NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Zelmac® (tegaserod) Advisory Committee Briefing Document

Document type:	Advisory Committee Briefing Document
Document status:	Final
Release date:	May 24, 2000
Number of pages:	93

TABLE OF CONTENTS

1 Introduction/Background

Novartis Pharmaceuticals Corporation (the sponsor) submitted a New Drug Application (NDA) on February 11, 2000, for Zelmac™ (tegaserod) tablets for the symptomatic treatment of irritable bowel syndrome (IBS) in patients who identify abdominal pain and discomfort and constipation as their predominant symptoms.

The purpose of this briefing document is to provide an overview of the tegaserod clinical program as contained in the dossier submitted to the Food and Drug Administration (FDA). The tegaserod clinical program for the treatment of constipation-predominant irritable bowel syndrome (C-IBS) included 48 studies, five of which were controlled clinical studies. At the core of the clinical program are three adequate and well-controlled studies, B351, B301 and B307, evaluating the safety and efficacy of tegaserod compared to placebo. The totality of the efficacy data across all studies provides strong evidence that tegaserod at a dose of 12 mg/ day produces clinically meaningful and statistically significant results on abdominal pain and discomfort, and altered bowel function in patients with C-IBS. Overall, tegaserod has an excellent benefit to risk ratio profile for treatment of this IBS population.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterized by chronic or recurrent abdominal pain or discomfort and disturbed defecation. The disorder has a broad range of severity, ranging from mild symptoms to severe and intractable symptoms. Although the pathophysiology of IBS is not fully understood, symptoms appear to be due to disturbances in GI motility and enhanced visceral sensitivity.[1] Psychosocial factors may also contribute to overall symptom expression.

IBS is highly prevalent in the general population and is associated with significant disability and health care costs. Prevalence estimates from surveys in the United States and Great Britain indicate that IBS affects 14-24% of women and 5-19% of men.[2] The Rome diagnostic criteria for IBS requires the presence for at least 3 months of continuous or recurrent symptoms of abdominal pain or discomfort relieved with defecation, or associated with a change in frequency or consistency of stool. Subgroups of IBS exist with clearly varying responses to particular forms of therapy. The most common subdivision is based on altered bowel habit, with classification into constipation-predominant IBS (C-IBS), diarrhea-predominant IBS (D-IBS) and alternating IBS. Physiological differences between patients with C-IBS and D-IBS have been demonstrated.[3]

Currently, there is no drug that is effective for treatment of all forms and all symptoms of IBS. Treatment is based on the physician's understanding of the individual patient's symptom pattern and associated psychosocial factors.[4] Current recommendations include: anticholinergics for acute episodes of pain; supplemental dietary fiber for constipation; opiates for diarrhea; and, in patients with sustained pain or bloating, low doses of antidepressants such as tricyclic agents and selective serotonin reuptake inhibitors (SSRIs).[2] Recently, a 5-HT_3 receptor antagonist has been approved for treatment of female patients with D-IBS.

Treatment of patients with C-IBS is usually based on increased dietary fiber and bulking agents, exercise, habit training, and psychological intervention. However, often only partial

relief is obtained, and the majority of patients use non-bulking laxatives on a regular basis without medical supervision. Side effects of frequent use of laxatives include dependency and progressive tolerance, electrolyte imbalance, and for the anthraquinones, melanosis coli. Chronic use of non-bulking laxatives is very unsatisfactory therapy, and additional therapeutic measures are needed.

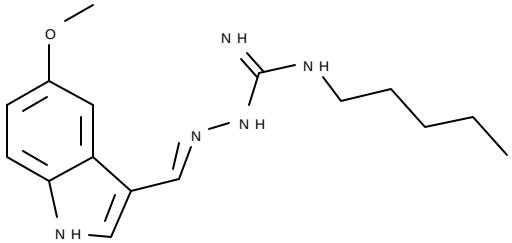
There is growing interest in and knowledge of the enteric nervous system as playing a pivotal role in the altered motility and visceral hypersensitivity of IBS. Rational pharmacotherapy for IBS may, therefore, be directed towards restoring normal motor activity and signal processing within the enteric nervous system.

Several neurotransmitters, including substance P, calcitonin gene-related peptide (CGRP) and serotonin (5-hydroxytryptamine, 5-HT) have been reported to be involved in the regulation of gut motility and visceral pain. The presence of 5-HT receptors throughout the human GI tract and the high amounts of serotonin in enterochromaffin cells, and also its presence in enteric nerves, suggest that 5-HT plays an important role in several physiological functions.[5] Recent investigations demonstrate the involvement of serotonin type-4 ($5\text{-}HT_4$)-receptors in gut motility, intestinal secretion, as well as visceral sensitivity.[6,7]

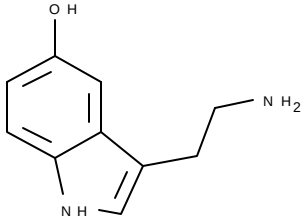
2 Pharmacological Class

Tegaserod is a potent partial agonist of serotonin type-4 (5-HT_4) receptors located in the GI tract.

Chemically designated as 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentyl-carbazimidamide, tegaserod is an aminoguanidine-indole derivative structurally similar to serotonin, as depicted below:



• $C_4H_4O_4$



Tegaserod

Serotonin (5-hydroxytryptamine)

It is structurally different from substituted benzamides, such as cisapride or metoclopramide. [8,9]

It also lacks relevant 5-HT_3 receptor and dopamine D_2 receptor blocking properties[10], as well as QT prolongation properties[11] typical of many substituted benzamide derivatives. Tegaserod binds with high affinity at human 5-HT_4 receptors.[12]

3 Preclinical Study Program

An extensive preclinical program consisting of pharmacodynamic, pharmacokinetic and safety/toxicological studies was completed for tegaserod.

3.1.1 Pharmacodynamics

The pharmacodynamic investigations in the GI tract demonstrated that tegaserod is a potent 5-HT_4 receptor partial agonist that exerts the following activities:

- modulation of both normal and altered motility throughout the GI tract
- modulation of intestinal secretion
- inhibition of visceral afferent responses upon colorectal distention.

Motility

Propulsion studies using isolated segments from Guinea pig colon demonstrated the promotile activity of tegaserod.[13] The compound potently and efficiently increased the propulsion velocity of artificial fecal pellets.

In vivo studies revealed tegaserod to exert promotile activity throughout the GI tract. It stimulated the gastric emptying rate in rats and dogs under normal and impaired conditions [10, 14, 15]. Mechanistic investigations confirmed the crucial involvement of 5-HT_4 receptors, consistent with its mode of action. Tegaserod stimulated small and large intestinal postprandial motility in a dose-dependent manner in dogs. Radioscintigraphy studies demonstrated a significant acceleration of colonic transit. Effects on impaired colonic motor activity and transit were examined in mice treated with the α_2 receptor agonist, lidamidine. Treatment with tegaserod offset the inhibitory effects of lidamidine.

Intestinal secretion

Tegaserod increased cyclic AMP (cAMP) and stimulated chloride and water secretion in crypt cells from rat distal colon at low nanomolar concentrations by activation of 5-HT_4 receptors.[16] These findings suggest a modulatory effect on intestinal secretion *in vivo.*

Visceral sensitivity

A study using decerebrate cats was performed to assess whether or not tegaserod, besides modulating intrinsic primary afferent neurons, had any effects on extrinsic afferents. The compound dose-dependently inhibited the firing rate of rectal afferents following rectal distension[7]. The effects were reversed by administration of a selective 5-HT_4 receptor antagonist, SB 203186. Tegaserod did not modify the pressure-volume relationship during rectal distension (barostat system). These data suggest a role of 5-HT_4 receptors in modulating visceral sensitivity without affecting compliance of the rectal wall. Data obtained in conscious rats (colorectal distension using a barostat system) confirmed the findings in decerebrate cats suggesting that tegaserod can exert antinociceptive activity during colorectal distension .[17]

3.1.2 Pharmacokinetics

The pharmacokinetics and metabolism of tegaserod were investigated in animal (rat, mouse, rabbit and dog) models and in vitro using human liver and intestinal slices as well as rat and human liver microsomes. In the rat, no major accumulation of tegaserod or its metabolites in organs was observed, with the possible exception of melanin-containing ocular membranes. This, however, does not seem to be of toxicological relevance as there were no toxicological findings in the pigmented dog eye. Furthermore, many drugs bind to eye melanin without being predictive of ocular toxicity. Brain penetration of both tegaserod and its metabolites was negligible in the rat. Oral treatment of pregnant rats and rabbits with tegaserod resulted in a low but measurable exposure of the embryos/fetuses to the parent drug (and metabolites, at least in rat). *In vitro* studies with human liver microsomes indicated a low potential of tegaserod to inhibit CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4. More potent effects were found for CYP1A2 and CYP2D6. These isoenzymes were further investigated in clinical studies, which however did not reveal clinically relevant drug-drug interactions (see page 12). The major circulating human metabolite, 5-methoxy-indole-3-carboxylic acid glucuronide, did not show any potential for inhibition of cytochrome P450 isoenzymes *in vitro*.

3.1.3 Safety/toxicology

The toxicological test species (mouse, rat, rabbit and dog) were systemically exposed to tegaserod to a much higher extent at their respective no observed adverse-effect level (NOAELs) than humans at the recommended therapeutic dose. The major human metabolites were observed in at least one of the test species. These data support the extrapolation of the animal toxicity data to humans.

In repeated dose toxicity studies, exaggerated pharmacological effects of tegaserod on the GI tract were observed in mice, rats and dogs without relevant target organ toxicity. The main metabolite has negligible affinity for 5-HT_4 receptors and is devoid of promotile activity in the dog. There was no evidence for effects on the immune system and therefore no specific immunotoxicity studies were performed. General toxicity, reproductive and carcinogenicity studies did not identify changes related to hormonal modifications.

There were no relevant effects on reproductive function, or embryofetal and neonatal development. However, tegaserod was detected in low amounts in fetuses and to a significant extent in milk. Therefore, caution should be taken when administered to a nursing woman.

Thorough *in vitro* and *in vivo* testing showed that tegaserod had no mutagenic and clastogenic potential, and did not induce DNA damage.

Doses used in the rat and mouse carcinogenicity studies satisfied (and exceeded) both maximum tolerated dose and exposure criteria as described in the ICH guidelines. The rat carcinogenicity study did not identify any carcinogenic potential. In mice, mucosal hyperplasia and adenocarcinoma were observed in the small intestine in respectively 12% and 7% of animals at the very high dose of 600 mg/kg p.o., which represents about 1800 times the human therapeutic dose (~ 70 times AUC). These effects were not observed at lower doses (60 and 200 mg/kg). The intestinal neoplastic changes are considered to be a result of an epigenetic effect. Tegaserod was shown to stimulate mucosal cell proliferation, possibly via

an increase in polyamine levels triggered by an inhibition of diamine oxydase activity by pentylaminoguanidine (PAG), a degradation product of tegaserod formed in the stomach. The adenocarcinomas appear thus as the consequence of an exaggerated and sustained effect on polyamine metabolism, with a clear threshold relationship. From the large margin of safety and from the postulated epigenetic pathogenesis, it can be concluded that adenocarcinomas observed in mice do not represent a relevant risk to human health.

Safety pharmacology studies indicated that tegaserod lacks relevant cardiovascular, renal, respiratory, central nervous system (CNS) and endocrine effects.

Together with the good clinical tolerance and efficacy, the data support the administration of tegaserod in patients with IBS, at the intended therapeutic dosage.

4 Rationale for the Use of Tegaserod in the Treatment of C-IBS

Due to limitations of currently available therapies, a significant clinical need remains for a safe, well-tolerated and effective drug to manage the abdominal pain and discomfort, bloating and constipation associated with C-IBS.

The mechanism of action of tegaserod is reflected in its stimulation of the peristaltic reflex [13, 18] intestinal secretion[16], as well as inhibition of visceral sensitivity[7,17] via activation of 5-HT_4 receptors in the gastrointestinal tract. Tegaserod acts as a partial agonist at neuronal 5-HT_4 receptors[18] triggering the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. In vivo studies showed that tegaserod enhanced basal motor activity and normalized impaired motility throughout the gastrointestinal tract.[14,15] In addition, studies demonstrated that tegaserod moderates visceral sensitivity during colorectal distention in animals.[7,17]

Based upon its pharmacodynamic activities exerted throughout the GI tract, tegaserod was selected for study in patients with C-IBS. It was hypothesized that by restoring and propagating motor activity, and moderating visceral sensitivity, tegaserod would be effective in relieving symptoms of IBS. Tegaserod was expected to have a dual effect in improving the altered bowel function and abdominal discomfort and pain that characterize C-IBS.

5 Clinical Pharmacology

The clinical pharmacology program for tegaserod included 25 studies, involving more than 540 healthy subjects, 13 patients with hepatic impairment and 11 patients with renal impairment. Studies were conducted to elucidate the dose-tolerability, absorption, distribution, metabolism and elimination, the effects of food and demography on the pharmacokinetics (PK) of tegaserod, the effects of possible co-administration with other drugs, and the PK of tegaserod in subjects with hepatic or renal impairment.

The final market formulation tablet was used in the Phase 3 efficacy trials. A similar tablet was used in late Phase 2 Clinical Pharmacology studies and two capsule formulations were used in Phase 1 and 2. The two tablet formulations are similar in terms of relative bioavailability and exceeded that of the Phase 1 and Phase 2 capsules by about 60% and 30%, respectively.

Pharmacokinetics

Tegaserod is rapidly absorbed following oral administration; peak plasma concentrations are reached after approximately 1 hour. The solubility of tegaserod is pH dependent. It is about 10-fold lower at pH 7.5 compared to pH 1 with a minimum solubility at pH 4.5 Below pH 3, tegaserod is rapidly degraded through hydrolytic breakdown. Absolute bioavailability is about 10 % under fasted conditions. Food reduced the systemic exposure to tegaserod by 40-65 % and C_{max} by approximately 20-40 %. Although there is a food effect on the PK of tegaserod, the relative timing of drug intake within 30 minutes before a meal is not critical. It is recommended to take tegaserod orally before a meal. Tegaserod is approximately 98 % bound to plasma proteins, primarily to α_1-acid glycoprotein. It is extensively distributed into tissues following intravenous administration with a volume of distribution at steady state of 368 ± 223 L. Tegaserod is metabolized mainly via two pathways. The first is a presystemic acid-catalyzed hydrolysis in the stomach followed by oxidation and conjugation, which produces the main metabolite of tegaserod, 5-methoxy-indole-3-carboxylic acid glucuronide. The main metabolite has negligible affinity for human 5-HT_4 receptors and is devoid of promotile activity in the dog. In man, systemic exposure to tegaserod was not statistically significantly altered at neutral gastric pH values. The second metabolic pathway of tegaserod degradation is direct glucuronidation, which leads to generation of three isomeric N-glucuronides. The plasma clearance of tegaserod is 77 ± 15 L/h, with an estimated terminal half-life ($t_{1/2}$) of 11 ± 5 h following intravenous administration. Approximately two-thirds of the orally administered dose of tegaserod is excreted unchanged in the feces, with the remaining one third excreted in the urine, primarily as the main metabolite.

The PK of tegaserod are dose proportional over the range 2 to 12 mg given twice daily for five days, with no relevant accumulation of tegaserod. The PK of tegaserod in IBS patients are comparable to those in healthy subjects. Inter-patient coefficients of variation in the PK parameters of tegaserod were comparable in C-IBS and D-IBS patients (40-50%) and healthy subjects.

Based on an analysis across several PK studies in healthy subjects (12 mg single dose, n=134), there is no effect of gender, age and ethnic origin on the PK of tegaserod when allowing for body weight as a covariate. Systemic concentrations of tegaserod are lower with

higher body weight. Given the variability in tegaserod PK and its wide safety margin, the data suggest that dose adjustment based on individual body weight is not needed.

Pharmacokinetics in special and other patient populations

Gender

Based on a special age/gender PK study, gender does not effect the PK of tegaserod in either the young or elderly population matched for height, weight, and gender. Then mean AUC_{0-} and C_{max} were 5% lower and 8% greater in young females compared to young malesl; for the elderly, in females mean AUC_{0-} and C_{max} were 2% and 30% greater than in males (for the latter see the effect of age below). Supportive information for no gender effect on the PK of tegaserod further is provided by pooled data from healthy subjects (12 mg dose, n=134) as discussed above.

Elderly

The PK of tegaserod are similar in elderly and young males, whereas the mean AUC_{0-} and C_{max} are 40 % and 22 % greater in elderly females than young females; young and elderly were matched for height, weight, and gender. No dosage adjustment is required in elderly patients.

Hepatic impairment

In subjects with mild (n=11) to moderate (n=1) hepatic impairment (liver cirrhosis, matched for age, gender, and weight withhealthy control subjects), mean AUC_{0-} was 43 % higher and C_{max} 18 % higher (not statistically significant). Both parameters showed positive correlations with dihydroxy bile acid concentrations. Given the variability in pharmacokinetic parameters in healthy subjects, and the wide safety margin of tegaserod, the data suggest that dose adjustment is not necessary in subjects with mild to moderate hepatic impairment. However, caution should be used in subjects with severe hepatic impairment.

Renal impairment

No change in the PK of tegaserod was observed in subjects with severe renal impairment requiring hemodialysis (matched for age, gender, and weight with healthy control subjects). No dosage adjustment is required in patients with any degree of renal impairment.

Drug-drug interactions

No clinically relevant drug-drug interactions have been identified in specific drug-drug interaction studies, or in concomitant use, during the clinical development of tegaserod. In vivo drug-drug interaction studies with theophylline (CYP1A2 prototype substrate), dextromethorphan (CYP2D6 prototype substrate), digoxin, warfarin, and oral contraceptives indicate no clinically relevant interactions. No dosage adjustment is required for either drug when tegaserod is co-administered with drugs metabolized by CYP1A2 (e.g. omeprazole, oestradiol, fluvoxamine) and CYP2D6 (e.g. fluoxetine, captopril, omeprazole), digoxin, warfarin, or oral contraceptives. Tegaserod is a substrate of P glycoprotein (Pgp), but its potential to inhibit Pgp is low. It could theoretically interact with other Pgp

substrates/inhibitors by competing for this transport protein. However, because of the relatively wide safety margin, the shallow dose-response relationship, and other factors limiting the maximum possible increase in systemic exposure to tegaserod, potential interactions with Pgp substrates/inhibitors are unlikely to have any clinically relevant effects. Although a substrate of Pgp, effects of tegaserod on systemic exposure to other substrates/inhibitors of this transport protein are unlikely because tegaserod is a weak inhibitor.

Pharmacodynamics in healthy subjects

Pharmacodynamic data in healthy subjects indicate that tegaserod has a maximum well-tolerated oral dose of 58 mg/day of the market formulation (tablet) and that higher doses may produce GI symptoms compatible with an exaggerated pharmacodynamic action. Furthermore the promotile action on the GI tract has been demonstrated at an oral dose of 6 mg b.i.d. and an i.v. dose of 0.6 mg b.i.d. Gastric emptying, small bowel transit, and colonic transit were enhanced to a clinically and statistically significant extent as compared to placebo. These effects were not statistically significant between the two tegaserod treatments. The effects on both stool consistency and frequency were more pronounced after the initial dose with the oral than i.v. route of administration.

Pharmacodynamics in patients

The PD properties of tegaserod have been evaluated primarily with respect to the effects on lower esophageal sphincter pressure (LESp), esophageal pH, rectal sensitivity and compliance, gastric emptying, small bowel transit, and colonic transit.

Study B252 explored the effects of tegaserod in patients with mild to moderate gastroesophageal reflux disorder. In this pilot study, tegaserod 1 mg/day and 4 mg/day decreased the post-prandial percentage of time that esophageal pH was <4 and the number of reflux episodes. The effects on esophageal acid exposure were not due to an increase in LESp, however a trend towards a decrease in lower esophageal sphincter relaxations was seen.

Study B304 was conducted to investigate the effect of tegaserod in comparison to placebo on rectal sensitivity measured by Barostat methodology inpatients with C-IBS. In this study, tegaserod at a dose of 4 mg/day did not have a significant effect on the perception of rectal distention in IBS patients with rectal hypersensitivity.

Study B357 was carried out to assess the effects of tegaserod on GI transit (gastric emptying, small bowel transit , colonic transit) in patients with C-IBS. Tegaserod 4 mg/day significantly accelerated small bowel transit without altering gastric emptying in patients with C-IBS. Results also suggested that tegaserod facilitates colonic transit.

6 Clinical Program Development

6.1 IBS Trial Methodology

Trial methodology for studies in functional GI disorders, and in particular IBS, has been extensively discussed in recent years in the scientific community. Nonetheless, to our knowledge, there are no regulatory guidelines available for clinical development of drugs in IBS. For this reason, the clinical development of tegaserod required numerous consultations with regulatory authorities and academia. Most of the scientific interactions with health authorities were initiated at the request of the sponsor to discuss methodological issues, especially related to the efficacy assessment.

A significant issue in designing and conducting clinical trials in IBS is the lack of consensus in the medical/scientific community on outcome measures. This relates both to the measurement of outcomes (i.e., how to define and record parameters that accurately assess patient's symptoms) as well as the specific symptom(s) to be assessed. At present, there is no outcome measure sufficiently well validated to be recommended for treatment trials in IBS.[19]

Outcomes for IBS trials have been assessed using ordinal scales (usually 5 or 7 items), visual analogue scales (VAS), and most recently, a binary scale (yes/no). At the September 1998 Vienna symposium on the Definition of a Responder in Clinical Trials for Functional Gastrointestinal Disorders, either a global assessment which integrates the patient's symptoms or a specific symptom measure (e.g., abdominal pain) were recommended as primary outcome measures.[20] No clear recommendations on measurement scales were given, although the difficulty of defining response on a VAS was noted. The most recent recommendation of the Rome Committee on the Design of Treatment Trials of Functional Gastrointestinal Disorders (Rome II) is that the primary outcome measure should "integrate" the symptoms of the disease. Because the symptoms that result in a diagnosis of IBS are varied and interact in complex ways, it was felt most appropriate that the primary outcome measure should allow the patient to "integrate the contribution of a disparate group of symptoms into a single global clinical rating."[19] In addition, it was recommended that a responder approach be used to assess outcome and that efficacy assessments should be made by the patient.

6.2 Tegaserod Phase 2 Program

Two double-blind Phase 2 studies (B251 and B202) evaluated four doses of tegaserod and placebo. A total of 894 patients were enrolled and a total of 670 patients with C-IBS were randomized in the two studies. Study B251 randomized 547 patients at 45 study sites in North America and Europe. Study B202 randomized 123 patients at 16 sites in Europe and Canada.

Study B251 was a dose-ranging study in which patients received one of four doses of tegaserod or placebo for 12 weeks. Study 202 utilized a dose-escalation design in which patients were randomized to receive tegaserod or placebo, and underwent dose-titration depending on efficacy response and tolerability.

A summary of the main features of the Phase 2 studies is given in Table 6-1.

Table 6-1. Main features of dose-finding studies

Study No.	Objective	Patients	Treatment Duration	Tegaserod dose/day	Population
B251	Dose-ranging	547	12 weeks	1, 4, 12, 24 mg/d, Placebo	C-IBS
B202	Dose-titration	123	20 weeks	1, 4, 12, 24 mg/d, Placebo	C-IBS

The Subject's Global Assessment (SGA) of overall GI symptoms was the primary efficacy assessment in both studies and was assessed by monthly patient interview:

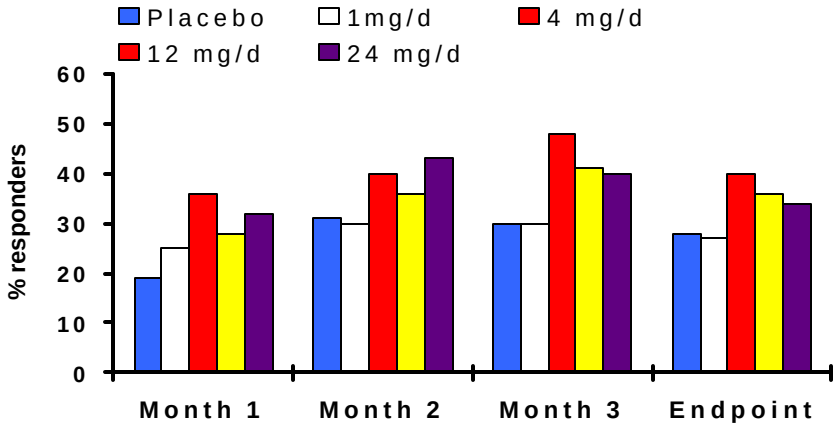
Patients responded to the following question:

"Compared to the way you usually felt during the 3 months before you entered the study, are your overall GI symptoms over the past 4 weeks: completely relieved, considerably relieved, somewhat relieved, unchanged or worse?"

Patients also responded to similar questions regarding abdominal discomfort/pain (SGA of abdominal discomfort/pain) and constipation (SGA of constipation). A patient with a score of "considerable" or "complete" relief at the study endpoint (the last month of treatment) was considered a responder.

In study B251, response rates on the SGA of overall GI symptoms were consistently higher in the tegaserod 4 mg/day, 12 mg/day and 24 mg/day treatment groups compared with placebo (Figure 6-1). Response rates on the SGA of abdominal/discomfort and SGA of constipation showed a similar pattern of response.

Figure 6-1. Study B251: Responder rate for SGA of overall GI symptoms by monthly interval and at endpoint



In the dose-titration study B202 (n=123), for all three SGA variables, there was a placebo response of approximately 30% which was sustained throughout the treatment period. After month 2 (optional dose-titration to 12 mg/day) and at endpoint, responder rates for tegaserod exceeded those of placebo by 10-17%.

Results of the dose-ranging study B251 indicated that tegaserod 4 mg/day was the most effective dose, while tegaserod 1 mg/day was similar to placebo. The dose-response was, however, relatively flat over the dose range 4 mg/day – 24 mg/day. Although not designed as a dose-response study, it was interesting to note that in study B202 the increase in response rates in the tegaserod group occurred during dose-titration from 4 mg/day to 12 mg/day.

Based on these results, tegaserod doses of 4 mg/day and 12 mg/day were chosen for further investigation in the Phase 3 program.

6.3 Tegaserod clinical program, regulatory guidelines and agreements

An End-of-Phase 2 meeting was held with representatives from the FDA. Results of two Phase 2 studies were reviewed, and proposed Phase 3 protocols were presented and discussed. Subsequent meetings were held primarily to discuss efficacy outcome measures. The design of the Phase 3 program was based on the results of these meetings and input received from expert consultants.

The primary efficacy measure used in the tegaserod Phase 2 trials was a 5-point ordinal scale, which captured the patient's relief of "overall GI symptoms." At the End-of-Phase-2 meeting, FDA recommended that abdominal pain should be the specific symptom assessment used as the primary efficacy variable, and suggested that improvement of 2 levels on a 5 level ordinal assessment scale define a responder for the Phase 3 program. Subsequently, an advisory panel of academic experts recommended that the sponsor use a VAS for the tegaserod trials. At a follow-up pre-Phase 3 meeting with the Agency to discuss clinically meaningful changes based on the VAS, FDA recommended use of a primary outcome measure that encompasses overall well-being, abdominal discomfort/pain, and altered bowel habit, and discouraged use of a VAS as a measurement tool for the primary outcome measure.

Faced with these disparate recommendations, the sponsor elected to adopt two primary outcome measures (see Section 6.5.2) for the Phase 3 clinical program:

- the Subject's Global Assessment (SGA) of relief, which encompassed overall well-being, abdominal pain/discomfort and altered bowel habit, measured with a 5-point ordinal scale (completely relieved, considerably relieved, somewhat relieved, unchanged, worse),
- the Subject's Global Assessment (SGA) of abdominal discomfort/pain, measured by a 100 mm VAS with verbal descriptors.

Although the same 5-point ordinal scale had been used in the Phase 2 trials to measure relief of overall GI symptoms, there were several important differences between the Phase 2 and Phase 3 relief efficacy variable. Unlike the Phase 2 relief efficacy variable, which focused on overall GI symptoms and was administered by monthly investigator interview of the patient, the Phase 3 SGA of relief efficacy variable included a component of overall well-being and was self-administered weekly in a patient diary.

Three Phase 3 trials, B351, B301 and B307, were planned using two primary efficacy variables, the SGA of relief and the SGA of abdominal discomfort/pain, to determine the efficacy of tegaserod in the treatment of patients with C-IBS.

6.3.1 Modification of analysis plan

Due to differing patient recruitment rates, results of study B351 became available before those of the other two trials. As a consequence of the findings in study B351, the sponsor, with FDA agreement, revised the definition of response and statistical analysis for the primary outcome measures in the remaining, rigorously blinded Phase 3 trials B301 and B307. Subsequently, prior to database lock, protocol amendments were submitted for the two studies. The rationale for the modification of the analysis plan is provided below in section 6.5.2.1.

6.4 Tegaserod Phase 3 program study design

Three large, multinational, parallel group, double-blind, placebo-controlled Phase 3 studies were conducted to evaluate the efficacy and safety of two doses of tegaserod. Each study consisted of a 4-week baseline period (with no placebo medication) and a 12-week double-blind treatment period. An overview of the major features of the adequate and well-controlled Phase 3 trials is given in Table 6-2.

Table 6-2. Summary of adequate and well-controlled trials

Study No.	Location	Design	N	Study duration	Treatment groups
B351	North America[1]	placebo-controlled, double-blind, parallel group	799	4-week baseline; 12-week treatment	tegaserod 4 mg/d; tegaserod 12 mg/d; placebo
B301	Europe, S Africa, US[2]	placebo-controlled, double-blind, parallel group	881	4-week baseline; 12-week treatment	tegaserod 4 mg/d; tegaserod 12 mg/d; placebo
B307	North America, Europe[3]	placebo-controlled, double-blind, parallel group, dose-titration	841[4]	4-week baseline; 12-week treatment	tegaserod 4 mg/d; tegaserod 4 to 12 mg/d (optional dose-titration); placebo

[1] 49 centers in US (47) and Canada (2); 97% of patients randomized from US.
[2] 92 centers in UK(18), Germany(15), Netherlands(12), Switzerland(9), US(9), Italy(7), Turkey(6), South Africa(6), Finland(4), Austria(3), Spain(2), Portugal(1); 90% of patients randomized from Europe.
[3] 67 centers in US (37), UK (10), France (8), Germany (5), Belgium (3), Canada (3), Spain (1); 66% of patients randomized from US.
[4] Excludes 4 randomized patients at one study center, which was terminated early due to concern with possible noncompliance with Good Clinical Practices.

A total of 3378 patients were enrolled and a total of 2521 patients with C-IBS were randomized in these studies.

Studies B351 and B301 had identical study designs: following the baseline period, eligible patients were randomized to receive either a fixed dose of tegaserod or placebo for 12 weeks.

Study B307 included a dose-titration in which patients were randomized to receive either a fixed dose of tegaserod 4 mg/day, a dose-titration regimen or placebo. Those patients randomized to dose-titration received tegaserod 4 mg/day and underwent dose titration at week 4 to 12 mg/day if the response on the SGA of relief was complete or considerable relief <50% of the time.

Selection criteria were similar for the 3 studies. Men and women $\geq$18 years ($\geq$12 years in Study B351) who satisfied Rome I criteria (abdominal discomfort/pain for at least 3 months relieved with a bowel movement or associated with a change in frequency or consistency of stool) for IBS were eligible to participate.[21]

In addition, patients were required to have at least 2 of 3 constipation symptoms (<3 bowel movements (BM)/week, hard/lumpy stools, straining with a BM, ≥25% of the time).

Patients underwent appropriate endoscopic or radiologic examinations to rule out other causes for the GI symptoms. Patients with significant diarrhea (loose stools and/or >3 BM/day with urgency, ≥25% of the time), diseases or conditions that affect bowel transit or other clinical evidence of significant disease, those using medications that interfere with the evaluations (i.e. narcotics analgesics, motility agents), and fertile women not using approved methods of contraception were excluded.

Following the 4-week baseline period in which patients recorded symptoms in a paper diary, patients who had at least mild abdominal discomfort/pain (as determined by a mean score $\geq$ 35 mm on a 100 mm VAS during the 4-week baseline period) were randomized. Given the fluctuation in the disease, patients were not required to meet specific bowel habit criteria during the baseline period and were not excluded based on their 4-week baseline bowel habit diary data.

Concomitant laxative use was not allowed during the study, unless requirements for rescue use were met (ie, no bowel movement for 4 consecutive days associated with bothersome abdominal discomfort/pain or bloating). Bulk-forming agents and use of tricyclic antidepressants and SSRIs were allowed if used in constant doses for at least one month prior to study entry and were to be taken in constant doses throughout the study.

Study medication was administered on a b.i.d. regimen and was to be taken within 30 minutes prior to meals. A double-dummy technique was used and patients took two tablets twice a day throughout the 12 week treatment period, including all 12 treatment weeks in study B307 (ie, patients took the same number of tablets before and after dose titration in study B307).

6.5 Phase 3 outcome measures and statistical methodology

6.5.1 Outcome measures evaluation in adequate and well-controlled studies

No outcome measure has been sufficiently validated to be recommended as the standard for treatment trials in IBS. At the time the Phase 3 tegaserod studies were initiated, both an overall integrative measure of symptoms and a specific measure of abdominal pain or discomfort were proposed as appropriate outcome measures. More recently, a consensus committee has recommended that the primary outcome measure should "integrate" the symptoms of the disease. Because the symptoms that result in a diagnosis of IBS are varied and interact in complex ways, it was felt most appropriate that the primary outcome measure should allow the patient to "integrate the contribution of a disparate group of symptoms into a global clinical rating".[19]

All efficacy assessments in the Phase 3 studies were recorded by the patients in paper diaries. The diaries were collected at the monthly visits. Three weekly self-assessments (SGA of relief, SGA of abdominal discomfort/pain, SGA of bowel habits) and 4 daily self-assessments (intensity of abdominal pain/discomfort, intensity of bloating, frequency of bowel movements and average stool consistency) were made by the patient throughout the 16-week study.

6.5.2 Primary efficacy variable(s)

SGA of relief efficacy variable

Patients responded weekly to the following question:

"Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?"

Possible answers were: completely relieved, considerably relieved, somewhat relieved, unchanged or worse.

The response definitions used in the Phase 3 trials are shown in Table 6-3.

Table 6-3. SGA of relief: response definition for primary efficacy variable

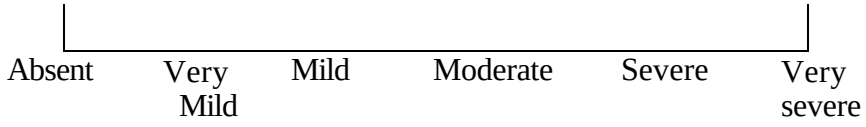
Study	Term	Response criteria
B351	***Original*** SGA of relief	complete or considerable relief $\geq$ 50% of the time at study endpoint[1]
B301 B307	SGA of relief	complete or considerable relief $\geq$ 50% of the time at study endpoint[1] OR complete or considerable or somewhat relief 100% of the time at study endpoint[1]

[1] Endpoint is defined as last 4 available weekly SGA scores, or all weekly SGA scores if fewer than 4 were available.

SGA of abdominal discomfort/pain

Efficacy was assessed weekly by a self-administered 100 mm VAS with verbal descriptors. Patients placed a vertical mark on the line in response to the following question:

"How much of a problem was your abdominal discomfort/pain over the last week?"



Patients were considered responders for the SGA of abdominal discomfort/pain if there was a reduction of $\geq$ 40% and an absolute reduction of $\geq$ 20 mm in mean VAS at endpoint compared with baseline. The SGA of abdominal discomfort/pain was a primary efficacy variable in study B351 and a secondary efficacy variable in studies B301 and B307.

- The ***original*** SGA of relief and the SGA of abdominal discomfort/pain were the two primary efficacy variables utilized in study B351.
- The SGA of relief was the single primary efficacy variable utilized in studies B301 and B307.

6.5.2.1 Rationale for modification of analysis plan

Study B351 was the first of the Phase 3 studies to be completed and analyzed. The results of study B351 showed a consistent pattern of improvement for tegaserod compared with placebo for the primary and secondary outcome measures (see Section 7.2.1 for study results). However, response rates in the tegaserod groups were not significantly different from placebo for the primary efficacy variables.

Response rates were relatively low in all treatment groups; in particular, the response rates in the placebo group (22%, ***original*** SGA of relief; 19%, SGA of abdominal discomfort/pain) were low compared to placebo response rates in Phase 2 tegaserod studies (30% - 34%) and available information in the literature for IBS trials (30% - 70%).[22] These findings suggested that the ***original*** response definition (complete or considerable relief $\geq$ 50% of the time at endpoint) for the SGA of relief and the response definition for the SGA of abdominal discomfort/pain were too stringent and, therefore, lacked sensitivity to detect a significant treatment difference.

To enhance the sensitivity of the SGA of relief efficacy variable, the "somewhat relieved" response was prospectively (ie, prior to database lock and unblinding) included in the responder definition for the SGA of relief in studies B301 and B307. Thus, the SGA of relief response definition was an attempt to capture not only significant relief in terms of magnitude of response ($\geq$ 50% complete/considerable relief) but also persistent positive relief (100% at least somewhat relief). Persistent improvement on a global endpoint that encompasses well being and integrates the patient's symptoms (abdominal discomfort/pain and altered bowel habit) was thought to represent an important clinical benefit to the patient.

The clinical relevance of the SGA of relief response definition was supported by the strong associations observed between a positive response on the SGA of relief and improvement in multiple secondary efficacy variables in study B351 (Table 6-4). Compared with nonresponders, responders reported clinically important and statistically significant greater improvement in days of significant abdominal discomfort and pain and average magnitude of the pain score, days of significant abdominal bloating and average magnitude of the bloating score, and altered bowel habit (reduction in days without a bowel movement and days with hard stools) . These strong associations were reproducible in studies B301 and B307, and so performed similarly on two continents. These results are comparable to published associations with an "adequate relief" endpoint.[23]

Table 6-4. Associations between SGA of relief response and other efficacy variables (B351)

Efficacy Variable	Responder		Nonresponder		P-value
	% change from baseline	N	% change from baseline	N	
VAS Score – SGA abd discomfort/pain	-47.5	314	-6.4	440	<0.0001
Days with significant pain	-35.4	314	9.2	445	<0.0001
Daily pain score	-40.5	314	-0.2	445	<0.0001
Days with significant bloating	-32.2	313	2.5	444	<0.0001
Daily bloating score	-38.1	313	-1.8	444	<0.0001
VAS Score – SGA bowel habit	-46.6	314	-6.0	440	<0.0001
Days with no bowel movement	-43.6	310	-15.1	439	<0.0001
Days with hard or very hard stool	-66.4	314	-22.7	444	<0.0001

Further, as shown in Table 6-5, the associations indicated that patients understood the scale and perceived somewhat relief as a positive response. Thus, a persistent (100% of the time), positive (at least somewhat) response seemed clinically appropriate to include as part of the response definition.

Table 6-5. Associations between SGA of relief response in last study week and other efficacy variables (B351)

Efficacy Variable	Response on SGA of relief				
	Complete	Considerable	Somewhat	Unchanged	Worse
(% change from baseline)	n = 48	n = 164	n = 222	n = 256	n = 61
VAS Score – SGA abd discomfort/pain	-78.6	-49.5	-22.6	-5.3	7.6
Days with significant pain	-73.0	-40.3	-7.4	18.1	2.5
Daily pain score	-71.8	-44.3	-15.6	3.6	8.0
Days with significant bloating	-61.2	-37.4	-7.4	6.1	2.7
Daily bloating score	-64.3	-41.2	-19.0	0.7	7.3
VAS Score – SGA bowel habit	-75.2	-49.5	-22.6	-3.4	6.2
Days with no bowel movement	-61.9	-46.1	-27.6	-10.2	-16.2
Days with hard or very hard stool	-71.2	-69.9	-50.3	-19.2	-2.9

A second change to the analysis plan for studies B301 and B307 was that the SGA of abdominal discomfort/pain was eliminated as a primary efficacy variable and retained as a secondary efficacy variable. Although not sensitive as a primary outcome measure, the SGA of abdominal discomfort/pain was thought to be useful to retain as a secondary efficacy variable to help assess effects on the specific symptom of abdominal discomfort and pain. The use of a global measure (ie, SGA of relief) for the primary efficacy variable in treatment trials of IBS is in accord with the recent recommendation of the Rome Committee on the Design of

Treatment Trials of Functional Gastrointestinal Disorders (Rome II).[19] Further, the SGA of relief efficacy variable already includes the consideration of abdominal discomfort/pain.

6.5.3 Secondary efficacy variables

The SGA of bowel habit was self-administered weekly using a VAS with descriptors (similar to SGA of abdominal discomfort/pain), in which patients responded to a question regarding their altered bowel habit.

Patients recorded on a daily basis the following:

- intensity of abdominal discomfort/pain (6-point scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe),
- intensity of abdominal bloating (6-point scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe),
- number of bowel movements, and
- average daily stool consistency (7-point scale: 1 = watery, 2 = loose, 3 = somewhat loose, 4 = neither loose nor hard, 5 = somewhat hard, 6 = hard, 7 = very hard)

Days with significant abdominal discomfort/pain and days with significant abdominal bloating were defined as $\geq$ mild (ie, $\geq$ 2 on a 6-point scale). The percent of days with hard/very hard stools was also calculated.

A tertiary variable was QOL scores, as measured by the IBS-QOL instrument, at randomization and at the end of the study.

6.5.4 Statistical methodology in adequate and well-controlled trials

Populations and endpoints:

The intent-to-treat (ITT) population, defined as all randomized patients, was the primary population.

Two types of endpoints were defined in the individual protocols:

Endpoint for SGA of scores: The last 4 available weekly SGA responses/scores in the post-randomization period, or all weekly responses/scores if fewer than 4 weekly scores were available.

Endpoint for daily diary scores: Daily diary scores obtained in the last 28 days of the post-randomization diary or all available daily scores obtained in the post-randomization diary, if fewer than 28 days were available.

Statistical methods:

All primary efficacy variables in the Phase 3 studies were dichotomous response variables based on SGA response criteria and adjustment rules.

Specifically, in study B351, two primary efficacy variables were prospectively defined and analyzed:

(1) ***Original*** SGA of relief (A responder for ***original*** SGA of relief was a patient who had considerable or complete relief $\geq$ 50% of the time at endpoint, and fulfilled the adjustment rules),

(2) SGA of abdominal discomfort/pain (A responder for SGA of abdominal discomfort/pain was a patient who had a reduction of $\geq$ 40% and an absolute reduction of $\geq$ 20 mm in mean VAS at endpoint compared with baseline, and fulfilled the adjustment rules).

In studies 301 and B307, a single primary efficacy variable was prospectively defined and analyzed:

(1) SGA of relief (A responder for SGA of relief was a patient who had considerable or complete relief $\geq$ 50% of the time at endpoint or had at least somewhat relief 100% of the time at endpoint, and fulfilled the adjustment rules).

The adjustment rules were:

- had at least one post-baseline SGA available,
- duration of exposure to study medication was ≥ 28 days,
- laxative intake was ≤ 5 days during the treatment period and no laxative intake during the last 4 weeks of treatment (adjustment for laxative intake was included as one of the adjustment criteria at the request of FDA).

As planned in the study protocol, each efficacy variable was analyzed by comparing the tegaserod groups versus the placebo group. The Mantel-Haenszel test stratified by center was performed. To ensure the overall two-sided type I error less than or equal to 0.05, Holm's multiple comparison procedure, adjusting for two primary variables and two tegaserod doses, was used in study B351, and Hochberg's multiple comparisons procedure, adjusting for two tegaserod doses, was used in studies B301 and B307.

Secondary efficacy variables, as specified in the protocol, were derived from the daily diary scores as well as from weekly SGAs. Each efficacy variable was analyzed by comparing the tegaserod groups versus the placebo group. The between-treatment comparisons for the dichotomous secondary variables were performed using the Mantel-Haenszel test stratified by center, while the numeric variables were analyzed by means of an Extended Mantel-Haenszel stratified by center. Holm's multiple comparison procedure, adjusting for two tegaserod comparisons, was used for each of the secondary efficacy variables in study B351. No multiple comparison procedure was used in the analysis for any of the secondary efficacy variables in studies B301 and B307.

Unadjusted responder rates

Provided as additional assessments, unadjusted responder rates at endpoint for the ***original*** SGA of relief, SGA of relief, and SGA of abdominal discomfort/pain were also calculated and similarly analyzed. The unadjusted responder rates were calculated by applying the corresponding SGA response criterion only. No adjustment rules were used in determining

the unadjusted responder status. Patients without any post-baseline SGAs were, therefore, not imputed as non-responders and were excluded from the unadjusted responder analysis.

Monthly responder rates for the ***original*** SGA of relief, SGA of relief, and SGA of abdominal discomfort/pain were summarized by treatment in each study. As the adjustment rules are endpoint specific, the monthly responder rates were unadjusted responder rates, i.e. the responders were determined by applying only the corresponding SGA response criterion to each monthly interval.

Mean scores for each of the daily diary variables were summarized weekly. The corresponding p-values comparing teagserod to placebo for change from baseline in mean score, are also presented for descriptive purposes.

7 Phase 3 efficacy analysis

A summary of the results of the individual Phase 3 studies (B351, B301 and B307) is provided, followed by sensitivity analyses, a comparative analysis of the efficacy variables, post-hoc analyses, responses in population subgroups and conclusions.

7.1 Phase 3 individual study results

Demographics and baseline variables

The demographics and baseline characteristics of the patients were similar among the 3 studies. As shown in Table 7-1, the patients in each study were largely female with a mean age of 43-46 years, had a mean duration of disease greater than 10 years and had similar baseline severity of disease. The percentage of black patients was highest in study B351. There were no relevant differences among treatment groups in demographics and baseline characteristics in the individual studies.

Table 7-1. Demographics and baseline characteristics in Phase 3 studies

Demographic/Baseline variable	B351 (N=799)	B301 (N=881)	B307 (N=841)
Age (yrs)	43 ± 13	46 ± 14	45 ± 13
Age ≥ 65 years	7%	11%	11%
Female	87%	83%	84%
Race: Caucasian	88%	98%	90%
Race: Black	9%	1%	6%
Race: Other	3%	1%	4%
Weight (kg)	71 ± 16	68 ± 14	70 ± 16
Duration of IBS (months)	175 ± 158	158 ± 147	166 ± 154
Abdominal discomfort/pain VAS score (mm)	63 ± 13	60 ± 13	61 ± 13
Bowel habit VAS score (mm)	64 ± 14	60 ± 14	62 ± 14
No. of days/28 days with significant[1] discomfort/pain	24 ± 6	24 ± 6	24 ± 6
No. of days/28 days with significant[1] bloating	25 ± 6	23 ± 7	24 ± 6
No. of days without bowel movements/28 days	13 ± 7	12 ± 7	11 ± 7
No. of bowel movements/28 days	23 ± 18	22 ± 16	25 ± 20
% of days[2] with hard/very hard stools	31 ± 29	28 ± 29	29 ± 28

Results expressed as mean ± SD
[1]defined as at least mild (daily score ≥ 2 on 6-point scale); [2] denominator is days with bowel movements

Laxative intake

As shown in Table 7-2, laxative use was similar among the treatment groups in each study.

Table 7-2. Number (and percentage of patients) with laxative use by study period

Study	Study period	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d
B351		n=267	n=265	n=267
	Baseline	83 (31.1)	76 (28.7)	74 (27.7)
	Treatment period	84 (31.5)	71 (26.8)	70 (26.2)
B301		n=288	n=299	n=294
	Baseline	83 (28.8)	91 (30.4)	89 (30.3)
	Treatment period	78 (27.1)	82 (27.4)	81 (27.6)
B307		n=284	n=282	n=275[1]
	Baseline	69 (24.3)	57 (20.2)	72 (26.2)[1]
	Treatment period	64 (22.5)	68 (24.1)	66 (24.0)[1]

[1]Study B307: 4-12 mg/d titration group

7.1.1 Study B351 Results

A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at two dose levels and placebo in subjects with constipation-predominant irritable bowel syndrome

A total of 1093 patients enrolled in the study of which 799 were randomized to tegaserod 4 mg/day, tegaserod 12 mg/day or placebo. Patient disposition by treatment for all randomized patients is displayed in Table 7-3.

The overall discontinuation rate from double-blind treatment was similar among the three treatment groups. The reasons for discontinuation were also generally similar among the groups, although more patients discontinued treatment due to adverse events in the 12 mg/day group (7%) compared to the 4 mg/day (3%) and placebo (3%) groups.

Table 7-3. Summary of patient disposition and primary reasons for discontinuations by treatment group (study B351)

	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d	Total
	N (%)	N (%)	N (%)	N (%)
Randomized into double-blind period (ITT population)	267	265	267	799
Completed the treatment period	214 (80.1%)	208 (78.5%)	211 (79.0%)	633 (79.2%)
Discontinued prematurely during the treatment period (total)	53 (19.9%)	57 (21.5%)	56 (21.0%)	166 (20.8%)
Adverse events	9 (3.4%)	9 (3.4%)	19 (7.1%)	37 (4.6%)
Abnormal laboratory values	0	1 (0.4%)	2 (0.7%)	3 (0.4%)
Unsatisfactory therapeutic effect	14 (5.2%)	10 (3.8%)	8 (3.0%)	32 (4.0%)
Subject withdrew consent	12 (4.5%)	15 (5.7%)	13 (4.9%)	40 (5.0%)
Lost to follow-up	13 (4.9%)	17 (6.4%)	8 (3.0%)	38 (4.8%)
Protocol violation	5 (1.9%)	5 (1.9%)	6 (2.2%)	16 (2.0%)

Efficacy results

The results for the two primary efficacy variables, the ***original*** SGA of relief and SGA of abdominal discomfort/pain at endpoint in the ITT population, are shown in Table 7-4. The responder rates for the tegaserod 4 mg/day and 12 mg/day groups were higher than for placebo for both efficacy variables. However, these differences did not reach statistical significance, according to the Holm's multiple comparison procedure.

Table 7-4. Responder rate for primary efficacy variables (*original* SGA of relief and SGA of abdominal discomfort/pain) at endpoint (study B351)

	Placebo (N=267)	Tegaserod 4 mg/d (N=265)	Tegaserod 12 mg/d (N=267)
***Original* SGA of relief**			
Responder rate[1] (n)	22.1% (59)	29.4% (78)	26.2% (70)
Treatment difference from placebo[2]		7.5%	4.1%
P-value[2]		0.050	0.266
SGA of abdominal discomfort/pain			
Responder rate[1] (n)	18.7% (50)	23.4% (62)	25.1%(67)
Treatment difference from placebo[2]		4.8%	6.4%
P-value[2]		0.185	0.075

[1] Adjusted for missing SGAs, treatment duration, laxative use.

[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint. Holm's multiple comparison procedure, adjusting for two primary variables and two tegaserod doses, was used to determine whether a treatment difference was statistically significant at the level of 0.05.

As previously discussed, the primary efficacy variables in this study established a high hurdle for response and may have lacked sensitivity to detect treatment differences. To explore this further, the SGA of relief definition of response (complete or considerable relief at least 50% of the time or at least somewhat relief 100% of the time at endpoint) was retrospectively analyzed. The results are summarized in Table 7-5. A positive dose-response was observed, with a 12% treatment difference for the tegaserod 12 mg/day group compared with placebo.

Table 7-5. Responder rate for SGA of relief at endpoint (study B351)

	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d
	N=267	N=265	N=267
Responder rate[1] (n)	33.3% (89)	38.9% (103)	45.7% (122)
Treatment difference from placebo[2]		6.0%	12.4%
P-value[2]		0.157	0.004*

[1] Adjusted for missing SGAs, treatment duration, laxative use.

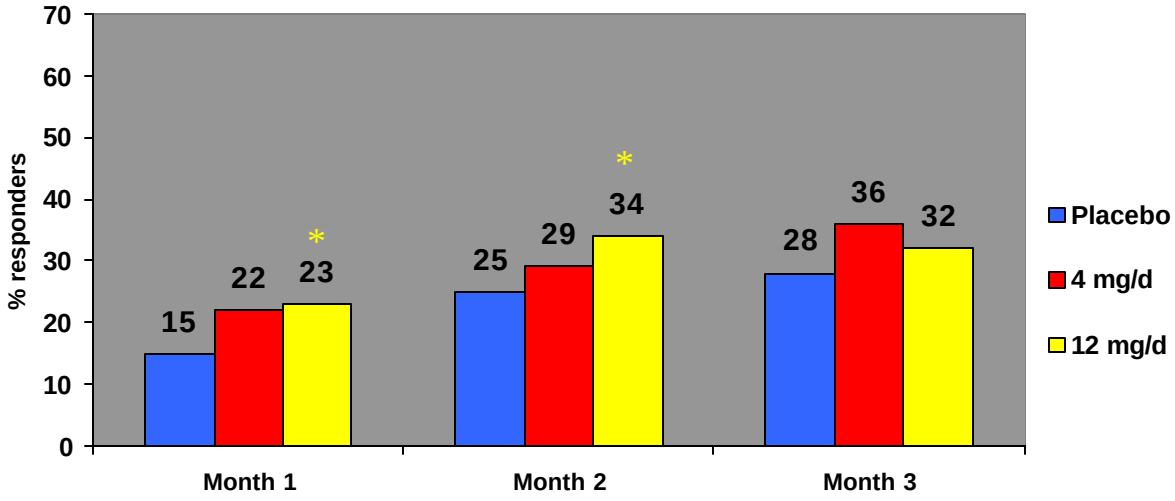
[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint. Holm's multiple comparison procedure, adjusting for two primary variables and two tegaserod doses, was used to determine whether a treatment difference was statistically significant at the level of 0.05.

* Indicates a statistically significant difference compared to placebo based on Hochberg's multiple comparison procedure, adjusting for two tegaserod doses, at the significance level of 0.05.

Monthly responder rates for both the ***original*** SGA of relief and the SGA of relief are shown in Figure 7-1. For the ***original*** SGA of relief (Figure 7-1A), both tegaserod groups had higher response rates compared with placebo at each monthly interval, but no clear dose-response profile was observed.

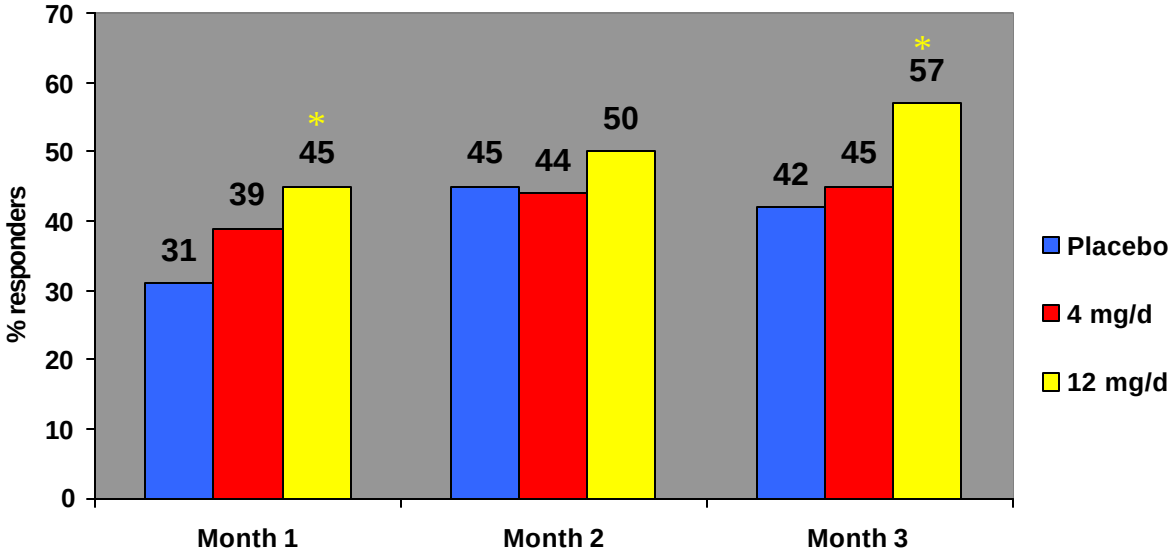
In contrast, for the SGA of relief (Figure 7-1B), a positive dose-response profile over time was observed with the tegaserod 12 mg/day group consistently having the highest response rates at each monthly interval.

Figure 7-1A. Unadjusted responder rate for *original* SGA of relief by monthly interval (study B351)



*p-value < 0.05 compared to placebo

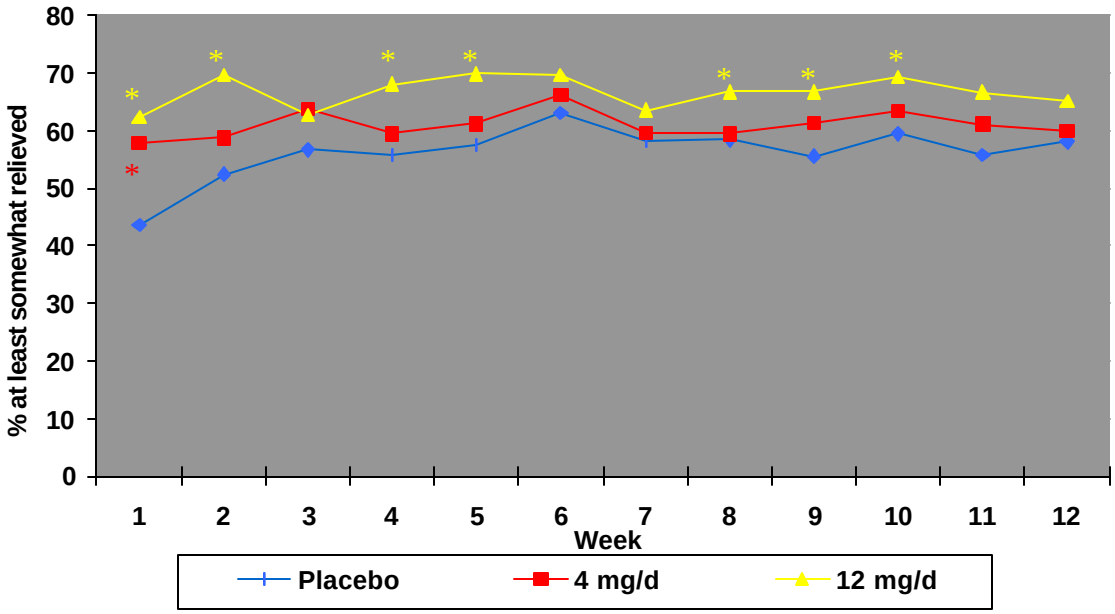
Figure 7-1B. Unadjusted responder rate for SGA of relief by monthly interval (study B351)



*p-value < 0.05 compared to placebo

Figure 7-2 presents the weekly percentage of patients with at least somewhat relief. A large placebo response was seen at week 1, which increased over the next several weeks and then stabilized. For the tegaserod 12 mg/day group, a significant difference from placebo was seen at week 1, and for most weeks in the study.

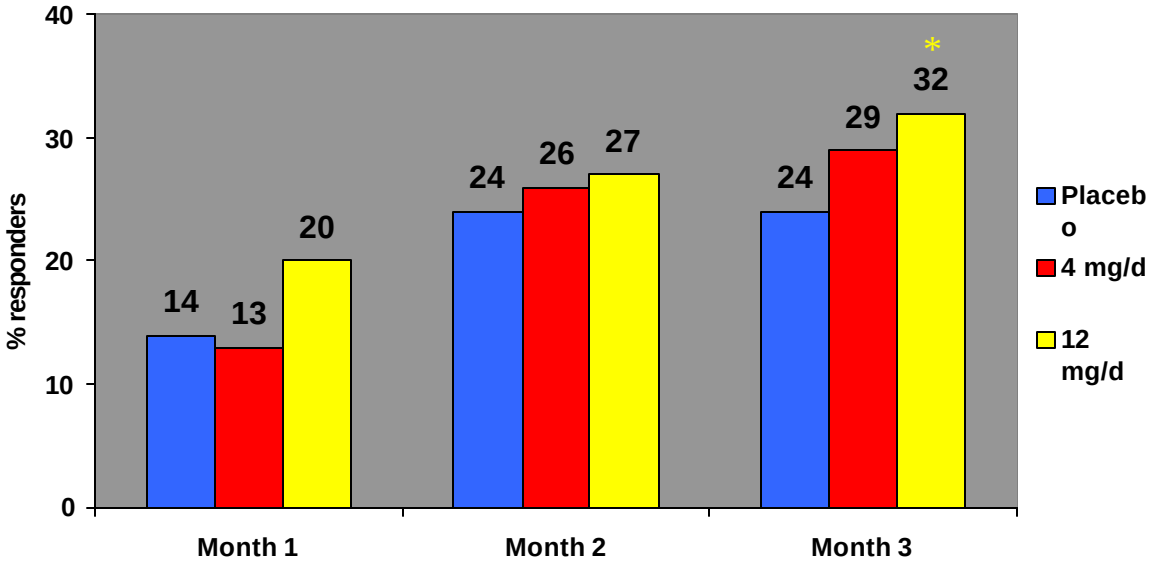
Figure 7-2. Weekly percentage of patients with at least somewhat relief (study B351)



*p<0.05 compared to placebo

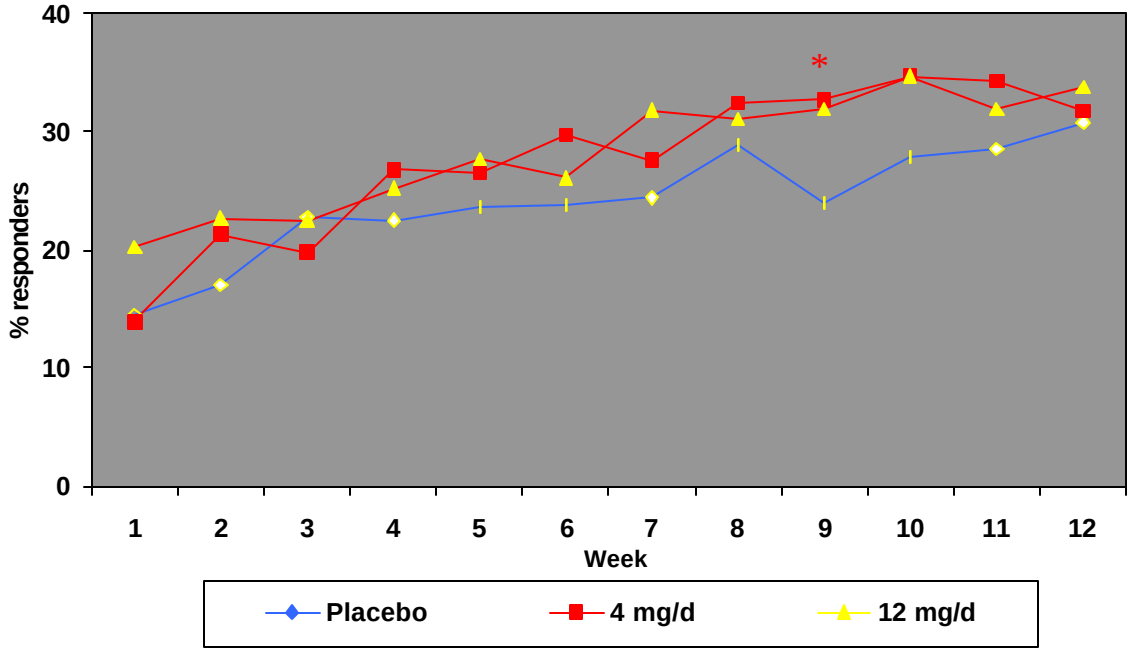
Monthly results for the SGA of abdominal discomfort/pain are shown in Figure 7-3A, with results shown weekly in Figure 7-3B. Response rates were higher in the tegaserod 12 mg/day group compared with placebo at all monthly timepoints and for many weekly timepoints.

Figure 7-3A. Unadjusted responder rate for SGA of abdominal discomfort/pain monthly interval (study B351)



*p< 0.05 compared to placebo

Figure 7-3B. SGA of abdominal discomfort/pain by week (study B351)



*p value <0.05 compared to placebo

Secondary efficacy variables

The results of between-treatment comparisons of the secondary efficacy variables at endpoint are shown in Table 7-6.

In addition to the SGA of abdominal discomfort/pain, abdominal discomfort/pain was also evaluated in the daily diary as days of significant abdominal discomfort/pain whereby significant was defined as at least mild. A similar evaluation was performed for days of significant abdominal bloating. The average decrease from baseline for both days of significant discomfort/pain and bloating was significantly greater in the tegaserod 12 mg/day group than in the placebo group; these differences were not statistically significant for the 4 mg/day group.

Effects of tegaserod on bowel habits were evaluated in several ways. Both tegaserod treatment groups had greater treatment responses than placebo patients with respect to the SGA of bowel habits, but differences from placebo did not reach statistical significance. Improvements in number of bowel movements, days without bowel movements and the percent of days with hard stools in the tegaserod 12 mg/day group were all significant at endpoint compared with the placebo group. For the 4 mg/day group, the increase in bowel movements was significant at endpoint compared with the placebo group.

Table 7-6. Summary of the between-treatment comparisons of secondary efficacy variables at endpoint (study B351, ITT population)

	Placebo	Tegaserod 4 mg/d	Difference from placebo[3]	Tegaserod 12 mg/d	Difference from placebo[3]
Mean percent change from baseline in number of days with significant[1] discomfort/pain	3.9%	-15.2% (p=0.147)	19.1%	-16.9% (p=0.017)*	20.8%
Mean percent change from baseline in number of days with significant[1] bloating	-5.6%	-14.9% (p=0.076)	9.3%	-15.1% (p=0.006)*	9.5%
Responder rate for SGA of bowel habit	20.2%	26.4% (p=0.082)	6.2%	24.7% (p=0.218)	4.5%
Mean percent change from baseline in number of days without bowel movements	-21.4%	-28.2% (p=0.053)	6.8%	-31.2% (p=0.002)*	9.8%
Mean percent change from baseline in number of bowel movements	44.8%	68.9% (p=0.003)*	24.1%	69.3% (p< 0.001)*	24.5%
Mean percent of days[2] with hard or very hard stool	18.9%	12.7% (p=0.068)	6.2%	11.3% (p=0.003)*	7.6%

[1] Defined as at least mild (daily score $\geq$ 2 on 6-point scale).

[2] Denominator is days with bowel movements.

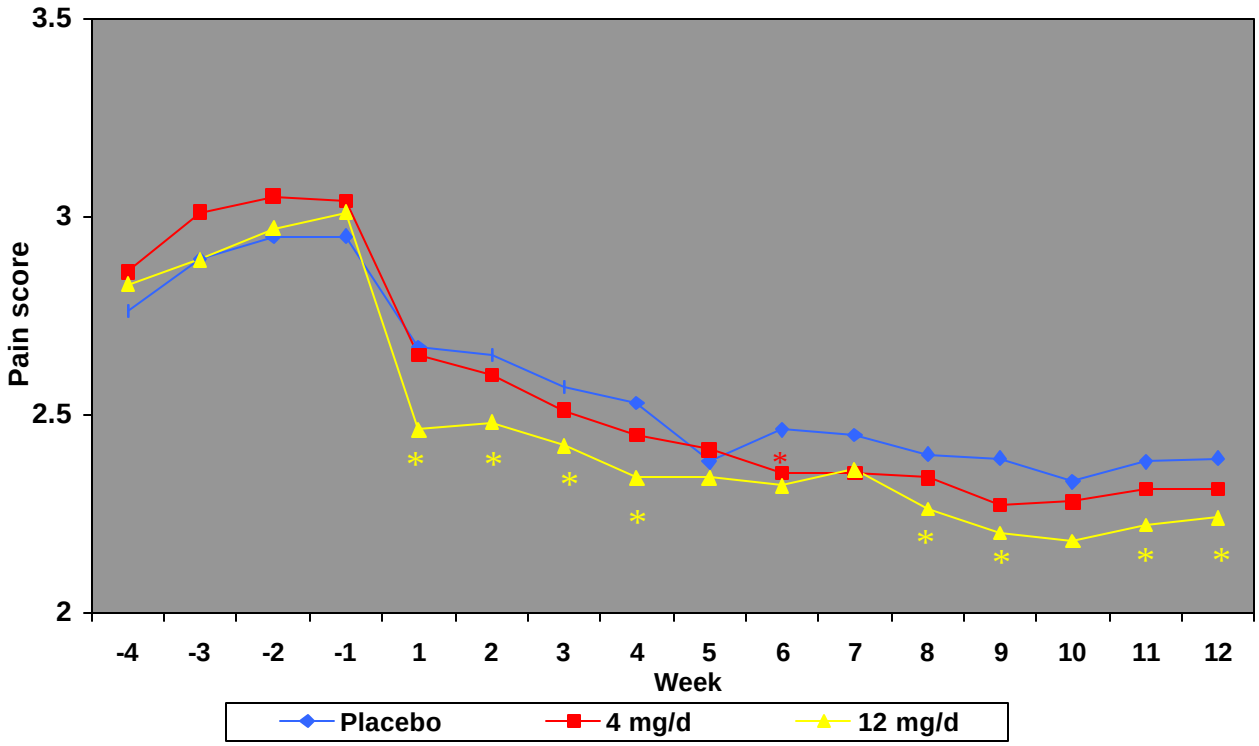
[3] Positive values in favor of tegaserod.

Note: P-values are the nominal p-values for the comparison between the tegaserod dose and placebo at endpoint.

* Indicates a statistically significant difference compared to placebo based on Holm's multiple comparison procedure, adjusting for two tegaserod doses, at the significance level of 0.05.

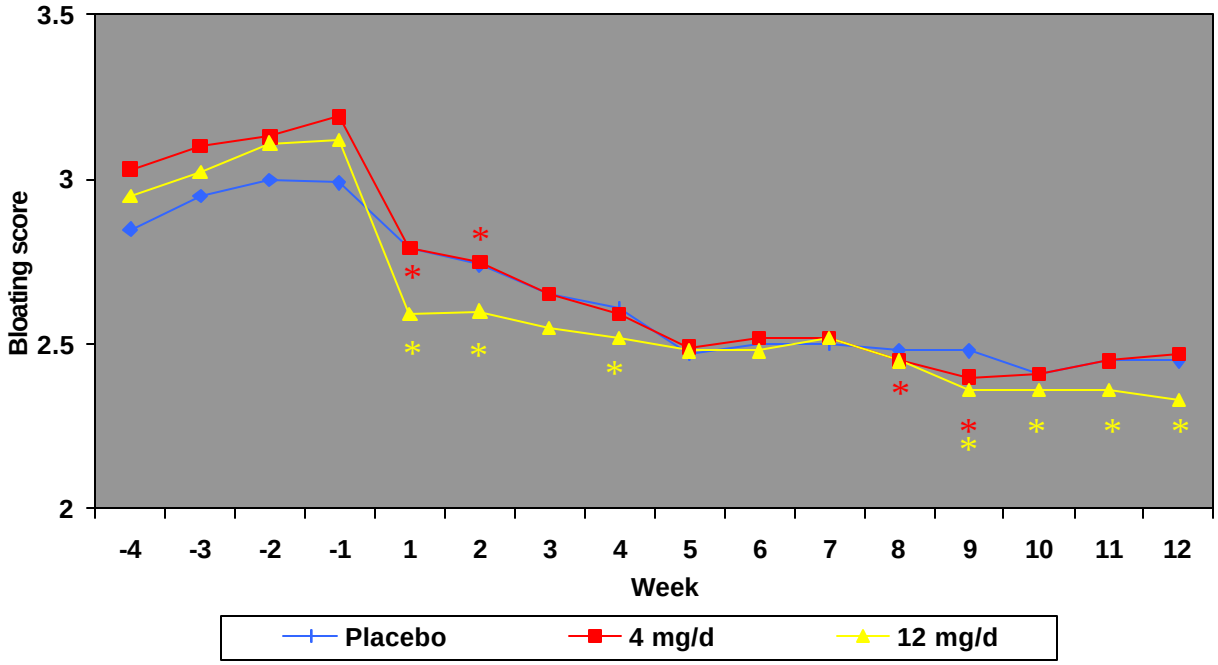
Weekly results for secondary efficacy variables are displayed in Figures 7-4 to 7-8. Mean daily abdominal discomfort/pain scores were consistently lower over the 12 weeks in the 12 mg/day group than in the placebo group, with an effect seen as early as Week 1 (Figure 7-4). Smaller differences from placebo in mean scores were seen for the 4 mg/day group. Mean daily bloating scores were lower for the 12 mg/day group than the placebo group during the first and third months of the study (Figure 7-5).

Figure 7-4. Mean daily abdominal pain scores by week (B351)



*p-value <0.05 compared to placebo (change from baseline)

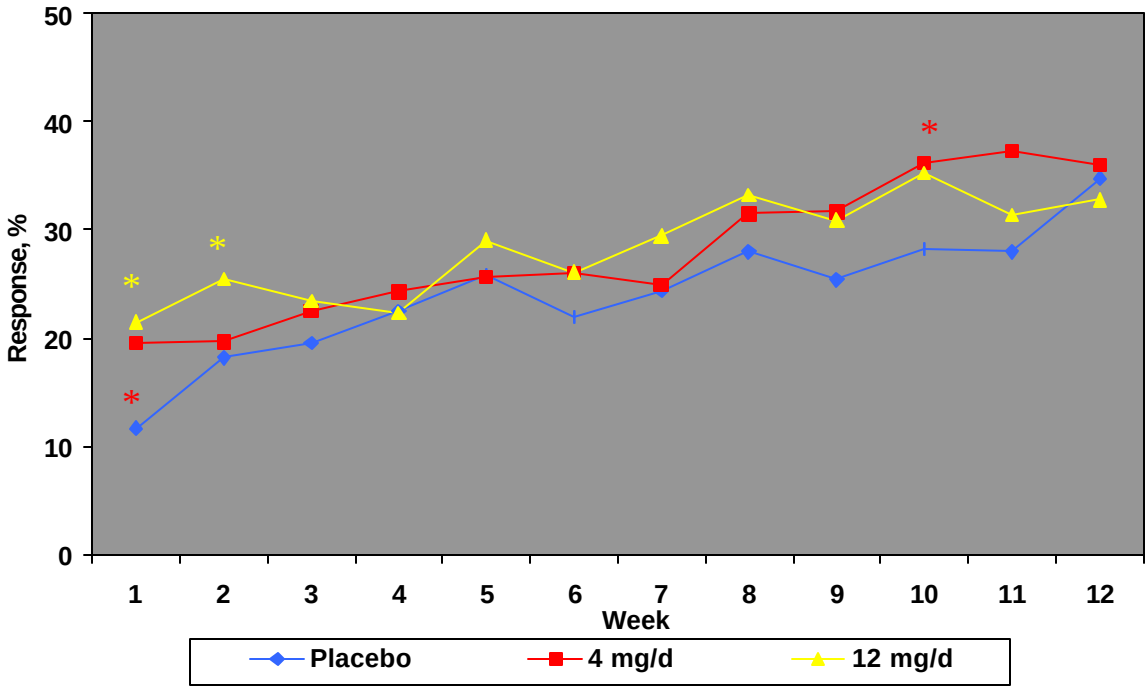
Figure 7-5. Mean daily bloating scores by week (B351)



*p-value compared to placebo (change from baseline)

Similar to the findings at endpoint, response rates on the SGA of bowel habits (Figure 7-6), were higher in the tegaserod groups compared with placebo, but not significantly so for most of the weeks in the study.

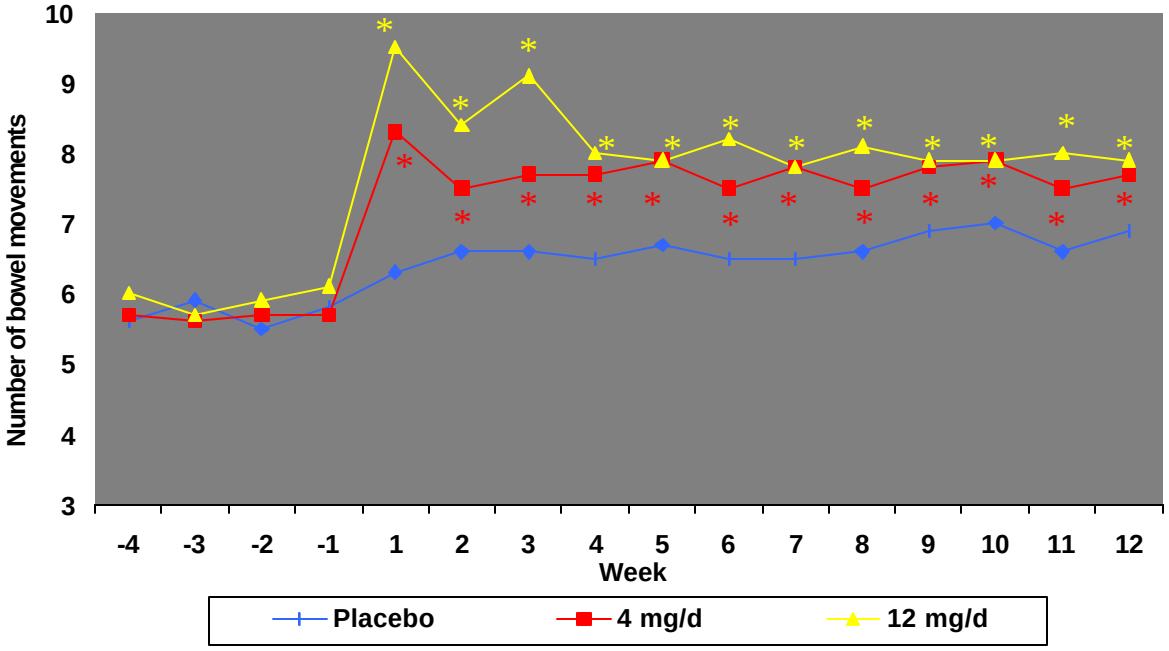
Figure 7-6. SGA of bowel habits by week (study B351)



*p < 0.05 compared to placebo

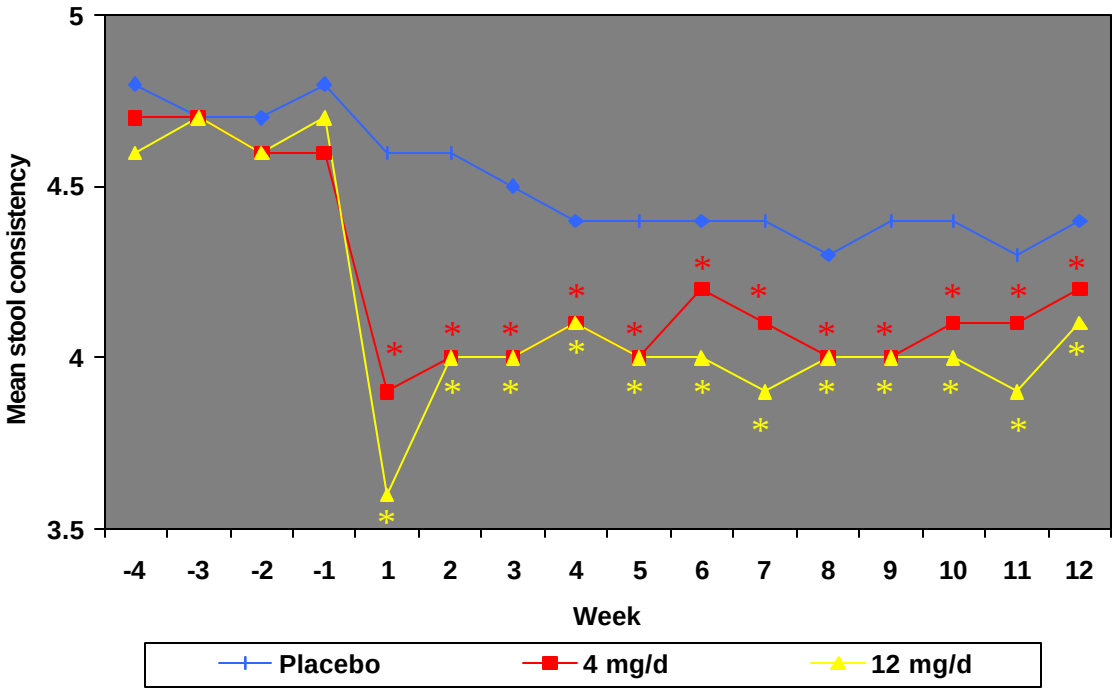
The effect of tegaserod on stool frequency is illustrated in Figure 7-7. A dose-dependent increase in the number of bowel movements was observed at Week 1, which decreased thereafter but remained significantly higher than placebo throughout the treatment period. The tegaserod groups had similar effects beyond Week 3. Results for stool consistency generally paralleled those for number of bowel movements (Figure 7-8). Tegaserod decreased stool consistency in a dose-dependent manner in Week 1, with similar effects for both tegaserod groups seen thereafter throughout the treatment period.

Figure 7-7. Weekly number of bowel movements (study B351)



*p-value <0.05 compared to placebo (change from baseline)

Figure 7-8. Weekly mean stool consistency (study B351)



*p-value <0.05 compared to placebo (change from baseline)
Scale: 1=watery, 2=loose, 3=somewhat loose, 4= neither loose nor hard, 5=somewhat hard, 6=hard, 7=very hard

Discussion/Conclusion, Study B351

Results for the primary efficacy variables, ***original*** SGA of relief and SGA of abdominal discomfort/pain, failed to reach statistical significance. However, a consistent pattern of improvement was observed in the tegaserod groups across the primary and secondary efficacy variables. Statistically significant improvements in the important symptoms of IBS, including abdominal discomfort/pain, abdominal bloating and bowel habits (stool frequency and stool consistency), were seen in the tegaserod 12 mg/day treatment group compared with placebo. The consistency of the data both in the weekly SGAs and the daily diary variables, as well as the effects at multiple timepoints, indicated that the data are robust. However, the low responder rates in the tegaserod groups and especially in the placebo group for the primary efficacy variables suggested that the definition of response was too stringent to detect true treatment effects. A retrospective analysis in which the responder definition for the SGA of relief was revised to include persistent somewhat relief was conducted; this analysis revealed clinically meaningful and statistically significant differences between the tegaserod 12 mg/day group and placebo. Since the revised definition of response was thought to be clinically meaningful and appeared to be a more sensitive measure of treatment effect, it was adopted as the primary efficacy variable in studies B301 and B307.

7.1.2 Study B301 Results

A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at two dose levels and placebo in subjects with constipation-predominant irritable bowel syndrome

A total of 1122 patients enrolled in the study of which 881 were randomized to tegaserod 4 mg/day, tegaserod 12 mg/day or placebo. Patient disposition by treatment for all randomized patients is displayed in Table 7-7.

More patients discontinued therapy in the tegaserod 4 mg/day group (18%) than in the tegaserod 12 mg/day group (14%) or placebo group (13%). The most common reason for discontinuation was adverse events, with a higher frequency in the 4 mg/day tegaserod group (9%) compared with the 12 mg/day (5%) and placebo (4%) groups. The number of discontinuations due to unsatisfactory therapeutic effect and other reasons was similarly distributed among the three treatment groups.

Table 7-7. Summary of patient disposition and primary reasons for discontinuations by treatment group (study B301)

	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d	Total
	N (%)	N (%)	N (%)	N (%)
Randomized into double-blind period (ITT population)	288	299	294	881
Completed the treatment period	251 (87.2%)	246 (82.3%)	254 (86.4%)	751 (85.2%)
Discontinued prematurely during the treatment period (total)	37 (12.8%)	53 (17.7%)	40 (13.6%)	130 (14.8%)
Adverse Events	12 (4.2%)	26 (8.7%)	15 (5.1%)	53 (6.0%)
Unsatisfactory therapeutic effect	8 (2.8%)	8 (2.7%)	7 (2.4%)	23 (2.6%)
Subject withdrew consent	7 (2.4%)	5 (1.7%)	10 (3.4%)	22 (2.5%)
Protocol Violation	4 (1.4%)	7 (2.3%)	5 (1.7%)	16 (1.8%)
Lost to follow-up	6 (2.1%)	5 (1.7%)	3 (1.0%)	14 (1.6%)
Patient's condition no longer required drug	0	1 (0.3%)	0	1 (0.1%)
Death	0	1 (0.3%)	0	1 (0.1%)

Efficacy results

The results for the primary efficacy variable, the SGA of relief at endpoint in the ITT population, are given in Table 7-8. Both tegaserod treatment groups had greater responder rates than the placebo group. The differences from placebo in responder rates for both the 4 mg/day and the 12 mg/day tegaserod group were statistically significant.

Table 7-8. Responder rate for SGA of relief at endpoint (study B301)

	Placebo (N=288)	Tegaserod 4 mg/d (N=299)	Tegaserod 12 mg/d (N=294)
Responder rate[1] (n)	30.2% (87)	38.8% (116)	38.4% (113)
Treatment difference from placebo[2]		9.1%	8.3%
P-value		0.018*	0.033*

[1] Adjusted for missing SGAs, treatment duration, laxative use.

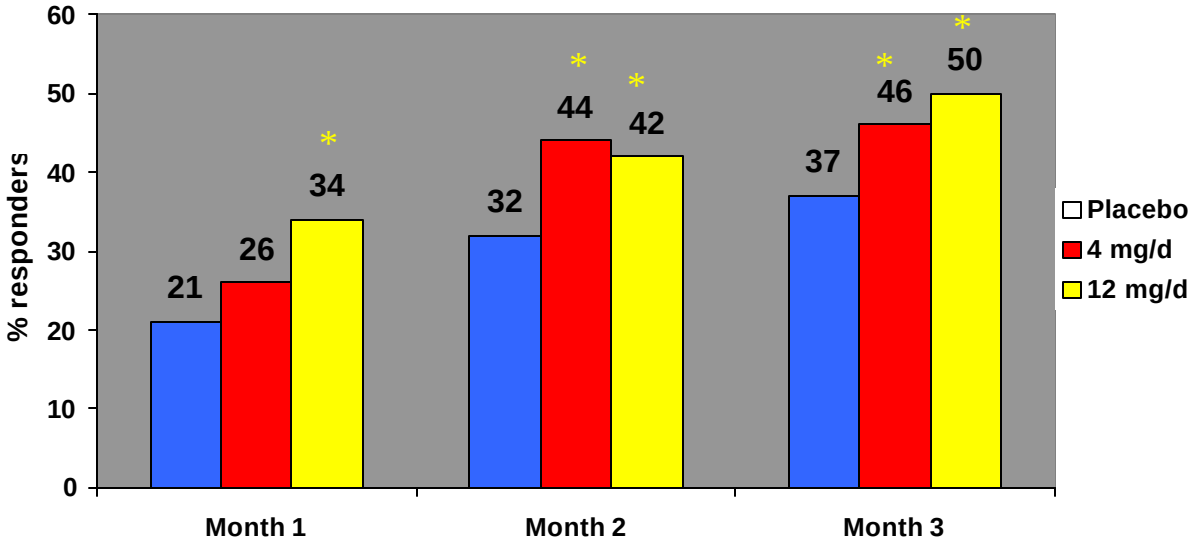
[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint.

* Indicates a statistically significant difference compared to placebo based on Hochberg's multiple comparison procedure, adjusting for two tegaserod doses, at the significance level of 0.05.

The adjustment rules reduced the responder rate to a greater extent in the tegaserod groups than in the placebo group. Despite the similarity in laxative use in the overall population (Table 7-2), it was the laxative adjustment rule (laxative use > 5 days during the treatment period and/or at least once during the last 4 weeks of treatment) that had the major impact on reducing the treatment differences in responder rates between the tegaserod groups and placebo. Responder rates not adjusted for laxatives (i.e., includes adjustment criteria for missing SGAs and treatment duration < 28 days but not the laxative adjustment) were 33.3%, 43.5% and 44.9% in the placebo, tegaserod 4 mg/day, and 12 mg/day groups, respectively with treatment differences from placebo of 10.2 for 4 mg/day and 11.6 for 12 mg/day. The impact of the adjustment rules on responder rates is discussed more fully in section 7.2 (Table 7-17).

Monthly responder rates are given in Figure 7-9. Responder rates for the 12 mg/day group were significantly higher for all months, and for the 4 mg/day group significantly higher for month 2 and month 3, than the corresponding placebo rates.

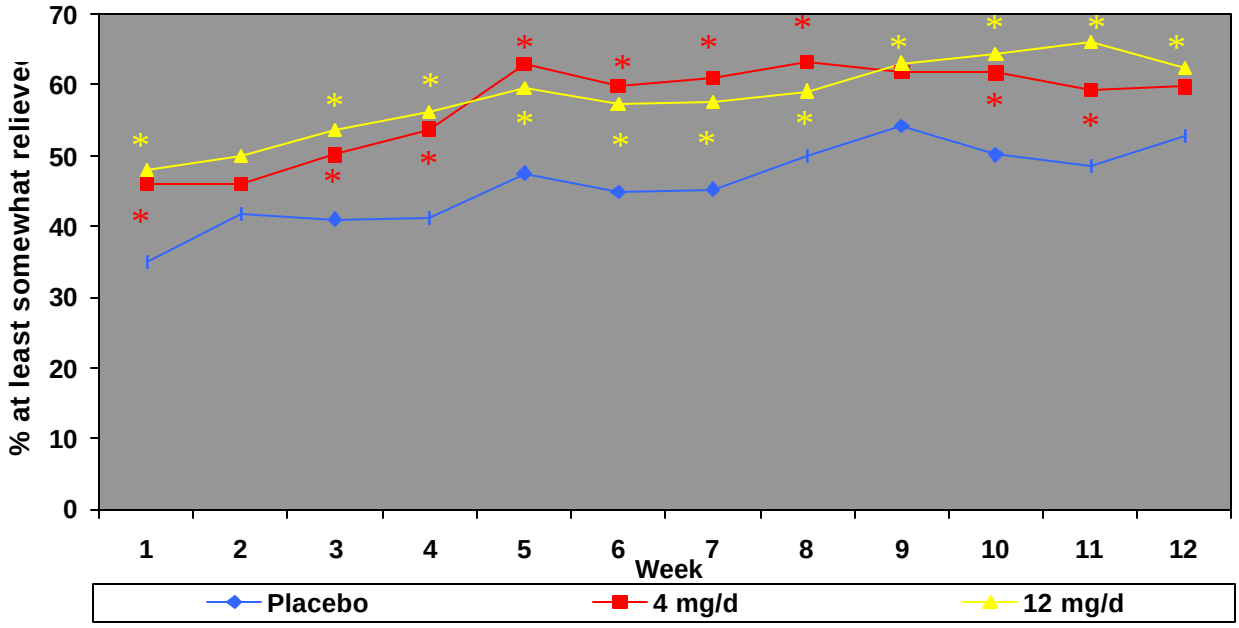
Figure 7-9. Unadjusted responder rate for SGA of relief by monthly interval (study B301)



*p-value <0.05 compared to placebo

Figure 7-10 displays the weekly percentage of patients who experienced at least somewhat relief. A treatment effect is seen at week 1, which persists for both tegaserod groups over the 12-week treatment period.

Figure 7-10. Weekly percentage of patients with at least somewhat relief (study B301, ITT population)



*p-value <0.05 compared to placebo

Responder rates for the ***original*** SGA of relief, considerably or completely relieved at least 50% of the time, at endpoint for the ITT population are shown below in Table 7-9.

Table 7-9. Responder rates for the *original* SGA of relief at endpoint (ITT population)

	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d
	N=288	N=299	N=294
Response rate[1] (n)	20.5% (59)	27.8% (83)	26.2% (77)
Treatment difference in responder rate[2]		7.6%	5.5%
P-value		0.028*	0.116

[1] Adjusted for missing SGAs, treatment duration, laxative use.

[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint.

* Indicates the nominal p-value < 0.05.

Secondary efficacy variables

As shown in Table 7-10, the responder rate for the SGA of abdominal discomfort/pain was higher than placebo for both tegaserod groups. This difference from placebo reached statistical significance for the tegaserod 12 mg/day treatment group.

Table 7-10. Responder rate for SGA of abdominal discomfort/pain at endpoint (study B301, ITT population)

	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d
	N = 287	N = 299	N = 294
Responder rate[1] (n)	22.6% (65)	29.8% (89)	29.9% (88)
Treatment difference in responder rate[2]		7.0%	7.3%
P-value		0.055	0.044*

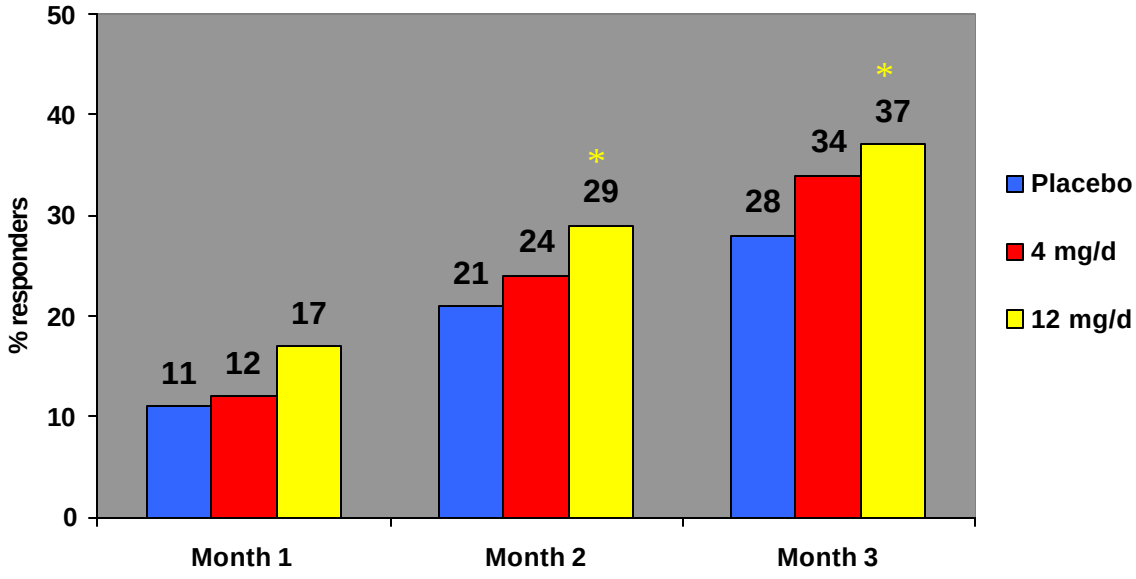
[1] Adjusted for missing SGAs, treatment duration, laxative use.

[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint.

* Indicates the nominal p-value < 0.05.

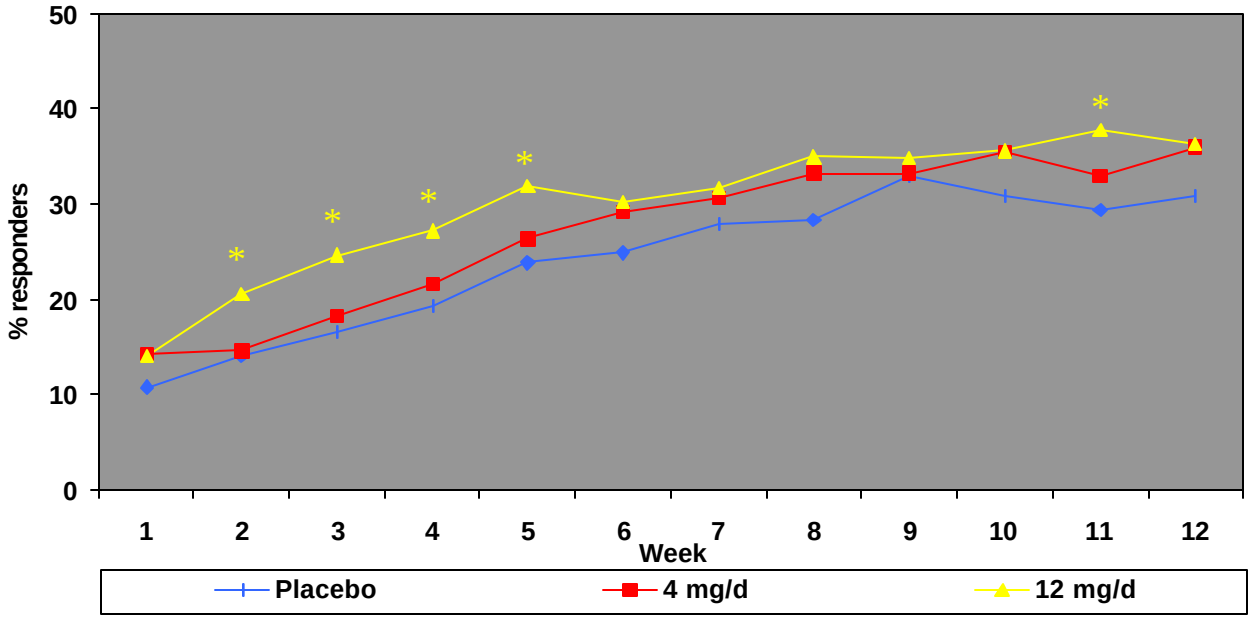
Monthly responder rates for the SGA of abdominal discomfort/pain are shown in Figure 7-11A, with the weekly responder rates shown in Figure 7-11B. Monthly responder rates were higher for the 12 mg/day group compared with placebo at all timepoints, with smaller treatment differences between the 4 mg/day and placebo groups. Weekly responder rates showed generally similar results.

Figure 7-11A. Unadjusted responder rate for SGA of abdominal discomfort/pain by monthly interval (study B301)



*p-value <0.05 compared to placebo

Figure 7-11B. SGA of abdominal discomfort/pain by week (study B301)



*p-value <0.05 compared to placebo

The results of between-treatment comparisons for the other secondary efficacy variables at endpoint are shown in Table 7-11. Although the average decrease from baseline for both days of significant discomfort/pain and bloating was greater in the tegaserod groups compared with

placebo, these differences were not statistically significant. For both tegaserod treatment groups, there was a higher treatment response than placebo in regard to the SGA of bowel habit, but the differences to placebo did not reach statistical significance. Number of bowel movements and days without bowel movements both significantly improved in the tegaserod groups compared with placebo.

Table 7-11. Summary of the between-treatment comparisons of secondary efficacy variables at endpoint (study B301)

	Placebo	Tegaserod 4 mg/d		Tegaserod 12 mg/d	
			Difference from placebo[3]		Difference from placebo[3]
Mean percent change from baseline in number of days with significant[1] discomfort/pain	-10.4%	-18.9% (p=0.180)	8.5%	-18.6% (p=0.116)	8.2%
Mean percent change from baseline in number of days with significant[1] bloating	4.0%	-10.7% (p=0.128)	14.7%	-8.3% (p=0.485)	12.3%
Responder rate for SGA of bowel habit	22.6%	28.8% (p=0.096)	6.2%	26.2% (p=0.337)	3.6%
Mean percent change from baseline in number of days without bowel movements	-19.2%	-30.6% (p=0.012)*	11.4%	-22.4% (p=0.013)*	3.2%
Mean percent change from baseline in number of bowel movements	42.0%	59.2% (p= 0.001)*	17.2%	54.6% (p= 0.009)*	12.6%
Mean percent of days[2] with hard or very hard stool	15.0%	12.8% (p=0.084)	2.2%	13.7% (p=0.803)	1.3%

[1] Defined as at least mild (daily score $\geq$ 2 on 6-point scale).

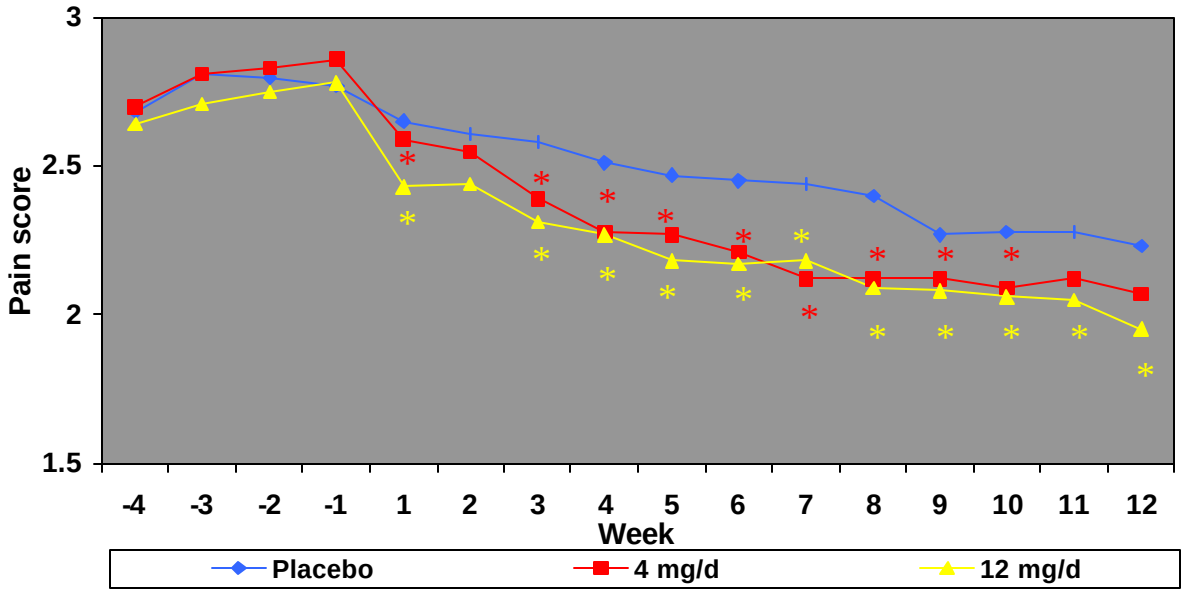
[2] Denominator is days with bowel movements.

[3] Positive values in favor of tegaserod.

Note: p-value (nominal p-value) refers to the comparison between the tegaserod dose and placebo at endpoint.
* Indicates the nominal p-value < 0.05.

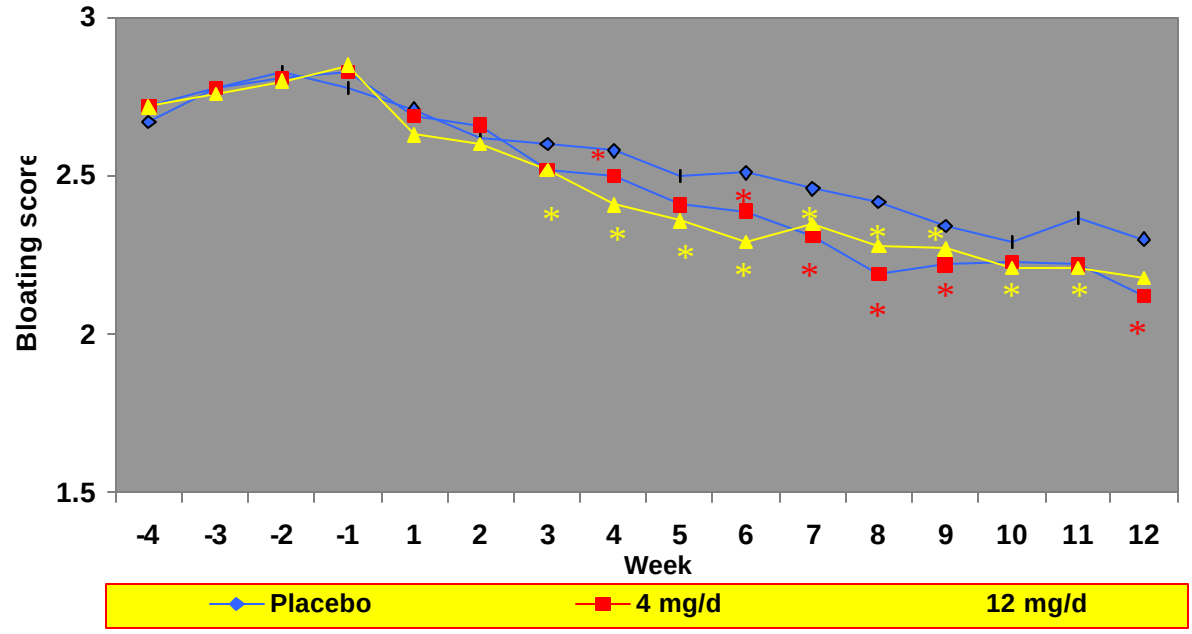
Weekly displays of the secondary efficacy variables are presented below. Mean daily abdominal discomfort/pain scores were lower in the tegaserod groups than in the placebo group throughout the 12 weeks (Figure 7-12). Similarly, bloating scores were lower in the tegaserod groups than in placebo (Figure 7-13).

Figure 7-12. Mean daily abdominal pain scores by week (study B301)



*p-value <0.05 compared to placebo (change from baseline)

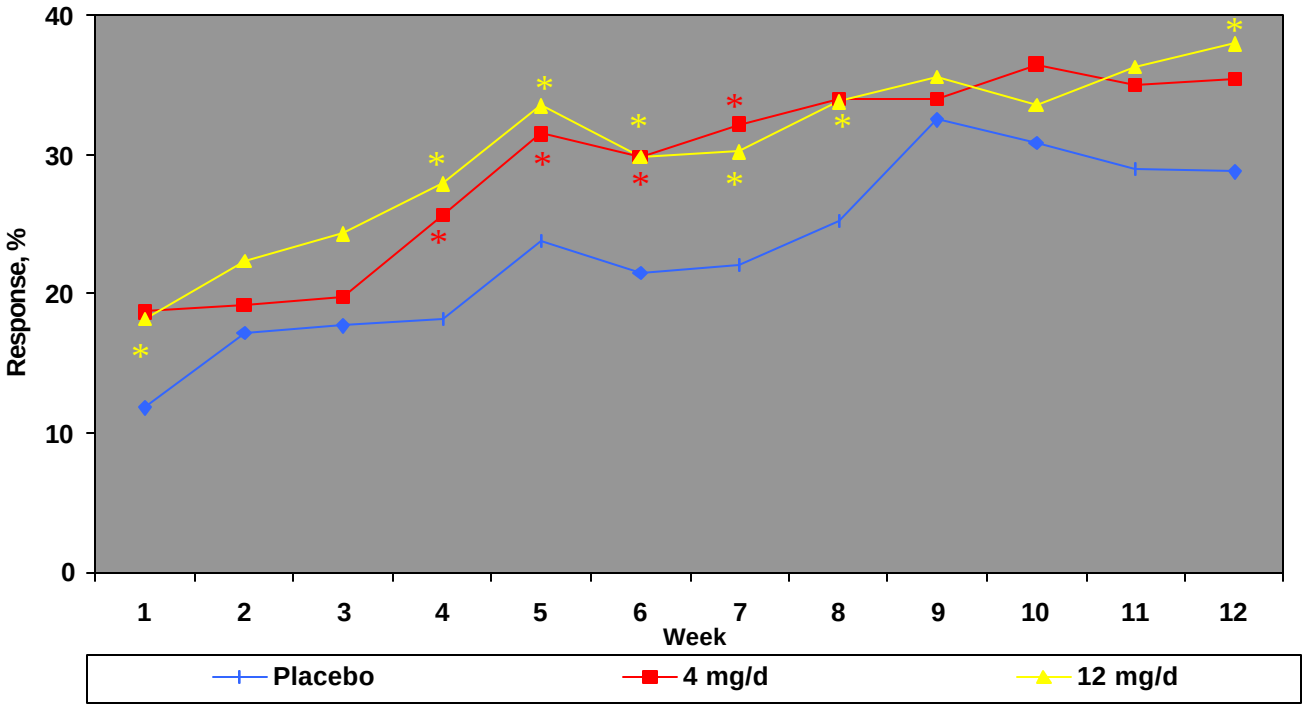
Figure 7-13. Mean daily bloating scores by week (study B301)



*p-value <0.05 compared to placebo (change from baseline)

Weekly response rates for the SGA of bowel habits were also higher in the tegaserod groups than in the placebo group (Figure 7-14).

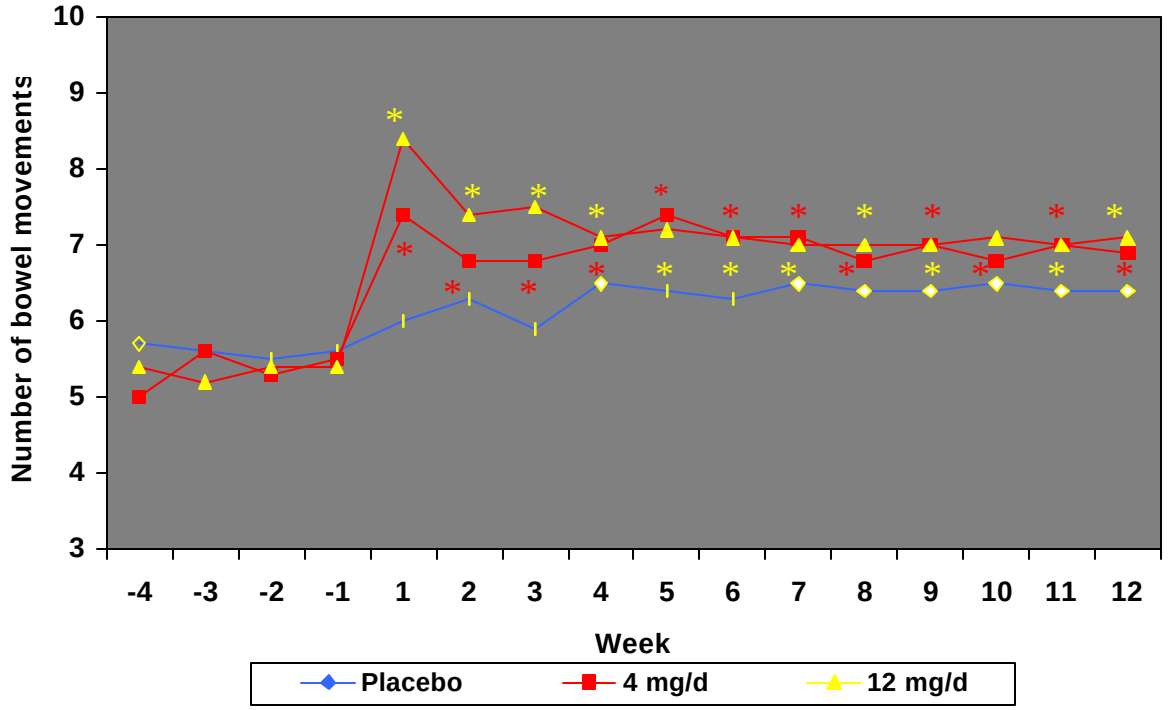
Figure 7-14. SGA of bowel habit by week (study B301)



*p-value <0.05 compared to placebo

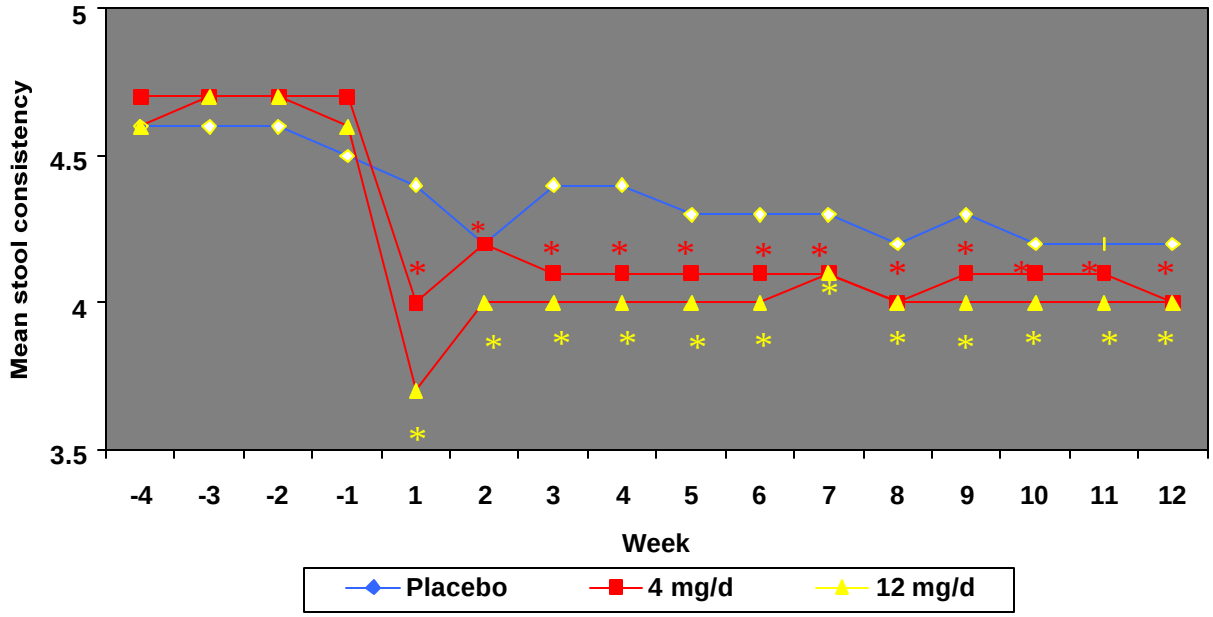
The effects of tegaserod on the number of bowel movements and on stool consistency are also illustrated in Figures 7-15 and 7-16. A dose-dependent increase in bowel movements and decrease in stool consistency occurred during Week 1, which remained different from placebo for the 12-week treatment period.

Figure 7-15. Weekly number of bowel movements (study B301)



*p-value <0.05 compared to placebo (change from baseline)

Figure 7-16. Weekly mean stool consistency (study B301)



*p-value <0.05 compared to placebo (change from baseline)
Scale: 1=watery, 2=loose, 3=somewhat loose, 4= neither loose nor hard, 5=somewhat hard, 6=hard, 7=very hard

Discussion/Conclusion, Study B301

Compared with placebo, both the tegaserod 4 mg/day and 12 mg/day groups had statistically significant higher response rates on the SGA of relief at endpoint, the primary efficacy variable in this study. This effect was observed in the tegaserod 12 mg/day group at the end of the first month and was sustained over the 3 month treatment period; higher response rates than placebo were seen at Month 1 ($p<0.01$), Month 2 ($p<0.05$) and at Month 3 ($p<0.01$). For the tegaserod 4 mg/day group, higher response rates than placebo were observed at Month 2 ($p<0.01$) and at Month 3 ($p<0.05$).

Response rates on SGA of relief were adjusted for several factors, including laxative intake. As overall laxative intake (both number of patients and number of days) was similar among treatment groups and laxatives are not clearly an escape medication for the abdominal pain of IBS, it maybe reasonable to use the non-laxative adjusted treatment difference to estimate the magnitude of effect. These differences, compared to placebo, were 12% for tegaserod 12 mg/day and 10% for tegaserod 4 mg/day (see Section 7.2, Table 7-17 Impact of adjustment criteria on responder rate for SGA of relief in individual studies).

For the daily diary variables days with significant abdominal discomfort/pain and days with significant bloating, trends in favor of tegaserod were observed but these results were not statistically significant at endpoint. Tegaserod 4 mg/day and 12 mg/day increased the number of bowel movements and decreased the number of days without bowel movements.

In summary, in this study, tegaserod 12 mg/day was effective in relieving overall IBS symptoms, abdominal discomfort and pain, and in improving stool frequency and stool consistency. Even though reaching statistical significance for the primary efficacy variable, tegaserod 4 mg/day showed a less consistent effect across variables and time.

7.1.3 Study B307 Results

A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at two dose regimens and placebo in subjects with constipation-predominant irritable bowel syndrome

A total of 1163 patients enrolled in the study of which 845 were randomized to tegaserod 4 mg/day, tegaserod 4-12 mg/day (titration group) or placebo. Patient disposition by treatment for all randomized patients is displayed in Table 7-12.

More patients discontinued double-blind treatment in the tegaserod 4 mg/day group (23%) than in the tegaserod 4-12 mg/day (17%) and placebo (19%) groups, although withdrawals due to adverse events and lack of efficacy were similar among the treatment groups.

Table 7-12. Summary of patient disposition and primary reasons for discontinuations by treatment group (study B307)

	Placebo N (%)	Tegaserod 4 mg/d N (%)	Tegaserod 4-12 mg/d N (%)	Total N (%)
Randomized into double-blind period[1]	285	283	277	845[1]
ITT population	284 (99.6%)	282 (99.6%)	275 (99.3%)	841 (99.5%)
Completed the double period	232 (81.4%)	217 (76.7%)	231 (83.4%)	680 (80.5%)
Discontinued prematurely during the treatment period (total)	53 (18.6%)	66 (23.3%)	46 (16.6%)	165 (19.5%)
Adverse Events	22 (7.7%)	25 (8.8%)	21 (7.6%)	68 (8.0%)
Abnormal laboratory values	0	0	2 (0.7%)	2 (0.2%)
Unsatisfactory therapeutic effect	4 (1.4%)	5 (1.8%)	3 (1.1%)	12 (1.4%)
Subject withdrew consent	13 (4.6%)	18 (6.4%)	10 (3.6%)	41 (4.9%)
Protocol violation	0	5 (1.8%)	1 (0.4%)	6 (0.7%)
Lost to follow-up	12 (4.2%)	11 (3.9%)	6 (2.2%)	29 (3.4%)
Administrative	2 (0.7%)	2 (0.7%)	3 (1.1%)	7 (0.8%)

[1] A total of 845 patients were randomized. One study center was terminated early due to concern with possible noncompliance with Good Clinical Practices. At the time of termination, 4 patients were randomized but had not completed the study; these four patients were not included in the ITT population.

Efficacy results

The responder rates for the primary efficacy variable, the SGA of relief at endpoint in the ITT population, are given in Table 7-13. The responder rate for the tegaserod 4-12 mg/day group was greater compared with placebo, but this difference was not statistically significant. The responder rates for the tegaserod 4 mg/day and placebo groups were similar.

Table 7-13. Responder rate for SGA of relief at endpoint (study B307)

	Placebo (N=284)	Tegaserod 4 mg/d (N=282)	Tegaserod 4-12 mg/d (N=275)
Responder rate[1] (n)	37.0% (105)	38.3% (108)	42.2% (116)
Treatment difference from placebo[2]		0.8%	6.0%
P-value[2]		0.837	0.142

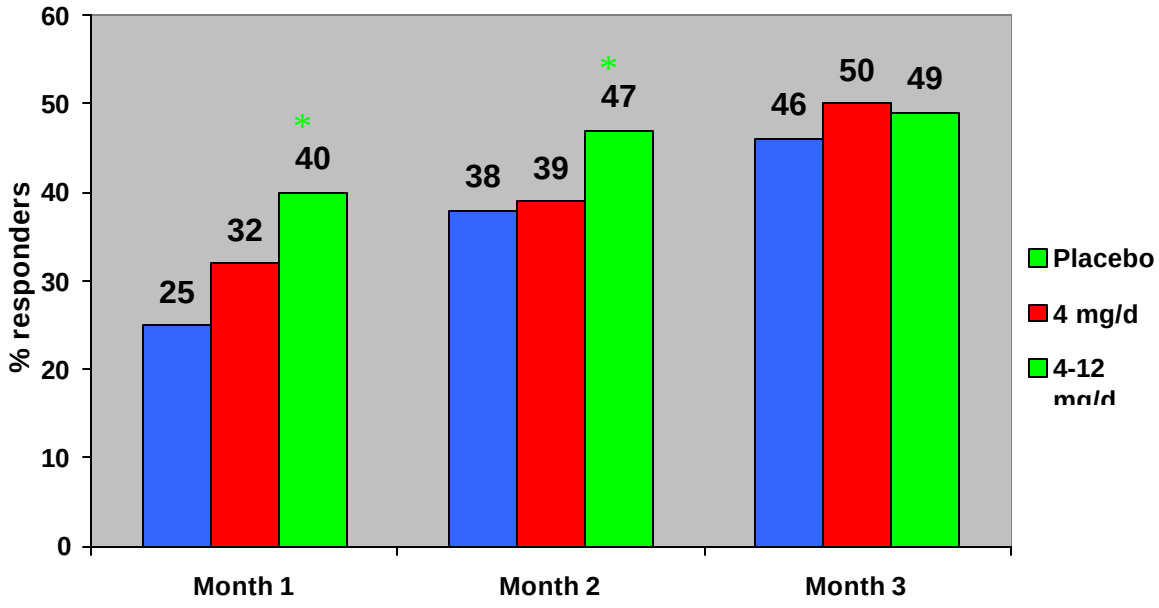
[1] Adjusted for missing SGAs, treatment duration, laxative use.

[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint.

The percentage of patients titrated at Month 1 were 68%, 65% and 73% in the tegaserod 4 mg/day, 4-12 mg/day and placebo groups, respectively. Monthly responder rates for the SGA of relief are shown in Figure 7-17. These monthly responder rates raise yielded two unusual findings:

- an inconsistency in Month 1 responder rates between the tegaserod groups, as both groups received identical treatment (i.e., tegaserod 4 mg/day) during study Month 1, and
- a large 13% increase in the placebo responder rate that occurred from Month 1 to Month 2 (after dose titration) compared to the 7% observed increase in responder rates in both tegaserod groups

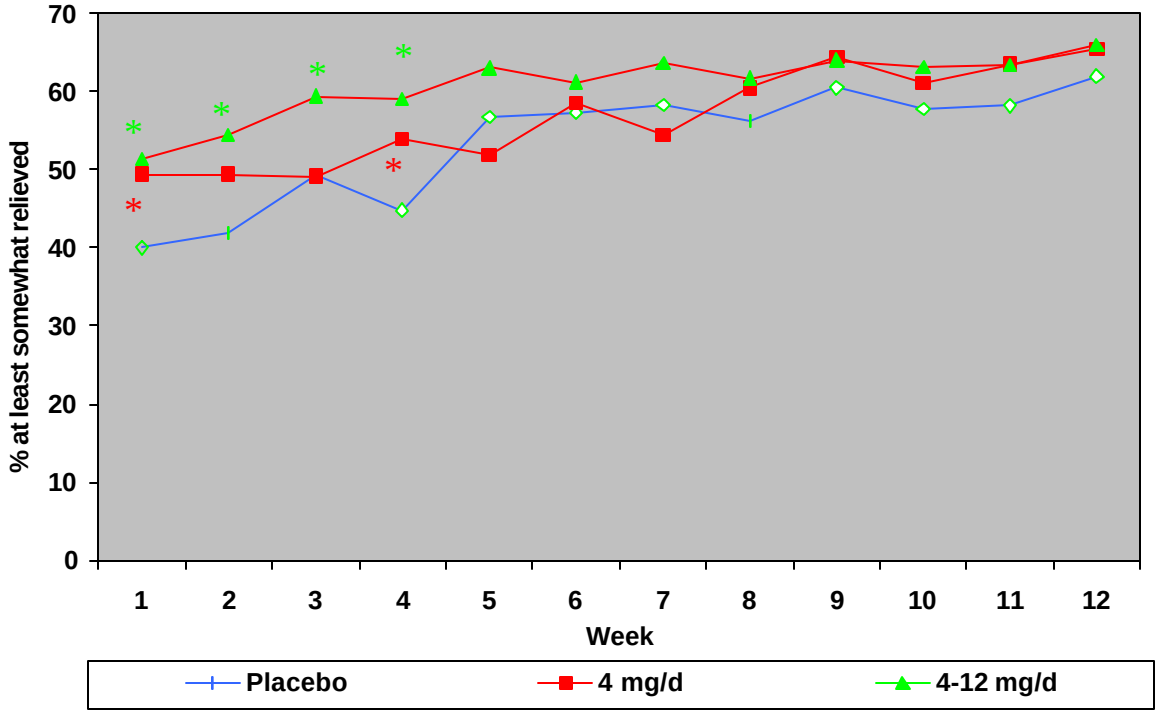
Figure 7-17. Unadjusted responder rate for SGA of relief by monthly interval (study B307)



*p-value <0.05 compared to placebo

The weekly percentage of patients that were at least somewhat relieved is shown in Figure 7-18.

Figure 7-18. Weekly percentage of patients with at least somewhat relief for SGA of relief (study B307)



*p-value <0.05 compared to placebo

As shown in Figure 7-18, at the time of dose-titration from Week 4 to Week 5, there was an unusually large increase of 12% in the placebo group compared with a decrease of 2% and increase of 4% in the tegaserod 4 mg/day and 4-12 mg/day groups, respectively. This increased placebo response then persisted for the remainder of the study.

Table 7-14 presents the results in the titrated (or mock titrated in tegaserod 4 mg/day and placebo groups) and non-titrated patients from Week 2 to Week 7. It is apparent that it was the titrated patients in the placebo group that had an unexpected increase in response at the time of titration. For the (mock) titrated placebo patients, there was an increase of 17% in the proportion of patients with at least somewhat relief from 36% to 53% immediately after (mock) dose-titration from Week 4 to 5. Similar increases were not observed in the titrated placebo patients at other weeks or in the titrated patients in the tegaserod groups. These findings may be explained by heightened expectations at the time of dose-titration, making interpretation of results after dose-titration difficult.

Table 7-14. Weekly percentage of patients with at least somewhat relief for SGA of relief in titrated and non-titrated patients (study B307)

Treatment	Week 2 % (N)	Week 3 % (N)	Week 4[1] % (N)	Week 5 % (N)	Week 6 % (N)	Week 7 % (N)
Placebo						
Titrated	35% (209)	40% (209)	**36% (209)**	**53% (206)**	54% (203)	53% (200)
Not titrated	84% (49)	86% (49)	83% (47)	81% (48)	69% (48)	83% (48)
Tegaserod 4 mg/d						
Titrated	44% (193)	42% (193)	46% (193)	45% (190)	50% (187)	49% (185)
Not titrated	86% (50)	86% (50)	90% (50)	82% (50)	84% (50)	84% (50)
Tegaserod 4-12 mg/d						
Titrated	43% (181)	49% (180)	48% (181)	53% (177)	53% (175)	53% (174)
Not titrated	93% (69)	93% (69)	94% (68)	93% (69)	88% (68)	84% (68)

N = total number of patients in titrated or nontitrated group for that week.
[1] Dose-titration at end of Week 4.

Results for the ***original*** SGA of relief, (complete or considerable relief at least 50% of the time), for the ITT population at endpoint are shown below in Table 7-15.

Table 7-15. Responder rates for the *original* SGA of relief at endpoint (ITT population)

	Placebo	Tegaserod 4 mg/d	Tegaserod 4-12 mg/d
	N=284	N=282	N=275
Response rate[1] (n)	28.2% (80)	25.5% (72)	26.5% (73)
Treatment difference in responder rate[2]		-3.0	-1.4
P-value		0.422	0.703

[1] Adjusted for missing SGAs, treatment duration, laxative use.

[2] Treatment difference (weighted by center) in responder rate and p-value (nominal p-value) refer to the comparison between the tegaserod dose and placebo at endpoint.

Secondary efficacy variables

Results for the secondary efficacy variables at endpoint are presented in Table 7-16. The results on the SGA of abdominal discomfort/pain, SGA of bowel habits and daily diary variables of abdominal pain and bloating were variable, but none of the differences at endpoint between tegaserod groups and placebo were statistically significant. Tegaserod 4-12 mg/day group did significantly increase the number of bowel movements and decrease the number of days without bowel movements compared with placebo at endpoint.

Table 7-16. Summary of the between-treatment comparisons of secondary efficacy variables at endpoint (study B307, ITT population)

	Placebo	Tegaserod 4 mg/d	Difference from placebo[3]	Tegaserod 4-12 mg/d	Difference from placebo[3]
Responder rate for SGA of abdominal discomfort/pain	30.6%	25.5% (p=0.141)	-5.1%	27.6% (p=.411)	-3.0%
Responder rate for SGA of bowel habits	25.0%	27.0% (p=0.661)	2.0%	24.0% (p=0.847)	-1%
Mean percent change from baseline in number of days with significant[1] discomfort/pain	-12.7%	-13.8% (p=0.884)	1.1%	-16.2% (p=0.273)	3.5%
Mean percent change from baseline in number of days with significant[1] bloating	-13.8%	-10.6% (p=0.196)	-3.2%	-8.0% (p=0.513)	-5.8%
Mean percent change from baseline in number of days without bowel movements	-14.4%	-20.7% (p=0.053)	6.3%	-22.0% (p=0.018)*	7.6%
Mean percent change from baseline in number of bowel movements	29.5%	67.2% (p=0.001)*	37.7%	59.4% (p<0.001)*	29.9%
Mean percent of days[2] with hard or very hard stool	16.2%	13.8% (p=0.692)	2.4%	13.0% (p=0.218)	3.2%

Note: P-values are the nominal p-values for the comparison between the tegaserod dose and placebo at endpoint.
* Indicates the nominal p-value <0.05.

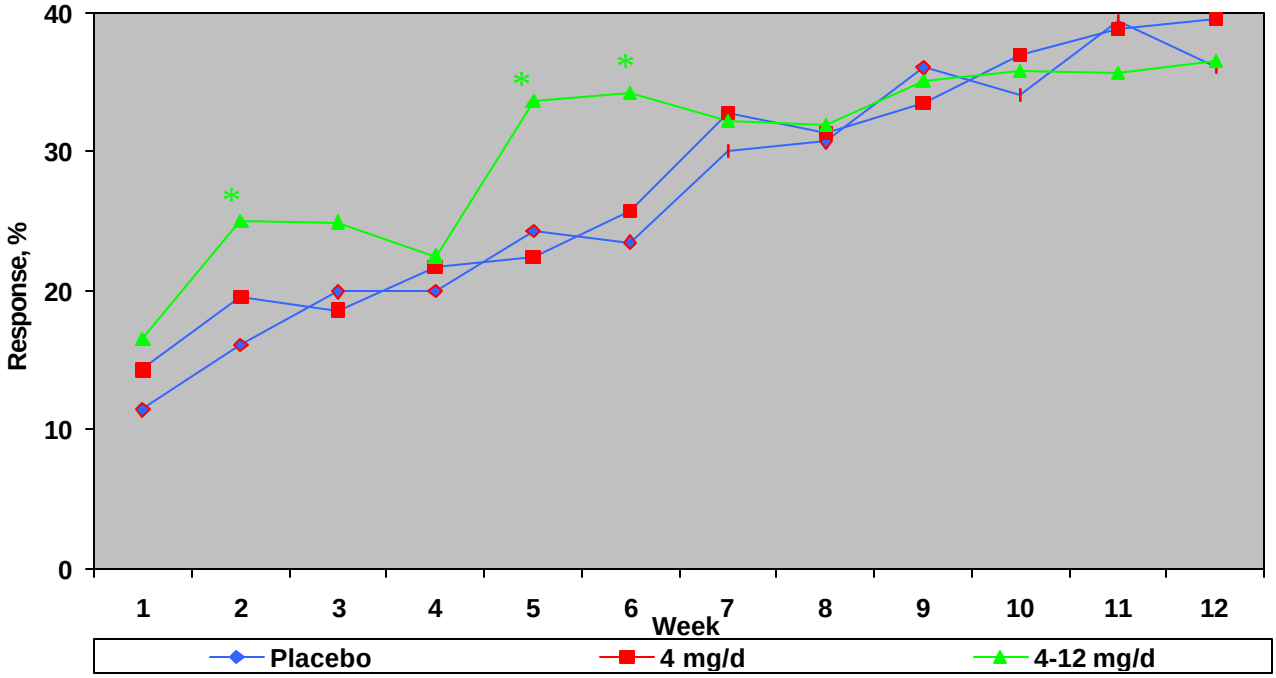
[1] Defined as at least mild (daily score $\geq$ 2 on 6-point scale);

[2] Denominator is days with bowel movements.

[3] Positive value in favor of tegaserod.

The secondary efficacy variables at weekly intervals are presented below. Of note, for the weekly SGA of abdominal discomfort/pain (Figure 7-19), a large increase (11%) in responder rate occurred in the tegaserod 4-12 mg/day group at the time of dose titration (ie, Week 4), which did not occur in the tegaserod 4 mg/day and placebo groups. These results are in contrast to those observed for the weekly percentage of patients with at least somewhat relief (Figure 7-18). Differences from placebo on the SGA of abdominal discomfort/pain were not apparent beyond Week 6.

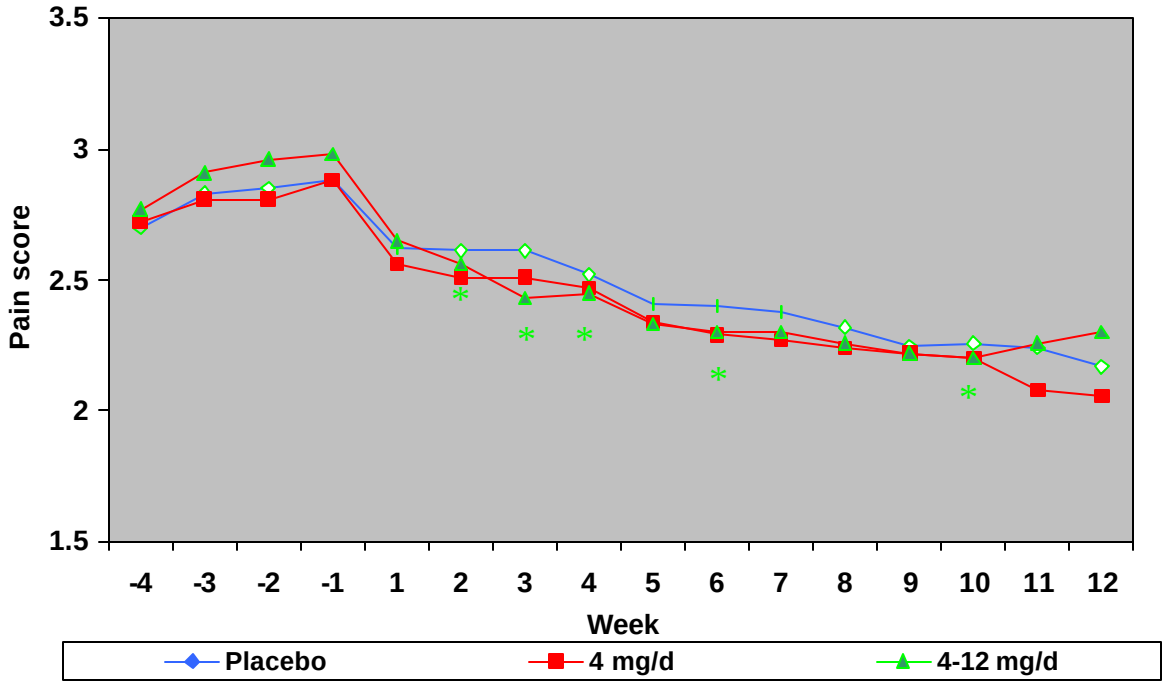
Figure 7-19. SGA of abdominal discomfort/pain by week (study B307)



*p-value <0.05 compared to placebo

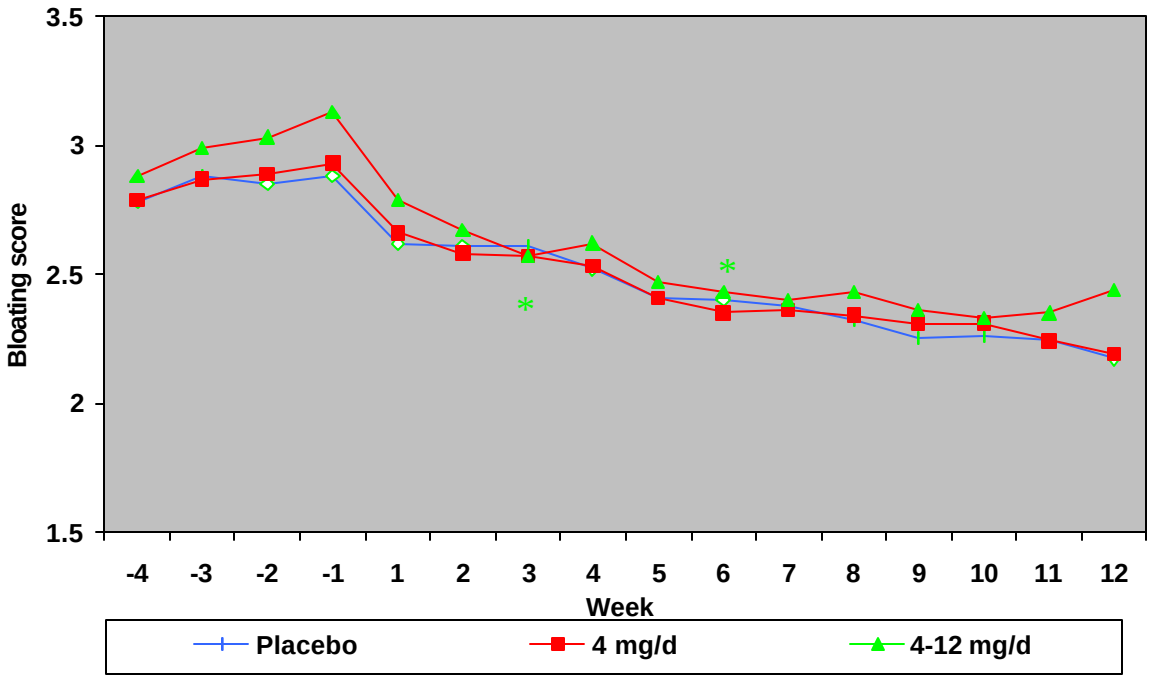
Mean abdominal discomfort/pain and bloating scores, weekly SGA of bowel habits, stool frequency and stool consistency scores are shown below in Figures 7-20 through 7-24. Pain scores were lower for the tegaserod 4-12 mg/day group than placebo for most of the study, with a higher score noted at Week 12. Bloating scores were variable and tended to be higher in the number of bowel movements and stool consistency scores were most prominent early in the study, but did persist over the 12 weeks.

Figure 7-20. Mean daily abdominal pain scores by week (B307)



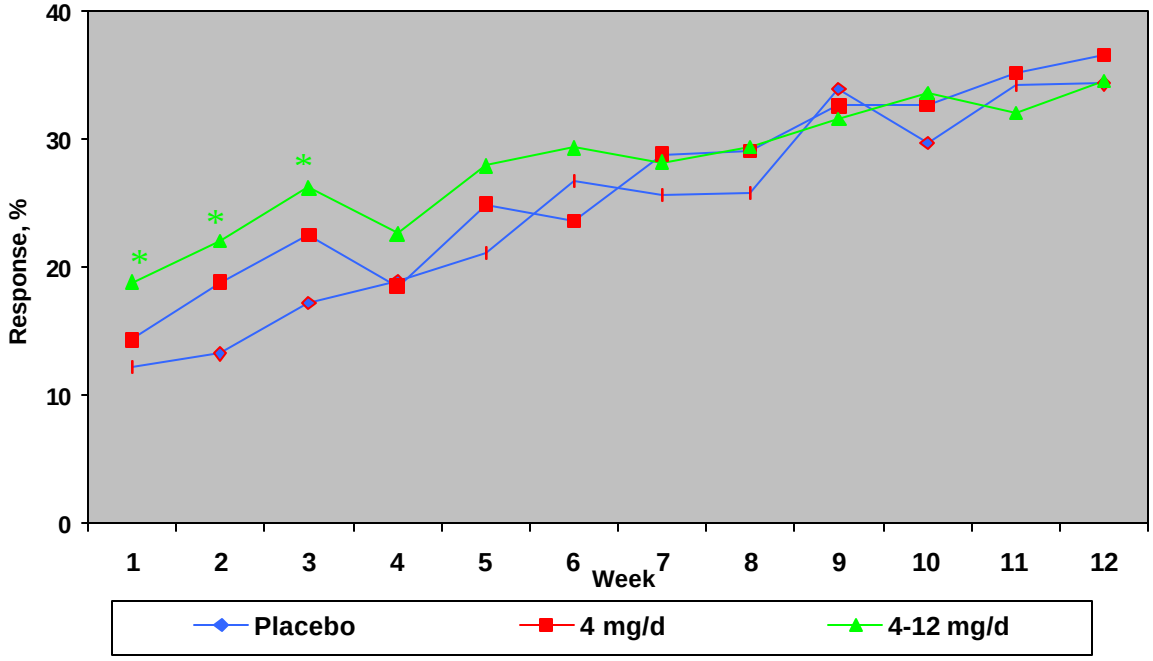
*p-value compared to placebo (change from baseline)

Figure 7-21. Mean daily bloating scores by week (B307)



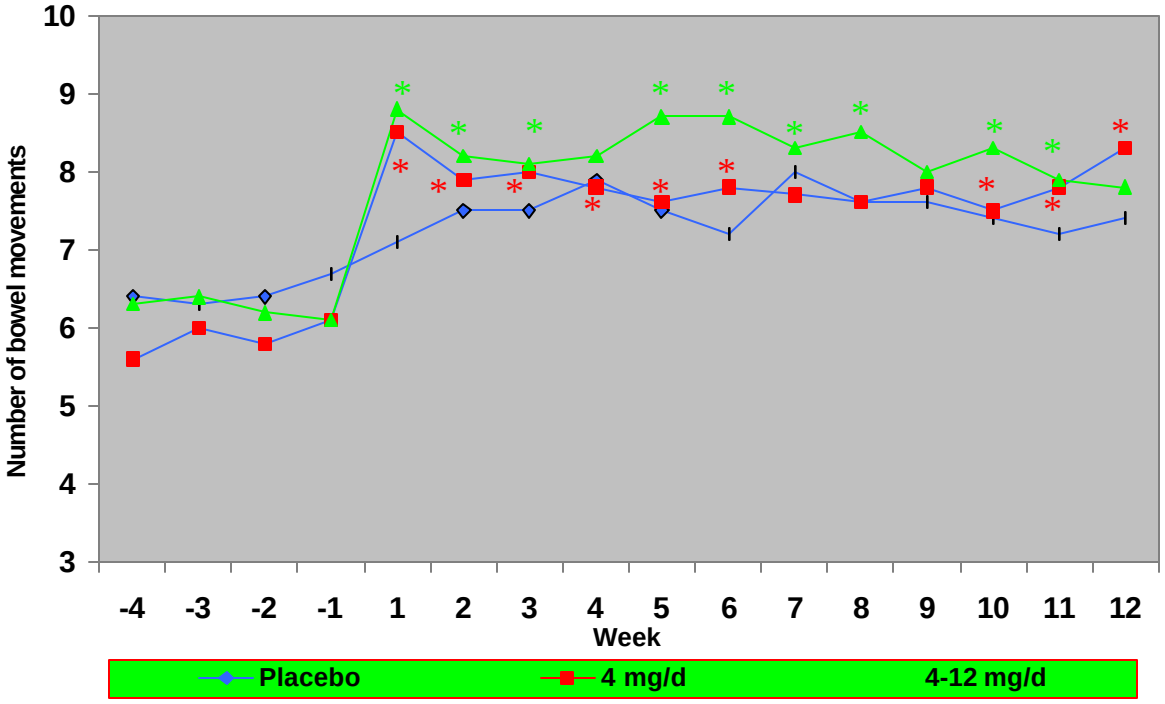
*p-value compared to placebo (change from baseline)

Figure 7-22. SGA of bowel habit by week (study B307)



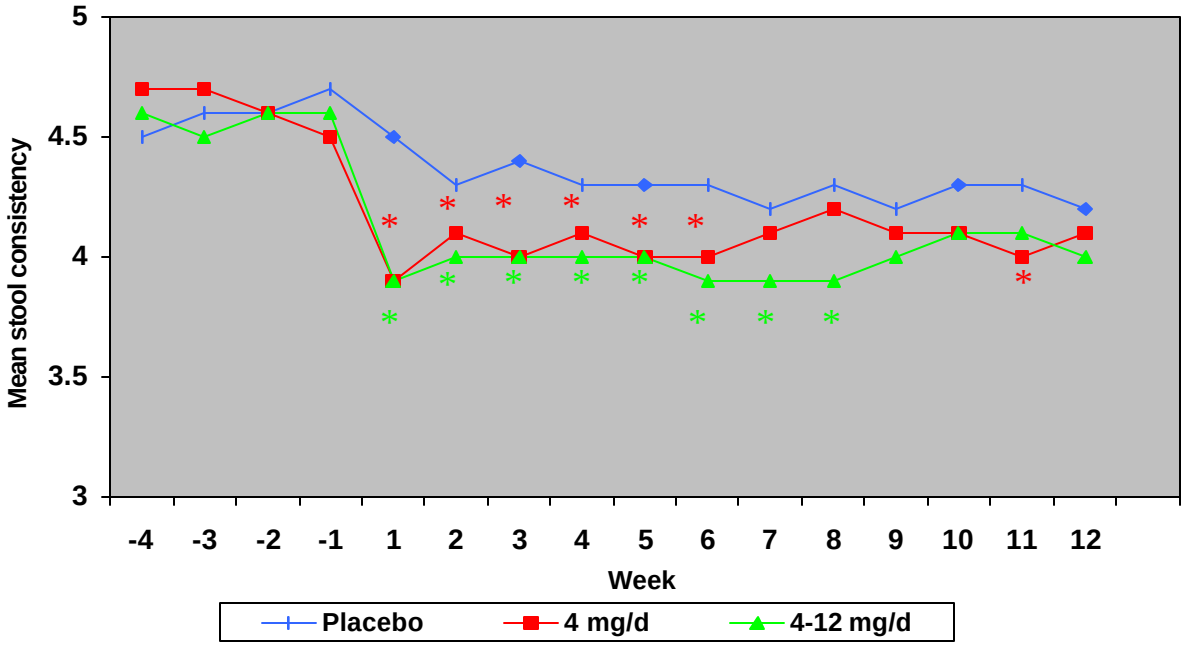
*p-value <0.05 compared to placebo

Figure 7-23. Weekly number of bowel movements (study B307)



*p-value <0.05 compared to placebo (change from baseline)

Figure 7-24. Weekly mean stool consistency (study B307)



*p-value <0.05 compared to placebo (change from baseline)
Scale: 1=watery, 2=loose, 3=somewhat loose, 4= neither loose nor hard, 5=somewhat hard, 6=hard, 7=very hard

Discussion/Conclusion, Study B307

At endpoint, treatment differences between the tegaserod groups and placebo on the primary and secondary outcome measures were variable and did not reach statistical significance for the primary efficacy variable for either tegaserod treatment group compared with placebo.

This study incorporated a dose-titration design. At Week 4, patients in the tegaserod 4-12 mg/day group underwent dose-titration and those in the tegaserod 4 mg/day and placebo groups underwent mock dose-titration, according to response on the SGA of relief. All patients in the study received the same number of tablets both before and after dose-titration. For unexplained reasons, the titrated patients in the placebo group had a substantial increase in response (% at least somewhat relief) immediately following dose-titration, which was not observed in the tegaserod groups and which persisted for the remainder of the study. However, for the SGA of abdominal discomfort/pain, a large increase in response was observed in the tegaserod 4-12 mg/day group at the time of titration. These mixed results may relate in some way to heightened expectations at the time of dose-titration, or other unknown reasons such as chance findings. Interpretations of results from this study are difficult.

7.2 Sensitivity Analyses

Impact of adjustment rules

The magnitude of the treatment difference between tegaserod and placebo was impacted by "adjustment rules" whereby a responder on the SGA of relief was declared a nonresponder in the primary analysis for the following:

- there were no SGAs available
- duration of treatment was < 28 days
- laxative intake was > 5 days during the treatment period or $\geq$ 1 day during the last 4 weeks of treatment.

The impact of these adjustment rules are shown in Table 7-17. Only unadjusted responder rates do not include the entire ITT population (ie, patients with missing SGAs were excluded from the unadjusted analysis, but were declared nonresponders in the other analyses). The type of adjustment factor applied did not affect statistical significance of the treatment comparisons.

Table 7-17. Impact of adjustment criteria on responder rate for SGA of relief in individual studies (ITT population)

	Study	placebo % response (N)	tegaserod 4 mg/d % response (N, diff. from placebo)	tegaserod 12 mg/d % response (N, diff. from placebo)
Unadjusted	B351	38.9 (257)	46.1 (245, 7.2)	53.2** (250, 14.3)
Adjusted for missing SGAs		37.5 (267)	42.6 (265, 5.1)	49.8** (267, 12.3)
Not adjusted for laxatives [1]		37.1 (267)	41.5 (265, 4.4)	48.7** (267, 11.6)
Adjusted[2]		33.3 (267)	38.9 (265, 5.6)	45.7** (267, 12.4)
Unadjusted	B301	34.5 (281)	46.7** (285, 12.2)	46.3** (285, 11.8)
Adjusted for missing SGAs		33.7 (288)	44.5** (299, 10.8)	44.9** (294, 11.2)
Not adjusted for laxatives [1]		33.3 (288)	43.5** (299, 10.2)	44.9** (294, 11.6)
Adjusted[2]		30.2 (288)	38.8* (299, 8.6)	38.4* (294, 8.2)
Unadjusted	B307	41.2 (274)	44.9 (267, 3.7)	48.5[3] (266, 7.3)
Adjusted for missing SGAs		39.8 (284)	42.6 (282, 2.8)	46.9[3] (275, 7.1)
Not adjusted for laxatives [1]		39.4 (284)	41.5 (282, 2.1)	45.8[3] (275, 6.4)
Adjusted[2]		37.0 (284)	38.3 (282, 1.3)	42.2[3] (275, 5.2)

N = total number of patients.
[1] Adjusted for missing SGAs and treatment duration
[2] Adjusted SGA of relief, all three adjustment rules applied (primary analysis). [3] 4-12 mg/d (titration group).
* Statistically significant at the significance level of 0.05, using Hochberg's multiple comparison procedure, adjusting for two tegaserod doses; ** Indicates nominal p-value is also < 0.01.

In general, however, the impact of the adjustment criteria was to decrease the treatment differences between the tegaserod groups and the placebo group. Differences from placebo in the 12 mg/day group response rates that were not adjusted for laxative use were 12% in both studies B351 and B301. Corresponding figures for differences from placebo in unadjusted response rates were 14% and 12%, respectively, in studies B351 and B301.

Impact of study withdrawals

Study withdrawals in the three Phase 3 studies ranged from 15%-21% over the 12-week treatment period, which is not unexpected for IBS studies. However, as it is important to assess the potential impact of these study withdrawals on response rates, a sensitivity analysis was conducted in which a) patients who discontinue due to adverse events or lack of efficacy are considered nonresponders and in which b) all discontinued patients were considered nonresponders. The results of these analyses are similar to the primary analysis and indicate that the discontinued patients did not impact study results (Table 7-18).

Table 7-18. Impact of premature withdrawals on results for SGA of relief in individual studies at endpoint

Study		Responder rate at endpoint		
		placebo % (N)	tegaserod 4 mg/d % (N)	tegaserod 12 mg/d % (N)
B351	SGA of relief	33.3 (267)	38.9 (265)	45.7** (267)
	Patients discontinued due to AE or lack of efficacy declared nonresponder	33.0 (267)	38.9 (265)	44.9** (267)
	All discontinued patients declared nonresponders	31.5 (267)	35.8 (265)	43.1** (267)
B301	SGA of relief	30.2 (288)	38.8* (299)	38.4* (294)
	Patients discontinued due to AE or lack of efficacy declared nonresponder	29.5 (288)	37.1* (299)	38.4* (294)
	All discontinued patients declared nonresponders	28.8 (288)	36.5* (299)	37.8* (294)
B307	SGA of relief	37.0 (284)	38.3 (282)	42.2[1] (275)
	Patients discontinued due to AE or lack of efficacy declared nonresponder	35.9 (284)	38.3 (282)	41.1[1] (275)
	All discontinued patients declared nonresponders	34.2 (284)	37.2 (282)	40.7[1] (275)

AE = adverse event. N = total number of patients. [1] 4-12 mg/d (titration group).
* Statistically significant at the significance level of 0.05, using Hochberg's multiple comparison procedure, adjusting for two tegaserod doses; ** indicates the nominal p-value is also < 0.01.

Patients completing the study

Results for those patients completing the studies, as shown below in Table 7-19, were generally similar to the ITT population, although differences from placebo were greater in the completers population.

Table 7-19. Response for SGA of relief in Phase 3 studies at endpoint for completed patients[1]

Study	placebo %	tegaserod 4 mg/d %	tegaserod 12 mg/d[2] %	p value: 4 mg/d vs placebo	p value: 12 mg/d vs placebo
B351	39.3	45.7	54.5	.140	.002*
B301	33.1	44.3	43.7	.007*	.012*
B307	41.8	48.4	48.5	.250	.111

[1] Primary analysis, using three adjustment rules (missing SGAs, treatment duration, laxative use); responder definition: $\geq$ 50% complete/considerable relief or at least 100% somewhat relief at endpoint.
[2] 4-12 mg/d (titration group) in study B307 included in 12 mg/d group.
* statistically significant at the significance level of 0.05, using the Hochberg's multiple comparison procedure; adjusting for two tegaserod doses.

7.3 Phase 3 studies comparative efficacy

7.3.1 Primary efficacy variable-SGA of relief

The SGA of relief was the primary efficacy measure in studies B301 and B307; results from study B351 were retrospectively analyzed using the SGA of relief definition of response. Response rates in the individual studies for the SGA of relief are shown in Table 7-20.

Table 7-20. Response for SGA of relief in individual studies at endpoint[1]

Study	Placebo %	Tegaserod 4 mg/d %	Tegaserod 12 mg/d[2] %	p value: 4 mg/d vs placebo	p value: 12 mg/d vs placebo
B351	33.3	38.9	45.7	.157	.004*
B301	30.2	38.8	38.4	.018*	.033*
B307	37.0	38.3	42.2	.837	.142

[1] Primary analysis, using three adjustment rules (missing SGAs, treatment duration, laxative use). Responder definition: $\geq$ 50% complete/considerable relief or at least 100% somewhat relief at endpoint.
[2] 4-12 mg/d (titration group) in study B307 included in 12 mg/d group.
* Statistically significant at the significance level of 0.05, using Hochberg's multiple comparison procedure, adjusting for two tegaserod doses.

In the individual studies B351 and B301, the tegaserod 12 mg/day group had a greater response rate than the placebo group at endpoint; the difference from placebo in responder rate for the 12 mg/day tegaserod group was statistically significant in both individual studies. The tegaserod 4 mg/day group had a more variable result in terms of a treatment effect compared with placebo in the two studies, with statistical significance observed in study B301 but not in study B351. Although a trend was noted for the 4-12 mg/day tegaserod (dose-titration) group in study B307, results were not statistically significant.

The weekly percentage of patients with at least somewhat relief for the 12 mg/day and 4-12 mg/day groups and placebo groups are shown in Figure 7-16. An early effect is apparent at Week 1. Despite differing placebo response rates, differences from placebo were quite similar for the 12 mg/day group in studies B351 and B301. Similar results were seen for the weekly percentage of patients with complete or considerable relief in studies B351 and B301. In study B307, response rates in the placebo group continued to increase throughout the study such that no treatment difference was seen over the last several weeks of the study.

Figure 7-16. Weekly percentage of patients with at least somewhat relief in Phase 3 studies

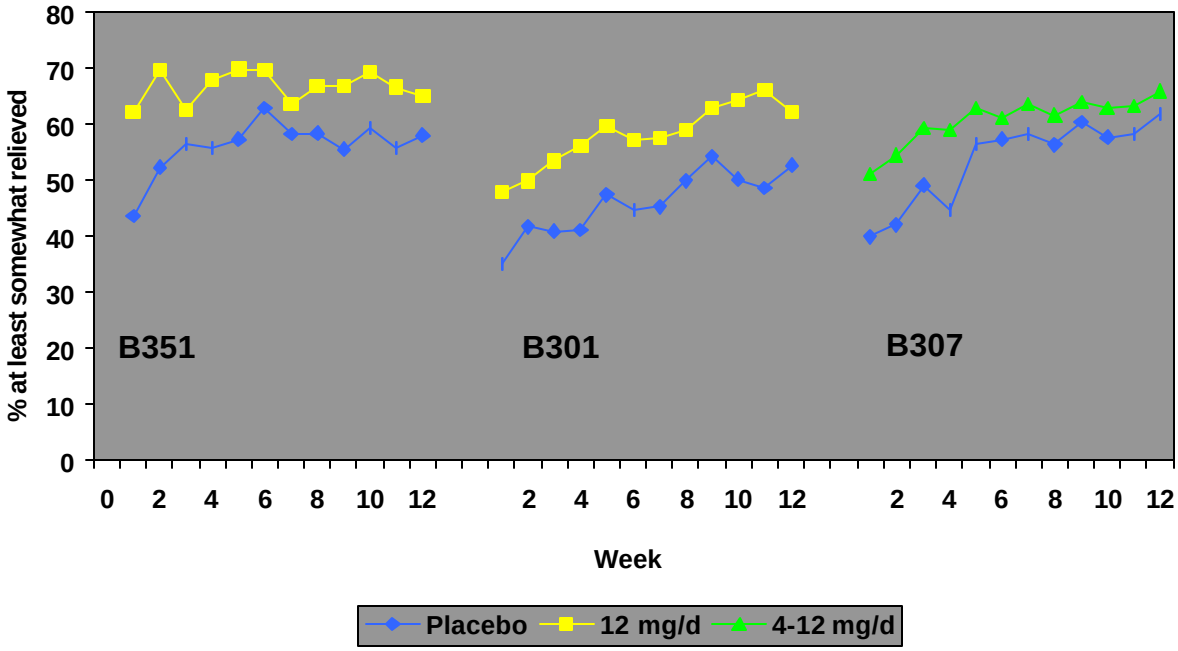
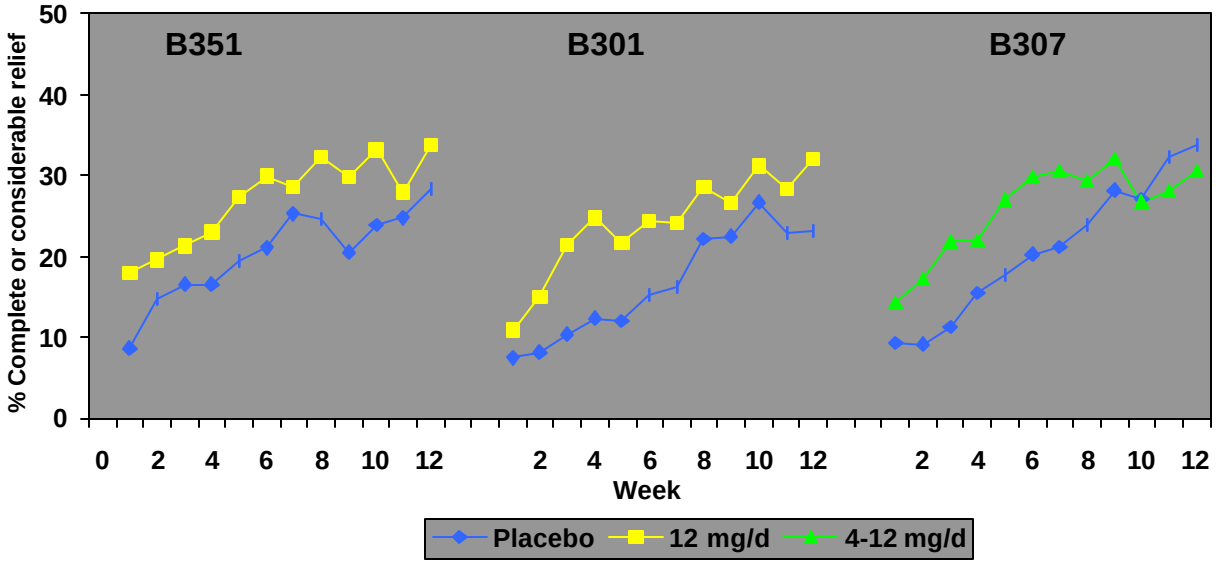


Figure 7-17. Weekly percentage of patients with complete or considerable relief in Phase 3 studies



7.3.2 Secondary efficacy variables

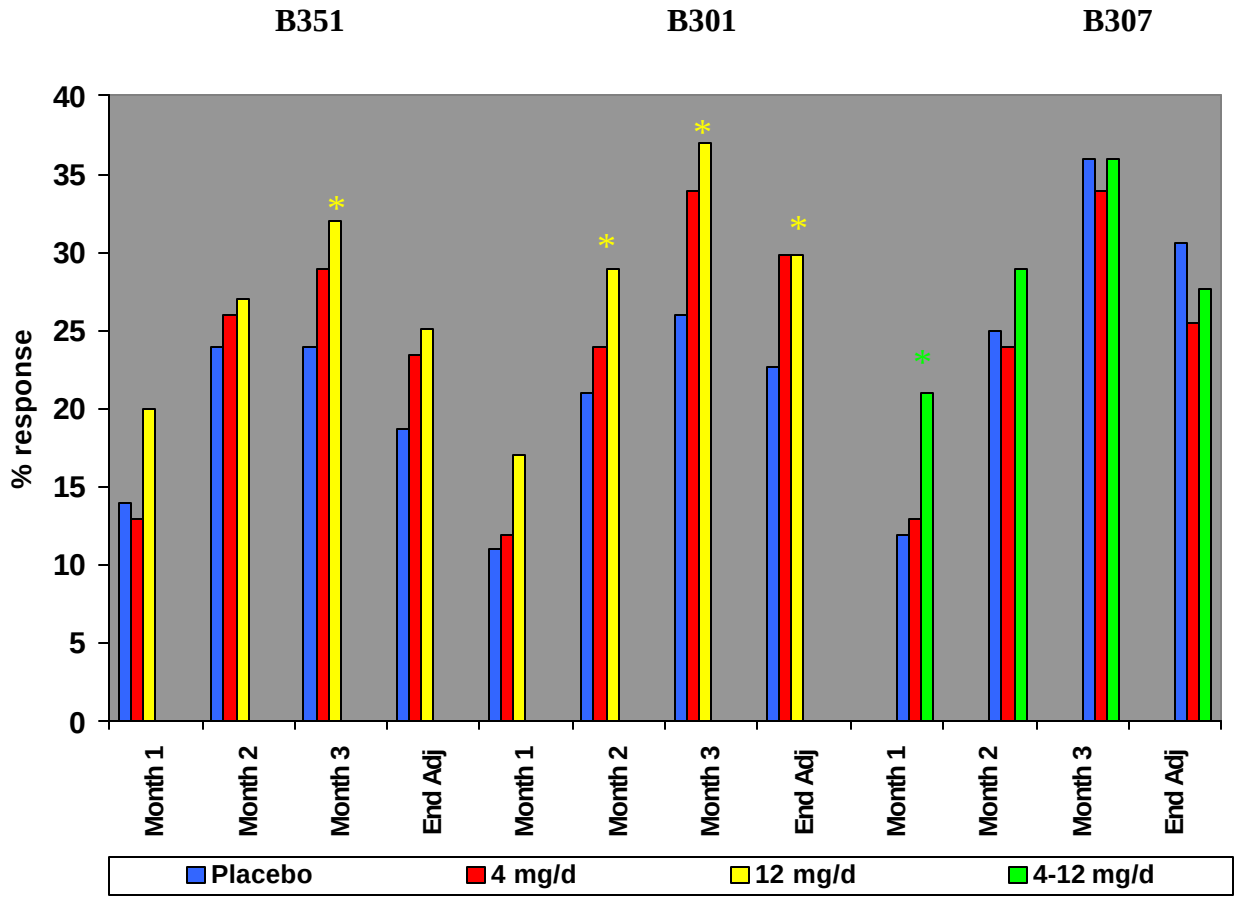
Abdominal discomfort/pain and abdominal bloating

Abdominal discomfort and pain was evaluated by the weekly SGA of abdominal discomfort/pain and daily by the number of days with significant (ie, at least mild) abdominal discomfort/pain. Abdominal bloating was evaluated by the number of days with significant bloating in the daily diary.

SGA of abdominal discomfort/pain

The SGA of abdominal discomfort/pain was a second primary efficacy variable in study B351 and designated as a secondary variable in studies B301 and B307. Reflective of the high hurdle for response on this efficacy variable, responder rates were low. However, results were consistent between studies B351 and B301. Responder rates were higher in the tegaserod 12 mg/day groups than the placebo groups at each monthly timepoint and at endpoint in both studies (Figure 7-18). In study B301, the treatment differences were significant at endpoint.

Figure 7-18. Response for SGA of abdominal discomfort/pain in Phase 3 studies by month and at endpoint

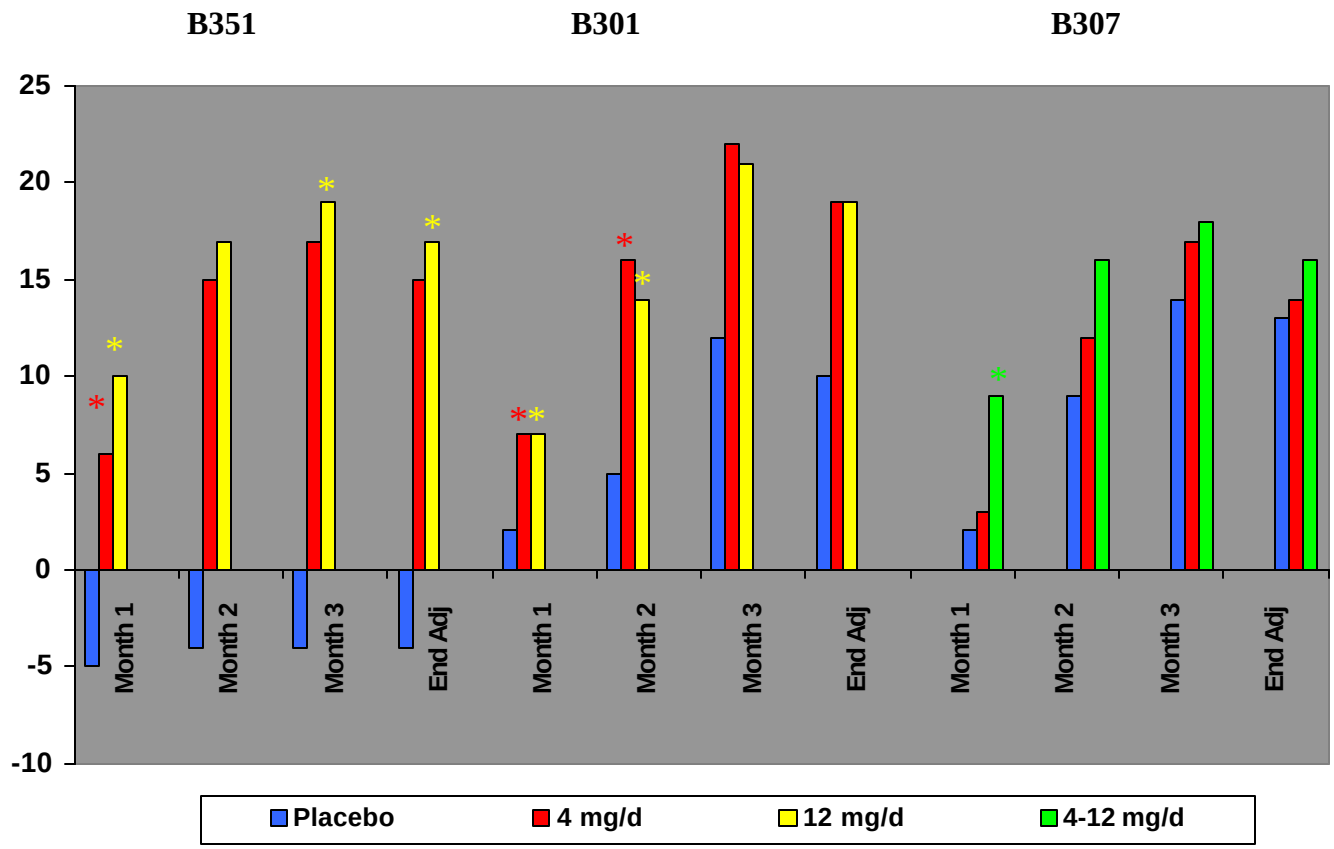


Endpt Adj - adjusted endpoint; adjusted for missing SGAs, treatment duration and laxative intake.
* $p < 0.05$ compared to placebo
Response: ≥ 40% reduction and at least 20 mm absolute reduction from baseline on 100 mm VAS

Daily diary variables: Days with significant abdominal discomfort/pain and days with significant bloating

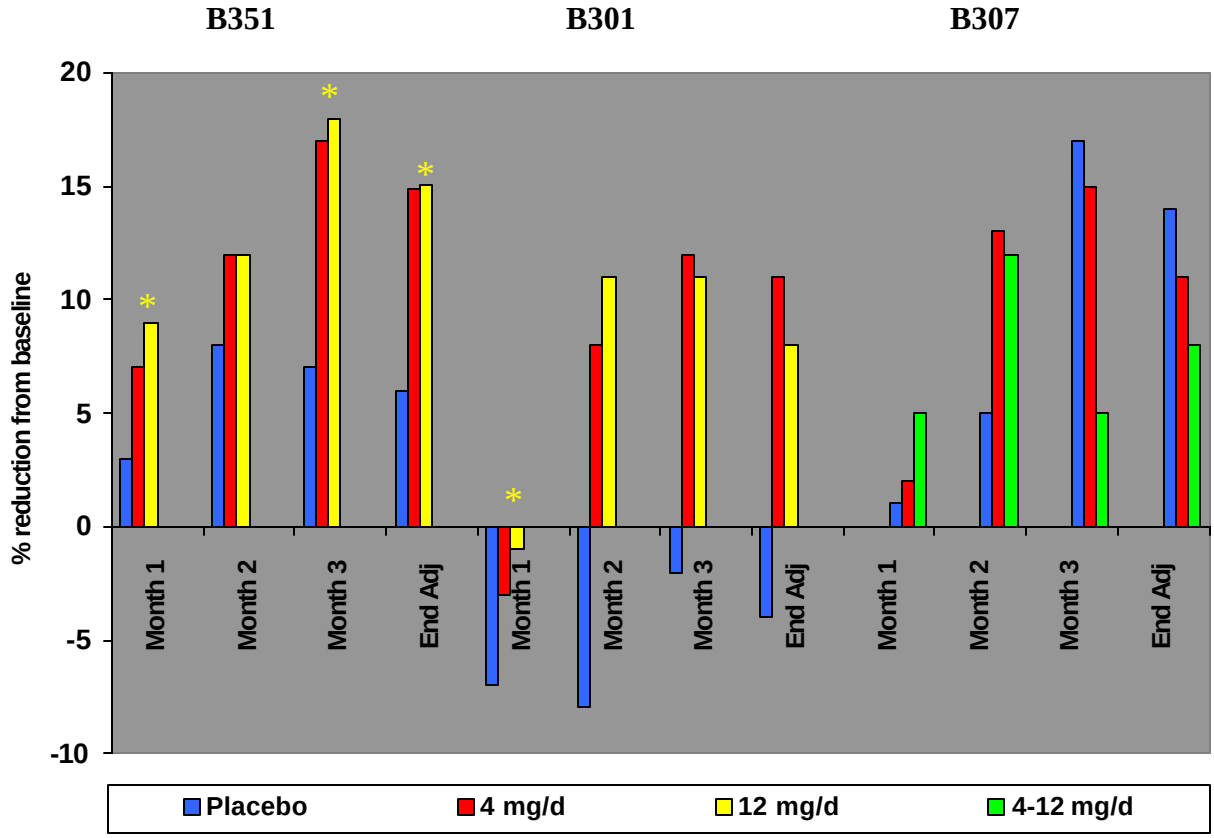
As shown in Figures 7-19 and 7-20, results were highly consistent in studies B351 and B301 with favorable effects seen in each study at all monthly timepoints and at endpoint. The differences were statistically significant at endpoint for the 12 mg/day-placebo comparison in study B351 for both abdominal discomfort/pain and bloating. In study B307, results were variable over time.

Figure 7-19. Days with significant abdominal discomfort/pain derived from daily diary in Phase 3 studies by month and at endpoint



*p < 0.05 compared to placebo
Significant: at least mild (≥ 2 on 6-point scale)

Figure 7-20. Days with significant abdominal bloating derived from daily diary in Phase 3 studies by month and at endpoint



* $p < 0.05$ compared to placebo
Significant: at least mild (≥ 2 on 6-point scale)

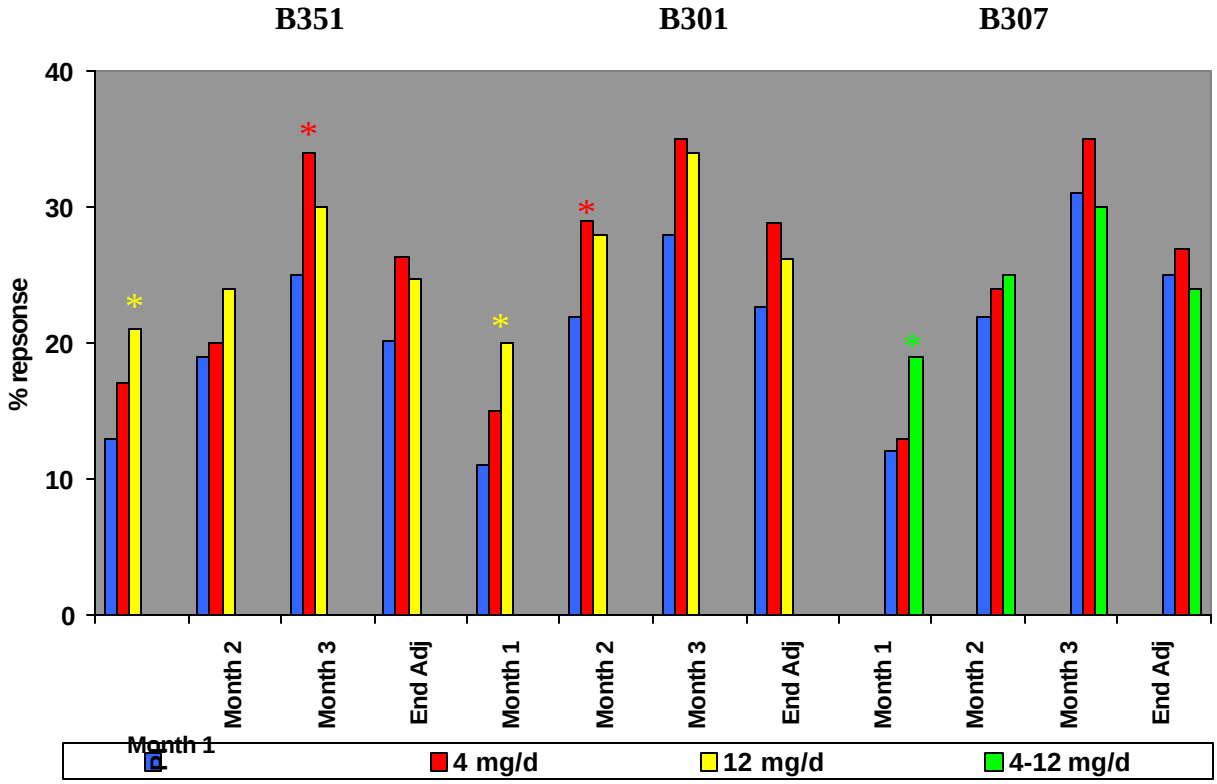
Bowel function

The effect of tegaserod on bowel function was evaluated by the weekly SGA of bowel habits and by daily recording of stool frequency and consistency.

SGA of bowel habits

Response rates tended to be higher for the tegaserod groups than placebo, but were not significantly different at endpoint (Figure 7-21). Once again, studies B351 and B301 yielded consistent results.

Figure 7-21. Response for SGA of bowel habits in Phase 3 studies by month and at endpoint



Adj endpt - adjusted endpoint; adjusted for missing SGAs, treatment duration and laxative intake.
* $p < 0.05$ vs. placebo
Response: ≥ 40% reduction and at least 20 mm absolute reduction from baseline on 100 mm VAS

7.3.3 Efficacy variables summary

The statistical significance of and direction of response for the weekly SGA assessments and daily diary efficacy variables are shown in Table 7-21. Results for studies B351 and B301 were highly consistent. Although statistical significance was not achieved for the treatment differences between the tegaserod groups and placebo for all efficacy variables, it is notable that the results were always more favorable for the tegaserod groups for all SGA and daily diary variables in these two studies of identical design. Results for study B307 at endpoint were variable across efficacy parameters.

Table 7-21. Summary of efficacy variables in Phase 3 studies at endpoint

	B351		B301		B307	
Efficacy variable	**4 mg/d**	**12 mg/d**	**4 mg/d**	**12 mg/d**	**4 mg/d**	**4-12 mg/d**
SGA efficacy variables (weekly)						
SGA of relief	**+**	<0.01	<0.05	<0.05	**+**	**+**
≥ 50% complete or considerable relief (***original*** SGA of relief)	<0.05	**+**	<0.05	**+**	**-**	**-**
100% At least somewhat relief	**+**	<0.01	<0.05	<0.05	**+**	**+**
SGA of abdominal discomfort/pain	**+**	**+**	**+**	<0.05	**-**	**-**
SGA of bowel habits	**+**	**+**	**+**	**+**	**+**	**-**
Daily diary variables						
Mean % change from baseline in days significant abdominal pain	**+**	<0.05	**+**	**+**	**+**	**+**
Mean % change from baseline in days significant abdominal bloating	**+**	<0.01	**+**	**+**	**-**	**-**
Mean % change from baseline in number of bowel movements	<0.01	<0.001	<0.001	<0.01	<.05	<.001
Mean % change from baseline in number of days without BMs	**+**	<0.01	<0.05	<0.05	**+**	<.05
Mean percent of days with hard or very hard stools	**+**	<0.01	**+**	**+**	**+**	**+**

+: Treatment difference in positive direction for tegaserod compared to placebo, nominal p ≥ 0.05 compared to placebo
-: Treatment difference in positive direction for placebo compared to tegaserod

7.4 Post-hoc analyses

After the unblinding of study B351, the data was examined and a more sensitive endpoint defined. The revised endpoint, the SGA of relief (>50% complete or considerable relief or 100% at least somewhat relief), was designated prospectively as the primary efficacy variable for studies B301 and B307. To gain more insight in the strength of evidence, several post-hoc analyses were performed. As these are post-hoc analyses, the sponsor acknowledges that the results need to be interpreted with caution.

7.4.1 Pooled analyses

Pooling of results of the three Phase 3 studies was performed to investigate the presence of a drug effect. Under the null hypothesis of no treatment effect, such a pooling is justified despite the difference in design between B307 and studies B301, B351 and further, as the pre-specified primary efficacy variables for each study were evaluated.

Thus, Studies B351, B301 and B307 were pooled by dose group and analyzed based on the respective primary efficacy variables. Accordingly, in this pooled analysis, for study B351 both the original SGA of relief (>50% complete or considerable relief) and the SGA of abdominal discomfort/pain were used; for studies B301 and B307, the SGA of relief (>50% complete/considerable relief or 100% at least somewhat relief) was used. The pooled population was analyzed at endpoint and also longitudinally. For the longitudinal analysis, the respective responder criteria were applied to Month 1, Month 2 and Month 3. Missing data were imputed by carrying the last observation forward. To adjust for laxative use, patients with more than 5 days of laxative use were considered as non-responders for any of the months.

Pooled results for the tegaserod 12 mg/day and 4-12 mg/day combined group showed highly statistically significant differences compared with the placebo groups, indicative of a positive drug effect (Table 7-22).

Table 7-22. Pooled analysis of Phase 3 primary efficacy variables: statistical significance of treatment comparisons

Endpoint analysis		Longitudinal analysis	
p-value: 4 mg/d vs. placebo	**p-value**: 12 mg/d[1] vs. placebo	**p-value**: 4 mg/d vs. placebo	**p-value**: 12 mg/d[1] vs. placebo
0.0141	0.0028	0.0085	<0.0001

Efficacy variables:

B351: Original SGA of relief; SGA of abdominal discomfort/pain (1 was assigned as the response score if responded to both variables, 0.5 if only responded to one of the variables, and 0 if no response to either variable.)

B301/B307: SGA of relief

[1]4-12 mg/d titration group in study B307

7.4.2 Supportive Analyses

To further evaluate the consistency of the SGA of relief response data, and to put these data into context, two additional post-hoc analyses were performed:

- At a recent (November 16, 1999) Gastrointestinal Drugs Advisory Committee meeting, the evaluation of a new drug (alosetron) for IBS was discussed. The primary analysis of the efficacy data presented at the meeting was based on a longitudinal analysis, using a monthly responder approach. Accordingly, this same analysis was subsequently performed for studies B351, B301 and B307. The number of months that a patient was a monthly responder was calculated and a score assigned: 0 = no monthly response, 1 = 1 monthly response, 2 = 2 monthly responses and 3 = 3 monthly responses. For months with all missing SGAs, the last month's value was carried forward. The scores were compared among the treatment groups. For the SGA of relief efficacy variable, treatment differences for the 12 mg/day and 4-12 mg/day tegaserod groups compared with placebo were statistically significant ($p<0.02$) in all three studies (Table 7-23).
- Since the SGA of relief was collected on a weekly basis, it is natural and logical to assess efficacy based on percent of weeks at which a patient showed a positive response Two cutoffs were used in this approach.

    (a) Percentage of weeks a patient was at least somewhat relieved was calculated, and compared between treatment groups.

    (b) Percentage of weeks a patient was completely relieved or considerably relieved was calculated, and compared between treatment groups.

As shown in Table 7-24, for weeks with at least somewhat relief, treatment differences between the 12 mg/day and 4-12 mg/day tegaserod groups and placebo were statistically significant ($p<0.01$) in all three studies. Similar results ($p<0.02$) were also obtained when comparing the percentage of weeks patients responded either completely relieved or considerably relieved.

Table 7-23. Statistical significance for between treatment comparison in number of months with response in individual studies

Study	Efficacy variable	p value: 4 mg/d vs. placebo	p value: 12 mg/d vs. placebo
B351	Original SGA of relief	.107 (N=265)	.047 (N=267)
B351	SGA of relief	.353 (N=265)	.013* (N=267)
B301	SGA of relief	.008* (N=299)	<.001* (N=294)
B307	SGA of relief	.479(N=282)	.008[1]* (N=275)

N = total number of patients.
Original SGA of relief: ≥50% complete/considerable relief
SGA of relief: ≥50% complete/considerable relief or 100% at least somewhat relief
[1] 4-12 mg/d (titration group).
* Indicates statistical significance at 0.05 level compared with placebo, with adjusting for multiple comparisons.

Table 7-24. Mean percentage of weeks with at least somewhat relief or with complete/considerable relief in individual studies

Study	Variable	placebo % (N)	tegaserod 4 mg/d % (N)	tegaserod 12 mg/d % (N)
B351	At least somewhat relief	53.2 (257)	59.7 (245) (p=0.021)*	65.0 (250) (p<0.001)*
	Complete/considerable relief	18.7 (257)	24.6 (245) (p=0.020)*	25.0 (250) (p=0.015)*
B301	At least somewhat relief	45.5 (281)	54.6 (285) (p=0.005)*	55.4 (285) (p<0.001)*
	Complete/considerable relief	15.7 (281)	19.2 (285) (p=0.061)	22.7 (285) (p<0.001)*
B307	At least somewhat relief	50.9 (274)	53.2 (267) (p=0.278)	59.7[1] (266) (p=0.003)*
	Complete/considerable relief	19.4 (274)	20.3 (267) (p=0.854)	24.9[1] (266) (p=0.018)*

N = total number of patients.
[1] 4-12 mg/d (titration group).
* Indicates a statistical significance at 0.05 level compared with placebo, with adjusting for multiple comparisons.

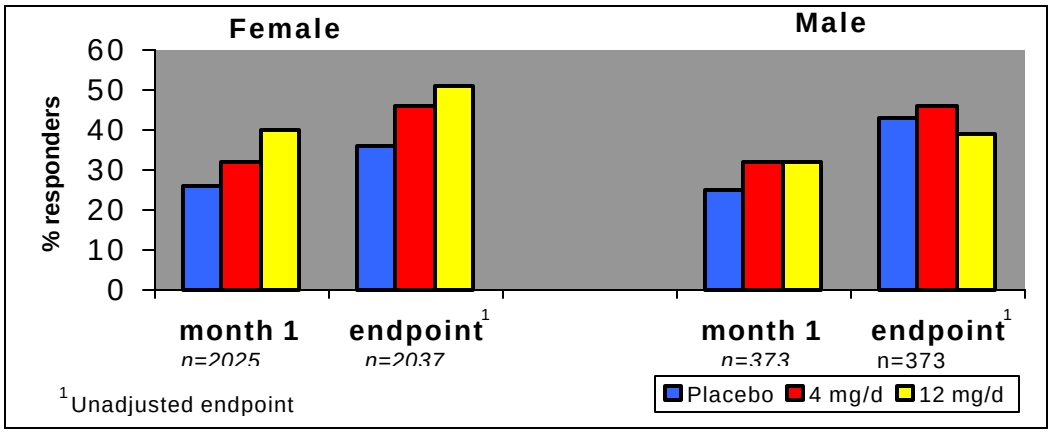
7.5 Responses in population subgroups

To explore treatment effects within subgroups, analyses assessing the SGA of relief was performed following stratification for gender, age, race, baseline severity of disease, baseline stool frequency and stool consistency, dietary fiber intake and use of concomitant psychotropic (SSRI and tricyclic antidepressant) and acid-suppressant medications.

Influence of demographic factors

Approximately 85% of the population in the three Phase 3 studies were female. Results for the pooled analysis by gender across the three Phase 3 studies at month 1 and at endpoint are shown in Figure 7-22. Among female patients, results were consistent across studies and over time. In contrast, results in male patients were less consistent. While no treatment effect was apparent at endpoint, a greater response was noted at month 1 for tegaserod than for placebo treated male patients.

Figure 7-22. Pooled (B351, B301, B307) response for unadjusted SGA of relief by gender at month 1 and at endpoint



Note: For B307, 4-12 mg/d group pooled with 4 mg/d group at month 1 and 4-12 mg/d at endpoint

Thus, the positive treatment effect observed with tegaserod was due primarily to its efficacy in females. While it appears that tegaserod may be more effective in female than in male IBS patients, given the relatively small number of male patients (15% of population), available data are insufficient to make firm conclusions regarding the efficacy of tegaserod in men. Differences in baseline variables, such as the degree of constipation symptoms, may account in part for the apparent smaller and less consistent treatment effect observed in males.

Elderly patients ($\geq$ 65 years of age) accounted for less than 10% of the population. Similar to the findings in male patients, results were not consistent over time, with a greater effect seen at endpoint than at month 1. No meaningful comparisons can be made for black patients, given the small number of black patients treated with tegaserod.

Influence of other factors

It has been suggested that those patients with more severe abdominal discomfort/pain are more resistant in terms of response to drug therapy; patients with more severe disease were not excluded from the Phase 3 studies. For the tegaserod 12 mg/day group, it did not appear

that those patients with more severe abdominal discomfort/pain responded less well than those with less severe discomfort/pain. Fiber intake also did not impact the efficacy of tegaserod. Similarly, it did not appear that frequently used concomitant medication (psychotropics and acid suppressants) impacted the efficacy of tegaserod.

However, patients (11% of study population) with looser stools during baseline (mean stool consistency < 3.5 on 7-point scale) did less well than those with more "normal" (consistency score of 3.5 – 4.5) and those with harder (> 4.5) stools during baseline.

7.6 Efficacy Discussion/Conclusions

The Phase 3 program was a global program conducted primarily in North America and in Europe. The studies were designed to enroll and randomize patients with a history of C-IBS by Rome criteria (ie, abdominal discomfort/pain and constipation). In this regard, the presence of at least mild abdominal pain during the baseline period (no exclusion for severe pain) was required to ensure the diagnosis of IBS; patients were not excluded based on baseline diary entries of stool consistency or number of bowel movements. Common concomitant medications in this population, such as tricyclic antidepressants and SSRIs were allowed. Thus, the Phase 3 program attempted to enroll a wide spectrum of patients that would reflect those likely to be treated with the drug in clinical practice.

Study B301 showed clear evidence for efficacy in a well-controlled prospective study on the primary efficacy endpoint. Both the tegaserod 4 mg/day and 12 mg/day groups had statistically significant higher response rates on the SGA of relief at endpoint than the placebo group. For the tegaserod 12 mg/day group, higher response rates compared with placebo were seen at each monthly interval. Secondary efficacy variables were consistently more favorable for the tegaserod groups than for placebo, although not all differences from placebo achieved statistical significance. For the tegaserod 12 mg/day group, statistically significant treatment differences compared with placebo were observed for the SGA of abdominal discomfort/pain.

Results in study B351 were highly consistent with those in study B301, especially for the tegaserod 12 mg/day group. For the SGA of relief (retrospective analysis in B351), the tegaserod 12 mg/day group had statistically significantly higher response rates than the placebo group. In addition, statistically significant improvements were noted in multiple daily diary variables, including days with significant abdominal discomfort/pain, days of significant abdominal bloating, stool frequency and consistency.

Response rates for the tegaserod groups in study B307, a dose-titration study, on the primary efficacy variable (SGA of relief) were not statistically significantly different from placebo. However, an unusual increase in placebo response after dose-titration make interpretation of study results difficult.

The SGA of relief results were consistent between studies B351 and B301 and consistent over time. To further evaluate the data, a number of sensitivity analyses and supportive analyses were performed.

- To assess the impact of early withdrawals, all such patients were declared nonresponders; treatment results for the SGA of relief in studies B351 and B301 were little changed and treatment differences between tegaserod groups and the placebo group remained statistically significant.
- An analysis was performed as a result of the presentation of efficacy data for the evaluation of a new drug (alosetron) for IBS at a recent (November 16, 1999) Gastrointestinal Drugs Advisory Committee meeting. The primary analysis of the efficacy data was based on a monthly responder approach. When a similar analysis was performed for the tegaserod studies, results were statistically significant ($p<0.02$) for the tegaserod 12 mg/day group, and 4-12 mg/day group, compared with the placebo group in all three studies for the SGA of relief.

In an additional supportive analysis, the percentage of weeks with at least somewhat relief and the percentage of weeks with complete or considerable relief over the entire 12-week treatment period were calculated. Both the percentage of weeks with at least somewhat relief and the percentage of weeks with complete or considerable relief were greater ($p<0.02$) in the tegaserod 12 mg/day group (and 4-12 mg/day group) than in the placebo group in all three studies.

Thus, the various supportive and sensitivity analyses confirmed that the results for the SGA of relief were consistent and robust.

The magnitude of the treatment difference for the SGA of relief at endpoint between the tegaserod 12 mg/day group and placebo group was 8% and 12% in studies B301 and B351, respectively. Response rates not adjusted for laxative use showed an identical treatment difference of 12% between tegaserod 12 mg/day and placebo at endpoint in the two studies.

The onset of action of tegaserod was apparent after one week of treatment. At Week 1, the percentage of patients with at least somewhat relief was greater in the tegaserod groups than in the placebo group in all three studies. This effect was sustained in the tegaserod 12 mg/day groups for the 12-week study duration in studies B351 and B301.

Finally, it is important to note that the secondary efficacy variables were used (ie, same question and scale for weekly SGAs and daily diary variables) and administered in the same way (ie, self-administered via patient diary) in each study. For the daily diary variables (days with significant abdominal discomfort/pain, days with significant bloating, stool frequency and consistency) and the SGA of abdominal discomfort/pain and SGA of bowel habits, favorable results for tegaserod 12 mg/day compared with placebo were consistently seen in study B351 and B301.

Overall, the totality of the data provides strong evidence that tegaserod is effective in the treatment of patients with C-IBS. The SGA of relief is a global assessment that integrates the important symptoms of IBS (abdominal discomfort and pain, altered bowel habit) and encompasses overall well being. Although performed as a retrospective analysis in study B351, results for the SGA of relief were consistent between studies B351 and B301, consistent over time and supported by the secondary efficacy variables in both studies.

8 Safety Analysis

The table below summarizes the number of subjects (patients and healthy subjects) exposed to tegaserod during the clinical development program.

Table 8-1. Duration of exposure: all subjects

Duration of exposure	Placebo n=1185 n (%)	Tegaserod All groups n=3510 n (%)	All treatments n =4606 n (%)
≥1 day	1185 (100.0)	3507 (100.0)	4603 (100.0)
≥7 days	1103 (93.1)	3113 (88.8)	4129 (89.7)
≥30 days	930 (78.5)	2541 (72.5)	3427 (74.5)
≥85 days	661 (55.8)	1874 (53.2)	2517 (54.7)
≥ 180 days	18 (1.5)	418 (11.9)	443 (9.6)
≥270 days	0	338 (9.6)	342 (7.4)
≥335 days	0	302 (8.6)	306 (6.7)
≥365 days	0	185 (5.3)	193 (4.2)

The evaluation of the safety of tegaserod in the treatment of C-IBS is based primarily on the results of studies of at least 12 weeks duration in patients with C-IBS: three placebo-controlled Phase 3 studies (B301, B307, B351), two placebo-controlled Phase 2 studies (B251, B202) and one long-term, open-label study (B209).

8.1 Demographics, disposition and exposure

8.1.1 Safety population demographics

The demographic characteristics of the pooled Phase 3 population were comparable in the different dosage groups, as is shown in Table 8-2.

Table 8-2. Demographic characteristics: pooled Phase 3 studies

Variable	Placebo N=837	Tegaserod 4 mg/d N=844	Tegaserod 12 mg/d N=560	Tegaserod titration 4/12 mg/d N=275	Tegaserod All groups N=1679	All N=2516
Sex n (%)						
Male	130 (15.5)	135 (16.0)	83 (14.8)	42 (15.3)	260 (15.5)	390 (15.5)
Female	707 (84.5)	709 (84.0)	477 (85.2)	233 (84.7)	1419 (84.5)	2126 (84.5)
Race n (%)						
Caucasian	770 (92.0)	774 (91.7)	532 (95.0)	244 (88.7)	1550 (92.3)	2320 (92.2)
Black	43 (5.1)	43 (5.1)	18 (3.2)	17 (6.2)	78 (4.6)	121 (4.8)
Other	24 (2.9)	27 (3.2)	10 (1.8)	14 (5.1)	51 (3.0)	75 (3.0)
Age (yr)						
Mean	45.0	44.3	44.8	45.6	44.7	44.8
SD	13.28	13.46	13.19	13.83	13.43	13.38
Range	18-85	17-89	13-85	19-83	13-89	13-89
Age category n (%)						
12-<18 yr	0	1 (0.1)	2 (0.4)	0	3 (0.2)	3 (0.1)
18-<65 yr	753 (90.0)	764 (90.5)	511 (91.3)	245 (89.1)	1520 (90.5)	2273 (90.3)
65-<75 yr	70 (8.4)	67 (7.9)	38 (6.8)	18 (6.5)	123 (7.3)	193 (7.7)
>=75 yr	14 (1.7)	12 (1.4)	9 (1.6)	12 (4.4)	33 (2.0)	47 (1.9)
Duration of C-IBS (yr)						
Mean	13.9	13.6	14.1	13.9	13.8	13.8
SD	12.86	12.46	12.97	13.03	12.72	12.76
Range	0.3-61.0	0.3-66.8	0.2-68.0	0.5-60.0	0.2-68.0	0.2-68.0

The population was predominantly female, Caucasian, middle-aged, with chronic disease. The characteristics of the Phase 2 population was similar.

8.1.2 Extent of exposure

The Phase 3 studies were of 12 weeks duration, with 81% of patients completing the studies; 67% completed 85 days as shown in Table 8-3. In the pooled Phase2/3 studies, 1470 patients had been treated with tegaserod overall for at least 85 days, with 74 of those patients on 24 mg/day.

Table 8-3. Duration of exposure: Pooled Phase 3 studies in C-IBS

Duration of exposure	Placebo N=837 n (%)	Tegaserod 4 mg/d N=844 n (%)	Tegaserod 12 mg/d N=560 n (%)	Tegaserod titration 4/12 mg/d N=275 n (%)	Tegaserod All groups N=1679 n (%)	All treatments N=2516 n (%)
>=1 day	837 (100)	843 (100)	560 (100)	274 (100)	1677 (100)	2514 (100)
>=7 days	825 (98.6)	816 (96.8)	541 (96.6)	270 (98.5)	1627 (97.0)	2452 (97.5)
>=30 days	781 (93.3)	759 (90.0)	511 (91.3)	255 (93.1)	1525 (90.9)	2306 (91.7)
>=85 days	564 (67.4)	555 (65.8)	380 (67.9)	184 (67.2)	1119 (66.7)	1683 (66.9)

For long-term study information, please see Section 8.7.

8.1.3 Disposition of patients

The disposition of patients, is summarized, by dosage group for the pooled Phase 3 studies in Table 8-4.

In the Phase 3 studies, discontinuations due to adverse events (AEs) were marginally more frequent in the tegaserod-treated patients than in those on placebo (6.8% v 5.1%) but without any dose-relationship. AEs, which led to discontinuations, are reviewed below. In Phase 2 the discontinuation rates due to AEs were similar with 8.3% for tegaserod and 9.3% for placebo.

Table 8-4. Disposition of patients: pooled Phase 3 studies in C-IBS

Disposition/Principal reason	Placebo groups	Tegaserod 4 mg/d	Tegaserod 12mg/d	Tegaserod titration 4-12 mg/d	Tegaserod All groups	All treatments
	N=837 n (%)	N=844 n (%)	N=560 n (%)	N=275 n (%)	N=1679 n (%)	N=2516 n (%)
Completed	697 (83.3)	671 (79.5)	465 (83.0)	231 (84.0)	1367 (81.4)	2064 (82.0)
Total discontinued	140 (16.7)	173 (20.5)	95 (17.0)	44 (16.0)	312 (18.6)	452 (18.0)
Adverse event	43 (5.1)	60 (7.1)	34 (6.1)	21 (7.6)	115 (6.8)	158 (6.3)
Death	0	1 (0.1)	0	0	1 (0.1)	1 (0.0)
Withdrawal of consent	32 (3.8)	38 (4.5)	23 (4.1)	10 (3.6)	71 (4.2)	103 (4.1)
Protocol violation	9 (1.1)	16 (1.9)	11 (2.0)	1 (0.4)	28 (1.7)	37 (1.5)
Unsatisfactory effect	26 (3.1)	22 (2.6)	15 (2.7)	3 (1.1)	40 (2.4)	66 (2.6)
Failure to return	29 (3.5)	33 (3.9)	10 (1.8)	6 (2.2)	49 (2.9)	78 (3.1)
Abnormal laboratory value	0	1 (0.1)	2 (0.4)	2 (0.7)	5 (0.3)	5 (0.2)
Administration problems	1 (0.1)	1 (0.1)	0	1 (0.4)	2 (0.1)	3 (0.1)
Subject's condition[1]	0	1 (0.1)	0	0	1 (0.1)	1 (0.0)

[1] Subject's condition no longer requiring further therapy.

8.2 Adverse events

8.2.1 Methodology

An adverse event (AE) was defined as any adverse medical change from the patient's baseline (or pretreatment) condition which occurred during the course of the study, after initiation of treatment, whether considered treatment-related or not.

8.2.2 Most commonly reported AEs

The most commonly reported AEs in the pooled Phase 3 studies (5% in either the tegaserod or placebo patients) are summarized in Table 8-5.

Table 8-5. Adverse events reported at frequency 5% in any dosage group: pooled Phase 3 studies

Adverse event	Placebo	Tegaserod 4 mg/d	Tegaserod 12 mg/d	Tegaserod titration 4/12 mg/d	Tegaserod All dosages
	N=837 n (%)	N=844 n (%)	N=560 n (%)	N=275 n (%)	N=1679 n (%)
Headache	177 (21.1)	181 (21.4)	130 (23.2)	47 (17.1)	358 (21.3)
Abdominal pain	152 (18.2)	168 (19.9)	105 (18.8)	59 (21.5)	332 (19.8)
Diarrhea	45 (5.4)	96 (11.4)	68 (12.1)	32 (11.6)	196 (11.7)
Nausea	72 (8.6)	78 (9.2)	55 (9.8)	21 (7.6)	154 (9.2)
Flatulence	55 (6.6)	63 (7.5)	40 (7.1)	22 (8.0)	125 (7.4)
Back pain	45 (5.4)	53 (6.3)	45 (8.0)	15 (5.5)	113 (6.7)
Influenza-like symptoms	46 (5.5)	55 (6.5)	42 (7.5)	10 (3.6)	107 (6.4)
URT infection	70 (8.4)	50 (5.9)	27 (4.8)	26 (9.5)	103 (6.1)
Dyspepsia	47 (5.6)	48 (5.7)	34 (6.1)	18 (6.5)	100 (6.0)
Dizziness	46 (5.5)	54 (6.4)	32 (5.7)	8 (2.9)	94 (5.6)
Pharyngitis	26 (3.1)	26 (3.1)	20 (3.6)	14 (5.1)	60 (3.6)

Diarrhea is the only AE that appears to be clearly more frequent in the tegaserod than in the placebo groups (11.7% v 5.4%) but without any apparent dose-relationship. The periods during which diarrhea was first reported by patients in the Phase 3 studies are summarized in Table 8-6. This shows that almost half of the cases of diarrhea in the tegaserod patients were reported for the first time during the first week of treatment, with over half of these being reported on the first day. After the first week, the frequency of first occurrence of diarrhea was only marginally greater in the tegaserod patients compared to the placebo patients. The median duration of the first diarrhea episode was the same for tegaserod and placebo (2 days each). The majority of patients (tegaserod 75%, placebo 72%) reported only a single episode of diarrhea.

Table 8-6. First occurrence of diarrhea (number and %), by time interval and treatment: pooled Phase 3 studies

Time at onset (days)	Placebo (N=837)	Tegaserod (N=1679)
	n (%)	n (%)
1	2 (0.2)	57 (3.4)
2-7	2 (0.2)	30 (1.8)
8-29	22 (2.6)	46 (2.7)
30-59	11 (1.3)	34 (2.0)
60	8 (1.0)	28 (1.7)

8.3 Discontinuations due to AEs

The rate of discontinuation due to AEs was not high overall, but the rate was marginally increased in the tegaserod-treated patients relative to placebo in the pooled Phase 3 studies. The same tendency is noted for the pooled Phase 2/3 studies.

The most frequent AEs leading to discontinuation (5% of patients treated) in the pooled Phase 2/3 studies are summarized in Tables 8-7. GI symptoms of IBS (diarrhea, abdominal pain, flatulence, nausea, and dyspepsia) were among the most frequent causes of discontinuation. Most of the other common AEs leading to discontinuation were non-specific (dizziness, headache, fatigue, dyspnea, non-specific back or chest pain, asthenia etc). The high rate of discontinuations because of female reproductive disorders reflects largely the obligatory discontinuation for any woman becoming pregnant while on study, this being recorded as an AE. The most evident imbalance between the tegaserod and placebo groups is that of discontinuations because of diarrhea, however the discontinuation rate due to diarrhea was low, 2.1%.

Table 8-7. Adverse events which led to discontinuation in at least 0.5% of patients in any treatment group: pooled Phase 2/3 studies

Body System/Adverse Event	Placebo N=988 n(%)	Tegaserod n=2198 n (%)
Discontinuations because of any AE	62 (6.3)	184 (8.4)
GI disorders	34 (3.4)	103 (4.7)
Diarrhea	6 (0.6)	46 (2.1)
Abdominal pain	19 (1.9)	37 (1.7)
Flatulence	7 (0.7)	25 (1.1)
Nausea	8 (0.8)	9 (0.4)
CNS disorders	20 (2.0)	37 (1.7)
Dizziness	12 (1.2)	16 (0.7)
Headache	9 (0.9)	16 (0.7)
General disorders	7 (0.7)	20 (0.9)
Skin disorders	9 (0.9)	16 (0.7)
Female reproductive disorders	6 (0.6)	11 (0.5)
Unintended pregnancy	5 (0.5)	8 (0.4)
Psychiatric disorders	7 (0.7)	7 (0.3)
Musculo-skeletal disorders	4 (0.4)	7 (0.3)

8.4 Deaths/Serious adverse events

8.4.1 Deaths

There was one death in the completed studies:

- A patient in study B301 committed suicide after 36 days in the study. She had a 14-year history of mild depression, and had received tricyclic antidepressant drug therapy. Her childhood had been marked by the suicide of her mother. The investigator did not consider this event to be related to tegaserod.

There were no other deaths in the studies ongoing up to 31 March 2000.

8.4.2 Serious adverse events

The frequency of serious adverse events (SAE) was similar between tegaserod and placebo both in Phase 2 and Phase 3. In the long-term studies, the frequency was approximately twice as high as would be expected because of the longer treatment duration (Table 8-8).

Table 8-8. Frequency of SAEs: All completed studies

	Placebo N=1185	Tegaserod
Phase 3	13/837 (1.6%)	30/1670 (1.8%)
Phase 2	5/151 (3.3%)	10/519 (1.9%)
Long-term	-	28/675 (4.1%)

Many AES, particularly GI disorders, were classified as serious because patients were hospitalized for diagnostic work-up of symptoms for which no serious organic cause could be identified. Those SAEs reported in tegaserod patients are summarized in Table 8-9. Overall 4 SAEs were considered to be possibly or probably related to the study medication: abdominal pain (n=2), gastritis (n=1), supraventricular tachycardia (n=1) and hypoglycemia (n=1). One SAE was fatal (see above).

Table 8-9. Individual SAEs in all completed studies (tegaserod patients)

Body System **Adverse event**	**Patient No (dose)**	**Adverse event**	**Patient No (dose)**
Gastrointestinal			
Abdominal pain	B301/104/9 (4); B351/513/34 (12); B307/748/21*(12); B209/13/14* (12); B251/40/6 (24)	Hiatal hernia	B351/529/13 (12)
Appendicitis	B209/11/39 (12)	Ileus	B209/28/6 (12)
Diverticulitis	B204/6/6 (12)	Nausea	B251/5/1 (24)
Constipation	B209/10/19 (12)	Pancreatic cyst	B301/112/9 (4)
Flatulence	B209/7/1 (4)	Rectocele	B351/517/24 (12)
Gastritis	W352/1/17* (12)	Sub-ileus	B251/30/3 (12); B251/42/7 (1)
Gastroenteritis	B351/531/24 (4)		
Cardiovascular			
Angina pectoris	B307/763/5 (4)	SV tachycardia, syncope	B204/10/5* (12)
Fluid overload & CHF	W354/1/17 (12)	Tachyarrhythmia, atrial fibrillation	B301/114/9 (4)
Hypertension	B209/28/23 (12)	Thrombophlebitis	B209/13/7 (12)
Myocardial infarction	B251/24/6 (4)		
Central nervous system			
Headache	B202/11/7 (24)	Neuropathy (cervical hernia)	B307/714/2 (4)
Endocrine			
Goiter	B209/31/18 (12)		

Body System Adverse event	Patient No (dose)	Adverse event	Patient No (dose)
Female reproductive			
Mastitis	B351/517/18 (12)	Threatened miscarriage	B209/13/19 (4)
Menorrhagia	B209/26/19 (12)	Ovarian cyst	B209/11/39 (12); B209/26/6 (12); B209/28/4 (12); B307/721/2 (12); B351/518/27 (12)
Miscarriage	B351/503/13 (12); B351/518/26 (12); B307/715/28 (4);		
General			
Accidental trauma	B209/4/4 (12); B251/44/5 (1); B301/134/15 (12)	Chest pain	B209/28/31(4); B209/27/7 (4); B301/174/1 (4); B307/734/15 (4)
Hematology			
Anemia (syncope)	B301/207/2(4)		
Liver/biliary			
Cholelithiasis	B209/21/6 (12); B209/28/31 (4)	Gallbladder dysfunction	B351/524/1 (12)
Metabolic			
Hypoglycemia	B251/32/4* (1)		
Musculoskeletal			
Abdominal hernia	B251/42/7 (1)	Costochondritis	B209/29/6 (4)
Back pain	B209/20/14 (12)		
Neoplasms			
Basal cell carcinoma	B209/28/18 (4)	Cervical carcinoma	B301/142/9 (12)
Breast carcinoma	B251/16/9 (24); B251/22/11 (24); B351/503/5 (4)		
Psychiatric			
Anxiety/bipolar disorder	B307/730/2 (4/12)	Suicide/attempted suicide	B301/147/1** (4)
Depression	B209/28/23 (12); B209/2/3 (4); B351/524/3 (4)		
Respiratory			
Pneumonia	B307/705/2 (4)	Pulmonary granuloma	B351/524/6 (4)
Skin & appendages			
Keratoacanthoma	B251/4/3 (4)	Urticaria	B209/2/13 (4)
Urinary system			
Nephrolithiasis	B251/33/1 (24)	Urinary tract infection	B209/20/8 (12)
Prostatitis	B209/4/5 (4)		
Vision			
Retinal hemorrhage	B301/102/10 (4)		
Elective procedures			
Abortion	B209/9/9 (12)	Hysterectomy	B307/792/7 (4); B204/2/8 (4)
Kidney transplant	W354/1/11 (12)	Rectocele surgery	B209/2/5 (4)

*) possibly or probably related to study drug. **) fatal

All SAEs reported to the sponsor for those studies ongoing on 31 October 1999, were judged to be unrelated or unlikely to be due to the study medication. None of the available histories suggest a drug relationship, with most of the events being expected or the consequence of circumstances extraneous to the studies. The SAEs observed in the ongoing studies had a similar pattern and frequency.

8.4.3 Pregnancies

A total of 20 pregnancies were reported (13 in the phase 3 studies and 7 in the long-term studies). Fifteen (0.4%) patients in the total tegaserod group and 5 (0.4%) patients in the placebo group became pregnant during these studies. The frequency of pregnancies was similar across treatment groups. All pregnant patients were withdrawn from the studies.

Four patients (3/15 in the total tegaserod group and 1/5 in the placebo group) experienced complications (miscarriages). Two of the three patients in the total tegaserod group who reported miscarriages had predisposing histories. Overall there were 4 and 1 elective abortions in the tegaserod and the placebo group, respectively and 6 and 3 healthy babies born, respectively. In two of the tegaserod cases, the outcome is unknown.

8.5 Clinical laboratory data

Standard laboratory variables of serum biochemistry, hematology and urinalysis were measured in all studies.

In Phase 3, pooled analyses of serum biochemistry and hematology showed the mean changes in both tegaserod and placebo groups to be negligible for all variables with notable abnormalities rare and no suggestion of a drug effect.

In particular, analysis of changes in liver enzyme values (serum transaminase activity, total bilirubin and alkaline phosphatases) did not indicate any treatment effect (data not shown).

Urinalysis did not show any treatment imbalance.

Results of the Phase 2 and long-term studies were similar.

Discontinuations for laboratory abnormalities

In Phase 2/3 and the long-term studies 11 patients discontinued because of laboratory abnormalities (Table 8-10). There was no evidence that these were due to treatment with tegaserod although for one of them, a case of hypereosinophilia without any clinical manifestation of hypersensitivity, the data did not allow an adequate assessment as no rechallenge was undertaken.

Table 8-10. Discontinuations due to laboratory abnormalities (Phase 2/3 and long-term studies)

Variable	Dose	Subj No.	Max. abnormal*	Comment
ALT	12 mg	B351/523/0033	100 U/L	baseline abnormal; no worsening on treatment
CPK	4 mg	B351/550/0003	626 U/L	baseline abnormal; normal on treatment
	12 mg	B351/522/0037	293 U/L	baseline abnormal; similar on treatment
	4 mg	B307/733/0028	6070 U/L	vigorous exercise
Bilirubin	PBO	B202/016/0004	2.9 mg/dL	Gilbert syndrome
Cholesterol	1 mg	B202/005/0004	8.0 mmol/L	similar at baseline
Glucose	1 mg	B251/032/0004	2.3 mmol/L	Continued after d/c
WBC	4 mg	B307/733/0007	2.1 10*9/L	baseline abnormal; similar on treatment
Eosinophils	4 mg	B209/017/0001	1.39 10*9/L	after d/c: 0.53 10*9/L
Platelets	4 mg	B301/167/0006	34 10*9/L	single value, probable lab error
Hct	4 mg	B301/207/0002	0.35 L/L	similar at baseline

*) after beginning of treatment with study medication

8.6 Other Safety Assessments

8.6.1 Blood Pressure

While animal studies did not show a cardiovascular effect of tegaserod at human therapeutic doses, early studies in healthy subjects using the i.v. formulation, and a few cases of healthy subjects exposed to single oral doses of $\geq$ 25 mg tegaserod indicated that in rare instances, tegaserod treatment may be associated with symptomatic reductions in blood pressure.

For this reason, in the Phase 2 and 3 programs, particular attention was paid to a comprehensive recording and analysis of the effects of tegaserod on blood pressure and pulse rate. An orthostatic blood pressure reduction was defined as a reduction in standing relative to supine systolic pressure of $\geq$20 mm Hg and/or a reduction in diastolic blood pressure of $\geq$10 mm Hg.[24]

In phase 2/3 studies, the frequency of notably abnormal systolic or diastolic blood pressures supine or standing (3-minute value) was very similar between the tegaserod and placebo groups. There was no suggestion for tegaserod having an effect on blood pressure or pulse rate. In the phase 3 studies, the frequency of orthostatic blood pressure lowering during the course of the 12-week treatment was 35% in the tegaserod group and 36% in the placebo group.

8.6.1.1 Symptoms suggestive of orthostatic hypotension (OH)

In the Phase 3 studies AEs suggestive of OH were reported with similar frequencies in the tegaserod and placebo groups. The most common AE was dizziness, which was reported with similar frequencies in both treatment groups; (postural) hypotension was more frequent with placebo (Table 8-11). On the other hand, syncope was more frequently reported in the tegaserod group than the placebo group (0.5% vs. 0.1%). In all but one case, fainting was reported as an isolated event and in no case was a therapy prescribed nor did any patient

discontinue the study prematurely because of this event. In the 8 patients on tegaserod the drug relationship was classified by the investigator as "none" (n=2), "unlikely" (n=4), and "possibly" (n=2); one patient was known to have an orthostatic dysregulation, and in one patient fainting occurred during blood sampling. In 6/8 patients the blood pressure was unchanged compared to baseline, in the remaining patients it was slightly reduced without signs for an orthostatic reaction.

Table 8-11. Number (%) of patients with adverse events suggestive of orthostatic hypotension in Phase 3 studies

	Tegaserod N=1679 n (%)	Placebo N=837 n (%)
Total patients with symptoms suggestive of orthostatic hypotension	107 (6.4)	55 (6.6)
Dizziness	95 (5.6)	46 (5.5)
Syncope	8 (0.5)	1 (0.1)
Hypotension	7 (0.4)	7 (0.8)
Hypotension postural	0	2 (0.2)
Circulatory failure	0	1 (0.1)

8.6.1.2 Discontinuations due to orthostatic hypotension in the Phase 2/3 and long-term study B209

The frequency of patients who discontinued from the studies due to a single AE suggestive of OH was slightly higher (0.4%) in the tegaserod group, than in the placebo group (0.1%). The frequency of patients discontinued from the studies due to one or more AEs including at least one AE suggestive of OH was the same in the tegaserod and placebo groups (1%). The percentage of tegaserod patients who discontinued long-term treatment for these symptoms was lower.

8.7 Long-term safety (study B209)

A total of 567 patients with C-IBS were safety analyzable in the 12-month open-label study B209. The selection criteria were similar to those in the Phase 3 studies, with the exception of an upper age limit of 70 years.

A total of 377 patients received tegaserod for 6 months (180 days) and 152 for 365 days. A total of 298 patients were treated for at least 335 days (Table 8-12). Compliance was good, with only 6% of patients receiving less than 75% of the prescribed tegaserod.

Table 8-12. Duration of exposure in long-term study B209

Duration of exposure	Tegaserod N=567 n (%)
≥1 day	567 (100)
≥7 days	560 (98.8)
≥30 days	530 (93.5)
≥85 days	466 (82.2)
≥180 days	377 (66.5)
≥270 days	329 (58.0)
≥335 days	298 (52.6)
≥365 days	152 (26.8)

Ninety-one percent were female, 93% Caucasian, mean age 44 years, and the mean disease duration of 12 years.

Overall, 304/579 (53%) of patients completed the study as planned. The main reasons for discontinuation were lack of effect (12%), adverse events (11%), withdrawal of consent (11%), and lost to follow-up (8%). The discontinuation rate due to AEs, was higher than the 7% of tegaserod-treated patients in Phase 2/3 studies (Table 8-6), but consistent when considering the longer duration of the study.

The overall proportion of patients reporting AEs was 80%. GI complaints were the most common (40% of patients), followed by CNS disorders (30%). Headache (30%) was the most frequently reported AE (Table 8-13).

Table 8-13. Most frequently (5% of patients) reported adverse events: long-term study (B209) in C-IBS

Adverse event	Tegaserod (N = 567) n (%)
Total patients with adverse events	452 (79.7)
Headache	167 (29.5)
Abdominal pain	97 (17.1)
Upper resp. tract. infection	92 (16.2)
Diarrhea	83 (14.6)
Back pain	49 (8.6)
Sinusitis	47 (8.3)
Nausea	46 (8.1)
Flatulence	43 (7.6)
Dyspepsia	41 (7.2)
Rhinitis	39 (6.9)
Influenza-like symptoms	34 (6.0)
Pharyngitis	30 (5.3)
Insomnia	29 (5.1)

Discontinuations because of AEs occurred in 11.5% of patients. The most frequent AEs responsible were diarrhea 3.5%, abdominal pain 2.8%, flatulence 2.6%, and headache 1.1%.

SAEs have been previously reviewed. Of note was the hospitalization of 3 women because of symptomatic ovarian cysts. The overall findings are discussed section 8.8.2.

Standard 12-lead ECGs were carried out before and during treatment and the findings together with AEs of cardiac arrhythmia have been analyzed and are discussed in section 8.8.1.

The second open-label long-term study (B204) was discontinued prematurely for administrative reasons. One-hundred seventy patients had been enrolled, and the maximal treatment duration for these subjects was less then 6 months. The results were similar to those obtained in study B209.

Overall, the safety profile obtained from the analysis of the long-term studies was consistent with that obtained from the placebo-comparative analyses in the pooled Phase 2/3 studies.

8.8 Notable safety issues

8.8.1 Electrocardiography

8.8.1.1 Preclinical cardiac repolarization studies

Some gastro-prokinetic drugs, like cisapride and erythromycin, are known to induce QT interval prolongation, sometimes associated with Torsade de Pointes (TdP). Recent evidence suggests that these drugs block delayed rectifier potassium currents (I_K) in the heart (without involvement of 5-HT_4 receptors), thereby causing a slowing of cardiac repolarization. Three *in vitro* studies were carried out to specifically address the potential to impair cardiac repolarization:

- The first study was designed to directly examine the effects of tegaserod on I_{Kr}, the component of the delayed rectifier potassium currents which were inhibited by drugs associated with QT interval prolongation and TdP. The effects on the corresponding potassium channel, encoded by the human ether-a-go-go-related gene (HERG) and stably transfected into mammalian cells (HEK 293 cells), were investigated using whole cell patch clamp methodology.
- Tegaserod was assessed for effects on intracellularly recorded action potential parameters in Guinea-pig isolated papillary muscle preparations electrically paced at 1 Hz.
- The effects of tegaserod, its main human metabolite (5-methoxyindole-3-carboxylic acid glucuronide), cisapride and erythromycin on cardiac repolarization were examined using the isolated perfused rabbit heart (Langendorff) model.

The results of the three *in vitro* models showed that tegaserod had no potential to impair cardiac repolarization at therapeutic concentrations. The results of an *in vivo* safety pharmacology study in conscious dogs addressing potential effects on ECG parameters also confirmed that tegaserod and its main human metabolite lack QT interval prolongation activity at therapeutic plasma concentrations.

8.8.1.2 Phase 3 and long-term ECG evaluations

In the Phase 3 studies an ECG was obtained 1.5 to 2.5 hours (corresponding to approximate T_{max}) after the first and last doses of study drug. In the Phase 3 studies, and in study B209, an independent company interpreted the ECG tracings using the Sigmascan technique. An abnormal PR interval was defined as an interval >200 msec, an abnormal QRS interval as an interval >120 msec, and an abnormal QTc interval as an interval >499 msec. A cutoff for the uncorrected QT interval was not defined. In addition, for the QTc interval, prolongations from baseline were classified as normal, borderline prolonged, or prolonged according to the Committee for Proprietary Medicinal Products (CPMP) recommendations[25].

Ventricular rate and PQ-, QRS-, and QT-intervals (Phase 3 and study B209)

In Phase 3 studies the changes in mean ventricular rate and mean PQ-, QRS-, and QT-intervals were comparable for the tegaserod and placebo groups. In the long-term study data were similar to the Phase 3 studies showing no treatment-related effect on ECG intervals.

QTc interval (Phase 3 and study B209)

The changes in mean QTc intervals were comparable in the tegaserod and placebo groups. The percentages of patients with an increase in the QTc interval of 30 to 60 msec or an increase of >60 msec from baseline, the percentage of patients with at least one borderline or prolonged QTc interval after the first dose of the study drug, the number of patients with normal baseline values and at least one borderline or prolonged QTc interval value were comparable in the tegaserod and placebo groups. The frequency of any newly occurring QTc intervals of >499 msec was low. There was no dose-response relationship between the tegaserod 4 and 12 mg/day groups. The long-term data (B209) was similar to the Phase 3 data showing no treatment effect on ECG intervals. QTc interval data are summarized, by treatment group, in Table 8-14.

Table 8-14. Summary of QTc interval data in Phase 3 and study B209

		Pooled Phase 3 studies			Study B209
	Placebo	4 mg/d	12 mg/d	All tegaserod	All tegaserod
	N=837	N=844	N=560	N=1679	N=675
	n(%)	n(%)	n(%)	n(%)	n(%)
Baseline (mean, SD, msec)	399 ± 22	401 ± 23	399 ± 24	400 ± 24	396 ± 22
Change from baseline, at endpoint (mean, SD, msec)	3.1 ± 22.7	1.6 ± 22.98	3.8 ± 21.2	2.1 ± 22.2	-0.7 ± 20.1
Increase by 30 to 60 msec	155 (18.7)	163 (19.6)	107 (19.5)	308 (18.6)	67 (12.5)
Increase by >60 msec	11 (1.3)	5 (0.6)	7 (1.3)	15 (0.9)	4 (0.7)
Normal at baseline to prolonged at least once during study[2]	5 (0.6)	3 (0.4)	2 (0.4)	7 (0.4)	0
Normal at baseline to borderline at least once during study[1]	33 (4.0)	31 (3.8)	20 (3.6)	59 (3.5)	9 (1.7)
Borderline at baseline to prolonged at least once during the study[1, 2]	3 (0.4)	4 (0.5)	0	5 (0.3)	0

[1] Borderline: males ≥430 to ≤450 msec; females ≥450 to ≤470 msec.
[2] Prolonged: males >450 msec; females >470 msec.

8.8.1.3 ECG abnormalities

Frequency of ECG abnormalities

In the Phase 3 studies, the frequency of newly occurring or worsening ECG abnormalities was similar for the tegaserod and the placebo groups.

The most frequent newly occurring ECG abnormalities were changes in T wave morphology (i.e., flattening, inversion, biphasic, or other) which however was similar between tegaserod and placebo. Other abnormalities seen in >1% of patients in the tegaserod group were ST-segment depression and first degree AV block. The frequency of ST-segment depression was slightly higher in the tegaserod group than in the placebo group .

In elderly patients (>65 years) the overall frequency of ECG abnormalities was higher in the tegaserod group than in the placebo group (21% vs. 12%) primarily due to a larger number of patients with ST-segment depression and/or T-wave alterations. According to an external consultant in cardiology (Dr. J. Morganroth, Philadelphia) there is no signal that tegaserod causes ST-T wave changes.

Similar results were obtained in the Phase 2 studies and the long-term studies.

8.8.2 Ovarian cysts

In the Integrated Summary of Safety (ISS) of the NDA submission, nine cases of ovarian cyst were reported (8 tegaserod, one placebo patient), all of them in women aged 50 or less. Five of these cases (all tegaserod patients) were considered as serious because they required

surgery. Since the submission, additional information (from case record forms, pathology and hospital discharge reports) has been obtained and submitted to the FDA, permitting a fuller interpretation.

Although more cases of ovarian cyst were reported in tegaserod patients, comparison of the reporting frequencies does not suggest a treatment effect (Table 8-15).

Table 8-15. Numbers (percentage) of female patients with ovarian cysts

	placebo	Tegaserod
Controlled studies		
Phase 3	1[(2)]/707 (0.14)	1[(1)]/1419 (0.07)
Phase 2	0/140	2[(3)]/456 (0.44)
Combined Phase 2/3	1/847 (0.12)	3/1875 (0.16)
Uncontrolled, long-term studies	-	1[(4)]/611 (0.16)

1: B351/518/27 2: B301/163/10 3: B251/32/2, B251/32/7 4: B209/28/4

Functional, non-neoplastic, ovarian cysts are a relatively common finding in women and are generally physiologic and related to ovulatory processes. Patients are normally managed by observation with surgical resection only in cases of large, symptomatic cysts not regressing spontaneously. Of the above patients only two (B351/518/27, B209/28/4) came into the category of having functional cysts requiring surgery and both of them had been shown to have the condition before entry into the study.

8.9 Safety summary and conclusions

The data presented have been drawn from over 4000 subjects of whom over 3000 were IBS patients in well-controlled studies. The dose range investigated in healthy subjects included multiples (more then 10 times) above the therapeutic dose. The focus of the safety analysis has been on the target population, which included both women and men, aged 18 years and older, including approximately 10% elderly patients. The characteristics of the study population were largely reflective of the general IBS population. In the Phase 3 studies, which formed the core of the safety database, patients, apart from fulfilling the criteria of C-IBS, were largely unselected with respect to concomitant diseases or co-medications. Thus, this study population was representative for what is seen in the general practice in terms of IBS.

Based on its pharmacological profile, tegaserod acts as a $5HT_4$-receptor partial agonist specifically in the GI tract in terms of stimulation of motility, intestinal secretion and inhibition of visceral afferents. Even though $5HT_4$-receptors can be found in other tissues (e.g., CNS, atria), the general pharmacology investigations revealed that tegaserod lacked systemic effects regarding CNS, renal function, the respiratory, cardiovascular or the endocrine system.

At therapeutic doses, the tolerability and safety profile of tegaserod has been proved to be favorable with, apart from a transient increase in bowel motility reported as diarrhea during the initiation of therapy, an AE profile similar to placebo. Analysis of the individual and pooled databases in the controlled and long-term studies did not suggest any pharmacological effect, which might indicate that tegaserod treatment induces organ dysfunction or toxicity.

- Of the AEs considered drug-related by the investigator or leading to discontinuation from the study, only diarrhea was identified as being clearly more frequent with tegaserod than with placebo. Tegaserod-induced diarrhea appears early after the start of treatment. It does not seem to represent a significant safety problem, seldom leading (3%) to patients discontinuing treatment.
- The frequency of SAEs was low, and comparable for tegaserod and placebo patients in the Phase 2/3 placebo-controlled studies (1.8%).
- Laboratory evaluations did not suggest that tegaserod had a systemic effect.
- As expected, and in line with the pharmacokinetic findings which had shown only negligible blood-brain barrier permeation in the rat, treatment tegaserod was devoid of any CNS effects.
- ECG analyses and the AE profile did not suggest that tegaserod had any proarrhythmic effect in general or one which may have suggested a stimulatory effect on the atria. Tegaserod exposure was associated with a slightly higher frequency ST-T-wave alterations, which were, however, not considered clinically relevant.

Special safety issues that had been identified during the development program as a result of preclinical or early clinical findings have been addressed in this document, and did not reveal any safety concerns, but rather confirmed the robustness of the safety profile:

- Analyses of the ECGs in Phase 3 and a regression analysis of plasma concentrations vs. QTc interval changes in several populations did not show any unfavorable effect on cardiac repolarization, especially the QTc interval.
- Orthostatic tests did not show any effect of tegaserod on the frequency of notably low blood pressures or episodes of symptoms that can be associated with OH. The overall frequency of AEs suggestive for OH was similar between tegaserod and placebo.

Tegaserod appears to be well tolerated at the doses recommended for therapy and devoid of any organ toxicity that would preclude its long-term use in the treatment of functional GI disorders.

9 Benefits/Risk Assessment

IBS is a common chronic GI disorder having a broad spectrum of severity, which can be associated with significant disability and health care costs. Since no drugs are available which have been shown to be globally effective in this disorder, there is a major medical need for an effective treatment.

The tolerability and safety profile of tegaserod proved to be very favorable. Apart from an initial increase in the bowel motility reported as diarrhea, the AE profile of tegaserod is similar to placebo. Hematological, biochemical, and cardiovascular parameters did not show any signs of specific toxicity. The absence of effects of tegaserod on the cardiac repolarization (QTc interval) is an important pharmacodynamic feature in comparison to other prokinetic agents, such as cisapride.

Overall, the totality of the data provides strong evidence that tegaserod is effective in the treatment of patients with IBS who identify abdominal pain and discomfort, and constipation as their predominant symptoms. This statement is supported by the consistency of the data between studies, at multiple timepoints (endpoint and monthly) and between the weekly SGA and daily diary efficacy variables. The SGA of relief is a global outcome measure that integrates the key symptoms of IBS and encompasses overall well-being. Tegaserod has been shown to have a clinically and statistically significant effect compared to placebo on the patient's assessment of relief. This effect was associated with a consistent improvement of the key symptoms of IBS, such as abdominal pain and discomfort and bowel function. This effect was evident already after the first week of therapy and was sustained throughout the treatment period.

In conclusion, tegaserod has a favorable risk-benefit ratio that appears to justify its recommendation for the treatment of IBS patients.

1 Camilleri M, Prather CM. The irritable bowel syndrome: mechanisms and a practical approach to management. Ann Intern Med 1992; 116:1001-1008.

2 Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997;112: 2120-2137.

3 Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhea and constipation predominant subjects. Gut 1990;31:458-462.

4 Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. Ann Intern Med 1992:; 116:1009-1016.

5 Talley NJ. Review article: 5-Hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation:clinical implications. Aliment Pharmacol Ther 1992;6:273-289.

6 Bockaert J, Fagni L, Dumuis A. 5-HT_4 receptors: an update. Serotonergic neurons and 5-HT receptors in the CNS (eds. HH Baumgarten and M Göthert) Springer-Verlag Berlin Heidelberg. Handbook of Exp Pharmacol 1997;129:439-474.

7 Schikowski A, Mathis C, Thewiâen M, Ross H-G, Pak MA, Enck P. Dose-dependent modulation of rectal afferent sensitivity by a 5-HT_4 agonist. Gastroenterol 1999;116:A643.

8 Buchheit K, et al. The serotonin $5HT_4$ receptor: 1. Design of a new class of agonists and receptor map of the agonist recognition site. J Med Chem 1995;38:2326-2330.

9 Buchheit K, et al. The serotonin $5HT_4$ receptor: 2. Structure-activity studies of the indole carbazimidamide class of agonists. J Med Chem 1995;38:2331-2338.

[10] Pfannkuche HJ, Buhl T, Gamse R, Hoyer D, Mattes H, Buccheit KH. The properties of a new prokinetically active drug, SDZ HTF 919. Neurogastroenterol Motil 1995;7:280.

[11] Drici MD, Ebert SN, Wang WX , Rodriguez I, Liu XK, Whitfield BH,Woosley RL. Comparison of tegaserod (HTF 919) and its main human metabolite with cisapride and erythromycin on cardiac repolarization in the isolated rabbit heart. J Cardiovasc Pharmacol 1999 Jul;34(1):82-8.

12 Hoyer D, Fehlmann D, Langenegger D, Kummer J, Giger R, Mattes H, Probst A, Pfannkuche HJ. High affinity of SDZ HTF 919 and related molecules for calf and human caudate 5-HT_4 receptors. Ann NY Acad Sci USA 1998;861:267-268.

13 Jin JG, Foxx-Orenstein AE, Grider JR. Propulsion in guinea pig colon induced by 5-hydroxytryptamine via 5-HT_4 and 5-HT_3 receptors. J Pharmacol Exp Ther 1999;288:93-97.

14 Nguyen A, et al. SDZ HTF 919 stimulates canine colonic motility and transit in vivo. J Pharmacol Exp Ther 1997;280:1270-1276.

15 Fioramonti J, Millian M, Bueno L. Investigations on a 5-HT_4 agonists (SDZ HTF 919) and its main metabolite in conscious dog: effects on gastrointestinal motility and impaired gastric emptying. Gastroenterol 1998;144:A752.

16 Stoner M, Arcuni JC, Lee J, Kellum JM. A selective 5-HT_4-receptor agonist induces cAMP medicated Cl- efflux from rat colonocytes. Gastroenterol 1999;116:A648.

17 Coehlo AM, Rovira P, Fioramonti J, Bueno L. Antinociceptive properties of HTF 919 (tegaserod) a 5-HT_4 receptor partial agonist on colorectal distention in rats. Gastroenterol 2000; AGA Abstract Presentation.

18 Grider JR, Foxx-Orenstein AE. A selective 5-HT_4-receptor agonist stimulates transmitter release and activates the intestinal peristaltic reflex. Gastroenterol 1996;110:A1075.

19 Veldhuyzen Van Zanten SJO, Talley N, Bytzer P et al. Design of treatment trials of functional gastrointestinal disorders. Gut 1999;45(Suppl II):II69-II77.

20 Whitehead WE. Definition of a responder in clinical trials for functional gastrointestinal disorders: report on a symposium. Gut 1999; 45(Suppl II): II78-II79.

21 Drossman DA, Thompson WG, Talley NJ, et al. Identification of sub-groups of functional gastrointestinal disorders. Gastroenterology Int 1990;3:159-172.

22 Talley NJ, Nyren O, Drossman DA, et al. The irritable bowel syndrome: toward optimal design of controlled treatment trials. Gastroenterology Int 1993;6(4):189-211.

23 Mangel AW, Hahn BA, Heath AT, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998;26:76-81.

24 Consensus statement on the definition of orthostatic hypotension, pure automatic failure, and multiple system atrophy. J Neurol Sci 1996;144:218-219.

25 Committee for proprietary medicinal products (CPMP). The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. EMEA, Dec 17, 1997.

Appendix 1

Rome Diagnostics Criteria for IBS

To qualify, subjects must meet all three criteria based on the IBS Questionnaire as described below:

Criterion 1.	Question 1 = yes; and
Criterion 2.	Question 2, 3, 4: yes for one or more; and
Criterion 3.	Question 5: yes for two or more of a, c, or e.

IBS Questionnaire

1. In the past three months have you had continuous or repeated discomfort or pain in your lower abdomen? (Caution: this includes diffuse (upper and lower) abdominal pain/discomfort. Purely epigastric/upper abdominal pain is not acceptable).
   a. Yes
   b. No (If no, stop, the subject does not meet the definition of IBS used for this study).
2. Is this discomfort or pain typically relieved by a bowel movement?
   a. Yes
   b. No
3. Is this discomfort or pain typically associated with a change in the frequency of bowel movements (i.e. having more or fewer bowel movements)?
   a. Yes
   b. No
4. Is this discomfort typically associated with a change in the consistency of the stool (i.e. softer or harder)?
   a. Yes
   b. No
5. Would you say that at least one fourth (1/4) of the occasions or days in the last three months you have any of the following? (Check all that apply)
   a. Less than 3 bowel movements a week (0 - 2)
   b. More than three bowel movements a day
   c. Hard or lumpy stools
   d. Loose or watery stools (see also Exclusion Criterion No. 1)
   e. Straining during a bowel movement
   f. Urgency - having to rush to the bathroom for a bowel movement
   g. Feeling of incomplete bowel movement
   h. Passing mucus (white material) during a bowel movement
   i. Abdominal fullness, bloating or swelling.