

Tegaserod in the treatment of irritable bowel syndrome (IBS) with constipation as the prime symptom

Peter Layer¹
Jutta Keller¹
Helena Loeffler²
Andreas Kreiss²

¹Department of Internal Medicine, Israelitisches Krankenhaus, Hamburg, Germany; ²Clinical Development, Novartis Pharma GmbH, Nuremberg, Germany

Abstract: Irritable bowel syndrome with constipation (IBS-C) as the predominant bowel symptom is a prevalent disorder, characterized by recurring abdominal pain/discomfort, bloating, and constipation, and imposes a significant socio-economic burden. Traditional treatments generally address just one of the multiple IBS symptoms. The efficacy and safety profile of tegaserod, a serotonin 5-HT₄ receptor agonist, has been demonstrated in several randomized, placebo-controlled, and open-label trials. This review discusses the major clinical trials of tegaserod, which have involved 8948 IBS patients. Overall, data reveal that tegaserod is an effective treatment for IBS-C, providing statistically significant relief of overall and multiple individual IBS-C symptoms (abdominal pain/discomfort, bloating, and constipation) in both placebo-controlled and “real-life” open-label settings. Repeat treatments with tegaserod were also shown to be effective, which is noteworthy given the chronic and episodic nature of IBS. Moreover, tegaserod was associated with improvements in patients’ quality of life and work productivity. Data also indicate that tegaserod is well tolerated over the short-term (4 weeks), long-term (12 months), and repeated treatments. Diarrhea is the only adverse event consistently associated with tegaserod and was generally mild and transient. Overall, tegaserod has been demonstrated to offer effective and well-tolerated treatment of IBS-C, providing patients with meaningful symptom relief.

Keywords: efficacy, IBS, safety, serotonin, tegaserod, Zelnorm

Introduction

Prevalence and impact of IBS

Irritable bowel syndrome (IBS) is a chronic and episodic gastrointestinal (GI) disorder. Cardinal symptoms include abdominal pain/discomfort, bloating, and altered bowel function, with the predominant bowel symptom determining the subclassification of IBS: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), or IBS with alternating symptoms of constipation or diarrhea (IBS-A). To date, no structural or specific biochemical markers have been identified for IBS and, therefore, its diagnosis is based on the recognition of key symptoms and exclusion of organic disease (Malagelada 2006). Several diagnostic guidelines have been established for IBS, including the Rome II criteria (Thompson et al 1999). Rome II criteria classify IBS as abdominal pain/discomfort associated with two out of three of the following features: relief with defecation, onset associated with a change in stool frequency (<3 bowel movements per week or >3 bowel movements per day) and/or onset associated with a change in stool form (lumpy/hard or loose/watery stool), occurring for at least 12 weeks (not necessarily consecutive) in the preceding 12 months (Thompson et al 1999).

IBS is a common disorder, thought to affect approximately 10%–15% of individuals in Western countries (Hungin et al 2003, 2005). In addition, IBS is

Correspondence: Peter Layer
Professor of Medicine, Medical Director,
Israelitic Hospital, Academic Hospital,
Hamburg University, Orchideenstieg 14,
D 22297 Hamburg, Germany
Tel: +49 40 5112 5211
Fax: +49 40 5112 5227
Email: layer@ik-h.de

detrimental to patients' quality of life (QoL), affecting their daily routines, social lives, and emotional well-being (Hahn et al 1999; Gralnek et al 2000; Frank et al 2002). IBS also has a major economic impact on society due to its prevalence and the chronic and recurring nature of the symptoms. Studies have demonstrated that the total direct costs of IBS are similar to those of Alzheimer's disease, asthma, and migraine (Kozma et al 2002; Müller-Lissner and Pirk 2002). Given the prevalence and substantial socioeconomic impact of IBS, it is essential that effective and well-tolerated treatments are available.

Current treatment options for IBS

Traditional pharmacological treatments

To date, there is no cure for IBS and so treatments are based on alleviating one or more of the multiple symptoms. A number of traditional pharmacological treatments are commonly used, including laxatives, antidiarrheal agents, antispasmodics, and low-dose antidepressants. Overall, these agents may be considered as suboptimal treatments for IBS since they each focus on just one symptom of this disorder (ie, constipation, diarrhea, or abdominal pain/discomfort), leaving other symptoms untreated. For example, the antidiarrheal agent, loperamide, has been demonstrated to be effective for diarrhea, but does not reduce other or overall symptoms of IBS (Brandt et al 2002; Lesbros-Pantoflickova et al 2004). Consequently, patients may have to take several different medications to address their multiple symptoms. Furthermore, although these agents are often used as first-line treatments for IBS, evidence for their efficacy is limited. This is due, in part, to a lack of randomized, controlled clinical trials or inadequate trial design, as highlighted by several reviews of clinical trials for IBS treatments (Brandt et al 2002; Lesbros-Pantoflickova et al 2004; Valenzuela et al 2004; Quartero et al 2005).

Along with efficacy, safety and tolerability are important issues for IBS pharmacologic therapies, as patients are likely to require long-term and repeated treatment. However, conventional IBS therapies can cause side effects that mimic or exacerbate other IBS symptoms. For example, bulking laxatives may increase bloating and abdominal pain/discomfort in some IBS patients, while some tricyclic antidepressants and antispasmodics may cause constipation (Brandt et al 2002).

Serotonergic agents

In addition to traditional pharmacotherapies, serotonergic agents are also used to treat IBS symptoms. Serotonin is a

key neurotransmitter in the GI tract, where it is released in response to changes in luminal pressure or content of the small intestine. Serotonin stimulates the release of other neurotransmitters and together these influence intestinal peristalsis, secretion of water, and visceral sensation (Gershon 1999, 2004; Crowell 2004). Recent findings suggest that patients with IBS have abnormalities in the synthesis and function of serotonin in the GI tract (Coates et al 2004; Camilleri 2005). This is thought to lead to the key symptoms of IBS, such as abdominal pain/discomfort and altered bowel motility.

Alosetron and cilansetron are serotonergic agents with serotonin type 3 (5-HT₃) receptor antagonist actions, while cisapride has a mixed 5-HT₃ antagonist/5-HT₄ receptor agonist action. Alosetron has been shown to relieve global and individual symptoms of IBS-D (Brandt et al 2002; Lesbros-Pantoflickova et al 2004; Valenzuela et al 2004; Quartero et al 2005), but has been associated with severe constipation and ischemic colitis and, since June 2002, the US Food and Drug Administration (FDA) restricted its license to women with severe IBS-D who fail to respond to other therapies. Cilansetron is currently in clinical development as a treatment for IBS-D, although it may also be associated with an increased incidence of ischemic colitis. Regulatory bodies have requested further clinical trials be conducted before they will consider licensing this treatment. Some, but not all, studies demonstrate that cisapride improves individual symptoms of IBS-C, including constipation and abdominal pain/discomfort. However, following reports of serious cardiac side effects unrelated to the 5-HT₃ antagonist/5HT₄ receptor agonist actions, cisapride is only available to patients who meet strict inclusion criteria in limited countries (Ferriman 2000; Wang et al 2001; Barbey et al 2002).

Tegaserod (Zelnorm®/Zelmac®, Novartis Pharmaceuticals Inc) has a different mode of action to alosetron and cisapride. It acts as a serotonin 5-HT₄ receptor agonist, and is without 5-HT₃ antagonistic properties or affinity for dopamine receptors (Pfannkuche et al 1995). Tegaserod is structurally similar to serotonin except it is more polar, which minimizes its potential to cross the blood-brain barrier. Preclinical and clinical studies reveal that tegaserod can facilitate GI motility and intestinal secretion and reduce visceral sensitivity, thereby increasing the frequency of bowel movements, softening stools, and reducing abdominal pain/discomfort (Fioramonti et al 1998; Grider et al 1998; Jin et al 1999; Schikowski et al 1999; Stoner et al 1999; Prather et al 2000; Degen et al 2001;

Coffin et al 2003; Sabate et al 2005). Recent reviews of clinical trial data suggest that tegaserod effectively relieves individual and global symptoms of IBS-C and has a favorable safety profile (Brandt et al 2002; Lesbros-Pantoflickova et al 2004; Valenzuela et al 2004; Schoenfeld 2005).

The aim of this paper is to review tegaserod as a treatment for IBS-C with particular focus on clinical trial data. The trials discussed in depth are divided into the four pivotal phase III trials involving 5859 IBS patients, three of which were the basis of FDA approval of tegaserod as a treatment for IBS-C, and six additional phase IIIb/IV trials involving 3089 IBS patients, which include open-label, repeat treatment studies to reflect “real-life” clinical practice. Data on the safety and tolerability of tegaserod following short- and long-term treatment are also discussed, along with special safety considerations.

Pivotal phase III clinical trials of tegaserod

Trial designs

The tegaserod clinical trial program includes four pivotal trials, which were conducted throughout 26 countries (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002; Tack et al 2005). They employed randomized, multicenter, double-blind, placebo-controlled designs and each involved large numbers of IBS-C patients (Table 1).

All the pivotal trials incorporated a treatment-free baseline period, during which IBS-C symptoms were assessed. This was followed by a 12-week treatment period in Studies 1–3 (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002) and a withdrawal period in Study 3 only (Novick et al 2002). The primary efficacy variable for Studies 1–3 was Subject’s Global Assessment (SGA) of Relief (Lefkowitz et al 1999; Müller-Lissner et al 2001;

Table 1 Overview of the design of the pivotal trials of tegaserod in IBS-C patients

	Study 1 (Müller-Lissner et al 2001)	Study 2 (Lefkowitz et al 1999)	Study 3 (Novick et al 2002)	ZENSAA (Tack et al 2005)
Location	Europe, South Africa, USA	North and South America America, South Africa	USA Europe, North and South	
Design	<ul style="list-style-type: none"> • 4-week baseline^a • 12-week treatment 	<ul style="list-style-type: none"> • 4-week baseline^a • 12-week treatment 	<ul style="list-style-type: none"> • 4-week baseline^a • 12-week treatment • 4-week withdrawal^a 	<ul style="list-style-type: none"> • 2-week baseline^a • Two 4-week treatment periods separated by treatment-free interval
Treatment ^b	Tegaserod 6 mg bid Tegaserod 2 mg bid Placebo	Tegaserod 6 mg bid Tegaserod 2 mg bid Placebo	Tegaserod 6 mg bid Placebo	Tegaserod 6 mg bid Placebo
Patients ^c	881 men and women	799 men and women	1519 women only	2660 women only
Primary outcome variable ^d	SGA of Relief	SGA of Relief	SGA of Relief	<ul style="list-style-type: none"> • Satisfactory relief of overall IBS symptoms • Satisfactory relief of abdominal discomfort/pain
Secondary outcome variables ^e	<ul style="list-style-type: none"> • SGA of Abdominal Pain/Discomfort • Effect on: <ul style="list-style-type: none"> - Abdominal discomfort/pain - Bloating - Stool frequency - Stool consistency 	<ul style="list-style-type: none"> • SGA of Abdominal Pain/Discomfort • Effect on: <ul style="list-style-type: none"> - Abdominal discomfort/pain - Bloating - Stool frequency - Stool consistency 	<ul style="list-style-type: none"> • SGA of Abdominal Pain/Discomfort • SGA of Bowel Habit • SGA of Satisfaction with Bowel Habit • Effect on: <ul style="list-style-type: none"> - Abdominal discomfort/pain - Bloating - Stool frequency - Stool frequency - Stool consistency 	<ul style="list-style-type: none"> • Effect on: <ul style="list-style-type: none"> - Abdominal discomfort/pain - Bloating - Stool frequency - Stool consistency - Overall satisfaction with treatment • IBS-QOL, EQ-5D, WPAI:IBS-C questionnaires

Notes: ^aTreatment-free; ^bRandomized, double-blind; ^cPatients fulfilled Rome I (Studies 1–3) or Rome II (ZENSAA) criteria for IBS-C; ^dPatient’s assessment; ^eAssessed using ordinal scales. Patients had broadly similar demographic characteristics and baseline symptoms between the four studies.

Abbreviations: bid, twice daily; EQ-5D, EuroQoL; IBS, irritable bowel syndrome; IBS-QOL, IBS-specific quality of life; WPAI: IBS-C, Work productivity activity impairment for IBS with constipation; SGA, Subject’s Global Assessment, measured by a patient’s response to the question “Please consider how you felt this last week in regard to your IBS, in particular your overall well-being and symptoms of abdominal pain/discomfort and altered bowel habit.” Compared with baseline, patients rated their symptoms on a 5-point scale: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse.

Novick et al 2002). This is an important outcome variable due to the varying importance that patients place on their different IBS symptoms (Dunger-Baldauf et al 2003). Responders were patients whose symptoms were “completely relieved” or “considerably relieved” at least 50% of the time or “somewhat relieved” 100% of the time during the final 4 weeks of the study. Patients also assessed their individual IBS symptoms as secondary efficacy variables (Table 1).

IBS patients often require repeat courses of therapy due to the chronic and episodic nature of their symptoms and, as recommended by the European Committee for Medicinal Products for Human Use (CHMP; formally known as the Committee for Proprietary Medicinal Products [CPMP]), it is important that treatment can be repeated without loss of efficacy (CPMP 2003). Therefore, Study 4 (ZENSAA, Zelnorm in Europe, North and South America and Africa) investigated the effects of repeat tegaserod treatment. Patients who responded to initial treatment (4 weeks) entered a treatment-free interval. Patients were randomized to receive a further 4 weeks of either tegaserod or placebo if their symptoms recurred during this interval. The ZENSAA trial utilized two primary efficacy variables: whether patients experienced satisfactory relief of their overall IBS symptoms, and whether patients experienced satisfactory

relief of their abdominal discomfort/pain during the last week (yes/no). Responders were patients with satisfactory relief during at least 3 weeks of each 4-week treatment cycle (Tack et al 2005). Effects of treatment on individual IBS symptoms were also assessed, along with patients’ QoL and work productivity, examined via IBS-QOL (IBS-specific QoL), EQ-5D (EuroQoL) and WPAI:IBS-C (Work Productivity Activity Impairment for IBS-C) questionnaires, along with their overall satisfaction with treatment (Table 1).

Efficacy data

Data from all four trials reveal that tegaserod was consistently and significantly better than placebo at relieving overall and key individual IBS symptoms (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002; Tack et al 2005). The main findings from each of the pivotal trials are summarized in Table 2.

In Studies 1–3, tegaserod provided significantly greater relief of overall IBS symptoms during nearly all weeks of treatment compared with placebo ($p<0.05$, Figure 1) (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002). Tegaserod also significantly improved individual IBS symptoms, including abdominal pain/discomfort, bloating, and constipation (increased stool frequency and

Table 2 Overview efficacy findings of the pivotal trials of tegaserod in IBS-C patients

	Primary efficacy variables ^a	Secondary efficacy variables
Study 1 (Müller-Lissner et al 2001)	<ul style="list-style-type: none"> Greater SGA of relief of overall IBS symptoms for 11 out of 12 weeks (tegaserod vs placebo, $p\leq 0.05$) At endpoint, treatment difference from placebo was 11.8% and 12.7% for 2 mg and 6 mg tegaserod, respectively 	<ul style="list-style-type: none"> Greater improvements in abdominal pain/discomfort, stool frequency, stool consistency during most weeks (tegaserod vs placebo, $p<0.05$) Favorable trend for tegaserod reducing the number of days with bloating
Study 2 (Lefkowitz et al 1999)	<ul style="list-style-type: none"> Greater SGA of overall relief at Months 1 and 2 (tegaserod vs placebo, $p<0.05$), but not at study endpoint 	<ul style="list-style-type: none"> Improved abdominal pain/discomfort, bloating, stool frequency, and stool consistency (tegaserod vs placebo, $p<0.05$)
Study 3 (Novick et al 2002)	<ul style="list-style-type: none"> Greater SGA of relief of overall IBS symptoms for 11 out of 12 weeks (tegaserod vs placebo, $p\leq 0.05$) At endpoint, treatment difference between tegaserod and placebo was 4.7% 	<ul style="list-style-type: none"> Improved SGAs of abdominal pain/discomfort, bowel habit and satisfaction with bowel habit, and symptoms of bloating, stool frequency, stool consistency and days with straining (tegaserod vs placebo, $p<0.05$)
ZENSAA (Tack et al 2005)	<ul style="list-style-type: none"> More tegaserod than placebo responders^a during initial and repeat treatment for satisfactory relief of overall IBS symptoms: 33.7% vs 24.2%, 44.9% vs 28.7%; and relief of abdominal discomfort/pain: 31.3% vs 22.1%, 42.4% vs 27.1%; all $p<0.0001$ 	<ul style="list-style-type: none"> Greater relief during initial and repeated treatment from abdominal discomfort/pain, bloating, and improvements in stool frequency and stool consistency (tegaserod vs placebo, $p\leq 0.001$) Greater treatment satisfaction, work productivity and improvements in QoL (tegaserod vs placebo, $p<0.05$)

Notes: ^aResponders had satisfactory relief of their overall IBS symptoms for at least 3 out of the 4 weeks in each treatment cycle.

Abbreviations: IBS-C, irritable bowel syndrome with constipation; SGA, Subject’s Global Assessment; QoL, quality of life.

softened stools) compared with placebo (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002). After withdrawal of treatment, IBS symptoms returned rapidly, but did not reach baseline levels (Novick et al 2002).

In the ZENSAA trial, tegaserod treatment was associated with significantly more responders for relief of overall IBS symptoms (Figure 1) and relief of abdominal discomfort/pain compared with placebo ($p<0.0001$). This occurred during both initial and repeat treatments (Tack et al 2005). Similar to the other pivotal studies, tegaserod was also superior to placebo for relief of individual IBS symptoms, including bloating and constipation, following initial and repeat treatments ($p\leq 0.001$). Furthermore, during both treatment cycles, more patients expressed overall satisfaction with tegaserod compared with placebo (56.2% vs 41.2%; 66.1% vs 50.1%, both $p<0.0001$) (Tack et al 2005). Similar to Study 3, IBS symptoms recurred gradually following cessation of treatment, with no evidence of a rebound effect (Tack et al 2005). Overall, these findings suggest that many patients who benefit from an initial course of tegaserod treatment are likely to benefit from a further course, should their symptoms recur (Tack et al 2005). It is noteworthy that no other IBS treatments have been shown to effectively address bloating, which is one of the symptoms IBS patients report as most bothersome (Schmulson et al 1999; Bijkerk et al 2003).

In the ZENSAA trial, the positive effect of tegaserod on IBS symptom relief was mirrored by significant improvements in QoL and health economic-related outcomes. In tegaserod-treated patients, IBS-QOL scores were significantly higher in five out of the eight domains (dysphoria, body image, health worry, food avoidance, and impact on relationships; $p<0.05$) compared with placebo (Patrick et al 2005; Tack et al 2005). Less presenteeism (impairment while at work), absenteeism (work time missed), and overall work productivity loss were also observed in tegaserod than placebo patients ($p<0.0001$), equating to an increase of 2.5 hours' work productivity per week (Reilly et al 2005; Tack et al 2005).

In all four pivotal trials, response to tegaserod was rapid and sustained. For each of the variables, response occurred within the first week of treatment (illustrated for stool frequency in Figure 2) and continued throughout the treatment period (illustrated for abdominal pain/discomfort in Figure 3), with no evidence of tachyphylaxis (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002; Tack et al 2005). Moreover, the response rate for tegaserod tended to increase during the course of treatment (Figure

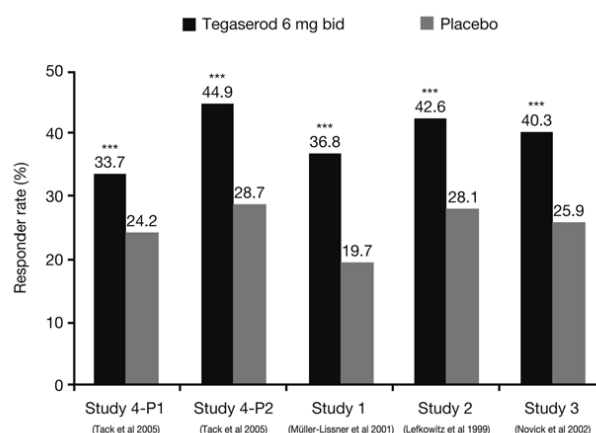


Figure 1 Subject's Global Assessment (SGA) of Relief demonstrates consistent improvement across tegaserod clinical trials.

Note: *** $p<0.001$.

Abbreviations: P1, first treatment cycle; P2, second treatment cycle.

4). These data indicate that patients who do not respond to tegaserod during the first few weeks of treatment may go on to respond a few weeks later if treatment is continued.

The placebo effect (a response to a pharmacologically inactive therapy) is well documented in trials of patients with functional bowel diseases (Patel et al 2005). Estimates of response to placebo in IBS trials are typically between 40% and 70%, making it difficult to detect a therapeutic gain with active treatment (Patel et al 2005). However, it is noteworthy that in each of the four key tegaserod IBS trials, a statistically significant greater response to treatment was observed for tegaserod compared with placebo. For overall symptom relief, response above placebo for tegaserod ranged between 4.7% and 16.2% (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002; Tack et al 2005). Numbers needed to treat (NNT) to derive benefit

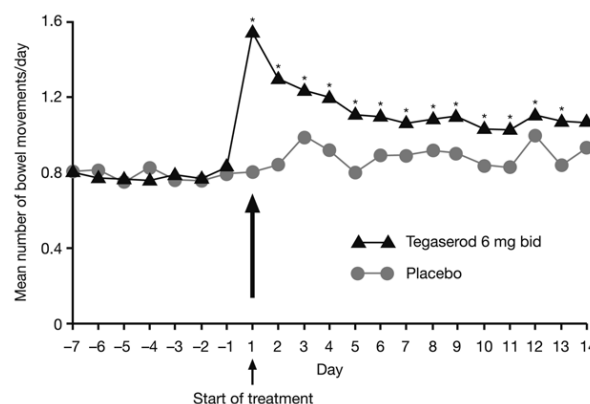


Figure 2 Rapid onset of action with tegaserod: increased number of bowel movements. Pooled data from Studies 1 and 2 (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novartis, Data on file).

Note: * $p<0.05$ vs placebo (change from baseline score).

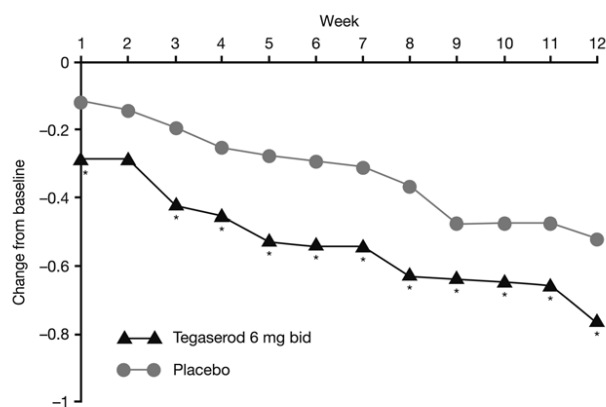


Figure 3 Sustained effect of tegaserod: improved abdominal pain and discomfort. Study 1. Copyright © 2001. Figure adapted with permission from the Blackwell Publishing Group from Müller-Lissner SA, Fumagalli I, Bardhan KD, et al. 2001. Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther*, 15:1655-66.

Note: 6-point scale: 0 = absent to 5 = very severe; *p<0.05 vs placebo (change from baseline score).

calculated for women aged ≤65 years in the pivotal trials were 5.6, 6.8, and 7.0 for Studies 1, 2, and 3, respectively, based on the definition of responder (patients whose symptoms were “completely relieved” or “considerably relieved” at least 50% of the time or “somewhat relieved” 100% of the time during the final four weeks of the study). NNT for Study 4 was 10.8 and 6.0 for initial and repeated treatment respectively, based on the definition of responder (patients with satisfactory relief during at least 3 weeks of each 4-week treatment cycle) (Novartis. Data on file).

Further phase IIIb/IV clinical trials of tegaserod in IBS-C

The aim of these six phase IIIb/IV studies was to further assess tegaserod treatment in IBS patients of differing race and culture from a wide range of countries (Kellow et al 2003; Uscanga-Dominguez and Cohen Munoz 2003; Bardhan et al 2004; Nyhlin et al 2004; Layer et al 2005; Müller-Lissner et al 2005). While two of these trials followed similar randomized, placebo-controlled designs to the pivotal IBS trials, the others were open-labeled and designed to evaluate the effectiveness of tegaserod under real-life conditions (Table 3).

Data from the two randomized, placebo-controlled trials (Kellow et al 2003; Nyhlin et al 2004) were consistent with the four pivotal trials (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002; Tack et al 2005). They demonstrated that significantly more patients taking tegaserod than placebo experienced satisfactory relief of their overall IBS symptoms and greater improvements in

individual symptoms, including abdominal pain/discomfort, stool frequency, stool consistency, and straining during defecation. These results confirm that tegaserod is an effective treatment for overall and individual symptoms of IBS, irrespective of factors such as geographical region, race, and culture. In addition, as two of these trials were conducted in IBS patients excluding those with diarrhea (non-IBS-D), they also indicate that tegaserod is effective in this subgroup of patients, as well as those diagnosed with IBS-C according to Rome II criteria.

Three of the phase IIIb/IV studies investigated the effects of repeated tegaserod treatment (Uscanga-Dominguez and Cohen Munoz 2003; Bardhan et al 2004; Müller-Lissner et al 2005). These were open-label studies and are more likely to reflect clinical practice than placebo-controlled trials. In the UK and Latin American retreatment studies, patients who responded to initial tegaserod therapy (satisfactory relief of overall IBS symptoms for at least 2 out of 4 weeks' treatment) were randomized to either continue on tegaserod or withdraw from treatment. In both studies, almost 60% more patients who withdrew from tegaserod experienced symptom recurrence compared with those who continued therapy (p<0.0001) (Uscanga-Dominguez and Cohen Munoz 2003; Bardhan et al 2004) (Table 3). A significant treatment benefit for abdominal pain/discomfort, bloating (both p≤0.02) (Uscanga-Dominguez and Cohen Munoz 2003; Bardhan et al 2004), stool frequency, and overall symptom relief (both p<0.0004) was observed in patients who continued tegaserod treatment compared with those who withdrew (Uscanga-Dominguez and Cohen Munoz

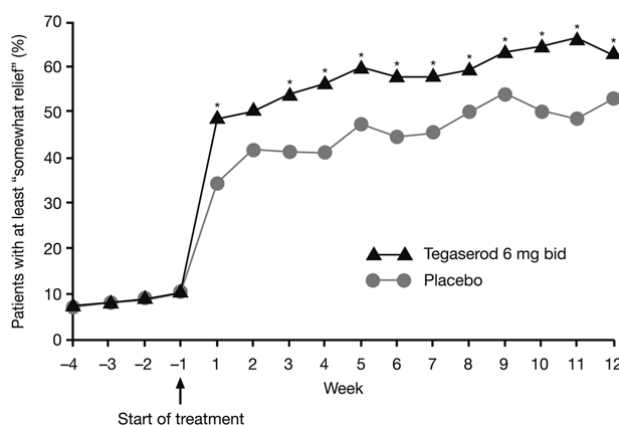


Figure 4 Subject's Global Assessment (SGA) of Relief during tegaserod treatment. Study 1. Copyright © 2001. Figure reproduced with permission from the Blackwell Publishing Group from Müller-Lissner SA, Fumagalli I, Bardhan KD, et al. 2001. Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther*, 15:1655-66.

Note: *p<0.05 vs placebo.

Table 3 Overview of the design and key efficacy outcomes of the additional Phase IIIb/IV trials of tegaserod in IBS patients

	Study characteristics		
	Patients ^a	Study design	Key findings
ZAP (Kellow et al 2003)	n=520 (non-IBS-D) Asia-Pacific countries	RCT <ul style="list-style-type: none"> 2-week baseline 12 weeks' treatment (tegaserod 6 mg bid or placebo) 4-week withdrawal 	<ul style="list-style-type: none"> More tegaserod than placebo responders^b over Weeks 1–4 (56% vs 35%) and Weeks 1–12 (62% vs 44%; $p<0.0001$) Greater reductions in days without bowel movements, hard/very hard stools, straining, sensation of incomplete evacuation for tegaserod vs placebo ($p<0.05$), but not for abdominal pain
TENOR (Nyhlin et al 2004)	n=647 (non-IBS-D) Nordic countries	RCT <ul style="list-style-type: none"> 2-week baseline 12 weeks' treatment (tegaserod 6 mg bid or placebo) 4-week withdrawal 	<ul style="list-style-type: none"> More tegaserod than placebo responders^b (54% and 78% higher for Weeks 1–4 and Weeks 1–12, respectively; $p<0.005$) Greater reductions in days without bowel movements, hard/very hard stools, straining, sensation of incomplete evacuation for tegaserod vs placebo patients ($p<0.05$), but not for abdominal pain/discomfort and bloating
German retreatment (Müller-Lissner et al 2005)	n=513 (IBS-C ^c) Germany	Open-label <ul style="list-style-type: none"> 2-week baseline 12 weeks' treatment (tegaserod 6 mg bid) 8-week withdrawal 4 weeks' treatment (tegaserod 6 mg bid) 	<ul style="list-style-type: none"> 85% were responders^b in first treatment cycle Recurrence of symptoms in 83.9% after a mean of 38 days without treatment 89.3% were responders^b during retreatment
UK retreatment (Bardhan et al 2004)	n=519 (IBS-C ^c) UK	Open-label, randomized <ul style="list-style-type: none"> 4-week baseline 4 weeks' treatment (tegaserod 6 mg bid) 8-week withdrawal or maintenance of tegaserod 6 mg bid 	<ul style="list-style-type: none"> Shorter time to symptom recurrence in withdrawal vs tegaserod patients. More tegaserod patients without symptom recurrence by Week 8 vs patients on intermittent (86.5% vs 58.1%) or withdrawal of treatment (69.2% vs 11.3%, $p<0.0001$) Significant reductions for bloating ($p<0.01$) and abdominal pain/discomfort ($p<0.02$)
LATAM (Uscanga-Dominguez and Cohen Munoz 2003)	n=678 (IBS-C ^c) Latin America	Open-label, randomized <ul style="list-style-type: none"> 2-week baseline 4 weeks' treatment (tegaserod 6 mg bid) 10-week withdrawal or maintenance of tegaserod 6 mg bid 	<ul style="list-style-type: none"> 82% experienced overall symptom relief Lower symptom recurrence in patients remaining on tegaserod vs those withdrawn (10% vs 67%, $p<0.0001$)
German primary care (Layer et al 2005)	n=212 (IBS-C) Germany	Open-label <ul style="list-style-type: none"> 2-week baseline 12 weeks' treatment (tegaserod 6 mg bid) 9-month optional treatment extension (tegaserod 6 mg bid) 	<ul style="list-style-type: none"> Response rates^b: 64.2% at Week 4, 70.3% at Week 12 After 12 weeks, significant reductions in abdominal pain/discomfort and bloating ($p<0.0001$) and improvements in stool frequency and stool consistency ($p<0.0001$)

Notes: ^aMen and women; ^bResponders had satisfactory relief of their overall IBS symptoms for at least 2 out of the 4 preceding weeks; ^cIBS-C classified according to Rome II criteria.

Abbreviations: bid, twice daily; IBS-D, irritable bowel syndrome with diarrhea; RCT, randomized, controlled trial; IBS-C, irritable bowel syndrome with constipation.

2003). In the German retreatment study, withdrawal of tegaserod resulted in symptom recurrence in the majority of patients (83.9%), while retreatment of responders to initial therapy, following symptom recurrence, was effective in over 90% of patients. Similar improvements from baseline in symptoms of abdominal pain, bloating, stool frequency and consistency were also observed following both the initial

($p\leq 0.0003$) and repeated treatments with tegaserod (Müller-Lissner et al 2005).

A second open-label study conducted in Germany investigated the effectiveness of tegaserod in “real-life” primary care settings, focusing on patients with mild or moderate IBS (Layer et al 2005). Response rates for overall IBS symptom relief (satisfactory relief of IBS symptoms

for 2 out of 4 of the previous weeks) increased during treatment and by Week 12, there were significant improvements in abdominal pain/discomfort, bloating, stool frequency, and consistency from baseline ($p < 0.0001$) (Layer et al 2005).

In summary, findings from these clinical trials demonstrate that tegaserod is an effective treatment for IBS. Tegaserod is associated with significant relief, compared with placebo or baseline, of overall and individual symptoms of IBS, in IBS-C and non-IBS-D patients from a wide range of countries throughout the world. Repeated use of tegaserod is effective, particularly in patients who previously responded to treatment.

Safety and tolerability of tegaserod: data from IBS clinical trials

Safety and tolerability were studied extensively throughout the tegaserod IBS clinical trial program. All reported adverse events (AEs) and serious adverse events (SAEs) were considered, alongside outcomes of physical examinations, standard hematology and biochemistry testing, urinalysis, blood pressure, and electrocardiogram (ECG) evaluations.

The available data demonstrate that tegaserod has a favorable safety profile and is well tolerated by IBS-C patients. Overall, the incidences of AEs and SAEs were comparable between patients who received tegaserod or placebo, with the exception of diarrhea, which was more frequent in patients taking tegaserod. A meta-analysis of three IBS-C trials of tegaserod revealed that diarrhea occurred in 10.0% and 4.2% of tegaserod and placebo patients, respectively, and was rated as severe in 3.1% and 0.9% of patients (Earnest et al 2002). Diarrhea is an anticipated AE associated with tegaserod use, given its promotile activity in the GI tract. In most cases diarrhea was experienced as a single episode, was mild and transient, and resolved without the need to interrupt the study drug or provide therapeutic intervention (Hasler and Schoenfeld 2004). The incidence of serious consequences of diarrhea, such as hypovolemia, hypotension, and syncope, was very rare, occurring in 3 out of 9267 patients (0.03%) who participated in phase II and III trials of tegaserod across all indications (Novartis. Data on file).

Along with diarrhea, headache was also one of the most frequently reported AEs in these trials. The effect of tegaserod on headache is inconclusive since the incidence was similar in tegaserod and placebo-assigned patients in

some studies (30.6% vs 27.3% [Müller-Lissner et al 2001] and 12.0% vs 11.1% [Kellow et al 2003] for tegaserod and placebo patients, respectively) but was more frequent with tegaserod in others (9.0% vs 5.7% [Novick et al 2002] and 8.0% vs 4.7% [Nyhlen et al 2004]). Other safety data from these trials indicated that no clinically relevant abnormalities in hematology, biochemistry, or ECG parameters were associated with tegaserod treatment.

Figure 5 shows a pooled analysis of AEs leading to discontinuation from the three pivotal IBS-C trials of 12 weeks' treatment duration (Studies 1–3) (Lefkowitz et al 1999; Müller-Lissner et al 2001; Novick et al 2002). Similar to overall AEs, the incidence of AEs leading to study discontinuation was comparable for tegaserod and placebo patients, with the exception of diarrhea and headache. Overall, 1.6% of patients taking tegaserod discontinued from the studies due to diarrhea compared with 0.3% of patients taking placebo ($p < 0.05$), and slightly more tegaserod patients also discontinued due to headache (1.0% and 0.8% of patients in the tegaserod and placebo groups, respectively). Tegaserod was also well tolerated in the repeat tegaserod treatment studies (Müller-Lissner et al 2005; Tack et al 2005). The AEs observed during initial and repeat treatment were comparable, while there was a tendency for their frequency to be lower upon repeat treatment (Table 4) (Tack et al 2005).

Two studies were also conducted to assess the long-term safety and tolerability of tegaserod, given that patients may require treatment for prolonged periods. Both were open-label, multicenter studies, recruiting patients from primary care or out-patient centers and comprised either 12 months of continuous tegaserod treatment (Tougas et al 2002) or 12 weeks of treatment with an optional 9-month extension (Layer et al 2005). In the first study, 567 patients received tegaserod and approximately half (52.5%) completed 12 months of treatment. The most common AEs reported reflect those observed in the short-term IBS trials (mild and transient diarrhea [10.1%], headache [8.3%], and abdominal pain [7.4%]). Only one SAE (abdominal pain) was reported as possibly related to tegaserod, and diarrhea was the most common reason for discontinuation (3.5%) (Tougas et al 2002). Safety data from the second study were similar, also reflecting findings in the placebo-controlled trials. Overall, 78.3% of patients completed the initial 12 weeks of tegaserod and 70.8% completed the 9-month extension period. Headache and diarrhea were the most commonly reported AEs in the 12-week phase (13.2% and 9.4%, respectively), while diarrhea was the third most frequent

AE in the 9-month extension phase, being reported by 7.5% of patients.

Overall, these data indicate that tegaserod is well tolerated by patients with IBS-C during short- and long-term treatment as well as repeat treatment. With the exception of diarrhea, which was generally mild and transient and resolved without the need for additional therapy, and possibly headache, the incidence of AEs was similar in tegaserod- and placebo-treated patients.

Special safety considerations: ischemic colitis

Recently, concerns have been raised regarding the potential risk of ischemic colitis associated with some serotonergic agents. This follows reports that patients taking alosetron and cilansetron have a higher incidence of ischemic colitis than patients taking placebo. These reports showed an incidence of ischemic colitis of 1.1 case per 1000 patient-years and 3.77 cases per 1000 patient-years for alosetron- and cilansetron-treated patients, respectively, which is much higher than that observed in IBS patients in general (43–48 cases per 100 000 patient-years) (Brinker et al 2004; Singh et al 2004; Chey et al 2005; Chey and Cash 2005).

In contrast to alosetron and cilansetron, which have a different mechanism of action to tegaserod, no cases of ischemic colitis have been reported in tegaserod-treated patients in the clinical trial program, which includes over 14 000 patients, equivalent to 4888 patient-years of exposure (Shetzline et al 2005). In addition, a review of post-marketing data reveals that the incidence of ischemic colitis in patients who have used tegaserod is comparable

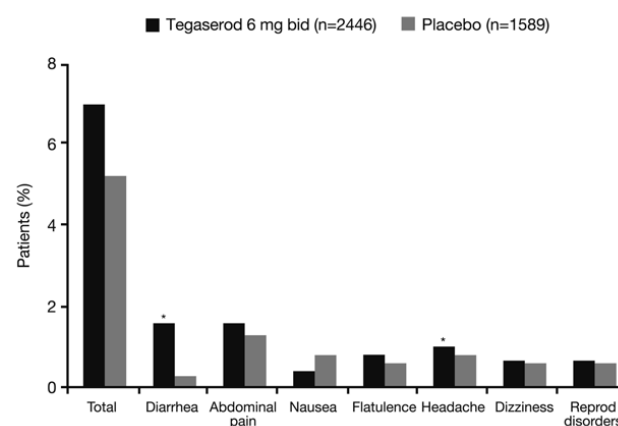


Figure 5 Adverse events (≥0.5%) leading to discontinuation in pivotal phase III trials of tegaserod. Pooled data from Studies 1, 2 and 3 (Müller-Lissner et al 2001; Leftkowitz et al 1999; Novick et al 2002; Novartis, Data on file).

Note: * $p < 0.05$ vs placebo.

Abbreviations: reprod, reproductive.

with, if not lower (8 cases per 100 000 patient-years) than, the incidence observed in the general IBS population (Shetzline et al 2005).

Special safety considerations: cardiac safety

Cisapride has been associated with fatal ventricular arrhythmias via a mechanism unrelated to its serotonergic action. This resulted in the suspension of its UK license, restricted license in several countries, and its withdrawal from the US market. This consequently has heightened interest in the cardiac safety of other serotonergic agents (Ferriman 2000; Wang et al 2001; Barbey et al 2002). In contrast to cisapride, tegaserod has a favorable cardiac safety

Table 4 Most frequent AEs during repeated tegaserod treatment (ZENSAA [Tack et al 2005]), regardless of study drug relationship

	First treatment		Repeated treatment ^a	
	Tegaserod (n=2132) n (%)	Placebo (n=525) n (%)	Tegaserod (n=487) n (%)	Placebo (n=494) n (%)
Headache	118 (5.5)	26 (5.0)	20 (4.1)	18 (3.6)
Diarrhea	81 (3.8) ^b	3 (0.6)	9 (1.8) ^c	2 (0.4)
Abdominal pain	48 (2.3)	13 (2.5)	5 (1.0)	6 (1.2)
Nausea	47 (2.2)	6 (1.1)	2 (0.4)	2 (0.4)
Nasopharyngitis	46 (2.2)	8 (1.5)	6 (1.2)	5 (1.0)
Influenza	24 (1.1)	7 (1.3)	1 (0.2)	2 (0.4)
Abdominal pain (upper)	23 (1.1)	3 (0.6)	3 (0.6)	2 (0.4)
Back pain	20 (0.9)	8 (1.5)	5 (1.0)	5 (1.0)
Dyspepsia	11 (0.5)	5 (1.0)	2 (0.4)	2 (0.4)
Urinary tract infection	11 (0.5)	6 (1.1)	5 (1.0)	3 (0.6)
Dysmenorrhea	11 (0.5)	3 (0.6)	2 (0.4)	5 (1.0)

Note: ^aRegardless of relationship to study drug; Includes only first treatment tegaserod patients who received repeated treatment; ^b $p < 0.0001$; ^c $p = 0.04$, tegaserod vs placebo. Copyright © 2005. Reproduced with permission from *BMJ* from Tack J, Müller-Lissner S, Bytzer P, et al. 2005. A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation (IBS-C). *Gut*, 54:1707-13.

profile and is not associated with any clinically significant cardiac abnormalities. In particular, no alterations of ECG parameters including QT-interval measurements have been observed (Morganroth et al 2002).

Special safety considerations: abdominal and pelvic surgery

Patients with IBS have a relatively high incidence of abdominal/pelvic surgeries. For example, they are twice as likely to undergo a cholecystectomy and four times more likely to undergo appendectomy than healthy people (Hasler and Schoenfeld 2003). In the US, prescribing information for tegaserod notes that trials in IBS-C patients demonstrated an increase in abdominal surgeries in tegaserod (0.3%) compared with placebo (0.2%) patients, primarily due to more cholecystectomies (0.17% and 0.06%, respectively). The FDA specified that tegaserod is contraindicated in patients with gallbladder disease, suspected sphincter of oddi dysfunction, or abdominal adhesions. However, a recent expert analysis of almost 10 000 patients in tegaserod clinical trials found the incidence of abdominal/pelvic surgery cases, including cholecystectomy, was comparable in tegaserod- and placebo-treated patients (Schoenfeld 2004), and there is no evidence that tegaserod has an effect on gallbladder or sphincter of oddi function in healthy women or those with IBS-C (Fisher et al 2003, 2004).

Special safety considerations: pregnancy and breast feeding

Pregnancy was investigated in preclinical studies of tegaserod in rats and rabbits at 90 and 360 times the human dose of 6 mg bid, respectively. No harmful effects of tegaserod were reported on pregnancy, embryonic or fetal development, parturition or postnatal development (Appel-Dingemanse 2002). Pregnancy was an exclusion factor in the tegaserod clinical trial program, and all participating women of child-bearing age were required to use a medically approved method of contraception. Despite this, there were 35 (0.43%) pregnancies in tegaserod and 18 (0.40%) pregnancies in placebo groups. Although these patients withdrew from the studies as protocol violators, there was no indication that tegaserod had a detrimental effect on pregnancy or fetal development (Novartis. Data on file). However, as no controlled studies of tegaserod have been performed in pregnant women, its use during pregnancy is not recommended.

Studies in lactating rats revealed that following oral administration of tegaserod, levels of the drug were approximately three-fold higher in milk than in plasma. This suggests that a suckling infant will ingest tegaserod via breast milk. Consequently, it is recommended that tegaserod is not prescribed to women who are breast-feeding.

Drug–drug interactions and special patient populations

The liver and kidneys play an important role in eliminating tegaserod from the body. Tegaserod can be metabolized by hepatic cytochrome P450 isozymes (CYP P450) or excreted in urine and feces (Appel-Dingemanse 2002). Other drugs are also metabolized by CYP P450, but there is no evidence of drug–drug interactions between tegaserod and such drugs, including theophylline (Zhou, Khalilieh, et al 2001), dextromethorphan (Kalbag et al 2000), digoxin (Zhou, Horowitz, et al 2001), warfarin (Ledford et al 2000), oral contraceptives (Zhou et al 2000), or antidepressants (Vickers et al 2001; Appel-Dingemanse 2002). These findings indicate that tegaserod can be safely administered alongside these commonly used drugs, with no need for dosage adjustments.

Due to the involvement of the liver and kidneys in the metabolism and excretion of tegaserod, the effects of tegaserod in patients with hepatic and renal disease were studied. Results showed that plasma concentrations of tegaserod in patients with mild-to-moderate liver disease, mild-to-moderate renal impairment, and in patients requiring renal dialysis were comparable with levels in healthy controls. Therefore, dose-adjustment of tegaserod is not required in these patients (Zhou et al 1999; Appel-Dingemanse 2002).

Concluding remarks

The efficacy and safety of tegaserod as a treatment for IBS-C have been extensively investigated. Data from randomized, placebo-controlled trials conducted in numerous countries suggest that compared with placebo, tegaserod provides rapid, sustained, and statistically significant relief of overall IBS symptoms as well as individual symptoms of abdominal pain/discomfort, bloating, and constipation. These effects are also observed during repeat treatment, which is important given the chronic and recurring nature of IBS symptoms. The improvements in IBS symptoms observed with tegaserod in comparison with placebo are within the range observed with other

serotonergic agents. Moreover, efficacy has been confirmed in open-label trials performed in real-life clinical settings, thereby reflecting the response to treatment physicians may observe in their patients. Tegaserod is associated with significant improvements in patients' QoL and work productivity and is well tolerated, including over long-term and repeated treatments. Diarrhea, the only AE consistently associated with tegaserod therapy, is generally mild, of short duration, and resolved without therapy. Overall, tegaserod provides significant improvements for patients with IBS-C, without compromising safety. Thus, it can be regarded as an appropriate treatment option from the current agents available for IBS-C.

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