

## *A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation*

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### SUMMARY

**Background:** Irritable bowel syndrome is a common functional gastrointestinal disorder which affects up to 20% of the population, with a predominance in females. **Aim:** To evaluate the efficacy and safety of tegaserod in female patients with irritable bowel syndrome characterized by symptoms of abdominal pain/discomfort and constipation.

**Methods:** In a randomized, double-blind, multicentre study, 1519 women received either tegaserod, 6 mg b.d. ( $n = 767$ ), or placebo ( $n = 752$ ) for 12 weeks, preceded by a 4-week baseline period without treatment and followed by a 4-week open withdrawal period. The primary efficacy evaluation was the patient's sympto-

matic response as measured by the Subject's Global Assessment of Relief. Other efficacy variables included abdominal pain/discomfort, bowel habits and bloating. **Results:** Tegaserod produced significant ( $P < 0.05$ ) improvements in the Subject's Global Assessment of Relief and other efficacy variables. These improvements were seen within the first week, and were maintained throughout the treatment period. After withdrawal of treatment, the symptoms rapidly returned. Overall, tegaserod was well tolerated. Diarrhoea was the most frequent adverse event; however, this led to discontinuation in only 1.6% of tegaserod-treated patients. **Conclusions:** Tegaserod, 6 mg b.d., produced rapid and sustained improvement of symptoms in female irritable bowel syndrome patients and was well tolerated.

### INTRODUCTION

Irritable bowel syndrome is a common functional gastrointestinal disorder that is estimated to affect up to 20% of the population. The disease affects three times as many women as men.<sup>1, 2</sup> It is characterized by chronically recurring key symptoms including abdominal pain and discomfort, bloating and altered bowel habits, such as constipation, diarrhoea or alternation between these symptoms. The pathophysiology of irritable bowel syn-

drome is believed to involve both altered gastrointestinal motility and visceral sensation in the small bowel and colon, which are modulated by input from the central nervous system, including the higher centres.<sup>3</sup> For diarrhoea-predominant irritable bowel syndrome, the 5-hydroxytryptamine-3 (5HT<sub>3</sub>) antagonists have been reported to be effective, whereas irritable bowel syndrome patients suffering primarily from pain may be treated with smooth muscle relaxants.<sup>4–6</sup> Currently, there is no therapy available that has proven efficacy in the treatment of the whole spectrum of symptoms in patients with irritable bowel syndrome and symptoms of abdominal pain/discomfort, bloating and constipation.

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Tegaserod, a potent and selective agonist at 5HT<sub>4</sub> receptors in the gastrointestinal tract, has been developed to relieve symptoms of abdominal pain/discomfort, bloating and constipation in patients with irritable bowel syndrome. In animal models, tegaserod has been shown to stimulate peristalsis in intestinal tissues at very low concentrations.<sup>7, 8</sup> In addition, data from animal models suggest that the mechanism by which tegaserod relieves abdominal pain and discomfort in irritable bowel syndrome patients may involve inhibition of the firing of afferent neurones involved in the transmission of pain signals from the gastrointestinal tract to the central nervous system.<sup>9</sup> In a rat model, tegaserod inhibited the response to colorectal distension.<sup>10</sup> In healthy male subjects, tegaserod accelerated gastric emptying and gastrointestinal transit.<sup>11</sup> The oro-caecal transit time was accelerated in constipation-predominant irritable bowel syndrome patients.<sup>12</sup>

The methodology in past irritable bowel syndrome treatment trials has been subject to several criticisms.<sup>13–15</sup> In this study, the primary measure of efficacy, called the Subject's Global Assessment (SGA) of Relief, integrates the symptoms of the disease and assesses overall or 'global' relief by taking abdominal pain/discomfort, altered bowel function and overall well-being into consideration (Müller-Lissner *et al.* 2002, unpublished observations). In a previous 12-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III clinical trial, tegaserod twice daily was shown to improve the symptoms of abdominal pain/discomfort, bloating and constipation in patients with irritable bowel syndrome and to improve the SGA of Relief.<sup>16</sup>

This current, large-scale, 12-week, multicentre, phase III study was conducted to confirm the efficacy and safety of tegaserod in female patients with irritable bowel syndrome and symptoms of abdominal pain/discomfort and constipation.

## MATERIALS AND METHODS

In this prospective, randomized, double-blind, placebo-controlled trial, female patients with symptoms of irritable bowel syndrome received either tegaserod, 6 mg b.d., or placebo for 12 weeks, preceded by a 4-week baseline period and followed by a 4-week withdrawal period. The study was conducted at 131 centres in the USA (71% primary care, 27% secondary care and 2% tertiary care).

## Patients

Patients were eligible if aged 18 years or older and diagnosed with irritable bowel syndrome of at least 3 months' duration (according to the Rome I criteria<sup>17</sup>), characterized by lower abdominal pain/discomfort and symptoms of constipation (at least two of the following: less than three bowel movements per week, hard or lumpy stools and/or straining during a bowel movement) at least 25% of the time which had not improved after at least 2 months of treatment with non-pharmacological therapies (high-fibre diet, exercise or bulking agents). Organic disease was ruled out by a colonoscopic examination or by sigmoidoscopy with double-contrast barium enema in patients over 50 years of age, performed after the appearance of symptoms and within the previous 5 years.

Patients were excluded if they had significant diarrhoea (loose or watery stools and/or more than three bowel movements daily associated with urgency for > 25% of days in the preceding 3 months), if they had structural abnormalities of the gastrointestinal tract or diseases/conditions that affected bowel transit, or if there was evidence of a cathartic colon or a history of laxative, drug or alcohol abuse. Pregnant or lactating women were also excluded and women of child-bearing potential practised a medically approved method of contraception. Concomitant use of any medication that could affect gastrointestinal motility and/or perception was disallowed. However, eligible patients on stable treatment with fibre or bulking agents were enrolled if their treatment was maintained and if they had been on bulking agent therapy for at least 3 months. Patients were required to have at least mild pain (> 1.5 on a seven-point scale) and at least normal stool consistency (> 3.5 on a seven-point scale; see *Evaluation, Efficacy*) during the baseline period.

All patients gave their written informed consent to participate in this study, which was performed in accordance with the principles of the Declaration of Helsinki concerning medical research in humans and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice.

## Study design

After the 4-week baseline period, patients were randomized (ratio 1 : 1) to receive double-blind treatment with either tegaserod, 6 mg b.d., or identical placebo

tablets for 12 weeks. Patient randomization was performed using blocking by centre to ensure equal treatment allocation within each centre.

Patients were instructed to take the medication with one glass of water within 30 min prior to the morning and evening meals. At the end of the double-blind treatment period, patients entered a 4-week withdrawal period during which they received no study medication. Visits were scheduled at monthly intervals for safety assessments. Patients provided weekly assessments of their overall well-being and daily and weekly symptoms of abdominal pain/discomfort, bloating and altered bowel function via the touch-tone telephone system (QTone™, Quintiles)<sup>18</sup> during the baseline, double-blind treatment and withdrawal periods.

### Evaluation

**Efficacy.** The primary efficacy assessment was the SGA of Relief that was recorded weekly by response to the following question using the touch-tone telephone system: 'Please consider how you felt this last 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.

Patients who were 'completely relieved' or 'considerably relieved' for at least 50% of the weeks at the end-point or 'somewhat relieved' for 100% of the weeks at the end-point were considered to be responders, as in previous studies.<sup>16</sup> The last 4 weeks of the double-blind period were used as the end-point. For the primary efficacy variable, patients who had no post-baseline SGAs, less than 28 days of exposure or took prohibited medication (non-bulking laxatives for at least 5 days during double-blind treatment or for more than 1 day during the last 4 weeks) were considered as non-responders. 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.<sup>19</sup> The SGA of Relief was also analysed on a monthly basis; patients were classified as responders within a month if they were considerably or completely relieved for at least 2 of the 4 weeks, or if they were at least somewhat relieved for each of the 4 weeks.

As secondary efficacy variables, symptoms were assessed weekly and daily via the touch-tone telephone system. On a weekly basis, patients were asked to assess: how 'bothersome' their abdominal pain/discomfort had been in the previous week (SGA of Abdominal Pain/Discomfort); how 'bothersome' their constipation had been in the previous week (SGA of Bowel Habit); and their level of 'satisfaction' with their bowel habit (SGA of Satisfaction with Bowel Habit). For the SGA of Satisfaction with Bowel Habit, patients were considered to be responders if they were 'very satisfied' or 'somewhat satisfied' at 50% of assessments. In addition, patients were asked to assess their symptoms of irritable bowel syndrome daily in terms of: intensity of bloating (on a seven-point ordinal scale; 0 = none and 6 = very severe); stool frequency (number of bowel movements per 28 days); stool consistency (on a seven-point scale, where 1 = watery, 2 = loose, 3 = somewhat loose, 4 = neither loose nor hard, 5 = somewhat hard, 6 = hard and 7 = very hard); and whether they had experienced straining during a bowel movement (yes or no).

**Safety and tolerability.** All spontaneously reported adverse events, as well as those elicited by the physician on questioning or detected by physical examination, were recorded and, as far as possible, their duration, severity and relationship to study treatment were established. Serious adverse events, defined as an event which was fatal or life-threatening, required prolonged hospitalization, caused permanent disability or incapacity, or required medical or surgical intervention to prevent death or serious/prolonged illness or disability, were recorded. Safety parameters assessed at scheduled visits included physical examinations, pregnancy screening, standard laboratory tests, sitting blood pressure and pulse rate and electrocardiogram evaluations.

**Statistical analysis.** The planned sample size calculated for this study was a total of 1528 patients (764 per treatment group), assuming a 33% placebo response for the SGA of Relief, using a two-sided chi-squared test to detect an 8% treatment difference with 90% power at the two-sided level of significance of  $\alpha = 0.05$ .

The efficacy evaluation was conducted on the intention-to-treat population of all patients randomized into the study. The primary efficacy variable was the response for the SGA of Relief, which was analysed by covariable-adjusted Mantel-Haenszel analysis<sup>20</sup> with baseline laxative use as a covariable, stratified by centre.

The end-point for SGA analyses was based on the last four available weekly SGA scores, but if fewer than four weekly scores were available, then all available weekly SGA scores in the treatment period were used. Monthly responder rates for the SGA of Relief were compared between treatments by the Mantel–Haenszel test with covariate adjustment of baseline laxative use performed at each month at the two-sided significance level of 0.05%. To estimate the relative benefit of tegaserod over control, the monthly ‘number needed to treat (NNT)’ values were calculated as shown below,<sup>21, 22</sup> including the 95% confidence intervals (CIs).<sup>23</sup>

The risk of an irritable bowel syndrome patient was to be a non-responder: risk in the treatment group  $RT = 100\% - \text{responder rate tegaserod (TEG)}$ ; risk in the control group  $RC = 100\% - \text{responder rate placebo (PLA)}$

$$\text{NNT} = 100(\text{RC} - \text{RT})$$

The supplemental analysis of the SGA of Relief included the weekly proportions of patients who were at least ‘somewhat relieved’ during the treatment period. These variables were analysed by covariable-adjusted Mantel–Haenszel statistics with baseline laxative use as the covariable at the two-sided significance level of 0.05. The end-point for daily diary scores was based on the daily scores obtained in the last 28 days of treatment, but if fewer than 28 days were available, then all daily scores obtained in the treatment period diary were used. Secondary efficacy variables were also analysed by two-sided Mantel–Haenszel statistics with a significance level of 0.05.

The safety population included all randomized patients who received at least one dose of study medication. Adverse events and changes in laboratory values, blood pressure, pulse rate and physical examination were analysed descriptively. For study discontinuations caused by any adverse event and by diarrhoea, the numbers needed to harm (NNH), i.e. the numbers needed to treat to experience such events, were calculated as given above for the NNT.<sup>21</sup>

## RESULTS

### *Patient characteristics at baseline*

A total of 3177 female patients were screened and 1519 randomized (tegaserod, 6 mg b.d.,  $n = 767$ ; placebo,  $n = 752$ ) in 131 centres. The types of centre were

distributed as follows: 71% primary care, 27% secondary care and 2% tertiary care. Most discontinuations during baseline were due to failure to comply with study entry criteria or failure to complete the touch-tone telephone diary system (712 patients) and withdrawal of consent (564 patients) (Figure 1).

The demographic characteristics and baseline data were comparable for both treatments, with the exception of laxative use (15% tegaserod vs. 11% placebo group;  $P < 0.05$ ). The severity of the patients’ irritable bowel syndrome symptoms was comparable between the tegaserod and placebo groups. Patients had moderately severe abdominal pain/discomfort and bloating and recorded approximately two-thirds of days with straining during a bowel movement and four bowel movements per week during the baseline period (Table 1).

More than 93% of randomized patients fulfilled the Rome II criteria for irritable bowel syndrome at baseline.<sup>24</sup> Overall, 20.6% of patients in the tegaserod group and 21.4% in the placebo group discontinued from the study prematurely (Figure 1) and 1401 continued into the withdrawal period.

### *Efficacy*

*Primary efficacy evaluation: SGA of Relief.* Treatment with tegaserod, 6 mg b.d., produced a statistically significantly greater response rate for the SGA of Relief than placebo at the end-point (43.5% vs. 38.8% of patients, respectively;  $P < 0.033$  vs. placebo) when laxative use was taken into account by declaring laxative users as non-responders. Without adjustment for laxatives, higher responder rates were observed (48.3% vs. 41.7% of patients, respectively;  $P < 0.009$  vs. placebo).

The monthly response rates for tegaserod and placebo, respectively, were as follows: month 1, 40.5% vs. 26.2%,  $P < 0.001$ ; month 2, 47.2% vs. 39.6%,  $P = 0.006$ ; month 3, 53.0% vs. 47.1%,  $P = 0.026$ . The NNT values (95% CIs) were: month 1, 7.0 (5.3–10.4); month 2, 13.3 (7.8–45.7); month 3, 17.1 (8.8–387.2).

Figure 2 illustrates the weekly percentages of patients who were at least ‘somewhat relieved’ of their irritable bowel syndrome symptoms (completely, considerably or somewhat relieved).

After the initiation of the study medication, a high placebo response was observed. At week 1, 59% of

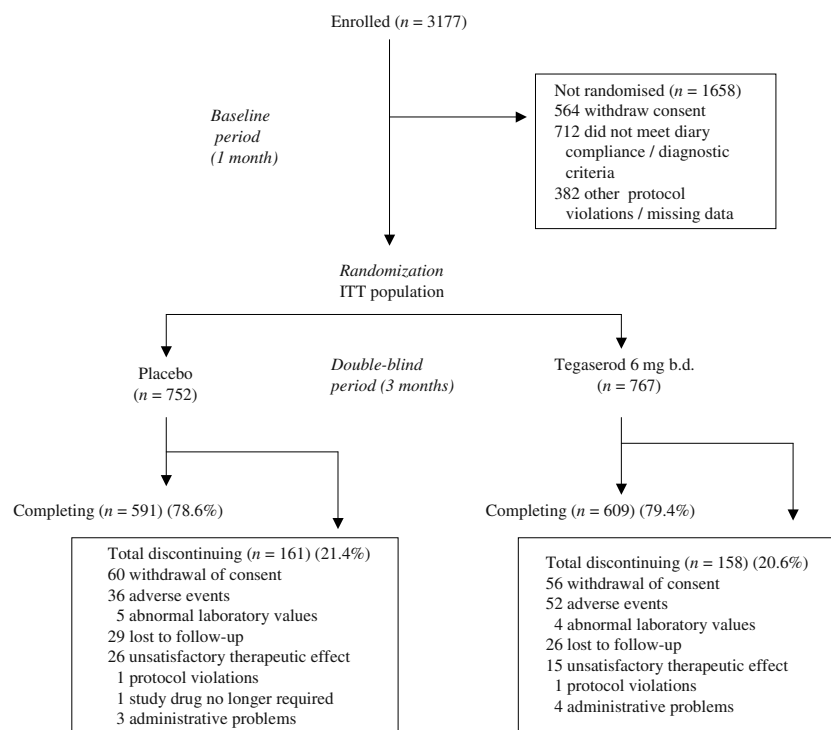


Figure 1. Patient flow during the study. ITT, intention to treat.

patients in the tegaserod group and 40% of patients in the placebo group were at least somewhat relieved. After 4 weeks, this difference was still 13%. Over the 12-week treatment period, the response to tegaserod increased slightly from 59% to 67%, whereas the placebo response increased substantially from 40% to 61%. Nevertheless, the proportion of patients who were at least 'somewhat relieved' remained statistically significantly greater with tegaserod than with placebo throughout the double-blind treatment period, with the exception of week 8 (Figure 2).

*Secondary efficacy variables: weekly assessments.* For the SGAs of Abdominal Pain/Discomfort, Bowel Habit and Satisfaction with Bowel Habit, tegaserod was associated with statistically significantly higher improvements from baseline vs. placebo. The following mean score differences (end-point minus baseline) after tegaserod and placebo treatment, respectively, were observed for the SGA of Abdominal Pain/Discomfort:  $-1.01$  and  $-0.80$  ( $P < 0.003$ ). For the SGA of Bowel Habit, the corresponding mean score differences were  $-1.30$  and  $-0.95$  ( $P < 0.001$ ).

The weekly effects of tegaserod vs. placebo on the SGAs of Abdominal Pain/Discomfort (Figure 3a) and

Bowel Habit (data not shown) indicated that the effects of tegaserod were statistically significantly greater than placebo at nearly all weeks during double-blind treatment ( $P < 0.05$ ).

The response rates for the SGA of Satisfaction with Bowel Habit for tegaserod and placebo, respectively, were as follows: month 1, 56.0% vs. 41.1%,  $P < 0.001$ ; month 2, 58.7% vs. 50.1%,  $P = 0.002$ ; month 3, 60.4% vs. 52.7%,  $P = 0.007$ .

*Secondary efficacy variables: daily gastrointestinal symptoms.* At end-point, tegaserod was also associated with statistically significant improvements from baseline vs. placebo in bloating scores ( $-1.59$  vs.  $-1.47$ ,  $P < 0.05$ ), number of bowel movements per 28 days ( $+9.8$  vs.  $+6.6$ ,  $P < 0.05$ ), stool consistency score ( $-0.91$  vs.  $-0.62$ ,  $P < 0.0001$ ) and number of days with straining ( $-4.3$  vs.  $-2.9$ ,  $P < 0.001$ ). There was an instantaneous improvement in stool consistency in the tegaserod group during the first week of double-blind treatment, which remained stable to the end of double-blind treatment, and which was statistically significantly greater than with placebo ( $P < 0.05$ ; Figure 3b). Consistently, a statistically significant reduction in days with straining was observed ( $P < 0.01$ ; Figure 4).

Table 1. Patient demographic characteristics and severity of gastrointestinal symptoms at baseline (intention-to-treat population)

	Placebo ( <i>n</i> = 752)	Tegaserod 6 mg b.d. ( <i>n</i> = 767)
<b>Demographic variables</b>		
Age (years), mean (s.d.)	41.0 (11.7)	41.5 (10.8)
By group		
< 65, <i>n</i> (%)	725 (96.4)	744 (97.0)
≥ 65, <i>n</i> (%)	27 (3.6)	23 (3.0)
Race		
Caucasian, <i>n</i> (%)	586 (77.9)	589 (76.8)
Black, <i>n</i> (%)	121 (16.1)	127 (16.6)
Oriental, <i>n</i> (%)	2 (0.3)	3 (0.4)
Other, <i>n</i> (%)	43 (5.7)	48 (6.3)
Smoker: Yes, <i>n</i> (%)	148 (19.7)	127 (16.6)
Weight (kg), mean (s.d.)	70.0 (13.9)	70.7 (15.4)
Duration of IBS symptoms (years), mean (s.d.)	16.3 (12.9)	16.0 (12.2)
<b>Mean (s.d.) baseline weekly assessments</b>		
Number of responders for SGA of Relief, <i>n</i> (%) <sup>*</sup>	0/752 (0)†	0/767 (0)†
SGA of Abdominal Pain/Discomfort‡	3.7 (1.0)	3.8 (1.0)
SGA of Bowel Habit‡	3.9 (1.1)	3.9 (1.1)
SGA of Satisfaction with Bowel Habit§	3.4 (0.6)	3.4 (0.6)
<b>Mean (s.d.) baseline¶ daily assessments</b>		
Bloating score <sup>**</sup>	4.1 (1.0)	4.2 (1.0)
Number of bowel movements/28 days¶	16.3 (13.0)	15.8 (11.6)
Stool consistency score††	4.9 (0.8)	5.0 (0.8)
Number of days with straining/28 days¶	17.5 (7.4)	17.9 (7.4)

IBS, irritable bowel syndrome; s.d., standard deviation; SGA, Subject's Global Assessment.

\* Completely or considerably relieved at least 50% of the time or at least somewhat relieved 100% of the time.

† Responders during baseline were excluded from the study.

‡ 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, 6 = a very great deal.

§ 1 = very satisfied, 2 = somewhat satisfied, 3 = somewhat dissatisfied, 4 = very dissatisfied.

¶ Baseline values normalized to a 28-day interval.

\*\* 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe.

†† 1 = watery, 2 = loose, 3 = somewhat loose, 4 = neither loose nor hard, 5 = somewhat hard, 6 = hard, 7 = very hard.

### Withdrawal of treatment

When patients entered the withdrawal period, there was a loss of effect, with a decline in responder rates in both groups in the first withdrawal week, which continued over the second and third withdrawal weeks and which then stabilized in the third and fourth withdrawal weeks (Figures 2 and 3). During the first week of the withdrawal period, the loss of effect was more marked in the tegaserod group than in the placebo group. No statistically significant difference was observed between the two groups for any of the efficacy variables during the 4-week withdrawal period. This pattern of effect was noted with most efficacy variables, but patients did not return to their baseline levels within 4 weeks. A similar time course was observed after termination of treatment with alosetron in diarrhoea-predominant irritable bowel syndrome patients.<sup>4</sup>

### Safety and tolerability

All 1519 patients in the intention-to-treat population were included in the safety analysis (tegaserod, *n* = 767; placebo, *n* = 752). Overall, there was a slightly higher reporting frequency of adverse events in the tegaserod group than in the placebo group (58.3% vs. 55.7%, respectively).

The numbers of patients (5% or more) reporting adverse events, whether or not drug related, are summarized in Table 2.

Headache, nausea and diarrhoea were more common in the tegaserod group, and upper respiratory tract infection was more common in the placebo group. Diarrhoea occurred in 6.4% of tegaserod-treated patients and in 2.9% of placebo-treated patients. The episodes of diarrhoea were mild and transient, uncomplicated and none led to hospitalization, significant

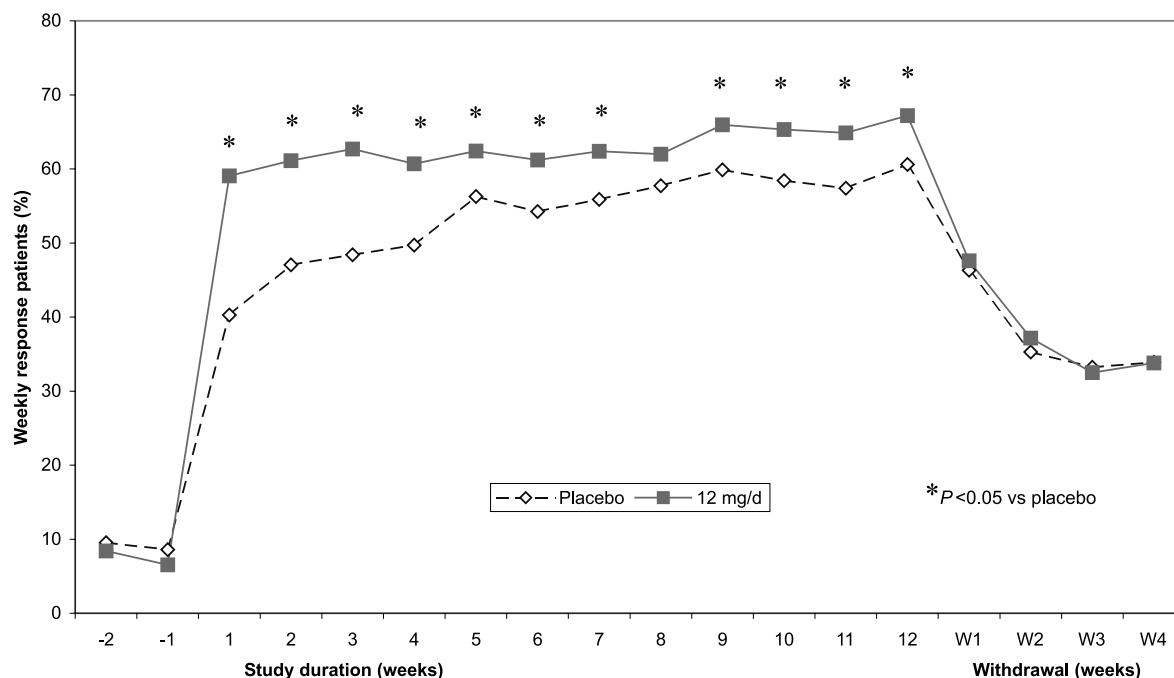


Figure 2. Subject's Global Assessment (SGA) of Relief: weekly percentage of patients who were completely, considerably or somewhat relieved with tegaserod, 6 mg b.d., and placebo (intention-to-treat population). \* $P < 0.05$  vs. placebo.

volume depletion or electrolyte abnormalities. The number of patients who discontinued due to adverse events was higher with tegaserod (52 patients, 6.8%) than with placebo (36 patients, 4.8%). Therefore, the number of patients needed to treat to experience one discontinuation was  $NNH_{disc} = 50$ . In particular, 12 patients (1.6%) in the tegaserod group discontinued due to diarrhoea compared with none in the placebo group ( $NNH_{disc \text{ diarrhoea}} = 62.5$ ).

As rare but medically relevant adverse events, patients underwent abdominal or pelvic surgery as follows: seven (0.9%) on tegaserod (four cholecystectomies, one appendectomy, one hiatal hernia and one hysterectomy) and four (0.5%) on placebo (two hysterectomy, one cholecystectomy and one lysis of adhesions). No causal relationship was suspected between the surgeries and the study medication by the investigators. All cholecystectomies were uncomplicated laparoscopic surgeries in patients with pre-existing symptoms. Only in one hospitalized patient was cholecystectomy assessed as a serious adverse event by the investigator.

An additional four serious adverse events were observed during the study. Three were reported in the tegaserod group: coronary artery disease (day 12), anxiety (day 25) and vertebral disc disorder (day 1). In the placebo group, one serious adverse event was

observed: seizures (days 32 and 35). All serious adverse events led to the discontinuation of study medication. However, none was suspected to be related to the study medication by the investigators. No deaths occurred during the study.

No clinically relevant changes in blood pressure, heart rate, clinical laboratory or electrocardiogram parameters were noted in either treatment group.

During the withdrawal period, 174 patients reported adverse events: 86 of 661 (13%) in the tegaserod group and 88 of 633 (14%) in the placebo group. The only adverse events reported by >1% of the tegaserod-treated patients were sinusitis (eight of 661, 1.2%) and nausea (seven of 661, 1.1%). The only adverse event reported by >1% of the placebo-treated patients was abdominal pain, which occurred in 12 of 633 (1.9%) patients.

## DISCUSSION

Tegaserod significantly improved abdominal pain/discomfort, constipation, bloating and stool consistency, i.e. multiple symptoms, in women suffering from irritable bowel syndrome with constipation. These effects were seen within the first week, persisted throughout the treatment period and the symptoms

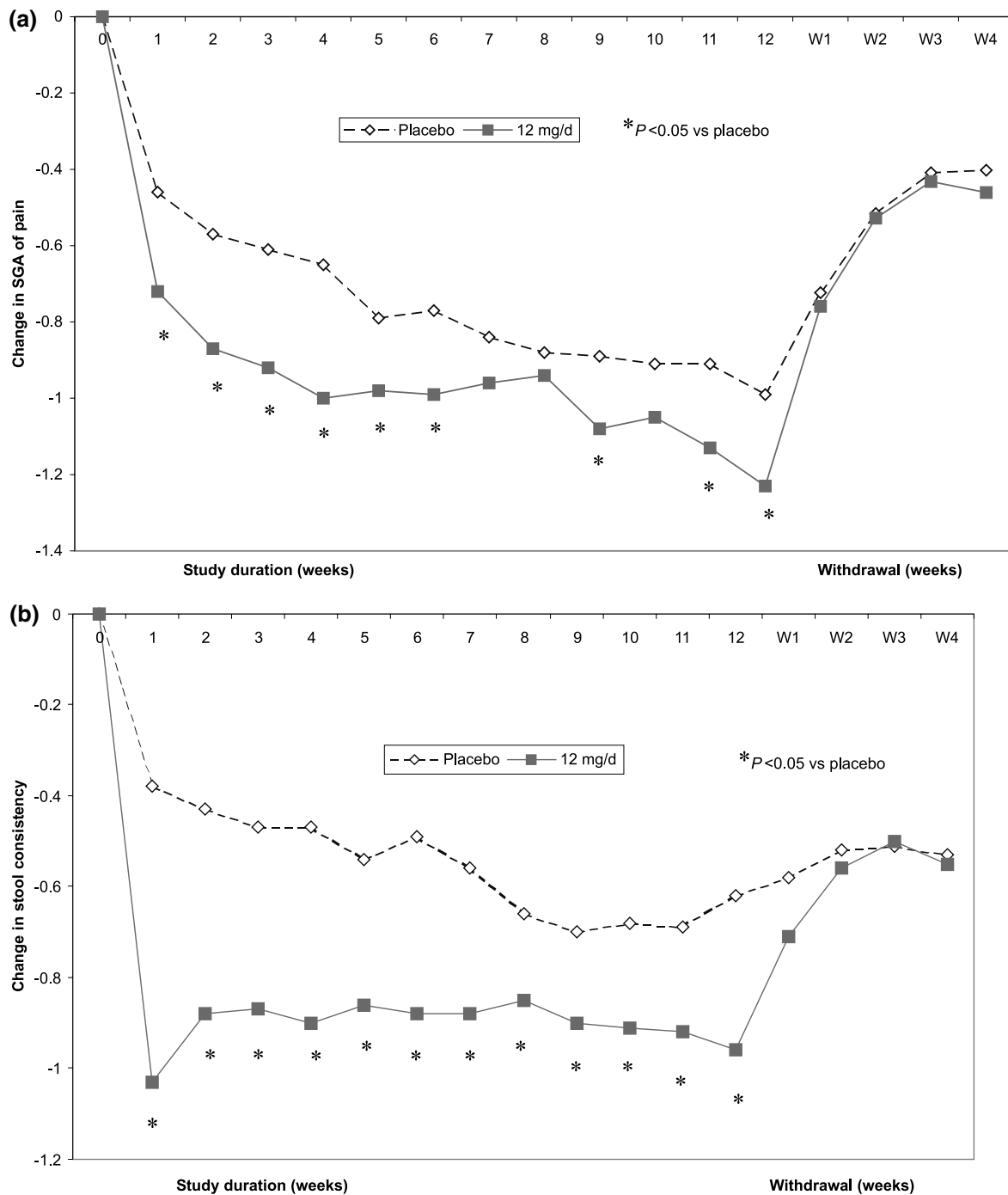


Figure 3. (a) Weekly mean changes from baseline in the Subject's Global Assessment (SGA) of Abdominal Pain/Discomfort with tegaserod, 6 mg b.d., and placebo (intention-to-treat population). \* $P < 0.05$  vs. placebo. (b) Weekly mean changes from baseline in stool consistency score with tegaserod, 6 mg b.d., and placebo (intention-to-treat population). \* $P < 0.05$  vs. placebo.

returned rapidly after cessation of therapy, but did not reach baseline levels within the 4-week washout period.

The study results are consistent with the findings of a previous 12-week, multicentre trial of tegaserod in both

male and female patients with irritable bowel syndrome and symptoms of abdominal discomfort/pain and constipation. However, in that study, a positive treatment effect for tegaserod was only seen in women; the

Table 2. Number (percentage) of patients reporting adverse events (reported in  $\geq 5\%$  of patients)

	Placebo (n = 752)		Tegaserod, 6 mg b.d. (n = 767)	
	n	%	n	%
Total patients with adverse events	419	55.7	447	58.3
Headache	43	5.7	69	9.0
Nausea	35	4.7	52	6.8
Abdominal pain	43	5.7	49	6.4
Diarrhoea	22	2.9	49	6.4
Flatulence	30	4.0	44	5.7
Upper respiratory tract infection	48	6.4	27	3.5

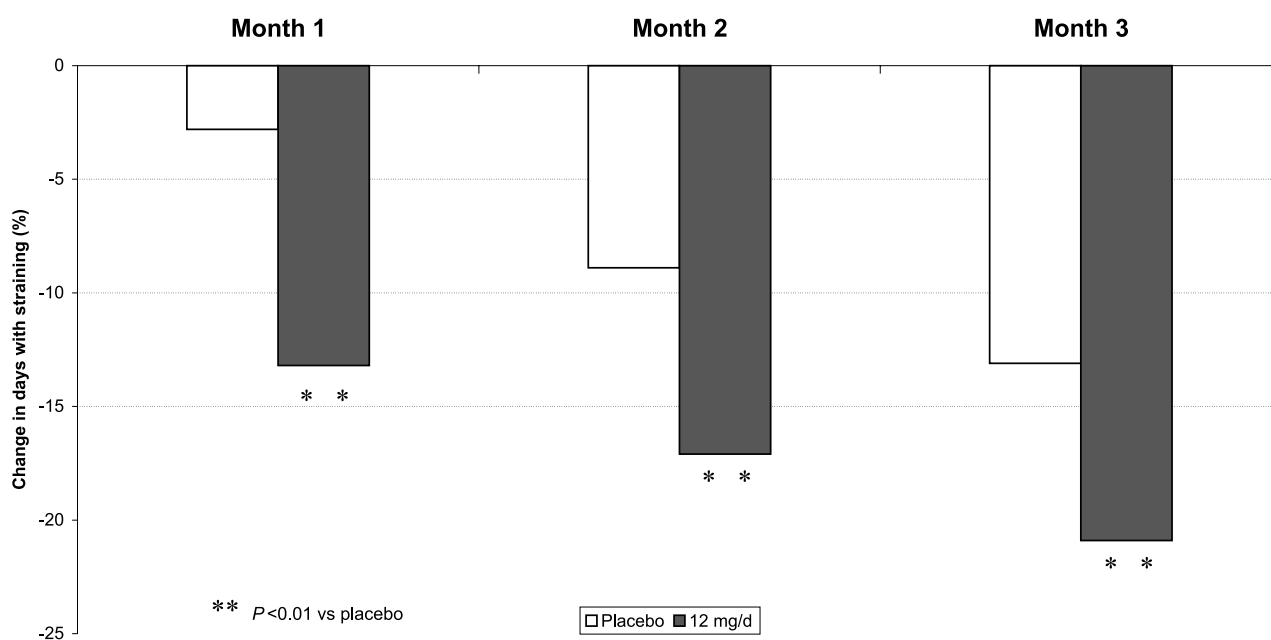


Figure 4. Monthly mean percentage changes from baseline in the number of days with straining with tegaserod, 6 mg b.d., and placebo (intention-to-treat population). \* $P < 0.05$  vs. placebo.

small number of men in the study did not permit any conclusion to be drawn with regard to efficacy in men (17% of the study population).<sup>16</sup> Because of this well-known gender distribution in the population, only women were included in this study. The higher prevalence in females may be explained by different symptoms and perceptual responses<sup>25</sup> and slower colonic transit times.<sup>26</sup>

Studies of the treatment of irritable bowel syndrome and other functional gastrointestinal disorders have at times experienced weakness in trial design, power, study execution and data analysis which have made it difficult to determine whether the treatments were truly effective.<sup>13–15</sup> In addition, the lack of identifiable tissue pathology, biological markers and feasible scientific

tools applicable in a setting similar to clinical practice, as well as the complexity of the disorder, makes it generally difficult to quantify therapeutic efficacy in clinical trials with irritable bowel syndrome.<sup>24, 27, 28</sup>

Another problem commonly associated with irritable bowel syndrome clinical trials is the high placebo response rate. In an analysis of 25 randomized, controlled studies, a median (range) placebo response of 47% (0–84%) was reported, and the optimum duration of treatment trials in irritable bowel syndrome was suggested to be at least 3 months, as placebo effects were expected to take approximately 12 weeks to start to tail-off.<sup>15</sup>

In the present study, as well as in a previous tegaserod clinical investigation, placebo responses showed a

tendency to rise during the study to a peak after 9–12 weeks with no tendency to decline.<sup>16</sup> A comparable time course of the placebo response was also observed in a group of diarrhoea-predominant irritable bowel syndrome patients when compared with a 5HT<sub>3</sub> antagonist.<sup>4</sup> This pattern may reflect the natural history of irritable bowel syndrome, which is a disorder of varying severity that fluctuates over time.<sup>2</sup> In another recent irritable bowel syndrome study with alosetron, the placebo response persisted for 12 months at around 50% and decreased only once therapy was discontinued.<sup>29</sup> As pointed out by Thompson in a review of the placebo response, the time course of the placebo effect in a chronic 'static' disorder, such as hypertension, may be very different from that in a chronic fluctuating disorder, such as irritable bowel syndrome, in which some patients undergo spontaneous improvement of their condition.<sup>30</sup>

Even though pain, as measured weekly by the SGA of Abdominal Pain/Discomfort, showed a sustained effect throughout this study<sup>14</sup> for the primary efficacy variable SGA of Relief, a smaller difference vs. placebo at the study end-point was observed than predicted from the earlier study.<sup>16</sup> Of note, in the current study, the placebo response rate increased to a substantially greater extent over time (40% to 61% from week 1 to week 12) than the response in the tegaserod group (59% to 67%). Thus, the smaller treatment difference vs. placebo at the end of the study appeared to be due to an increasing placebo response. In contrast with the paper-based diary used in previous tegaserod studies, an electronic telephone diary system was used.<sup>18</sup> The impact of the electronic diary system on the placebo response rate, if any, is unknown. However, there was a higher dropout rate (> 50%) during the screening phase which was probably partly due to this system as compared with the previous tegaserod study.<sup>16</sup> A screen failure rate of > 50% has also been reported in another irritable bowel syndrome study using an electronic diary system.<sup>4</sup>

Tegaserod, 6 mg b.d., was safe and well tolerated in this study. Blood pressure, pulse rate and clinical laboratory results were similar in the placebo and tegaserod groups. Tegaserod was associated with a higher frequency of diarrhoea than placebo, which was consistent with the results of previous studies.<sup>16</sup> This was not an unexpected finding, as the 5HT<sub>4</sub> agonist tegaserod accelerated colonic transit in clinical studies.<sup>11, 12</sup> Only 1.6% of patients in the tegaserod group discontinued due to diarrhoea.

After the end of treatment, no rebound phenomena were observed. The frequency of adverse events remained comparable in the tegaserod and placebo groups. Only two tegaserod-treated patients complained of constipation in the first week of the washout period. In addition, no clinically relevant changes in electrocardiogram parameters were associated with tegaserod treatment in this study, confirming the results of a systematic review of electrocardiogram data from irritable bowel syndrome patients included in three randomized, double-blind, placebo-controlled trials of tegaserod.<sup>31</sup> The NNT values were reasonably smaller (7–17) than the NNH values (50–62.5) showing a positive benefit–risk relation.

In conclusion, this trial in a population reflecting general practice has confirmed the findings of previous studies. Tegaserod, 6 mg b.d., was both effective and well tolerated in the rapid relief of overall irritable bowel syndrome symptoms and in the improvement of abdominal discomfort/pain, bloating and constipation in women. After discontinuation of treatment, the difference vs. placebo disappeared within 1–2 weeks. These findings indicate that the efficacy of tegaserod in irritable bowel syndrome patients persists for at least 12 weeks of treatment.

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