

Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation

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SUMMARY

Aim: To investigate the efficacy and safety of tegaserod, a novel 5-HT₄ receptor partial agonist, in a randomized, double-blind, placebo-controlled, 12-week treatment, multicentre study.

Methods: Eight hundred and eighty-one patients with irritable bowel syndrome, characterized by abdominal pain, bloating and constipation, received tegaserod, 2 mg b.d. or 6 mg b.d., or placebo for 12 weeks.

Results: Tegaserod, 2 mg b.d. and 6 mg b.d., showed a statistically significant relief of overall irritable bowel syndrome symptoms, measured by a weekly, self-administered questionnaire. At end-point, treatment differences from placebo were 12.7% and 11.8% for

2 mg b.d. and 6 mg b.d., respectively. The effect of tegaserod was noted as early as week 1, and was sustained over the 12-week treatment period. Individual irritable bowel syndrome symptoms assessed daily also showed a statistically significant improvement of abdominal discomfort/pain, number of bowel movements and stool consistency, and a favourable trend for reducing days with significant bloating. Adverse events were similar in all groups, with transient diarrhoea being the only adverse event seen more frequently with tegaserod than placebo.

Conclusions: Based upon the results of this study, tegaserod offers rapid and sustained relief of the abdominal pain and constipation associated with irritable bowel syndrome. Tegaserod is also well tolerated.

INTRODUCTION

Irritable bowel syndrome is one of the most common functional gastrointestinal disorders, and is characterized by recurrent abdominal pain and discomfort, bloating and altered bowel function.¹ It has been estimated in epidemiological studies that as many as 22% of people report symptoms consistent with irritable bowel syndrome.² In clinical practice in Western countries, irritable bowel syndrome is gener-

ally reported more frequently by women.^{2, 3} The disease can have a significant impact on an individual's quality of life, with profound social and economic consequences.^{4–6}

The diagnosis of irritable bowel syndrome is challenging because of the lack of histopathological or biochemical markers to characterize the disorder.^{1, 7} Physicians therefore rely on exploring the symptomatology expressed by individual patients, the predominant symptom being abdominal pain or discomfort.¹ The subclassification of irritable bowel syndrome patients by their primary symptoms can be clinically meaningful in order to select the appropriate treatment.² In terms

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of bowel function, some patients may experience constipation more often and others diarrhoea more often. However, there is a large group of patients who alternate between constipation and diarrhoea during the course of their illness.⁸

The underlying mechanisms which contribute to the pathophysiology of irritable bowel syndrome are currently emerging with the advent of novel therapeutic agents. Recent methodological advances and interdisciplinary studies have led to a greater understanding of gastrointestinal physiology, in particular the interplay between the enteric and the central nervous system (the 'brain-gut axis'). As a result, it is now accepted that disturbances in gastrointestinal motility and enhanced perception of visceral stimuli (visceral hypersensitivity) both make important contributions to irritable bowel syndrome symptoms.^{2, 7, 9}

In the past, treatment decisions were often based on the patient's individual symptoms because there was no single drug that was effective in relieving abdominal pain, bloating and constipation associated with irritable bowel syndrome.¹⁰ However, there is growing evidence that serotonin (5-HT), via its subtype 4 (5-HT₄) receptors, plays a pivotal role in the maintenance of overall gastrointestinal motor function.^{11, 12} The advent of innovative 5-HT₄ receptor agonists has demonstrated that 5-HT₄ receptor stimulation can trigger the peristaltic reflex in both animal and human gastrointestinal tract.¹³ Moreover, recent studies performed in cats and rats suggest a modulating role of 5-HT₄ receptors in visceral sensation.^{14, 15}

Tegaserod [3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentyl-carbazimidamide] hydrogen maleate is a new compound designed as a selective 5-HT₄ receptor partial agonist.^{16, 17} Preclinical and clinical investigations have demonstrated that tegaserod can stimulate motility throughout the gastrointestinal tract.¹⁸⁻²² Partial agonists may have the effect of normalizing altered gastrointestinal motility and, in addition, may also modulate visceral sensation.^{14, 15} Therefore, tegaserod was investigated in the treatment of irritable bowel syndrome.

The purpose of this study was to evaluate the efficacy and safety of tegaserod in a large, international, randomized, placebo-controlled, double-blind, multicentre study in patients with symptoms of abdominal pain, bloating and constipation associated with irritable bowel syndrome.

METHODS

Patients

Patient selection was based on a 3-month history of irritable bowel syndrome symptoms, diagnosed using the Rome criteria.²³ Male and female patients, 18 years or older, were required to have lower abdominal pain or discomfort either relieved by a bowel movement, or associated with a change in the frequency of bowel movements. Patients were also required to have at least two of three constipation symptoms at least 25% of the time during the 3 months prior to study entry: less than three bowel movements per week, hard/lumpy stools, straining.

Normal colonic anatomy had to be confirmed by colonoscopy, sigmoidoscopy or barium enema, performed within the previous 5 years and after the onset of symptoms.

Patients were excluded from the study if they presented with a history of diarrhoea (defined as loose or watery stools and/or more than three bowel movements per day associated with urgency on 25% of days), or planned to use drugs that affect gastrointestinal motility and/or perception. Female patients were excluded if they were pregnant, breast-feeding or did not use an adequate method of contraception. Patients with a condition affecting gastric, small bowel or colonic transit, or with a history of drug, alcohol or laxative abuse, were also excluded. Concomitant use of any medication primarily affecting gastrointestinal motility and/or perception was disallowed. However, patients experiencing severe constipation were permitted to use pre-defined laxatives as rescue medication, while patients with bothersome diarrhoea were allowed loperamide in addition to study medication. Patients taking chronic stable doses of bulking agents could continue to do so. Common concomitant medications in this population, such as tricyclic antidepressants and selective serotonin re-uptake inhibitors, were allowed. The target population was a wide spectrum of patients who represented those likely to be treated with the drug in clinical practice.

Study design

Following a 4-week treatment-free baseline period, patients were randomly assigned to receive either tegaserod, 4 mg/day (given as 2 mg b.d.), tegaserod, 12 mg/day (given as 6 mg b.d.), or placebo tablets, using a double-dummy packaging technique. Patients were instructed to

take the study medication with water, within 30 min prior to the morning and evening meal. During the entire study period, patients recorded their irritable bowel syndrome symptoms in a paper diary on a weekly and daily basis. Diaries were provided in the local languages. Visits were at monthly intervals, at which time the investigator reviewed the entries from the diaries and performed safety assessments. These included physical examinations, pregnancy screening, standard laboratory tests, pulse and blood pressure. In addition, standard 12-lead electrocardiograms were obtained at screening, and on three occasions during the treatment period. Electrocardiograms were analysed centrally, using the Sigmascan technique, by an independent experienced cardiologist blind to the treatment group (Premier Research World-wide, Pennsylvania, USA).

Throughout the study, patients evaluated their response to tegaserod by completing weekly assessments: the Subject's Global Assessment (SGA) of Relief and the SGA of Abdominal Pain and Discomfort. The SGA of Relief variable has been shown to be a reproducible and responsive efficacy measure, highly correlated with clinically meaningful changes in other efficacy measures.²⁴

Patients assessed their SGA of Relief by answering the following question: 'Please consider how you felt this past week in regard to your irritable bowel syndrome, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?' Possible answers were: completely relieved; considerably relieved; somewhat relieved; unchanged; or worse.

The SGA of Abdominal Pain and Discomfort was evaluated by completing a self-administered visual analogue scale (100 mm in length) with severity descriptors (absent, very mild, mild, moderate, severe and very severe), adapted from Talley *et al.*²⁵

At the end of the baseline period, the presence of at least mild abdominal pain and discomfort (no exclusion for severe pain) was required to permit inclusion. Patients were to have completed at least three weekly assessments to be randomized.

In addition, patients were asked to record daily the following information, during both baseline and the double-blind phase: number of bowel movements; stool consistency (1, watery; 2, loose; 3, somewhat loose; 4, neither loose nor hard; 5, somewhat hard; 6, hard;

7, very hard); severity of abdominal pain and discomfort and severity of bloating (0, none; 1, very mild; 2, mild; 3, moderate; 4, severe; 5, very severe).

Patients with missing data for 10 or more days during baseline were excluded from entering the double-blind treatment period.

Statistical methods/data analysis

Efficacy analyses were by intention-to-treat, and included all patients randomized. The primary efficacy variable was defined as the response for SGA of Relief at end-point (last four assessments).

The definition of a responder took into account both the magnitude and persistence of effect. In order to be classified as a responder, patients were to have described, at end-point, at least 50% of their SGA of Relief assessments as either 'considerably relieved' or 'completely relieved' (magnitude of effect) or 100% at least 'somewhat relieved' (persistence of effect). Furthermore, the primary efficacy variable was defined as 'adjusted response', i.e. patients were classified as non-responders if one of the following criteria was fulfilled: (i) laxatives had been taken as concomitant medication on more than 5 days during the double-blind treatment phase; (ii) laxatives had been taken during the last 28 days of the treatment phase; (iii) the duration of study treatment was less than 28 days; (iv) no post-baseline SGA of Relief was available.

Patients were classified as responders for the secondary efficacy variable, the SGA of Abdominal Pain and Discomfort, if they reported at least a 20-mm and a 40% reduction in mean visual analogue scale score at end-point, compared with the baseline score.

A total of 693 randomized patients (231 patients per treatment group) were required to detect a 15% difference in the proportion of responders at end-point with a statistical power of 80%, using a two-sided chi-squared test and assuming a 30% placebo response. An overall significance level of $P < 0.05$ was ensured, taking into account adjustment for multiple comparisons. The Cochran-Mantel-Haenszel test, stratified by centre, was used to compare each of the two doses of tegaserod with placebo. Hochberg's procedure for multiple comparisons was used to ensure that the overall two-sided type 1 error was < 0.05 for the SGA of Relief at end-point. Centres were pooled if the minimum requirements for analysis were not fulfilled.

Daily and weekly efficacy parameters were summarized at end-point. Comparisons of binary data were performed using the Mantel–Haenszel test, while non-binary data were analysed by means of an extended Mantel–Haenszel test. All tests were stratified for centres. Analogous calculations were performed summarizing the percentage change from baseline to end-point in days with significant abdominal pain and discomfort, daily bloating score, number of bowel movements and mean stool consistency. In addition, weekly summaries, normalized to 7-day intervals, were calculated, and daily and weekly efficacy parameters were summarized at months 1, 2 and 3. Abdominal pain and discomfort or bloating were considered to be significant if at least mild.

The safety analyses were performed for all randomized patients who received at least one dose of study medication and underwent at least one post-randomization safety assessment.

RESULTS

Study demographics

A total of 1122 patients were enrolled in 92 centres in Europe, South Africa and the USA. Of these, 881 patients were assigned treatment with either tegaserod, 2 mg b.d., tegaserod, 6 mg b.d., or placebo. An overview of the trial is illustrated in Figure 1.

The baseline demographics of the patients were comparable amongst all treatment groups (Table 1).

The population was predominantly Caucasian (98%) and female (83%). Baseline irritable bowel syndrome symptoms were also similar across all treatment groups. Patients presented on average a moderate severity of abdominal pain and discomfort, and a high proportion of days with significant discomfort/pain and bloating.

Constipation was also confirmed by the number of days without bowel movements, and the percentage of days with hard or very hard stools. Patients entering the study typically had a long duration of irritable bowel syndrome symptoms (approximately 10 years). This symptom profile indicates that the patients studied were very representative of irritable bowel syndrome patients seen in clinical practice.

Although patients with a history of significant diarrhoea in the 3 months preceding baseline were excluded from entering the study, subsequent analysis showed that approximately 14% of the randomized patients presented with diarrhoea symptoms (more than three daily bowel movements for at least 25% of the days, and/or watery/loose stools in at least 25% of the days) during the baseline period. This finding is in keeping with observations that many irritable bowel syndrome patients experience alternating periods of diarrhoea and constipation.

All randomized patients in the study fulfilled the Rome I criteria for irritable bowel syndrome.²³ The majority of these patients (88.1%) also fulfilled the more stringent Rome II requirement of at least two abdominal discom-

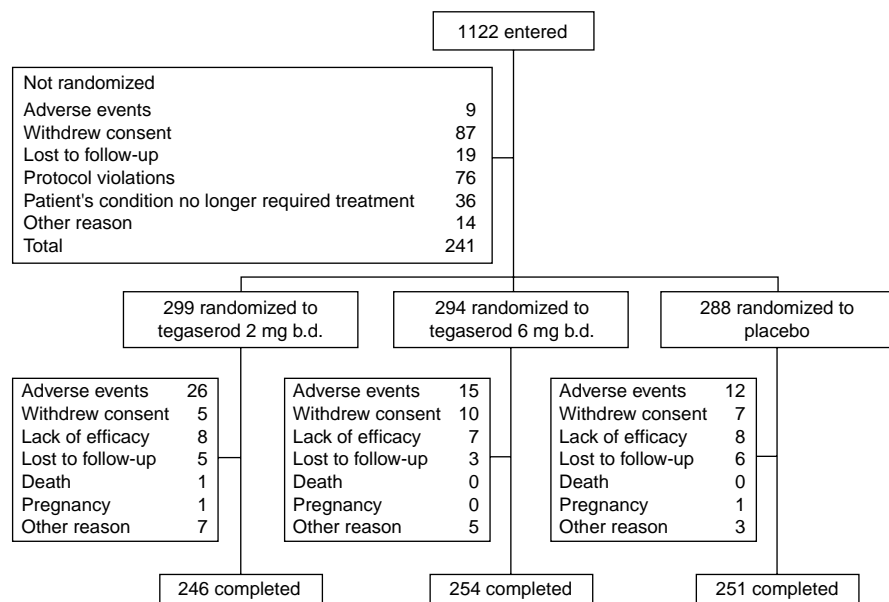


Figure 1. Trial overview.

Table 1. Baseline characteristics of participants

	Tegaserod		
	2 mg b.d. <i>n</i> = 299	6 mg b.d. <i>n</i> = 294	Placebo <i>n</i> = 288
Mean (s.d.) age (years)	45.7 (14.4)	45.6 (13.6)	46.1 (13.6)
Gender			
Male	52 (17.4%)	50 (17.0%)	48 (16.7%)
Female	247 (82.6%)	244 (83.0%)	240 (83.3%)
Median duration of IBS symptoms (years)	10.0	10.0	8.2
Patients (%) fulfilling the Rome II criteria for IBS	89.3%	88.8%	87.5%
Patients (%) who used bulking agents during the baseline period	35 (11.7%)	35 (11.9%)	30 (10.4%)
Mean (s.d.) abdominal pain and discomfort score (mm)	60.5 (13.2)	59.8 (12.5)	60.3 (13.8)
Mean (s.d.) percentage of days with at least mild abdominal pain and discomfort	85.0 (22.0)	82.9 (22.4)	84.3 (23.2)
Mean (s.d.) percentage of days with at least mild bloating	83.2 (25.4)	83.2 (24.3)	82.9 (25.3)
Mean (s.d.) percentage of days without bowel movements	43.9 (26.1)	43.6 (25.4)	43.9 (26.6)
Mean (s.d.) number of bowel movements per 28 days	21.1 (15.3)	21.9 (15.1)	22.3 (16.4)
Mean (s.d.) percentage of days with hard or very hard stools*	28.9 (29.3)	29.4 (29.3)	26.0 (27.1)
Number of patients (%) with diarrhoea† during baseline period	36 (12.0%)	42 (14.3%)	46 (16.0%)

*Denominator is number of days with stool.

†More than three bowel movements for at least 25% of the days, and/or watery/loose stools in at least 25% of the days. IBS, irritable bowel syndrome.

fort/pain symptoms, with a similar distribution across the treatment groups. This is shown in Table 1.

SGA of Relief

Patients treated with tegaserod experienced greater relief of their overall irritable bowel syndrome symptoms than patients treated with placebo. Responder rates for the SGA of Relief at end-point were 46.5%, 46.3% and 34.5% for the 2 mg b.d., 6 mg b.d. and placebo groups, respectively. The difference between each tegaserod group and placebo was statistically significant [12.7% for 2 mg b.d. ($P = 0.002$, 95% CI 4.8–20.7) and 11.8% for 6 mg b.d. ($P = 0.004$, 95% CI 3.8–19.8), taking into account the centre effect]. When the patients' laxative intake, minimum duration of treatment and availability of SGA of Relief evaluations were taken into account (primary efficacy variable), the responder rates observed in patients treated with tegaserod were 38.8% and 38.4% for 2 mg b.d. and 6 mg b.d., respectively, and 30.2% for patients who received placebo. This difference between each of the tegaserod groups and placebo was also statistically significant (95% CI for 2 mg b.d. vs. placebo: 1.6–16.5; 6 mg b.d. vs. placebo: 0.5–16.0).

This effect was observed as early as the first week of treatment, as illustrated in Figure 2(A). The percentage

of patients with an SGA of Relief at least 'somewhat relieved' remained constant during the baseline period, with a marked increase in responders occurring as soon as treatment began.

Both tegaserod groups maintained a consistently higher response rate than the placebo group throughout the 3 months of treatment (Table 2).

In females, the responder rates for the SGA of Relief at end-point were 37.7%, 38.9% and 27.5% for the 2 mg b.d., 6 mg b.d. and placebo groups, respectively. The difference between each tegaserod group and placebo was statistically significant [10.2% ($P = 0.017$) for 2 mg b.d. and 11.4% ($P = 0.008$) for 6 mg b.d., taking into account the centre effect]. The efficacy results in males were more variable across treatments and over time and do not allow a meaningful comparison to be made due to the relatively small numbers of male patients enrolled.

Abdominal pain and discomfort

The SGA of Abdominal Pain and Discomfort, assessed weekly, was significantly improved in patients treated with tegaserod, 6 mg b.d. Responder rates at end-point were 29.8% ($P = 0.055$), 29.9% ($P = 0.044$) and 22.6% for the 2 mg b.d., 6 mg b.d. and placebo groups, respectively. This effect on abdominal pain and discom-

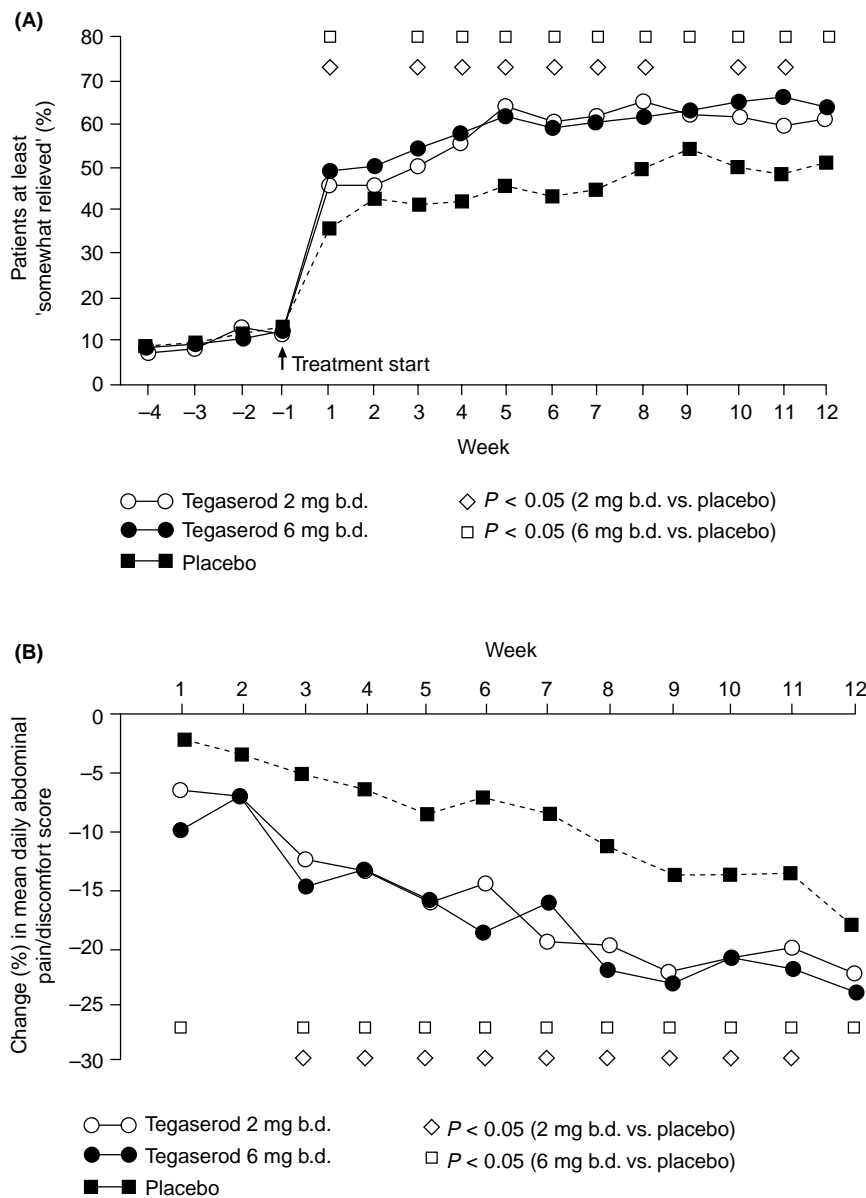


Figure 2. (A) Weekly percentage of patients with an SGA of Relief at least 'somewhat relieved'. (B) Change from baseline in the severity of daily abdominal pain and discomfort.

fort was sustained throughout the 3 months of treatment (Table 2).

The severity of abdominal pain and discomfort, assessed daily, was also significantly reduced in patients treated with tegaserod. This effect was observed early after the initiation of treatment, and was sustained throughout the 12 weeks of treatment, as shown in Figure 2(B).

In addition, patients treated with tegaserod had significantly fewer days with significant abdominal pain and discomfort at month 1 and month 2, with a strong favourable trend at month 3 (Table 2).

Effect on bloating

A favourable trend in the reduction in the number of days with significant abdominal bloating was observed in patients treated with tegaserod compared with those who received placebo (Table 2).

Effect on bowel movements

Patients receiving placebo reported little change in the number of bowel movements throughout the study. However, patients treated with tegaserod experienced a

Table 2. Monthly results for efficacy variables

	Treatment group	Monthly response (%)		
		Month 1	Month 2	Month 3
Responder rate for SGA of Relief (%)	2 mg b.d.	26.1	44.4*	46.4*
	6 mg b.d.	34.2*	41.5*	50.0*
	Placebo	21.0	31.6	36.6
Responder rate for SGA of Abdominal Pain and Discomfort (%)	2 mg b.d.	11.5	24.4	34.3
	6 mg b.d.	17.3	29.1*	36.7*
	Placebo	11.4	21.4	28.3
Reduction in percentage of days with significant abdominal pain and discomfort	2 mg b.d.	6.8*	16.4*	21.7
	6 mg b.d.	6.8*	13.8*	20.8
	Placebo	2.3	4.9	11.8
Reduction in percentage of days with significant bloating	2 mg b.d.	-3.2*	7.8	14.8
	6 mg b.d.	-1.3	11.1	11.3
	Placebo	-7.5	-7.7	-2.1

* $P < 0.05$ compared with placebo.

A negative reduction represents an increase in bloating.

SGA, subject's global assessment.

significant increase in the number of bowel movements as early as the first week of treatment. The effect stabilized after 2 weeks and persisted throughout the 12 weeks of treatment (Figure 3A).

This effect on bowel movements was accompanied by a significant decrease in stool consistency, as shown in Figure 3(B).

Safety

The most common reason for discontinuation during the treatment phase was adverse events (8.7%, 5.1% and 4.5% of patients from the tegaserod, 2 mg b.d., tegaserod, 6 mg b.d., and placebo groups, respectively). The most common adverse events during the course of the study are listed in Table 3.

Diarrhoea was the only adverse event which clearly appears to have increased in frequency with tegaserod (7.1%, 9.6% and 2.5% of patients from the tegaserod 2 mg b.d., tegaserod 6 mg b.d., and placebo groups, respectively). The median duration of the first diarrhoea episode was 2 days in the 2 mg b.d. group, 4 days in the 6 mg b.d. group and 2 days in the placebo group. However, after the initial onset, the number of recurrent episodes was small. The drop-out rates due to diarrhoea were only 2.0% and 2.4% in the 2 mg b.d. and 6 mg b.d. groups respectively, while there were no placebo patients who discontinued due to diarrhoea. No serious drug-related adverse events were reported during the study. Body weight, blood pressure, pulse

rate, haematology, biochemistry and electrocardiogram analyses showed no clinically relevant differences between treatment groups.

Thirteen patients out of 876 (1.5%) reported a total of 14 serious adverse events. No cases of ischaemic colitis were reported. None of these events were suspected by the investigators to be related to the study drug.

DISCUSSION

This study was designed to evaluate the effects of the novel selective 5-HT₄ receptor partial agonist, tegaserod, on the multiple symptoms of irritable bowel syndrome. Patients with irritable bowel syndrome typically complain of abdominal pain and discomfort, bloating and altered stool frequency and consistency (constipation, diarrhoea or both). In this study, patients were characterized by a symptom profile of abdominal pain/discomfort, bloating and constipation. Both doses of tegaserod used in the study (2 mg b.d. and 6 mg b.d.) were effective against these symptoms and were well tolerated. However, the higher dose of tegaserod, 6 mg b.d., offered more consistent efficacy over time and across the major symptoms examined. The clinical benefits of tegaserod in relieving abdominal pain/discomfort and constipation were noted during the first week of treatment, demonstrating a rapid onset of action. These effects were sustained over the entire 12-week treatment period.

Improvement in the symptoms of irritable bowel syndrome has traditionally been difficult to quantify

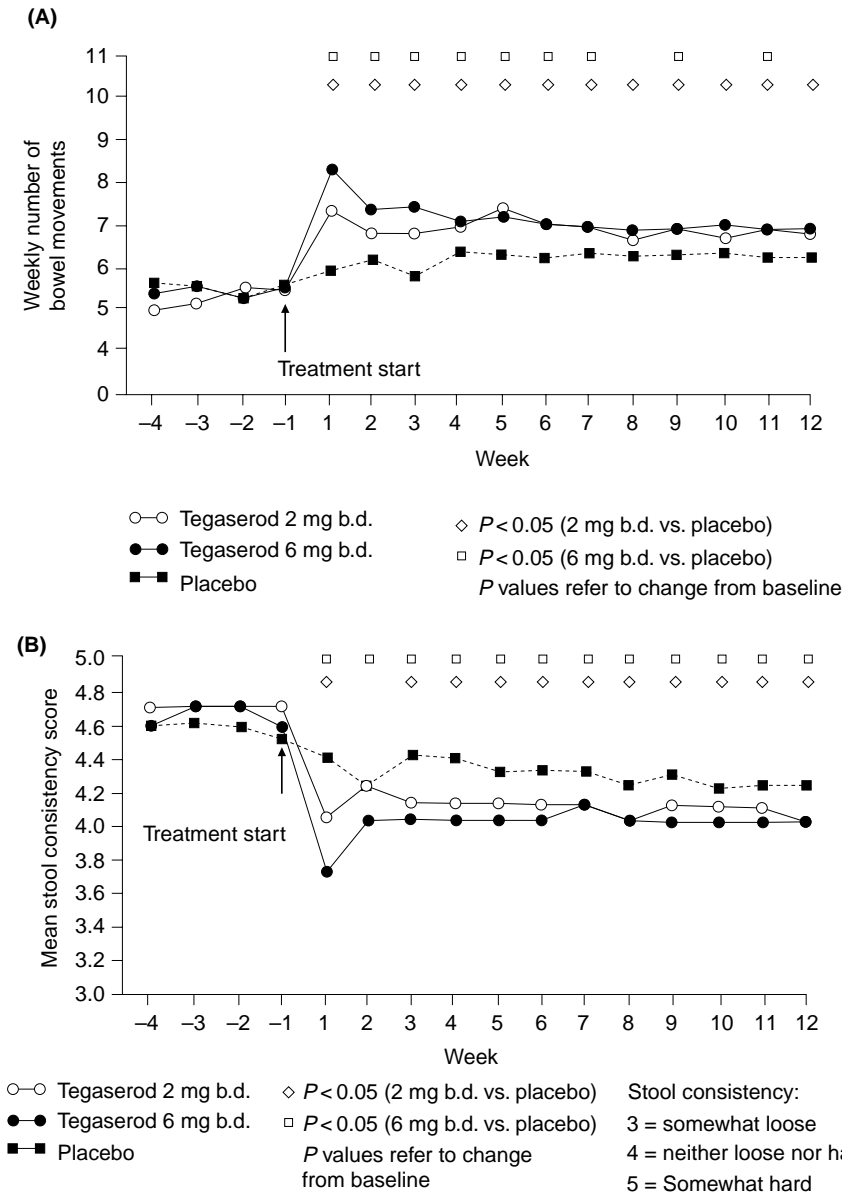


Figure 3. (A) Effect of tegaserod on the weekly number of bowel movements. (B) Effect of tegaserod on the weekly stool consistency score.

in clinical trials, because of the lack of biological markers in patients,^{1, 7} and the complex nature of the condition. Indeed, there has been much concern in recent years over the lack of an agreed universal endpoint by which to classify responders in clinical trials. Assessing treatment effects by single variables, such as pain scores, is useful but may not provide an accurate reflection of the overall symptom improvement because individual symptoms can vary from patient to patient and from time to time.²⁶ However, it has been reported that global assessments of efficacy allow the multiple symptoms of irritable bowel syndrome to be captured in a single measure.²⁷

The global relief measure used in the pivotal tegaserod clinical trials (the SGA of Relief) takes into account the three central factors in irritable bowel syndrome: abdominal pain and discomfort, altered bowel function and overall well-being. Furthermore, the SGA of Relief has shown a high correlation with clinically relevant improvements in the daily diary measures of abdominal pain and bowel function.²⁴ This finding is further substantiated by the results of this study.

Another problem commonly associated with irritable bowel syndrome clinical trials is the high placebo response rate. The placebo effect in our study varied

Table 3. Number (%) of patients with most common adverse events

	Tegaserod 2 mg b.d.	Tegaserod 6 mg b.d.	Placebo
Headache	91 (30.6%)	80 (27.3%)	78 (27.3%)
Abdominal pain	49 (16.5%)	49 (16.7%)	49 (17.1%)
Influenza-like symptoms	25 (8.4%)	33 (11.3%)	28 (9.8%)
Diarrhoea*	21 (7.1%)	28 (9.6%)	7 (2.5%)
Nausea	22 (7.4%)	21 (7.2%)	25 (8.7%)
Back pain	21 (7.1%)	21 (7.2%)	21 (7.3%)
Upper respiratory tract infection	21 (7.1%)	13 (4.4%)	21 (7.3%)
Dizziness	17 (5.7%)	13 (4.4%)	11 (3.9%)

*Diarrhoea includes all degrees of increased bowel movements and looseness reported as an adverse event.

between 25 and 40%, depending on the duration of treatment and the variable examined. This is consistent with placebo rates reported in previous clinical trials of functional gastrointestinal disorders,^{28, 29} and is thought to be due, at least in part, to the types of patients recruited in clinical trials and also the underlying variability of the severity of the disorder.²⁵ The superiority of tegaserod, 6 mg b.d., over placebo (drug-placebo treatment difference) was 13.4% on the SGA of Relief after 12 weeks of treatment. In clinical practice, therefore, an absolute response rate of approximately 50% can be anticipated with tegaserod, 6 mg b.d. This effect is clinically meaningful, especially in view of the fact that no other treatment is available to simultaneously manage the multiple symptoms of abdominal pain and constipation associated with irritable bowel syndrome.

In the updated Rome criteria for functional gastrointestinal disorders (Rome II criteria), irritable bowel syndrome is defined as a group of symptoms in which abdominal discomfort or pain is associated with altered bowel function.¹ It is pointed out that irritable bowel syndrome is a heterogeneous disorder and there is probably no pathophysiology common to all patients fulfilling the definition of irritable bowel syndrome. Hence, it is reasonable to tailor treatments towards the primary symptom pattern (e.g. abdominal pain, bloating and constipation) by using specific drugs with different pharmacodynamics to effectively treat the symptoms expressed.

Because of its known ability to increase intestinal motility,^{18–20} tegaserod was selected for clinical development in irritable bowel syndrome patients who experience abdominal pain, bloating and constipation. A previous study with tegaserod demonstrated a

significant reduction in oro-caecal transit times in irritable bowel syndrome patients with constipation.²² The effects of tegaserod on gastrointestinal motility were confirmed by the results of this study: patients treated with tegaserod showed an increase in stool frequency as early as the first week of treatment. This was accompanied by a significant improvement in stool consistency, the effects of which were also evident during the first week of treatment.

The pathogenesis of abdominal pain and discomfort in irritable bowel syndrome is understood to a lesser degree than the abnormal motility component. It has been previously reported that abnormal motility, intestinal distension and visceral hypersensitivity are among the most important underlying mechanisms.^{2, 30–32} Because most irritable bowel syndrome patients who suffer from constipation frequently complain about abdominal pain and bloating related to their bowel function,⁸ a beneficial effect of a prokinetic agent on these symptoms, via increased peristalsis, might be anticipated. Interestingly, the mixed 5-HT₄ receptor agonist/5-HT₃ receptor antagonist, cisapride, has proven gastro-prokinetic activity.³³ It also improved constipation³⁴ and appeared to improve irritable bowel syndrome symptoms in one study.³⁵ However, the clinical efficacy of cisapride in irritable bowel syndrome patients could not be confirmed in a subsequent trial.³⁶

In contrast, tegaserod is a selective 5-HT₄ receptor partial agonist devoid of 5-HT₃ receptor antagonist properties,^{17, 20} and therefore offers an innovative pharmacological profile. In animal models investigating the effect of tegaserod on visceral sensitivity, tegaserod triggered propagating motor activity in the gastrointestinal tract,¹³ reduced the firing rate in spinal rectal

afferent nerves in the cat,¹⁴ and increased the pain threshold to colorectal distension in rats,¹⁵ thus suggesting a modulating role of the 5-HT₄ receptor in nociception. It is tempting to speculate that these pharmacodynamic effects contributed to the therapeutic activity observed in the present study of irritable bowel syndrome. A visceral pain perception effect may correlate with the significant reduction in patients' abdominal pain or discomfort compared with placebo.

Although not classed as one of the central diagnostic symptoms of irritable bowel syndrome, bloating (also known as a feeling of abdominal distension or fullness)³⁷ is one of the key supportive symptoms.¹ In a recent study evaluating the occurrence of various gastrointestinal symptoms in irritable bowel syndrome patients, Schmulson and colleagues identified bloating-type symptoms in 88.6% of irritable bowel syndrome patients with constipation.⁸ In the present study, tegaserod showed a favourable trend in reducing the number of days with significant abdominal bloating compared with placebo.

Tegaserod showed a highly favourable safety profile in this study. The overall incidence of adverse events in the two tegaserod treatment groups was similar to placebo. The only adverse event reported more frequently with tegaserod was diarrhoea (as defined/considered by patients). The diarrhoea typically occurred early during treatment, and quickly resolved without intervention or interruption of therapy. The early onset of diarrhoea in some patients is consistent with the rapid pharmacodynamic action of the drug. Tegaserod also showed a favourable cardiac safety profile, with no clinically relevant effects on electrocardiogram parameters, QTc interval or cardiac repolarization. Concern over the cardiac safety profile of gastro-prokinetic agents arose from the association of cisapride with rare disturbances in electrocardiogram parameters (such as prolonged QTc intervals), which may lead to potentially fatal dysrhythmias.^{38, 39}

CONCLUSION

Based upon the results of this study, tegaserod offers rapid and sustained relief of the abdominal pain and constipation associated with irritable bowel syndrome. Tegaserod is also well tolerated.

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