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ORIGINAL CONTRIBUTIONS

Stomach

Tegaserod Treatment for Dysmotility-Like Functional Dyspepsia: Results of Two Randomized, Controlled Trials

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OBJECTIVES: Therapies for dysmotility-like functional dyspepsia (FD) are limited. We studied tegaserod, a selective serotonin type 4 receptor agonist, in patients with FD.

METHODS: Two identical multicenter, double-blind, randomized, placebo-controlled trials enrolled women ≥18 yr with recurring mid-upper abdominal discomfort characterized by postprandial fullness, early satiety, and/or bloating. Patients were randomized to tegaserod 6 mg b.i.d. or placebo. Two patient-reported primary variables were assessed: percentage of days with satisfactory symptom relief, and symptom severity using the composite average daily severity score (CADSS).

RESULTS: In total, 2,667 women were randomized with no differences between trials in terms of recruitment method, *Helicobacter pylori* status, heartburn, or medication use. Mean percentage of days with satisfactory symptom relief for tegaserod *versus* placebo in Trial 1: 32.2% *versus* 26.6% (95% CI of treatment difference 2.82, 9.27; $P < 0.01$), Trial 2: 31.9% *versus* 29.4% (95% CI of treatment difference −0.21, 6.53; $P = 0.066$). Mean CADSS in Trial 1: 3.14 *versus* 3.35 (95% CI of treatment difference −0.29, −0.10; $P < 0.0001$), Trial 2: 3.15 *versus* 3.23 (95% CI of treatment difference −0.18, 0.01; $P = 0.094$). Meta-analysis showed significant benefit for both end points: increase in days with satisfactory relief 4.6% (95% CI 2.29, 6.96); decrease in CADSS 0.14 (95% CI 0.21, 0.07). Treatment effect was greater in patients with severe baseline symptoms. Diarrhea requiring study discontinuation was more common with tegaserod than placebo (4.1% *vs* 0.3%).

CONCLUSIONS: Some improvement in dysmotility-like FD was observed with tegaserod treatment. The clinical implication of this improvement is uncertain.

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INTRODUCTION

Dyspepsia is a common disorder, experienced by approximately 25% of the general population in Western countries (1). The cardinal manifestation is pain or discomfort centered in the upper abdomen, which may be associated with other upper gastrointestinal (GI) symptoms.

While some patients have a known cause for their dyspepsia (*e.g.*, peptic ulcer, gastro-esophageal reflux disease [GERD], or malignancy), others have no explanation despite clinical testing. These patients are classified as having functional dyspepsia (FD) (2, 3). FD can be subdivided based on symptom characteristics. The ROME II Committee on Functional Gastrointestinal Disorders recognized dysmotility-like (discomfort centered in the upper abdomen, which may be associated with meal-related symptoms such as postprandial fullness, early satiety, bloating, or nausea) and ulcer-like (pain centered in the upper abdomen as the predominant symptom) subgroups of FD (2). The ROME III definition of FD distinguished a postprandial distress syndrome from an epigastric pain syndrome (4).

While dyspepsia symptoms can impair numerous aspects of patients' daily activities and well-being, dysmotility-like symptoms are reported to have the greatest negative impact on health-related quality of life (HRQoL) (5, 6). A single causative mechanism for FD symptoms has not been defined, although several abnormalities in upper GI sensory and motor function have been reported (4, 7–11). Given the absence of a distinct, single pathophysiologic mechanism for FD and the diversity of symptoms, it is likely that different patient subgroups may require different management approaches (4).

Current therapy for FD is limited and largely consists of empirical treatment with proton pump inhibitors (PPIs) and eradication of *Helicobacter pylori* infection (12, 13). While these approaches can offer benefit to some patients with ulcer-like FD or symptoms of coexisting GERD, treatment results are variable (14–16). Furthermore, no currently available agent has been documented to improve dysmotility-like FD.

Tegaserod, a selective serotonin type 4 receptor agonist, is an effective treatment for irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (17–21). Tegaserod has been shown to improve gastric and small intestinal motility by normalizing delayed gastric emptying, enhancing gastric accommodation, and improving impaired antroduodenal motility (4, 22–27). Tegaserod may also decrease visceral hypersensitivity (28, 29). Pilot studies suggest that tegaserod can improve dysmotility-like FD symptoms in women (24, 30). These data provided the rationale to investigate further the potential value of tegaserod in large-scale clinical trials in women with dysmotility-type FD symptoms.

METHODS

Design Overview

The two multicenter, double-blind, randomized, placebo-controlled trials (ClinicalTrials.gov NCT00232024 [Trial 1] and NCT00232089 [Trial 2]) were conducted between January 2004 and June 2006 at 675 sites in the United States, United Kingdom, Canada, and South Africa. The trials were of identical design. Both comprised a 4-wk screening period, a 2-wk baseline period, and a 6-wk treatment period (Fig. 1) and were developed according to recommendations made by the ROME II committee (2).

Randomization and Concealed Allocation

Patients were assigned randomly to tegaserod 6 mg twice daily (b.i.d.) or placebo; both treatments were identical in appearance. Randomization (1:1 allocation ratio) was performed using a computer-generated sequence in each treatment center using permutated blocks of size 4. The randomization scheme was reviewed by a biostatistics quality assurance group, locked on their approval, and concealed from patients and study personnel at both the site and the sponsor offices until after both trials were completed.

Patient Population

Patients were English-speaking women ≥18 yr of age with recurring mid-upper abdominal discomfort characterized by at least two of the following symptoms: postprandial fullness, early satiety, and/or bloating. Symptoms had to be present for at least 12 wk, not necessarily consecutive, during the previous 12 months. Thus, symptom characteristics were compatible with dysmotility-like FD, as defined by the ROME II Committee (2).

Key exclusion criteria included a history of erosive esophagitis, erosive gastroduodenitis, gastric or duodenal ulceration (confirmed by negative upper GI endoscopy during screening); previous abnormal 24-h esophageal pH metry assessment; complaint of their most bothersome symptom being heartburn, nausea, or vomiting, or epigastric/ulcer-like pain; frequent heartburn (>2 times per week); current IBS or IBS-like symptoms; use of antisecretory or prokinetic medications; and concomitant serious medical conditions. Also, pregnant or breastfeeding women and those of childbearing

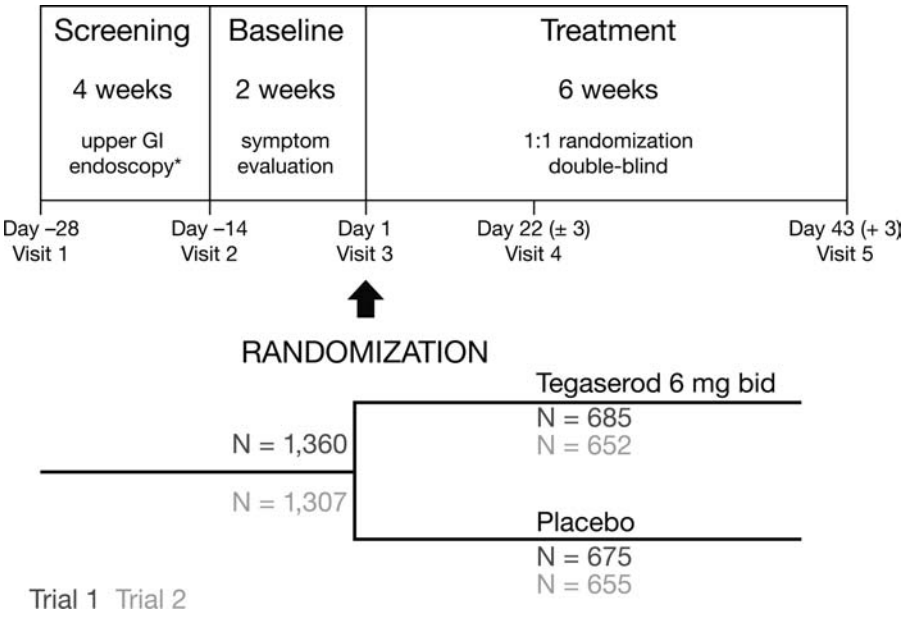

Figure 1. Study design. *Upper GI endoscopy was performed to exclude patients with gastric, esophageal, or duodenal abnormalities unless the patient had a normal endoscopy in the preceding 24 wk.

Table 1. Questions on Dyspepsia Symptoms

Verbatim Question		Explanation Given to Patients
Daily Individual Symptom Questions:		
	. . .early fullness while eating?	Early fullness while eating is a feeling the stomach is uncomfortably full soon after starting a normal size meal so that it is difficult to finish the meal
	. . .postmeal fullness?	Postmeal fullness is an uncomfortable feeling of being overly full after a meal
*How much discomfort have you had today from. . .	. . .bloating?	Bloating is an uncomfortable feeling of tightness or pressure in the stomach or belly like it is swollen; clothing may feel too tight on the stomach or belly, which could appear visibly larger or distended
	. . .abdominal pain?	No explanation given
	. . .nausea?	Nausea is a sick feeling as if you were going to vomit or throw-up
Did you have any occurrence of vomiting today?		No explanation given
Daily Satisfactory Relief Question:		
†Today did you have satisfactory relief of your mid-upper abdominal discomfort, which may include early fullness while eating, postmeal fullness, or bloating?		Satisfactory relief means your dyspepsia symptoms were not bothersome today
Weekly Global Assessment of Change Question:		
‡Compared with how you felt prior to entering this study, how would you rate your dyspepsia symptoms during the last week?		No explanation given

CADSS = composite average daily severity score.
*1 = no discomfort at all, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort, 5 = moderately severe discomfort, 6 = severe discomfort, 7 = very severe discomfort.
†Yes/No.
‡3 = a lot better, 2 = better, 1 = a little better, 0 = unchanged, −1 = a little worse, −2 = worse, −3 = a lot worse.

age who were not using an approved method of contraception were excluded.

During the 2-wk observational baseline period and the 6-wk treatment period, patients rated the discomfort caused by their dyspepsia symptoms (postprandial fullness, early satiety, bloating, abdominal discomfort/pain, and nausea) on a 7-point Likert scale (1 = no discomfort to 7 = very severe discomfort). This was done each day using an interactive voice response system. On a weekly basis, patients completed the Global Assessment of Change question, rating any change in their dyspepsia symptoms on a 7-point Likert scale (−3 = a lot worse to 3 = a lot better) (Table 1). The descriptions of the dyspepsia symptoms were developed and tested with FD patients (N = 74) prior to initiating the trials in order to ensure that the medical terms used were understandable (Table 1) (31). During the baseline observation period, patients who reported an average of at least "mild discomfort" (≥3 on a 7-point Likert scale) for two or more of the cardinal dyspepsia symptoms (postprandial fullness, early satiety, and bloating), who responded "no" ≥50% of the time to the daily satisfactory relief question (Table 1), and who recorded an assessment of their symptoms on ≥11 of 14 days, were eligible for randomization.

Efficacy Assessments

Two patient-assessed primary variables were used: (a) percentage of days with satisfactory relief of dyspepsia symptoms, and (b) composite average daily severity score (CADSS) for the three cardinal dyspepsia symptoms (postprandial fullness, early satiety, and bloating). CADSS was calculated by averaging the responses to the daily questions regarding individual dyspepsia symptom severity (Table 2). This composite end point had not been validated formally prior to the trials commencing. These primary variables were based on recommendations made in 2000 by the ROME II Committee (2). The secondary variables are listed and described in Table 2.

HRQoL

The impact of study medication on patients' HRQoL was assessed using the Short Form-36 Nepean Dyspepsia Index questionnaire (SF-NDI), a validated, disease-specific HRQoL measure (32, 33). SF-NDI comprises five domains (tension, interference with daily activities, eating/drinking, knowledge/control, and work/study), with each domain comprising two items. Patients rated each item, recalling the previous 2 wk, on 5-point Likert scales, providing individual domain scores ranging from 2 to 10. SF-NDI was administered at baseline, week 3 of study medication, and at end of treatment.

Tolerability and Safety Assessments

All adverse events (AEs) and serious AEs (SAEs, *i.e.*, a medically significant event that was life-threatening, required

Table 2. Efficacy Variables

Efficacy Variable	Assessment
Primary Variables:	
Percentage of days with satisfactory relief of dyspepsia symptoms	Responded "Yes" to the daily satisfactory relief question
CADSS of postprandial fullness, early satiety, and bloating	Based on responses to the daily questions on individual symptoms*
Secondary Variables:	
Overall and weekly responder rates for percentage of days with satisfactory relief	Responded "Yes" to the daily satisfactory relief question ≥50% of the time
Overall and weekly responder rates for CADSS	≥1.0 point improvement from baseline*
Overall and weekly responder rates for individual symptom severity scores for early satiety, postprandial fullness, bloating, and nausea	≥1.0 point improvement from baseline*
Overall and weekly responder rates for global assessment of change in dyspepsia symptoms	Responded "Better" or "A lot better" to the global assessment of change question†

CADSS = composite average daily severity score.
*1 = no discomfort at all, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort, 5 = moderately severe discomfort, 6 = severe discomfort, 7 = very severe discomfort.
†Global assessment of change question responses: 3 = a lot better, 2 = better, 1 = a little better, 0 = unchanged, −1 = a little worse, −2 = worse, −3 = a lot worse.

hospitalization, or caused significant incapacity) were recorded. In addition, vital signs, hematology, urinalysis, blood chemistry, and electrocardiograph data were evaluated. Stool frequency and form, using the Bristol Stool Scale, were recorded daily (34). Patients were withdrawn from the trials if they interrupted study medication for >5 consecutive days, and reasons for patient dropout were recorded.

Statistical Analysis

Target enrollment for each trial was 1,296 (648 per treatment arm) patients per trial. This was calculated using a Bonferroni adjustment for type 1 errors to detect a 10% difference between tegaserod and placebo groups with 90% power, assuming a 30% placebo response rate. The decision to power the study to detect a 10% difference was based on results from the phase II FD studies with tegaserod, and by the minimal level of improvement suggested by clinicians involved in designing the trials and considered necessary for indication approval by Health Authorities. Efficacy outcomes were analyzed in the intention-to-treat (ITT) population of all randomized patients. AEs were evaluated in all patients who received at least one dose of study medication (safety analyzable population).

Data from each trial were analyzed separately. Primary efficacy variables were evaluated over the entire treatment period using analysis of covariance (ANCOVA) models that included treatment, baseline measurements, and pooled treatment center as variables. Hochberg's procedure was used to control for a type 1 error rate of 5%. Treatment effects (differences in least square means [LSM]) and 95% confidence intervals (CIs) were obtained for each variable. Predefined nonparametric sensitivity analyses were conducted to evaluate the robustness of data, *i.e.*, skewness and outliers. As the percentage of days data were skewed right, median data are provided in addition to mean data.

For each variable, three predefined response criteria were evaluated: ≥50%, ≥66%, and ≥75% of days with satisfactory symptom relief; and ≥1-point, ≥1.5-point, and ≥2-point improvements from baseline for CADSS and for change in individual symptoms. Results for ≥50% of days with satisfactory relief and ≥1-point improvement from baseline for CADSS and individual symptoms are reported in this article. Response was analyzed using logistic regression models with treatment, baseline symptom score, and pooled center as covariates. Change in global assessment of dyspepsia symptoms was evaluated using Mantel-Haenszel tests. SF-NDI domain scores were analyzed using ANCOVA models including treatment, baseline measurements, and pooled treatment center as variables.

Interactions between treatment results and various baseline factors were analyzed within each trial for each primary efficacy variable. In addition, the data were pooled in a *post hoc*, patient-level, meta-analysis and reanalyzed to provide the best estimates of treatment effects and to test for interaction between treatment and baseline disease and demographic factors (including study). These meta-analyses were performed using models identical to those used within each study and by including a factor to account for study variability. A significant interaction ($P = 0.0060$) between treatment and baseline CADSS was identified for the CADSS primary variable. To investigate this treatment interaction further, patients were subgrouped arbitrarily according to baseline symptom severity: mild (CADSS 1 to <4), moderate (CADSS 4 to <5), severe (CADSS 5–7).

The study protocols were approved by ethics committees at all participating centers and performed according to the Declaration of Helsinki and the principles of Good Clinical Practice. All patients gave written informed consent.

RESULTS

Patient Characteristics

Patient disposition is summarized in Figure 2. The most frequent reasons for exclusion prior to randomization were failure to meet the diagnostic criteria (*e.g.*, presence of GERD or erosive gastritis or duodenitis) and dyspepsia symptoms that

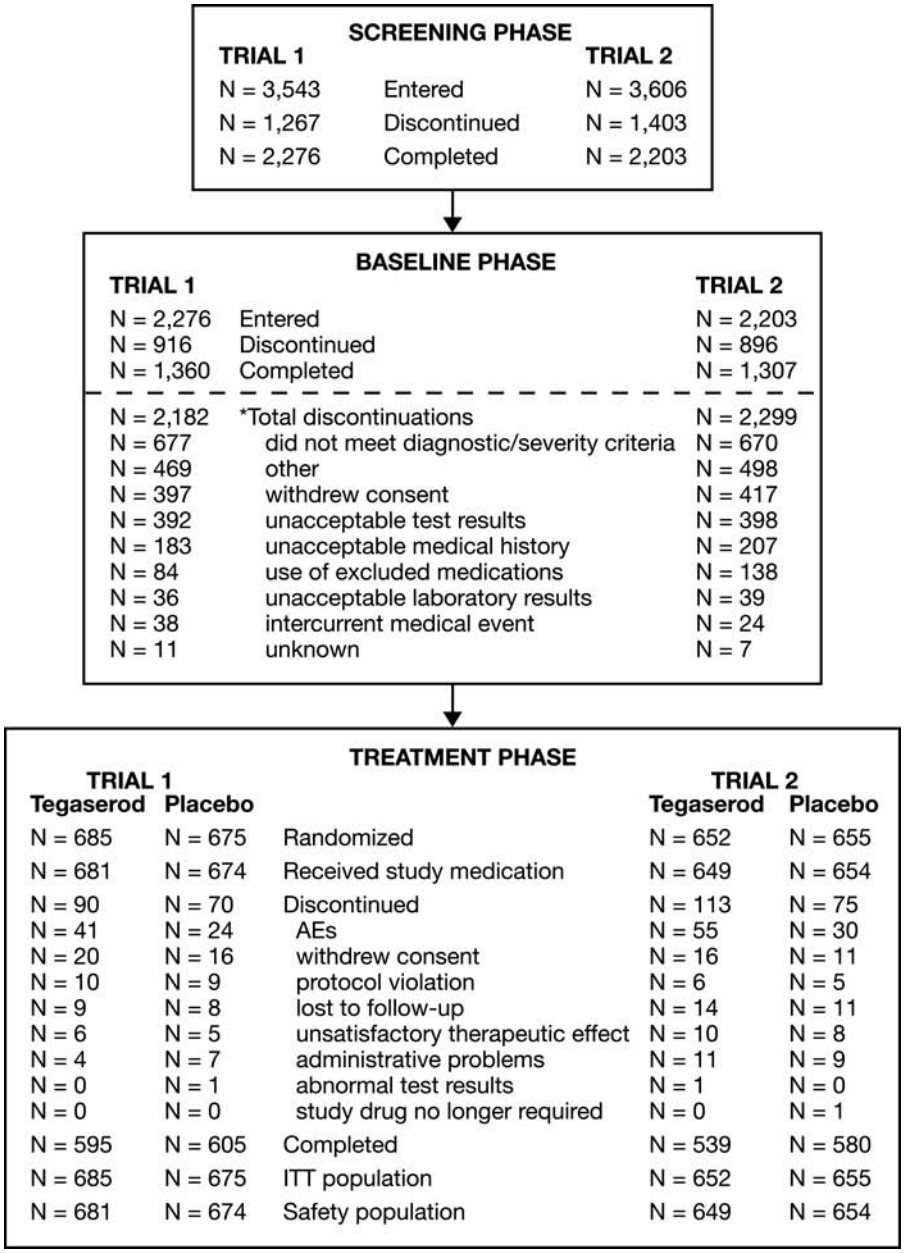

Figure 2. Summary of patient flow. *Discontinuations are shown for the screening and baseline phases combined. A patient may have more than one reason for not continuing into the randomization phase. AEs = adverse events; ITT = intention-to-treat.

did not meet the severity criteria during the baseline period. Most randomized patients (1,134 [84.8%] tegaserod, 1,185 [89.1%] placebo) completed the trials. Patients randomized to placebo or tegaserod had similar demography, body mass index, and symptom scores at baseline. Prior use of medication was similar between treatment groups and the individual studies at baseline. The medications most commonly used by patients prior to the trials were PPIs (Trial 1: 11.4% tegaserod *vs* 15.3% placebo; Trial 2: 10% tegaserod *vs* 10.1% placebo) and H2 receptor antagonists (Trial 1: 5.3% tegaserod *vs* 5.3% placebo; Trial 2: 3.5% tegaserod *vs* 4.1% placebo).

Patients were recruited into the trials from a variety of sources. Most were recruited from print, radio, or TV advertisements (Trial 1: 48%, Trial 2: 51%) or from the study investigators' own practices (Trial 1: 30%, Trial 2: 27%). Referral directly from physicians who were not investigators for the study accounted for $\leq$10% of recruitment across Trial 1 and Trial 2. Of these referrals, a majority were from primary care (Trial 1: 30%, Trial 2: 27%) rather than tertiary care (Trial 1: 10%, Trial 2: 6%).Tests for interaction revealed no association between source of patient recruitment and treatment outcome.

Approximately 80% of patients reported $<$1 day with satisfactory relief during the 14-day baseline observation period, the mean baseline CADSS scores were identical across treatment groups and trials and most patients

Table 3. Patient Baseline Demographic Characteristics and Dyspepsia Symptom Scores (ITT Population)

	Trial 1		Trial 2	
Parameter	Tegaserod 6 mg b.i.d.	Placebo	Tegaserod 6 mg b.i.d.	Placebo
N	685	675	652	655
Age (mean ± SD), yr	43.7 ± 13.2	44.2 ± 14.5	43.4 ± 13.7	43.6 ± 13.2
Range, yr	18–80	18–87	18–85	18–82
Ethnic Origin, N (%)				
White	537 (78.4)	524 (77.6)	510 (78.2)	511 (78.0)
Black	81 (11.8)	67 (9.9)	69 (10.6)	68 (10.4)
Asian	5 (0.7)	8 (1.2)	7 (1.1)	13 (2.0)
Other	62 (9.1)	76 (11.3)	66 (10.1)	63 (9.6)
BMI (mean ± SD), kg/m^2	27.5 ± 6.6	27.6 ± 6.7	27.2 ± 6.2	27.2 ± 6.5
Range, kg/m^2	16.5–62.1	15.5–58.0	15.2–62.4	16.1–63.4
Measurements at Baseline (mean ± SD)				
Percentage of days with satisfactory relief	6.6 ± 12.3	7.1 ± 13.5	5.9 ± 11.2	6.6 ± 12.0
Mean CADSS*	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 0.9

Missing values are excluded from the table.
*CADSS = composite average daily severity score (1 = no discomfort at all, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort, 5 = moderately severe discomfort, 6 = severe discomfort, 7 = very severe discomfort); b.i.d. = twice daily; BMI = body mass index; ITT = intention-to-treat; SD = standard deviation.

reported dyspepsia symptoms of at least moderate severity (Table 3).

Primary Efficacy Variables

Patients receiving tegaserod experienced a greater mean percentage of days with satisfactory symptom relief during the 6-wk treatment period compared with those receiving placebo. This treatment difference was statistically significant (32.2% *vs* 26.6%, 95% CI of treatment difference 2.82, 9.27; $P = 0.0002$) in Trial 1, but not in Trial 2 (31.9% *vs* 29.4%, 95% CI of treatment difference −0.21, 6.53; $P = 0.066$) (Table 4). In view of the skewed distribution of data for percentage of days with satisfactory relief, the median data are also presented for tegaserod and placebo, respectively: Trial 1: 25.3% and 9.8% ($P = 0.0004$), Trial 2: 22.5% and 15.4% ($P = 0.0633$).

Mean CADSS reported by tegaserod patients during the treatment period (3.14) was significantly lower than that of placebo patients (3.35) in Trial 1 (95% CI of treatment difference −0.29, −0.10; $P < 0.0001$), but not in Trial 2 (tegaserod 3.15 *vs* placebo 3.23, 95% CI of treatment difference −0.18, 0.01; $P = 0.094$) (Table 4).

The results of a *post hoc*, patient-level, meta-analysis using primary efficacy variable data from Trial 1 and Trial 2 are shown in a petogram (Fig. 3). Also shown are the 95% CIs relating to the two individual trials. When the data from both trials were combined, the 95% CIs around the point estimates were narrowed relative to each individual trial and the differences were statistically significant for both primary variables: mean percentage of days with satisfactory symptom relief (95% CI of treatment difference of 2.29, 6.96), mean CADSS (95% CI of treatment difference −0.21, −0.07).

Secondary Efficacy Variables

RESPONDER RATE: PERCENTAGE OF DAYS WITH SATISFACTORY RELIEF. The responder rate for percentage of days with satisfactory relief (≥50%) was significantly greater with tegaserod than placebo (32.5% *vs* 25.9%; OR 1.45, 95% CI 1.13, 1.85; $P = 0.003$) in Trial 1, but not in Trial 2 (tegaserod 32.0%, placebo 30.8%; OR 1.10, 95% CI 0.86, 1.41; $P = 0.430$).

RESPONDER RATE: COMPOSITE AVERAGE DAILY SEVERITY SCORE. In Trial 1 there were significantly more responders (change ≥1.0-point improvement in the severity of patients' symptoms from baseline) to tegaserod than placebo, as assessed by CADSS (49.9% *vs* 41.9%; OR 1.42, 95% CI 1.14, 1.77; $P = 0.002$). In contrast, while the responder rate to tegaserod was numerically greater than placebo in Trial 2, the difference was not statistically significant (50.3% *vs* 45.8%; OR 1.21, 95% CI 0.97, 1.51; $P = 0.092$).

INDIVIDUAL DYSPEPSIA SYMPTOMS. Tegaserod reduced the severity of all individual symptoms of dyspepsia. The response rate (≥1.0-point improvement from baseline) was significant for all symptoms (early satiety [$P = 0.001$], postprandial fullness [$P = 0.0001$], bloating [$P = 0.002$], abdominal pain [$P = 0.027$], and nausea [$P = 0.014$]) in Trial 1, but only for postprandial fullness in Trial 2 ($P = 0.04$) (Fig. 4).

GLOBAL ASSESSMENT OF CHANGE IN DYSPEPSIA SYMPTOMS. In 5 out of the 6 wk in Trial 1 and in all 6 wk in Trial 2, tegaserod was statistically superior to placebo (Fig. 5) for improving the patients' rating of global change in dyspepsia symptoms (improvement was defined as a response of "a lot better" or "better" on the 7-point Likert scale) compared with baseline (Trial 1 $P < 0.001$, Trial 2 $P = 0.004$).

As described earlier, results for ≥50% of days with satisfactory relief and ≥1-point improvement from baseline for CADSS and individual symptoms are reported here; however, results using the other predefined responder definitions

Table 4. Primary Outcome Variables

Variable	Trial 1					Trial 2					Meta-Analysis				
	Tegaserod 6 mg b.i.d.	Placebo	Least Square Mean (LSM) Difference			Tegaserod 6 mg b.i.d.	Placebo	Least Square Mean (LSM) Difference			Tegaserod 6 mg b.i.d.	Placebo	Least Square Mean (LSM) Difference		
			Mean	95% CI	*P* value			Mean	95% CI	*P* value			Mean	95% CI	*P* value
N	680	673				651	652				1331	1325			
Patients with satisfactory relief, % ± SD (Median, %)	32.2 ± 32.3 (25.3)	26.6 ± 31.2 (9.8)	6.1	2.82, 9.27	0.0002 (0.0004)	31.9 ± 32.6 (22.5)	29.4 ± 32.1 (15.4)	3.2	−0.21, 6.53	0.066 (0.0633)	32.1 (24.0)	28.0 (12.5)	4.6	2.29, 6.96	0.0001
Mean CADSS ± SD (Median)	3.14 ± 1.1 (3.1)	3.35 ± 1.2 (3.3)	−0.19	−0.29, −0.10	<0.0001	3.15 ± 1.1 (3.1)	3.23 ± 1.1 (3.2)	−0.08	−0.18, 0.01	0.094	3.15	3.29	−0.14	−0.21, 0.07	<0.0001

CADSS = composite average daily severity score (1 = no discomfort at all, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort, 5 = moderately severe discomfort, 6 = severe discomfort, 7 = very severe discomfort); b.i.d. = twice daily; CI = confidence interval; SD = standard deviation.

(≥66% and ≥75% of days with satisfactory relief, and ≥1.5-point, and ≥2-point improvement from baseline for CADSS and individual symptoms) did not alter the overall response picture (data not shown).

Treatment Response in Relation to Baseline Dyspepsia Symptom Severity

Analyses of pooled data suggested that the treatment effect of tegaserod may be greater in patients who had more severe dyspepsia symptoms at baseline. Tegaserod provided the greatest improvement in percentage of days with satisfactory relief of symptoms in patients who reported severe baseline symptoms (treatment effect −6.7% *vs* placebo; $P = 0.01$) compared with patients whose baseline symptoms were rated as only moderate (treatment effect −2.4% *vs* placebo; $P = 0.075$) or mild (treatment effect −4.2% *vs* placebo; $P = 0.02$).

Treatment with tegaserod also provided the greatest improvement in CADSS in patients who reported severe symptoms of dyspepsia at baseline: severe (treatment effect −0.28; $P = 0.005$), moderate (treatment effect −0.12; $P = 0.012$), and mild (treatment effect −0.07; $P = 0.105$).

The effect of tegaserod treatment on improving individual symptoms was also most pronounced for those patients who reported severe symptoms at baseline. A greater proportion of these patients experienced a reduction in severity (≥1.0-point improvement from baseline) with tegaserod *versus* placebo. Improvement in four of the five dyspepsia symptoms (postprandial fullness, bloating, abdominal pain, and nausea) was significantly greater with tegaserod compared with placebo in these patients ($P \leq 0.016$) while only postprandial fullness had a significantly higher response with tegaserod among patients with mild baseline symptoms (Table 5).

When baseline data were pooled, HRQoL domain scores, as assessed by the SF-NDI, were comparable for tegaserod and placebo patients within each symptom severity subgroup and were comparable to other studies investigating the effect of FD symptoms on sufferers' QoL (5). All five SF-NDI domain scores were highest in patients who reported severe baseline dyspepsia symptoms ($P < 0.0001$), indicative of greatest impairment of all the measured aspects of HRQoL (tension, interference with daily activities, eating/drinking, knowledge, work/study). Importantly, the treatment benefit with tegaserod for all five SF-NDI domains was greatest in those patients with severe baseline dyspepsia symptoms. In relation to HRQoL symptom domains that might be expected to be adversely affected by dyspepsia, the greatest improvement during tegaserod *versus* placebo therapy was observed in the eating/drinking domain for this subgroup of patients (0.77 point, $P = 0.0005$).

Treatment Exposure, Safety, and Tolerability

Exposure to study medication was high; approximately 87% of patients reported ≥42 days of exposure to tegaserod or placebo, consistent with the 6-wk treatment duration.

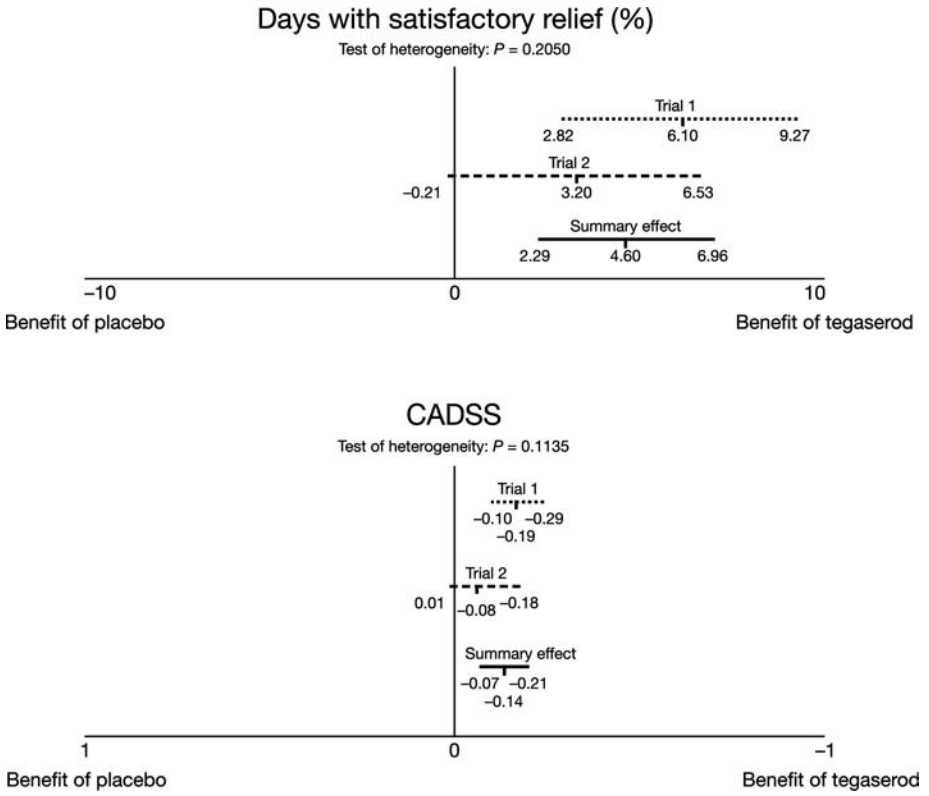

Figure 3. Petogram illustrating confidence intervals for the two primary efficacy variables (percentage of days with satisfactory relief of dyspepsia symptoms and mean CADSS) for both trials and for the meta-analysis (point estimates are shown between each set of confidence intervals). *P* values for meta-analysis data: satisfactory relief of dyspepsia symptoms $P = 0.0001$; mean CADSS $P < 0.0001$.

During treatment with study drug, the most commonly reported AEs in both trials were diarrhea, headache, and nausea. Only diarrhea was more common with tegaserod than with placebo treatment (Table 6). Significantly more patients treated with tegaserod than placebo discontinued the study because of diarrhea (54/1330 [4.1%] *vs* 4/1328 [0.3%]; $P < 0.001$). Of note, when analyzed by baseline symptom severity, more discontinuations because of diarrhea in tegaserod-treated patients occurred in the mild/moderate rather than severe dyspepsia symptom subgroups (mild 22/579 [3.8%] *vs* moderate 24/485 [4.9%] *vs* severe 7/265 [2.6%]). SAEs were reported by four patients (0.6%) in each treatment group of

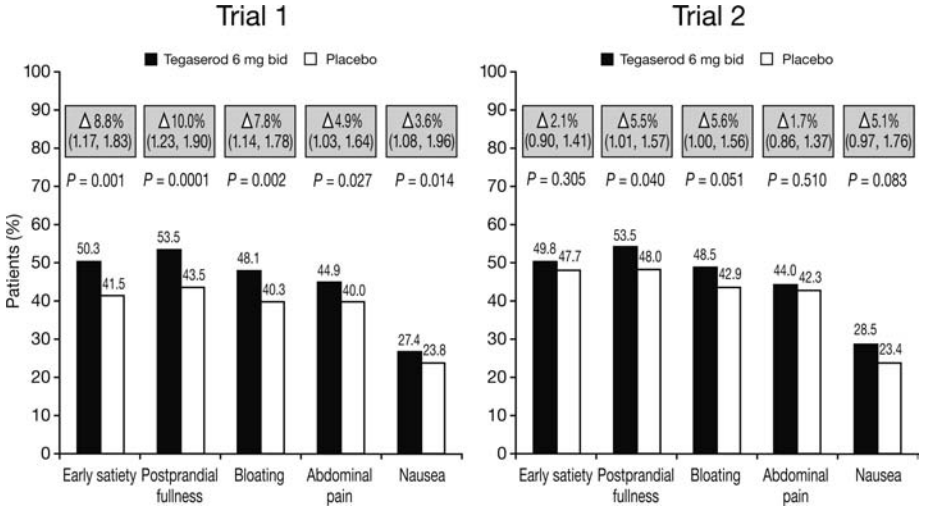

Figure 4. Proportion of patients with ≥1-point improvement from baseline in individual symptom severity scores. Symptoms were assessed on a 7-point scale: 1 = no discomfort at all, 2 = minimal discomfort, 3 = mild discomfort, 4 = moderate discomfort, 5 = moderately severe discomfort, 6 = severe discomfort, 7 = very severe discomfort Δ represents treatment differences between tegaserod and placebo with confidence intervals included in parentheses below.

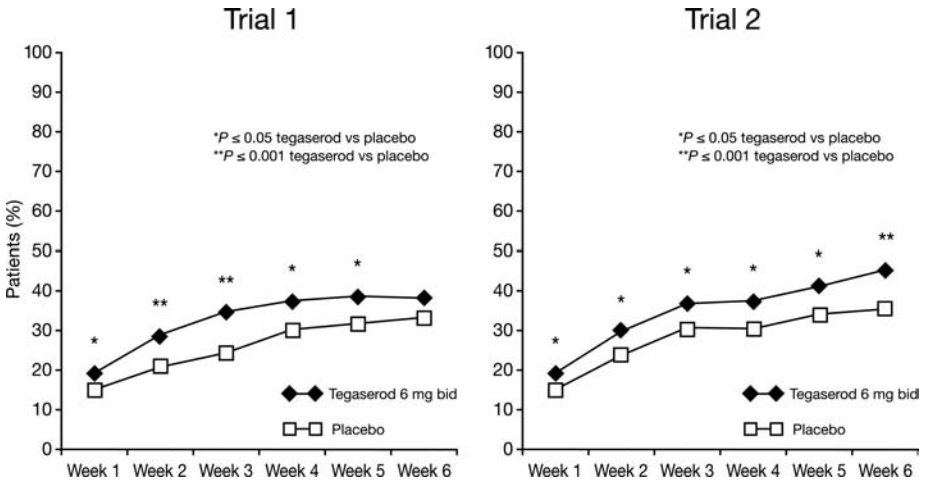

Figure 5. Proportion of patients with a response of "better" or "a lot better" on global assessment of change in dyspepsia symptoms. "Compared with how you felt prior to entering this study, how would you rate your dyspepsia symptoms during the last week?" (3 = a lot better, 2 = better, 1 = a little better, 0 = unchanged, −1 = a little worse, −2 = worse, −3 = a lot worse.). Response defined as "better" or "a lot better". $^{*}P \leq 0.05$, $^{**}P \leq 0.001$ tegaserod *versus* placebo.

Trial 1, and by two tegaserod patients (0.3%) and five placebo patients (0.8%) in Trial 2. No deaths and no cases of ischemic colitis were reported.

There was one AE in Trial 1 initially reported as a cardiovascular event. A 35-yr-old woman randomized to placebo reported chest pain on Day 14 of the double-blind treatment period. She was evaluated in the emergency room and investigations were negative for a cardiovascular event. This patient completed the trial. There were two SAEs reported as cardiovascular events in Trial 2. One case, later determined to be musculoskeletal chest pain, occurred in a patient taking tegaserod, and one case of chest discomfort occurred in a patient taking placebo. Both patients discontinued the study prematurely.

DISCUSSION

The term "dyspepsia" defines a set of symptoms commonly observed in primary care and has been estimated to account for 2–5% of all family practice consultations (12). Most of these patients have no identifiable explanation for their symptoms, and hence are described as having FD. The management of FD can be both expensive and unsatisfactory because treatment options are limited and symptom patterns do not correlate well with pathophysiological abnormalities (12). For example, while the use of prokinetic agents in patients with dysmotility-type FD symptoms may lead to improvement in delayed gastric emptying, there is little correlation between changes in gastric emptying and symptom improvement (35). Predictors of response to treatment are also problematic, making it difficult for clinicians and investigators to identify patients who are likely to respond to treatment in general or to a specific therapeutic approach based on their presenting symptoms (36).

Other treatment approaches for FD include eradication of *H. pylori*, and acid inhibition with PPIs (13, 37). However, both *H. pylori* eradication and PPIs have limited efficacy in FD, with randomized trials indicating that, as compared with placebo, approximately one of every 15 patients receiving active therapy reports improvement in symptoms (38, 39). Furthermore, PPIs are no more effective than placebo in patients with dysmotility-type FD (40). Because of the limited efficacy of *H. pylori* eradication and acid inhibition in patients with dysmotility-type FD, a large proportion of patients remain symptomatic with current treatment approaches.

Table 5. Improvement (≥1.0 Point) in Individual Symptoms by Baseline Symptom Severity* (Pooled Data)

	Mild			Moderate			Severe		
Response (%) (≥1.0-point)	Tegaserod 6 mg b.i.d.	Placebo	*P* Value	Tegaserod 6 mg b.i.d.	Placebo	*P* Value	Tegaserod 6 mg b.i.d.	Placebo	*P* Value
Early satiety	38.8	35.2	0.229	56.5	49.2	0.009	63.1	55.1	0.065
Postprandial fullness	45.9	39.4	0.031	56.1	48.4	0.013	65.8	54.0	0.005
Bloating	39.5	35.0	0.108	52.0	44.6	0.030	60.8	49.4	0.009
Abdominal pain	31.2	31.8	0.776	49.5	44.6	0.046	64.3	54.0	0.016
Nausea	16.9	14.3	0.096	30.0	27.2	0.092	48.3	36.2	0.009

*Severity definition for composite average daily severity score (CADSS): mild (CADSS 1 to <4), moderate (CADSS 4 to <5), severe (CADSS 5–7).

Table 6. Frequency of Adverse Events (≥3% in Any Group), and Analysis of Diarrheal Episodes

	Trial 1		Trial 2	
Adverse Event	Tegaserod 6 mg b.i.d.	Placebo	Tegaserod 6 mg b.i.d.	Placebo
N	681	674	649	654
AE Frequency, N (%)				
Diarrhea	129 (18.9)	26 (3.9)	125 (19.3)	34 (5.2)
Headache	40 (5.9)	27 (4.0)	30 (4.6)	33 (5.0)
Nausea	29 (4.3)	33 (4.9)	28 (4.3)	31 (4.7)
Abdominal pain	16 (2.3)	18 (2.7)	21 (3.2)	10 (1.5)
Vomiting	9 (1.3)	20 (3.0)	12 (1.8)	13 (2.0)
Time to Onset of First Diarrhea Episode (Days)				
Median	2.0	18.0	2.0	8.0
Range	1–47	1–48	1–42	1–45
Number of Diarrhea Episodes per Patient, N (%)				
1	111 (16.3)	22 (3.3)	101 (15.6)	33 (5.0)
2	16 (2.3)	5 (0.7)	18 (2.8)	1 (0.2)
3	5 (0.7)	0	6 (0.9)	1 (0.2)
4	0	0	1 (0.2)	0
5	1 (0.1)	0	0	0
6	2 (0.3)	0	1 (0.2)	0
Classification of Diarrhea, N (%)				
Mild diarrhea	62 (9.1)	15 (2.2)	64 (9.9)	24 (3.7)
Moderate diarrhea	45 (6.6)	7 (1.0)	48 (7.4)	9 (1.4)
Severe diarrhea	22 (3.2)	4 (0.6)	13 (2.0)	1 (0.2)
Diarrhea leading to discontinuation	22 (3.2)	1 (0.1)	33 (5.1)	3 (0.5)
Diarrhea as SAE	0	0	0	0

Diarrhea was defined as any AE with the following preferred terms: diarrhea, loose stools, loose bowel, watery stools, fecal incontinence, frequent bowel movements, gastroenteritis, watery diarrhea. For episodes marked as "continuing" at study end, the last visit date is imputed as the end date of the diarrheal episode.

The results of this study demonstrated some improvement in patients' dysmotility-like FD symptoms and HRQoL following treatment with tegaserod, with a trend toward an enhanced response in patients with severe dysmotility symptoms at baseline. Based on the treatment response for the primary variables, the effect of treatment with tegaserod was statistically significant in Trial 1, but not in Trial 2. A prespecified analysis identified baseline symptom severity and the presence of heartburn (both represented equally in the patients of both trials) as affecting the response to treatment. This analysis failed to identify any other differences between Trial 1 and Trial 2 that may have modified response to treatment. Furthermore, testing for heterogeneity revealed no difference between the two trials, a result that supported the decision to combine the primary variable data from both trials as part of a *post hoc*, patient-level, meta-analysis. The results of the meta-analysis suggest that the "true" effect of treatment with tegaserod lies between the results of Trial 1 and Trial 2. The meta-analysis demonstrated a statistically significant result when data from the two trials were combined. However, whether the observed effect would be clinically meaningful for individual patients in a clinical setting remains to be determined, particularly because the primary variables have yet to be validated against recognized clinically meaningful parameters. Nevertheless, it is important to note that when treatment response is assessed by stratifying patients according to their baseline symptom severity, the response to treatment for most variables was consistent across both Trial 1 and Trial 2. Furthermore, consistent treatment differences favoring tegaserod were observed across most of the primary and secondary variables including HRQoL. This result supports the suggestion that while tegaserod may not be an appropriate treatment for all patients with dysmotility-type FD, there may be some patients, particularly those with severe symptoms, who could benefit. Using a responder definition of ≥1 point from baseline for CADSS, the number-needed-to-treat (NNT) in this study was 9 for the FD patients with severe symptoms, and 16 for the ITT population.

As with all drugs, the benefit of tegaserod must be weighed against its side effects. Diarrhea was the principal side effect in these studies, with approximately 4% of patients discontinuing tegaserod because of diarrhea. Patients with severe FD symptoms had lower discontinuation rates because of the side effects and had the greatest potential to benefit from treatment. However in patients with mild-moderate FD symptoms, an acceptable balance between benefit and side effects may be more difficult to achieve. The result of the meta-analysis that is based on ITT data (*i.e.*, all dropouts are considered failures) suggests that for the group as a whole, some benefit is seen with tegaserod.

As observed in most FD trials, our study had a high placebo response rate. As also seen in this and prior FD trials, the magnitude of symptom improvement was modest when compared with that of drugs for other therapeutic areas where altering the underlying pathophysiology is the goal, such as in GERD where treatment with PPIs reduce esophageal acid exposure (41).

While the underlying pathophysiology of FD symptoms is incompletely understood, the mechanism(s) responsible for a significant therapeutic response are also unresolved.

Treatment strategies for improving dysmotility-type FD symptoms have been directed at accelerating gastric emptying, enhancing gastric accommodation to a meal, and changing meal-related gastric volume. However, such strategies have had limited success. Tegaserod was chosen for study in FD as several early mechanistic trials showed that in addition to stimulating gastric emptying and small bowel transit, tegaserod also reduced hyperalgesia in the upper GI tract and, in some patients, improved gastric accommodation (4, 22–27). Some studies have shown that cisapride, a nonselective serotonin type 4 receptor agonist, improves dysmotility-like FD symptoms, but a recent meta-analysis suggested that the benefit attributed to cisapride in this condition may, in part, be related to publication bias (42). Other gastroprokinetic agents such as the motilin receptor agonist, ABT-229, have been unsuccessful in the treatment of FD (43). Another agent that has been studied in dyspepsia is itopride, a dopamine D2 antagonist and acetylcholinesterase inhibitor that in healthy people reduces postprandial gastric volume without accelerating gastric emptying or significantly altering gastric motor and sensory function (44, 45). Although itopride was effective in improving symptoms of FD and heartburn in a Phase II trial, no significant improvement over placebo in reduction of FD symptoms was observed in two subsequent Phase III trials (46, 47).

At present there is no established outcome measure to evaluate treatment efficacy in dysmotility-like FD. This may result from our limited understanding of the causes of the disorder as well as limited knowledge of factors modifying symptom severity and related impact on patients. Recently, there has been a new focus on prospectively determining such parameters. In 2007, the U.S. FDA mandated the use of validated, patient-reported outcome (PRO) measures when assessing symptom improvement in conditions like FD (48). The most appropriate PROs for use in dyspepsia trials have not been defined. In this study we used several end points, all of which were PRO measures and recommended by the ROME II expert group (2). The advantage of the binary satisfactory relief variable is that it has been well studied in IBS trials. However, it may fail to capture more subtle degrees of improvement in upper GI symptoms. While the CADSS assessment may capture changes in selected FD symptoms, the equal weighting of individual symptom scores and the omission of other symptoms may have limitations. When symptoms are strongly correlated, considering them separately and assigning each an equal weight may lead to overrating, a problem that would not occur if the symptoms occurred independently of each other. Furthermore, the CADSS scale has neither been validated nor has the minimum clinically important difference been determined for this scale. We have no information to indicate that the small difference in CADSS between tegaserod and placebo found in these studies is a clinically important difference.

The most consistent improvements with tegaserod were seen with the global assessment of change in individual dyspepsia symptoms during treatment compared with baseline. This result was significant for both trials and for all weeks except one. The main disadvantage of this variable is the inherent recall of pretreatment symptom severity, which may lead to bias. However, this outcome variable closely resembles the way treatment benefit is evaluated by physicians in clinical practice. In light of the new guidance from the FDA (48), additional evaluation of end points and validation studies will be required to determine the optimal outcome measure(s) for use in clinical trials assessing treatment effects in dysmotility-like FD.

Because observed rates of treatment response have been limited in all previous FD trials, it is reasonable to ask whether better patient selection could improve the outcome of clinical trials in FD. Because there is no unifying pathogenic mechanism that explains the symptoms under evaluation, and as improvements in some physiologic measures do not readily translate into symptom improvement, patient selection on clinical grounds may need to be considered further. In our study, exploratory analyses show that patients with severe symptoms have a better response to tegaserod than do patients with mild symptoms. To our knowledge, baseline symptom severity has not been identified as an important variable in previous FD treatment trials. Although these symptom severity-related responses are viewed as hypothesis generating and not confirmatory, future trials may benefit from considering symptom severity in patient recruitment.

The strengths of our trials include the large sample size and the careful selection of patients without symptoms or endoscopic findings of GERD, a problem that has complicated previous trials in FD. Also, we did not attempt to control for *H. pylori* status so the results stand alone and are not affected by this consideration. The patient population we studied (those with dysmotility-type symptoms) has the greatest need for an effective therapy because available treatments are of limited or no efficacy (12, 13). Furthermore, the trials were of identical design and there were no identifiable differences between the trials in terms of patient characteristics or demographics. A weakness is the inclusion of only women. However, this choice was based on Phase II tegaserod data that demonstrated greatest efficacy in women with dyspepsia symptoms and on the approval of tegaserod for use only in women with IBS at the time the study program was designed.

No cardiovascular toxicity was observed in tegaserod-treated patients in either trial. The trials were completed before March 30, 2007, when Novartis announced it was complying with a request from the FDA to suspend U.S. marketing and sales of tegaserod owing to a potential signal suggesting increased cardiovascular ischemic events with tegaserod use. Obviously, the benefit *versus* the risk of any treatment choice for dyspepsia, as well as for other conditions, needs to be considered carefully.

In conclusion, the results from Trial 1 demonstrate that tegaserod significantly improved some dyspepsia symptoms in women with dysmotility-type FD, while a significant treatment effect was not seen in Trial 2. A meta-analysis of

the two trials shows a small statistically significant benefit with tegaserod. The clinical importance of improvements in FD symptoms of the magnitude seen in these trials is uncertain. Any potential benefit with tegaserod appeared to be most pronounced in those patients with severe baseline symptoms.

FOOTNOTE

On March 30, 2007, Novartis complied with a request from the Food and Drug Administration (FDA) to suspend U.S. marketing and sales of Zelnorm (tegaserod maleate) because the analysis of clinical trial data had identified a small imbalance that was statistically significant in the number of cardiovascular ischemic events in patients taking Zelnorm. The data showed that events occurred in 13 out of 11,614 patients treated with Zelnorm (0.11%), compared with one case in 7,031 placebo-treated patients (0.01%). These events included heart attack, stroke, and unstable angina. These cardiovascular ischemic events occurred in patients who had preexisting cardiovascular disease and/or cardiovascular risk factors. There is no demonstrated causal relationship between Zelnorm and these events.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Treatment options for patients with dysmotility-like FD are limited.
- Serotonergic agents modulate GI motility, secretion and sensation.
- Tegaserod has been shown to improve the symptoms of patients with IBS-C and CC.

What Is New Here

- Tegaserod improved some dysmotility-like FD symptoms in Trial 1 but the effect was not reproduced in Trial 2.
- The greatest improvement in FD symptoms and HRQoL with tegaserod occurred in patients with the most severe symptoms.
- A meta-analysis of Trial 1 and Trial 2 results showed that the "true" effect of treatment with tegaserod may lie between the results of the individual trials.

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CONFLICT OF INTEREST

Guarantor of the article: Nimish Vakil.

Specific author contributions: Nimish Vakil has made substantial contributions to the intellectual content of the paper (conception and design, acquisition of the data, analysis and interpretation of the data, drafting and critical revision of the manuscript). He wrote the first draft and made significant contributions to all subsequent versions of the manuscript. He has also given his final approval for the manuscript to be submitted. Loren Laine has made substantial contributions to the intellectual content of the paper (conception and design, acquisition of the data, analysis and interpretation of the data, drafting and critical revision of the manuscript). He has

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