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<b>Study No.:</b> S3B20032
<b>Title:</b> A four-week, open, multicenter study to assess the safety and efficacy of 1 mg once daily (QD) of GR68755 in female subjects with severe diarrhea-predominant irritable bowel syndrome (IBS) who have frequent bowel urgency
<b>Rationale:</b> This study is an exploratory study aiming (i) to obtain clinical experience of alosetron/GR68755 in Japanese subjects with severe d-IBS to explore the feasibility of the next phase study and (ii) to obtain reference data for endpoints and dosage and administration of a next phase study.
<b>Phase:</b> II
<b>Study Period:</b> 18-Sep-2003 to 14-May-2005
<b>Study Design:</b> This study is a multicenter, open study.
<b>Centres:</b> 12 in Japan
<b>Indication:</b> Women with Severe Diarrhea-Predominant IBS
<b>Treatment:</b> Subjects underwent observation and examinations during the screening phase, and subjects who met the eligibility criteria were entered into the treatment phase. During the treatment phase, subjects took alosetron 1 mg tablets once daily (QD), every morning for 28 days.
<b>Objectives:</b> To obtain the clinical experience of alosetron 1 mg QD in Japanese female subjects with severe d-IBS who have frequent bowel urgency and to obtain exploratory efficacy and safety data that can be used as reference for endpoints and dosage and administration of a next phase clinical study in Japan.
<b>Primary Outcome/Efficacy Variable:</b> 1) Global Improvement Scale(GIS), 2) Satisfactory control of IBS related bowel urgency
<b>Secondary Outcome/Efficacy Variable(s):</b> 1) Adequate relief of IBS pain and discomfort,2) Days without abdominal pain and discomfort,3) Severity score of abdominal pain and/or discomfort,4) Intestine function (Number of bowel movements, Stool form, Feeling of incomplete evacuation, Abdominal bloating)
<b>Statistical Methods:</b> With a sample size of n=30, assuming that the population incidence of constipation was 10%, 15% or 20%, the power to detect constipation in at least 1 subject would be 95.8%, 99.2% or 99.9%, respectively (based on binominal distribution). Also assuming the population incidence of abdominal discomfort or abdominal pain was 5% or 10%, the power would be 78.5% or 95.8%. The populations for efficacy analysis were Full Analysis Set (FAS) and Per Protocol Set (PPS) The FAS consisted of all patients who entered the treatment phase and did not fall under any of the following conditions: <ul style="list-style-type: none"> <li>• Patients who did not have severe d-IBS with bowel urgency and abdominal pain or discomfort during the screening phase.</li> <li>• Patients who failed to take at least one dose of the investigational product.</li> <li>• Patients for whom all data were missing after the start of study treatment.</li> <li>• Others who were considered ineligible for the FAS population.</li> </ul> The Per Protocol Set (PPS) consisted of the subset of the FAS population who did not fall under the following condition. <ul style="list-style-type: none"> <li>• Patients who were considered ineligible for efficacy assessments because of protocol violations.</li> </ul> PPS population was used to confirm the results of FAS population. The primary population was the FAS. The efficacy results based on the FAS population and on the PPS population were investigated for the robustness. The population for safety analysis was SP. For the primary analyses, missing data were estimated by carrying forward the last observation (LOCF). Furthermore, the observed cases (OC) dataset was also analyzed. For the primary and secondary efficacy variables, summary statistics were calculated at each time point, and changes from baseline or % changes from baseline were presented visually using summary statistics. The association of the primary and secondary efficacy variables was investigated by using Spearman rank-order correlation coefficient.
<b>Study Population:</b> Female subjects aged 20-64 years who had been diagnosed with severe d-IBS (at least 6 months of d-IBS symptoms as defined by the Rome II Criteria), and failed conventional IBS therapy. <ol style="list-style-type: none"> <li>1) An average stool consistency score recorded during the screening phase is <math>\geq 3.0</math>.</li> <li>2) Average "severity of abdominal pain or discomfort" score recorded during the screening phase is <math>\geq 1.0</math>.</li> <li>3) Has frequent "bowel urgency" (has urgency <math>\geq 50\%</math> of the days during the screening phase)</li> </ol> The key exclusion criteria are below <ol style="list-style-type: none"> <li>1) Does not have severe d-IBS</li> <li>2) Has current evidence of or history of chronic or severe constipation, or a history of sequela from constipation</li> </ol>

3) Is currently constipated or did report no stool for three or more consecutive days during the screening phase.	
Number of Subjects:	
Planned, N	30
Entered, N	32
Completed, n (%)	28 (87.5)
Total Number Subjects Withdrawn, N (%)	4 (12.5)
Withdrawn due to Adverse Events n (%)	3 (9.4)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	1 (3.1)
Demographics	
N (FAS)	32
Females: Males	32:0
Mean Age, years (SD)	37.3 (10.44)
Oriental, n (%)	32 (100)
<b>Primary Efficacy Results:</b>	
<b>A responder for GIS of IBS symptoms</b>	
FAS population, n	32
GIS responder, n	21
Rate of GIS responder %	65.6
(95% CI)	(46.8 ,81.4)
<b>The proportion of days that a subject has satisfactory control of bowel urgency (responder rate)</b>	
FAS population, n	32
Mean(SD)	72.21 (25.249)
(95% CI)	(63.11, 81.31)
<b>Secondary Efficacy Results:</b>	
<b>The proportion of days with incomplete evacuation The proportion of days with relief of IBS pain and discomfort</b>	
FAS population, n	32
Mean(SD)	75.00 (32.379)
<b>The proportion of days with abdominal pain and/or discomfort</b>	
FAS population, n	32
Screening phase, Mean(SD)	88.41 (14.430)
Week 1, Mean(SD)	69.64 (26.354)
Week 2, Mean(SD)	63.62 (30.648)
Week 3, Mean(SD)	56.03 (36.291)
Week 4, Mean(SD)	52.90 (35.960)
<b>The average of severity of abdominal pain and/or discomfort</b>	
FAS population, n	32
Screening phase, Mean(SD)	1.76 (0.532)
Week 1, Mean(SD)	1.35 (0.884)
Week 2, Mean(SD)	1.12 (0.721)
Week 3, Mean(SD)	0.94 (0.736)
Week 4, Mean(SD)	0.83 (0.691)
<b>The average of bowel movement</b>	
FAS population, n	32
Screening phase, Mean(SD)	2.41 (1.034)
Week 1, Mean(SD)	1.73 (0.895)
Week 2, Mean(SD)	1.76 (1.053)
Week 3, Mean(SD)	1.73 (0.918)
Week 4, Mean(SD)	1.82 (1.040)
<b>The average of stool form score</b>	
FAS population, n	32
Screening phase, Mean(SD)	3.75 (0.427)
Week 1, Mean(SD)	3.11 (0.768)

Week 2, Mean(SD)	3.13 (0.695)
Week 3, Mean(SD)	2.99 (0.693)
Week 4, Mean(SD)	3.08 (0.638)
<b>The proportion of days with incomplete evacuation</b>	
FAS population, n	32
Screening phase, Mean(SD)	56.88 (35.702)
Week 1, Mean(SD)	51.19 (39.169)
Week 2, Mean(SD)	47.43 (42.975)
Week 3, Mean(SD)	39.84 (41.938)
Week 4, Mean(SD)	39.11 (42.260)
<b>The proportion of days with abdominal bloating</b>	
FAS population, n	32
Screening phase, Mean(SD)	51.17 (37.997)
Week 1, Mean(SD)	56.70 (35.271)
Week 2, Mean(SD)	44.64 (40.528)
Week 3, Mean(SD)	50.89 (40.721)
Week 4, Mean(SD)	49.11 (40.559)
<b>The proportion of days with bowel urgency</b>	
FAS population, n	32
Screening phase, Mean(SD)	74.93 (18.941)
Week 1, Mean(SD)	42.41 (33.745)
Week 2, Mean(SD)	35.71 (28.571)
Week 3, Mean(SD)	22.77 (28.074)
Week 4, Mean(SD)	28.13 (31.316)
<b>Safety Results:</b> On-therapy AEs were events that occurred on the first day of treatment and up to follow-up visit.	
<b>Most Frequent Adverse Events – On-Therapy</b>	
N	32
Subjects with any AE(s), n(%)	25 (78.1)
Constipation	6 (18.8)
Nasopharyngitis	5 (15.6)
Headache	3 (9.4)
Abdominal distension	2 (6.3)
Malaise	2 (6.3)
Eosinophil percentage increased	2 (6.3)
Dizziness	2 (6.3)
Somnolence	2 (6.3)
Hypertension	2 (6.3)
<b>Serious Adverse Events - On-Therapy</b> <b>n (%) [n considered by the investigator to be related to study medication]</b>	
Subjects with non-fatal SAEs, n (%)	0
Subjects with fatal SAEs, n (%)	0

**Conclusion:**

To obtain the clinical experience with alosetron 1mg once daily, alosetron was administered to a total of 32 Japanese female subjects with severe diarrhea-predominant IBS. Twenty-one (21) of the 32 subjects (65.6%) were GIS responders. The proportion of days with satisfactory control of bowel urgency was 72.21%. Adverse events were reported in 25 (78.1%) subjects, with the most frequently reported events being constipation and nasopharyngitis. No fatal or non-fatal serious adverse events were reported.

**Publications:**

No publication

Date Updated: 04-Apr-2006