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Study No.: S3B30006
Title: A 1-Year Randomized, Double-Blind, Placebo-Controlled Study of Alosetron (GR68755) 1mg BID in Female Subjects With Irritable Bowel Syndrome
Rationale: Studies in the Phase III program (S3BA3001 and S3BA3002) support the use of alosetron for up to 12 weeks for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). However, given the chronic intermittent nature of the syndrome in some subjects, it is important to know the efficacy and safety of alosetron over a longer treatment period. While the 1-year safety study (S3BA3003) established the safety profile of alosetron for continued-use, this study was conducted to evaluate the efficacy and safety of alosetron 1mg twice a day (<i>bis in die</i> [BID]) in non-constipated female IBS subjects during a 48-week treatment period.
Phase: III
Study Period: 03 Dec 1998 to 15 Jun 2000
Study Design: A 1-year randomized, double-blind, placebo-controlled study in female subjects; with a 2-week screening phase, a 48-week treatment phase, and a 4-week follow-up phase.
Centres: The study was initiated at 160 centers in the US and rest of world (ROW); 138 sites randomized subjects including 28 sites from ROW countries (United Kingdom, Sweden, New Zealand and Canada).
Indication: Non-Constipated IBS
Treatment: After the 2-week screening phase, eligible subjects were randomized to receive 1 of the following 2 blinded treatments: alosetron 1mg tablets by mouth (<i>per os</i> , [PO]) BID or placebo tablets PO BID.
Objectives: The primary objectives of the study were to compare the 2 treatment groups with respect to adequate relief of IBS pain and discomfort and to compare the tolerability of the 2 treatments with respect to the incidence of adverse events (AEs) and abnormalities in clinical laboratory values.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the 48-week average adequate relief rate of IBS pain and discomfort during the treatment phase. The primary safety endpoints were the incidence of AEs and shifts in laboratory values.
Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints were the 48-week average rates of satisfactory control of gastrointestinal (GI) symptoms (urgency, stool frequency, stool consistency, and bloating). Health outcome endpoints evaluated the 2 treatment groups with respect to changes in subject-assessed, health-related quality of life (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 38%. The number of subjects per group necessary to detect a 10% difference between alosetron and placebo with 90% power at the $\alpha=0.05$ significance level was N=300 per group for a total sample size of N=600 subjects.
<p>The intent-to-treat population (ITT) included all subjects who were randomized to 1 of the 2 treatment groups. The diarrhea-predominant ITT population (DITT) included all subjects in the ITT population who were categorized by the investigator (based on the subjects' IBS disease history) as being of the diarrhea-predominant subtype of IBS. The safety population included all subjects in the ITT population who consumed at least 1 dose of study drug.</p> <p>The primary efficacy endpoint was the 48-week 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.</p> <p>Secondary efficacy endpoints were the 48-week average rates of satisfactory control of GI symptoms (urgency, stool frequency, stool consistency, and bloating) using the LOCF approach for missing data.</p> <p>The primary health outcome endpoint was the change from baseline in the 9 transformed scales of , the IBSQOL at 12 months,. The IBSQOL scales were compared using analysis of covariance (ANCOVA).</p> <p>Adverse events and clinical laboratory findings were compared between treatment groups using Fisher's exact test. Adverse events and laboratory results were also assessed by age, race, and hormone use subgroups.</p>

Study Population: Subjects were female ambulatory outpatients, age ≥ 18 years who reported at least 6 months of recurrent symptoms that fulfilled the Rome 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) and had an average stool consistency score of ≥ 2.5 (consistency between hard [2] to formed [3] or looser).		
Number of Subjects:	Placebo	Alosetron 1mg
Planned, N	300	300
Randomised, N	363	351
Completed, n (%)	219 (60)	212 (60)
Total Number Subjects Withdrawn, n (%)	144 (40)	139 (40)
Withdrawn Due to Adverse Events, n (%)	36 (10)	67 (19)
Withdrawn Due to Lack of Efficacy, n (%)	58 (16)	21 (6)
Withdrawn for Other Reasons, n (%)	50 (14)	51 (15)
Demographics:	Placebo	Alosetron 1mg
N (ITT)	363	351
Females:Males, n:n	363:0	351:0
Mean Age, Years (SD)	46.6 (13.0)	45.9 (13.5)
Caucasian, n (%)	341 (94)	332 (95)
Time Since Onset of IBS Symptoms, Years, n	363	351
Mean (SD)	11.62 (10.78)	10.34 (10.05)
Subtype of IBS, n	363	351
Diarrhea-Predominant, n (%)	290 (80)	279 (79)
Alternating Constipation/Diarrhea, n (%)	73 (20)	72 (21)
Constipation Predominant, n (%)	0	0
Primary Efficacy Results (DITT Population With LOCF): Adequate Relief of IBS Pain and Discomfort		
	Placebo N=290	Alosetron 1mg N=279
48-Week Average		
Mean (Standard Error [SE])	43.86 (2.27)	52.13 (2.33)
CI (Mean)	39.42, 48.30	47.57, 56.70
Treatment Difference	8.27	
CI (Treatment Difference)	1.99, 14.55	
p-value ^a	0.010	
a. t-test stratified by cluster.		
Secondary Outcome Variables (DITT Population With LOCF):		
	Placebo N=290	Alosetron 1mg N=279
Satisfactory Control of Urgency		
Mean (SE)	52.03 (2.23)	63.79 (2.29)
CI (Mean)	47.66, 56.39	59.30, 68.28
Treatment Difference	11.76	
CI (Treatment Difference)	5.59, 17.94	
	Placebo N=290	Alosetron 1mg N=279
Satisfactory Control of Stool Consistency		
Mean (SE)	45.16 (2.18)	50.06 (2.24)
CI (Mean)	40.90, 49.42	45.67, 54.44
Treatment Difference	4.90	
CI (Treatment Difference)	-1.14, 10.93	
	Placebo N=290	Alosetron 1mg N=279
Satisfactory Control of Stool Frequency		
Mean (SE)	49.55 (2.23)	54.22 (2.29)
CI (Mean)	45.18, 53.92	49.73, 58.71
Treatment Difference	4.67	
CI (Treatment Difference)	-1.52, 10.85	
	Placebo N=290	Alosetron 1mg N=279
Satisfactory Control of Bloating		
Mean (SE)	45.88 (2.32)	48.70 (2.39)
CI (Mean)	41.33, 50.44	44.02, 53.38

Treatment Difference	2.82	
CI (Treatment Difference)	-3.63, 9.26	
Health Outcome Variables (DITT Population):		
IBSQOL Transformed-Specific Scores at Month 12	Placebo N=290	Alosetron 1mg N=279
Emotional		
n	273	265
Baseline Mean (SE)	47.4 (1.4)	46.7 (1.5)
Mean Change From Baseline (SE)	15.3 (1.5)	21.6 (1.5)
Treatment Difference Mean (SE)	6.2 (2.0)	
95% CI Treatment Difference	2.2, 10.2	
Mental Health		
n	273	265
Baseline Mean (SE)	67.9 (1.3)	68.0 (1.3)
Mean Change From Baseline (SE)	10.4 (1.2)	12.3 (1.2)
Treatment Difference Mean (SE)	1.9 (1.7)	
95% CI Treatment Difference	-1.4, 5.1	
Sleep		
n	289	273
Baseline Mean (SE)	68.9 (1.2)	66.9 (1.3)
Mean Change From Baseline (SE)	12.2 (1.1)	11.9 (1.2)
Treatment Difference Mean (SE)	-0.4 (1.6)	
95% CI Treatment Difference	-3.5, 2.8	
Energy		
n	289	274
Baseline Mean (SE)	51.0 (1.6)	49.0 (1.7)
Mean Change From Baseline (SE)	19.0 (1.5)	19.5 (1.6)
Treatment Difference Mean (SE)	0.5 (2.2)	
95% CI Treatment Difference	-3.7, 4.7	
Physical Functioning		
n	285	267
Baseline Mean (SE)	69.6 (1.4)	68.8 (1.5)
Mean Change From Baseline (SE)	12.0 (1.2)	13.2 (1.3)
Treatment Difference Mean (SE)	1.2 (1.7)	
95% CI Treatment Difference	-2.2, 4.5	
Food		
n	289	271
Baseline Mean (SE)	55.4 (1.3)	55.1 (1.3)
Mean Change From Baseline (SE)	14.1 (1.2)	17.9 (1.2)
Treatment Difference Mean (SE)	3.8 (1.7)	
95% CI Treatment Difference	0.5, 7.0	
Social Functioning		
n	289	271
Baseline Mean (SE)	43.5 (1.4)	44.5 (1.6)
Mean Change From Baseline (SE)	19.9 (1.4)	23.9 (1.5)
Treatment Difference Mean (SE)	4.0 (2.0)	
95% CI Treatment Difference	0.1, 7.9	
Role Physical		
n	287	271
Baseline Mean (SE)	43.9 (1.6)	41.1 (1.6)
Mean Change from Baseline (SE)	20.7 (1.5)	21.1 (1.6)
Treatment Difference Mean (SE)	0.4 (2.2)	
95% CI Treatment Difference	-3.9, 4.7	

Sexual Relations		
n	193	153
Baseline Mean (SE)	59.8 (1.8)	60.6 (2.1)
Mean Change from Baseline (SE)	14.3 (1.4)	15.9 (1.6)
Treatment Difference Mean (SE)		1.6 (2.2)
95% CI Treatment Difference		-2.6, 5.8
<p>Safety Results: An on-therapy AE or SAE was defined as an AE or SAE with onset during the 48-week treatment and 4-week follow-up phases. Events occurring during the 2-week screening phase meeting the definition of an AE were considered to be non-treatment-emergent. The Safety Population included >99% (710/714) of the subjects randomized. One subject randomized to the placebo BID group, and three subjects randomized to the alosetron 1mg BID group, did not consume study drug and were excluded from the Safety Population.</p>		
	Placebo N=362	Alosetron 1mg N=348
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects With Any AEs	261 (72)	297 (85)
Constipation	17 (5)	79 (23)
Nausea	41 (11)	38 (11)
Abdominal Discomfort & Pain	31 (9)	34 (10)
Diarrhea	31 (9)	27 (8)
Vomiting	22 (6)	22 (6)
Gastrointestinal Discomfort & Pain	13 (4)	23 (7)
Ear, Nose, & Throat Infections	68 (19)	49 (14)
Viral Ear, Nose, & Throat Infections	25 (7)	21 (6)
Headaches	32 (9)	31 (9)
Musculoskeletal Pain	37 (10)	26 (7)
Viral Respiratory Infections	32 (9)	23 (7)
Bronchitis	18 (5)	12 (3)
Depressive Disorders	17 (5)	10 (3)
Serious Adverse Events - On-Therapy	Placebo N=362	Alosetron 1mg N=348
n (%) [n considered by the investigator to be related to study medication]	n (%) [n]	n (%) [n]
Subjects With Non-Fatal SAEs	14 (4) [0]	18 (5) [1]
Nausea	1 (<1) [0]	2 (<1) [0]
Vomiting	1 (<1) [0]	2 (<1) [0]
Abdominal Discomfort & Pain	0	2 (<1) [0]
Abdominal Cysts, Lumps, & Masses	1 (<1) [0]	0
Decreased GI Motility & Ileus	1 (<1) [0]	0
Dental and Gum Inflammation	0	1 (<1) [0]
Diarrhea	0	1 (<1) [0]
Peritoneal Adhesions	1 (<1) [0]	0
Viral GI Infections	0	1 (<1) [0]
Angina Pectoris	0	1 (<1) [0]
Cerebrovascular Accidents	0	1 (<1) [0]
Hypertension	0	1 (<1) [0]
Palpitations	1 (<1) [0]	0
Tachyarrhythmias	0	1 (<1) [0]
Thrombosis	0	1 (<1) [0]
Wounds & Lacerations	1 (<1) [0]	0
Contusions & Hematomas	0	1 (<1) [0]
Ligament, Tendon, or Cartilage Injuries	1 (<1) [0]	0
Postoperative Infections	1 (<1) [0]	0
Inflammation of Cervix Uteri	1 (<1) [0]	0
Menstruation Symptoms	0	1 (<1) [0]

Polyps of Female Reproductive Tract	1 (<1) [0]	0
Primary Malignant Breast Neoplasia	1 (<1) [0]	0
Primary Malignant Female Reproductive Neoplasia	1 (<1) [0]	0
Cholelithiasis	2 (<1) [0]	1 (<1) [0]
Headache	0	1 (<1) [0]
Hypoesthesia	0	1 (<1) [1]
Sleep Disorders	1 (<1) [0]	0
Chest Symptoms	0	2 (<1) [0]
Faintness	0	1 (<1) [0]
Anxiety	0	1 (<1) [0]
Depressive Disorders	1 (<1) [0]	0
Suicide & Attempted Suicide	1 (<1) [0]	0
Asthma	0	1 (<1) [0]
Chronic Obstructive Airways Disease	0	1 (<1) [0]
Bone & Cartilage Disorders	0	1 (<1) [0]
Musculoskeletal Inflammation	0	1 (<1) [0]
Blindness & Low Vision	0	1 (<1) [0]
Urinary Calculi	0	1 (<1) [0]
	n (%) [n]	n (%) [n]
Subjects With Fatal SAEs	1 (<1) [0]	0
Bilateral Pulmonary Emboli	1 (<1) [0]	0
Conclusions: See publications below.		
Publications:		
Long-term Safety and Efficacy of Alosetron in Women with Severe Diarrhea-Predominant Irritable Bowel Syndrome, WD Chey, WY Chey, A Heath, G Dukes, E. Carter, A Northcutt, V Ameen Am J Gastro,99:2195-2203,2004		

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