American Journal of Gastroenterology

Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2008.01808.x

ORIGINAL CONTRIBUTIONS

Functional GI Disorders

# Tegaserod for Female Patients Suffering From IBS With Mixed Bowel Habits or Constipation: A Randomized Controlled Trial

William D. Chey, M.D.,[1] Pierre Paré, M.D.,[2] Andrea Viegas, Pharm.D.,[3] Gregory Ligozio, M.S.,[3] and Michael A. Shetzline, M.D., Ph.D.[3]

[1] *University of Michigan Health System, Division of Internal Medicine, Ann Arbor, Michigan;* [2] *University Laval, Division of Gastroenterology, CHAUQ- Hôpital du St-Sacrement, Quebec City, Canada; and* [3] *Novartis Pharmaceuticals Corporation, East Hanover, New Jersey*

**OBJECTIVES:** Though the greatest proportion of irritable bowel syndrome (IBS) patients report a mixed bowel pattern (IBS-Mixed), no available therapies have been rigorously evaluated in this subgroup. This study aimed to evaluate the efficacy and safety of the 5-$HT_4$ agonist tegaserod in women with IBS-Mixed and IBS with constipation (IBS-C).

**METHODS:** This prospective, double-blind, randomized, placebo-controlled, multicenter study was conducted in 100 centers in North America, South America, and Europe. Women with IBS-Mixed or IBS-C received tegaserod 6 mg or placebo twice daily. The primary efficacy variable was the patient's assessment of satisfactory relief over the 4-wk treatment period. The proportion of patients reporting satisfactory relief for $\geq$3 of 4 treatment weeks (75% rule) and individual IBS symptoms were assessed.

**RESULTS:** In total, 661 women were randomized (IBS-Mixed 324, IBS-C 337). Baseline symptom assessments identified clear differences between the two cohorts. Tegaserod provided significant improvement in satisfactory relief of IBS symptoms over 4 wk (OR 1.75, 95% CI 1.35–2.25, $P < 0.001$) in both IBS-Mixed and IBS-C patients. Using the 75% rule, 52.3% of tegaserod-receiving IBS-M patients and 43.3% of IBS-C patients were responders (*vs* 36.3, OR 1.88, 95% CI 1.16–3.04, $P < 0.010$; and 28.9, OR 1.90, 95% CI 1.19–3.05, $P < 0.008$ for placebo, respectively). The most frequent adverse events leading to study discontinuation in tegaserod-treated patients were diarrhea (1.5%) and abdominal pain (0.9%). Overall 7% of IBS-C patients reported diarrhea compared to 12% of IBS-Mixed (placebo 2.4%, 1.8%, respectively).

**CONCLUSIONS:** Tegaserod is effective in treating overall IBS symptoms in patients with IBS-Mixed and IBS-C.

(Am J Gastroenterol 2008;103:1217–1225)

## INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain and/or discomfort in association with altered bowel habits (1, 2). Recent estimates suggest that 10–15% of the general population experience symptoms suggestive of IBS (3, 4). In clinical practice, health-care providers base management decisions upon a patient's predominant bowel-related symptoms. All of the recently approved IBS therapies have been developed for the treatment of patients with IBS with diarrhea *or* constipation. Unfortunately, 30–50% of IBS patients report a mixture of diarrhea and constipation (1, 5, 6). This subgroup is now referred to as IBS with a "mixed" bowel pattern (IBS-Mixed) (7). There have been no large, prospective methodologically rigorous studies that have evaluated the efficacy of medical therapies in IBS-Mixed patients.

The pathophysiology of IBS remains incompletely understood. Factors that appear to play a role in IBS include alterations in GI motility, visceral perception, and psychosocial factors (8, 9). Serotonin has been found to play a critical role in GI motility, secretion, and sensation in health and functional bowel disorders like IBS (10–12). Medical therapies that target the regulation of serotonin have demonstrated

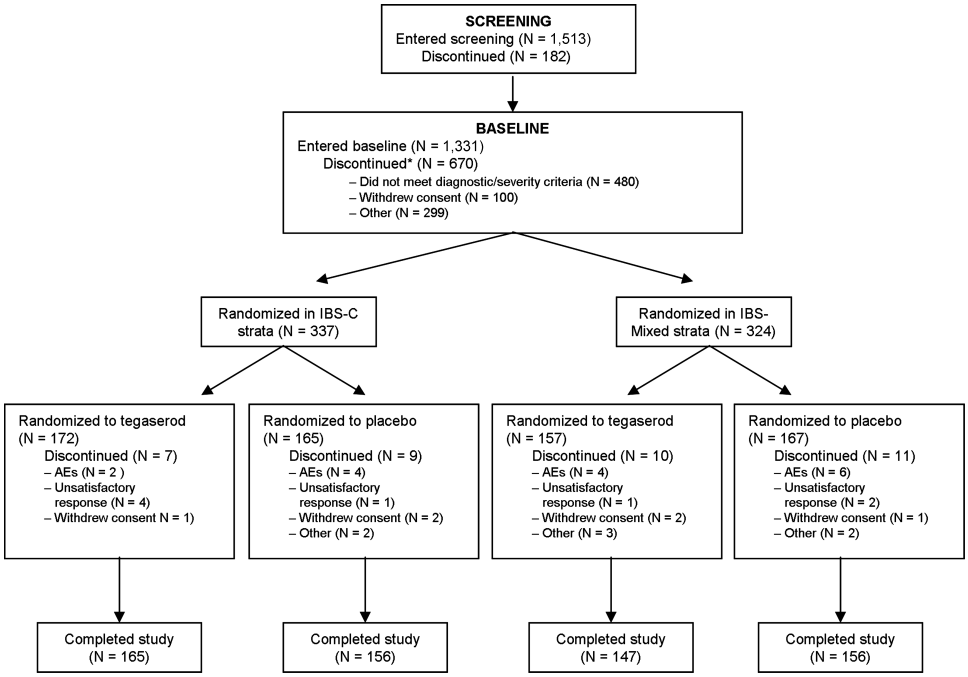



**Figure 1.** Study overview. *More than one reason for discontinuation can be included. AEs = adverse events.

efficacy in IBS with constipation (IBS-C) (13–16) and IBS with diarrhea (IBS-D) (17–19).

Tegaserod is an aminoguanidine-indole compound that acts as a selective 5-$HT_4$ receptor agonist (20). Tegaserod augments the peristaltic reflex and accelerates orocecal and colonic transit (21, 22). Animal and human data suggest that tegaserod may also exert effects on visceral sensation (23–25). Tegaserod has proven more effective than placebo at improving global and individual symptoms in IBS-C patients (13, 14, 26–28). Though tegaserod has been studied in patients with nondiarrhea IBS (26, 28), the efficacy of tegaserod in IBS-Mixed patients has not previously been specifically assessed.

This large, placebo-controlled study was designed to evaluate the efficacy and safety of tegaserod in women with IBS-Mixed and IBS-C.

**Table 1.** Stratification for Randomization by the Number of Constipation and Diarrhea Criteria Met

| Number of Diarrhea Criteria Met | Number of Constipation Criteria Met | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| 0 | NE | IBS-C | IBS-C | IBS-C |
| 1 | NE | IBS-Mixed | IBS-C | IBS-C |
| 2 | NE | NE | IBS-Mixed | IBS-Mixed |
| 3 | NE | NE | IBS-Mixed | IBS-Mixed |

NE – indicated that the patient had either IBS-D or normal bowel habits by history and was not eligible for the study.
IBS-C = irritable bowel syndrome (IBS) with constipation predominance; IBS-D = IBS with diarrhea predominance.
Constipation criteria: <3 bowel movements (BMs) per week, hard or lumpy stools and/or straining.
Diarrhea criteria: >3 BMs per day, loose/mushy or watery stools and/or urgency.

## MATERIALS AND METHODS

### *Protocol*

This was a prospective, double-blind, randomized, placebo-controlled, parallel-group, multicenter study in women with IBS-Mixed or IBS-C. The study comprised a 2-wk screening period (no medication or placebo), a 2-wk baseline period to assess symptom severity (no medication or placebo), followed by a 4-wk treatment period (Fig. 1). During the 4-wk treatment period, patients received either tegaserod 6 mg or placebo twice daily (b.i.d.). Patients were stratified to IBS-Mixed or IBS-C based on the physician–investigator's assessment of their self-reported IBS symptoms using criteria established prior to study initiation (Table 1). Patients in each stratum (IBS-Mixed or IBS-C) were randomized to tegaserod or placebo in a 1:1 ratio.

Visits took place at screening (day 28), the start of baseline (day 14), and on the first and last day of the 4-wk treatment period. On a daily basis, patients recorded their symptoms, as well as any laxative or antidiarrheal medication intake, using a touch-tone telephone system.

To assess primary efficacy, patients responded (yes/no) weekly to the following question: "Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?" Patients were instructed that "satisfactory" relief meant that compared to their previous typical IBS symptoms, they felt that their IBS symptoms over the past week had been improved to an extent that they would take a medication to maintain that state of improvement.

Patients were also asked to characterize on a daily basis their abdominal discomfort or pain, bloating, stool frequency, stool consistency, straining, and urgency. Abdominal discomfort or pain and bloating were assessed using a

7-point scale (0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, and 6 = very severe). Stool consistency was assessed using the Bristol Stool Form Scale (29), ranging from 1 (separate hard lumps, like nuts) to 7 (watery, no solid pieces). Straining and urgency were recorded using a binary scale (yes/no).

Safety assessments involved monitoring and recording all adverse events (AEs), serious AEs, baseline assessments of hematology and blood chemistry, and regular assessments of vital signs, physical condition, and body weight.

Patients' perception of study medication was also assessed at the end of the study using a six-item questionnaire.

This study was performed in accordance with the Declaration of Helsinki and the U.S. 21 Code of Federal Regulations regarding informed patient consent and institutional review board approval.

### *Setting and Participants*

Women, 18–65 yr of age, with a history of IBS, excluding those with Rome II-defined IBS-D, were eligible for this study. IBS-C was defined using the Rome II criteria (2). Patients who did not fulfill the Rome II criteria for IBS-C or IBS-D were classified as suffering from IBS-Mixed based on the assessment by the physician–investigator (Table 1). Subjects with symptoms of IBS with a normal bowel pattern, that is, no evidence of diarrhea or constipation, were excluded from this study.

All patients were also required to meet the following IBS Rome II classification (2): In the preceding 12 months, at least 12 wk or more (not necessarily consecutive) of abdominal discomfort or pain with two of the following features: (a) relieved with defecation, (b) onset associated with a change in stool frequency, (c) onset associated with a change in stool form. Inclusion for entry into the double-blind treatment period was also dependent on patients' responses to IBS symptom assessments during the baseline period. Patients providing responses for 11 of 14 baseline days including the 3 days prior to randomization, having an abdominal discomfort or pain score of $\geq$3 (moderate) on a 7-point scale recorded on at least 8 days, and having a mean stool consistency score of $\leq$4 on a 7-point scale (not including laxative-induced stool), were eligible for randomization. Patients were not eligible for randomization if they experienced watery stool during the 3 days prior to the randomization visit (unless documented to be laxative induced) or 3 or more bowel movements (BMs) per day during the 3 days prior to the randomization visit (unless hard stools documented using the Bristol Stool Form Scale) (29), took antidiarrheal medication for $>$2 days during the baseline period or used any of laxatives during the 3 days prior to randomization, or took prohibited medications (*i.e.*, drugs affecting GI motility) during the baseline period. Medications affecting GI motility and/or visceral perception were not permitted during the study.

### *Assignment and Masking*

Patients were assigned to treatment groups at the investigative site according to a random allocation sequence, by strata. The allocation sequence was generated by Novartis Drug Supply Management using a validated system that automated the random assignment of treatment to randomization numbers. Randomization data were kept strictly confidential and all personnel involved in this study remained blinded until the study had been completed, the data file verified, and the protocol violations determined.

### *Statistical Analysis*

The primary efficacy variable was the Patient's Overall Satisfactory Relief, a binary variable. The variable was collected weekly (weeks 1–4). The null hypothesis was that the odds of responding to treatment (*i.e.*, responding "yes" to the assessment) was the same on tegaserod 6 mg b.i.d. and placebo (*i.e.*, the odds ratio is equal to 1) over 4 wk of treatment. The alternative hypothesis was that the odds ratio was not equal to 1. The hypothesis was tested using a 2-sided test with a 5% significance level.

The null hypothesis was tested using a generalized linear model with logistic regression. The response profile for satisfactory relief was analyzed by a longitudinal analysis over the 4 wk of treatment using a logistic regression model (generalized estimating equation). Besides treatment, covariates included in the model were week, IBS stratification factor (IBS-C or IBS-Mixed), baseline abdominal pain, age, pooled center, prior use of tegaserod, and body mass index (BMI). Centers were pooled prior to database lock based on geographical region. The significance of between-treatment differences was analyzed by means of the Wald test based on the robust estimator of the covariance matrix. The analysis for the intention-to-treat (ITT) population was considered as primary; however, the analysis was also performed within each stratum (IBS-C or IBS-Mixed).

The "overall responder" definition analyzed was the proportion of patients who responded at least 75% of the weeks. This responder definition was analyzed using a logistic regression model with the same covariates as in the primary model (except week). Daily assessments were summarized on a weekly and overall treatment basis using all available data during that period. Between-treatment comparisons for continuous variables were performed by means of an analysis of covariance (ANCOVA) model with random subject effect. Covariates in the models included treatment, week, IBS stratification factor (constipation only or mixed), baseline score or number of days (specific to the variable being analyzed), age, pooled center, prior use of tegaserod, and BMI.

Treatment groups were also compared at day 28 (end of treatment) with respect to the responses to their perception of study medication, using a Cochran-Mantel-Haenszel test adjusted for pooled centers for each item. The difference in IBS symptoms at baseline between strata (IBS-C or IBS-Mixed) was evaluated by performing ANOVA with the factors stratum and pooled center for continuous variables and by Fisher's exact test for proportions.

The Pan method was used to calculate the sample size based on generalized estimating equations methods under the assumption of an exchangeable structure (30). The

**Table 2.** Patient Demographics and Baseline Characteristics

| | Tegaserod 6 mg b.i.d. (N = 329) | Placebo (N = 332) |
|---|---|---|
| Age (yr) | | |
| Mean (SD) | 40.6 (11.34) | 41.6 (12.31) |
| Median | 42.0 | 42.0 |
| Race, N (%) | | |
| White | 200 (60.8) | 204 (61.4) |
| Black | 6 (1.8) | 12 (3.6) |
| Asian | 2 (0.6) | 1 (0.3) |
| Other* | 121 (36.8) | 115 (34.6) |
| Mean body mass index, kg/m$^2$ | 25.7 | 25.7 |
| Premenopausal women, N (%) | 217 (66.0) | 209 (63.0) |
| Duration of IBS symptoms (yr) | | |
| Mean (SD) | 9.7 (9.4) | 10.5 (9.3) |
| Median | 6.0 | 8.0 |
| Prior use of tegaserod, N (%) | 40 (12.2) | 43 (13.0) |

b.i.d. = twice daily; SD = standard deviation; IBS = irritable bowel syndrome.
*Other category includes 76 of 121 subjects that reported that they were Hispanic (63%).

**Table 3.** IBS Symptoms During Baseline by Strata (ITT)

| | IBS-C (N = 337) Mean | IBS-Mixed (N = 324) Mean | Total (N = 661) Mean |
|---|---|---|---|
| Abdominal discomfort/ pain score* | 3.77 | 3.66 | 3.71 |
| Bloating score* | 3.90 | 3.71 | 3.81 |
| No. of BMs/week§ (mean/median) | 4.57/3.77 | 7.22/4.44 | 5.87/5.09 |
| No. of days/week with no BMs§ | 3.43 | 2.42 | 2.93 |
| Stool consistency score† | 2.40 | 3.28 | 2.83 |
| Days/week with normal stool consistency‡,§ | 2.08 | 3.06 | 2.56 |
| Days/week with straining§ | 4.22 | 3.75 | 3.99 |
| Days/week with urgency§ | 1.12 | 2.05 | 1.58 |

*7-point scale: 0 = none and 6 = very severe.
†7-point scale: 1 = separate hard lumps like nuts and 7 = watery, no solid pieces.
‡Defined as 3–5 inclusive.
§Normalized to 7 days.
*P* value <0.01 for all comparisons.

response rate for placebo in a previous study was found to be approximately 33% (27). Thus, this study was powered to detect a treatment difference of 11% (or an odds ratio of approximately 1.6). The acceptable type I error rate was estimated to be 5% based on a 2-sided test and the acceptable type II error rate was 10% (*i.e.*, power is 90%). Under these assumptions and allowing for a dropout rate of approximately 10%, 664 randomized patients were planned.

### *Patients' Perception of Study Medication*

The patient's perception of study medication was assessed with a questionnaire that asked patients about their satisfaction with and preference for the study medication relative to symptoms of IBS and whether or not patients would use the study medication again and would recommend it to family or friends who have IBS.

Using the ITT population, overall treatment groups were compared at day 28 (end of treatment) with respect to the expectation and satisfaction with the study medication as well as to the patient's decision to continue and recommend treatment with study medication using the Mantel-Haenszel test. A similar analysis was performed for the IBS-M and IBS-C subgroups.

For subanalysis purposes, responses for survey questions were dichotomized as follows: response choices 1 and 2 (*i.e.*, "far above expectations," and "above expectations," "extremely satisfied" and "satisfied") *versus* other response choices.

## RESULTS

### *Participant Flow and Follow-Up*

In total, 1,513 women from 100 primary care and gastroenterology centers in 11 countries, including North America, South America, and Europe, were screened and 661 were randomized. Patients were recruited from April 2005 until April 2006. In total, 337 patients were included in the IBS-C subset and 324 patients in the IBS-Mixed subset (Fig. 1). Of the 661 randomized patients, 624 (94.4%) completed the study.

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS. Demographic and baseline characteristics were similar across treatment groups (Table 2). The majority of patients were whites, premenopausal, and between the ages 25 and 55 yr (mean age 41.1 yr). The median duration of IBS symptoms was 7.0 yr.

During the baseline period, 120 (35.6%) IBS-C patients took laxatives compared to only 54 (16.7%) IBS-Mixed patients. Compared to IBS-C patients, those with IBS-Mixed reported a greater daily BM frequency during baseline. In addition, IBS-Mixed patients had fewer days with no BM, greater stool consistency, more days with normal stool consistency (Bristol Stool Score 3, 4, or 5), and fewer days with straining. Small but statistically significant differences in abdominal pain and bloating were noted between groups. There was also a greater number of patients with urgency among IBS-Mixed patients (Table 3).

PATIENTS' OVERALL SATISFACTORY RELIEF. The overall odds of reporting satisfactory relief of IBS symptoms over the 4 wk of active treatment was greater with tegaserod than placebo (odds ratio 1.75, 95% CI 1.35–2.25, $P < 0.001$) and during each of weeks 2, 3, and 4 of treatment ($P < 0.001$). The number and percentage of patients who were responders for relief of overall IBS symptoms were significantly higher in the tegaserod group compared with placebo overall and during weeks 2, 3, and 4. Subgroup analyses by strata showed the odds of responding were significantly greater in the tegaserod group for IBS-Mixed patients over the 4-wk treatment period (odds ratio 1.50, 95% CI 1.03–2.19, $P = 0.034$) and at weeks 2 and 4. For IBS-C patients, tegaserod led to significant improvements over the 4-wk treatment period (odds ratio 1.97,

**Table 4.** Patients' Assessment of Satisfactory Relief by Strata (ITT Patients)

| Week | Tegaserod 6 mg b.i.d. N = 329 n/m (%) | Placebo N = 332 n/m (%) | Odds Ratio | 95% CI of Odds Ratio | *P* Value |
|---|---|---|---|---|---|
| IBS-C | | | | | |
| 1 | 76/168 (45.2) | 53/158 (33.5) | 1.60 | (1.01–2.55) | 0.047 |
| 2 | 88/165 (53.3) | 56/152 (36.8) | 1.98 | (1.24–3.17) | 0.004 |
| 3 | 98/162 (60.5) | 58/151 (38.4) | 2.49 | (1.57–3.95) | <0.001 |
| 4 | 93/159 (58.5) | 63/146 (43.2) | 1.89 | (1.19–3.00) | 0.007 |
| Overall | | | 1.97 | (1.39–2.81) | <0.001 |
| IBS-Mixed | | | | | |
| 1 | 74/151 (49.0) | 72/159 (45.3) | 1.10 | (0.68–1.79) | 0.698 |
| 2 | 92/148 (62.2) | 69/157 (43.9) | 2.00 | (1.23–3.23) | 0.005 |
| 3 | 84/144 (58.3) | 77/153 (50.3) | 1.28 | (0.80–2.07) | 0.306 |
| 4 | 85/134 (63.4) | 65/140 (46.4) | 1.87 | (1.13–3.09) | 0.015 |
| Overall | | | 1.50 | (1.03–2.19) | 0.034 |

n = number of patients with satisfactory relief.
m = number of patients assessed.

95% CI 1.39–2.81, $P < 0.001$) and at each of the 4 wk (Table 4).

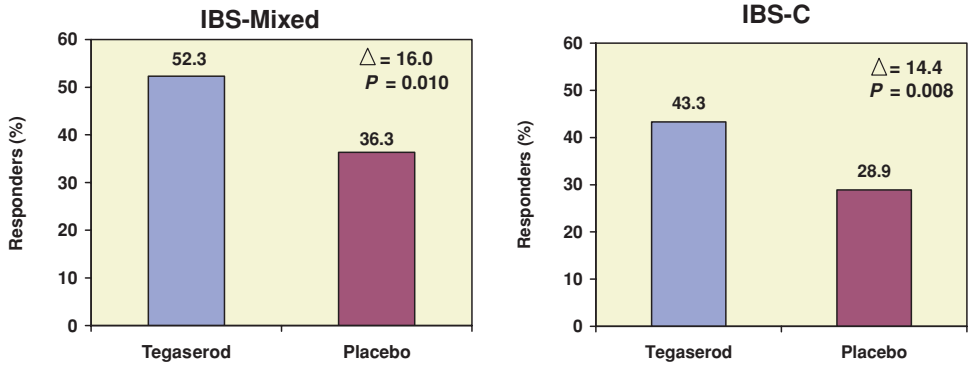
The percentage of patients who experienced satisfactory relief of IBS symptoms in at least 3 of 4 wk of treatment (75% rule) was significantly higher in patients treated with tegaserod compared with placebo in ITT patients (47.5% *vs* 32.6%, $P < 0.001$) and in both the IBS-Mixed and IBS-C subsets (Fig. 2). The number needed to treat (NNT) based on these response rates was 7.0 (95% CI 4.6–14.3).

IBS SYMPTOMS OVER THE ENTIRE TREATMENT PERIOD. For the IBS-Mixed group, there were statistically significant differences between the tegaserod and placebo groups for stool frequency (<0.001), number of days with no BMs (0.001), stool consistency (<0.001), number of days with straining (0.023), and number of days with urgency (0.030). For the IBS-C group, statistically significant differences between groups were observed for stool frequency (<0.001), number of days with no BMs (0.020), stool consistency (<0.001), and number of days with straining (0.018) (Table 5).

SAFETY AND TOLERABILITY. Overall, 28% of patients experienced at least one AE during treatment. The most frequently reported AEs with tegaserod were diarrhea (9.4%), headache (5.5%), abdominal pain (3.0%), and nausea (2.1%). For patients who received placebo, the most prevalent AEs were diarrhea (2.1%), headache (6.6%), abdominal pain (2.1%), and nausea (3.3%). For patients with IBS-Mixed, the most frequent AEs were diarrhea, headache, nausea, abdominal pain, and abdominal distension (Table 6).

During treatment, 13.7% of patients who received tegaserod and 9.4% of patients who received placebo had AEs suspected to be related to study drug. Of the individual AEs suspected to be related to study drug, only diarrhea occurred more frequently in the tegaserod group compared with placebo (7.0% *vs* 1.2%). In comparison, AEs reported for diarrhea overall (regardless of relationship to study medication) were for IBS-Mixed, 12.1% of those receiving tegaserod compared to 1.8% in the placebo group, and for 7% of IBS-C patients randomized to tegaserod compared to 2.4% of those receiving placebo.

Seventy-nine percent of tegaserod patients who experienced their first episode of diarrhea reported as an AE did so




IBS-C = irritable bowel syndrome with constipation predominance.

**Figure 2.** Responder rates for patients' overall satisfactory relief (75% rule). IBS-C = irritable bowel syndrome with constipation predominance.

**Table 5.** IBS Symptoms Over the Entire Treatment Period (ITT Patients)

| | IBS-Mixed | | | IBS-C | | |
|---|---|---|---|---|---|---|
| Assessment | Tegaserod 6 mg b.i.d. | Placebo | *P* Value | Tegaserod 6 mg b.i.d. | Placebo | *P* Value |
| Abdominal discomfort/pain | 2.66 | 2.83 | 0.310 | 2.84 | 2.95 | 0.588 |
| Bloating | 2.83 | 2.99 | 0.303 | 3.08 | 3.16 | 0.335 |
| No. of bowel movements* | 9.78 | 8.34 | <0.001 | 6.88 | 6.06 | <0.001 |
| No. of days with no bowel movements* | 1.39 | 1.68 | 0.001 | 2.31 | 2.48 | 0.020 |
| Stool consistency | 3.95 | 3.49 | <0.001 | 3.53 | 2.89 | <0.001 |
| No. of days with normal stool consistency*† | 3.90 | 3.91 | 0.731 | 3.69 | 3.39 | 0.120 |
| No. of days with straining* | 2.42 | 2.87 | 0.023 | 3.08 | 3.55 | 0.018 |
| No. of days with urgency* | 2.01 | 1.88 | 0.030 | 1.37 | 1.16 | 0.057 |

Mean values are presented, unless noted.
*Normalized to 7 days.
†Normal stool consistency is defined as stool consistency score 3–5 inclusive.
ITT = intention-to-treat; IBS-C = irritable bowel syndrome with constipation predominance; b.i.d. = twice daily.

during days 1–7 of treatment, as compared to 57% of placebo patients. The mean duration of diarrheal episodes was longer in the tegaserod group than the placebo group. Subjects in both the IBS-C and IBS-M cohorts reported similar findings in regards to diarrhea onset, duration, and severity. There were no significant differences in episodes of diarrhea reported as AEs in patients with IBS-Mixed (23 tegaserod, 4 placebo) and patients with IBS-C (18 tegaserod, 5 placebo).

Other AEs suspected to be treatment related that occurred in ≥2% of patients were abdominal pain (2.7% in tegaserod *vs* 1.8% in placebo) and headache (2.4% in tegaserod *vs* 3.0% in placebo). Similar results were reported in the IBS-Mixed and the IBS-C subsets.

Discontinuation due to AEs occurred in 1.8% of tegaserod-treated patients and 3.0% of placebo-treated patients. The AEs that most commonly led to discontinuation were diarrhea (1.5% for tegaserod and 0.6% for placebo), abdominal pain (0.9% tegaserod *vs* 0.6% placebo), and headache (0.3% tegaserod *vs* 0.9% placebo). In the IBS-Mixed subset, 2.5% of tegaserod-treated patients and 0.6% of placebo-treated patients discontinued because of diarrhea. In patients with IBS-C, diarrhea led to discontinuation in 0.6% of tegaserod-treated patients and 0.6% of placebo-treated patients.

No deaths occurred during the study. Only two serious AEs were reported, both in the IBS-Mixed subset (costochondritis in a patient receiving tegaserod and appendicitis in a patient receiving placebo), and neither event was felt to be related to study treatment. No cases of ischemic colitis were reported.

PATIENTS' PERCEPTION OF STUDY MEDICATION. A significantly greater proportion of ITT patients treated with tegaserod than placebo considered relief of their symptoms far above/above expectations (33.6% *vs* 20.7%, $P = 0.001$). A statistically significantly higher percentage of patients treated with tegaserod than placebo were extremely satisfied/satisfied with their treatment (55.3% *vs* 41.9%, $P = 0.02$). In addition, a significantly greater percentage of tegaserod patients than placebo patients said they would recommend their medication to family or friends with IBS (71.4% *vs* 60.8%, $P = 0.007$). More IBS-Mixed patients on tegaserod than placebo considered that the study medication was far above/above expectations (36.7% *vs* 21.5%, $P = 0.051$).

**Table 6.** Frequency of Reported AEs (>1% Total in Any IBS Subgroup) by IBS Subgroup and Treatment

| | IBS-Mixed | | | IBS-C | | |
|---|---|---|---|---|---|---|
| | Tegaserod 6 mg b.i.d. N = 157 N (%) | Placebo N = 167 N (%) | Total N = 324 N (%) | Tegaserod 6 mg b.i.d. N = 172 N (%) | Placebo N = 164 N (%) | Total N = 336 N (%) |
| Any preferred term | 51 (32.5) | 41 (24.6) | 92 (28.4) | 46 (26.7) | 44 (26.8) | 90 (26.8) |
| Diarrhea | 19 (12.1) | 3 (1.8) | 22 (6.8) | 12 (7.0) | 4 (2.4) | 16 (4.8) |
| Headache | 10 (6.4) | 14 (8.4) | 24 (7.4) | 8 (4.7) | 8 (4.9) | 16 (4.8) |
| Abdominal pain | 5 (3.2) | 3 (1.8) | 8 (2.5) | 5 (2.9) | 4 (2.4) | 9 (2.7) |
| Influenza | 2 (1.3) | 3 (1.8) | 5 (1.5) | 3 (1.7) | 2 (1.2) | 5 (1.5) |
| Back pain | 2 (1.3) | 1 (0.6) | 3 (0.9) | 2 (1.2) | 2 (1.2) | 4 (1.2) |
| Abdominal distension | 3 (1.9) | 2 (1.2) | 5 (1.5) | 0 (0) | 4 (2.4) | 4 (1.2) |
| Nasopharyngitis | 1 (0.6) | 0 (0) | 1 (0.3) | 0 (0) | 4 (2.4) | 4 (1.2) |
| Nausea | 7 (4.5) | 4 (2.4) | 11 (3.4) | 0 (0) | 7 (4.3) | 7 (2.1) |

Denominator used in the percentage calculations: patients in the safety population.
b.i.d. = twice daily.

## DISCUSSION

The results of this large, multinational, randomized, placebo-controlled study show that tegaserod effectively relieved overall symptoms and was well tolerated in patients with IBS-M. The study population included patients with IBS symptoms and symptoms of diarrhea and/or constipation. Patients with IBS and a normal bowel pattern, that is, no criteria for diarrhea or constipation, were excluded. Though tegaserod has previously been studied in patients with "nondiarrhea" IBS (26, 28), the design of these trials did not allow a specific analysis of treatment efficacy in patients with IBS-Mixed. Unlike these previous trials with tegaserod, the design of the current trial allowed us to clearly demonstrate benefits of tegaserod in patients with IBS-Mixed as well as IBS-C. This is one of the first studies to identify an efficacious medical therapy for this challenging subset of IBS sufferers.

IBS is a disorder of heterogeneous pathogenesis and symptom expression. According to the Rome criteria, all patients with IBS experience some degree of abdominal pain or discomfort. However, bowel-related symptoms are highly variable with some patients endorsing predominantly constipation-related complaints (reduced stool frequency, hard or lumpy stools, straining to pass a BM), others reporting a predominance of diarrhea-related complaints (increased stool frequency, decreased stool consistency, or urgency), and still others reporting a mixture of constipation and diarrhea-related complaints. Epidemiological studies have reported that 30–50% of IBS sufferers do not fulfill diagnostic criteria for IBS-C or IBS-D. In fact, most studies have reported that the greatest proportion of IBS patients fits into the IBS-Mixed category (1, 5, 6). Recent work suggests that the clinical characteristics of IBS-Mixed more closely resemble IBS-C than IBS-D (1, 5, 6). In addition, "natural history" studies suggest that there is migration of IBS patients from one subgroup to another and that the IBS-Mixed subgroup is the least stable. Further, migration between IBS-C and IBS-Mixed appears to occur more commonly than between IBS-D and IBS-Mixed or IBS-C (1).

Despite being the most prevalent subgroup of IBS, the management of patients with IBS-Mixed is less well defined than for IBS-C or IBS-D patients. There are currently no medical therapies that have been rigorously evaluated in patients with IBS-Mixed. Not surprisingly then, there are currently no therapies that have been approved in the United States or elsewhere for this IBS subgroup.

The literature addressing the IBS-Mixed group is challenging to interpret related to inherent differences in study populations and the varied definitions of IBS-Mixed used in the different studies. Formal criteria for IBS-Mixed have recently been published as part of the Rome III process (7). Unfortunately, the Rome III criteria were not available at the time this study was designed. In this study, IBS was defined using the Rome II criteria (2). While Rome II offered criteria for defining IBS-C and IBS-D, there was no recommendation for IBS-Mixed (2). After excluding patients with normal bowel habits, we defined IBS-Mixed as those patients who did not fulfill the Rome II criteria for IBS-C or IBS-D.

Using these definitions, we found clear clinical differences between the IBS-Mixed and IBS-C subgroups during the 2-wk baseline period, supporting the notion that they indeed represent distinct patient subgroups. In the absence of any drug interventions, patients with IBS-Mixed reported a greater daily stool frequency, fewer days without a BM, a higher stool consistency score on the Bristol Stool Form Scale, more days with a normal stool consistency, and fewer days without straining compared to IBS-C patients. There were also a greater number of patients with urgency among IBS-Mixed patients. There were statistically significant differences in abdominal pain/discomfort and bloating scores between the IBS-Mixed and IBS-C subgroups, though the clinical relevance of these small differences is questionable.

Results from this study indicate that tegaserod was more effective than placebo at improving the patient's assessment of overall satisfactory relief in patients with IBS-M. The number and percentage of patients who were responders for relief of overall IBS symptoms were significantly higher in the tegaserod than the placebo group. Overall, a higher percentage of tegaserod patients achieved overall satisfactory relief compared with placebo at each week of treatment.

Tegaserod provided satisfactory relief of IBS symptoms in more patients than placebo for subsets of patients with IBS-Mixed and IBS-C. The percentage of tegaserod patients achieving satisfactory relief was statistically significantly higher at weeks 2 and 4, and overall in patients with IBS-Mixed and at all weeks and overall in patients with IBS-C. Patients with IBS-Mixed and IBS-C treated with tegaserod had significantly more BMs, fewer days with no BMs, a higher stool consistency score, fewer days with straining, and a higher number of days with urgency than those randomized to placebo. No differences were observed in mean abdominal discomfort and pain scores and mean bloating scores between the tegaserod and placebo groups.

Given the baseline differences in clinical characteristics between patients with IBS-Mixed and IBS-C, a review of AEs reported in association with tegaserod is of considerable interest. Similar to previous studies, the most commonly reported AE in association with tegaserod was diarrhea. Diarrhea in patients taking tegaserod tended to occur during the first week of therapy and usually was transient. Only 1.5% of tegaserod-treated subjects discontinued therapy due to diarrhea. In addition, there were no clinically relevant consequences (hospitalization, fluid and electrolyte imbalance, or dehydration) reported due to diarrhea.

An issue worthy of discussion is the duration of the trial. Most previous trials with tegaserod have employed randomized treatment periods of 12 wk. This trial employed a randomized treatment period of 4 wk. The Rome III recommendations on the design of treatment trials for functional GI disorders (31) suggest that trial duration should be based on the natural history of symptomatic episodes for the disorder in question. The Rome III document also points out that the

European Agency for the Evaluation of Medicinal Products (EMEA) is accepting 4-wk trials when considering short-term efficacy indications. For these reasons, we feel that the data generated by this trial offer information that is relevant to the treatment of IBS-Mixed and IBS-C patients.

In conclusion, IBS-Mixed and IBS-C patients can be distinguished by differences in bowel-related symptoms such as stool frequency, stool consistency, straining, and urgency. Tegaserod 6 mg b.i.d. for 4 wk was more effective than placebo in relieving the symptoms of IBS in women with either IBS-Mixed or IBS-C. Tegaserod was well tolerated in these IBS populations. Tegaserod offers a viable treatment option for women with IBS and a mixed bowel pattern.

## ACKNOWLEDGMENTS

We would like to thank Stephane Levy, M.D. (Novartis Pharmaceuticals Corporation, East Hanover, NJ) for his scientific expertise in the design and implementation of this study.

### STUDY HIGHLIGHTS

**What Is Current Knowledge**

- The largest proportion of irritable bowel syndrome (IBS) patients suffer with a mixture of constipation and diarrhea (IBS with a mixed bowel pattern [IBS-Mixed]).
- No available treatments have been specifically evaluated in patients with IBS-Mixed.
- Tegaserod is more effective than placebo for global and individual symptoms in patients with IBS with constipation (IBS-C).

**What Is New Here**

- Compared to IBS-C, IBS-Mixed patients reported greater stool frequency, differences in stool consistency, less straining, and more urgency.
- Tegaserod 6 mg b.i.d. was more effective than placebo in relieving IBS-Mixed.
- Diarrhea was the most common adverse event and was reported in 12% of IBS-Mixed and 7% of IBS-C patients.

**Reprint requests and correspondence:** William D. Chey, M.D., University of Michigan Health System, Division of Internal Medicine, 3912 Taubman Center, Ann Arbor, MI 48109-0632.
*Received March 8, 2007; accepted October 25, 2007.*

## REFERENCES

1. Drossman DA, Morris CB, Hu Y, et al. A prospective assessment of bowel habit in irritable bowel syndrome in women: Defining an alternator. Gastroenterology 2005;128:580–9.
2. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and D. functional abdominal pain. In: Drossman DA, Talley NJ, Thompson WG, et al, eds. Rome II: Functional gastrointestinal disorders: Diagnosis, pathophysiology, and treatment, 2nd Ed. McLean, VA: Degnon Associates, Inc., 2000:351–432.
3. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence patterns and impact of irritable bowel syndrome: An international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–50.
4. Hungin APS, Chang L, Locke GR, et al. Irritable bowel syndrome in the United States: Prevalence, symptom patterns and impact. Aliment Pharmacol Ther 2005;21: 1365–75.
5. Mearin F, Balboa A, Badia X, et al. Irritable bowel syndrome subtypes according to bowel habit: Revisiting the alternating subtype. Eur J Gastroenterol Hepatol 2003;15:165–72.
6. Tillisch K, Labus JS, Naliboff BD, et al. Characterization of the alternating bowel habit subtype in patients with irritable bowel syndrome. Am J Gastroenterol 2005;100:896–904.
7. Longstreth G, Thompson WG, Chey WD, et al. Rome III: Functional bowel disorders. Gastroenterology 2006;130:1480–91.
8. Camilleri M, Prather CM. The irritable bowel syndrome: Mechanisms and a practical approach to management. Ann Intern Med 1992;116:1001–8.
9. Kellow JE, Azpiroz F, Delvaux M, et al. Applied principles of neurogastroenterology: Physiology/motility sensation. Gastroenterology 2006;130:1412–20.
10. Gershon M. Review article: Serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. Aliment Pharmacol Ther 2004;20(Suppl 7):3–14.
11. Crowell MD, Shetzline MA, Moses PL, et al. Enterochromaffin cells and 5-HT signaling in the pathophysiology of disorders of gastrointestinal function. Curr Opin Investig Drugs 2004;5:55–60.
12. Coates MD, Johnson AC, Greenwood-Van Meerveld B, et al. Effects of serotonin transporter inhibition on gastrointestinal motility and colonic sensitivity in the mouse. Neurogastroenterol Motil 2006;18:464–71.
13. Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2002;16:1877–88.
14. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. Aliment Pharmacol Ther 2001;15:1655–66.
15. Muller-Lissner S, Holtmann G, Rueegg P, et al. Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. Aliment Pharmacol Ther 2005;21:11–20.
16. Kellow JE. Advances in the management of irritable bowel syndrome. J Gastroenterol Hepatol 2002;17:503–7.
17. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. Aliment Pharmacol Ther 1999;13:1149–59.
18. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. Lancet 2000;355:1035–40.
19. Chey WD, Chey WY, Heath AT, et al. Long-term efficacy and safety of alosetron in women with severe diarrhea-

predominant irritable bowel syndrome. Am J Gastroenterol 2004;99:2195–203.
20. Buchheit KH, Buhl T. Prokinetic benzamides stimulate peristaltic activity in the isolated guinea pig ileum by activation of 5-HT4 receptors. Eur J Pharmacol 1991;205:203–8.
21. Prather CM, Camilleri M, Zinsmeister AR, et al. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterology 2000;118:463–8.
22. Degen L, Matzinger D, Mertz M, et al. Tegaserod, a 5-HT4 receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. Aliment Pharmacol Ther 2001;15:1745–51.
23. Thewissen M, Ruehl A, Enck P. On the adequate stimulus for rectal mechanoreception and perception: A study in cat and humans. Neurogastroenterol Motil 2000;12:43–52.
24. Schikowski A, Thewissen M, Mathis C, et al. Serotonin type-4 receptors modulate the sensitivity of intramural mechanoreceptive afferents of the cat rectum. Neurogastroenterol Motil 2002;14:221–7.
25. Coffin B, Farmachidi JP, Rueegg P, et al. Tegaserod, a 5-HT4 receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. Aliment Pharmacol Ther 2003;17:577–85.
26. Kellow J, Lee OY, Chang FY, et al. An Asia Pacific, double blind, placebo controlled, randomized study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. Gut 2003;52:671–6.
27. Tack J, Muller-Lissner S, Bytzer P, et al. A randomized controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation (IBS-C). Gut 2005;54:1707–13.
28. Nyhlin H, Bang C, Elsborg L, et al. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. Scand J Gastroenterol 2004;39:119–26.
29. O'Donnell LJD, Virjee J, Heaton KW. Detection of pseudodiarrhea by simple clinical assessment of intestinal transit rate. BMJ 1990;300:439–40.
30. Pan W. Sample size and power calculations with correlated binary data. Control Clin Trials 2001;22:211–7.
31. Irvine JE, Whitehead WE, Chey WD, et al. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology 2006;130:1538–51.

## CONFLICT OF INTEREST

**Guarantor of the article:** William D. Chey, M.D.
**Specific author contributions:** The responsible author helped to design the study, was the primary investigator at his study site, and was responsible for writing the manuscript. Pierre Paré assisted in the design of the study, was the primary investigator at his study site, and reviewed and revised the manuscript. Andrea Viegas assisted in design of the study and reviewed and revised the manuscript. Gregory Ligozio assisted in design of the study and performed statistical analyses. Michael Shetzline helped contribute to surveillance and interpretation of the study data and reviewed and revised the manuscript.
**Financial support:** This study was funded by Novartis Pharmaceuticals Corporation. Novartis participated in the design of the study and the reporting of outcomes. The study was conducted independently at research centers. This manuscript is supported by a grant from Novartis; AV, GL, and MAS are employees of Novartis.
**Potential competing interests:** Dr. Chey is a consultant and serves on the speaker's bureau for Novartis Pharmaceuticals.

**Author's Note:** On March 30, 2007 Novartis announced it would comply with a request from the Food and Drug Administration (FDA) to suspend US marketing and sales of tegaserod maleate (Zelnorm). An analysis of clinical trial data identified a small, but statistically significant imbalance in the number of cardiovascular ischemic events in patients taking tegaserod. There is no demostrated causal relationship between tegaserod and these events.