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Effect of tegaserod on work and daily activity in irritable bowel syndrome with constipation

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SUMMARY

Background: Tegaserod is a promotility agent with proven efficacy and safety in patients with irritable bowel syndrome with constipation.
Aim: To assess tegaserod's effect on work productivity and daily activity.
Methods: Women, 18–65 years old and meeting Rome II criteria for irritable bowel syndrome with constipation, were randomized to a double-blind, placebo-controlled, multicentre study of tegaserod 6 mg b.d. or placebo. Productivity loss and daily activity impairment because of irritable bowel syndrome were measured with the Work Productivity and Activity Impairment questionnaire for irritable bowel syndrome, modified to exclude diarrhoea as a symptom. Assessments were made at baseline, weeks 2 and 4.
Results: A total of 2660 women were randomized and, of these, 1675 [tegaserod ($n = 1363$), placebo ($n = 312$)] were employed and completed Work Productivity and Activity Impairment for irritable bowel syndrome questionnaires. Compared with placebo, tegaserod significantly reduced work and daily activity impairment at weeks 2 and 4. Tegaserod reduced absenteeism by 2.6% ($P = 0.004$), presenteeism by 5.4% ($P < 0.0001$), overall work productivity loss by 6.3% ($P < 0.0001$), and activity impairment by 5.8% ($P < 0.0001$) at week 4 (vs. baseline). Assuming a 40-h workweek, tegaserod reduced work productivity loss by 2.5 h/week.
Conclusions: Tegaserod significantly reduced work productivity loss and daily activity impairment at 2 weeks, and this benefit was maintained at 4 weeks.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic and episodic gastrointestinal (GI) dysmotility and sensory disorder characterized by abdominal pain or discomfort associated with altered bowel habit, i.e. constipation, diarrhoea, or alternating constipation and diarrhoea.[1] Most estimates from population-based studies indicate that IBS occurs in 10–15% of the population.[2–4] IBS affects more women than men, at an approximate ratio of 2:1, and patients are generally between the ages of 30 and 50 years when they first consult a doctor.[2–4] Estimates indicate that 75% of IBS patients are between 25 and 64 years of age.[5] Thus, the majority of patients with IBS are of working age.

IBS imposes a substantial economic burden on society,[5–7] in addition to the cost borne by patients. IBS has been shown to be associated with significant direct costs (use of health care resources) and indirect costs (work productivity).[5] The direct annual cost of IBS in the USA is estimated to be between $1.7 and $10 billion (1999$), excluding the cost of prescription and over-the-counter (OTC) drugs.[5, 7] The indirect costs associated with absenteeism (missed days of

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work) and presenteeism (impairment while at work) attributable to IBS are estimated to be as high as $20 billion (2000$).[5]

From an employer perspective, direct and indirect costs are 50% higher for an employee with IBS than for an employee without IBS.[8] Disability and absenteeism costs for employees with IBS account for 37% of total overall costs to the employer (health care and lost productivity costs).[8] In 1992, IBS was the second leading cause of health-related workplace absenteeism,[9] and by the year 2000, absenteeism because of IBS was equivalent to that caused by the common cold.[10]

In addition to absenteeism, IBS symptoms are responsible for significant presenteeism, which actually results in greater costs for employers than does absenteeism.[11–13] Patients with IBS tend to miss work sporadically rather than for long-term disability.[8] One study of both absenteeism and presenteeism in employees of a large company showed a reduced work productivity rate of 19.8% among employees with IBS, which is equivalent to working only 4 days of a 5-day workweek.[11, 13] Furthermore, many individuals with IBS have made job decisions that they would not otherwise have made, such as cutting back on days of work, working fewer hours, turning down promotions or advancements, and working from home.[5, 12, 14–16]

Also IBS has a significant negative impact on patient quality of life (QoL).[5–7] IBS symptoms restrict or otherwise negatively affect many aspects of patients' lives, including diet, travel, sleep, intimacy and leisure activities.[5, 12, 14–16] The QoL of IBS patients has been demonstrated to be substantially diminished compared not only with the general population, but also with patients who have other chronic and episodic conditions such as gastro-oesophageal reflux disease (GERD), asthma or migraine.[17, 18]

Tegaserod is a promotility agent acting at the serotonin type 4 (5-HT_4) receptor, with proven efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C),[19–21] and more recently chronic idiopathic constipation.[22] Treatment with tegaserod has been associated with significant improvement in symptom relief and QoL relative to placebo,[23, 24] but its effect on work-related productivity and daily activity is unknown until now. The objective of this analysis was to evaluate the effect of tegaserod on work productivity and daily activity impairment in patients with IBS with constipation.

METHODS AND MATERIALS

Subject enrolment and study design

This was a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicentre study that compared tegaserod 6 mg b.d. and placebo in females with IBS-C. The study was conducted in 257 centres in 24 countries, including the USA, Canada, New Zealand, five South American countries, 14 European countries and two African countries. The study comprised a 2-week baseline period (no medication weeks −2 to 0), and two 4-week placebo-controlled treatment periods, which were separated by a treatment-free interval of 2–12 weeks. During first treatment, patients were randomly assigned to either tegaserod 6 mg b.d. or placebo in the ratio 4:1. Patients who responded to treatment then entered the treatment-free interval (2–12 weeks). If symptoms recurred within 12 weeks, patients were re-randomized. During repeated treatment, patients who received tegaserod during first treatment were re-randomized to either tegaserod 6 mg b.d. or placebo in the ratio 1:1; and those who received placebo during first treatment were assigned (mock randomized) to tegaserod.

Women 18–65 years of age who met the Rome II diagnostic criteria for IBS-C[25] were eligible to participate in the study. The Rome II criteria for IBS-C stipulate that patients in the 12 months preceding study entry have at least 12 weeks (not necessarily consecutive) of abdominal discomfort or pain with two of three of the following features.

1. Relieved with defecation and/or
2. Onset associated with a change in frequency of stools and/or
3. Onset associated with a change in form (appearance) of stool.

Patients were excluded if they had significant diarrhoea at least 25% of the time during the 3 months preceding study entry.

Using hand-held electronic data entry devices, patients completed the Work Productivity and Activity Impairment questionnaire for IBS[26] at baseline, weeks 2 and 4 of both treatment cycles. The results of the work productivity and daily activity impairment analysis for the first treatment period are reported here. Because of a programming error in the hand-held devices, data were not evaluable for repeated treatment and therefore the

analysis of treatment differences could not be performed.

Questionnaires

As IBS patients with diarrhoea-predominant symptoms were excluded from this trial, the validated WPAI:IBS was modified (by eliminating the word 'diarrhoea' from the description of IBS symptoms in the introduction) to make it appropriate for a patient population with constipation (WPAI:IBS-C). The WPAI:IBS-C was self-administered and consisted of six questions that elicited employment status, and for the prior 7 days: hours missed because of IBS; hours missed due to other reasons; hours actually worked; degree IBS affected presenteeism using a scale from 0 (no effect) to 10 (completely prevented me from working) and degree IBS affected regular daily activities, from 0 (no effect) to 10 (completely prevented me from doing daily activities). Scores for absenteeism, presenteeism, overall work productivity loss and impairment in regular (non-work) daily activities, such as work around the house, shopping, childcare, exercising, studying, etc. were derived as follows:

$$\text{Absenteeism} = \text{hours missed}/\text{hours missed} + \text{hours worked}$$

$$\text{Presenteeism} = \text{scale score}/10$$

$$\text{Work productivity loss} = \text{absenteeism} + (\text{hours worked} \times \text{presenteeism})$$

$$\text{Daily activity impairment} = \text{scale score}/10$$

Scores were transformed into percentages, with higher percentages indicating greater work impairment and daily activity impairment.

Bilingual translators created the questionnaires for 14 languages through a harmonization process of forward- and back-translations.[27]

Statistical methods

As the number of patients randomized at some centres was relatively small, pooled centres were created based on size and geographic location so that there were at least 20 patients randomized into each centre at baseline. In total, 24 centres were created from the original 267 centres. To test for regional differences, the 24 centres were further combined into four regions as follows.

1 USA.
2 Europe: Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, UK, Hungary, Italy, the Netherlands, Norway, Sweden.
3 South America: Argentina, Chile, Colombia, Ecuador, Peru.
4 Other: Canada, Egypt, New Zealand, South Africa.

Results for the 'other' category are not included in the analysis of regional differences because of the small sample size ($n = 95$) and the geographically dispersed population.

An ANCOVA was performed for the change from baseline to weeks 2 and 4 for each WPAI:IBS-C measure. In the case of a missing week 4 assessment, data from the last observation (week 2 assessment) were carried forward (LOCF). Treatment and pooled centre as factors, and age and baseline score as covariates were included in the analysis. All employed patients with a baseline and at least one postbaseline completed questionnaire were included in these analyses.

RESULTS

Characteristics of the population

A total of 2660 patients were randomized to first treatment, and of these, 1675 (63%) were currently employed, completed a baseline and at a least one follow-up WPAI:IBS-C, and are included in the analysis. The participation rate among the 2135 patients randomized to tegaserod was 61.8%, while 59.4% of the 525 patients randomized to placebo participated. As shown in Table 1, the majority of the patients were Caucasian

Table 1. Demographic characteristics of the population at baseline

Characteristic	Tegaserod 6 mg b.d. ($N = 1363$)	Placebo ($N = 312$)	Total ($N = 1675$)
Age [years; mean (s.d.)]	40.8 (10.7)	40.7 (10.6)	40.8 (10.7)
Race, *n* (%)			
Caucasian	1162 (85.3)	269 (86.2)	1431 (85.4)
Black	45 (3.3)	10 (3.2)	55 (3.3)
Asian	12 (0.9)	3 (1.0)	15 (0.9)
Other	144 (10.6)	30 (9.6)	174 (10.4)

(85.4%), with a mean age of 40.8 years. The two treatment groups were comparable for all measures.

Work productivity and activity impairment outcomes

At baseline, 39.4% of patients reported missing time from work because of IBS in the previous week; 94.6% reported reduced productivity while working and 86.9% reported impairment in daily activities. WPAI:IBS-C results indicated that patients had approximately 5% absenteeism, 40% presenteeism, 42% overall work productivity loss and 48% daily activity impairment during the prior 7 days because of IBS.

The overall impact of tegaserod on the employed population is represented in Table 2. Patients in the tegaserod group reported a significant decrease in all impairment measures, relative to placebo ($P = 0.01$–0.0004) at week 2 (Table 2). These results were maintained at week 4: treatment with tegaserod was associated with a 2.6% decrease in absenteeism ($P = 0.004$); a 5.4% reduction in presenteeism ($P < 0.0001$); a 6.3% reduction in overall work productivity loss ($P < 0.0001$) and a 5.8% reduction in daily activity impairment ($P < 0.0001$; Table 3).

The data were also analysed by region (USA, Europe and South America) and are displayed in Tables 2 and 3. The USA patients in the tegaserod group reported a significant decrease in all impairment measures, relative to placebo, at both weeks 2 and 4 ($P = 0.01$–0.05). European patients in the tegaserod group reported non-significant decreases in all work impairment measures and a significant decrease in daily activity impairment ($P = 0.04$), relative to placebo, at week 2, and significant decreases in all measures at week 4 ($P = 0.003$–0.04). South American patients in the tegaserod group reported a significant decrease in absenteeism ($P = 0.004$) at week 2, relative to placebo: the decreases in the other impairment measures were not significant relative to placebo, at week 2 or week 4.

The results of the significance testing were identical for week 4 when the last observation was not carried forward and only those with week 4 data were included in the analysis (not displayed).

DISCUSSION

IBS is a significant cause of morbidity, dramatically affecting patients' QoL, and in turn imposing a substantial economic burden on society, as well as, individuals with the disorder. In this study, 39.4% of the patients enrolled reported missing time from work because of IBS symptoms (absenteeism) in the week prior to randomization. Importantly, nearly all of the patients reported that IBS affected their productivity while working (presenteeism) as well as their ability to perform regular daily activities, such as housework, schoolwork, shopping, childcare, etc. Compared with the general population of IBS patients seeking care from gastroenterologists reported previously,[26] the IBS-C population in this clinical trial study was more likely to report absenteeism (39.4% vs. 27.1%), but the percentage of patients with presenteeism (94.6% vs. 86.5%) and daily activity impairment (86.9% vs. 93.3%) were similarly high in both populations. Together, the data from both studies indicate that among those patients seeking health care for IBS, almost all will experience work and daily activity impairment.

Previous studies have understated the productivity loss of IBS patients by failing to take partial-day absences and presenteeism into account.[26] In the working population participating in this study, tegaserod significantly reduced work and daily activity impairment after 2 weeks, an improvement that was maintained through the 4-week tegaserod treatment period when compared with placebo. Assuming a 40-h workweek, tegaserod treatment reduced work productivity loss (absenteeism + presenteeism) by 2.0 h/week at week 2 and 2.5 h/week at week 4. Applying a potential inflation rate for work productivity loss in IBS patients because of errors in 1-week recall, i.e. a possible 33.7% inflation observed by Reilly *et al.*[26] a conservative estimate of the difference in work productivity loss between placebo and tegaserod treatment groups is 1.7–2.5 h/week at week 4.

The positive effect of tegaserod on work productivity and daily activity impairment was also observed when analysing the data by region (USA, Europe and South America). Although not all differences between tegaserod treatment and placebo reached statistical significance at the two time points for the regions, the data consistently showed a larger reduction in impairment for each of the four impairment measures in each region following tegaserod treatment. For the USA, all differences between treatment groups were significant at both time assessments. Within the European region, which included 721 patients in 14 countries, the differences were significant for all measures at week 4

Table 2. Work productivity and activity impairment IBS-specific with constipation outcomes (WPAI:IBS-C) at baseline and week 2

Region	*N**	Baseline, mean (s.d.)	Week 2 follow-up, mean (s.d.)	Treatment effect	*P*-value†
All regions‡					
Absenteeism					
Teg 6 mg b.d.	1143	5.4 (15.4)	3.4 (11.5)	−2.1	0.01
Placebo	232	5.3 (12.7)	5.3 (16.2)		
Presenteeism					
Teg 6 mg b.d.	1256	40.4 (25.4)	28.8 (24.5)	−4.1	0.004
Placebo	272	38.7 (25.0)	31.8 (26.0)		
Work productivity loss					
Teg 6 mg b.d.	1139	42.7 (26.0)	31.1 (25.4)	−5.1	0.002
Placebo	232	42.7 (25.4)	35.7 (28.0)		
Daily activity impairment					
Teg 6 mg b.d.	1292	48.3 (25.3)	34.1 (25.3)	−5.1	0.0004
Placebo	282	45.7 (25.9)	37.7 (25.8)		
USA					
Absenteeism					
Teg 6 mg b.d.	464	3.6 (11.6)	2.5 (9.9)	−2.4	0.05
Placebo	92	5.9 (15.6)	5.3 (17.2)		
Presenteeism					
Teg 6 mg b.d.	507	38.8 (23.9)	29.3 (23.8)	−6.9	0.003
Placebo	109	40.5 (26.5)	36.3 (26.1)		
Work productivity loss					
Teg 6 mg b.d.	463	40.5 (24.2)	30.8 (24.8)	−7.3	0.004
Placebo	92	44.6 (27.1)	39.5 (28.1)		
Daily activity impairment					
Teg 6 mg b.d.	519	47.8 (24.9)	34.7 (25.3)	−6.07	0.007
Placebo	117	49.2 (25.1)	40.7 (26.7)		
Europe§					
Absenteeism					
Teg 6 mg b.d.	468	5.1 (16.1)	3.4 (12.7)	−0.6	0.58
Placebo	104	4.0 (9.5)	3.3 (9.4)		
Presenteeism					
Teg 6 mg b.d.	526	38.1 (25.4)	26.7 (24.3)	−2.2	0.28
Placebo	125	35.0 (21.9)	27.1 (23.8)		
Work productivity loss					
Teg 6 mg b.d.	466	40.4 (25.8)	29.4 (25.1)	−2.6	0.25
Placebo	104	39.2 (21.8)	30.9 (25.1)		
Daily activity impairment					
Teg 6 mg b.d.	544	45.7 (24.3)	31.9 (24.4)	−4.3	0.04
Placebo	127	41.3 (25.4)	34.1 (23.3)		
South America¶					
Absenteeism					
Teg 6 mg b.d.	126	11.8 (21.1)	4.9 (9.0)	−9.6	0.004
Placebo	24	7.4 (12.3)	14.5 (30.8)		
Presenteeism					
Teg 6 mg b.d.	133	51.0 (26.9)	31.2 (23.9)	−5.8	0.27
Placebo	24	46.7 (32.1)	35.4 (33.4)		
Work productivity loss					
Teg 6 mg b.d.	125	55.1 (27.3)	33.8 (24.4)	−10.6	0.06
Placebo	24	49.1 (32.8)	42.4 (37.2)		

Table 2. Continued

Region	*N**	Baseline, mean (s.d.)	Week 2 follow-up, mean (s.d.)	Treatment effect	*P*-value†
Daily activity impairment					
Teg 6 mg b.d.	138	56.7 (27.3)	37.6 (26.5)	−5.4	0.33
Placebo	24	50.0 (30.1)	40.0 (32.7)		

* Sample size varies due to missing information.
† ANCOVA with pooled centre, age, baseline value and treatment.
‡ Includes USA, Europe, South America, Canada, Egypt, New Zealand, South Africa.
§ Europe: Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, UK, Hungary, Italy, the Netherlands, Norway, Sweden.
¶ South America: Argentina, Chile, Colombia, Ecuador, Peru.
IBS, irritable bowel syndrome; Teg, tegaserod.

Table 3. Work productivity and activity impairment IBS-specific with constipation outcomes (WPAI:IBS-C) at baseline and week 4*

Region	*N*†	Baseline, mean (s.d.)	Week 4 follow-up, mean (s.d.)	Treatment effect	*P*-value‡
All regions§					
Absenteeism					
Teg 6 mg b.d.	1171	5.1 (14.4)	3.5 (12.4)	−2.6	0.004
Placebo	244	5.4 (13.4)	6.1 (17.8)		
Presenteeism					
Teg 6 mg b.d.	1270	40.4 (25.4)	24.7 (23.3)	−5.4	<0.0001
Placebo	279	38.9 (25.1)	29.4 (26.2)		
Work productivity loss					
Teg 6 mg b.d.	1165	42.8 (26.1)	27.4 (24.9)	−6.3	<0.0001
Placebo	244	42.5 (25.9)	33.4 (27.9)		
Daily activity impairment					
Teg 6 mg b.d.	1312	48.3 (25.3)	28.3 (24.5)	−5.8	<0.0001
Placebo	289	46.0 (26.2)	32.9 (25.4)		
USA					
Absenteeism					
Teg 6 mg b.d.	489	3.7 (11.4)	3.2 (11.5)	−2.9	0.04
Placebo	97	5.6 (15.2)	6.5 (20.2)		
Presenteeism					
Teg 6 mg b.d.	514	39.1 (24.0)	25.8 (22.9)	−5.5	0.01
Placebo	113	40.4 (26.1)	31.2 (26.8)		
Work productivity loss					
Teg 6 mg b.d.	487	41.3 (24.8)	27.6 (24.3)	−7.3	0.003
Placebo	97	44.2 (27.0)	35.5 (28.7)		
Daily activity impairment					
Teg 6 mg b.d.	529	48.1 (24.9)	28.8 (24.4)	−6.13	0.005
Placebo	120	49.5 (26.0)	35.1 (26.1)		
Europe¶					
Absenteeism					
Teg 6 mg b.d.	466	4.6 (14.9)	3.2 (13.0)	−2.6	0.04
Placebo	110	4.4 (11.8)	5.8 (15.9)		
Presenteeism					
Teg 6 mg b.d.	530	38.1 (25.4)	23.0 (23.3)	−5.7	0.005
Placebo	128	35.3 (21.9)	27.7 (25.2)		
Work productivity loss					
Teg 6 mg b.d.	464	40.2 (25.9)	25.8 (24.5)	−7	0.003
Placebo	110	39.1 (23.1)	32.3 (26.6)		

Table 3. Continued

Region	*N*†	Baseline, mean (s.d.)	Week 4 follow-up, mean (s.d.)	Treatment effect	*P*-value‡
Daily activity impairment					
Teg 6 mg b.d.	549	45.6 (24.4)	26.8 (24.2)	−6.05	0.004
Placebo	131	41.5 (25.3)	31.0 (23.6)		
South America**					
Absenteeism					
Teg 6 mg b.d.	131	10.5 (19.3)	5.8 (15.2)	−1	0.79
Placebo	24	7.4 (12.3)	6.6 (20.4)		
Presenteeism					
Teg 6 mg b.d.	136	50.6 (27.1)	25.0 (23.0)	−5.4	0.29
Placebo	24	46.7 (32.1)	29.2 (28.7)		
Work productivity loss					
Teg 6 mg b.d.	130	54.0 (27.3)	29.5 (26.0)	−3.9	0.5
Placebo	24	49.1 (32.8)	31.7 (31.4)		
Daily activity impairment					
Teg 6 mg b.d.	141	56.5 (27.2)	29.3 (25.2)	−5.53	0.29
Placebo	24	50.0 (30.1)	32.5 (27.9)		

* Last postbaseline was carried forward (LOCF).
† Sample size varies due to missing information.
‡ ANCOVA with pooled centre, age, baseline value and treatment.
§ Includes USA, Europe, South America, Canada, Egypt, New Zealand, South Africa.
¶ Europe: Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, UK, Hungary, Italy, the Netherlands, Norway, Sweden.
** South America: Argentina, Chile, Colombia, Ecuador, Peru.
IBS, irritable bowel syndrome; Teg, tegaserod.

and for daily activity impairment at week 2, and there was a trend for improvement in the work impairment measures at week 2. For the South American region, which included 171 patients in five countries, the positive trends associated with tegaserod were generally not significant. The small sample sizes and the 4:1 ratio of tegaserod to placebo, particularly in the pooled South American region, make these results inconclusive. However, the positive trends associated with tegaserod in the European region at week 2 and the South American region at weeks 2 and 4 are noteworthy and warrant additional investigation with larger sample sizes.

A limitation of this study is that the data from the repeated treatment period were not available for analysis due to a programming error in the hand-held devices used for data collection. However, given that statistically significant differences between the tegaserod and placebo groups were observed for IBS symptom relief during all treatment weeks, including the repeated treatment cycle,[28] we speculate that the beneficial effect of tegaserod on work productivity and daily activity impairment would also persist with repeated treatment. Work productivity and daily activity impairment have been shown to vary with symptom severity[26] so it is reasonable to assume that the beneficial effect of tegaserod on symptom relief in the repeated treatment cycle would be associated with reduced impairment of both work and daily activity.

CONCLUSION

Nearly all patients seeking health care for IBS-C have notable work and daily activity limitations. IBS is a chronic and episodic disorder associated with high disease burden, a detrimental and negative impact on patients' QoL and significant economic costs. These factors should be taken into consideration when selecting appropriate treatment and management strategies. Only by relieving the multiple symptoms of IBS can improvements in patient well-being, and subsequently, improvements in productivity, be achieved. Tegaserod treatment reduces absenteeism (missed time at work), presenteeism (impairment while at work) and daily activity impairment at 2 weeks and these beneficial effects are maintained at 4 weeks.

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