Table 2

Diagnostic Criteria for Irritable Bowel Syndrome

Rome criteria
At least 3 months of continuous or recurrent symptoms of the following:
Abdominal pain or discomfort
Relieved with defecation, or
Associated with a change in frequency of stool, or
Associated with a change in consistence of stool
Two or more of the following, at least on one fourth of occasions or days:
Altered stool frequency (for research purposes "altered" may be defined as more than 3 bowel movements each day or less than 3 bowel movements each week), or
Altered stool form (lumpy/hard or loose/watery stool), or
Altered stool passage (straining, urgency, or feeling of incomplete evacuation), or
Passage of mucus, or
Bloating or feeling of abdominal distention

Manning criteria
Abdominal pain relieved by defecation
Looser stools with onset of pain
More frequent stools with onset of pain
Abdominal distention,
Passage of mucus in stools
Sensation of incomplete evacuation

Evaluation also includes a complete physical examination, sigmoidoscopy, and additional testing when indicated. Other recommended studies include examination of the stool (ova and parasites, occult blood, laxatives), complete blood count, sedimentation rate, and serum chemistries. In certain cases imaging studies (e.g., upper gastrointestinal series), colonoscopy with rectal biopsy will be needed.

IBS is truly a common chronic gastrointestinal disorder with a wide variety of severity and different pathophysiologies. Different patients have different predominant symptoms: pain/gas/bloating, diarrhea or constipation. Currently, the treatment of IBS is tailored to relieve the predominant symptom. Various forms of fiber supplementation afford only partial relief for those patients with constipation - predominant symptoms. A large segment of constipation-predominant IBS patients resort to laxative use for relief of symptoms and this is fraught with problems long term, the most significant of which is melanosis coli. Currently no prokinetic agents are approved for the treatment of constipation-predominant IBS.

The data in Table 1 demonstrate that, in Britain and the United States, IBS affects 14 to 24% of women and 5 to 19% of men. There are very few data that deal with the prevalence of IBS in non-western countries. Studies do suggest that IBS is rare in Uganda, but seem common in Japan, China, South America, and the Indian subcontinent. In the US, IBS is the most common complaint seen in an outpatient gastrointestinal practice. The majority of patients present to the physician between the ages of 30 and 50 y and prevalence decreases beyond the age of 60. IBS has a long list of associated conditions: gastroesophageal reflux disease, dysphasia, globus hystericus, fatigue, non-cardiac chest pain, urologic dysfunction, gynecologic disease (chronic

pelvic pain) and fibromyalgia. A discussion of these associated conditions is beyond the scope of this review. However, patients with irritable bowel syndrome, when compared with persons without bowel symptoms, have more non-g.i. complaints and they consult physicians more for these problems as well. In the U.S., Householder Study persons with IBS visited physicians 1.64 times per year for g.i. and 3.88 times for non-g.i. complaints compared with 0.09 and 1.77 times, respectively, for persons without bowel symptoms. In addition, this study showed that people with symptoms of IBS had missed 3 times as many work days in the year before the survey than those without bowel symptoms (13.4 days vs 4.9 days). Also, a higher proportion reported that they were too sick to work (11.3% vs 4.2%).

Table 3
Effects of Stress on IBS Symptoms

Reference	Experimental design	Summary of Results
Mendeloff et al	Unvalidated stress interview administered to IBS, IBD , controls	More stress in IBS than in IBD or healthy controls
Fava and Pavan	Standardized life event scale given to 20 IBS, 20 IBD, 20 appendicitis patients	More stressful events reported by IBS patients than other two groups
Drossman et al.	Self-report that stress affects bowel symptoms in 135 IBS and 654 controls	72.6% of IBS and 54.4% of controls reported stress led to change in stool pattern, 84.4% of IBS and 67.6% of controls reported stress led to abdominal pain
Ford et al.	Bedford College life events and difficulties interview given to 36 IBS, 12 dyspepsia, and 16 organic GI disorder patients	No relationship between stress and functional bowel disorder
Drossman et al.	Standardized life event scale given to 72 IBS patients, 82 IBS nonconsulters, and 84 controls	IBS patients reported fewer negative stressful events and perceived them as less severe; IBS nonconsulters reported more negative life events than controls; IBS patients also reported fewer positive life events
Creed et al.	Psychiatric interview based on the life events and difficulty schedule	60%-66% had experienced severe life events preceding onset of IBS vs 25% of controls for an arbitrary time
Drossman et al.	Questionnaire used to detect physical and sexual abuse among 206 female GI clinic patients	Patients with functional GI disorders were more likely to report a history of physical or sexual abuse as compared to patients with organic GI disorders
Whitehead et al.	Life event questionnaire given every 3 months for 1 year (5 times)	Stressful events more common in IBS; stress significantly correlated with number of bowel symptom, disability days, and physician visits, people with IBS showed greater reactivity to stress than people without IBS
Suls et al.	Daily rating of stress and bowel symptoms, analyzed between - and within-subjects	Daily stress was not significantly correlated with bowel symptoms in IBS patients

Psychological stress compounds gastrointestinal symptoms in everyone, but to a greater degree in patients with IBS. Although psychological stress has no diagnostic value for IBS, its identification may help in planning psychological and pharmacological adjunctive

treatment. Table 3 summarizes results of studies on the effects of the stressful life events on IBS symptoms. In general, these studies support the premise that psychological stress or emotional responses to stress affect g.i. function and produce symptoms in virtually everyone. Because the effects of stress on gut function are universal, they have no diagnostic value in IBS.

Table 4 summarizes results of studies that relate to findings of abnormal motility in IBS. This literature is indeed vast, but the key points are as follows:

a. The types of motility patterns in the colon or small intestine in patients with IBS are qualitatively similar to the contractions seen in healthy controls.

b. There is no consensus on the patterns of motility responsible for diarrhea or constipation.

c. There are some patients with diarrhea predominant IBS who have accelerated transit in the small bowel and/or colon.

d. There are some patients with constipation-predominant IBS who have slowed or delayed transit.

e. Recent studies do not support previous findings that IBS is characterized by 3 cycles per minute cooling motor activity.

f. Persons with IBS experienced increased motility when environmental or enteric stimuli factors such as psychological stress, meals, balloon inflation, and cholecystokinin lead to an exaggerated intestinal motor response.

The lack of correlation between motor disturbances and symptoms led to studies on the potential role of sensitivity (hyperalgesia). Various balloon distention studies commencing with studies in sigmoid colon and subsequently moving to the ileum and the rest of the colorectum demonstrated a significant number of patients with IBS experience awareness of distention and painful symptoms at pressure and volumes that are significantly lower than control subjects.

TABLE 4
Altered Motility Studies

	Study	Comments
ALTERED SMALL BOWEL MOTILITY		
DCC	Kumar and Wingate	Increased frequency of DCC pattern compared to healthy subjects; DCCs associated with reports of pain
	Kellow et al.	
	Gorard et al.	
PPC	Kellow et al.	No increase in prevalence of DCC during ambulatory 24 hour studies
Increased phasic pressure activity to distention and neostigmine	Kellow et al.	PPC associated with pain among IBS + D patients; no difference in frequency of PPC
	Kellow et al.	
	Gorard et al.	
MMC	Cann et al.	↑ in nonperistaltic contractions
Delayed transit	Cann et al.	
Accelerated transit	Vassallo et al.	Increased number of MMCs in IBS patients
		No increase in MMCs in IBS patients
		Delayed orocecal transit in IBS + C
		Orocecal transit measured by bean-H2 breath test in IBS + D
		Small bowel transit of solid residue accelerated in subgroup of IBS + D
ALTERED COLONIC MOTILITY		
Electrical activity	Chaudhary and Truelove	Increased phasic contraction postprandially in those with prominent gastrocolonic reflex
	Weigan et al	Refuted myoelectric hypothesis
	Snape et al.	3 cycles/minute, electrical activity more common in IBS
	Bueno et al.	Increased long spike bursts in diarrhea, irregular short spike burst activity with constipation
	Latimer et al.	Myoelectric activity similar in IBS and 'psychologic' controls
Phasic pressure activity	Connell et al.	Increased colonic contractions in constipation, reduced contractions in diarrhea
	Whitehead et al.	Increased rectosigmoid response to distention in IBS + D > IBS + C > Controls
	Bazzocchi et al.	Reduced higher amplitude contractions in constipation
	Rogers et al.	Increased sigmoid phasic activity postprandially in IBS
	Bazzocchi et al.	Increased higher amplitude (>35 mm Hg) contractions in functional diarrhea
Compliance and tone	Whitehead et al.	Rectal compliance normal
	Vassallo et al.	Fasting and postprandial colonic (descending) tone normal accelerated and delayed whole gut transit in IBS + D and IBS + C respectively
Colonic transit	Cann et al.	

DCC, discrete clustered contractions; IBS + C, constipation-predominant IBS, IBS + D, diarrhea-predominant IBS; MMC, migrating motor complex; PPC, prolonged propagated contractions.

A synopsis to the literature to date suggests the following:

i) Increased sensitivity to painful distentions in the small bowel and colon

ii) Increased sensitivity in normal intestinal function (e.g., spontaneous migrating motor complexes)

iii) Increased or unusual area of somatic referral of visual pain.

The exact mechanisms for the increased visceral sensitivity remain unknown at this time. Also, it is not known whether psychological or neurophysiological mechanisms work singularly or together in the perception of incoming signals of this sensitivity. Indeed, the complexity of these interactions provides the basis for the need to integrate education, psychological, dietary, and pharmacologic approaches to target the central and peripheral functions for patients if management in these IBS patients is to be successful. Because no psychologic phenomenon permits the clinician to identify IBS, this syndrome must be diagnosed by identifying certain symptoms consistent with the disorder and excluding other medical conditions having a similar clinical presentation. There is, of course, a risk of overdoing the diagnostic evaluation to rule out organic disease. Ergo, now-a-days- most physicians recommend a subsequential diagnostic strategy that includes the use of symptom-based criteria, a conservative evaluation strategy based on predominant symptom(s), and initiation of symptomatic treatment with reassessment in several weeks. This approach may result in misdiagnosing of preexisting colonopathies or conditions that might worsen with new therapeutic approaches.

There are multiple factors that can help in planning a diagnostic strategy.

i) The duration and severity of symptoms. New onset of symptoms, particularly in an older patient or more severe and disabling symptoms may require more extensive studies.

ii) The change of the symptoms over time.

iii) Demographic features. IBS is more common in women than men and in younger than in older patients.

iv) Referral status of the patients. Patients seen in primary care setting are less likely to require extensive evaluation.

v) Previous diagnostic evaluation.

vi) Colon cancer history in the family, especially of those cases that occurred at a younger age.

vii) the nature and extent of any psychosocial difficulties.

The initial diagnostic approach involves identification of IBS using positive symptom criteria and limited diagnostic screen. More diagnostic studies will depend on the predominant symptom subgroup, namely constipation, diarrhea, or pain/bloating. At first a minimal evaluation in patients with diarrhea predominant symptoms could include a small bowel radiograph to rule out Crohn's disease or a lactose hydrogen breath test and if negative, a therapeutic trial of loperamide. For patients with constipation-predominant symptoms a therapeutic trial of fiber supplement may be all that is required. For patients with pain as a predominant symptom, a plain abdominal radiograph during an acute episode to exclude small bowel obstruction and other abdominal pathology, and if negative, a therapeutic trial of an antispasmodic may be indicated. Treatment can be started and patients condition re-evaluated in three to six weeks. If treatment is unsuccessful or further evaluation seems needed, additional studies based on symptoms subtype can be performed at that time (Fig. 1).

IRRITABLE BOWEL SYNDROME

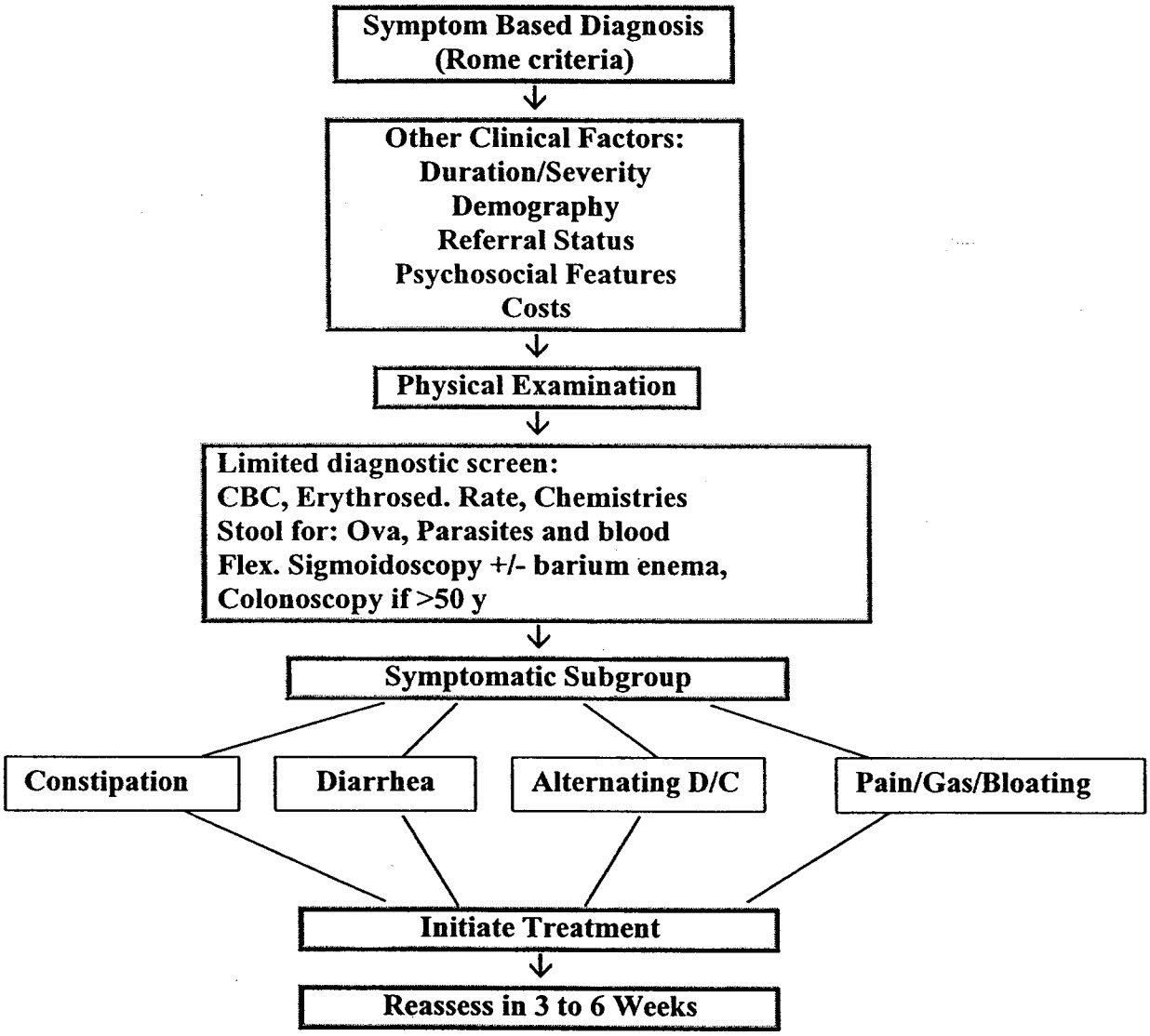

Fig. 1 - Work up of IBS

2. Treatment

The need for an effective physician-patient relationship is supported by the observation that patients with IBS have a 30 to 88% placebo response rate regardless of treatment. For all patients, the physician should establish an effective therapeutic relationship, provide patient education, reassurance, and help with dietary and lifestyle modifications when needed. Currently, the treatment strategy is based on the nature and severity of the symptoms, the degree of psychological disturbance and functional impairment, and the presence of psychosocial difficulties affecting the course of the illness. Those patients with mild symptoms usually respond to education, reassurance and simple treatments not requiring prescription medication. A smaller proportion of patients with moderate symptoms have more disability and require pharmacologic treatment directed at altered gut physiology or psychological treatments. A small proportion of patients with severe and refractory symptoms are frequently seen at referral centers, and have more constant pain and psychosocial disablement. They may require anti-depressant treatment, psychological treatments and support, and in occasional cases, referral to a multidisciplinary pain center.

When pain and bloating predominate, one could consider an antispasmotic (anticholinergic medication) particularly when symptoms are exacerbated by meals or a tricyclic (TCA) or serotonin-reuptake inhibitor antidepressant (SSRI), particularly when pain is frequent or severe. Increase dietary fiber (25 g per day) is recommended for simple constipation, although its effectiveness is inconsistent, based on several studies in reducing pain in patients with constipation-predominant IBS. Currently, there is no prokinetic medication that has proven efficacy in constipation-predominant IBS.

For diarrhea, loperamide (2 to 4 mg, up to 4 times a day) can reduce loose stools, urgency and fecal soiling and in low doses does not seem to have central nervous system effects. Cholestyramine may be considered for a subgroup of patients with cholecystectomy or who may have idiopathic bile acid malabsorption. Alosetron (LOTRONEX®) 1 mg b.i.d. po may be used in females with diarrhea-predominant IBS.

Psychological treatments are usually initiated when symptoms are severe enough to impair health-related quality of life. A patient may be referred to a mental health professional for treatment of associated psychiatric disorders, such as major depression or history of abuse that interfers with adjustment to illness. To increase patient motivation for psychological treatment, the physician must explain that along with primary care physician, a mental health professional is indeed part of a treatment team involved in the patients overall plan of care. Several psychological treatments have been studied in patients with IBS. There are no comparative data to determine which treatments are superior. Additional studies are needed to determine the relevance of efficacy of psychological treatments for various subgroups of patients with IBS.

Antidepressants (mentioned above) are recommended for severe or refractory symptoms of pain, and may be helpful for less severe symptoms. They have neuromodulatory and analgesic

properties independent of their psychotropic effect, and these effects may occur sooner and in lower dosages than is the case when these drugs are used for treatment of depression. Most studies have evaluated treatment with tricyclic antidepressants rather than SSRIs in patients with IBS, but no comparative studies have been performed. However the selective serotonin reuptake inhibitors are now in common use because of their low side effect profile and better safety than tricyclic antidepressants. Anxiolytics are generally not recommended because of weak treatment effects, a potential for physical dependence, and interaction with other drugs and alcohol.

B. Tegaserod (Zelmac™)

1. Introduction

Zelmac™ Tegaserod hydrogen maleate (tablets) contain tegaserod as a hydrogen maleate. Categorized as an oral gastrointestinal pro-motility agent, tegaserod hydrogen maleate is chemically designated as 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylearbazimidamide hydrogen maleate. The empirical formula is $C_{16}H_{23}N_5).C_4H_4O_4$, Mw=417.47.

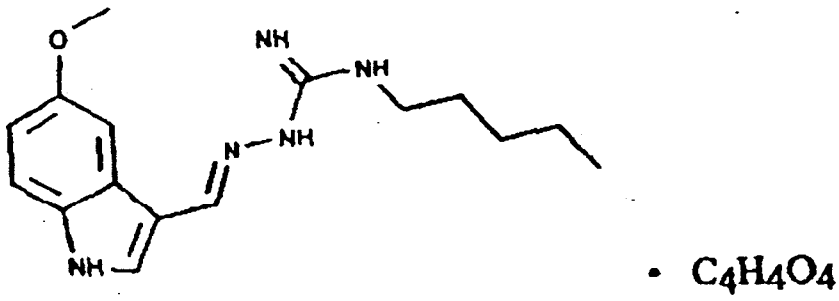

Fig. 2 - Chemical structure of tegaserod

Tegaserod as a hydrogen maleate is a white to off-white crystalline powder in itself slightly soluble in ethanol and very slightly soluble in water. Each 1.385 mg of tegaserod as the hydrogen maleate is equivalent to 1 mg of tegaserod. Zelmac is available for oral use as tablets containing 6 mg of tegaserod. Inactive ingredients are crospovidone, glycerol monostearate, hydroxypropyl methyl cellulose, lactose monohydrate ——— and polyethylene glycol 4000.

2. Mechanism of Action

According to the sponsor, clinical investigations have shown that motor and sensory functions of the gut appear to be altered in patients suffering from IBS. Both the enteric nervous system, which acts to integrate and process information in the gut, and 5-hydroxy tryphtophan (5-HT, Serotonin) are thought to represent key elements in the etiology of IBS. Serotonin is found throughout the gastrointestinal tract primarily stored in enterochromaffin cells but also in enteric nerves acting as a neurotransmitter. Serotonin has been shown to be involved in regulating

In repeated dose toxicity studies 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. No relevant effects were reported on reproductive function, or embryo/fetal and neonatal development. Tegaserod was detected in low amounts in fetuses and to a significant extent in milk.

Preclinical Safety Issues

NOTE: In a two-year oral (dietary) carcinogenicity study in mice, (CD-1), treatment with SDZ HFT 919 at 600 mg/kg/day produced mucosal hyperplasia (in 13.3% males and 11.7% females) and adenocarcinoma (in 10% males and 3.3% females) of small intestines. Treatment with lower doses of 200 and 60 mg/kg/day did not produce such effects. Adenocarcinoma of small intestine is a rare tumor for mice and as well as humans. The implications of the findings in the context of human safety are unclear at present.

Treatment of female rats (HanIbm Wistar) with SDZ HTF 919 at 20, 80 and 180 mg/kg/day (in diet) for 110 weeks produced dose-related increase in the incidence of "Ovarian" cysts (12, 14 and 20%, respectively) when compared to incidence in controls (0 to 4%). In rats, ovarian follicular cysts can be produced by exposure to constant light, or androgens during neonatal period, or by induced hypothyroidism. The sponsor has conducted histopathology reevaluation of the ovarian material from the rat studies. The relevance of the findings in rats and the implications in the context of the incidences of ovarian cysts noted in women treated with tegaserod are unclear.

III. SUMMARY OF HUMAN PKs AND BIOAVAILABILITY

[The material reproduced below represents sponsor's conclusions.]

The pharmacokinetics (PK) and many pharmacodynamics (PD) effects of tegaserod have been characterized in man. The PK of tegaserod in healthy subjects are representative of those patients with IBS who are generally healthy except for specific disease-related symptoms.

1. Pharmacokinetics

- Following intravenous administration, plasma tegaserod concentrations exhibited triphasic decay with the terminal t½ of about 11 h. The terminal t½ was more difficult to characterize after oral dosing mainly because of the limited sensitivity of the analytical assay. Tegaserod was extensively distributed into tissues (steady-state volume of distribution 368 ± 223 L) and had a moderate clearance (total plasma clearance 77±15 L).

- Tegaserod was rapidly absorbed with the medium T_{max} of 1 hour. The absorption seems pH dependent with increased passage of diffusion in lower g.i. segments (at higher pH). The absolute bioavailability was about 10%.

- Tegaserod absorption was reduced when given with medium to high fat containing meals (by 40 to 65% and 20 to 40% for the $AUC_{0-\infty}$ and C_{max} respectively). Although there was a food effect on the PK of tegaserod relative timing of drug intake within 30 minutes before a meal was not critical. It is recommended to take tegaserod before a meal.

- There was no change in the PK of tegaserod on repeated twice daily dosing. For the therapeutic dose 6 mg b.i.d. there was no relevant accumulation of tegaserod in plasma.

- After an oral ^{14}C-labeled dose of tegaserod, unchanged tegaserod accounted for only a few percent of total radioactivity in plasma. The predominant compound in plasma was the metabolite 5-methoxyindole-3-carboxylic acid glucuronide (m29.0). Four other metabolites, the 5- hydroxyindole-3-carboxylic acid glucuronide and three isomeric N-glucronides have been identified in plasma. The bulk of the radioactivity labeled material was excreted in feces (58%, mainly unchanged tegaserod) and 27% in urine (mainly metabolite m29.0, no unchanged tegaserod). Total recovery of an orally administered 2 mg dose was 85% within 168 h. The initial hydrolytic breakdown of tegaserod to form 5-methoxyindo 3-carboxylic acid, which is further metabolized to metabolite m29.0, presumably occurs in the stomach (under acidic conditions). Metabolite m29.0 shows negligible affinity for the $5\text{-}HT_4$ receptor and is devoid of promotility activity in the dog. Direct N-glucuronidation seems to be the major route of elimination for systemically available tegaserod.

- Tegaserod is highly bound to the plasma protein α 1-acid glycoprotein. In concentrations exceeding those of the parent drug, m29.0 does not displace tegaserod from its binding sites. The plasma/blood distribution to tegaserod is concentration independent.

- Based on the analysis across several PK studies in healthy subjects (n=134, single dose data), there was no effect of gender, age and ethnic origin on the PK of tegaserod when allowing for body weight as a covariate. Mean $AUC_{0-\infty}$ and C_{max} of tegaserod were 40 and 22% greater in elderly females than young females, but within the variability in tegaserod PK in healthy subjects. The data suggest that dose adjustment in elderly is not needed.

- Multiple PK of tegaserod 6 mg b.i.d. for 6 days in healthy Japanese subjects was comparable to those in Caucasians.

- In subjects with mild to moderate hepatic impairment (liver cirrhosis) mean $AUC_{0-\infty}$ increased by 43% and C_{max} by 18% (both not statistically significant). The sponsor concluded that given the variability in PK parameters in healthy subjects and the wide safety margin of tegaserod, dose adjustment is not needed in subjects with mild to moderate hepatic impairment. However, the PKs of the drug in patients with moderate or severe hepatic impairment have not been adequately assessed.

- Several renal impairment (creatinine clearance less than 15 ml per min.) did not affect PK of tegaserod. The data suggest that the dose adjustment in subjects with impaired renal function is not needed. Due to the large distribution volume of tegaserod and its extensive binding to plasma protein it is unlikely that tegaserod could be removed efficiently by dialysis.

- *In vitro* studies with human liver microsomes indicated a low potential of tegaserod to inhibit CYP2C9, CYP2C19, CYP23A and CYP3A4 isoenzymes. More potent effects were found for CYP1A2 and CYP2D6. However, no clinically relevant drug-drug interactions have been observed with dextromethorphan (CYP2D6 prototype substrate), theophylline (CYP1A2 prototype substrate), digoxin, oral contraceptives, or warfarin. The data suggest that dose adjustment of the drugs belonging to the different classes and tegaserod is not needed.

- The PK of tegaserod in patients (drug intake within 30 min. before meals) with constipation-predominant IBS and [redacted] are compatible to those in healthy subjects (fasting condition) when taking the food effect into account.

- The sponsor concluded and the reviewer agrees that based on dose and exposure ratios in animals and man, a wide safety margin exists with the clinical use of tegaserod (6 mg b.i.d. as — tablet).

Biopharmaceutics

- The solubility of tegaserod is pH-dependent; it is about 10-fold lower at pH 7.5 compared to pH 17.1 with a maximum solubility at pH 4.5. Below pH 3.5 tegaserod is rapidly degraded through hydrolytic breakdown.

- *In vitro* dissolution of tegaserod tablets in water is rapid and complete.

Pharmacodynamics

- *Healthy subjects:* tegaserod enhanced gastric emptying, small bowel transit time, and colonic transit to a clinically and statistically significant extent in healthy subjects. Tegaserod dose-dependently increased stool frequency and decreased stool consistency (produced looser stools), more pronounced effects were observed with higher doses. Effect on stool frequency and stool consistency were most prominent in early treatment.

- *Irritable Bowel Syndrome (IBS) patients:* tegaserod significantly accelerated oral-cecal transit time without altering gastric emptying in patients with C-IBS. Trends were also seen for an increase in proximal colonic emptying and reduction in colonic transit time.

NOTE: Some of these PD findings, especially those related to safety, will be reviewed in detail in the clinical section of the present review. Again, the sponsor's conclusions are summarized below because at this juncture there is no PD review available.

Mechanism of Action

- Tegaserod is a partial agonist at the 5-HT_4 receptor site. Preclinical investigations using human g.i. tissue specimens suggest an involvement of the 5-HT_4 receptors in at least 3 different processes:

  i) Triggering of the peristaltic reflex

  ii) Modulation of smooth muscle tone

  iii) Modulation of intestinal secretion

- Overall, pharmacodynamic data indicate that tegaserod enhances gastric emptying, small bowel transit time, and colonic transit to a clinically and statistically significant extent.

- In studies assessing stool frequency and stool consistency tegaserod increased stool frequency and decreased stool consistency. At different dose levels these effects showed a dose response relationship, more pronounced effects being observed with the higher doses. These effects on stool frequency and consistency were most prominent during early treatment (i.e., the first week).

- Studies using 2 mg tegaserod vs placebo in twice daily rectal sensitivity measurements by Barostat methodology, failed to show statistically significant differences between the treatment groups.

- In studies designed to assess effects on g.i. transit in patients with C-IBS, the effect of tegaserod did not achieve statistical significance, did not accelerate regional or total colonic transit period. Tegaserod significantly accelerated oral-cecal transit (percentage colonic filling at 6 h) but did not affect gastric emptying. This indicates that tegaserod's effect on oral cecal transit was predominantly due to acceleration of small bowel transit.

IV. FOREIGN MARKETING HISTORY

- Currently tegaserod (Zelmac™) is not approved or marketed in any other country.

V. REQUESTED LABELING FOR THE INDICATION SOUGHT

Indications and Usage

[ ]

Dosage and Administration

[ ]

VI. COMMENTS ON MAIN DESIGN FEATURES OF CLINICAL TRIALS

The main design features of the Phase II and Phase III clinical trials are featured in Tables 5 and 6. The design of the long-term studies is summarized in Table 7. Table 8 shows the design of clinical trials in other patient populations.

TABLE 5
Key Design Feature in Phase II and Phase III Studies

	Phase II (n=251)	Phase III (Main Studies)
Design	Double-blind, parallel groups, randomized	Double-blind, parallel groups, randomized
Baseline period	4 weeks, no placebo	4 weeks, no placebo
Treatment duration	12 weeks	12 weeks
Visit interval	2 weeks	4 weeks
Age	18-65 y	≥12 y (B351), ≥18 y (B301, B307)
Selection criteria	C-IBS based on Rome criteria; diarrhea excluded	C-IBS based on Rome criteria; diarrhea excluded
Doses	–, 2, 6, 12 mg b.i.d., placebo	2, 6 mg b.i.d., placebo
Primary efficacy variables	Subjective overall global assessment of GI symptoms, 5-point ordinal scale, comparison to baseline	Subjective overall global assessment of relief; 5-point ordinal scale, comparison to baseline
Data collection for primary endpoint	Monthly interview	Weekly by patient diary

The main differences between Phase III and Phase II studies regarding patient selection design can be summarized as follows:

- Primary outcome variable based on subjective healing "overall well-being" assessed by the patient;
- collection of information on additional symptoms as secondary variables;
- further restriction in concomitant laxative intake;
- site selection, predominantly primary care centers with a gastroenterologist rather than tertiary referral centers. Table 6 provides additional details of the key trials carried out in Phases II and III of the Development Plan.

TABLE 6
Summary and Design of Key Placebo-controlled Phase II/III Studies in C-IBS

Study No.	Objective	No. of Patients	Treatment Duration (Weeks)	Tegaserod daily dose (Drug administered in two divided daily doses)
B251	Dose-ranging	547	12	– 4, 12, 24 mg, placebo. Fixed doses
B202	Dose-titration	123	20	– 4, 12, 24 mg, placebo. Starting dose – mg (or placebo). In non-responders increase of dose each month. 2:1 randomization (experimental drug: PL)
B301	Efficacy/safety and dose confirming	881	12	Fixed doses, 4 mg, 12 mg or placebo
B307	Efficacy/safety and dose confirming	845	12	4 mg, 12 mg, or placebo. Up-titration from 4 to 12 mg in non-responders at Week 4
B351	Efficacy/safety and dose confirming	799	12	Fixed doses, 4 mg, 12 mg, or placebo

Long-term Safety Studies (Table 7)

Two long-term studies B204, B209 with a similar design were conducted in C-IBS patients.

TABLE 7
Summary and Design of Long-term Safety Studies in C-IBS

Study No.	Objective	No. of Patients	Treatment Duration (Months)	Tegaserod daily dose (administered in two daily doses)
B204	Long-term safety	170	12	– 4, 12, 24 mg, titration based on effect
B209	Long-term safety	579	12	4 and 12 mg, titration based on effect

Study B204 was discontinued for administrative reasons. Study B209 was completed as planned. Table 8 summarizes clinical studies in other patient populations.

TABLE 8
Summary and Design of Clinical Studies in

Study No.	Study Objective	No. of Patients	Treatment Duration (Weeks)	Tegaserod Dose

VII. REVIEW OF KEY PHASE II TRIALS (DOSE RANGING AND EARLY EFFICACY)

A. Study B251

This 5-arm study was designed to determine the dose-response relationship of efficacy, safety and tolerability among four different dose levels of SDZ HTF919 and placebo. Test medication was administered for 12 weeks. The Subjects Global Assessment (SGA) of overall GI symptoms was the primary efficacy assessment 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 dosing/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.

Table 9 shows the effect of SGA of overall g.i. symptoms, SGA abdominal comfort and SGA of constipation. Displayed are the percent responder rates of graded doses of SDZ HTF919

compared to placebo. This Table also shows therapeutic gain with each of the dose levels of the drug vs placebo. The therapeutic gain ranged from 3% to 12% for overall GI symptoms (the primary efficacy variable), 1% to 8% for abdominal discomfort and 5% to 12% for constipation, the two secondary efficacy variables.

TABLE 9
Study B251
Efficacy Results

	Treatment Response on Subjective Global Assessments at End of Study (%) Tegaserod (mg/day)					Therapeutic Gain (vs PL) %			
	— n=103	4 n=99	12 n=101	24 n=99	Placebo n=104	— mg	4 mg	12 mg	24 mg
SGA of overall GI symptoms[1] % responder	28	43+	40	37	31	3	12	9	6
SGA of abdominal discomfort % responder	34	41	38	38	33	1	8	5	5
SGA of constipation % responder	40	47+	48+	43	35	5	12	13	8

[1] Primary efficacy variable. +pf<0.01 vs placebo

From this study, it was concluded that there is consistency between the data obtained in the SGA and the diary variables. The method of evaluation, the SGA responder approach, is a reasonable technique to evaluate efficacy in trials of IBS given its positive association with multiple secondary variables. The — mg/d dose was not differentiated from placebo; 4 mg/d appeared to be an effective dose. The dose response was flat over the 4 mg/d to 24 mg/d dose-range.

B. Study B202

Study B202 was a 26 week, prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter study in which subjects with constipation-prone IBS were treated. The study consisted of a 1-week screen period, a 5-week pretreatment period and 26 weeks of randomized double-blind treatment with four flexible doses of SDZ HTF919 or matching placebo. The 26-week phase of the experimental treatment was divided into a 16-week dose adjustment phase, a 4-week dose maintenance phase, and a 6-week withdrawal phase, each of these phases being randomized.

In the protocol design the primary efficacy endpoints were to be the number of days without bowel movement and the average daily abdominal pain/discomfort score. Secondary endpoints were to be based on abdominal distention (or bloating), straining during defecation, sense of incomplete evaluation and global assessment of overall well being.

In the study that was performed the objectives were changed in that the primary efficacy variable was the responder rate based on subjects global assessment (SGA) of overall g.i. symptoms compared to the three month period prior to ending the study. The secondary efficacy variable was then the SGA of constipation and the SGA of abdominal discomfort, number of days without a bowel movement and average daily abdominal pain discomfort score.

Study Population

The study population, including inclusion and exclusion criteria were similar to study 251.

COMMENT

There was a suggestion however that further increase from 12 to 24 mg per day dosage did not afford further benefit. There were some positive effects observed on constipation and abdominal discomfort, but other symptoms such as bloating were not at all affected. There was a significant difference in the effect of concomitant laxatives between treatments a possible confounding effect that must be taken into account when interpreting results using the present experimental design. also a randomized withdrawal phase was planned but due to internal decision made by the sponsor, the trial was stopped prematurely and the withdrawal phase was not carried out. In summary, as stated, no definitive conclusions can be reached in this study due to:

i) Small sample size

ii) Premature discontinuation of the study

iii) The similarities of pharmacologic effect between treatment groups and the use of concomitant laxative medication, which could be confounding.

Results of these Phase II studies suggested that the HDZ HTF119 is well tolerated at all doses tested. There were no major differences between dropout rates and adverse effects between the treatment group vs placebo. Study B251 showed a moderate improvement in constipation and abdominal pain and these effects were sustained throughout the 12-week treatment period. Also observed was an increase in the number of bowel movements, and this effect was more pronounced during the first 2 weeks of the treatment.

Because of the reasons seen above, no definite conclusion can be drawn from this study. Study 251 showed 4 mg/d to be the most effective dose; and in addendum, study 202 showed that there was an increase in responder rate with a titration from 4 mg/d to 12 mg/d. It was therefore concluded that 4 mg/d and 12 mg/d would be the dose levels to be studied in the Phase III clinical trials.

VIII. CRITICAL CLINICAL TRIALS IN NDA 21-200

In support of the approval of Zelmac™ for the indication sought, the sponsor has presented the information from the following three critical trials. In Table 11 the protocol no., study population, main features of the trials, the groups being compared and reviewer's remarks as to the utility of the trial to assist the Division in a Regulatory Action are included.

TABLE 11

NDA 21-200

Main Features of Design and Execution and Initial Assessment of the Utility of the Critical Clinical Trials Submitted by the Sponsor for the Approval of the Marketing of Zelmac™ (Tegarerod) for the Treatment of Constipation Predominant Irritable Bowel Syndrome (C-IBS)

Protocol No. Country	No. Patients Entered per Gender	Main Features of Trial	Groups Being Compared	Remarks
B-351 52 Centers 49 - USA 3 - Canada	F 691 M 108 n= 799 ≥ 12 years	Randomized, multicenter, 16-week, prospective, 3-arm parallel group, double-dummy study in outpatients with constipation-predominant irritable bowel syndrome (C-IBS) Study population: C-IBS patients defined as per Rome Criteria, Evaluations - Weekly diary cards - Subjects Global Assessment (SGA)/month - Physical exam, ECG and laboratory evaluation - day 28 and every month Endpoints of Efficacy The primary endpoint of efficacy: 1) SGA of relief 2) SGA of abdominal discomfort/pain Secondary efficacy variables included: 1) SGA of bowel habit 2) No. of days with significant abdominal discomfort/pain 3) No. of days with significant bloating 4) No. of bowel movements + stool consistency The Tertiary efficacy variable was the Quality-of-Life score	All given p.o. 30 min A.C. BID for 12 weeks Tegarerod (4 mg/d) [n=265] Tegarerod (12 mg/d) [n=267] Placebo [n=267]	• Useful design Same as for B301. NOTE: The results of this trial were initially analyzed as per protocol prospectively stipulated statistical methodology. When this approach yielded negative results, the statistical approach used in the analysis of this and the other two Phase III trials, was changed [see review of individual Phase III trials]..

Protocol No. Country	No. Patients Entered per Gender	Main Features of Trial	Groups Being Compared	Remarks
B301 92 Centers 18 - UK 15 - Germany 12 - Netherlands 9 - Switzerland 7 - USA 6 - Italy 4 - Turkey 3 - Finland 3 - Austria 2 - Spain 1 - Portugal	F 734 M 147 n= 881 ≥ 18 years	Randomized, multicenter, 16-week, prospective, 3-arm parallel group, double-dummy study in outpatients with constipation-predominant irritable bowel syndrome (C-IBS) Study population: C-IBS patients, defined as per Rome criteria. Evaluations - Weekly diary cards - Subjects Global Assessment (SGA)/month - Physical exam, EKG and laboratory evaluation - day 28 and every month Endpoints of Efficacy The primary endpoint of efficacy was response or non-response based on SGA of relief Secondary Efficacy Variables Included: 1) SGA of abdominal discomfort/pain 2) A clinical evaluation of bowel habits 3) Daily diary variables 4) An IBS-specific Quality-of-Life survey	All given p.o. 30 min A.C. BID for 12 weeks Tegarerod (4 mg/d) [n=299] Tegarerod (12 mg/d) [n=294] Placebo [n=287]	• Useful design - Experimental conditions (raindomized, double-blind) are designed to minimize bias - Efficacy is shown by comparing results of each dose level of experimental drug to placebo - Dose-response (two dose levels of the experimental drug) compared to placebo. - Length of treatment (3 mo.) • The difference in pill size irrelevant because of the double dummy approach

Protocol No. Country	No. Patients Entered per Gender	Main Features of Trial	Groups Being Compared	Remarks
B-307 79 Centers 41 - USA 12 - France 11 - UK 6 - Germany 4 - Belgium 3 - Canada 2 - Spain	F 706 M 139 n= 845 ≥ 18 years	Randomized, multicenter, 16-week, prospective, 3-arm parallel group, double-dummy study in outpatients with constipation-predominant irritable bowel syndrome (C-IBS) The study consisted of:: ● 4 wk baseline period ● 12 wk treatment program ● a dose titration after 4 weeks Study population: C-IBS patients (by Rome Criteria) Evaluations - Weekly diary cards - Subjects Global Assessment (SGA)/month - Physical exam, ECG and laboratory evaluation - day 28 and every month Endpoints of Efficacy - The primary endpoint of efficacy was the SGA of relief response rate at endpoint. Secondary efficacy variables Included: 1) SGA of abdominal discomfort/pain 2) SGA of bowel habits 3) Percentage of days with significant abdominal bloating 4) No. of bowel movements + stool consistency The Tertiary efficacy variable was the Quality-of-Life score	All given p.o. 30 min A.C. BID for 12 weeks Tegarerod (4 mg/d) [n=283] Tegarerod (12 mg/d) [n=277] Placebo [n=285]	● Less useful design - Although the experimental conditions are geared to minimize bias, the study has less power because of the less No. of observations in the 12 mg group - Results in the 4 mg/d arm may be compared to placebo to assess efficacy - Results with the 4 mg/d in the 4→12 mg/d arm can be compared to placebo to assess efficacy - An additional weakness of this trial is that, during the assessment of efficacy, the results of the 4 mg/day arm alone cannot be pooled with those of the 4 mg/d pts from the 4 to 12 mg/d arm..

IX. REVIEW OF CLINICAL TRIALS FOR THE INDICATION TREATMENT OF CONSTIPATION-PREDOMINANT IRRITABLE BOWEL SYNDROME (C-IBS)

A. Study 301

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.

1. Objectives

i) Primary Objective

To determine the efficacy of two dose levels of SDZ HTF 919 and placebo as measured by the patients global assessment (SGA) of relief.

ii) Secondary Objectives

To determine the efficacy of two dose levels of SDZ HTF 919 and placebo as measured by

1) The SGA of bowel habit and number of days with significant abdominal discomfort/pain.

2) The daily diary measures of symptoms.

3) To determine the safety and tolerability of two dose levels of SDZ HTF 919 and placebo.

iii) Tertiary Objective

To determine the effect of two dose levels of HDZ HTF 919 and placebo on the quality of life.

2. Study Population

The initial target enrollment into the randomized double-blind portion of the study was to be 591 ITT patients with constipation-predominant IBS in approximately 45 centers. Each center aimed to randomize a minimum of 15 and maximum of 30 ITT subjects.

a. Inclusion Criteria (from original protocol)

Inclusion criteria will be assessed on Day -28. Subjects may be included if the following apply:

1. Male and female subjects 18 years and older.

2. Subjects meet the definition of IBS as defined by his/her response to the questionnaire below adapted from Drossman et al. (1990). 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 Nr. 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.

3. Previous use of non-pharmacological therapy (eg. high-fiber diet, exercise or bulking agents) of at least two months duration that has not resulted in adequate improvement in symptoms of constipation-predominant IBS (as judged by the subject) due to either ineffectiveness or intolerance.

   Subjects who are on stable treatment with a daily fiber supplementation or bulking agents might be enrolled provided that:
   - *they have the symptoms mentioned above (inclusion criterion #2) while on treatment.*
   - *the administration schedule is intended to be maintained throughout the study.*

4. Endoscopic/Radiologic bowel evaluation in order to rule out cancer, obstruction or other structural disease:

   a) All subjects over the age of 50 years must have had
      i) a colonoscopy or
      ii) a sigmoidoscopy plus double-contrast barium enema.

   All subjects 50 years of age or less must have had
      i) a colonoscopy or
      ii) a sigmoidoscopy.

   These evaluations must have been performed after the lower gastrointestinal symptoms began and no longer than 5 years prior to screening (whichever came last).

   b) For subjects with guaiac positive stool on digital rectal examination or with evidence of occult blood at stool analysis. If obvious hemorrhoidal bleeding is excluded, colonoscopy or sigmoidoscopy plus barium enema is required unless there has been a normal colonoscopy or sigmoidoscopy plus barium enema in the past one year.

   (Note: these examinations are considered part of standard of care; if needed they have to be conducted prior to the first visit).

5. Ability to communicate well with the investigator and to comply with the requirements of the entire study.

6. The subject has given written informed consent to participate and is willing to participate in the entire study.

b. Exclusion criteria (also from original protocol)

Exclusion criteria will be assessed on Day -28. A subject must not be entered if any of the following apply:

1. Significant diarrhea associated with C-IBS, i.e. over the past three months at least 25% of the days or occasions
   - loose or watery stools and/or
   - more than 3 bowel movements per day associated with urgency.

2. *Diseases/conditions that affect bowel transit including:*
   - Gastric, small bowel or colonic resection
   - Known history of colon cancer (ruled out as outlined above, Section 5.3.2 Inclusion Criterion # 4.)
   - Diabetes mellitus: *insulin dependent and/or associated with neuropathy*
   - Known history of inflammatory bowel disease (Crohn's disease or ulcerative colitis)
   - Poorly controlled hypo- or hyperthyroidism
   - Known history of Hirschsprung's disease, progressive systemic sclerosis (scleroderma), anorexia nervosa
   - Other diseases or conditions that in the opinion of the investigator significantly affect bowel transit.

3. Planned use during the study period of drugs or agents that affect GI motility and/or perception including:
   - Antacids containing magnesium or aluminum salts *(only calcium containing ones are allowed)*
   - Anthraquinones (senna, cascara, danthron, aloe)
   - Prokinetics (metoclopramide, ———— , cisapride).
   - Erythromycin
   - Opioids *(sporadic use of codeine containing analgetics is allowed)*
   - Anticholinergics
   - Adsorbents (kaolin, resins)
   - Ondansetrone and other 5-HT_3 antagonists
   - Antispasmotic agents (e.g. peppermint oil, mebeverine)
   - Octreotide
   - Calcium antagonists *(in constant doses throughout trial allowed)*
   - Serotonin re-uptake inhibitors or tricyclic antidepressants *(in constant doses throughout trial allowed)*

4. Evidence of cathartic colon or a history of laxative use, that in the investigator's opinion is consistent with severe laxative dependence such that the subject is likely to require or use laxatives during the study.

5. Current or recent history (within 12 months) of drug or alcohol abuse.

6. Clinical evidence (including physical exam, ECG, laboratory tests) of significant cardiovascular (including bradyarrhythmias and tachyarrhythmias), respiratory, renal, hepatic, gastrointestinal, hematologic, neurologic or of any disease that may interfere with the subject successfully completing the trial.

7. Other clinically relevant intercurrent medical conditions that interfere with the objectives of the study.

8. Symptoms of a significant clinical illness in the preceding two weeks.

9. Psychosis, schizophrenia, mania or major psychiatric illness needing pharmacological treatment. Well-compensated depression does not exclude a potential subject.

10. Existence of surgical or medical conditions which interfere with the absorption, distribution, metabolism and excretion of the study drug.

11. Pregnancy or breast feeding.

12. Fertile women not currently using or complying with a medically approved method of contraception.

13. Participation in other clinical trials during the previous three months in which investigational or commercially available drugs were tested.

14. Previous participation in any clinical trial with SDZ HTF 919.

15. A history of positive HIV serology (test not mandatory).

c) Exclusion criteria for entry into double-blind treatment period

These exclusion criteria will be assessed on Day 1. A subject must not be entered if any of the following apply:

1. During baseline the mean score for the SGA of abdominal discomfort/pain is less than mild/moderate (i.e. VAS score <40 mm at end of Weeks -4, -3, -2, and -1).

   (Note: The investigator is requested to calculate the arithmetic mean of the assessments at the end of Weeks -4, -3, -2 and -1; if mean <40 mm from the left end of the VAS, the subject does not qualify for randomization).

2. Failure to complete the daily Diary Cards: defined as missing data for ten or more days during the baseline period (Day -28 to 1) and/or inability to reliably complete the VAS at least 3 times during the baseline period.

3. Use of disallowed medication affecting GI motility and/or perception (i.e. laxatives, prokinetics, antidiarrheals, antispasmodic, or antiafferent drugs) on more than four days during the baseline period (Days -28 to 1).

(Note: for list of disallowed medication, see Table_).

Impact of intake of prohibited concomitant medication on efficacy analyses

Class	Prohibited Medication affecting GI motility and / or perception (ATC code[5])		Number of days with prohibited medication per study period leading to classification "Non-responder"[1]	
	Not recommended as rescue medication	Rescue medication	Weeks 1-8[2]	Weeks 9 - 12[3]
Laxatives & cathartics	- Antacids containing magnesium salts A02AA - Phenolphthalein, bisacodyl, sodium picosulfate A06AB - Anthraquinones (senna, cascara, danthron, aloe) A06AB - Sorbitol, lactulose A06AD - Bisacodyl tablets A06AB - Softeners (paraffin, docusate) A06AA - Contact laxatives in comb. w. bulk producer A06AC50 - Contact laxatives in comb. w. liquid paraffin A06AA - Contact laxatives in comb. w. other softeners A06AB	- Mg sulfate A06AG - Lactulose A06AD - Go-lytely A06AD - Sodium picosulfate A06AD - Bisacodyl supp. A06AG - Glycerol supp. A06AX - Enemas A06AG	>5 days	any
Prokinetic agents	- Cholinergic agents - Benzamides (metoclopramide, cisapride). -	none	not applicable[4]	not applicable[4]
Antidiarrheals	- Kaolin, charcoal, cholestyramine, other resins - Antacids containing aluminum salts - Diphenoxylate HCl, - Ondansetron, granisetron & other 5HT$_3$ antagonists	- Loperamide	not applicable[4]	not applicable[4]
Antispasmodics	- Anticholinergics - Octylonium bromide, peppermint oil, pinaverium - Mebeverine	none	not applicable[4]	not applicable[4]
Antiafferents	- Opioids *(sporadic use of codeine containing analgetics is allowed)* - Octreotide	none	not applicable[4]	not applicable[4]

1) Note: An individual subject will be declared Non-responder, if any of the criteria below is fulfilled.
2) For subjects with early discontinuation: active treatment period excluding the last 4 weeks.
3) For subjects with early discontinuation: last 4 weeks of active treatment period.
4) Protocol violators regarding these medications will be declared invalid for the Per-Protocol analysis, criteria to be defined (see statistical section).
5) ATC = Anatomical Therapeutic Chemical classification

3. Overall Study Design and Schedule of Evaluations

This was designed as a 16-week (4-week baseline period plus a 12-week randomized, double-blind treatment 3-arm) with either placebo or one of two dose levels of SDZ HTF 919 (prospective, parallel group, multicenter) trial in subjects with C-IBS.

For the purpose of this study, constipation-predominant IBS was defined by the Rome criteria as assessed in a questionnaire with focus on subjects having constipation as a predominant symptom of their altered bowel habit.

The dose regimen consisted of treatment for 12 weeks with a fixed dose level of 4 or 12 mg per day SDZ HTF 919 or placebo using a double-dummy technique. All patients were to take one small (6 mm) and large (7 mm) tablet within 30 minutes before meal time in the morning and evening. During the baseline period, patients received neither test medication nor placebo.

The visit schedule was conducted such that all patients were seen on an outpatient basis. Details of evaluations and procedures are listed in Table 11.

TABLE 11
Study 301
Schedule of Evaluations and Procedures

EVALUATION	Visit:	1	2	3	4	5
	Day:	-28	1	29	57	85 or Time of Med. Discon.
		BOOK 1		BOOK 2		
Informed Consent		X				
Inclusion/Exclusion		X	X			
Background information/ History		X				
Dietary survey		X				X
IBS-specific Quality of Life survey			X			X
Physical examination[1]		X	X[2]	X[2]	X[2]	X
SGA GI Symptoms (VAS)[3]		X	X[4]	X	X	X
Handout of Diary Cards for 4 weeks		X	X	X	X	
Collection Diary Cards of last 4 weeks			X	X	X	X
Clin. evaluation based on Diary Cards			X	X	X	X
Vital signs[5]		X	X	X	X	X
ECG evaluation		X	X[6]	X		X[6]
Laboratory evaluations[7]		X	X	X	X	X
Comments		X	X	X	X	X
Randomization			X			
End of Screening/Study			X			X
Dispensing of study medication			X	X	X	
Study medication label page			X	X	X	
Drug accountability				X	X	X
Prior/concomitant medication		X	<—Update as necessary—>			
Adverse events assessment[8]		<—— Update As Necessary ——>				

1) Physical Examination abnormalities to be entered into the following CRFs:
Day -28: Past/Coexistent diseases CRF.
Baseline and active treatment period: Adverse Event CRF.
2) Examination of the subjects general appearance, lungs, heart, and abdomen
3) To be completed by subject weekly.
4) SGA of discomfort/pain end of Weeks -4, -3, -2 and -1 is criterion for subject inclusion and reference baseline.
5) BP and pulse supine and standing each visit, on Day 1 BP profile during 3 hours after first dose; body weight Days -28, 1, and 85.
6) 2 ± 0.5 hours post dosing
7) Including pregnancy screen (for women only)
8) Including all SAEs occuring within 1 month after the final dose of study medication

4. Treatment Assignment/Randomization/Blinding

The methods for treatment assignment, randomization procedures and maintenance of blinding were all adequate. Details of these procedures are given below.

Each patient was assigned a two-part subject identifier on day -28. The first part consisted of a center number (assigned to the investigator by Norvatis) and the second part consisted of a sequential number (assigned by the investigator). The second part of the patient identifier was assigned upon obtaining the signed informed consent, and was not reused.

On Day 1 a medication number was assigned to each patient who met the inclusion criteria and was randomized. The medication number consisted of seven digits. The first 3 digits were always 700, and remaining 4 represented a randomization number associated with a specific treatment group. The entire number appeared on the medication dispensed to each patient. A randomization list was generated per country.

The blinding of the study was preserved by the use of corresponding placebos of identical aspect (taste, size, smell and appearance) and therefore indistinguishable from the test medication..

The randomization list was made available only to the authorized personnel at Norvatis. The decode of each medication number was provided to the investigator in the code breaker labels for use in case of a medical emergency only.

Three code breaker labels were made; one set of code breaker labels was distributed to the investigator. Another was maintained by Novartis clinical and safety epidemiological department, and the third set was stored in the standard study file for this study. A code breaker label was to be opened by the investigator only in an emergency.

All study personnel directly involved in the conduct of the study was to remain blinded to the treatment until all patients had completed the study and all data had been retrieved and finalized for analysis, i.e., at the time of data base lock.

Upon database lock, the information contained in the randomization list was to be merged into the data base and the patient's true treatment assignment was then associated with his/her data, i.e., the database was unblinded at database lock.

5. Concomitant Therapy

Use of concomitant medication affecting g.i. motility and/or perception was not permitted. In case of severe constipation or diarrhea, if needed, rescue medication may be taken by the patient. Patients using prohibited medication beyond the maximum number of days outlined in the study were to be declared non-responders with respect to the primary efficacy outcome.

The following agents were allowed provided they had been taken in constant doses for at least one month prior to study date (day -28) and if the dose remained unchanged during the trial:

- bulk forming agents, such as methylcellulose, psylium, and bran
- calcium antagonists (verapamil) dihydropyridines, diltiazem (for indications other than IBS)
- tricyclic antidepressants
- serotonin reuptake inhibitors

Any concomitant medication and therapy was to be recorded on the prior and concomitant medication/therapy form. This form was to be used as an on-going log and had to be updated as necessary to reflect any changes in the medication/therapy (or the dosage) taken by the subject.

Patients taking laxatives more than five days during weeks 1-8 and/or any laxative during weeks 9-12 (or during the last 4 weeks of treatment) were to be classified as "non-responders" with respect to the primary efficacy criterion irrespective of the outcome of the SGA.

If the patient has not had a bowel movement for at least 4 consecutive days and his/her lower abdominal discomfort or bloating/distention were highly bothersome, the following rescue medications were allowed: magnesium sulfate, 10 g (1 tablespoon), lactulose (15 to 30 ml), Go-lytely (250 to 2000 ml), sodium picosulfate (7.5 to 15 mg), glycerol suppositories or bisacodyl: 1 suppository before going to bed. Patients who did not experience adequate relief overnight were permitted to initiate other forms of laxatives (including enemas) in consultation with the investigator.

Patients receiving a chronic stable dose of bulking agents (e.g., psylium seed extract) were to be instructed to continue using the same dose of these agents throughout the study period. Patients were told not to change their diet any time during the study.

In case of bothersome diarrhea during the study, if needed, the use of an antidiarrheal (i.e., loperamide max 4 x 2 mg per day) in addition to the test medication was allowed. If the combination was not successful the test medication had to be discontinued. The test compound may have been reintroduced after the resolution of the diarrhea episode.

Bothersome diarrhea was defined as four or more loose or watery bowel movements with the sense of urgency for three or more consecutive days. If solid stools were passed or after a stool free interval of at least 12 h the anti-diarrheal should have been stopped. Upon resolution, patients were to resume the dose schedule within three days.

While medications for indications other than constipation or diarrhea were permitted, drugs with a narrow therapeutic window were to be carefully monitored as part of good clinical practice, for adequacy of therapeutic effect, adverse drug reactions, and blood levels if appropriate.

6. Evaluation Criteria

a) Efficacy

i) Primary Efficacy Variable

The primary efficacy variable was subject's global assessment (SGA) of relief, which was collected on a weekly basis (weeks -4, -3, -2, -1, 1, 2, 3, etc. to 12).

Patients were asked to answer the following question in their diary. *"Please consider how you felt the 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:

- Complete relief
- Considerably relieved
- Somewhat relieved
- Unchanged
- Worse

Patients being "completely relieved or considerably relieved" for at least 50% of the last four SGA of relief available, or "somewhat relieved" for the last four SGA of relief available were defined as "responders" if they fulfilled the specific criteria regarding laxative intake, duration of treatment, and the minimal number of efficacy assessments.

COMMENTS

The SGA of relief is a good primary efficacy variable in that it encompasses the patients overall well-being, his/her abdominal pain and altered bowel habits. The SGA of relief is the patient's assessment, not the interviewer's assessment and is therefore more reliable as to the patient's response.

ii) Secondary Efficacy Variables

The SGAs of abdominal discomfort/pain and SGA of bowel habits assessed the symptoms experienced during the previous week using a self-administered Visual Analog Scale (VAS), 100 mm length with severity descripters. Efficacy was assessed at the end of weeks -4, -3, -2, -1, 1, 2, 3, etc. to 12 or at discontinuation. The VAS was provided to patients with the diary cards. The VAS read as follows: absent, very mild, mild, moderate, severe, very severe.

The patient was asked *"How much of a problem was your abdominal discomfort/pain over the last week?" Then the patient made a vertical mark on the VAS scale.*

Additional secondary efficacy variables were a clinical evaluation of bowel habits, which were recorded and analyzed as follows:

- Daily number of bowel movements
- Daily stool consistency (7-ordinal scale: 1=watery, 7=very hard)
- Daily severity of abdominal pain (6-ordinal scale: 0=none, 5=very severe)
- Severity of bloating daily (6-ordinal scale: 0=none, 5=very severe).

The following were derived from the above variables:

- Change from baseline to endpoint in mean VAS of abdominal discomfort/pain.
- Change from baseline to endpoint in mean VAS of bowel habit.
- Greater than or equal to categories improvements from baseline to endpoint in mean VAS of abdominal discomfort/pain (using 6 equally spaced intervals on SGA scale).
- Greater than or equal to categories improvement from baseline to endpoint in mean VAS of bowel habits (using six equally spaced intervals on SGA scale).
- Normalization of bowel habits during the last four weeks of treatment.
- Number of days with significant abdominal discomfort/pain (score of greater than or equal to 2).
- Number of days with significant bloating (score of greater than or equal to 2).
- Days with no bowel movement.
- Number of bowel movements (normalized per 24-day interval).
- Percentage of days with stool consistency between 3 and 5 (inclusive).
- Percentage of days with hard or very hard stools (stool consistency 6 or 7).

iii) Tertiary Efficacy Variable

The tertiary efficacy variable was an IBS specific quality of life consisting of a questionnaire using a 5-point response scale (not at all=1, slightly=2, moderately=3, quite a bit-4, and extremely/a great deal=5) to describe the feelings of the patient where higher responses represented greater "distress".

b. Safety Assessments

The safety assessments were the following: adverse events, vital signs, physical examination, ECG evaluation, pregnancy screen and standard laboratory safety test including urinalysis, stool analysis. A central laboratory performed the hematology, chemistry, urinalysis and pregnancy

test. Stool analysis were performed locally. Blood samples were obtained from fasting patients if possible. ECGs were analyzed centrally.

i) Adverse Events
(As per Novartis clinical study report)

An adverse event (AE) was any adverse medical change from the patient's baseline (or pretreatment) condition which occurred during the course of the study, after study enrollment, whether considered treatment-related or not. AEs were volunteered spontaneously by the patient, or discovered as a result of the general questioning by the investigator or by physical examination. They were recorded in the AE form. Where a laboratory or vital sign abnormality constituted the main indicator of a severe or serious adverse event or led by itself to premature withdrawal of treatment, this was noted also as an AE on the AE form in the patient's CRF.

As far as possible, each AE was described by its duration, its frequency, its severity, its relationship to test medication, whether it influenced the course of the study, medication or whether it required specific therapy.

Symptoms typical for IBS occurring at the same intensity and/or frequency as before the trial were not reported as AEs.

Narratives were provided for all adverse events related to dizziness, hypotension, or arrhythmia.

ii) Serious Adverse Events (SAEs)

The following was considered an SAE: an (untoward unfavorable) event which:

- Was fatal or life-threatening,
- Required or prolonged hospitalization
- Was slightly or permanently disabling or incapacitating
- Constituted a congenital anomaly or a birth defect
- May have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

An event not considered to be a serious adverse event was a hospitalization occurring under the following circumstances:

- Was planned before entry into the clinical study
- Was for elective treatment of pre-existing condition unrelated to the study, indication or its treatment
- Occurred on an emergency, outpatient basis and did not result in admission, unless fulfilling the criteria above

- Was part of the normal treatment or monitoring of the studies indication and not associated with any deterioration in condition. Any SAE, including a serious clinical laboratory abnormality, which occurred in a patient receiving test medication was required to be reported to Novartis within 24 h of learning of the event, even if the SAE did not appear to be drug-related. Follow-up information pertaining to a previously reported SAE was to be reported to Novartis within 24 h of receipt.

The investigator faxed the completed SAE form to the local Clinical Safety & Epidemiology department along with any follow-up information at a later stage.

Both the original and copy of the SAE form, along with the fax confirmation sheet, were retained in the CRF binder. The event was also recorded on the standard AEs form in the patient's CRF.

Narratives were provided for all deaths and SAEs occurring during the administration of test medication and during a 30 day follow-up period; post-study SAEs were considered on an individual basis.

iii) Laboratory Evaluations

Standard hematologic and chemistry tests and urinalyses were conducted at screening, before administration of the first dose of test medication (baseline) and at periodic intervals during treatment. The analysis of the blood and urine samples was performed by a central laboratory (——— in Europe, — in USA, and ——— for South Africa). Blood samples were obtained with the patient in a fasting state, if possible. It was noted in the CRF whether a blood sample was obtained under fasting conditions. The following laboratory variables were determined:

- Hematology: Hb, Hct, erythrocyte, WBC with differential count, and platelet count.

- Biochemistry: ALT, AST, total bilirubin, creatinine, urea, uric acid, AP, total CPK (creatinine phosphokinase), albumin, total protein, glucose, total cholesterol, Ca, Cl, K and Na.

- Urinalysis: pH, protein, glucose, and blood. A stool analysis for occult blood was performed locally at the start of the study.

In the event of a significant laboratory abnormality or clinical or laboratory evidence of toxicity, the investigator was instructed to collect additional specimens for repeat analysis at appropriate intervals. The patient was closely followed until sufficient information was obtained to determine the cause or until the return to normality was observed. If necessary, appropriate or remedial measures were taken and response recorded. Clinical and laboratory diagnostic measures were employed as needed in an attempt to elucidate the etiology of the problem. A standard set of normal reference ranges and alert values was defined by the central laboratory.

When the presence of blood or protein was identified in the urine sample using the dip stick method, the results reported in North America, in five categories negative to very positive (negative, trace 1+, 2+, 3+). In Europe while the blood and urine was reported in the same fashion as in North America, when a sample showed positive results for protein, a second analysis was performed in the exact quantity of protein present in the urine was determined. When the laboratory value or vital sign abnormality was the main indicator of a severe or SAE or led to premature discontinuation of study medication, this abnormal finding was recorded on the AE form in the patient's CRF. Narratives were provided for all patients who discontinued due to an abnormal laboratory value.

A serum pregnancy test was conducted in all female patients at screening and periodically throughout the study duration by the central laboratory. If the pregnancy test was positive at screening, the patient was not allowed to enter the study. If the pregnancy test was positive during the study, the patient was discontinued immediately from the trial. Information was obtained from the investigator regarding the pregnancy. Narratives were provided for all patients who had a positive pregnancy test during the study.

iv) Electrocardiogram

Standard 12-lead EKGs were obtained on day -28 (baseline evaluation), on day 1, day 29, day 85, and during any additional visits scheduled due to a patient reporting symptoms of fainting or unusual dizziness. On day 1 and day 85, EKG was performed two hours (±30 min) after the morning dose. However, following protocol amendment #2, the day 1 EKG was no longer required and day 85 EKG was performed regardless of the time test medication was taken. All 12-lead EKGs were interpreted by an independent cardiologist affiliated with [redacted] Ventricular rate was determined based on three consecutive RR intervals, RR, PR, QRS and QT intervals were measured. QT_c was calculated by the BAZETT formula. All measurements and interpretations were done according to standard American Heart Association guidelines. Narratives were provided for all patients with arrhythmias or a QT_c interval greater than 499 ms, and those who discontinued due to an abnormal EKG finding. (NOTE: drug level and PK assessments were not performed in this study.)

7. DATA MANAGEMENT

Investigators entered the information required by the protocol onto the CRF that were printed on 3-part, non-carbon required (NCR paper). Novartis monitors reviewed the CRFs for completeness and accuracy, and instructed site personnel to make any required corrections or additions. One NCR copy of the CRF was retained at the investigational site. The original copy and one NCR copy were collected by Novartis monitors or by the investigational site, and then forwarded to the medical document reception center (MDRC) of Novartis. The receiver was recorded in the [redacted] tracking system, the original copy was placed in the central files and the NCR copy was forwarded by express mail to the responsible medical data management staff at [redacted] for processing. [redacted] handled the data

management of this study. For the last part of the study, the sites were requested to send the express mail CRFs directly to ———— After the initial logging of the CRF data, the original CRF pages were sent to Novartis to be entered into the tracking system and filed. The sites were also requested to send the final copy of the life questionnaires and dietary surveys by fax to ———— Again the original CRF data followed, arriving from the site at Novartis (NDA Vol. 157, page 35).

Concomitant medications entered into the database were coded using the World Health Organization (WHO) and anatomical therapeutic chemical (ATC) dictionary. Co-existent diseases and adverse events were coded using the Sandoz medical terminology thesaurus (SMTT) coding dictionary.

The database was declared complete on 5-July-99. Database lock occurred on 25-July-99.

8. STATISTICAL METHODOLOGY (AS SPECIFIED IN THE STUDY PROTOCOL)

(The information is that of the sponsor as the full FDA's statistical analysis is not available at the time of this writing)

a. Statistical Methods

These statistical analyses for this trial were performed according to the protocol. The data from all centers conducted under this protocol were combined as planned and analyzed by Novartis personnel. The original statistical methodology was revised August 22, 1997 and July 12, 1999.

Because validated efficacy endpoints in IBS studies are lacking, as a result of other tegaserod study results (from Study B351), extensive changes in the primary and secondary efficacy variables and the QOL analyses were introduced. These included changes in the primary and secondary efficacy variables and in the statistical adjustment procedure for multiple testing. All these adaptations were decided under conditions blind to the treatment assignment.

[Details of the statistical method originally proposed in the protocol and the modifications introduced are given below in the statistical methodology section of the review of Study B351.]

b. Populations

Three analysis populations were considered in this trial:

Intent-to-treat (ITT) population: Defined as all patients who were randomized to test medication or PL. The ITT population was considered as the primary population.

Per Protocol (PP) population: Defined as all ITT patients except those who fulfilled any of the following:

- Baseline mean VAS for SGA of discomfort/pain less than 35 mm.
- Rome criteria for C-IBS as not fulfilled.
- Less than 3 baseline measurements for VAS discomfort/pain.
- Compliance to test medication less than 75% during the double-blind period based on drug dispensing data.
- Less than or equal to measurements during the last four weeks of experimental treatment for the primary variable.
- Less than eight weeks of double-blind treatment.

Safety analyzable population: Defined as all randomized patients who receive at least one dose of test medication and underwent at least one post-baseline safety assessment.

c. Analyses of Background and Demographic Characteristics

The analysis of demographic and background information comprised the following:

- Age, sex, body weight, and race (white, black or other)
- any past/co-existent medical condition (yes/no)
- Smoker (yes/no)

The following variables were used for the analysis of the disease background of IBS:

- Duration of main IBS symptoms
- Baseline values for efficacy variables
- Dietary fiber score as derived from the dietary assessment on day -28 based on the concomitant medication records (during the last 28 days of the baseline period).

All above variables were summarized by treatment. F-tests or Chi-square tests were performed to assess the homogenicity of the treatment groups.

In addition, answers to the IBS questionnaire were summarized by treatment.

Summary statistics for the amount of test medication taken and compliance were provided by treatment group. Compliance was calculated based on the number of tablets taken vs tablets that were to be taken.

Concomitant therapy, i.e., any other medication taken other than the test medication taken by patient during the treatment period, was summarized in frequency tables. The frequency tables summarized the number of patients receiving concomitant therapy by treatment group, classifying the concomitant medication by body system, according the ATC coding system. The

number of patients taking prohibited medication (including non-bulking laxative) was summarized by class and treatment group. The proportion of patients taking prohibitive laxatives during treatment was compared between the two tegaserod treatment groups and placebo using the Cochran Mantel-Haenszel test with a significance level of 0.05. The number of days with laxative use during treatment was analyzed using an extended Mantel-Haenszel test.

9. STUDY RESULTS

a. Protocol Violations

A total of 71 patients (8.1%) had at least one protocol violation during the study. The number of protocol violators was 31 and 23 in the 4 mg per day and 12 mg tegaserod groups respectively, and 17 in the placebo group. The most frequently observed protocol violation was inadequate compliance: patients taking less than 75% of required study medication. This was observed in 56 patients (6.4%), and referred to 23, 19 and 14 patients in the 4 mg per day, 12 mg per day and placebo group, respectively.

b. Baseline Demographic and Background Characteristics

The demographic variables were comparable among the three and between any two of the treatment groups. All in all, 10.7% of patients were older than 65 years. The majority of patients were female (83%) and Caucasian (98%). For their mean duration of IBS symptoms the score was 13 years.

TABLE 13
Study No. 301
Demographics and Baseline Characteristics by Treatment
(ITT population)

Demographic Variable	Category/ Summary Statistics	Tegaserod (mg/d) 4 [n=299]	Tegaserod (mg/d) 12 [n=294]	Placebo [n=288]	Overall [n=881]
Age group	<65	89.0%	90.1%	88.9%	89.3%
	≥65	11.0%	9.9%	11.1%	10.7%
Age (years)	Mean	45.7	45.6	46.1	45.8
Sex	Male	17.4%	17.0%	16.7%	17.0%
	Female	82.6%	83.0%	83.3%	83.0%
Race	Caucasian	97.3%	99.0%	97.6%	98.0%
	Black	0.3%	0.3%	1.7%	0.8%
	Oriental	1.7%	0.3%	0.3%	0.8%
	Other	0.7%	0.3%	0.3%	0.5%
Smoker	Yes	28.1%	28.2%	21.2%	25.9%
	No	71.9%	71.8%	78.8%	74.1%
Weight (kg)	Mean	67.0	68.4	67.9	67.8
Duration of IBS symptoms (months)	Mean	162.1	156.2	156.0	158.1
Use of bulking agents during baseline period	Yes	11.7%	11.9%	10.4%	11.4%
Source: Sponsor's Post-text Table 7.4-1					

The mean VAS score for abdominal discomfort/pain and the mean VAS score for bowel habit were very similar among the treatment groups, and corresponded with moderate symptoms (Table 14).

TABLE 14
Study No. 301

Summary of Baseline SGA of Relief, Abdominal Discomfort/pain, and Bowel Habit by Treatment Group (ITT population)

Subject Global Assessment	Statistics	Tegaserod (mg/d)		Placebo [n=288]
		4 [n=299]	12 [n=294]	
Number of responders for SGA of relief[1]	n (%)	7/292 (2.4%)	9/291 (3.1%)	10/285 (3.5%)
Abdominal discomfort/pain, VAS (mm)	Mean SD	60.5 13.2	59.8 12.5	60.3 13.8
Bowel havit, VAS (mm)	Mean SD	60.9 13.2	60.3 14.9	60.0 14.7

[1] Patients with a SGA of relief at least "considerably relieved" for at least 50% of the assessments during baseline, or at least "somewhat relieved" in 100% of SGAs of relief during baseline. Denominator represents the number of patients who had at least one SGA of relief during baseline.

As noted in Table 14, approximately 3.0% of patients (26) were already responders at baseline, with no differences among the treatment arms..

c. Concomitant Medication

A majority of patients took at least 1 concomitant medication, for example 94.0% in the 4 mg per day group, 93.2% in the 12 mg per day group and 96.2% in the placebo group. Table 15 shows the most commonly used concomitant medications (greater than 5% of the patients in any treatment group).

TABLE 15
Study B301

Number and Percentage of Patients Who Took the Most Common Concomitant Medications (>5% of the Patients) (ITT population)

Therapeutic class	Preferred term	Tegaserod (mg/d)				Placebo [n=288]	
		4 [n=299]		12 [n=294]			
		n	%	n	%	n	%
Anilides	Paracetamol	68	22.7	67	22.8	72	21.5
Contact laxatives	Bisacodyl	23	7.7	28	9.2	29	9.7
Contact laxatives	Sodium picosulfate	18	6.0	12	4.1	18	5.9
Natural and semisynthetic estrogens	Estrogens conjugated	11	3.7	4	1.4	15	5.2
Osmotically acting laxatives	Lactulose	14	4.7	17	5.8	14	4.9
Other laxatives	Glycerol	20	6.7	21	7.1	16	5.6
Propionic acid derivatives	Ibuprofen	31	10.4	33	11.2	36	12.5
Salicylic acid	Acetylsalicylic acid	26	8.7	25	8.5	26	9.0
Thyroid hormones	Levothyroxine Sodium	19	6.4	24	8.2	10	3.5

Obvious increase in percentages of drug usage are seen in the category of estrogens and thyroid hormones. Estrogens were taken by a smaller percentage of patients in the 12 mg and 4 mg group than in the placebo, whereas thyroid hormones were taken more often in the tegaserod groups. These imbalances are not expected to have an impact on efficacy results.

The number of patients taking bulking agents was comparable between the three treatment groups. Two bulking agents most frequently recorded by patients were psyllium hydrophilic (4.7% in the 4 mg per day group, 4.4% in the 12 mg per day group, and 4.2% in the placebo group), and Ispaghula used more frequently in the 4 mg per day group and placebo group (2.3% and 2.1%, respectively) compared with the 12 mg per day treatment group (0.3%).

d. Results of Efficacy Analyses

i) Primary Efficacy Analysis

The primary efficacy variable was reached for both the 4 mg/d and the 12 mg/d dose levels. Adjusting the SGA of relief for laxative use resulted in decreasing the therapeutic gain for the 4 mg/d dose level from 12.2% to 8.6%, and for the 12 mg/d dose level from 11.8% to 8.2%.

TABLE 16
Study B301
Subject Global Assessment of Relief

	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
Study 301 (n=881)						
Responder Rate % (n)	27.8 (299)	26.2 (294)	20.5 (288)	38.8	38.4	30.2
Difference (se)[1]	7.7 (3.5)	5.9 (3.5)		9.0 (3.8)	8.6 (3.9)	
p-value[2]	0.029	0.092		0.020	0.028	
Adjusted p-value[3]	0.058	0.092		0.028	0.028	

1) Difference is the weighted difference of responder rates between the active treatment group and placebo group. The weights used are for each country and the weight for a country is proportional to the number of patients in each treatment group.
2) Nominal p-value based on Mantel-Haenszel test stratified by country in studies 301 and 307 and based on Fisher's Exact test in study 351.
3) p-value adjusted using: 1) Hockberg's multiple comparison procedure adjusting for two doses in studies 301 and 307 for both definitions and in study 351 for the new definition of SGA of Relief; or 2) using Holm's multiple comparison procedure adjusting for two doses and co-primary efficacy variable of SGA of abdominal discomfort/pain in Study 351 for the original definition of SGA of Relief

ii) Secondary Efficacy Analyses

As shown in Table 17, the daily diary variables of days with significant abdominal discomfort/pain and days with significant bloating trends yielded indeed in favor of tegaserod over placebo. However, these results were not statistically significant at endpoint. On the other hand, tegaserod 4 mg per day and 12 mg per day increased - significantly - the number of bowel movements and decreased the number of days without bowel movements. The effect on the number of bowel movements was seen in the first few days following the test medication. The number of BMs in the tegaserod group remained greater than the placebo group throughout the 12 week study period.

There was no clear superiority for either the 4 mg/d or 12 mg/d dose levels. These effects were more prominent early but were sustained throughout the 12-week treatment (Fig. 2 and 3).

TABLE 17
Study 301

Summary of Secondary Variables Derived From Daily Diary Data (ITT population)

	Tegaserod 4 mg/d n=299	Tegaserod 12 mg/d n=294	Placebo n=287
Responder rate	29.8%	29.9%	22.6%
Treatment difference in responder rate[1]	7.0%	7.3%	
p-value[2]	0.055	0.044*	
Mean percent change from baseline to endpoint in number of days with significant discomfort/pain	-18.9% (p=-0.180)	-18.6% (P=0.116)	-10.4%
Mean percent change from baseline to endpoint in number of days with significant bloating	-10.7% (p=0.128)	-8.3% (P=0.485)	4.0%
Mean percent change from baseline to endpoint in number of days with no bowel movements	-30.6% (p=0.012*)	-22.4% (P=0.013*)	-19.2%
Mean percent change from baseline to endpoint in number of bowel movements	59.2% (p<0.001*)	54.6% (P=0.009*)	42.0%
Mean percent of days with hard or very hard stool[1]	12.8% (p=0.084)	13.7% (P=0.803)	15.0%
Mean percent of days with stool consistency score between 3 and 5[1]	73.0% (p=0.385)	69.8% (P=0.009)	76.0%
Proportion of patients with normalized bowel habit at endpoint	70.2% (P=0.863)	65.5% (P=0.257)	68.9%

1) Denominator is the number of days with a bowel movement within the 28-day interval.
NOTE: p-value (nominal p-value) refer for the comparison between the tegaserod groups and placebo group at endpoint.
* Indicates the nominal p-value <0.05.

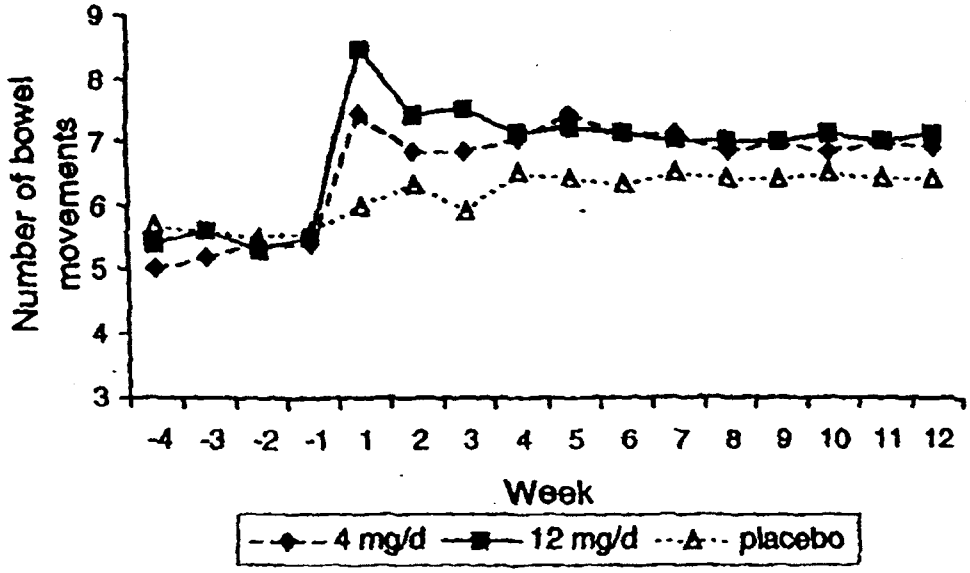

Fig. 2: *Weekly number of bowel movements (ITT population)*

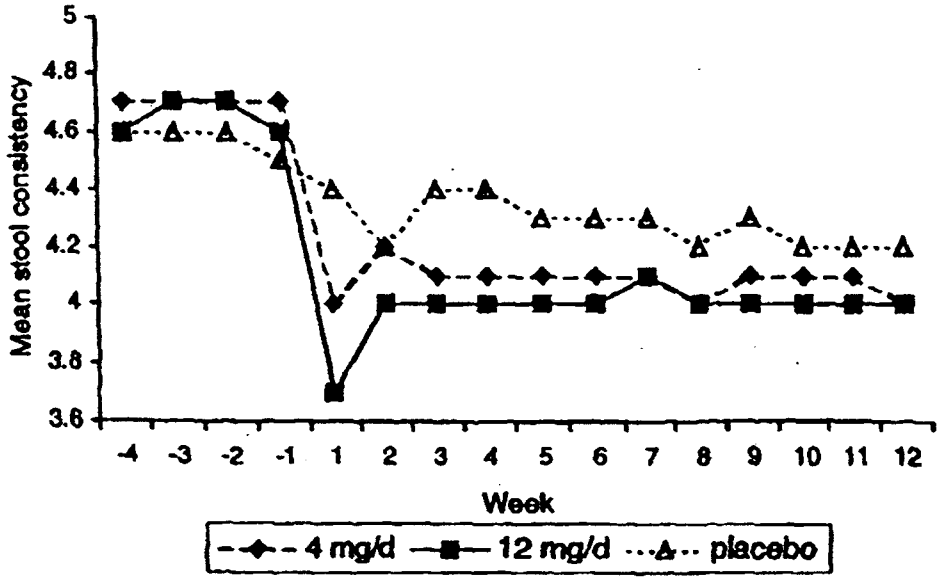

Fig. 3: *Weekly stool consistency (ITT population)*

e. Results of Safety Evaluations

i) Adverse Events (AEs).

The most commonly reported treatment-emergent events were gastrointestinal disorders [310 patients out of 876, (35.4%)]. Other organ systems more commonly affected were central and peripheral nervous system (291 patients, 33.2%), body as a whole (181 patients, 20.7%), respiratory system disorders (150 patients, 17.1%) and muscular-skeletal disorders (127 patients, 14.5%). Overall there was a higher reporting frequency of treatment-emergent events in the 4 than in the 12 mg per day and placebo groups. Almost all of this difference in the 4 mg per day group could be explained by central peripheral nervous system disorders: dizziness, headache and migraine (Table 18).

TABLE 18
Study No. 301

Number and Percentage of Patients Reporting Common (5% or more per Treatment Group) Treatment-emergent Adverse Events, Whether or Not Drug Related (Safety population)

	Tegaserod (mg/d)				Placebo [n=286]	
	4 [n=297]		12 [n=293]			
	n	%	n	%	n	%
Total patients with AEs	220	74.1	206	70.3	192	67.1
Headache	91	30.6	80	27.3	78	28/3
Influenza-like symptoms	25	8.4	33	11.3	28	9.8
Diarrhea	21	7.1	29	9.6	7	2.5
Dizziness	17	5.7	13	4.4	11	3.9

The reporting frequencies were similar among/between treatment groups with the exception of diarrhea which was reported more frequently in the tegaserod group than in the placebo group.

Drug-related AEs occurring on $\geq$1% of patients are listed in Table 19. More treatment-emergent adverse events occurred in the 12 mg/d group. The most common reported adverse events were: abdominal pain, headache, diarrhea, dizziness, nausea and flatulence. Only the incidence of diarrhea was dose-related as well as statistically significantly greater in both tegaserod groups than placebo.

TABLE 19
Study No. 301

Number and Percentage of Patients Reporting Common (≥1% in any Treatment Group) Drug Related Treatment-emergent Adverse Events (Safety population)

	Tegaserod (mg/d)				Placebo [n=286]	
	4 [n=297]		12 [n=293]			
	n	%	n	%	n	%
Total patients with drug-related treatment-emergent AEs	65	21.9	87	29.7	58	20.3
Abdominal pain	17	5.7	19	6.5	17	5.9
Diarrhea	12	4.0	24	8.2	2	0.7
Dizziness	10	3.4	8	2.7	9	3.2
Flatulence	7	2.4	8	2.7	6	2.1
Vomiting	4	1.4	2	0.7	2	0.7
Dyspepsia	3	1.0	4	1.4	4	1.4
Fatigue	3	1.0	4	1.4	1	0.4
Irritable colon	3	1.0	3	1.0	0	
Albuminuria	3	1.0	1	0.3	1	0.4
Antropathy	1	0.3	3	1.0	0	

ii) Deaths and Other Serious Events (SAEs)

- One death occurred in the study, patient identification No. 147/0001, from the 4 mg per day group.

- 13 patients out of 876 (1.5%) reported a total of 14 serious events, 7 in the 4 mg per day group, 2 in the 12 mg per day group and 4 patients in the placebo group.

- None of these events were suspected by the investigators to be related to the test medication.

iii) Results of Laboratory Evaluation

1) Hematology

There were no clinically relevant changes observed in the mean value for hematology parameters in any of the treatment groups. Seven patients developed low hematocrit, 5 (1.7%) in the 4 mg tegaserod group and 2 (0.7%) in the 12 mg per day tegaserod group. One patient (0.4%) in the 4 mg per day tegaserod group had high erythrocytes whereas 5 others developed low erythrocyte counts, two (0.7%) in the 4 mg per day tegaserod group, two (0.7%) in the 12 mg per day tegaserod group and one (0.4%) in the placebo group.

Nine patients had reduced leukocyte values during treatment, 4 (1.6%) in the 4 mg per day group, 2 (0.8%) in the 12 mg per day group and 3 (1.2%) in the placebo treatment group. In addition four patients developed low neutrophils; 2 (0.7%) in the 4 mg per day and 2 (0.7%) in the 12 mg per day tegaserod group. All in all, 13 patients had a high eosinophile account during treatment, but the incidence in the experimental arms were higher than those seen with PL.

2) Biochemistry

There were no clinically relevant changes in mean values for biochemistry parameters in any of the treatment groups. Five patients developed abnormal high ALT values, 1 (0.3%) in the 4 mg per day tegaserod group, 2 (0.7%) in the 12 mg per day tegaserod group, and 2 (0.7%) in the placebo group. Four patients developed high bilirubin values, 1 (0.3%) in the 4 mg per day group and 3 (1.1%) in the 12 mg per day tegaserod group and none in the placebo group.

3) Urinalysis

Urinary pH remained normal for all patients. There was no difference in the urine protein and urine glucose levels across treatment groups.

iv) Vital Signs

No clinically relevant changes were observed in vital signs in any of the treatment groups. The number of patients with orthostatic hypertension was similar across treatment groups.

v) EKG Evaluations

During the treatment phase of the study there were 66 (7.5%) patients for which the EKGs were classified as worse when compared to baseline. Twenty-five patients (8.6%) in the 4 mg group, 20 (7.0%) in the 12 mg per day group, and 21 (7.4%) in the placebo group. ST depression was reported in 11 patients (3.3%) in the 4 mg per day tegaserod group vs 3 patients (1.0% and 1.1%) in the two other groups. Changes from baseline in QTc interval are listed in Table 20. The

number and proportion of patients with increases in the QT_c interval were similar among the three treatment arms. There were no clinically relevant differences observed between the treatment groups. One patient (4 mg per day group) presenting with a normal QTc (i.e., less than 499 msec) values at baseline had abnormal values during the study.

TABLE 20
Study 301

Number and Percentage of Patients With Increase in QTc Intervals by Category (Safety population)

	Tegaserod (mg/d)				Placebo [n=286]	
	4 [n=297]		12 [n=293]			
	n	%	n	%	n	%
With any increase	201	69.3	200	70.7	203	72.2
Increase <15%	197	67.9	192	67.8	194	69.0
Increase ≥15% to <25%	3	1.0	8	2.8	9	3.2
Increase ≥25%	1	0.3	0		0	

vi) Other

There were 2 unintended pregnancies in the study, one occurred in the 4 mg per day group (116/0003) and one in the placebo group (171/0003). Test medication was discontinued in both and the patients were withdrawn from the study. The placebo treated patient experienced a spontaneous abortion; the other gave birth to a healthy baby boy.

10. Discussion and Overall Conclusions (Sponsor)

"The patients entered into the study were predominantly female (83%), and a mean age of 46 years and an average 13 year history of IBS. All of the randomized patients fulfilled the Rome criteria for C-IBS and had an average score of 60 mm on 100 mm VAS which corresponded to moderate discomfort/pain. The demographics and baseline variables were similar between the treatment groups.

"Compared with placebo the tegaserod 4 mg per day and 12 mg per day group had statistically significant higher response rates on the SGA of relief at endpoint, the primary efficacy of variable. This effect was seen early in the first week and was sustained over the three month treatment period.

"Response rates on the SGA of relief were adjusted for several factors, including patients missing all SGAs, treatment duration less than 28 days, and laxative intake. Although laxative intake (both number of patients and number of days) were similar among treatment groups, laxative adjustment decreased the weighted treatment difference between tegaserod 12 mg per day and placebo from 12% to 85. Two factors that favored the use of unadjusted or non-laxative adjusted treatment differences of 13 and 12 were:

1. The arbitrary nature of laxative treatment (greater than 5 days during the treatment period and greater than 1 day over the last 4 weeks).

2. Laxatives not clearly being an escape medication for abdominal pain of IBS.

"The results of the SGA of relief were thought to be robust. When early withdrawals due to lack of efficacy or adverse events were considered non-responders, or when all early withdrawals were considered non-responders, there were little changes in the treatment result, treatment differences between tegaserod groups and the placebo group remained statistically significant.

"Tegaserod in doses of 4 mg per day and 12 mg per day was safe and well tolerated. The overall reporting frequency of AEs was similar in the two tegaserod treatment groups (4 mg per day: 74%; 12 mg per day: 70%) and was slightly higher in the tegaserod treatment groups when compared with placebo (67%). The AE reported more frequently in the tegaserod groups compared to placebo was diarrhea, which occurred in 7%, 10% and 2% of the patients in the tegaserod 4 mg, 12 mg per day and placebo groups, respectively. the diarrhea early in the tegaserod treatment groups and in most cases was transient, self-limiting, rarely recurred, and seldom led to discontinuation from the study (2%). Other frequent reported AEs, with the exception of headache, were mainly related to the disease under investigation and the reporting frequencies of all AEs except diarrhea were similar in all treatment groups. Higher frequencies of discontinuations due to AEs were seen in the 4 mg and 12 mg per day groups, however, this was felt to be due to various events and no one particular AE in the treatment patients.

"Extensive blood pressure measurements failed to reveal any differences between the treatment groups and placebo. No clinically relevant effects of tegaserod were observed on any of the EKG parameters."

11. Reviewer's Additional Comments

Study 301, one of the two critical trials in NDA 21-200, was a well-designed, well-executed trial of sufficient duration to evaluate response to therapy for C-IBS.

There did not appear to be any significant demographic or other irregularities in the composition of the treatment or placebo groups. Therefore, valid conclusions on efficacy and safety can be drawn. As shown in Table 16, where results of primary efficacy analyses are summarized, there was evidence of therapeutic gain in both the 4 mg and 12 mg/d groups. With the inclusion of the "somewhat relieved" category there was evidence that the effects of tegaserod are sustained throughout the treatment period. This is graphically demonstrated in the weekly number of bowel movements (Fig. 2) and the weekly stool consistency (Fig. 3).

There was an overall higher reporting frequency of treatment-emergent adverse events in the 4 mg/d group than in the 12 mg/d and placebo groups (74.1 mg in the 4 mg/d, 70.3% in the 12 mg/d and 67.1% in the placebo group).

The reporting frequencies were similar between treatment groups with the exception of diarrhea which was reported more frequently in the active treatment groups than in the placebo group (7.1% in the 4 mg/d group, 9.6% in the 12 mg/d group and 2.5% in the placebo group).

Of note, the reporting frequencies for abdominal pain were similar in all treatment groups (4.6 to 6.1%)

B. Study B351

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.

1. Objectives

The primary, secondary and tertiary objectives of this study were as in Study 301.

2. Study Population and Overall Study Design and Schedule of Evaluations

These were as per Study 301, with the post hoc modification to efficacy analyses mentioned above.

Sample Size: The target enrollment was 591 intent-to-treat (ITT) patients in approximately 45 centers. All patients randomized into the study, receiving at least one dose of medication, were considered as ITT subjects.

3. Randomization/Selection and Timing of Dosage

A randomization list was generated per country via the randomization process.

The randomization list was made available only to the authorized personnel at Novartis. The discipher code of each medication number was provided to the investigator and the code breaker label for use in case of medical emergency only.

The randomization schedule was computer-generated by Novartis Technical Research and Development (TRD) using the ——— program. Two copies of the complete randomization list were prepared, one for use of the Novartis TRD which performed packaging and second to be maintained in a locked confidential location at the ——————— office in the Novartis-Horsham Research Center.

In addition, two sets of code breaker labels, containing the actual treatment assignment were prepared. One set of code breaker labels was distributed to the investigator, another complete set was maintained by the Novartis Clinical Safety and Epidemiologic Department. A code breaker label to be opened by the investigator only in case of emergency (e.g., a code breaker - a serious adverse event) when it was judged necessary to know the subject's treatment. If the code breaker label was opened, the investigator had to immediately provide a full explanation to the Novartis as the reason to do so.

All study personnel directly involved in the conduct of the study remained blinded to the treatment until all subjects had completed the study and all data had been retrieved and finalized for analyses; i.e., at the time of data base log.

4. Dosage and Duration

The following doses were used during the 12-week experimental treatment period: placebo, 2 mg b.i.d. and 6 mg b.i.d.

Each dose consisted of a small and a large tablet, both were to be taken with one glass of water within 30 min. before mealtimes, in the morning and in the evening. Patients received the same dosage throughout the 12-week randomized, double-blind treatment period. Treatment began on the morning of dose of day 1 and ended on the morning of dose of day 85. The first dose on day 1 and the last on day 85 were administered in the clinic. Patients were asked to record daily in the diary card whether or not they had taken the morning and evening doses.

5. Prior and Concomitant Therapy (Prohibited Concomitant Medication)

This was as per Study 301.

6. Evaluation Criteria

a. Efficacy Variables

i) Primary Efficacy Variables

In addition to the SGA of relief, the SGA of abdominal discomfort/pain efficacy was assessed by a self-administered VAS at the end of weeks -4, -3, -2, -1, 1, 2, 3, etc. to 12, or until discontinuation. To ensure the timely completion of the diary cards patients were counseled by the Center as to the importance to compliance in completing the VAS at its weekly interval. The VAS was provided to patients with the diary cards. Patients were asked to complete the weekly interval of VAS for abdominal discomfort/pain and bowel habit during the prior week. The VAS was read: on a 100 mm line with reading from absent to very mild, mild, moderate, severe and very severe. The patient was asked the following: *"How much of a problem was your abdominal discomfort/pain over the last week? Please insert (I) anywhere on the line between the extremes"*. The distance between the mark and the left end of the line (distance A) was measured by the investigator for each patient at each time point as the data were entered into the appropriate CRF. To be eligible the patient had to have at least a mild/moderate severity of abdominal discomfort/pain (i.e., $\geq$40 mm).

Patients with a greater than or equal to 40% relative reduction on the VAS at end of study compared to baseline were considered "responders" provided no use of laxative during the last 4 weeks had occurred.

The same approach was used for the assessment of the SGA of bowel habit. The VAS instructions were available in the local language required.

ii) Secondary Efficacy Variables (Table 21)

TABLE 21
Study B351

Secondary Efficacy Variables: Information to be Recorded on Diary Cards and in CRFs

Variable	Diary Card (to be completed daily by subject; with calendar date)	CRF (to be completed by investigator every 28 days)
Stool frequency	Number of bowel movements (BM) per day	Transcription of all data into "Clinical Elevation - Bowel Habits Diary" CRF.
Abdominal discomfort/pain	Abdominal discomfort/pain based on a 0-5 point scale, whereby: 0=none, 1=very mild; 2=mind; 3=moderate; 4=severe, 5=very severe. Patients chose a number between 0 and 5 (inclusive) that best described the overall severity of their lower abdominal discomfort/pain for the day.	
Bloating	Bloating based on a 0-5 point scale, whereby: 0=none; 1=very mild; 2=mild; 3=moderate; 4=severe, 5=very severe. Patients chose a number between 0 and 5 (inclusive) that best described. the overall severity of their bloating or abdominal distension for the day.	
Stool consistency	Stool consistency on a 1-7 point scale, whereby: 1=watery, 2=loose; 3=somewhat loose; 4=neither loose nor hard, 5=somewhat hard; 6=hard; 7=very hard. Patients chose a number that best described the average consistency of their stools for the day. If no stools were passed they were to mark: 99.	
Use of laxative and/or bulking agents	Use of taxative and/or bulking agents for that day: Yes/No	
Intake test medication	Intake test medication both tablets	
Laxatives and/or bulking agents	Note details of any medication taken in "Concomitant medication Log"	Name, dose, and start and stop date of medication, into Prior & Conc. Med. CRF
Concomitant Medication	Note details of any medication taken in "Concomitant medication Log"	Name, dose, and start and stop date of medication, into Prior & Conc. Med. CRF
AEs	Record all unusual symptoms in "Unusual Symptoms Log"	Complete Adverse Event CRF

For interpretation cards the following definitions were used:

- Discomfort/pain or "significant bloating" or days with a score of greater than or equal to 2 points.
- Patients had "normalized" bowel habit if all of the following criteria were fulfilled at the end of study.

- VAS score for bowel habit at least 40% improvement from baseline, an absolute value of 20 mm or less on VAS.
- Less than 3 bowel movements per week during at most 25% of the time.
- More than 3 bowel movements per week during at most 25% of the time.
- Median stool consistency between 3 and 5 points.

iii) Tertiary, Efficacy Variable, Quality of Life Survey

This was assessed as per Study B301.

b. Safety Variables/Discontinuations

The safety variables used in this study included measurements of vital signs, physical examination, EKG evaluations, pregnancy screen, adverse events, serious adverse events and laboratory evaluations. These variables were assessed as a Study 301. Discontinuations were handled as in study 301.

c. Statistical Methods

i) Populations Analyzed

Safety analyzable: All patients who were randomized into the study, received at least one double blind dose of medication, and underwent at least one assessment of the AEs they may have experienced.

Intent-to-treat (ITT): All patients randomized into the study, receiving at least one dose of test medication were considered as ITT subjects.

Per-protocol (PP): All patients of the ITT population who (1) met the major eligible criteria: constipation-predominant IBS as assessed by the Rome criteria; negative endoscopy-radiology; no diarrhea or relevant disease/condition affecting bowel habit, (2) had a baseline measurement of the primary efficacy variable, (3) had at least 8 weeks (2 28-day periods) of double-blind treatment, (4) had at least 75% of the prescribed medication, (5) were compliant with respect to the keeping of diaries, (6) did not take disallowed concomitant medication in such a way that the primary efficacy relation would be deemed to be compromised.

To investigate adequacy of the randomization, inferential statistics was to be applied (nominal significance level 0.05) to the variables mentioned in the protocol. For continuous, ordinal, or categorical variables, the KRUSKAL-WALLIS test and the two sided Fishers exact test, respectively were to be used to test homogenity of the groups.

ii) Hypothesis Tested

The primary hypothesis were: H_0: the proportions of responders are equal between each of the SDZ HTF 919 dose groups and the placebo group vs H_1 the proportions of responders are not equal between at least one of the SDZ HTF 919 dose groups and the placebo group.

The primary hypothesis were to be tested through the following family of pair-wise comparisons:

- SDZ HTF 919 4 mg vs placebo
- SDZ HTF 919 12 mg vs placebo

The Mantel-Haenszel test stratified percent was to be performed for each of the pair-wise comparisons. To adjust for multiplicity, the Dunn-Sidak in equality was to be used to insure an overall 2-sided significance level less or equal to 0.05. Statistical calculations were to be done for the ITT subjects and for the per-protocol subjects separately.

8. Compliance

The methods used to assess compliance to the prescribed regimen were adequate. Compliance was assessed by counting the number of tablets returned at each visit, subtracting this number from the total dispensed and comparing the results number with the number expected to have been consumed for that visit. Summary statistics by group and visit in categorical analysis over the entire study was to be conducted (proportionately less than 75% compliant greater than or equal to 75% to less than 125% greater or equal to 125%).

9. Results

a. Efficacy

i) Primary Efficacy Variables (Table 22)

The results for the two primary efficacy variables, the original SGA of relief and SGA of abdominal discomfort/pain for the ITT population did not reach statistical significance according to the protocol-stipulated HOLM'S multiple comparison procedure. Consequently, a new statistical approach was proposed.

At a meeting with the Division (July 1999), the sponsor and their consultant believed that the definition of response was too stringent. A change was made such that in addition to complete or considerable relief at least 50% of the time, the category of **somewhat relief 100% of the time** at endpoint was added to the responder definition. When the data were analyzed in this manner, statistically significant difference between the tegaserod 12 mg group and placebo was achieved (lower panel of Table 22).

NOTE: This revised definition of response was thought to be more sensitive to measure treatment effect in C-IBS patients and it was therefore adopted to re-define the primary efficacy variable in studies B301 and B307.