

Tegaserod relieves multiple chronic constipation symptoms in men

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BACKGROUND

- Chronic constipation (CC) is a common gastrointestinal (GI) problem affecting 2–28% of individuals in Western countries^{1,4}
- Dietary fiber and bulking agents are common treatments, although they only offer partial relief. Non-bulking laxatives are frequently used, but these can be associated with unpredictable responses and exacerbation of other CC symptoms. Furthermore, laxatives are unlikely to offer better long-term symptom relief of CC than placebo⁵
- Clinical studies have demonstrated that tegaserod accelerates GI transit in patients with irritable bowel syndrome with constipation,⁶ reduces the sensitivity to rectal distension,⁷ accelerates bowel transit in healthy subjects⁸ and this is particularly more pronounced in men⁹
- Two pivotal CC trials have shown tegaserod to be effective and well tolerated.^{10,11} The objectives of the two pivotal studies were to evaluate the efficacy, safety and tolerability of tegaserod 2 mg b.i.d. and 6 mg b.i.d., compared with placebo in female and male patients with CC. A total of 2,603 (n=861 tegaserod 2 mg b.i.d., n=881 tegaserod 6 mg b.i.d., n=861 placebo) patients were randomized in these studies, of whom, 308 (11.8%) were men

OBJECTIVE

- To evaluate the efficacy and safety of tegaserod 6 mg b.i.d. compared with placebo in male patients with CC

METHODS

Study design

- Randomized, double-blind, placebo-controlled, multicenter trial of the efficacy and safety of tegaserod (6 mg b.i.d.)
- Two-week baseline phase without study medication; 12-week randomized treatment phase

Patient recruitment

- Men 18 years or older with a history of constipation for at least 6 months before screening
- Constipation was defined as <3 complete spontaneous bowel movements (CSBM)/week plus one or more of the following symptoms for at least 25% of the time:
 - very hard and/or hard stools (Type 1 and/or 2 on the Bristol Stool Form Scale)¹²
 - sensation of incomplete evacuation
 - straining

Efficacy endpoints

- Assessment of bowel habits (frequency, stool form, straining and feeling of complete evacuation)
 - patients kept a daily electronic diary (eDiary) record of their bowel movements, stool form, use of laxatives or enema, and straining habits
- Primary endpoint:**
 - response rate for CSBM during weeks 1–4, where responders were those patients who achieved a mean increase of ≥ 1 CSBM/week compared with baseline
- Secondary endpoints:**
 - response rates for CSBM and spontaneous bowel movements (SBM) in terms of absolute number and an increase ≥ 1 CSBM or SBM per week during weeks 1–12
 - time to first CSBM and SBM after first intake of study medication
 - stool form was rated on the 7-point Bristol Stool Form Scale: 1 corresponds to hard lumps and 7 to watery stools
 - straining was rated on a 3-point scale: no straining (0), acceptable straining (1), and too much straining (2)
 - patient's assessment of bowel habits, constipation, abdominal distension/bloating and discomfort/pain, and satisfaction of relief of symptoms. Patients used a 5-point scale – a lower score indicated less bothersome symptoms

Safety assessments

- Adverse events (AEs) and serious AEs (SAEs) were recorded
- Standard laboratory evaluations, vital signs and physical examinations were made

Statistical analysis

- The primary efficacy variable was analyzed using a logistic regression model with number of CSBMs at baseline, pooled center and treatment included in the model
- P-values by week were calculated using Cochran-Mantel-Haenszel tests stratified by center

RESULTS

Patient recruitment and baseline demographics

- Male patients with CC (n=322) were randomized to tegaserod (n=158) or placebo (n=164), from which 269 (83.5%) patients completed to study end (Figure 1)

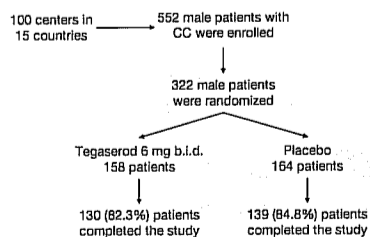


Figure 1. Patient flow chart.

- The mean age of the tegaserod and placebo group was 51.1 years and 51.8 years, respectively. The mean duration of constipation was 10.98 years for tegaserod patients and 10.02 years for placebo patients. Further baseline demographic data are shown in Table 1
- Overall, 30.1% of patients reported straining as their most bothersome symptom in the 6 months preceding the study (27.2% tegaserod, 32.9% placebo), whereas 20.8% of patients (19.0% tegaserod, 22.6% placebo) reported infrequent defecation as their most bothersome symptom
- During the 14-day baseline period, the mean number of CSBM/week was 0.3 and 0.4 for patients randomized to tegaserod and placebo, respectively (Table 2)
- During the 14-day baseline period, the mean number of SBM/week was 2.8 and 2.7 for patients randomized to tegaserod and placebo, respectively (Table 2)

RESULTS (cont'd)

Table 1. Baseline demographic data for all ITT patients.

Demographic variable	Tegaserod 6 mg b.i.d. (n=158)	Placebo (n=164)	Total (n=322)
Age (years)			
Mean (SD)	51.1 (17.17)	51.8 (17.16)	51.5 (17.14)
Age group (n, %)			
<35	33 (20.9)	36 (22.0)	69 (21.4)
≥ 35 and <65	86 (54.4)	81 (49.4)	167 (51.9)
≥ 65	39 (24.7)	47 (28.7)	86 (26.7)
Race (n, %)			
Caucasian	84 (53.2)	79 (48.2)	163 (50.6)
Black	4 (2.5)	1 (0.6)	5 (1.6)
Oriental	63 (39.5)	75 (45.7)	138 (42.9)
Other	7 (4.4)	9 (5.5)	16 (5.0)
Duration of constipation symptoms (months)			
Mean (SD)	131.7 (158.03)	120.2 (149.20)	125.8 (153.47)
Median	66.0	60.0	60.0
Most bothersome symptom in preceding 6 months (n, %)			
Straining	43 (27.2)	54 (32.9)	97 (30.1)
Infrequent defecation	30 (19.0)	37 (22.6)	67 (20.8)
Feeling of incomplete evacuation	35 (22.2)	28 (17.1)	63 (19.6)
Abdominal distension/bloating	29 (18.4)	26 (15.9)	55 (17.1)
Hard stools	20 (12.7)	16 (9.8)	36 (11.2)
Other	1 (0.6)	3 (1.8)	4 (1.2)
Abdominal discomfort/pain	0 (0.0)	0 (0.0)	0 (0.0)

ITT = intent-to-treat; SD = standard deviation

Table 2. Comparison of the mean number of CSBM, SBM and BM during weeks 1–12 and baseline by treatment.

Mean (SD)	Tegaserod 6 mg b.i.d.		Placebo	
	Baseline	Weeks 1–12	Baseline	Weeks 1–12
CSBM/week	0.3 (0.59)	1.6 (1.66)	0.4 (0.68)	1.2 (1.48)
SBM/week	2.8 (2.80)	3.9 (2.71)	2.7 (2.58)	3.5 (2.74)
BM/week	3.9 (3.06)	4.9 (3.06)	3.8 (2.77)	4.3 (2.88)

BM = bowel movements; CSBM = complete spontaneous bowel movements; SBM = spontaneous bowel movements; SD = standard deviation

Change in bowel frequency

- Significantly more tegaserod-treated patients were responders, defined as a mean increase of ≥ 1 CSBM/week in weeks 1–4 (primary efficacy endpoint) compared with placebo-treated patients (40.5% vs 29.3%, respectively; $p < 0.05$)
- The responder rate for weeks 1–12 was also significant (43.0% tegaserod versus 31.1% placebo; $p = 0.0359$) (Figure 2)
- Tegaserod-treated patients experienced a greater weekly increase from baseline in CSBM compared with placebo-treated patients; results were significant for the majority of weeks ($p < 0.05$; Figure 3)
- A superior response rate for the absolute number of CSBM and an increase from baseline in CSBM (≥ 1 CSBM/week and > 3 CSBM/week) was seen with tegaserod, achieving significance in the majority of weeks (Figure 4)

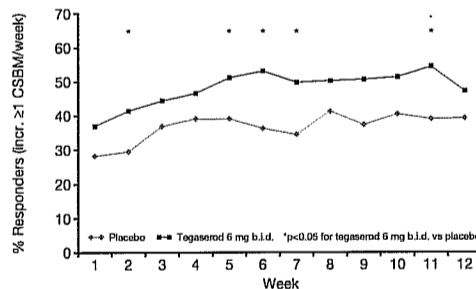


Figure 2. Weekly response rate for CSBM during weeks 1–12 by treatment.

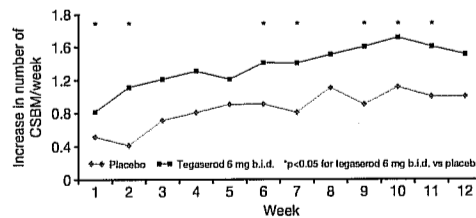


Figure 3. Weekly increase from baseline in the number of CSBMs during weeks 1–12 by treatment.

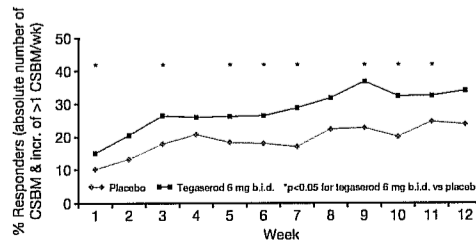


Figure 4. Weekly response rate in absolute number of CSBMs (> 3 CSBM/week) and an increase from baseline of ≥ 1 CSBM/week during weeks 1–12 by treatment.

RESULTS (cont'd)

- Tegaserod-treated patients had a greater mean number of SBM/week during weeks 1–12 compared with placebo-treated patients (Table 2)
- Tegaserod was associated with a greater mean increase from baseline in SBM/week than placebo, but this was only significant at week 9 (data not shown)
- Men using tegaserod demonstrated a greater increase from baseline in the number of bowel movements (BM)/week compared with placebo-treated patients ($p < 0.05$ for 4 of 12 weeks)
- Patients treated with tegaserod experienced their first CSBM and SBM earlier than placebo-treated patients (data not shown)

Effect on stool consistency and straining

- Tegaserod was significantly superior to placebo in softening stool form during SBM for 10 out of 12 weeks ($p < 0.05$; Figure 5)
- Analysis of straining data from SBMs demonstrated that tegaserod was generally associated with greater improvements during weeks 1–12 in:
 - mean weekly straining score, significant ($p < 0.05$) for 5 out of 12 weeks
 - mean number of days/week with 'too much straining' (data not shown)
 - mean number of days/week with straining but no passage of stool (Figure 6)

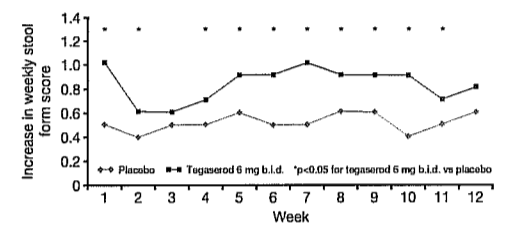


Figure 5. Weekly improvement in stool form of SBMs.

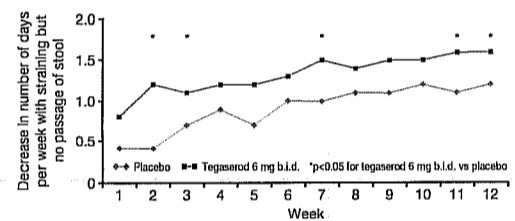


Figure 6. Weekly decrease from baseline in the number of days/week with straining but no passage of stool.

Patient satisfaction

- Tegaserod treatment was associated with a greater improvement from baseline in the global constipation relief score for 8 out of 12 weeks compared with placebo; the difference being significant ($p < 0.05$) for 3 of 12 weeks
- Tegaserod significantly reduced the bothersomeness of constipation compared with placebo ($p < 0.05$) during 3 out of 12 weeks
- Tegaserod treatment was associated with a greater improvement from baseline in abdominal discomfort/pain for 8 out of 12 weeks, and in abdominal distension/bloating for 7 out of 12 weeks compared with placebo (not statistically significant)
- Tegaserod treatment was associated with greater overall satisfaction with bowel habits than placebo (10 of 12 weeks), although the differences between the groups only reached significance at week 6
- Patients treated with tegaserod reported a greater overall satisfaction with their CC symptoms than placebo-treated patients at all study weeks ($p < 0.05$ at weeks 2 and 12)
- More placebo-treated patients (42.1%) used laxatives than tegaserod-treated patients (35.4%), although similar proportions in both groups used enemas

Safety

- Tegaserod was well tolerated
- Similar proportions of patients in both groups experienced AEs (tegaserod 37.3%; placebo 32.3%), with the most common being diarrhea (4.3%), abdominal pain (4.0%) and headache (2.8%)
- Discontinuations due to AEs were infrequent in both treatment groups (tegaserod 4.4%; placebo 1.2%)
- One patient (0.6%) receiving tegaserod discontinued due to diarrhea, two patients (1.3%) receiving tegaserod discontinued due to abdominal pain, and no patients discontinued due to headache
- GI-related AEs were reported by 17.1% of tegaserod patients and by 8.5% of placebo patients. Mild-to-moderate diarrhea was reported (tegaserod 8.2%, placebo 0.3%), which was mostly transient and usually resolved with continued therapy
- Seven SAEs were reported (tegaserod 3.2%; placebo 1.2%): adenocarcinoma of the lung (death), coronary heart disease (two patients), chest pain, left ventricular end diastolic dysfunction, chronic stable angina, subacute thyroiditis
- There were no cases of clinically significant diarrhea and no reports of colitis of any type. One case of melena was reported in the tegaserod group

CONCLUSIONS

This was the first clinical trial to evaluate the efficacy and safety of tegaserod specifically in men with CC. Significantly more tegaserod patients had an increase of ≥ 1 CSBM/week in weeks 1–4 and weeks 1–12. Tegaserod provides rapid relief of the multiple symptoms (stool form, straining, bowel movements) associated with CC. Tegaserod was well tolerated in men with CC.

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