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Study No.: S3B10945	
Title: A Double-Blind, Randomised, 2-Way Crossover Study to Determine the Effect of Alosetron 1mg BID for 14 days Versus Placebo BID on Visceral Hypersensitivity Following Duodenal Lipid Infusion in Female Diarrhea-Predominant IBS Patients	
Rationale: Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder that is characterised by abdominal pain or discomfort and disturbed bowel habit (diarrhea or constipation or both alternating). Postprandial symptoms are common. Simren et al. showed infusion of lipids in the duodenum lowered the colonic perception thresholds and changed the viscerosomatic referral patterns of discomfort and pain following colonic distension in IBS subjects compared with saline infusion, but not in controls. Alosetron hydrochloride has been shown to decrease vasoactive nociceptive responses in animal models of visceral pain. In IBS subjects undergoing left colonic distension using a barostat, alosetron significantly increased compliance of the colon. Compared with placebo, alosetron 0.25 or 4mg twice a day (<i>bis in die</i> , BID) for 7 days increased the median volume at which pain was perceived (by 71 and 84ml, respectively; $p=0.039$ and 0.017 , respectively). Alosetron 1mg BID has been shown to be effective in reducing the abdominal pain and discomfort of IBS in non-constipation-predominant female subjects. This study therefore investigated the effect of alosetron versus placebo on visceral sensitivity to colonic distension following duodenal infusion of lipids in diarrhea-predominant, female IBS subjects.	
Phase: I	
Study Period: 17 May 2000 to 01 Nov 2000	
Study Design: A double-blind, randomized, placebo-controlled, 2-way crossover study.	
Centres: This study was conducted in 1 centre in Sweden.	
Indication: Diarrhea-Predominant IBS in Female Subjects	
Treatment: Eligible subjects were randomized to receive a course (15 [\pm 2] days) of each of the 2 treatments with a 14-day washout period between treatments: alosetron 1mg orally BID and matching placebo BID.	
Objectives: The primary objective was to compare the change in colonic sensitivity to distensions following duodenal lipid infusion in subjects receiving treatment with alosetron versus placebo.	
Statistical Methods: The primary pharmacodynamic endpoints were the change in the pressure perception thresholds of first sensation, discomfort, pain, and gas following the lipid infusion; discomfort was considered an important endpoint. The change in the perception threshold was analyzed using repeated measures analysis of covariance (ANCOVA) with factors for the pre-lipid infusion pressure, treatment sequence, period, treatment, and subject within sequence. The secondary PD endpoints of change in relative area of referred discomfort and pain and colonic compliance were analyzed using the same procedure as described above for the primary endpoints. Colonic tone was analyzed using a similar method to evaluate the treatment effect, with an additional repeated factor for the various time intervals (0 to 10, 10 to 20, 20 to 30, 40 to 50, 50 to 60 minutes) within each phase (pre-infusion and during infusion). The number of phasic volume events was analyzed as above (primary endpoint), with the exception that there was no factor for the pre-lipid infusion value (ie, an ANOVA approach); there was only 1 measure of this outcome in each treatment period. Twenty four subjects received at least 1 dose of study medication and were therefore included in the safety population. Fifteen of these subjects had evaluable PD data in both treatment periods and were therefore included in the pharmacodynamic population.	
Study Population: Female subjects ≥ 18 years with diarrhea-predominant IBS (as defined by Rome II criteria). Females were to be of non-childbearing potential or childbearing potential with negative pregnancy test and using acceptable contraception methods.	
Number of Subjects:	Alosetron 1mg
Planned, N	16
Dosed, N	24

Completed, n (%)	16 (67)		
Total Number Subjects Withdrawn, n (%)	8 (33)		
Withdrawn Due to AEs, n (%)	2 (25)		
Withdrawn Due to Lack of Efficacy, n (%)	0		
Withdrawn For Other Reasons, n (%)	6 (75)		
Demographics:	Alosetron 1mg		
N (Safety)	24		
Females:Males, n:n	24:0		
Mean Age, Years (SD)	40.8 (12.6)		
Mean Weight, kg (SD)	65.09 (9.68)		
Caucasian, n (%)	24 (100)		
Summary of Pharmacodynamic Data (PD):			
Sensation	Placebo	Alosetron 1mg	
Perception Threshold (mmHg)	N=15	N=15	
First Sensation			
Pre, Mean (SD)	20.1 (6.4)	17.7 (9.1)	
Post, Mean (SD)	16.7 (2.9)	15.0 (4.9)	
LS Mean Change (95% CI)	-2.7 (-4.8, -0.6)	-3.2 (-5.3, -1.1)	
Gas			
Pre, Mean (SD)	26.9 (7.9)	23.0 (10.1)	
Post, Mean (SD)	21.7 (7.7)	20.6 (5.7)	
LS Mean Change (95% CI)	-4.5 (-8.7, -0.4)	-3.1 (-7.2, 1.1)	
Discomfort			
Pre, Mean (SD)	33.9 (10.1)	33.3 (11.9)	
Post, Mean (SD)	26.9 (9.3)	27.0 (8.1)	
LS Mean Change (95% CI)	-7.1 (-10.9, -3.4)	-6.2 (-9.9, -2.4)	
Pain			
Pre, Mean (SD)	40.9 (9.0)	39.0 (11.7)	
Post, Mean (SD)	31.5 (10.8)	34.4 (11.8)	
LS Mean Change (95% CI)	-9.1 (-13.9, -4.4)	-4.1 (-8.9, 0.8)	
Colonic Compliance (mL/mmHg)			
Pre, Mean (SD)	4.616 (1.566)	5.105(2.920)	
Post, Mean (SD)	5.533 (2.018)	5.177 (3.325)	
LS Mean Change (95% CI)	.833 (-0.143, 1.808)	0.071 (-0.907, 1.049)	
Area of Referred Sensation (cm²)			
Discomfort			
Pre, Mean (SD)	6.01 (8.84)	3.57 (3.80)	
Post, Mean (SD)	8.20(10.22)	5.44 (8.23)	
LS Mean Change (95%CI)	2.05 (-1.64, 5.74)	2.17 (-1.52, 5.87)	
Area of Referred Sensation (cm²)			
Pain			
Pre, Mean (SD)	4.36 (9.38)	1.19 (1.52)	
Post, Mean (SD)	9.69(12.91)	6.35 (11.34)	
LS Mean Change (95% CI)	5.48 (-1.11, 12.07)	5.11 (-1.47, 11.70)	
Summary of Statistical Analysis:			
	LS Mean	LS Mean	
Sensation	Alosetron	Placebo	
	N=15	N=15	p value
Change in Perception Threshold (mmHg)			
First Sensation	-3.18	-2.71	0.794
Gas	-3.09	-4.54	0.700
Discomfort	-6.16	-7.15	0.751
Pain	-4.06	-9.15	0.102
Change in Colonic Compliance (mL/mmHg)	0.0710	0.8327	0.225
Change in Area of Ref. Sensation (cm ²)			
Discomfort	2.1736	2.0508	0.961
			Difference (90% CI)
			p value

Pain	5.1141	5.4812	0.3671 (-6.7380, 6.0038)	0.920
Change in Colonic Tone (mL)	-14.0578	-8.7195	5.3384 (-14.5458, 3.8691)	0.337
Safety Results: Adverse events were collected from screening through post-study.				
Adverse Events	Placebo N=23	Alosetron 1mg N=21		
	n (%)	n (%)		
Subjects With AEs	0	2 (10)		
Serious Adverse Events (SAEs), n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]	Placebo N=23	Alosetron 1mg N=21		
	n (%) [n]	n (%) [n]		
Subjects With SAEs	0	0		

Publications: No publication

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