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Study No.: S3B20023
Title: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging, Phase II Study to Assess the Clinical Efficacy of Alosetron (GR68755) in Male Subjects With Irritable Bowel Syndrome
Rationale: The purpose of the study was to establish whether alosetron provides adequate relief from abdominal pain and discomfort and improves bowel function in males with diarrhea-predominant irritable bowel syndrome (IBS). Selection of this sub-group of male IBS subjects was prompted by post hoc analyses from Phase II studies (ie, S3BP12 and S3BA2001). These data suggested that a proportion of male subjects who presented with average stool consistency scores ≥ 3.0 (formed to loose, watery) along with average abdominal pain scores ≥ 1.0 (at least mild) exhibited clinical benefit in response to alosetron treatment. Thus, these screening parameters were chosen to define the diarrhea-predominant male population for this study.
Phase: II
Study Period: 08 Oct 1999 to 16 Nov 2000
Study Design: This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, study; with a 2-week screening phase, a 12-week treatment phase, and a 4-week follow-up phase.
Centres: This study was initiated at 223 centers in the United States (US) and Canada; 186 sites randomized subjects, including 163 sites from the US and 23 sites from Canada.
Indication: Diarrhea-Predominant IBS in males
Treatment: Blinded alosetron tablets (0.5mg, 1.0mg, 2.0mg, and 4.0mg) administered orally twice a day (<i>bis in die</i> [BID]); blinded placebo tablets administered orally BID
Objectives: The primary objectives of the study were as follows: Identify the optimal dose of alosetron, which provided adequate relief from pain and discomfort in male subjects with diarrhea-predominant IBS Evaluate the safety and tolerability of alosetron in male subjects with IBS
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the average weekly rate of adequate relief of IBS pain and discomfort during Weeks 5 to 12 of the treatment period.
Secondary Outcome/Efficacy Variable(s): The secondary endpoints were the changes in self-ratings of lower gastrointestinal (GI) symptoms, (urgency, stool frequency, stool consistency, incomplete evacuation, and bloating) during Weeks 5 to 12 of the treatment period, and changes in health-related quality of life using the Irritable Bowel Syndrome Quality of Life (IBSQOL) questionnaire
Statistical Methods: The sample size for this study was based on an anticipated treatment difference of 15% in average adequate relief rate with a standard deviation (SD) of 40%. The number of subjects per group necessary to detect a 15% difference between alosetron groups and placebo with 80% power at the $\alpha=0.05$ significance level was N=120 per group for a total sample size of N=600 subjects. Two populations were analyzed. The intent-to-treat population (ITT) included all subjects who were randomized to 1 of the 5 treatment groups. The safety population included all subjects in the ITT population who consumed at least 1 dose of study drug. The primary efficacy endpoint was the average weekly rate of adequate relief of IBS pain and discomfort during the last 8 weeks of the treatment period (ie, Weeks 5 to 12) using the last observation carried forward (LOCF) approach for missing data; treatment groups were compared using Dunnett's t-test with stratification for geographical cluster. Secondary efficacy endpoints were the changes from baseline during the last 8 weeks of the treatment period (ie, Weeks 5 to 12) in lower GI symptoms (urgency, stool frequency, stool consistency, incomplete evacuation, and bloating) using the LOCF approach for missing data. Health outcome endpoints were the change from baseline in the Irritable Bowel Syndrome Quality of Life (IBSQOL) scale scores. Adverse events (AEs) and clinical laboratory findings were compared between treatment groups using Fisher's exact test.

Study Population: Male outpatients who reported symptoms fulfilling the Rome (I) Criteria for IBS over a period of at least 6 months and whose abdominal pain or discomfort and functional bowel symptoms during screening averaged at least mild pain (≥ 1 on a 4-point scale), and who exhibited formed to loose/watery stools (stool consistency ≥ 3 on a 5-point scale) with a normal, age-appropriate colon procedure, were randomized to receive 0.5, 1.0, 2.0, or 4.0mg BID of alosetron or matching placebo.					
Number of Subjects:	Placebo	Alosetron 0.5mg BID	Alosetron 1.0mg BID	Alosetron 2.0mg BID	Alosetron 4.0mg BID
Planned, N	120	120	120	120	120
Randomised, N	128	127	131	136	140
Completed, n (%)	110 (86)	105 (83)	107 (82)	105 (77)	119 (85)
Total Number Subjects Withdrawn, n (%)	18 (14)	22 (17)	24 (18)	31 (23)	21 (15)
Withdrawn Due to Adverse Events, n (%)	5 (4)	7 (6)	15 (11)	13 (10)	11 (8)
Withdrawn Due to Lack of Efficacy, n (%)	3 (2)	6 (5)	1 (<1)	6 (4)	3 (2)
Withdrawn for Other Reasons, n (%)	10 (8)	9 (7)	8 (6)	12 (9)	7 (5)
Demographics:	Placebo	Alosetron 0.5mg BID	Alosetron 1.0mg BID	Alosetron 2.0mg BID	Alosetron 4.0mg BID
N (ITT)	128	127	131	136	140
Females:Males, n:n	0:128	0:127	0:131	0:136	0:140
Mean Age, Years (SD)	42.9 (12.0)	43.9 (11.7)	43.8 (11.7)	43.0 (12.9)	45.2 (14.6)
Caucasian, n (%)	118 (92)	118 (93)	123 (94)	128 (94)	128 (91)
Time Since IBS Onset, Years Mean (SD)	11.0 (10.5)	10.4 (11.4)	11.0 (10.0)	11.0 (11.1)	11.3 (11.7)
Primary Efficacy Results (ITT With LOCF):					
Adequate Relief Rate of IBS Pain and Discomfort Weeks 5-12 Average	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	131	136	140
Mean (SE)	39.66 (3.17)	48.93 (3.72)	52.84 (3.68)	48.37 (3.61)	49.85 (3.57)
CI (Mean)	32.38, 46.95	41.61, 56.24	45.60, 60.07	41.28, 55.46	42.85, 56.86
Tmt Diff	-	9.26	13.18	8.71	10.19
CI (Tmt Diff)	-	-3.56, 22.08	0.45, 25.90	-3.90, 21.32	-2.34, 22.72
p-value ^a	-	0.229	0.040	0.265	0.147
t-test stratified by cluster for pairwise comparisons with placebo using Dunnett's multiple comparison method.					
Secondary Outcome Variables (ITT With LOCF):					
IBS Stool Frequency Weeks 5-12 Average	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	130	136	140
Baseline Mean (SD)	3.32 (1.45)	3.18 (1.44)	3.33 (1.62)	3.35 (1.50)	3.36 (1.64)
Mean (SD)	2.71 (1.16)	2.46 (1.45)	2.54 (1.50)	2.57 (1.42)	2.50 (1.68)
CI (Mean)	2.51, 2.91	2.20, 2.71	2.29, 2.80	2.34, 2.81	2.22, 2.78
Change Mean (SE)	-0.60 (0.09)	-0.72 (0.09)	-0.78 (0.09)	-0.77 (0.09)	-0.85 (0.09)
CI (Change Mean)	-0.77, -0.42	-0.90, -0.54	-0.96, -0.60	-0.94, -0.59	-1.02, -0.68
Tmt Diff Change	-	-0.12	-0.18	-0.17	-0.25
CI (Tmt Diff)	-	-0.37, 0.13	-0.43, 0.07	-0.42, 0.08	-0.50, -0.01
IBS Stool Consistency Weeks 5-12 Average	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	130	136	140
Baseline Mean (SD)	3.77 (0.41)	3.79 (0.47)	3.82 (0.46)	3.84 (0.4)	3.75 (0.45)
Mean (SD)	3.28 (0.50)	2.98 (0.77)	2.94 (0.81)	2.94 (0.74)	2.81 (0.88)

CI (Mean)	3.19, 3.36	2.85, 3.12	2.80, 3.08	2.82, 3.07	2.66, 2.95
Change Mean (SE)	-0.49 (0.06)	-0.81 (0.06)	-0.87 (0.06)	-0.90 (0.06)	-0.94 (0.06)
CI (Change Mean)	-0.61, -0.37	-0.93, -0.69	-0.99, -0.75	-1.02, -0.78	-1.05, -0.82
Tmt Diff Change	-	-0.31	-0.38	-0.41	-0.44
CI (Tmt Diff)	-	-0.48, -0.14	-0.55, -0.21	-0.57, -0.24	-0.61, -0.28
Percentage of Days Urgency Experienced Weeks 5-12 Percentage	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	130	136	140
Baseline Mean (SD)	82.07 (18.27)	78.10 (23.72)	74.10 (29.01)	76.59 (25.70)	78.47 (24.81)
Mean (SD)	46.13 (34.97)	38.67 (31.86)	36.49 (33.40)	41.49 (33.99)	40.91 (33.85)
CI (Mean)	40.07, 52.19	33.13, 44.22	30.75, 42.23	35.78, 47.20	35.31, 46.52
Change Mean (SE)	-35.54 (2.98)	-39.06 (2.99)	-37.07 (2.97)	-34.65 (2.90)	-37.02 (2.87)
CI (Change Mean)	-41.40, -29.69	-44.94 (-33.18)	-42.91, -31.24	-40.35, -28.96	-42.65, -31.39
Tmt Diff Change	-	-3.51	-1.53	0.89	-1.48
CI (Tmt Diff)	-	-11.77, 4.74	-9.74, 6.68	-7.23, 9.01	-9.55, 6.59
Percentage of Days Incomplete Evacuation Experienced Weeks 5-12 Percentage	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	130	136	140
Baseline Mean (SD)	76.75 (26.65)	78.71 (27.15)	73.93 (26.43)	76.19 (27.83)	74.77 (29.18)
Mean (SD)	51.44 (37.09)	46.73 (35.60)	42.32 (36.90)	47.17 (36.94)	43.82 (36.51)
CI (Mean)	45.01, 57.86	40.54, 52.92	35.98, 48.67	40.96, 53.38	37.77, 49.87
Change Mean (SE)	-24.86 (3.22)	-31.53 (3.23)	-30.97 (3.21)	-28.36 (3.13)	-30.39 (3.09)
CI (Change Mean)	-31.18, -18.55	-37.88, -25.19	-37.26, -24.67	-34.50, -22.21	-36.47, -24.31
Tmt Diff Change	-	-6.67	-6.10	-3.49	-5.52
CI (Tmt Diff)	-	-15.58, 2.24	-14.96, 2.76	-12.26, 5.27	-14.23, 3.18
Percentage of Days Bloating or Abdominal Distension Experienced Weeks 5-12 Percentage	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
n	128	127	130	136	140
Baseline Mean (SD)	73.61 (34.92)	80.20 (25.37)	70.50 (33.97)	71.21 (34.89)	69.74 (34.43)
Mean (SD)	51.19 (39.03)	52.15 (37.56)	44.42 (39.21)	47.42 (37.81)	45.60 (38.13)
CI (Mean)	44.43, 57.95	45.62, 58.69	37.68, 51.16	41.06, 53.77	39.29, 51.92
Change Mean (SE)	-22.30 (3.09)	-27.96 (3.10)	-25.96 (3.08)	-23.76 (3.00)	-23.99 (2.97)
CI (Change Mean)	-28.36, -16.24	-34.04, -21.87	-32.00, -19.92	-29.66, -17.89	-29.82, -18.16
Tmt Diff Change	-	-5.66	-3.66	-1.46	-1.69
CI (Tmt Diff)	-	-14.21, 2.89	-12.16, 4.84	-9.87, 6.95	-10.05, 6.66
Health Outcomes Variables (ITT With LOCF):					
	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=131	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
IBSQOL					
Emotional					
n	121	125	129	130	137
Baseline Mean (SE)	43.8 (2.1)	46.0 (1.9)	45.1 (1.9)	41.6 (2.0)	46.0 (1.8)
Change from Baseline Mean (SE)	16.0 (2.1)	18.6 (2.0)	19.7 (2.0)	18.2 (2.0)	19.1 (2.0)
Tmt Diff (SE)	-	2.6 (2.9)	3.7 (2.9)	2.2 (2.9)	3.2 (2.8)
95% CI	-	-3.1, 8.3	-2.0, 9.3	-3.5, 7.8	-2.4, 8.7
Mental Health					
n	122	125	128	130	137
Baseline Mean (SE)	67.7 (1.9)	71.4 (1.8)	68.7 (1.7)	66.8 (1.7)	69.0 (1.8)
Change from Baseline Mean (SE)	10.0 (1.5)	10.7 (1.4)	12.3 (1.4)	10.9 (1.4)	12.3 (1.4)
Tmt Diff (SE)	-	0.7 (2.0)	2.3 (2.0)	0.8 (2.0)	2.3 (2.0)
95% CI	-	-3.3, 4.7	-1.7, 6.3	-3.1, 4.8	-1.7, 6.2
Sleep					

n	128	127	130	135	139
Baseline Mean (SE)	66.9 (1.9)	66.5 (2.0)	65.6 (2.2)	66.2 (2.0)	65.0 (1.9)
Change from Baseline Mean (SE)	9.3 (1.6)	12.9 (1.6)	13.9 (1.6)	9.9 (1.6)	11.5 (1.6)
Tmt Diff (SE)	-	3.6 (2.3)	4.6 (2.3)	0.6 (2.2)	2.2 (2.2)
95% CI	-	-0.8, 8.1	0.2, 9.0	-3.8, 5.0	-2.2, 6.5
Energy					
n	128	127	130	135	139
Baseline Mean (SE)	53.1 (2.5)	54.7 (2.5)	53.1 (2.3)	50.4 (2.2)	55.2 (2.2)
Change from Baseline Mean (SE)	15.9 (2.0)	18.5 (2.0)	19.8 (2.0)	16.7 (2.0)	18.4 (1.9)
Tmt Diff (SE)	-	2.6 (2.8)	4.0 (2.8)	0.9 (2.8)	2.6 (2.8)
95% CI	-	-2.9, 8.2	-1.5, 9.5	-4.6, 6.3	-2.8, 8.0
Physical Functioning					
n	127	126	124	135	137
Baseline Mean (SE)	73.2 (2.1)	75.9 (1.9)	74.3 (2.0)	72.0 (1.9)	72.0 (2.0)
Change from Baseline Mean (SE)	7.8 (1.5)	11.9 (1.5)	11.0 (1.5)	8.0 (1.4)	12.1 (1.4)
Tmt Diff (SE)	-	4.1 (2.1)	3.2 (2.1)	0.2 (2.0)	4.4 (2.0)
95% CI	-	0.1, 8.2	-0.9, 7.3	-3.8, 4.2	0.4, 8.3
Food					
n	128	127	130	135	139
Baseline Mean (SE)	56.7 (1.8)	60.9 (1.7)	59.8 (1.9)	59.4 (1.9)	58.0 (1.9)
Change from Baseline Mean (SE)	8.6 (1.6)	13.2 (1.6)	15.3 (1.6)	12.4 (1.6)	13.1 (1.5)
Tmt Diff (SE)	-	4.6 (2.3)	6.7 (2.3)	3.8 (2.2)	4.6 (2.2)
95% CI	-	0.2, 9.1	2.3, 11.2	-0.6, 8.2	0.2, 8.9
Social Functioning					
n	128	127	130	135	139
Baseline Mean (SE)	45.1 (2.1)	46.1 (2.2)	44.4 (2.3)	43.7 (2.2)	46.1 (2.2)
Change from Baseline Mean (SE)	17.0 (2.0)	20.6 (2.0)	25.5 (2.0)	17.8 (2.0)	22.7 (2.0)
Tmt Diff (SE)	-	3.6 (2.9)	8.6 (2.9)	0.8 (2.8)	5.7 (2.8)
95% CI	-	-2.0, 9.3	2.9, 14.2	-4.8, 6.4	0.2, 11.2
Role Physical					
n	128	127	130	135	139
Baseline Mean (SE)	42.9 (2.4)	47.0 (2.4)	41.7 (2.2)	39.5 (2.4)	44.5 (2.2)
Change from Baseline Mean (SE)	16.7 (2.2)	17.5 (2.2)	21.7 (2.2)	17.1 (2.2)	15.7 (2.1)
Tmt Diff (SE)	-	0.8 (3.1)	5.0 (3.1)	0.5 (3.1)	-1.0 (3.0)
95% CI	-	-5.3, 6.9	-1.0, 11.1	-5.6, 6.5	-6.9, 5.0
Sexual Relations					
n	100	103	99	97	115
Baseline Mean (SE)	73.0 (2.6)	71.3 (2.4)	68.0 (2.4)	73.0 (2.2)	72.3 (2.3)
Change from Baseline Mean (SE)	8.0 (1.7)	10.9 (1.7)	12.0 (1.7)	8.4 (1.7)	9.2 (1.6)
Tmt Diff (SE)	-	3.0 (2.4)	4.0 (2.4)	0.4 (2.4)	1.2 (2.3)
95% CI	-	-1.7, 7.6	-0.7, 8.8	-4.3, 5.2	-3.4, 5.8
Safety Results: The investigator was responsible for recording and reporting AEs observed before, during, and after study drug treatment. During the screening period, only serious adverse events (SAEs) were assessed by the investigator as related to study participation were transcribed into the CRF and reported to the Sponsor. During the 12-week treatment and 4-week follow-up periods all AEs, regardless of causality or seriousness, were transcribed into the CRF and reported to the Sponsor.					
Most Frequent Adverse Events – On-Therapy	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=130	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects With Any AE(s)	65 (51)	73 (57)	86 (66)	80 (59)	87 (62)
Constipation	0	12 (9)	19 (15)	15 (11)	29 (21)
Abdominal Discomfort & Pain	4 (3)	6 (5)	16 (12)	7 (5)	10 (7)
Gastrointestinal Discomfort & Pain	2 (2)	3 (2)	8 (6)	4 (3)	13 (9)
Diarrhea	4 (3)	2 (2)	7 (5)	5 (4)	1 (<1)
Hemorrhoids	2 (2)	7 (6)	2 (2)	3 (2)	3 (2)
Regurgitation & Reflux	3 (2)	4 (3)	4 (3)	7 (5)	1 (<1)

Ear, Nose & Throat Infections	6 (5)	8 (6)	10 (8)	10 (7)	8 (6)
Headache	10 (8)	8 (6)	9 (7)	11 (8)	7 (5)
Musculoskeletal Pain	8 (6)	4 (3)	3 (2)	5 (4)	5 (4)
Malaise & Fatigue	5 (4)	1 (<1)	5 (4)	5 (4)	3 (2)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	Placebo N=128	Alosetron 0.5mg BID N=127	Alosetron 1.0mg BID N=130	Alosetron 2.0mg BID N=136	Alosetron 4.0mg BID N=140
	n(%) [n]	n(%) [n]	n(%) [n]	n(%) [n]	n(%) [n]
Subjects With Non-Fatal SAEs	0	2 (2) [0]	5 (4) [0]	1 (<1) [0]	2 (1) [0]
Ear, Nose & Throat Infections	0	1 (<1) [0]	0	0	0
Primary Malignant Male Reproductive Neoplasia	0	1 (<1) [0]	1 (<1) [0]	0	0
Cholecystitis	0	0	1 (<1) [0]	0	0
Chest Symptoms	0	0	1 (<1) [0]	0	1 (<1) [0]
Diarrhea	0	0	1 (<1) [0]	0	0
Nausea	0	0	1 (<1) [0]	0	0
Vomiting	0	0	1 (<1) [0]	0	0
Pneumonia	0	0	1 (<1) [0]	0	0
Tachyarrhythmias	0	0	1 (<1) [0]	0	0
Pericarditis	0	0	0	1 (<1) [0]	0
Fractures	0	0	0	0	1 (<1) [0]
Subjects With Fatal SAEs	0	0	0	0	0
Conclusion: See publication below.					

Publications:

Phase II Dose-ranging Study of Efficacy and Safety of Alosetron in Men with Diarrhea-Predominant Irritable Bowel Syndrome, L Chang, V Ameen, G Dukes, D McSorley, E. Carter, E Mayer, Am J Gastro,100:115-123,2005

12-week randomized, double-blind, placebo-controlled, parallel,-group, dose-ranging, Phase II study to assess the clinical efficacy of alosetron in male subjects with IBS, Edwards EB, Heitman CK, Hall P, Hamedani AG, Dukes G, Mangel, Am J Gastro 96(9 supp 1): S317, 2001

Abstract: Gender differences in placebo response in patients with diarrhea-predominant irritable bowel syndrome (d-ibs). Ameen, V. Z. MD, Heath, A. T., and Chang, L. Digestive Disease Week 2005: American Association for the Study of Liver Diseases, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy, Society for Surgery of the Alimentary Tract 5/15/2005 Chicago, IL; USA

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