Effect of Tegaserod in Chronic Constipation: A Randomized, Double-Blind, Controlled Trial

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Background & Aims: Chronic constipation is a common gastrointestinal disorder. The aim of this study was to evaluate the efficacy, safety, and tolerability of tegaserod, a serotonin subtype 4 receptor partial agonist in patients with chronic constipation.

Methods: This was a randomized, double-blind, placebo-controlled study. After a 2-week baseline, patients received tegaserod 2 mg twice daily (n = 450), tegaserod 6 mg twice daily (n = 451), or placebo (n = 447) for 12 weeks, followed by a 4-week withdrawal period. Responders were those patients having been treated for at least 7 days with an increase of ≥1 complete spontaneous bowel movement/week vs. baseline during weeks 1–4 (primary variable) and weeks 1–12 (secondary variable). Other secondary variables included patient assessment of constipation symptoms (number of bowel movements, stool form, abdominal bloating/distention, straining, and abdominal pain/discomfort), and global assessment of constipation and bowel habits.

Results: Responder rates for complete spontaneous bowel movement/week vs. baseline during weeks 1–4 (primary variable) and weeks 1–12 (secondary variable). Other secondary variables included patient assessment of constipation symptoms (number of bowel movements, stool form, abdominal bloating/distention, straining, and abdominal pain/discomfort), and global assessment of constipation and bowel habits. Results: Responders rates for complete spontaneous bowel movement during weeks 1–4 were significantly greater (P < 0.0001) in the tegaserod 2 mg twice daily (41.4%) and 6 mg twice daily groups (43.2%) vs. placebo (25.1%). This effect was maintained over 12 weeks. Statistically significant improvements over placebo were observed across the majority of secondary variables for both tegaserod doses. No rebound effect was observed after treatment withdrawal. Tegaserod was well tolerated; headache and nasopharyngitis, the most frequent adverse events, were more common in the placebo group than in either tegaserod group. Conclusions: Over 12 weeks, tegaserod treatment produced significant improvements in chronic constipation symptoms and was also safe and well tolerated.

Constipation is a common problem. Population-based studies indicate that approximately 10%–20% of otherwise healthy people report 1 or more symptoms of chronic constipation, with some reports in the U.S. suggesting a prevalence rate exceeding 30%. Definitions of this disorder vary markedly, likely explaining the wide variation in prevalence, but generally include infrequent passage of stools associated with persistent symptoms of straining, hard or lumpy stools, and a feeling of incomplete evacuation.

Constipation is associated with substantial direct and indirect health care costs. In the U.S., the disorder prompts an estimated 2.5 million physician visits per year, with 100,000 referrals to gastroenterologists. It has been estimated that the majority of these visits (85%) result in a prescription for a laxative. Indeed, the annual expenditure for laxatives in the U.S. is estimated at $800 million. These figures probably underestimate the true treatment costs associated with chronic constipation, because individuals typically attempt to treat this persistent condition themselves before seeking medical attention.

Traditional treatments such as laxatives and dietary modifications have been primarily directed towards increasing gastrointestinal (GI) motility and stool frequency. Although such treatment approaches lead to improvement in stool frequency, they can be associated with side effects, including abdominal distention and discomfort. Available data regarding the efficacy of laxatives and fiber in treating constipation are limited, with many randomized trials using short treatment durations. There is an unmet medical need for a well-tolerated and effective therapy for patients with chronic constipation that not only increases bowel frequency but also relieves the multiple symptoms associated with the disorder, such as straining, bloating, hard stools, feelings...
of incomplete evacuation, and abdominal pain/discomfort.

Tegaserod is a selective agonist at the serotonin subtype 4 (5-HT₄) receptor and has been shown to augment the peristaltic reflex, enhance intestinal secretion, and reduce visceral hypersensitivity. Tegaserod interacts with enteric 5-HT₄ receptors, resulting in amplification of peristaltic and secretory reflexes in response to endogenous mucosal stimulation. Previous studies with tegaserod have shown enhanced promotile activity in animals, healthy volunteers, and patients suffering from irritable bowel syndrome with constipation (IBS-C). Given the known pharmacodynamic actions of tegaserod, and its documented efficacy profile in IBS-C, the aim of the current study was to assess the efficacy, safety, and tolerability of tegaserod in patients with chronic constipation.

**Materials and Methods**

**Study Design**

This was a randomized, double-blind, placebo-controlled study involving patients with chronic constipation recruited from 105 centers in North and South America (Argentina, Brazil, Canada, Chile, Colombia, United States, and Venezuela). The study comprised a 2-week baseline period followed by a 12-week treatment period. Patients who completed the treatment period or discontinued from the study prematurely were encouraged to enter a 4-week withdrawal period, during which no medication was taken. During the treatment phase, patients were randomized to receive either tablets containing tegaserod 2 mg, tegaserod 6 mg, or placebo, twice daily, within 30 minutes of morning and evening meals. A double-dummy packaging technique was used to mask the slightly different sizes of the 2 and 6 mg tablets. After initiation of therapy, each patient was seen by a study investigator at weeks 4, 8, 12, and 16 to collect and verify diary data and to assess safety and tolerability.

Randomization was performed using a validated computerized system that automated the random assignment of treatment groups. All personnel involved remained blinded to study medications until the time of unblinding. Drug codes were broken and data were made available for analysis after the study was complete, the data file verified, and protocol violations determined. The study was performed in accordance with the Declaration of Helsinki and the US 21 Code of Federal Regulations regarding informed patient consent and institutional review board approval.

**Study Population**

Eligible patients were men or women ≥18 years of age with a history of constipation of ≥6 months. Constipation was defined as an average of ≤3 complete spontaneous bowel movements (CSBM)/week, associated with at least 1 of the following symptoms on ≥25% of occasions: straining, incomplete evacuation, and hard and/or very hard stools. A bowel movement (BM) was considered to be complete if it was associated with a feeling of complete evacuation and spontaneous if the patient had not used a laxative or undergone an enema within the preceding 24 hours.

Before entering the study, patients answered a questionnaire related to their constipation symptoms during the preceding 6 months. The questions specifically inquired about the duration of constipation, the patient’s main symptoms associated with constipation, the patient’s use of laxatives and other medications for constipation, the number of spontaneous bowel movements (SBM)/week, and the percentage of SBM with hard/very hard stools, incomplete evacuation, or straining.

Investigators were asked to record relevant medical conditions affecting each patient. Patients whose constipation and symptoms were associated with a known disease of the colon, and those with documented pelvic floor dysfunction, metabolic or neurologic disturbances, or any other disease that could interfere with study completion, were excluded from entering the study. Individuals who were not constipated during the baseline period, as well as those experiencing loose or watery stools for ≥3 days during baseline, those who were not compliant with completion of their diary assessments during baseline, and those taking prohibited medication (i.e., drugs affecting GI motility) for ≥2 days during baseline were also excluded from the study.

The use of medications affecting GI motility was not allowed during the study; such medications were discontinued before baseline. Patients were instructed to use bisacodyl as a rescue medication only if they had not experienced a bowel movement in the previous 96 hours. Nonpharmacologic therapies affecting the GI system (e.g., acupuncture, colonic irrigation) were not allowed during the study, and patients were instructed not to change their lifestyle, diet, or fiber intake.

**Efficacy and Safety/Tolerability Assessments**

Throughout the study (including the baseline and withdrawal periods), patients recorded their symptoms in a paper diary. On a daily basis, they recorded the time of BM (if any) and associated characteristics (sensation of incomplete evacuation [yes/no], straining, and stool form). Straining was evaluated using a 3-point scale (no straining/acceptable straining/too much straining). Stool form was assessed using the 7-point Bristol Stool Form scale, ranging from 1 (separate hard stools, like nuts) to 7 (watery, unformed stools). In addition, patients recorded on a daily basis the intake of other medications and, in the case of laxatives, the time of intake.

On a weekly basis, patients assessed their satisfaction with bowel habits using a 5-point ordinal scale (0 = a great deal satisfied, 1 = a good deal satisfied, 2 = moderately satisfied, 3 = hardly satisfied, 4 = not at all satisfied) and the bothersomeness of constipation, abdominal distention/bloating, and abdominal pain/discomfort (each measured using a 5-point ordinal scale in which 0 = not at all bothersome, 1 = hardly bothersome, 2 = moderately bothersome, 3 = a good deal bothersome, 4 = a very great deal bothersome).
To assess the effect of treatment on quality of life and health status, patients also completed quality of life questionnaires at baseline, week 4, and week 12. The results of these assessments will be presented in a subsequent publication.

All adverse events (AEs) and serious AEs (SAEs), either reported by the patient or discovered by the physician following questioning or by physical examination, were recorded and described by duration, severity, and relationship to study treatment. Safety evaluations included standard laboratory tests (hematology, biochemistry, and urinalysis), measurement of vital signs, physical examinations, and central evaluation of electrocardiogram (ECG) parameters.

Statistical Analysis

The primary efficacy variable was the responder rate for CSBM during the first 4 weeks (weeks 1–4) of double-blind treatment. Responders were those with a mean increase of ≥1 CSBM/week compared with baseline, provided that they had completed at least 7 days of treatment. Prospectively planned secondary efficacy variables included the responder rate for CSBM during the whole 12 weeks of active treatment (weeks 1–12), and at each weekly time point in the study; the change from baseline in mean number of CSBM, SBM, and BM over weeks 1–4, weeks 1–12, and at each weekly time point; weekly evaluations of individual constipation symptoms; days of laxative intake; and median time to first CSBM and SBM. In addition, the percentages of patients with ≥3 CSBM/week during weeks 1–4 and weeks 1–12, and ≥7 days of treatment were determined for each treatment group. The percentage improvement from baseline in mean number of CSBM, SBM, and BM per week was calculated in a post-hoc analysis.

Sample size calculations were performed using the nQuery Advisor software (Statistical Solutions, Saugus, MA), based on the primary efficacy variable. Assuming a response rate of 30% in the placebo group and 42% in at least 1 of the tegaserod groups, it was calculated that 395 patients per treatment arm in the placebo group and 42% in at least 1 of the tegaserod groups, respectively. This effect was maintained over the entire treatment period (i.e., during weeks 1–12) with a P value of 0.025 (0.025 was used to maintain the overall significance level at 5% when using the Hochberg correction for multiple testing). Efficacy analyses were performed using the intent-to-treat (ITT) population, defined as all randomized patients, irrespective of whether or not they actually took study medication. Safety/tolerability analyses were conducted using data only from randomized patients who received ≥1 dose of study medication (safety population).

The CSBM responder rates (those with an increase of ≥1 CSBM/week compared with baseline) and the percentage of patients with ≥3 CSBM/week during weeks 1–4 and weeks 1–12 were analyzed using logistic regression models adjusting for center, gender, and baseline number of CSBM/week. Because each dose of tegaserod was compared with placebo separately in these analyses, the Hochberg adjustment for multiple comparisons was used to assess the statistical significance of these multiple tests, although the P values presented here are the nominal (unadjusted) P values. Analyses of time to CSBM and SBM were performed using survival analysis methods, censoring patients at the end of treatment. Estimates for these variables derive from Kaplan–Meier survival curves, and P values derive from log-rank tests. Analyses of the other secondary efficacy variables were performed weekly and over weeks 1–4 and weeks 1–12 using van Elteren tests, stratified by center. In these cases, values for each patient over the period of interest were summarized by the mean over the period, normalized to a 7-day period.

Results

A total of 1954 patients were screened, and of these, 1348 were randomized to receive treatment with tegaserod 2 mg twice daily (n = 450), tegaserod 6 mg twice daily (n = 451), or placebo (n = 447) (Figure 1). Overall, 82.9% completed the double-blind treatment phase and 97.2% completed the withdrawal period.

Patient Demographics and History of Constipation Symptoms

Patient demographics were similar across the 3 treatment groups (Table 1). The majority of patients were women and Caucasian, with a mean age of approximately 47 years. Patients were chronically constipated, as the mean duration of constipation before study entry was approximately 19 years (Table 2). Symptoms of constipation and the use of laxatives (based on the 6 months before study entry) were also comparable among the treatment groups. Abdominal bloating/distention and infrequent defecation were the main complaints. A previous medical history of IBS was reported in 4.2% of randomized patients.

Effect of Tegaserod on Frequency of Bowel Movements

Tegaserod treatment resulted in a marked effect on the frequency of BM, as assessed by a number of efficacy parameters.

Complete spontaneous bowel movement responder rate. The percentage of patients who experienced an increase from baseline of ≥1 CSBM/week during the first 4 weeks of treatment (primary efficacy variable) was significantly higher in both tegaserod groups compared with placebo (P < 0.0001 for both doses; Figure 2). In the tegaserod 6 mg twice daily group, 43.2% were responders, compared with 41.4% and 25.1% in the tegaserod 2 mg twice daily and placebo groups, respectively. This effect was maintained over the entire treatment period (i.e., during weeks 1–12) with a significantly higher responder rate in the tegaserod 6 mg twice
daily group (44.8%; \( P < 0.0001 \)) and 2 mg twice daily group (40.3%; \( P < 0.0001 \)) compared with placebo (26.9%) (Figure 2).

The percentage of CSBM responders for each individual week of the study is shown in Figure 3. From week 1, a significantly greater percentage of tegaserod-treated patients experienced an increase from baseline of ≥1 CSBM/week, compared with the placebo group. This effect was generally sustained throughout the 12-week treatment period. After the end of treatment, the percentage of responders decreased in both tegaserod treatment groups during treatment withdrawal, reaching a similar level as the placebo group within 2 weeks (W2).

A similar pattern of effect was noted for all constipation-related symptoms during the withdrawal period. Patients did not return to their baseline level of symptom severity. At baseline, the mean number of CSBM/week was 0.5–0.6 across the 3 treatment groups (Table 3). The proportion of patients who reached a level of ≥3 CSBM/week during weeks 1–4 was significantly greater with tegaserod 2 mg twice daily (23.0%) and 6 mg twice daily (21.8%) than with placebo (12.9%) (\( P < 0.0001 \) vs. placebo for each dose). Similar results were seen over the whole treatment period (weeks 1–12), where 22.7%, 22.0%, and 13.1% in each treatment group, respectively, reached a level of ≥3 CSBM/week (\( P < 0.0001 \) vs. placebo for each dose).

Effect on number of complete spontaneous bowel movements, spontaneous bowel movements, and bowel movements. In patients treated with either dose of tegaserod, a significant increase from baseline was seen in the weekly number of CSBM, SBM, and BM (Table 3).
Onset of action. The median time to first CSBM (± 95% confidence intervals) was significantly shorter in patients treated with tegaserod 6 mg twice daily (73 ± 45 hours; \(P < 0.0001\)) and 2 mg twice daily (117 ± 66 hours; \(P < 0.01\)) than in the placebo group (229 ± 123 hours).

Patients receiving tegaserod also experienced their first SBM significantly faster than patients receiving placebo (Figure 4). As with CSBM, the 95% confidence interval widths were much smaller in the tegaserod groups (approximately 3.5 hours in both tegaserod groups) than in the placebo group (approximately 15 hours).

Effect of Tegaserod on Other Aspects of Bowel Function

Tegaserod not only significantly improved the frequency of BM, but also the quality of BM, as assessed by secondary efficacy variables. Significant differences in favor of both doses of tegaserod were seen across the majority of these variables during the study (Table 4). In general, changes from baseline were slightly greater with the 6 mg twice daily dose compared with the 2 mg twice daily dose.

Laxative Use

At baseline, the use of rescue laxatives (mean number of days/week) was comparable across the 2 mg twice daily group (0.6 days/week), 6 mg twice daily group (0.6 days/week), and the placebo group (0.6 days/week). During the double-blind treatment period, use of laxatives decreased compared with baseline (to 0.3 days/week, 0.4 days/week, and 0.4 days/week, respectively). Although a greater reduction in laxative use was seen in the tegaserod 2 mg twice daily group, the difference was not significantly different from placebo.

Safety and Tolerability

Overall, 62.0% of patients in the safety population reported ≥1 AE during the 12-week treatment period (61.2%, 62.2%, and 62.6% in the tegaserod 2 mg twice daily group, 6 mg twice daily group, and placebo group, respectively). The most frequently reported AEs in the tegaserod 2 and 6 mg twice daily groups were headache (9.2% and 9.8%, respectively) and nasopharyngitis (7.6% and 8.4%, respectively), both of which occurred more frequently with placebo (12.8% and...
Diarrhea was more common in tegaserod 2 and 6 mg twice daily groups (4.5% and 7.3%, respectively) than in the placebo group (3.8%). In general, episodes of diarrhea were of mild to moderate severity, occurred early (median of 5.5 days after the start of tegaserod 6 mg twice daily treatment), did not require treatment with antidiarrheal drugs, and in the majority of cases (86.1% in the 6 mg twice daily group), occurred only once during the study. The median duration of diarrhea in all treatment groups was 2.0 days. Tegaserod treatment did not result in any cases of electrolyte imbalance.

The percentage of patients who discontinued treatment due to AEs was similar across all 3 treatment groups (3.1%, 3.8%, and 2.5% for tegaserod 2 mg twice daily, 6 mg twice daily, and placebo, respectively). Individual AEs leading to discontinuation were also similar across treatment groups with the exception of diarrhea (0.4%, 0.9%, and 0% for tegaserod 2 mg twice daily, 6 mg twice daily, and placebo, respectively) and abdominal pain (1.1%, 0%, and 0%, respectively). SAEs were reported for 13 patients (1.0% overall; 4 patients in each of the tegaserod groups and 5 in the placebo group) during the double-blind phase, none of which were deemed by the investigators as being related to study treatment. There were no clinically relevant changes observed in any of the treatment groups for hematology, biochemistry, urinalysis, vital signs, or ECG parameters. No deaths occurred during the study.

AEs reported during the withdrawal period were similar among the 3 groups (15.8%, 20.8%, and 20.2% of patients in the tegaserod 2 mg twice daily, 6 mg twice daily, and placebo groups, respectively), with no evidence of a rebound effect. Seven patients (0.6% overall) experienced SAEs during the withdrawal period, none of which were suspected by the investigators to be related to study treatment.

Discussion

The results of this large multinational, randomized, double-blind, placebo-controlled study show that tegaserod, a selective, partial agonist at the 5-HT4 receptor, is an effective and well-tolerated treatment for patients with chronic constipation. This prospective study demonstrates an effective treatment for chronic constipation over 12 weeks.

Although chronic constipation is associated with a wide spectrum of persistent symptoms, infrequent BM are generally viewed as a defining and clinically significant symptom. This study evaluated the effects of tegaserod treatment on the frequency of BM by assessing the weekly number of CSBM, SBM, and BM. The primary efficacy variable (percentage of patients reporting an increase of ≥1 CSBM/week over baseline during the first 4 weeks of treatment) is a reliable and objective measure of bowel frequency that has been used in investigational studies of prucalopride in chronic constipation. The definition of CSBM used in this study combines a subjective measure of BM associated with a sense of complete evacuation with an objective measure of the number of BM, thereby identifying BM that relieve symptoms caused by chronic constipation. By excluding BM that were produced by the patient taking laxatives or undergoing enemas, the primary endpoint accurately reflected the effect of tegaserod on bowel frequency and facilitated the analysis of multiple constipation symptoms in a single measure.

Results for the primary efficacy variable significantly favored both doses of tegaserod over placebo, and this effect was sustained over the entire study duration. Tegaserod demonstrated a rapid and predictable effect on bowel function, with patients experiencing their first CSBM and SBM significantly faster than placebo pa-

Figure 2. Complete spontaneous bowel movement responder rates during weeks 1–4 (primary efficacy variable) and weeks 1–12.

Figure 3. Weekly responder rate throughout the study.
patients. The widths of 95% confidence intervals for median time to first CSBM were narrower in the tegaserod groups, particularly 6 mg twice daily, than in the placebo group, suggesting that the occurrence of first CSBM was less variable. A similar trend was seen for time to first SBM.

For patients with chronic constipation, who on average experience only 0.5 CSBM/week, an increase of ≥1 CSBM from baseline represents a clinically significant improvement. However, it may be argued that patients having <3 CSBMs/week are still constipated and response should therefore be defined as an increase to ≥3 CSBM/week. Even when this more stringent definition was examined, tegaserod remained significantly superior (\( P < 0.0001 \)) to placebo during the first 4 weeks of treatment and over the entire study duration.

A large proportion of patients with chronic constipation also complain of symptoms such as bloating, straining, and abdominal pain/discomfort, and report passing hard stools. Indeed, in this study abdominal bloating/distention was the main complaint reported by patients in the 6 months before study entry. Statistically significant improvements (\( P < 0.05 \)) were seen for both doses of tegaserod over placebo across the majority of symptoms assessed, supporting the results of the primary efficacy variable.

As expected from the findings of previous clinical studies in patients with IBS-C, tegaserod also showed a beneficial effect on abdominal bloating/distention and abdominal pain/discomfort. Only 125 patients (9.3%) reported abdominal pain as their main symptom complaint during the 6 months before study entry. Because abdominal pain is a feature of IBS, this small group of patients may include those with IBS as well as those reporting some form of abdominal pain at baseline. A very small proportion of enrolled patients were also known to have a prior or current history of formally diagnosed IBS (56/1348, 4.2%). If all patients selecting abdominal pain as their main complaint at baseline had undiagnosed IBS, the overall number of patients with IBS would, at most, still be a minority (181 patients, or 13.4% of the population at baseline, assuming no overlap of patients).

Stool form and straining were improved, as were satisfaction with bowel habits and overall bothersomeness of constipation. Furthermore, the proportion of patients reporting a sense of complete evacuation with a BM was significantly higher in the tegaserod groups compared with placebo.

A 4-week withdrawal period, during which patients did not take any study medication, assessed whether cessation of tegaserod treatment would cause a rebound effect (i.e., symptoms becoming worse or more severe than when the patient entered the study). Consistent with the findings from a similarly designed study in patients with IBS-C, symptoms did not return to their baseline level of severity during treatment withdrawal and were comparable in severity to those seen in the placebo group within 2 weeks.

The ability of tegaserod to improve the multiple symptoms of chronic constipation was expected, based on the pharmacodynamic profile of this agent, the findings of early mechanistic studies, and the results of several studies in patients with IBS-C. These effects include augmentation of peristaltic motor activity throughout the GI tract and increased intestinal secretion, both of which are important targets in the effective management of chronic constipation.

Traditionally, laxatives have been the primary approach to the treatment of chronic constipation, despite
the fact that a meta-analysis has shown they do not demonstrate efficacy beyond 4 weeks. It is therefore important to recognize that treatment with tegaserod resulted in sustained improvement across all the key symptoms of constipation over the entire 12-week treatment period.

In addition to being effective in relieving the multiple symptoms of chronic constipation, tegaserod was safe and well tolerated. The most frequently reported AEs were headache and nasopharyngitis, both of which occurred more frequently with placebo than tegaserod. Diarrhea occurred more frequently with tegaserod than with placebo, likely representing an enhanced physiologic response to treatment. In general, however, diarrhea was mild, transient (typically occurring a few days after initiation of treatment and resolving after approximately 2 days), and self-limited. Only 0.4% and 0.9% of patients treated with tegaserod 2 mg twice daily and 6 mg twice daily, respectively, were discontinued from the study because of diarrhea. Treatment with tegaserod did not result in electrolyte imbalance, an abnormality which may be associated with the frequent use of osmotic laxatives.5

In conclusion, this prospective study shows that tegaserod provides rapid, predictable, and consistent relief of the persistent symptoms of chronic constipation, including BM, straining, incomplete evacuation, hard/lumpy stools, abdominal bloating/distention, and abdominal pain/discomfort. Significant benefits over placebo were demonstrated during the first week of treatment and were generally maintained throughout the 12-week treatment period. Tegaserod was also safe and well tolerated in this population.

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