Synopsis

Identifier: RM2005/00190/00 **Study Number:** SB-223412/068

Title: An Eight Week, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate Efficacy and Safety of Talnetant in Subjects with Irritable Bowel Syndrome.

Investigators: Multicenter study

Study centers: A total of 109 centers enrolled subjects: 53 in the United States (US), 28 in Europe [8 in Germany, 7 in France, 4 in the United Kingdom, 4 in Spain, 4 in Sweden, and one in the Netherlands], 16 in Canada, 11 in Australia, and one in South Africa.

Publications: None at the time of this report

Study Period: 25 October 2004 (first subject screened) – 21 July 2005 (last subject completed)

Phase of Development: IIB

Objectives: The primary objective was to determine whether Talnetant (SB-223412) provided adequate relief from IBS pain and discomfort for at least one of three Talnetant dose groups compared with placebo and to determine the safety and tolerability of Talnetant in subjects with IBS. Secondary objectives were to explore the differentiation in response among subgroups of subjects with IBS, obtain dose-response information for design of subsequent studies, evaluate the positive treatment effects within bowel subgroups for secondary symptoms; compare treatment groups for global improvement of IBS symptoms (Global Improvement Scale, GIS), improvement of IBS pain or discomfort, changes in bowel patterns and improvement of subjects' IBS-related quality of life (IBSQoL). Another secondary objective was to estimate the plasma concentration of Talnetant in IBS subjects and to characterize the relationship between plasma concentration and response (adequate relief).

Methodology: This was an 8-week, randomized, double-blind, placebo-controlled, dose-ranging study to compare three oral twice-daily doses of Talnetant (100, 200, and 400mg) with placebo in subjects with IBS. Male and female subjects, ≥18 years of age, with recurrent symptoms meeting the Rome II criteria for IBS entered a 2-week Screening Period during which they recorded their IBS pain or discomfort scores and other GI symptoms daily via a touch-tone telephone data entry system. Subjects meeting the screening requirements and all other inclusion/exclusion criteria were equally randomized to one of the four treatment groups for an 8-week Treatment Period followed by a 4-week Follow-up Period of no treatment. During the Treatment and Follow-up Phases, subjects recorded daily and weekly self-assessments of IBS pain and discomfort and lower GI symptoms, as well as weekly assessments of adequate relief of IBS pain and discomfort, improvements in bowel pattern, bowel symptoms and IBS pain, and global improvement in IBS symptoms (using GIS). Subject's quality of life (QoL) was assessed at Randomization and end of treatment via the IBSQoL questionnaire. Total

study duration was up to 14 weeks. For those subjects requiring a colon examination between screening and randomization, total study duration was up to 15 weeks.

Number of subjects: A total of 1396 subjects were screened, 732 subjects were randomized: 182 to Talnetant 100mg, 185 to Talnetant 200mg, 183 to Talnetant 400mg, and 182 to placebo. Most subjects completed the study: 147 (81%) in the Talnetant 100mg group, 155 (84%) in the Talnetant 200mg group, 155 (85%) in the Talnetant 400mg group, and 150 (82%) in the placebo group.

Diagnosis and main criteria for inclusion: Male or female adult subjects ≥18 years of age diagnosed with IBS consistent with Rome II criteria were eligible for this study. During the 2-week screening phase, subjects must have documented an average IBS pain or discomfort score ≥1.5 and conducted self-assessments on at least 12 days using the telephone data entry system. All subjects randomized to treatment had a normal colonic examination within 2-years prior to randomization. At the end of the 2-week Screening Phase, for the purpose of subgroup analyses, subjects were classified by IBS subtype as diarrhea-predominant subtype (D-IBS) or constipation-predominant subtype (C-IBS), based on at least 70% of days with diarrhea or constipation, respectively. Subjects not meeting the 70% threshold were classified as "other" (O-IBS).

Treatment administration: Subjects received Talnetant (Phase IIB formulation) 100mg BID, 200mg BID, or 400mg BID, or Placebo BID. Talnetant was supplied as 100mg (Batch: 041040278, 041056821) and 200mg (Batch: 041040281, 041056822, 041040686) tablets. Batch numbers for the matching placebo tablets were 041040307 and 041056823.

Criteria for evaluation: The primary efficacy endpoint was the proportion of subjects that recorded adequate relief of IBS pain and discomfort on each of the last 4 weeks of treatment (i.e., Week 5 through Week 8) of the Treatment Phase. Safety was assessed by monitoring adverse events and clinical laboratory (hematology, clinical chemistry, and sex hormones) tests. Blood samples were collected to evaluate the relationship between Talnetant exposure and treatment response.

Statistical methods: The sample size was based on modeling the dose-response relationship in the proportions of subjects with adequate relief of IBS pain and discomfort on each of the last 4 weeks of treatment using quantal logistic regression and estimates from a previous IBS study with Talnetant. In the previous study, a responder was defined as a subject who had reported adequate relief on each week of the last 4 weeks of treatment (Week 5 trough Week 8 or 4/4 weeks with adequate relief). The 4/4 adequate relief response rate for placebo was approximately 20% and the 4/4 adequate relief response rate for Talnetant 100mg QD was 35%. In the present study, assuming a 20% response rate for placebo, a 35% response rate for Talnetant 100mg BID, a 40% response rate for Talnetant 200mg BID, and a 45% response rate for Talnetant 400mg BID, n=113 subjects per group was needed to detect a significant dose-response relationship with 90% power at the two-sided α=0.05 significance level. To allow for a small percentage of dropouts, a target sample size of n=125 subjects/group was chosen for a total of n=500 O-IBS subjects (primary population for efficacy analyses).

The primary efficacy endpoint was the proportion of O-IBS subjects that recorded adequate relief of IBS pain and discomfort on each of the last 4 weeks of treatment (i.e., Week 5 through Week 8) of the Treatment Phase using the LOCF approach for missing data. The significance of a dose-response relationship for adequate relief across the placebo and Talnetant dose groups was determined using a quantal logistics regression model. If significant, each Talnetant dose, beginning with the 100mg BID dose, was compared with placebo using Fisher's exact test. The next higher dose was analyzed only if the lower dose was significantly different from placebo. The following summary statistics were provided for each treatment group: mean, standard error, 95% confidence interval (CI) for the mean, treatment difference versus placebo, and 95% CI for the treatment difference.

Secondary efficacy measures included weekly adequate relief and average adequate relief rate of IBS pain and discomfort during Week 5 through Week 8, GIS responders, changes in bowel symptoms and improvements in bowel function, pain severity scores, pain/discomfort-free days; improvements in pain or discomfort; and changes in IBSQoL domains. Each bowel symptom and function, pain severity, pain improvement and pain-free days, and change from baseline was summarized by treatment group for both the last 4 weeks on treatment (i.e., Weeks 5 to 8) and for each week of the Treatment and Follow-up Phases; pairwise comparisons between each Talnetant dose group with placebo were made using Wilcoxon rank sum tests. The proportions of GIS responders were summarized at each week of the Treatment and Follow-up Phases and compared between each Talnetant dose and placebo using Fisher's exact test. In addition, the complete 7-point scale was summarized by treatment group for each week of the Treatment and Follow-up Phases and compared between each Talnetant dose group and placebo using the Wilcoxon rank sum test. Change from baseline in IBSQoL scores for each Talnetant group versus placebo was evaluated using analysis of covariance.

AEs were classified by body system and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term and were tabulated by treatment group, maximum intensity, seriousness, and attribution to study drug. Comparison of the incidence of AEs for each Talnetant group versus placebo were made using Fishers exact test. Summary statistics of clinical laboratory evaluations (hematology, clinical chemistry, and sex hormone levels) data were reported.

The relationship between trough plasma concentrations of Talnetant and response (e.g., adequate relief, global improvement, pain severity) was evaluated graphically by IBS subtype.

Summary: A total of 732 subjects were randomized in this study (ITT Population); the majority of subjects (74%) were women. The study population was predominantly White (96%) and <65 years of age (92%); the mean age was 46 years; and the mean time since IBS onset was 11 years. Subjects were diagnosed with IBS using the Rome II Criteria and had normal findings from an age-appropriate colon exam within 2 years of being randomized to treatment. Approximately two-thirds of the subjects (67%, 488/732) had a bowel pattern classified as O-IBS at the end of screening and comprised the primary population for analysis. Subjects with D-IBS (96/732) and C-IBS (148/732) were randomized for exploratory purposes.

Efficacy: Talnetant, up to 400mg BID, failed to provide a statistically significant difference in adequate relief of IBS pain and discomfort during the last 4 weeks of treatment compared with placebo in the O-IBS ITT, D-IBS ITT, C-IBS ITT, or ITT populations.

There were no statistically significant differences between any of the Talnetant dose groups compared with placebo in the proportion of responders as measured by GIS at any treatment week in any IBS subtype. No treatment effects were detected for other bowel-related symptoms such as average stool frequency and consistency and days with urgency, bloating and straining. Additionally, there were no treatment differences for changes or improvements in average pain severity or the proportion of pain-free days.

Safety: Doses of Talnetant up to 400mg BID were well tolerated by subjects with IBS. The overall incidence of AEs across the treatment groups ranged from 58% (Talnetant 400mg) to 67% (placebo). The most common AEs were headache (14-19%), nasopharyngitis (6-11%), nausea (4-9%), and abdominal pain (4-8%). The majority of these most common AEs were considered drug-related by the investigator. The incidence of AEs leading to withdrawal from the study was comparable across the treatment groups (7-10%). One percent of subjects (10/732) experienced SAEs during treatment. Half of these subjects had SAEs considered related to study drug by the investigator.

One subject in the Talnetant 100mg group died from thrombosis of multiple abdominal vessels (superior and inferior mesenteric arteries, celiac artery and splenic vein) resulting in complete bowel infarction involving the esophagus down to the rectum and also the liver and spleen. The investigator considered the death possibly caused by study drug. An autopsy was performed and the pathologist cited the cause of death as acute mesenteric ischemia and concluded "It is possible that the patient's protracted bowel symptoms diagnosed as IBS were related to mesenteric ischemia. The thrombi in this case are severely fibrotic and acellular consistent with chronicity. Although a drug effect causing hypercoagulability cannot be ruled out, the chronicity of the thrombi in this case most likely predates the start of the drug trial. A full hypercoagulable work up is not possible at this time; however, a hypercoagulable state of unknown etiology is favored".

Few subjects reported events of bloody diarrhea/rectal bleeding (2%) or severe worsening of abdominal pain (4%). Etiologies of bloody diarrhea/rectal bleeding included anal fissures and hemorrhoids, and the disease under study accounted most often for severe worsening of abdominal pain. None of these events were associated with an event of colonic ischemia/ischemic colitis, and there were no apparent dose-related trends.

No treatment or dose-related trends were apparent for the few subjects who experienced worsening of constipation, diarrhea, or bowel pattern compared with baseline.

No clinically significant changes in hematology or clinical chemistry, including hepatic function, were observed during the study.

In the male population as a whole, there appeared to be a treatment related but not dose related decrease in testosterone levels, with recovery occurring with the cessation of treatment. Using the threshold-defined decrease in total or free testosterone levels, decreases were observed in all treatment groups, including placebo, but appear to be

related to treatment but not to dose. In these subjects, testosterone levels partially recovered upon cessation of treatment.

No treatment-related or dose-related decreases in estradiol or FSH were observed for female subjects.

Pharmacokinetics/Pharmacodynamics: Plasma trough concentrations were as expected based on data from healthy volunteers. Concentrations increased less than proportionally with increasing dose. There were 130 subjects who received various doses of Talnetant, yet had trough concentrations similar to those expected for 600mg BID.

There was no relationship between plasma concentrations and response, including adequate relief, global improvement, or pain severity. Response did not appear to be any better in those subjects with exposures similar to 600mg BID.

Health Outcomes: There were no significant differences between any dose of Talnetant and placebo in any of the nine IBSQoL scales for any of the four populations examined.

Conclusions: Talnetant, up to 400mg BID, failed to provide evidence of efficacy as measured by Adequate Relief of IBS pain and discomfort, global improvement of IBS symptoms (using GIS), bowel-related parameters, or IBS-related quality of life. There was no relationship between plasma concentrations and response, including adequate relief, global improvement, or pain severity. Talnetant was well tolerated by subjects with IBS.

Date of Report: 08 February 2006