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Study No.: S3B30013
Title: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study of Alosetron in Female Subjects With Alternating Diarrhea/Constipation Irritable Bowel Syndrome
Rationale: Post hoc analyses in the alosetron Phase III Irritable Bowel Syndrome (IBS) studies indicated that female subjects, with alternating diarrhea and constipation IBS and a mean baseline stool frequency of ≥ 2 bowel movements per day and stool consistency which was formed, loose, or watery, reported greater adequate relief of IBS pain and discomfort with alosetron treatment as compared with subjects whose bowel parameters in screening showed a more constipated bowel pattern. The current study was conducted to further evaluate the efficacy and safety of alosetron in the treatment of this subset of female IBS subjects who exhibit non-constipated alternating bowel patterns.
Phase: III
Study Period: 20 Oct 1999 to 11 Jan 2001
Study Design: A multi-center, randomized, double-blind, placebo-controlled study in female subjects with alternating diarrhea/constipation IBS; with a 2-week screening phase, a 12-week treatment phase, and a 4-week follow-up phase.
Centres: The study was initiated at 220 centers in the United States (US) and Canada; 164 centers randomized subjects (149 centers in the US and 15 centers in Canada).
Indication: Alternating Diarrhea/Constipation IBS
Treatment: At the end of the 2-week screening period, eligible subjects were randomized (ratio: 1:1) to receive treatment with either alosetron 1mg twice a day (<i>bis in die</i> [BID]) or placebo BID for 12 weeks.
Objectives: The primary objectives of the study were as follows: Compare the 2 treatment groups with respect to adequate relief of IBS pain and discomfort Compare the tolerability of the 2 treatments with respect to the incidence of adverse events (AEs) and abnormalities in laboratory tests
Primary Outcome/Efficacy Variable: The primary measure of efficacy was adequate relief of IBS pain and discomfort between the 2 treatment groups.
Secondary Outcome/Efficacy Variable(s): Secondary efficacy variables included lower GI symptoms (sense of urgency, stool frequency, stool consistency, sense of incomplete evacuation, and bloating or abdominal distension). Health outcomes variables evaluated the 2 treatment groups with respect to changes in health-related QOL.
Statistical Methods: The sample size for the study was based on an anticipated treatment difference of 10% in average adequate relief rate and a standard deviation (SD) of 40%. The number of subjects necessary to detect a 10% difference between alosetron and placebo with 80% power at the $\alpha=0.05$ significance level was N=251 per treatment group. To allow for a 15% dropout rate, a target sample size of 300 subjects per treatment group was chosen for a total sample size of N=600 subjects. Two populations were analyzed. The intent-to-treat population (ITT), which included all subjects who were randomized to 1 of the 2 treatment groups. The safety population, which included all subjects in the ITT population who consumed at least 1 dose of study drug. The primary efficacy endpoint was the last 8 weeks (ie, Weeks 5 through 12) average adequate relief rate of IBS pain and discomfort during the treatment phase using the last observation carried forward (LOCF) approach for missing data; treatment groups were compared using a t-test with stratification for geographical cluster.
Adverse events and clinical laboratory findings were compared between treatment groups using Fisher's exact test, and were also assessed by age, race, and hormone use subgroups.

Study Population: Subjects were female ambulatory outpatients ≥ 18 years of age, who reported at least 6 months of recurrent symptoms that fulfilled the Rome (I) criteria for IBS, had normal sigmoidoscopic/colonoscopic results within 7 years, had an overall average pain and discomfort severity score ≥ 1.0 (representing mild pain, on a 4-point scale), an average stool consistency score of ≥ 3.0 (consistency of formed [3] or looser on a 5-point scale), and an average stool frequency of ≥ 2.0 per day.

Number of Subjects:	Placebo	Alosetron 1mg
Planned, N	300	300
Randomized, N	281	280
Completed, n (%)	175 (62)	185 (66)
Total Number Subjects Withdrawn, n (%)	106 (38)	95 (34)
Withdrawn Due to Adverse Events, n (%)	17 (6)	35 (13)
Withdrawn Due to Lack of Efficacy, n (%)	19 (7)	4 (1)
Withdrawn for Other Reasons, n (%)	70 (25)	56 (20)
Demographics:	Placebo	Alosetron 1mg
N (ITT)	281	280
Females:Males, n:n	281:0	280:0
Mean Age, Years (SD)	46.1 (14.1)	47.1 (13.3)
Caucasian, n (%)	251 (89)	254 (91)
Use of Hormonal Replacement or Contraceptive, n (%)	125 (44)	149 (53)
Time Since Onset of IBS Symptoms n	281	280
Mean years(SD)	10.3 (9.8)	10.0 (9.5)
Primary Efficacy Results (ITT With LOCF):		
Adequate Relief Rate of IBS Pain & Discomfort Weeks 5-12	Placebo	Alosetron 1mg
Week 5-12 Average, N	281	280
Mean (Standard Error, SE)	39.15 (2.58)	54.72 (2.58)
Confidence Interval (CI, 95%) (Mean)	34.09, 44.22	49.65, 59.79
Treatment Difference	15.56	
CI (Treatment Difference)	8.66, 22.46	
p-value ^a	<0.001	
a. The t-test was stratified by cluster for pairwise comparisons with placebo.		
Secondary Outcome Variable(s) (ITT With LOCF):		
% of Days Urgency Experienced Weeks 5-12	Placebo	Alosetron 1mg
Baseline, N	281	280
Mean (SD)	77.62 (20.32)	77.85 (21.72)
CI (Mean)	75.25, 80.00	75.30, 80.39
Treatment Difference	0.37	
CI (Treatment Difference)	-3.09, 3.83	
Week 5-12 Average, N	281	280
Mean (SD)	52.66 (33.99)	39.63 (33.63)
CI (Mean)	48.68, 56.63	35.69, 43.57
Change Mean (SE)	-24.00 (1.91)	-37.46 (1.91)
CI (Change Mean)	-27.76, -20.25	-41.22, -33.70
Treatment Difference Change	-13.45	
CI (Treatment Difference)	-18.56, -8.35	
IBS Stool Frequency Weeks 5-12	Placebo	Alosetron 1mg
Baseline, N	281	280
Mean (SD)	3.37 (1.34)	3.36 (1.29)
CI (Mean)	3.21, 3.52	3.21, 3.51
Treatment Difference	-0.01	
CI (Treatment Difference)	-0.22, 0.21	
Week 5-12 Average, N	281	280
Mean (SD)	2.73 (1.44)	2.12 (1.15)
CI (Mean)	2.57, 2.90	1.98, 2.25
Change Mean (SE)	-0.57 (0.07)	-1.19 (0.07)

CI (Change Mean)	-0.72, -0.43	-1.33, -1.05
Treatment Difference Change	-0.62	
CI (Treatment Difference)	-0.81, -0.42	
IBS Stool Consistency Weeks 5-12	Placebo	Alosetron 1mg
Baseline, N	281	280
Mean (SD)	3.58 (0.46)	3.64 (0.46)
CI (Mean)	3.53, 3.64	3.58, 3.69
Treatment Difference	0.06	
CI (Treatment Difference)	-0.02, 0.13	
Week 5-12 Average, N	281	280
Mean (SD)	3.13 (0.71)	2.58 (0.88)
CI (Mean)	3.04, 3.21	2.48, 2.68
Change Mean (SE)	-0.45 (0.05)	-1.06 (0.05)
CI (Change Mean)	-0.55, -0.36	-1.15, -0.96
Treatment Difference Change	-0.60	
CI (Treatment Difference)	-0.73, -0.48	
% of Days Incomplete Evacuation Experienced Weeks 5-12	Placebo	Alosetron 1mg
Baseline, N	281	280
Mean (SD)	77.09 (24.36)	78.01 (23.91)
CI (Mean)	74.25, 79.94	75.21, 80.81
Treatment Difference	0.96	
CI (Treatment Difference)	-3.03, 4.96	
Week 5-12 Average, N	281	280
Mean (SD)	57.99 (35.04)	49.99 (35.52)
CI (Mean)	53.89, 62.08	45.83, 54.15
Change Mean (SE)	-18.21 (2.06)	-27.16 (2.06)
CI (Change Mean)	-22.25, -14.17	-31.20, -23.12
Treatment Difference Change	-8.95	
CI (Treatment Difference)	-14.44, -3.46	
% of Days Bloating or Abdominal Distension Experienced Weeks 5-12	Placebo	Alosetron 1mg
Baseline, N	281	280
Mean (SD)	80.54 (24.28)	81.15 (23.87)
CI (Mean)	77.70, 83.38	78.35, 83.94
Treatment Difference	0.55	
CI (Treatment Difference)	-3.45, 4.55	
Week 5-12 Average, N	281	280
Mean (SD)	59.33 (35.70)	55.53 (36.39)
CI (Mean)	55.16, 63.51	51.27, 59.79
Change Mean (SE)	-20.22 (1.96)	-24.83 (1.96)
CI (Change Mean)	-24.07, -16.37	-28.69, -20.98
Treatment Difference Change	-4.61	
CI (Treatment Difference)	-9.85, 0.62	
Health Outcome Variable(s) (ITT With LOCF):		
IBSQOL at Endpoint – Transformed Scale-Specific Scores	Placebo N=281	Alosetron 1mg N=280
Emotional, n	262	266
Baseline, Mean (SE)	44.9 (1.5)	42.9 (1.4)
Change From Baseline, Mean (SE)	15.4 (1.5)	18.9 (1.5)
Treatment Difference (SE)	3.5 (2.1)	
95% CI	-0.6, 7.6	
Mental Health, n	263	266
Baseline, Mean (SE)	63.4 (1.4)	62.0 (1.4)
Change From Baseline, Mean (SE)	11.0 (1.3)	15.2 (1.3)

Treatment Difference (SE)	4.2 (1.7)	
95% CI	0.8, 7.6	
Sleep, n	275	278
Baseline, Mean (SE)	60.5 (1.3)	59.7 (1.4)
Change From Baseline, Mean (SE)	14.2 (1.2)	15.9 (1.2)
Treatment Difference (SE)	1.8 (1.6)	
95% CI	-1.4, 5.0	
Energy, n	275	278
Baseline, Mean (SE)	47.7 (1.6)	41.2 (1.6)
Change From Baseline, Mean (SE)	18.2 (1.6)	21.7 (1.6)
Treatment Difference (SE)	3.5 (2.2)	
95% CI	-0.9, 7.8	
Physical Functioning, n	265	262
Baseline, Mean (SE)	66.2 (1.4)	61.8 (1.5)
Change From Baseline, Mean (SE)	13.8 (1.4)	16.3 (1.4)
Treatment Difference (SE)	2.5 (1.9)	
95% CI	-1.2, 6.2	
Food, n	273	277
Baseline, Mean (SE)	53.6 (1.4)	51.9 (1.3)
Change From Baseline, Mean (SE)	13.3 (1.4)	17.8 (1.3)
Treatment Difference (SE)	4.6 (1.8)	
95% CI	0.9, 8.2	
Social Functioning, n	272	276
Baseline, Mean (SE)	40.8 (1.5)	38.4 (1.4)
Change From Baseline, Mean (SE)	17.2 (1.6)	22.5 (1.6)
Treatment Difference (SE)	5.3 (2.2)	
95% CI	1.0, 9.6	
Role Physical, n	272	277
Baseline, Mean (SE)	39.1 (1.5)	36.2 (1.4)
Change From Baseline, Mean (SE)	18.1 (1.7)	21.6 (1.6)
Treatment Difference (SE)	3.5 (2.2)	
95% CI	-0.9, 7.9	
Sexual Relations, n	155	148
Baseline, Mean (SE)	60.1 (2.2)	53.2 (2.2)
Change From Baseline, Mean (SE)	9.9 (1.7)	12.7 (1.7)
Treatment Difference (SE)	2.8 (2.3)	
95% CI	-1.7, 7.4	
Safety Results (Safety): An on-therapy adverse event (AE) and serious adverse event (SAE) were defined as any event with onset during the 12-week treatment and 4-week follow-up phases.		
	Placebo N=280	Alosetron 1mg N=280
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects With Any AE(s)	146 (52)	170 (61)
Constipation	10 (4)	46 (16)
Abdominal Discomfort & Pain	10 (4)	21 (8)
Nausea	15 (5)	15 (5)
Diarrhea	14 (5)	11 (4)
	8 (3)	12 (4)
Gastrointestinal Discomfort & Pain	7 (3)	10 (4)
Vomiting	10 (4)	6 (2)
Gastrointestinal Gaseous Symptoms	4 (1)	7 (3)
	16 (6)	22 (8)
Ear, Nose, & Throat Infections	9 (3)	14 (5)
	3 (1)	9 (3)
Musculoskeletal Pain	9 (3)	6 (2)

Arthralgia & Articular Rheumatism	8 (3)	1 (<1)
Urinary Infections	4 (1)	10 (4)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	Placebo N=280	Alosetron 1mg N=280
	n (%) [related]	n (%) [related]
Subjects With Non-Fatal SAEs	5 (2) [0]	8 (3) [4]
Abdominal Discomfort & Pain	1 (<1) [0]	1 (<1) [0]
Colitis	0	2 (<1) [2]
Appendicitis	0	1 (<1) [0]
Diverticulosis	0	1 (<1) [0]
	0	1 (<1) [0]
	1 (<1) [0]	0
	1 (<1) [0]	0
Pain	0	1 (<1) [1]
Chronic Obstructive Airways Disease	1 (<1) [0]	0
Pneumonia	1 (<1) [0]	0
Thrombophlebitis	0	1 (<1) [0]
	0	1 (<1) [0]
	0	1 (<1) [1]
	0	1 (<1) [0]
Abortion & Stillbirth	1 (<1) [0]	0
Skin Infections	0	1 (<1) [0]
	0	0

Conclusion:

Efficacy

Alosetron 1mg BID provided a significantly greater average adequate relief rate of IBS pain and discomfort during Weeks 5 through 12 than placebo in female subjects with alternating diarrhea/constipation IBS. Alosetron 1mg BID use resulted in significantly fewer days with urgency, fewer stools, and firmer stools than placebo. A significantly greater reduction in the percentage of days with incomplete stool evacuation was reported in 8 out of the 12 weeks during treatment with alosetron compared to placebo. Due to the high screen failure rate based on the average daily stool frequency and consistency entry criteria, the appropriate characterization of the population may be alternators in their diarrheal phase, which is probably not different during this study than from diarrhea-predominant IBS subjects.

The incidence of adverse events was 60% in the alosetron group vs. 52% in the placebo group. Constipation, headache and abdominal pain and discomfort were the most frequently reported adverse events in the alosetron group. Headache, nausea and vomiting were the most frequently reported events in the placebo group. SAEs were reported in similar proportions between alosetron-treated subjects (8/280, 3%) and those receiving placebo (5/280, 2%). Two subjects in the alosetron treated group reported colitis which was the only SAE reported by more than one subject in a group. No deaths were reported.

Publications:

Efficacy and safety of alosetron in female patients with alternating diarrhea/constipation IBS: a randomized, placebo-controlled trial, Hamm LR, Dukes GE, Mangel AW, Northcutt, A, Am J Gastro 96(9 supp 1): S318, 2001

Abstract: Efficacy and safety of alosetron in female patients with alternating diarrhea/constipation irritable bowel syndrome: a randomized, placebo controlled study. Hamm, L R, Dukes, G E, Hamedani, A G, Harding, J P, Jeter, B J, Mangel, A W, and Northcutt, A R 66th Annual Meeting of the American College of Gastroenterology 10/19/2001 Las Vegas, NV; USA

Date Updated: 06-May-2005