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Study No.: S3B30011
Title: A Twelve Week Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Tolerability of Alosetron Hydrochloride 1mg Twice Daily for Control of Bowel Urgency in Females with Nonconstipated Irritable Bowel Syndrome
Rationale: Subjects with irritable bowel syndrome (IBS) manifest a variety of symptoms including abdominal pain and discomfort, and changes in stool frequency or stool form. Previous studies of alosetron reported constipation as the most common side effect. This study evaluated the efficacy of alosetron in controlling bowel urgency, and included subjects' self-evaluation of their overall improvement from IBS, subject satisfaction over previous treatment, and interventions to manage constipation.
Phase: IIIb
Study Period: 13 Sep 1999 to 21 Apr 2000
Study Design: A 12-week, randomized, double-blind, placebo-controlled study, with a 2-week screening phase, a 12-week treatment phase, and a 2-week follow-up phase.
Centers: This study was initiated at 210 centers in the United States; 180 sites enrolled subjects.
Indication: Nonconstipated IBS
Treatment: Eligible subjects were randomized (2:1) to receive either blinded alosetron 1mg tablets taken orally twice a day (<i>bis in die</i> [BID]) or blinded placebo tablets taken orally BID for 12 weeks.
Objectives: The primary objective of the study was to compare treatment with alosetron 1mg BID to placebo BID with respect to the proportion of days subjects reported satisfactory control of bowel urgency.
Primary Outcome/Efficacy Variable: The primary measure of efficacy was the proportion of days subjects reported satisfactory control of bowel urgency.
Secondary Outcome/Efficacy Variable(s): Secondary efficacy measures included the proportion of subjects who were IBS Global Improvement Responders, daily analysis of satisfactory control of bowel urgency, and lower gastrointestinal symptoms (stool consistency, stool frequency, and sense of incomplete evacuation).
Statistical Methods: The sample size for this study was based on the primary endpoint and 1 safety endpoint. Using the nonparametric Wilcoxon Rank Sum test, 200 subjects per treatment group were needed to detect a 0.10 difference in the proportion of days with satisfactory control of bowel urgency with 90% power at the $\alpha=0.05$ significance level. To allow for a 20% dropout rate, a target sample size of 250 per treatment group was needed. A safety endpoint was the management of constipation. Since the Phase III clinical trials showed that 25% of the subjects randomized to alosetron reported constipation, more subjects were needed in the alosetron group to adequately assess constipation management. Thus, a 2:1 (alosetron 1mg BID: placebo BID) randomization was used with a target sample size of 500 in the alosetron group and 250 in the placebo group, for a total of 750 subjects. This allowed for more precise estimates of the proportions of subjects who reported constipation and who obtained relief of constipation following the implementation of a constipation management regimen. Following this increase in sample size, the power for the primary endpoint was 96%.
The 2 populations used for analysis were: 1) Intent-to-Treat (ITT) population was comprised of all randomized subjects and was the primary population used for efficacy analyses. Subjects who participated in the Screening Phase but who were not subsequently randomized to treatment were excluded from this population. 2) Safety population was comprised of subjects in the ITT population who received at least 1 dose of study drug. Subjects with no treatment start date were excluded from this population.
The proportion of days with satisfactory control of bowel urgency was compared between treatment groups using the van Elteren method of the Wilcoxon rank-sum test with stratification by geographic cluster (ie, West, North Central, South Central, Southeast, and Northeast/Mid-Atlantic US). Responders for the Global Improvement of IBS symptoms were defined as subjects who reported their IBS symptoms were substantially or moderately improved on a 7-point scale (1=substantially worse, 2=moderately worse, 3=slightly worse, 4=no change, 5=slightly improved, 6=moderately improved, 7=substantially improved). Proportions of IBS Global Improvement Responders were compared between treatment groups using a Mantel-Haenszel test stratified by cluster. Gastrointestinal function results were compared between treatments using a van Elteren test stratified by cluster. Safety results were summarized by treatment and were not compared inferentially.
Study Population: Subjects were female ambulatory outpatients, aged ≥ 18 years who were diagnosed with

<p>nonconstipated IBS, had consistent or recurrent symptoms (for ≥ 12 weeks in the previous 12 months) that fulfilled the Rome criteria for IBS, had documented lack of satisfactory control of bowel urgency on at least 50% of days during the Screening Phase, had normal sigmoidoscopic/colonoscopic results within 5 years, and recorded at least 12 out of 14 days (4 out of 5 days for antidiarrheal-dependent subjects) of daily self-assessments for the Screening Phase. Subjects were not eligible if they had a diagnosis of IBS with subtype constipation, had used alosetron previously, or had evidence of a biochemical or structural abnormality of the digestive tract.</p>		
Number of Subjects:	Placebo	Alosetron 1mg
Planned, N	250	500
Randomized, N	269	532
Completed, n (%)	219 (81)	433 (81)
Total Number Subjects Withdrawn, n (%)	50 (19)	99 (19)
Withdrawn Due to AEs, n (%)	16 (6)	52 (10)
Withdrawn Due to Lack of Efficacy, n (%)	13 (5)	12 (2)
Withdrawn For Other Reasons, n (%)	21 (8)	35 (7)
Demographics:	Placebo	Alosetron 1mg
N (ITT)	269	532
Females, n	269	532
Mean Age in Years (SD)	47.65 (12.77)	48.02 (13.20)
Caucasian, n (%)	253 (94)	495 (93)
Subtype of IBS, n	269	532
Alternator, n (%)	7 (3)	11 (2)
Diarrhea Predominant, n (%)	262 (97)	521 (98)
Time Since Onset of IBS Symptoms in Years, n	268	530
Mean (SD)	11.21 (10.50)	11.20 (10.06)
Primary Efficacy Results (ITT Population With LOCF):		
Satisfactory Control of Urgency Over 12 Weeks		
	Placebo N=269	Alosetron 1mg N=532
Proportion of Days		
Mean (SE)	0.52 (0.295)	0.65 (0.283)
p-value ^a	<0.001	
Obtained using van Elteren Test stratified by cluster.		
Change from Baseline in Satisfactory Control of Urgency Over 12 Weeks		
	Placebo N=269	Alosetron 1mg N=532
Proportion of Days	Mean (SE)	Mean (SE)
Baseline	0.21 (0.177)	0.22 (0.181)
Week 1	0.37 (0.298)	0.47 (0.325)
Week 2	0.45 (0.343)	0.56 (0.353)
Week 3	0.51 (0.336)	0.62 (0.351)
Week 4	0.52 (0.348)	0.64 (0.352)
Week 5	0.54 (0.355)	0.67 (0.348)
Week 6	0.56 (0.361)	0.69 (0.343)
Week 7	0.58 (0.371)	0.68 (0.346)
Week 8	0.55 (0.386)	0.69 (0.349)
Week 9	0.56 (0.364)	0.70 (0.342)
Week 10	0.57 (0.359)	0.71 (0.336)
Week 11	0.55 (0.368)	0.71 (0.341)
Week 12	0.58 (0.366)	0.71 (0.350)
Follow-up Week 1	0.56 (0.357)	0.61 (0.336)
Follow-up Week 2	0.57 (0.364)	0.54 (0.361)
Secondary Outcome Variables (ITT Population With LOCF):		
	Placebo N=269	Alosetron 1mg N=532
IBS Global Improvement Responder by Month	n (%)	n (%)
Week 4, n	251	497

Responder	105 (42)	332 (67)
Non-responder	146 (58)	165 (33)
Week 8, n	258	509
Responder	106 (41)	369 (72)
Non-responder	152 (59)	140 (28)
Week 12, n	258	509
Responder	113 (44)	379 (74)
Non-responder	145 (56)	130 (26)
Proportion of Subjects with Satisfactory Control of Urgency on Each of the First 14 Days of Treatment	Placebo N=269	Alosetron 1mg N=532
	Mean	Mean
Day 1	0.23	0.29
Day 2	0.33	0.41
Day 3	0.38	0.49
Day 4	0.41	0.52
Day 5	0.41	0.54
Day 6	0.45	0.55
Day 7	0.46	0.55
Day 8	0.39	0.53
Day 9	0.44	0.57
Day 10	0.48	0.58
Day 11	0.44	0.55
Day 12	0.53	0.59
Day 13	0.47	0.60
Day 14	0.52	0.60
Lower Gastrointestinal Functions		
Stool Consistency^{a,b}	Placebo N=269	Alosetron 1mg N=532
	Mean (SD)	Mean (SD)
Weekly Change from Baseline		
Week 1	-0.28 (0.514)	-0.77 (0.674)
Week 2	-0.30 (0.606)	-1.00 (0.835)
Week 3	-0.36 (0.537)	-0.99 (0.821)
Week 4	-0.35 (0.561)	-0.98 (0.798)
Week 5	-0.36 (0.582)	-0.94 (0.793)
Week 6	-0.36 (0.586)	-0.90 (0.812)
Week 7	-0.43 (0.612)	-0.90 (0.794)
Week 8	-0.37 (0.591)	-0.86 (0.796)
Week 9	-0.36 (0.566)	-0.92 (0.798)
Week 10	-0.37 (0.578)	-0.90 (0.791)
Week 11	-0.35 (0.613)	-0.89 (0.800)
Week 12	-0.37 (0.616)	-0.89 (0.808)
Follow-up Week 1	-0.33 (0.584)	-0.41 (0.694)
Follow-up Week 2	-0.35 (0.566)	-0.26 (0.696)
Average Consistency by Week		
Baseline	3.86 (0.477)	3.85 (0.517)
Week 1	3.58 (0.609)	3.08 (0.806)
Week 2	3.56 (0.653)	2.85 (0.923)
Week 3	3.50 (0.555)	2.86 (0.904)
Week 4	3.50 (0.578)	2.88 (0.890)
Week 5	3.50 (0.607)	2.91 (0.872)
Week 6	3.50 (0.641)	2.95 (0.869)
Week 7	3.43 (0.647)	2.96 (0.839)
Week 8	3.49 (0.610)	2.99 (0.837)
Week 9	3.50 (0.606)	2.93 (0.837)

Week 10	3.49 (0.636)	2.95 (0.832)
Week 11	3.51 (0.623)	2.97 (0.845)
Week 12	3.49 (0.620)	2.97 (0.833)
Follow-up Week 1	3.52 (0.594)	3.44 (0.717)
Follow-up Week 2	3.50 (0.636)	3.60 (0.682)

Stool consistency scale: 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery.
Negative values represent a hardening of the stool consistency.

Stool Frequency ^{a,b}	Placebo N=269	Alosetron 1mg N=532
	Mean (SD)	Mean (SD)
Weekly Change from Baseline		
Week 1	-0.30 (0.907)	-0.89 (1.275)
Week 2	-0.33 (0.994)	-1.01 (1.447)
Week 3	-0.39 (0.967)	-1.05 (1.433)
Week 4	-0.47 (1.078)	-1.10 (1.511)
Week 5	-0.45 (1.116)	-1.11 (1.434)
Week 6	-0.51 (1.137)	-1.15 (1.494)
Week 7	-0.60 (1.123)	-1.12 (1.550)
Week 8	-0.53 (1.159)	-1.17 (1.511)
Week 9	-0.44 (1.322)	-1.15 (1.525)
Week 10	-0.50 (1.142)	-1.17 (1.564)
Week 11	-0.49 (1.232)	-1.15 (1.504)
Week 12	-0.52 (1.280)	-1.16 (1.508)
Follow-up Week 1	-0.48 (1.222)	-0.69 (1.595)
Follow-up Week 2	-0.52 (1.324)	-0.60 (1.529)
Average Frequency by Week		
Baseline	3.20 (1.562)	3.23 (1.746)
Week 1	2.91 (1.573)	2.34 (1.348)
Week 2	2.87 (1.597)	2.21 (1.420)
Week 3	2.81 (1.517)	2.18 (1.462)
Week 4	2.74 (1.503)	2.13 (1.416)
Week 5	2.75 (1.621)	2.11 (1.433)
Week 6	2.69 (1.621)	2.07 (1.397)
Week 7	2.60 (1.530)	2.11 (1.520)
Week 8	2.67 (1.589)	2.06 (1.420)
Week 9	2.76 (1.647)	2.08 (1.440)
Week 10	2.70 (1.573)	2.06 (1.434)
Week 11	2.72 (1.689)	2.08 (1.461)
Week 12	2.68 (1.683)	2.07 (1.431)
Follow-up Week 1	2.68 (1.583)	2.52 (1.431)
Follow-up Week 2	2.63 (1.665)	2.63 (1.678)

a. Stool frequency measured as the number of stools per day.

b. Negative values represent a decrease in stool frequency.

Sense of Incomplete Evacuation	Placebo N=269	Alosetron 1mg N=532
	Mean (SD)	Mean (SD)
Weekly Change from Baseline		
Week 1	-0.05 (0.255)	-0.07 (0.302)
Week 2	-0.10 (0.292)	-0.14 (0.354)
Week 3	-0.14 (0.321)	-0.20 (0.371)
Week 4	-0.17 (0.360)	-0.24 (0.393)
Week 5	-0.19 (0.359)	-0.26 (0.398)
Week 6	-0.17 (0.376)	-0.29 (0.396)
Week 7	-0.19 (0.366)	-0.28 (0.397)
Week 8	-0.19 (0.373)	-0.30 (0.416)

Week 9	-0.19 (0.376)	-0.31 (0.411)
Week 10	-0.20 (0.374)	-0.30 (0.406)
Week 11	-0.18 (0.373)	-0.30 (0.407)
Week 12	-0.21 (0.396)	-0.33 (0.425)
Follow-up Week 1	-0.18 (0.363)	-0.26 (0.396)
Follow-up Week 2	-0.18 (0.385)	-0.22 (0.390)
Proportion of Days Symptom Experienced by Week		
Baseline	0.69 (0.298)	0.71 (0.285)
Week 1	0.64 (0.338)	0.64 (0.332)
Week 2	0.58 (0.364)	0.57 (0.358)
Week 3	0.55 (0.369)	0.51 (0.367)
Week 4	0.52 (0.371)	0.47 (0.378)
Week 5	0.50 (0.374)	0.45 (0.384)
Week 6	0.52 (0.389)	0.42 (0.382)
Week 7	0.50 (0.381)	0.43 (0.377)
Week 8	0.50 (0.386)	0.41 (0.389)
Week 9	0.50 (0.386)	0.40 (0.386)
Week 10	0.49 (0.386)	0.41 (0.383)
Week 11	0.50 (0.382)	0.41 (0.380)
Week 12	0.48 (0.395)	0.38 (0.387)
Follow-up Week 1	0.50 (0.377)	0.46 (0.373)
Follow-up Week 2	0.50 (0.393)	0.50 (0.392)

Safety Results: An on-therapy AE or SAE was defined as an AE or SAE with onset during the 12-week treatment and 2-week follow-up phases. Events occurring during the 2-week screening phase meeting the definition of an AE were considered to be non-treatment.

	Placebo N=269	Alosetron 1mg N=532
Most Frequent AEs – On-Therapy	n (%)	n (%)
Subjects With Any AEs	178 (66)	409 (77)
Constipation	37 (14)	206 (39)
Ear Nose & Throat Infections	30 (11)	71 (13)
Gastrointestinal Discomfort & Pain	21 (8)	65 (12)
Viral Respiratory Infections	23 (9)	44 (8)
Headaches	15 (6)	46 (9)
Nausea	10 (4)	32 (6)
Diarrhea	11 (4)	23 (4)
Vomiting	8 (3)	19 (4)
Gastrointestinal Gaseous Symptoms	5 (2)	19 (4)
Bronchitis	11 (4)	19 (4)
Viral Ear Nose & Throat Infections	11 (4)	16 (3)
Musculoskeletal Pain	14 (5)	13 (2)
Serious Adverse Events (SAEs) - On-Therapy n (%) [n considered by the investigator to be related to study medication]	Placebo N=269	Alosetron 1mg N=532
	n (%) [n]	n (%) [n]
Subjects with Non-fatal SAEs	6 (2) [2]	12 (2) [3]
Chest Symptoms	2 (<1) [0]	2 (<1) [0]
Cholecystitis	0	1 (<1) [0]
Colitis	0	1 (<1) [0]
Depressive Disorders	1 (<1) [0]	0
Disorders of Equilibrium	0	1 (<1) [0]
Diverticulitis	0	1 (<1) [1]
Fractures	0	1 (<1) [0]
Gastrointestinal Discomfort and Pain	1 (<1) [1]	0

Gastrointestinal Hemorrhage	1 (<1) [1]	0
Headaches	0	1 (<1) [0]
Hypoesthesia	0	1 (<1) [0]
Increased Blood Pressure	0	1 (<1) [1]
Infections	0	1 (<1) [0]
Medical Substances Non-specific Effects	0	1 (<1) [0]
Migraines	0	1 (<1) [1]
Musculoskeletal Pain	0	1 (<1) [0]
Pneumonia	0	1 (<1) [0]
Primary Malignant Breast Neoplasia	1 (<1) [0]	0
Thrombosis	0	1 (<1) [0]
Visual Disturbances	0	1 (<1) [0]
Subjects with Fatal SAEs	1 (<1) [0]	0
Death of Unknown Cause	1 (<1) [0]	0

Conclusion:

See publications below.

Publications:

T Lembo, K Olden, V Ameen, S Gordon, A Heath, E Carter. Effect of Alosetron on Bowel Urgency and Global Symptoms in Women with Severe Diarrhea-Predominant Irritable Bowel Syndrome: Analysis of Two Controlled Trials. Clin Gastro and Hepatol, 2(8):675-82, 2004.

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Lembo T, Wright R, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. Am J Gastro 2001 Sep;96(9):2662-70.

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Northcutt A, Mangel A, Hamm L, et al. Validation of Global Improvement Scale in Irritable Bowel Syndrome (IBS) as an Endpoint in IBS Clinical Trials. Program and abstracts of Digestive Disease Week 2001; May 20-23, 2001; Atlanta, Georgia. Poster #3243

Jhingran P, Bagby B, Decker C, Gordon S, Markowitz M, Carter E. Patient Satisfaction in Lotronex treated nonconstipated IBS females. Am J Gastro 95(9):2631-2, 2000

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Markowitz M, Bagby B, Gordon, Decker C, Jhingran P, Carter E. Satisfactory control of bowel urgency and global symptom improvement in IBS with Lotronex therapy. Am J Gastro 95(9): 2543, 2000

Jhingran P, Bagby B, Gordon S, Markowitz M, Thompson B, Carter E. Impact of Lotronex on workplace productivity and activity time in females with nonconstipated IBS. Am J Gastro 95(9): 2537, 2000

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