack of Efficacy n (%)		0		
Withdrawn for Other Reasons n (%)		1 (5)		
Demographics				
N (safety)		20		
Females		20		
Mean Age in Years (SD)		33 (8.9)		
Mean Weight in kg (SD)		62.20 (9.39)		
White n (%)		19 (95)		
Pharmacodynamic Endpoints: The effects of alosetron on QTcF and QTcB compared with placebo are presented in the following tables.				
Machine-read ECG msec	Weighted Mean QTcF (95% CI)	Maximum QTcF (95% CI)	QTcF changes from baseline > 30 msec	
			No. of subjects	No. of ECGs
Placebo	406.8 (400.0, 413.6)	416.9 (409.7, 424.1)	0	0
Alosetron 1 mg	408.2 (401.4, 415.0)	415.2 (408.0, 422.5)	0	0
Alosetron 2 mg	407.7 (400.9, 414.5)	416.4 (409.2, 423.7)	0	0
Alosetron 4 mg	409.1 (402.2, 415.9)	418.1 (410.9, 425.4)	0	0
95% CI = 95% confidence interval; ECG = electrocardiogram.				

Manually-read ECG msec	Weighted Mean QTcF (95% CI)	Maximum QTcF (95% CI)	QTcF changes from baseline > 30 msec	
			No. of subjects	No. of ECGs
Placebo	402.1 (393.5, 410.8)	416.4 (407.9, 425.0)	0	0
Alosetron 1 mg	403.7 (395.1, 412.4)	414.9 (406.3, 423.4)	0	0
Alosetron 2 mg	404.3 (395.7, 413.0)	416.4 (407.9, 425.0)	1 of 20	2 of 140
Alosetron 4 mg	404.9 (396.2, 413.5)	418.3 (409.8, 426.9)	0	0

95% CI = 95% confidence interval; ECG = electrocardiogram.

Machine-read ECG msec	Weighted Mean QTcB (95% CI)	Maximum QTcB (95% CI)	QTcB changes from baseline > 30 msec	
			No. of subjects	No. of ECGs
Placebo	407.6 (402.4, 412.8)	419.8 (413.4, 426.1)	1 of 19	1 of 133
Alosetron 1 mg	406.9 (401.8, 412.1)	416.3 (409.9, 422.6)	0	0
Alosetron 2 mg	405.4 (400.3, 410.6)	417.3 (411.0, 423.7)	1 of 20	1 of 140
Alosetron 4 mg	408.1 (402.9, 413.3)	420.3 (413.9, 426.6)	0	0

95% CI = 95% confidence interval; ECG = electrocardiogram.

Manually-read ECG msec	Weighted Mean QTcB (95% CI)	Maximum QTcB (95% CI)	QTcB changes from baseline > 30 msec	
			No. of subjects	No. of ECGs
Placebo	404.1 (396.6, 411.5)	424.4 (416.7, 432.1)	3 of 19	3 of 133
Alosetron 1 mg	403.6 (396.2, 411.1)	420.1 (412.4, 427.8)	1 of 20	1 of 140
Alosetron 2 mg	403.0 (395.6, 410.4)	421.9 (414.3, 429.6)	2 of 20	3 of 140
Alosetron 4 mg	405.1 (397.7, 412.6)	424.3 (416.6, 431.9)	2 of 20	2 of 140

95% CI = 95% confidence interval; ECG = electrocardiogram.

The following tables summarise the statistical analysis of differences between alosetron and placebo in weighted mean and maximum QTcF and QTcB.

Treatment	Weighted Mean QTcF (msec)		Maximum QTcF (msec)	
	Difference	90%CI	Difference	90%CI

Machine-read ECG

Alosetron 1 mg	1.4	-2.3, 5.1	-1.6	-5.5, 2.3
Alosetron 2 mg	0.9	-2.8, 4.6	-0.4	-4.3, 3.5
Alosetron 4 mg	2.3	-1.4, 6.0	1.2	-2.6, 5.1

Manually-read ECG

Alosetron 1 mg	1.6	-3.3, 6.6	-1.6	-7.0, 3.8
Alosetron 2 mg	2.2	-2.7, 7.2	0.0	-5.4, 5.4
Alosetron 4 mg	2.7	-2.2, 7.7	1.9	-3.5, 7.3

90% CI = 90% confidence interval; ECG = electrocardiogram.

Treatment	Weighted Mean QTcB (msec)		Maximum QTcB (msec)	
	Difference	90%CI	Difference	90%CI
Machine-read ECG				
Alosetron 1 mg	-0.7	-4.3, 3.0	-3.5	-8.8, 1.8
Alosetron 2 mg	-2.2	-5.8, 1.5	-2.4	-7.7, 2.8
Alosetron 4 mg	0.5	-3.2, 4.2	0.5	-4.8, 5.8
Manually-read ECG				
Alosetron 1 mg	-0.4	-6.1, 5.2	-4.3	-10.7, 2.2
Alosetron 2 mg	-1.1	-6.7, 4.6	-2.4	-8.9, 4.1
Alosetron 4 mg	1.1	-4.6, 6.7	-0.1	-6.6, 6.4
90% CI = 90% confidence interval; ECG = electrocardiogram.				
Pharmacokinetic Endpoints: Cmax values for alosetron are summarised in the following table.				
Mean (SD)	Placebo	Alosetron 1 mg	Alosetron 2 mg	Alosetron 4 mg
Cmax (ng/mL)	0	5.60 (2.42)	16.02 (6.67)	45.81 (16.17)
Safety results: Adverse events were collected from screening to the post-study visit.				
Adverse Events:				
N (safety)	20			
	Placebo	Alosetron 1 mg	Alosetron 2 mg	Alosetron 4 mg
No. subjects with AEs n (%)	7 (35)	7 (35)	7 (35)	6 (30)
Most Frequent AEs				
Headache	2 (10)	4 (20)	2 (10)	2 (10)
Constipation	1 (5)	3 (15)	1 (5)	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	0	0
Publications: No publication				

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