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<b>Study No.:</b> S3B30012
<b>Title:</b> A 6-Week Trial of Alosetron Hydrochloride 1mg Twice Daily as Empirical Therapy in Female Subjects With Symptoms of Non-Constipated Irritable Bowel Syndrome
<b>Rationale:</b> This study was conducted to predict the probability that a female subject with symptoms consistent with non-constipated irritable bowel syndrome (IBS), who responded to a 6-week course of alosetron, would subsequently be confirmed with a diagnosis of IBS.
<b>Phase:</b> IIIb
<b>Study Period:</b> 05 Oct 1999 to 28 Sep 2000
<b>Study Design:</b> A multi-center, open-label study in female subjects with symptoms of non-constipated IBS; with a 1-week screening phase, a 6-week treatment phase followed by a 2-week period for gastrointestinal (GI) assessment (totalling up to 8 weeks for all subjects). Subjects who responded to alosetron and had a normal GI assessment continued on therapy for a 4 month follow-up phase (totalling up to 24 weeks for responders diagnosed with non-constipated IBS).
<b>Centres:</b> The study was initiated at 121 centers in the United States (US); 91 centers enrolled subjects
<b>Indication:</b> Non-Constipated IBS
<b>Treatment:</b> At the end of the 1-week screening period, eligible subjects received open-label alosetron 1mg tablets to be taken orally twice daily ( <i>bis in die</i> [BID]) for 6 weeks starting on Day 1.
<b>Objectives:</b> The primary objective of the study was to predict the probability that a female subject with symptoms consistent with non-constipated IBS, who responded to a 6-week course of alosetron, would subsequently be confirmed with a diagnosis of IBS. The secondary objectives were to evaluate the safety and tolerability of alosetron over the study period and described the demographic and symptom profile of subjects who were subsequently diagnosed with organic GI disease.
<b>Primary Outcome/Efficacy Variable:</b> This study evaluated the proportion of subjects who responded to treatment and subsequently had a normal GI assessment (defined as the positive predictive value [PPV] of a confirmed diagnosis of IBS). The primary response measure was adequate relief of pain and discomfort. During the first 6 weeks of the treatment phase, subjects responded weekly through an interactive voice response system (IVRS) to the question "Over the past 7 days, have you had adequate relief of your IBS pain and discomfort (yes/no)?" Responders were subjects who completed the 6-week empiric treatment phase of the study and reported adequate relief of IBS pain and discomfort for at least 3 of the 6 weeks of treatment. The GI assessment was considered normal if the evaluating gastroenterologist did not detect abnormalities that were considered likely to contribute to symptoms of abdominal pain and discomfort and altered bowel dysfunction.
<b>Secondary Outcome/Efficacy Variable(s):</b> The secondary efficacy and outcome variables of the study were as follows: Proportion of subjects diagnosed with IBS at Week 8 who maintained a diagnosis of IBS at the final visit Changes in specified GI symptoms (bowel urgency, stool frequency, stool consistency, and sense of incomplete evacuation) in the first 6 weeks Adverse events (AEs) grouped by body system and preferred term
<b>Statistical Methods:</b> The sample size for this study was based on an estimate of the proportion of evaluable subjects who responded to alosetron at Week 6 and who were subsequently confirmed to have a diagnosis of IBS (defined as the positive predictive value [PPV] of a confirmed diagnosis of IBS). Based on a clinically relevant proportion of 95% with a 3% level of precision, 225 evaluable (ie, completing the 6-week treatment phase, demonstrating a positive response to alosetron, and undergoing the required GI work-up) subjects were required. Given an approximate 60% response rate in the 2 Phase III clinical trials, an estimated 10% dropout rate during treatment with an additional 15% dropout rate prior to completing the GI work-up, the total sample size was increased to at least 490 subjects.  For the primary endpoint, the numbers of Responders and Non-responders were calculated. The PPV of responding to alosetron was calculated as follows: # of Responders with a confirmed diagnosis of IBS divided by # of Responders who completed the GI work-up.

All subjects who were enrolled in the study were included in the intent-to-treat (ITT) population. The safety population comprised subjects in the ITT Population who received study drug. The primary efficacy (PE) population included all subjects in the safety population who completed the 6 weeks of treatment, responded to treatment, and completed the GI work-up.	
<b>Study Population:</b> Subjects were female ambulatory outpatients aged 18 to 60 years, inclusive who reported consistent or recurrent symptoms (for $\geq 12$ weeks in the previous 12 months) of abdominal pain or discomfort associated with 2 or more of the following: relief with defecation, change in stool frequency, change in stool consistency and were suggestive of non-constipated IBS. Subjects with a diagnosis and/or treatment of IBS within the previous 5 years were ineligible for study participation.	
<b>Number of Subjects:</b>	<b>Alosetron 1mg</b>
Planned, N	490
Enrolled, N	426
Dosed, N	422
Week 8, N	426
Completed, n (%)	281 (66)
Total Number Subjects Withdrawn, n (%)	145 (34)
Withdrawn Due to Adverse Events, n (%)	65 (15)
Withdrawn Due to Lack of Efficacy, n (%)	15 (4)
Withdrawn for Other Reasons, n (%)	65 (15)
Week 24, N	235
Completed, n (%)	205 (87)
Total Number Subjects Withdrawn, n (%)	30 (13)
Withdrawn Due to Adverse Events, n (%)	3 (1)
Withdrawn Due to Lack of Efficacy, n (%)	1 (<1)
Withdrawn for Other Reasons, n (%)	26 (11)
<b>Demographics:</b>	<b>Alosetron 1mg</b>
N (ITT)	426
Females:Males, n:n	426:0
Mean Age, Years (SD)	40.3 (11.6)
Caucasian, n (%)	380 (89)
Time Since Onset of IBS Symptoms	n = 425
Mean years (SD)	8.14 (8.44)
<b>Primary Efficacy Results (PE):</b>	
	<b>Alosetron 1mg</b>
<b>N (PE)</b>	238
<b>PPV (N, %)</b>	238 (100)
<b>Secondary Outcome Variable(s) (PE &amp; ITT):</b>	
<b>Proportion of Subjects Maintaining Diagnosis of IBS at Final Visit</b>	<b>Alosetron 1mg</b>
ITT Population, N	426
Final Diagnosis, N	336
IBS, n (%)	331 (99)
<b>Proportion of Days With Bowel Urgency Overall After 6 Weeks of Treatment</b>	<b>Alosetron 1mg</b>
Baseline, ITT population	426
<25%	24 (6)
25-<50%	87 (20)
50-<75%	123 (29)
$\geq 75\%$	192 (45%)
PE Population, N	238
Overall, n	238
Mean (SD)	0.40 (0.304)
<b>Proportion of Days With Sense of Incomplete Evacuation Overall After 6 Weeks of Treatment</b>	<b>Alosetron 1mg</b>

Baseline, ITT population, N	426
<25%	80 (19)
25-<50%	95 (22)
50-<75%	131 (31)
≥75%	120 (28)
PE Population, N	238
Overall, n	238
Mean (SD)	0.37 (0.262)
<b>Average Stool Consistency<sup>a</sup> Overall After 6 Weeks of Treatment</b>	<b>Alosetron 1mg</b>
Baseline, ITT population, N	426
Hard	3 (<1)
Loose	14 (3)
Formed	262 (62)
Watery	147 (35)
PE Population, N	238
Overall, n	238
Mean (SD)	2.74 (0.589)
<b>Average Stool Frequency Overall After 6 Weeks of Treatment</b>	<b>Alosetron 1mg</b>
Baseline, ITT Population, N	426
Mean (SD)	5.0 (2.9)
PE Population, N	238
Overall, n	238
Mean (SD)	1.98 (0.799)
a. Stool Consistency Scale: 1=Very Hard; 2=Hard; 3=Formed; 4=Loose; 5=Watery	
Safety Results (Safety): The Safety Population comprised subjects in the ITT Population who received study drug (n=422). Events by body system and study phase are summarized in the following tables.	
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>Alosetron 1mg</b>
	<b>N=422</b>
	<b>n (%)</b>
Subjects With Any AE(s)	269 (64)
Constipation	114 (27)
Gastrointestinal Discomfort & Pain	54 (13)
Ear, Nose, & Throat Infections	33 (8)
Nausea	28 (7)
Headache	26 (6)
Gastrointestinal Gaseous Symptoms	23 (5)
Diverticulosis	16 (4)
Diarrhea	14 (3)
Gastrointestinal Polyps of Uncertain Behavior	13 (3)
Abdominal Distension	12 (3)
Hemorrhoids	12 (3)
<b>Serious Adverse Events - On-Therapy</b> <b>n (%) [n considered by the investigator to be related to study medication]</b>	<b>Alosetron 1mg</b>
	<b>N=422</b>
	<b>n (%) [related]</b>
Subjects With Non-Fatal SAEs	4 (<1) [1]
Cancer of Large Intestine	1 (<1) [0]
Gastrointestinal Discomfort & Pain	1 (<1) [1]
Vomiting	1 (<1) [1]
Fluid Disturbances	1 (<1) [1]
Abortion & Stillbirth	1 (<1) [0]
Subjects With Fatal SAEs	1 (<1) [0]
Unknown Cause	1(<1)[0]

**Conclusion:**

See publication below.

**Publications:**

Northcutt A, Mangel A, Hamm L, et al. Confirmation of Presumptive Diagnosis of Irritable Bowel Syndrome (IBS) Utilizing Rome II Criteria and Simple Laboratory Screening Tests with Diagnostic (GI) Evaluation Program and abstracts of Digestive Disease Week 2001; May 20-23, 2001; Atlanta, Georgia.

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