

**TABLE 22**  
**Study B351**

**Subject Global Assessment of Relief**

	Original Definition of SGA of Relief			New Definition of SGA of Relief		
	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
Study 351 (n=775)						
Responder Rate % (n)	30.0 (257)	26.2 (259)	21.6 (259)	39.7	45.2	32.4
Difference (se) <sup>1</sup>	8.4 (3.8)	4.6 (3.7)		7.3 (4.2)	12.8 (4.2)	
p-value <sup>2</sup>	0.035	0.257		0.099	0.004	
Adjusted p-value <sup>3</sup>	0.140	0.492		0.099	0.008*	
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) Hochberg'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 (Table 23)**

As seen in Table 23 the 4 mg per day and the 12 mg per day tegaserod treatments showed statistical significance compared to placebo for the mean percent change from baseline in the number of bowel movements. In addition, the 12 mg per day group also showed statistical significance in 4 other secondary efficacy variables (Table 23).

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**TABLE 23**  
**Study B351**

**Secondary Variables Derived From Daily Diary Data At Endpoint  
(ITT population)**

	Tegaserod (mg/d)		Placebo
	4	12	
Mean percent change from baseline in mean VAS of SGA of abdominal discomfort/pain	-24.8% (p=0.211)	-25.3% (p=0.044)	-20.7%
Mean percent change from baseline in number of days with significant <sup>1</sup> discomfort/pain	-15.2% (p=0.147)	-16.9% (p=0.017)*	3.9%
Mean percent change from baseline in number of days with significant <sup>1</sup> bloating	-14.9% (p=0.076)	-15.1% (p=0.006)*	-5.6%
Mean Percent change from baseline in number of days without bowel movements	-28.2% (p=0.053)	-31.2% (p=0.002)*	-21.4%
Mean percent change from baseline in number of bowel movements	68.9% (p=0.003)*	69.3% (p<0.001)*	44.8%
Mean percent of days <sup>2</sup> with hard or very hard stool <sup>1</sup>	12.7% (p=0.068)	11.3% (p=0.730)	18.9%
Mean percent of days with stool consistency score between 3 and 5 <sup>1</sup>	74.5% (p=0.168)	76.3% (p=0.730)	74.3%
Proportion of patients with normalized bowel habit	72.1% (p=0.441)	76.6% (p=0.079)	69.1%

NOTE: Nominal p-values are presented for the comparison between the tegaserod dose and placebo at endpoint.  
\* Indicates a statistically significant difference compared to placebo based on Holm's multiple comparison procedure, adjusting for two doses, at significance level of 0.05.  
1) Denominator is the number of days with a bowel movement.

Figures 4 and 5 show the changes in number of bowel movements and weekly stool consistency in study 351.

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ON ORIGINAL**

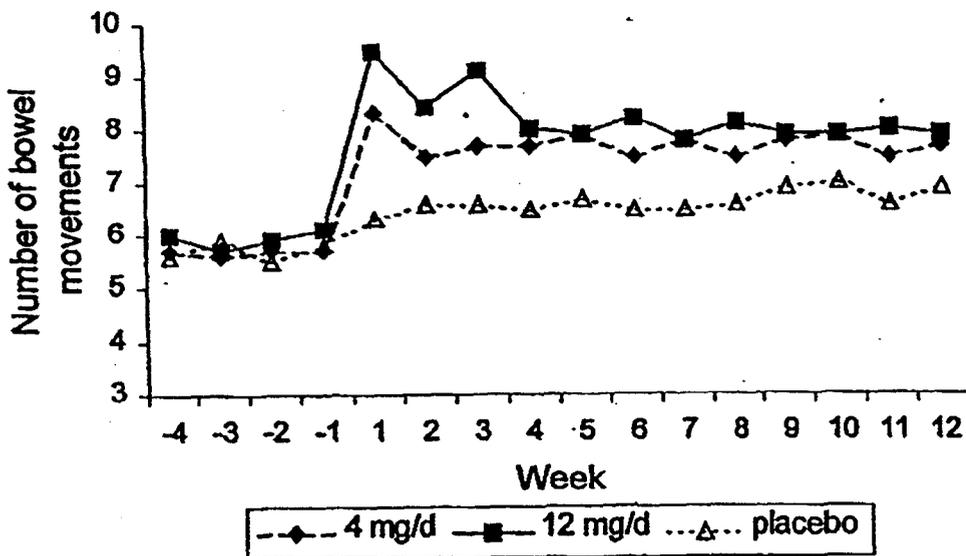


Fig. 4. - Weekly number of bowel movements (ITT population).

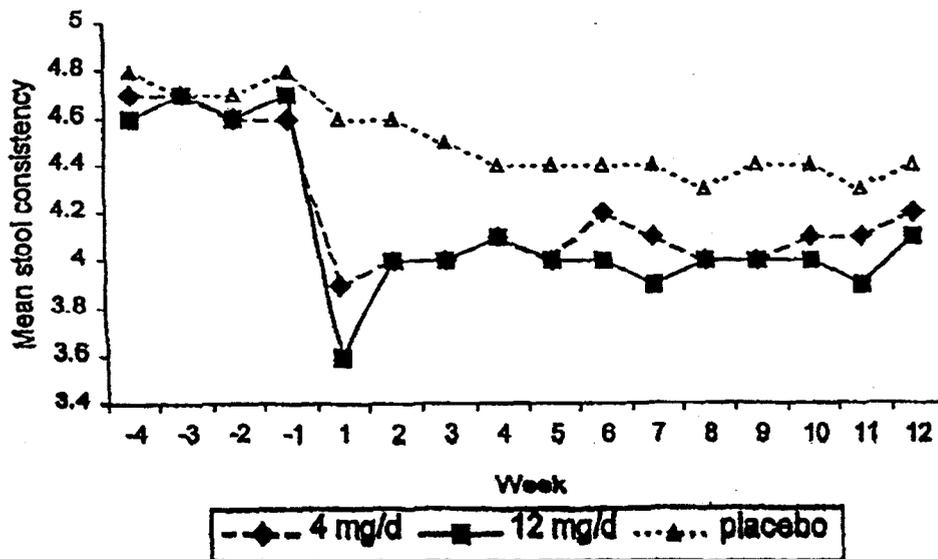


Fig. 5 - Weekly mean stool consistency (ITT Population)

## b. Safety Analyses

As mentioned above, safety variables that were analyzed included: (1) adverse events, (2) vital signs, (3) EKG evaluations, (4) clinical laboratory tests (hematology, blood chemistry, urinalysis) and (5) discontinuation from the trial. These variables were dealt with in a fashion similar as described in study 301.

The safety profile was similar to that in Study 301. Once again, diarrhea was the one AE which occurred more than twice as frequently as in the placebo group. There were no deaths in the study, and none of the SAEs reported were thought to be due to the medication.

## 10. Discussion and Overall Conclusions (Sponsor)

"According to the sponsor, Study 351 consisted predominantly (87%) of female patients with a mean age of 43.2 y and a 14.5 y history of IBS. All randomized patients met the Rome criteria for C-IBS and had at least mild abdominal discomfort/pain during the baseline period, with a mean of 63.2 mm (corresponding to moderate discomfort/pain) on a 100 mm VAS. Demographic and disease baseline characteristics were similar among treatment groups.

"The consistency of the data both in the weekly SGAs and the daily diary variables, as well as the consistency at multiple time points indicate a treatment difference for tegaserod compared with placebo. However, the low responder rate of the original SGA of relief in the tegaserod group (29.4%, 4 mg per day and 26.2%, 12 mg per day) and especially the placebo group (22.1%), suggested that the definition of response might have been too stringent to detect true treatment effects. Consequently, the ASGA of relief definition of response was revised and retrospectively analyzed. When the comparison between placebo and tegaserod was made, the difference in responder rate for the 12 mg per day treatment group was statistically significant. The SGA of relief at each month time point also showed a dose response relationship with the 12 mg per day treatment group having the highest responder rate.

"Responder 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. The impact of the adjustment criteria was on the placebo treatment group, with minimal impact on the tegaserod treatment groups. The laxative adjustment decreased responder rates to a similar extent in all three treatment groups, whereas there were more patients who had no SGA assessments and therefore were declared non-responders in the tegaserod groups compared with placebo. When all early withdrawals were considered non-responders, treatment differences between the 12 mg per day treatment group and placebo remained statistically significant. The daily diary variables days with significant abdominal discomfort/pain at study endpoint showed a decrease for patients in the tegaserod treatment groups and a mean increase for patients in the placebo from baseline. The effect of tegaserod 12 mg per day treatment group compared to placebo was statistically significant. Also in the 12 mg per day tegaserod group statistically significant differences with placebo were seen for **significant bloating** at endpoint. Tegaserod 4 mg per day and 12 mg per day increased the number of bowel movements and decreased the number of days without bowel movements; these effects were most common early but were sustained throughout the 12-week treatment period.

"Tegaserod in doses of 4 and 12 mg per day were well tolerated, the most frequent adverse events were those which can be ascribed to the pharmacodynamic action of the compound. For several adverse events, the frequency was somewhat higher with 12 mg per day than the 4 mg per day, the differences, however, were not conclusive. Laboratory safety parameters and EKG did not show any clinically relevant findings suggesting toxicity. There were no serious adverse events in which their causality was related to the exposure to the study compound.

"The PK data showed that in the subset of patients tested there was no difference in the pharmacokinetics of tegaserod in C-IBS patients and healthy volunteers.

"The primary and secondary efficacy variables showed consistent trends for the treatment effect of tegaserod compared with placebo. A post-analysis in which the responder definition of the SGA of relief was revised to include persistent "somewhat relieved" was conducted. This analysis demonstrated clinically meaningful differences between the 12 mg per day treatment group and placebo.

"The sponsor concluded that overall, tegaserod treatment was well tolerated; only diarrhea occurred more frequently in the tegaserod groups compared with the placebo group. The safety profile of tegaserod 4 mg per day and 12 mg per day was similar."

### **11. Reviewer's Additional Comments**

Because the study was unblinded and subject to a post-hoc analyses with changes in the primary efficacy variable, 351 cannot be considered pivotal.

Also, the results of the secondary variables evaluations were similar to the results in Study 301, that is they gave support to the effects of the 12 mg/d dose level. For the 12 mg/d dose level there were statistically significant results for the absolute number of bowel movements, the percentage of days with hard stools and the number of days with significant bloating. This is compared to the 4 mg/d dose-level which showed only statistically significant difference in the mean percent of change from baseline in the number of bowel movements.

No significant safety issues arose from safety analyses from this study.

#### **C. Study B307**

*A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at 2 dose regimens and placebo in subjects with constipation-predominant irritable bowel syndrome.*

##### **1. Primary Objectives**

The primary objective was to determine the efficacy of two dose levels of tegaserod (HTF 919) by comparison to placebo as measured by the subject's global assessment (SGA) of relief from IBS symptoms.

##### **2. Secondary Objectives**

The secondary objectives were to determine the:

- Efficacy of two dose levels of tegaserod as measured by SGA of abdominal discomfort/pain, SGA bowel habit and percentage of days with significant abdominal discomfort/pain.

- Efficacy of two dose levels of tegaserod as measured by the daily diary measures of symptoms.
- Efficacy of increasing the dose of tegaserod in patients not sufficiently responding to a lower dose (4 mg per day).
- Safety and tolerability of two dose levels of tegaserod.

### **3. Tertiary Objective**

The tertiary objective was to determine the effect of two dose levels of tegaserod on the quality of life.

### **4. Study Population**

#### **a. Number of Patients:**

There were 845 patients randomized (tegaserod 4 mg per day: 283; 12 mg per day: 277; and placebo: 285).

#### **b. Main Criteria for Inclusion**

The study recruited male and female patients aged 18 years or older with C-IBS with a least mild abdominal discomfort/pain as determined the VAS during the baseline period. Patients with C-IBS associated diarrhea with diseases/conditions affecting bowel transit, who planned to use drugs or agents that effect g.i. motility, lactating or pregnant, or patients who were HIV positive or had previously participated in a study with tegaserod were also excluded. Patients with a mean VAS score less than 35 mm at the end of weeks -4, -3, -2, and -1 for the SGA of abdominal discomfort/pain, who failed to complete the daily diary cards or who used disallowed medication affecting g.i. motility and/or perception were excluded from the double-blind treatment period.

### **5. Duration of Treatment**

During the 12-week randomized, double-blind period, patients in one arm took tegaserod 2 mg b.i.d. (4 mg per day) or placebo b.i.d. tablets with water within 30 minutes prior to meals in the morning and evening. Patients in the third arm also started with 4 mg per day for weeks 1 through 4. Non-responders in this dose titration group were switched to 12 mg per day during weeks 5 through 12 if they were considered non-responders by the original criteria of SGA of relief.

## 6. Evaluation Criteria

### a. Efficacy

The primary efficacy variable was the SGA of relief. Secondary efficacy variables were the SGA of abdominal discomfort/pain, SGA of bowel habit, the percentage of days with significant abdominal discomfort/pain, number of days with significant abdominal bloating, bowel movements and stool consistency. The tertiary efficacy variable was the QOL score.

The primary (SGA of relief response rated endpoint) and secondary efficacy variables were evaluated using a standard Mantel-Haenszel test taking into account center effect, for comparison of both tegaserod treatment groups to placebo. Hochberg's procedure for multiple comparisons was used to adjust the overall significant level of 0.05 for the primary efficacy variable only. Monthly and weekly summaries of the efficacy variable daily diary variables were presented. Quality of life scores were analyzed by means of a general linear model.

### b. Safety

As in the two previously described trials, safety variables in Study B307 included adverse events, vital signs, physical examination, EKG evaluations, and clinical laboratory tests. Safety variables were analyzed descriptively. The frequencies of AEs and abnormal findings for laboratory, vital signs, and EKG evaluations were tabulated. Numeric laboratory, vital sign and EKG parameters were presented showing mean, standard deviation, median minimum and maximum.

## 7. Results

### a. Efficacy

#### i) Primary Efficacy Analysis (Table 24)

With regard to the primary efficacy variable (SGA of relief) neither the 4 mg/d dose level or the 12 mg/d dose level were significantly better than placebo.

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**TABLE 24**  
**Study B307**

**Subject Global Assessment of Relief**

	Original Definition of SGA of Relief			New Definition of SGA of Relief		
	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
<b>Study 307 (n=835)</b>						
Responder Rate % (n)	25.7 (280)	26.7 (273)	28.0 (282)	-38.2	42.1	36.9
Difference (se)	-2.4 (3.7)	-1.2 (3.8)		1.2 (4.0)	5.4 (4.2)	
p-value	0.524	0.753		0.768	0.193	
Adjusted p-value	0.753	0.753		0.768	0.386	

**ii) Secondary Efficacy Analyses (Table 25)**

The results of this analyses of the secondary variables at endpoint showed a statistically significant change for both the 4 mg/d and 12 mg/d dose levels with regard to the number of bowel movements. Neither treatment doses had significant effects on abdominal pain, bloating or stool consistency.

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ON ORIGINAL**

**TABLE 25**  
**Study B307**

**Secondary Variables at Endpoint (ITT population)**

	Tegaserod (mg/d)		Placebo
	4	4→12	
Mean percent change from baseline in number of days with significant abdominal discomfort/pain	-13.8% (N.S.)	-16.2% (N.S.)	-12.7%
Mean percent change from baseline in number of days with significant abdominal bloating	-10.6% (N.S.)	-8.0% (N.S.)	-13.8%
Mean percent change from baseline in number of days without bowel movements	-20.7% (N.S.)	-22.0% (p=0.018)*	-14.4%
Mean percent change from baseline in number of bowel movements	67.2% (p<0.001)**	59.4% (p<0.001)**	29.5%
Mean percent of days with hard or very hard stool <sup>1</sup>	13.8% (N.S.)	13.0% (N.S.)	16.2%
Mean percent of days with stool consistency score between 3 and 5 <sup>1</sup>	71.6% (N.S.)	74.1% (N.S.)	73.9%
Proportion of patients with normalized bowel habit	67.3% (N.S.)	73.7% (N.S.)	67.9%

Note: p-value (nominal p-value) refers to the comparison between each of the tegaserod groups and placebo at endpoint  
1) denominator is number of days with stool  
\* indicates the nominal p-value <0.05, and  
\*\* indicates the nominal p-value <0.01.

**b. Safety**

The safety profile of tegaserod 4 mg/d and 4 → 12 mg/d were similar. The overall safety results were similar to those in Study B301 with (once again) diarrhea being the most prominent AE occurring more than twice as frequently in the tegaserod treatment groups than in the placebo treated group.

**8. Sponsor's Conclusion**

"Tegaserod provided early relief of overall C-IBS symptoms. The onset of relief was approximately 1 week. There were no statistically significant results between the tegaserod treatment groups and placebo; trends favoring tegaserod were seen during the treatment period. The safety profile for tegaserod 4 mg per day and the 4 → 12 mg groups were similar."

### 9. Reviewer's Additional Comments:

Study B307 was a well-designed and apparently well-executed properly randomized study where the inclusion criteria/reason for exclusion fit the Rome criteria for C-IBS. Conclusions on efficacy and safety of the test medication are valid because there appeared to be no demographic differences and baseline variables between the different treatment groups. One difference between 307 and the other two trials is that this study utilized a dose-titration design. That is, patients in the tegaserod 4 → 12 mg per day group underwent a dose-titration at week 4 for unsatisfactory response and those in the tegaserod 4 mg per day group and the placebo group underwent mock titration. This approach resulted in a placebo group that - in comparison to the other pivotal trials - had a significant increase in response immediately following dose-titration; that such high placebo response persisted for the remainder of the study. Since this increase in titration response was not seen in the other two experimental arms of the trial; neither the 4 nor the 4 → 12 mg per day tegaserod groups showed statistically significant difference from placebo. Factors contributing to this high placebo response without a concomitant increase in response to tegaserod are not understood.

Tegaserod, in doses of 4 mg and 4 → 12 mg was safe and well tolerated. The overall reported frequency of AEs was similar across the treatment groups. Of note, diarrhea was reported twice more frequently in both tegaserod groups when compared to placebo; this finding is no longer surprising (see ISS). Diarrhea occurred early in the tegaserod groups and in most cases was transient, self-limiting it did not recur (less than 12%) and rarely led to discontinuation (less than 2.5% vs PL 0.6%). Essentially all AEs otherwise were similar between the tegaserod groups and placebo.

There were no differences in the orthostatic blood pressure measurements, reported frequency of dizziness and EKG changes across the three treatment arms, in particular there was no evidence of QT<sub>c</sub> prolongation.

In conclusion, the therapeutic gain for the 4 mg per day and the 4→12 mg per day tegaserod group were clinically insignificant and - statistically - could not be differentiated from placebo.

## X. INTEGRATED SUMMARY OF EFFICACY

### A. Introduction

The applicant summarized the clinical effectiveness of Zelmac™ tablets 6 mg po twice daily before a meal in volume #200. Following a 117-week dose ranging study (B251) done in Europe and North America, and a 26-week dose-titration study done in Europe and Canada (B202) it was concluded that positive effects on constipation-predominant irritable bowel syndrome (C-IBS) were seen with both the 4 mg as well as the 12 mg per day dose. The latter seemed to be associated with the maximum efficacy. Also, in these Phase II trials, moderate improvement

in constipation and abdominal discomfort/pain were noted and these effects were sustained throughout the treatment period. Therefore, Phase III studies (B351, B301, B307) were carried out with men and women with constipation-predominant IBS over a 12 week treatment period. Table 26 summarizes the main features of the design of these three Phase III controlled trials.

**TABLE 26**  
**NDA 21-200**

**Summary of Adequate and Well-controlled Trials Submitted in Support of the Approval of Tegaserod for the Treatment of C-IBS**

Study No.	Location	Design	n	Study duration	Treatment groups (mg/d)
B351	North America <sup>1+</sup>	placebo-controlled, double-blind, parallel group	799	4-week baseline, 12-week treatment	tegaserod 4 tegaserod 12 placebo
B301	Europe, S. Africa, US <sup>2</sup>	placebo-controlled, double-blind, parallel group	881	Ibid	tegaserod 4 tegaserod 12 placebo
B307	North America, Europe <sup>3</sup>	placebo-controlled, double-blind, parallel group, dose-titration	841 <sup>4</sup>	Ibid	tegaserod 4 tegaserod 4→12 (optional dose-titration), placebo
<p>1) 49 centers in US(47) and Canada(2), 97% of patients randomized at US sites                  2) 92 centers in UK(18), Germany(15), Netherlands(12), Switzerland(9), US(9), Italy(7), Turkey(6), South Africa(6), Finland(4), Austria(3), Spain(2), Portugal(1), 90% of patients randomized from Europe                  3) 67 centers in US(37), UK(10), France(8), Germany(5), Belgium(3), Canada(3), Spain(1); 66% of patients randomized from US                  4) Excludes 4 randomized patients at one study center. This site was terminated early due to concern with possible non-compliance with Good Clinical Practices.</p>					

The Phase III studies utilized similar inclusion and exclusion criteria. They were performed in different geographical areas but the demographic and baseline characteristics of the patients were generally similar among the three studies. As shown in Table 27 patients in each study were largely female, with a mean age of 43 to 46 years and had a duration of disease greater than 10y and similar baseline severity of disease. Of note, the percentage of black patients was highest in Study B351.

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**TABLE 27**  
**NDA 21-200**

**Demographics and Baseline Characteristics in Adequate and Well-Controlled Studies**

	<b>B351 (n=799)</b>	<b>B301 (n=881)</b>	<b>B307 (n=841)</b>
Age (y)	43 ± 13	46 ± 14	45 ± 13
Age ≥65 y	7%	11%	11%
Female	87%	83%	84%
Race: Caucasian	88%	98%	90%
Black	9%	1%	6%
Other	3%	1%	4%
Weight (kg)	71 ± 16	68 ± 14	70 ± 16
Duration of IBS (months)	175 ± 158	158 ± 147	166 ± 154
Abdominal discomfort/pain VAS score (mm)	63 ± 13	60 ± 13	61 ± 13
Bowel habit VAS score (mm)	64 ± 14	60 ± 14	62 ± 14
No. of days/28 days with significant <sup>1</sup> discomfort/pain	24 ± 6	24 ± 6	24 ± 6
No. of days/28 days with significant <sup>1</sup> bloating	25 ± 6	23 ± 7	24 ± 6
No. of days without bowel movements/28 days	13 ± 7	12 ± 7	11 ± 7
No. of bowel movements/28 days	23 ± 18	22 ± 16	25 ± 20
% of days <sup>2</sup> with hard/very hard stools	31 ± 29	28 ± 29	29 ± 28
Note: results expressed as mean ± SD			
1) Defined as at least mild (daily score > on 6-point scale).			
2) Denominator is days with bowel movements.			

There were no relevant differences in demographic and other baseline characteristics.

Studies B301 and B351 were similar with respect to study design: following a baseline period, patients were randomized to receive either a fixed dose of tegaserod 4 mg per day, a fixed dose of tegaserod 12 mg per day or placebo for a 12-week period. Study B307 was different in design since it included a dose-titration arm. In this trial, patients were randomized to receive either a fixed dose of tegaserod 4 mg per day, a dose-titration regimen or placebo. The patients who were randomized to the dose-titration regimen received tegaserod 4 mg per day and underwent dose-titration at week 4 to tegaserod 12 mg per day if the response to the SGA of relief was complete or considerable relief of less than 50% of the time. Otherwise patients remained on tegaserod 4 mg per day for the remaining 8 weeks of the trial. In this dose-titration study, patients in the tegaserod 4 mg per day and placebo arms remained on their original assigned medication for the entire 12 weeks.

The randomized study populations (entry criteria and reasons for exclusion from the studies) were similar for the three trials. Men and women greater than or equal to 18 years (greater than or equal to 12 y in study B351) who satisfied Rome I criteria (1991) for C-IBS were eligible to participate in the trials. Additionally, patients were required to have at least two of three constipation symptoms (at least 25% of the time during 3 months prior to study entry: less than 3 bowel movements per week, hard/lumpy stools, straining with a bowel movement). Most

(approximately 90%) of the patients in these three trials also satisfied the Rome II (1999) criteria which required that abdominal discomfort or pain be associated with two of the following three: relieved by a bowel movement, associated with a change of frequency of bowel movements, or associated with the change in consistency of stool.

In all three trials, patients underwent appropriate endoscopic or radiologic procedures to rule out other causes of G.I. symptoms. Patients with diarrhea (greater than 25% of the time: loose stools and/or greater than 3 bowel movements per day associated with urgency), diseases or conditions that affect bowel transit or other evidence of significant medical disease, patients using medications that would effect bowel transit or interfere with clinical evaluations (i.e., narcotic analgesics) and women of childbearing age not using medically approved contraception were not randomized into these trials.

Following the 4-week baseline period in which patients used a paper diary to record symptoms, those who had at least mild abdominal discomfort/pain (greater than or equal to 35 mm on a 100 mm VAS scale) during the 4-week baseline period were randomized.

Laxative use was allowed if requirements for rescue were met (i.e., no bowel movement for 4 consecutive days associated with bothersome abdominal discomfort/pain or bloating). Bulk-forming agents and use of tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) were allowed if used in constant doses for at least one month prior to randomization and were taken in constant doses throughout the study.

All test medication was given po b.i.d. to be taken within 30 minutes prior to meals. A double-dummy technique was used throughout and patients took two tablets twice a day during the 12-week treatment period, even in study 307 with its dose-titration design.

#### B. Summary Results of Study B351

- 1,093 patients were enrolled into this trial; 799 of these were randomized to tegaserod 4 or 12 mg per day or placebo:

	<u>n</u>
Tegaserod 4 mg/d	= 283
4-12 mg/d	= 277
Placebo	= <u>285</u>
Total n	= 845

Study B351 was the first of the Phase III studies to be completed. Although the results showed a consistent pattern of improvement for tegaserod compared with placebo for the primary and secondary outcome measures, the response rates were considered to be low in all treatment groups, in particular the response in the placebo group (22% original SGA of relief, 19% SGA of

abdominal discomfort/pain). The sponsor reasoned that the original response definition (complete or considerable relief greater than or equal to 50% of the time at endpoint) for the original SGA of relief and the response definition of the SGA of abdominal discomfort/pain was **too strict** and hence did not have the sensitivity to detect a significant treatment difference. To enhance the sensitivity of the SGA of relief efficacy variable the "somewhat relieved" response 100% of the time was prospectively included in the responder definition for the SGA of relief for the assessment of results of studies B301 and 307. An additional modification for the evaluation of the latter trials was that the SGA of abdominal discomfort/pain was eliminated as a primary efficacy variable and retained as a secondary efficacy variable. The sponsor has not provided an adequate explanation for this apparently arbitrary approach.

In Study B351, although the responder rates for the tegaserod 4 mg per day and the 12 mg per day groups were numerically higher than placebo for both efficacy variables, these comparisons did not reach statistical significance using the Holm's multiple comparison procedure (upper panel of Table 22).

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Responder Rate % (n)	30.0 (257)	26.2 (259)	21.6 (259)	39.7	45.2	32.4
Difference (se) <sup>1</sup>	8.4 (3.8)	4.6 (3.7)		7.3 (4.2)	12.8 (4.2)	
p-value <sup>2</sup>	0.035	0.257		0.099	0.004	
Adjusted p-value <sup>3</sup>	0.140	0.492		0.099	0.008*	
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) Hochberg'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.						

As previously mentioned, primary efficacy variables in Study 351 were thought to lack sensitivity to detect treatment differences. Using the new SGA of relief definition of response (complete or considerable relief at least 50% of the time or at least somewhat relief 100% of the time at the time of endpoint) the data were re-analyzed. In this re-analysis treatment with 12 mg per day achieved statistical significance when compared to placebo (lower panel of Table 22).

As seen in Table 23 the 4 mg per day and the 12 mg per day tegaserod treatments showed statistical significant difference compared to placebo for the mean percent change from baseline in the number of bowel movements. In addition, the 12 mg per day group also showed statistical significant difference in 4 additional secondary efficacy variables (Table 23).

**TABLE 23**  
**Study B351**

**Secondary Variables Derived From Daily Diary Data At Endpoint  
(ITT population)**

	Tegaserod (mg/d)		Placebo
	4	12	
Mean percent change from baseline in mean VAS of SGA of abdominal discomfort/pain	-24.8% (p=0.211)	-25.3% (p=0.044)	-20.7%
Mean percent change from baseline in number of days with significant <sup>1</sup> discomfort/pain	-15.2% (p=0.147)	-16.9% (p=0.017)*	3.9%
Mean percent change from baseline in number of days with significant <sup>1</sup> bloating	-14.9% (p=0.076)	-15.1% (p=0.006)*	-5.6%
Mean Percent change from baseline in number of days without bowel movements	-28.2% (p=0.053)	-31.2% (p=0.002)*	-21.4%
Mean percent change from baseline in number of bowel movements	68.9% (p=0.003)*	69.3% (p<0.001)*	44.8%
Mean percent of days <sup>2</sup> with hard or very hard stool <sup>1</sup>	12.7% (p=0.068)	11.3% (p=0.730)	18.9%
Mean percent of days with stool consistency score between 3 and 5 <sup>1</sup>	74.5% (p=0.168)	76.3% (p=0.730)	74.3%
Proportion of patients with normalized bowel habit	72.1% (p=0.441)	76.6% (p=0.079)	69.1%
NOTE: Nominal p-values are presented for the comparison between the tegaserod dose and placebo at endpoint.			
* Indicates a statistically significant difference compared to placebo based on Holm's multiple comparison procedure, adjusting for two doses, at significance level of 0.05.			
1) Denominator is the number of days with a bowel movement.			

**C. Summary Results of Study B301**

- 1,122 patients were considered for enrollment into the trial; 881 of these were randomized to tegaserod 4 or 12 mg per day or placebo. The disposition by treatment for all randomized patients showed no significant differences among the three treatment arms:

Tegaserod 4 mg	=	<u>n</u> 299
12 mg	=	294
Placebo	=	<u>288</u>
Total n		881

- Results of the primary efficacy variable (SGA of relief at endpoint) assessments were shown in Table 16.

**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
<b>Study 301 (n=881)</b>						
Responder Rate % (n)	27.8 (299)	26.2 (294)	20.5 (288)	38.8	38.4	30.2
Difference (se) <sup>1</sup>	7.7 (3.5)	5.9 (3.5)		9.0 (3.8)	8.6 (3.9)	
p-value <sup>2</sup>	0.029	0.092		0.020	0.028	
Adjusted p-value <sup>3</sup>	0.058	0.092		0.028	0.028	
<p>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.</p> <p>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.</p> <p>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</p>						

In this study both tegaserod treatment groups had significantly greater responder rates than the placebo group.

- The results of secondary efficacy evaluations were displayed in Table 17.

The only two secondary variables to reach statistical significance, and this occurred for both the 4 mg per day and 12 mg per day tegaserod groups, were the mean percent change from baseline in the number of days without bowel movements and the mean percent of change in number of bowel movements. The effect on number of days without bowel movements and number of bowel movements were noticeable early and were sustained throughout the 12-week treatment period. In spite of the fact of reaching statistical significance with the primary efficacy variable, tegaserod 4 mg per day was thought to show less consistent effects across variables and time.

**TABLE 17**  
**Study 301**

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

	<b>Tegaserod 4 mg/d n=299</b>	<b>Tegaserod 12 mg/d n=294</b>	<b>Placebo n=287</b>
Responder rate	29.8%	29.9%	22.6%
Treatment difference in responder rate <sup>1</sup>	7.0%	7.3%	
p-value <sup>2</sup>	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 <sup>1</sup>	12.8% (p=0.084)	13.7% (P=0.803)	15.0%
Mean percent of days with stool consistency score between 3 and 5 <sup>1</sup>	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.			

**D. Summary Results of Study B307**

- 1,163 patients were considered for enrollment into this trial; 845 of these were randomized to tegaserod 4 mg per day, tegaserod 4-12 mg per day (titration group) or placebo. Patient disposition analysis showed comparability among the three experimental arms. The distribution of patients per arm was:

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	<u>n</u>
Tegaserod 4 mg	= 283
12 mg	= 277
Placebo	= 285
Total n	= 845

Withdrawals from the study due to adverse events and lack of efficacy were similar among the three treatment groups.

With regards to the primary efficacy variable neither the tegaserod 4 mg per day nor the 4-12 mg per day groups could be differentiated from placebo (Table 24).

**TABLE 24**  
**Study B307**

**Subject Global Assessment of Relief**

	Original Definition of SGA of Relief			New Definition of SGA of Relief		
	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
Study 307 (n=835)						
Responder Rate % (n)	25.7 (280)	26.7 (273)	28.0 (282)	-38.2	42.1	36.9
Difference (se)	-2.4 (3.7)	-1.2 (3.8)		1.2 (4.0)	5.4 (4.2)	
p-value	0.524	0.753		0.768	0.193	
Adjusted p-value	0.753	0.753		0.768	0.386	

Of note, there was a large (13%) increase in the placebo responder rate that occurred from month 1 to month 2 (after dose titration) compared with the 7% observed increase in responder rates in both tegaserod groups. The increased placebo response then persisted for the remainder of study 307.

The only secondary variable that reached statistical significance with both the 4 and 12 mg per day groups was the mean percentage change from baseline in number of bowel movements (Table 25). In addition, the mean percent change from baseline in number of days without bowel movements reached statistical significance for the 4-12 per day group.

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**TABLE 25**  
**Study B307**

**Summary of the Between-Treatment Comparisons of Secondary Efficacy Variables at Endpoint (ITT population)**

	Tegaserod (mg/d)		Placebo
	4 mg/d	12 mg/d	
Responder rate for <b>original</b> SGA of relief (>50% complete or considerable relief)	25.5% (p=N.S.)	26.5% (p=N.S.)	28.2%
Responder rate for 100% at least somewhat relief	35.1% (p=N.S.)	40.0% (p=N.S.)	33.9%
Responder rate for SGA of abnormal discomfort/pain	25.5% (p=N.S.)	27.6% (p=N.S.)	30.6%
Responder rate for SGA of bowel habits	27.0% (p=N.S.)	24.0% (p=N.S.)	25.0%
Mean percent change from baseline in number of days with significant <sup>1</sup> discomfort/pain	-13.8% (p=N.S.)	-16.2% (p=N.S.)	-12.7%
Mean percent change from baseline in number of days with significant <sup>1</sup> bloating	-10.6% (p=N.S.)	-8.0% (p=N.S.)	-13.8%
Mean percent change from baseline in number of days without bowel movements	-20.7% (p=N.S.)	-22.0% (p=0.018)	-14.4%
Mean percent change from baseline in number of bowel movements	67.2% (p=0.001)	59.4% (p<0.001)	29.5%
Mean percent of days <sup>2</sup> with hard or very hard stool	13.8% (p=N.S.)	13.0% (p=N.S.)	16.2%
Note: p-values are the nominal p-values for the comparison between the tegaserod dose and placebo at endpoint			
1) Defined as at least mild (daily score $\geq 2$ on 6-point scale);			
2) Denominator is days with bowel movements.			

**OVERALL CONCLUSION ON EFFICACY**

In conclusion, the data evaluated here provide evidence that tegaserod is effective in the treatment of patients with C-IBS. The SGA of relief is a global assessment endpoint that combines the important symptoms of IBS (abdominal discomfort/pain, altered bowel habits and overall well-being). With the SGA of relief that was calculated on a post-hoc analyses in Study 351 there was consistency seen between the SGA of relief in Studies 301 and 351 and these changes were persistent overtime and generally supported by secondary efficacy variables in both studies.

**E. Long-Term (L-T) Efficacy (Study B209)**

*Study B209: a 12-month open label-dose-titration study to assess the safety and efficacy of SDZ HTF 919 in subjects with constipation-predominant irritable bowel syndrome.*

This study was designed to provide L-T efficacy/safety data under an open-label design. Participating patients were treated with tegaserod during a 12-month period following an initial 7-day screening period. Visits took place at months 1, 2, 4, 6, 8, 10 and 12 after the start of drug administration. Efficacy was judged by monthly investigator interview using the SGA of overall GI symptoms, SGA of abdominal discomfort, and SGA of constipation. No daily efficacy data were collected. Treatment was started with 4 mg per day of tegaserod with the possibility of a dose increase to 12 mg per day at month 1 through month 10. Patients who were completely relieved or considerably relieved with the SGA of overall g.i. symptoms remained on the 4 mg per day dose while those somewhat relieved, unchanged or worse received the 12 mg per day dose.

Of 601 patients considered for enrollment in study B209, 579 received tegaserod treatment. Table 28 summarizes the disposition of patients in this study.

**TABLE 28  
Study B209**

**Summary of Patient Disposition and Primary Reasons for Discontinuations**

	n (%)
Patients entering study treatment phase	580
ITT population	567 (09%)
Patients completing 12-month study period	304 (53%)
Total patients discontinued during the treatment period	274 (47%)
Lack of efficacy	72 (12%)
Adverse event	65 (11%)
Withdrawal of consent	61 (11%)
Failed to return	49 ( 8%)
Protocol violation	18 ( 3%)
Other	10 ( 2%)
ITT population: all treated patients with at least one efficacy assessment during the treatment phase	

- 53% of the patients who began treatment with tegaserod completed the 12-month study; nearly one-half [n=274] were withdrawn from the trial (Table 28), for reasons that included insufficient therapeutic effect, adverse events and consent withdrawal. At the end of the study, 80% of the patients had been titrated from the 4 to the 12 mg per day. Of the patients completing the trial, 62% reported "complete" or "considerable" relief of the overall g.i. symptoms. Study 204 was discontinued due to administrative problems.

**XI. INTEGRATED SUMMARY OF SAFETY**

**A. Clinical Studies**

The studies contributing to analyses groupings are identified in Table 29.

**TABLE 29**  
**NDA 21-200**  
**Populations and Groupings of Studies for Analysis**

Database	Subpopulations	Studies	Number of patients		
			Tegaserod	Placebo	Totals
<b>Key Safety Population (C-IBS patients in studies ±12 weeks)</b>					
1	Placebo-controlled Phase III studies	B301, B307, B351	1679	837	2516
2	Placebo-controlled Phase II studies	B202, B251	519	151	670
3	Phase II and III studies combined	B202, B251, B301, B307, B351	2198	988	3186
4	Long-term uncontrolled studies	B204, B209	675	-	675
<b>Total number of patients<sup>1</sup></b>			<b>2665</b>	<b>988</b>	<b>3596</b>
<b>Other Populations/Groupings for Analysis</b>					
	Placebo-controlled Phase II study	—	52	24	76
	All multiple-dose, placebo-controlled Phase II and III studies and parallel-group studies in healthy volunteers	B202, — B251, — — B301, — B307, B351, —	2424 <sup>2</sup>	1117	3510 <sup>2</sup>
	[	]	211	41	252
	[	]	119	-	119
	[	]	160	5	165
	All completed studies	All studies listed in sponsor's Tables 1 through 6	<b>3510</b>	<b>1185</b>	<b>4606</b>
<p>1) Some patients from study B204 also participated in study B209. Some patients from the Phase II studies B202, B207, and B251 also participated in studies B204 and B209. A patient being counted only once in any value, the "totals" are not necessarily the sum of the values in the columns. For databases with crossover studies, the totals are not the sum of the cells in each row, these being the same patients receiving tegaserod and placebo.</p> <p>2) Database 6 value excludes 3 patients from study W106 who participated only in the uncontrolled pilot phase.</p>					

The key safety population (KSP) was drawn from studies of patients with C-IBS designed to last at least 12 weeks. The selection criteria for the KSAP are listed in Table 30.

**TABLE 30**  
**NDA 21-200**

**Main Selection Criteria of Patients**  
**(Key Safety Population)**

Inclusion criteria	Phase 3			Phase 2		Long-term	
	B301	B351	B307	B202	B251	B204	B209
Age (yr)	≥ 18	≥ 12	≥ 18	18 - 65	18 - 65	≥ 18	18 - 70
Diagnosis of C-IBS <sup>1</sup>	a	a	a	b	b	c	c
Inadequate improvement through use of non-pharmacological therapy (bulking agents, high-fiber diet, exercise) for ≥2 months	x	x	x	x	x	x	x
<b>Exclusion criteria</b>							
Significant associated diarrhea <sup>2</sup>	a	a	a	b	b	na	a
Cancer, structural bowel disease or other diseases significantly affecting bowel transit	x	x	x	x	x	x	x
Planned medication significantly affecting GI motility	x	x	x	x	x	x	x
Pregnancy/inadequate contraception	x	x	x	x	x	x	x
Major psychiatric illness requiring therapy <sup>3</sup>							
Other major illness compromising trial participation	x	x	x	x	x	x	x
History of syncope, orthostatic hypotension, autonomic neuropathy, carotid sinus hypersensitivity	na	na	na	x	x	x	x
Orthostatic hypotension at pre-trial single 24-mg challenge	na	na	na	x	na	na	na
<p>Note: "x" implies criteria required and na=not applicable.</p> <p>1) Based on 1992 Rome criteria: Patient must have had over previous 3 months: continuous or repeated lower abdominal pain/discomfort which is relieved by bowel movement (BM) and/or associated with change in BM frequency, and/or associated with a change in stool consistency, and for at least 25% of that time:</p> <p>a: 2/3 of following: &lt;3 BM/week, hard or lumpy stools, straining during BM.</p> <p>b: &lt;3 BM week, plus ≥2/3 of following: hard or lumpy stools, straining during BM or feeling of incomplete BM, abdominal bloating/swelling</p> <p>c: &lt;3 BM/week, plus ≥1/3 of following: hard or lumpy stools, straining during BM or feeling of incomplete BM, abdominal bloating/swelling</p> <p>2) a: Over past 3 months, for ≥25% of time: loose/watery stools and/or &gt;3 BM/day associated with urgency.</p> <p>b: Over past 6 months, for ≥25% of time: &gt;3 BM/day and/or loose/watery stools and/or urgency for BM.</p> <p>3) Well-compensated depression was not an exclusion criterion.</p> <p>Source: Study reports for studies B202, B204, B209, B251, B301, B307, and B351</p>							

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The visit schedule and evaluations for the studies adding to the KSP are shown in Tables 31 and 32.

**TABLE 31**  
**NDA 21-200**  
**Visit Schedule**  
**(Key Safety Population)**

	Screening (days)	First Dose (days)	Treatment Period
<b>Phase III</b> B301, B351, B307	-28	1	Days 29, 57, 85 (or at discontinuation)
<b>Phase II</b> B202	-35*, -1	1	Days 28, 56, 84, 112, 140, 154, 168, 182/discontinuation
B251	-35, -38, -14	1	Days 14, 28, 42, 56, 70, 84/discontinuation
<b>Long-Term</b> B204	-7	1	Day 14, Months 1, 2, 3, 4, 6, 8, 10, 12/discontinuation
B209	-7	1	Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12/discontinuation
*Challenge dose (24 mg tegaserod)			
Source: Study reports for studies B202, B204, B209, B251, B301, B307 and B351			

**TABLE 32**  
**NDA 21-200**  
**Safety Evaluations**  
**(Key Safety Population)**

Evaluation	Timing
Full physical examination	All studies: screening and at end of treatment
Adverse event solicitation	All studies: at all visits
Concomitant medication	All Studies: at all visits
Vital signs Blood pressure and pulse, supine and sitting 3-h blood pressure profile	All studies: at all visits Phase III studies: Day 1 (post-first dose) B202: Day -35 (post 25-mg challenge dose) B251: Day 1 (post-first dose), Day 42 Screening and end treatment (and intermediate visits in B204 and 209)
Body weight	
Laboratory <sup>a</sup>	Phase III studies: at all visits B202: Days -35, -1, 28, 56, 112, 140, 182 B251: Day -35, 1, 14, 28, 42, 56, 70, 84 B204: Day -7, Months 2, 4, 6, 8, 10, 12 B209: Days -7, 1, Months 1, 2, 4, 6, 8, 12, 12
Pregnancy test	Phase III studies: at all visits B202: Days -35, -1, 28, 56, 84, 112, 140, 168, 182 B251: Days -35, 1, 28, 56, 84 B204: Day -7, Months 1, 2, 3, 4, 6, 8, 10, 12 B209: Day -7, Months 1, 2, 4, 6, 8, 10, 12
EKG (standard 12-lead)	Phase III studies: Days -28, 1 (1.5 to 2.5 hours post-first dose,=), 29, 85 (1.5 to 2.5 h post-last dose) B202: Days -35, 182 B251: Days -28, 1, 28, 56 B204 and 209: Day -7, Months 2, 6, 12
a) Laboratory: serum biochemistry (transaminases, total bilirubin, creatinine, urea, uric acid, alkaline phosphatases, creatinine phosphokinase, albumin, total protein, glucose, total cholesterol, calcium, chloride, potassium, sodium), hematology (hemoglobin, hematocrit, red blood cells, white blood cells and differential, and platelets), urinalysis (pH, protein, glucose, blood). Day 1 sample was pre-first dose.	

In the key safety population ca. 10% of the randomized patients were equal to 65 y of age, in the L-T studies 6% of the patients were greater than or equal to 65 y of age.

Although the overall studies consisted approximately of 85% female patients, the percentages of males/females who received test medication for at least 85 days were comparable.

The majority of patients (greater than 90%) were Caucasians and there were very few patients of other races.

Overall, a total of 4,306 patients received test medication of whom 3,507 received tegaserod. The KSP of patients with C-IBS comprised 3,861 patients of whom 2,873 received tegaserod (mainly 2,516 of patients from Phase III studies, 67% of which equally in the placebo and tegaserod groups were exposed to test medication over the 85-day study duration. Exposure rates for the Phase II studies were similar: 418 patients from the KSP received tegaserod for 6 months. The 12 month figure was 185 patients with 302 patients treated for 335 days. Compliance showed 90% of patients taking at least 75% of their prescribed medication.

The disposition of patients in the Key Safety Population is shown in Table 33, which shows the proportion of patients completing the studies; the different treatment groups were comparable to each other.

**TABLE 33**  
**NDA 21-200**

**Disposition of Patients: Pooled Phase II Studies (Database 1)**

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

1) Subject's condition no longer requiring therapy.

About 1/3 of the Phase III patients discontinuing prematurely, 6.3% of the study population, did so because of AEs. The rates of AE attributed to discontinuation were marginally higher in the tegaserod than in the placebo group (6.8 vs 5.1%). One tegaserod patient died (a case of suicide), 7 were withdrawn because of laboratory abnormality, and a relatively large portion of Phase III patients (7.1% of tegaserod vs 7.3% placebo) discontinued due to withdrawal of consent for failure to attend as required. Further evaluation of the reasons for these withdrawals showed that the most common were g.i. events or headache.

The disposition of patients in the pooled Phase II studies is given in Table 34. There was a lower AE-related discontinuation rate (1.9%) in the tegaserod ~ mg per day group compared with the 4 mg, 12 mg and 24 mg per day groups (8 to 10%), which suggests a dose effect.

**TABLE 34**  
**NDA 21-200**

**Disposition of Patients: Pooled Phase II Studies**  
**(Database 2)**

Disposition/ Principal Reason	Tegaserod (mg/d)					Tegaserod groups n=519 n (%)	Placebo n=151 n (%)	All treatment n=670 n (%)
	— n=107 n (%)	4 n=107 n (%)	12 n=110 n (%)	24 n=110 n (%)	— >12 titration n=85 n (%)			
Completed	89 (83.2)	85 (79.4)	89 (80.9)	87 (79.1)	42 (49.4)	392 (75.5)	104 (68.9)	496 (74.0)
Discontinued	18 (16.8)	22 (20.6)	21 (19.1)	23 (20.9)	43 (50.6)	127 (24.5)	47 (31.1)	74 (26.0)
Adverse event	2 ( 1.9)	11 (10.3)	10 ( 9.1)	9 ( 8.2)	11 (12.9)	43 ( 8.3)	14 ( 9.3)	57 ( 8.5)
Withdrawal of consent	6 ( 5.6)	2 ( 1.9)	2 ( 1.8)	3 ( 2.7)	4 ( 4.7)	17 ( 3.3)	7 ( 4.6)	24 ( 3.6)
Protocol violation	0	0	0	0	2 ( 2.4)	2 ( 0.4)	3 ( 2.0)	5 ( 0.7)
Treatment failure	2 ( 1.9)	4 ( 3.7)	4 ( 3.7)	2 ( 1.8)	9 (10.6)	20 ( 3.9)	10 ( 6.6)	30 ( 4.5)
Failure to return	6 ( 5.6)	3 ( 2.8)	3 ( 2.8)	6 ( 5.5)	1 ( 1.2)	21 ( 4.0)	5 ( 3.3)	26 ( 3.9)
Other	2 ( 1.9)	2 ( 1.9)	2 ( 1.9)	3 ( 2.7)	16 (18.8)	24 ( 4.6)	8 ( 5.3)	32 ( 4.8)

For L-T study B209 (Table 35) the overall 12 month completion rate was about half (54%). The AE discontinued rate at 10% of all discontinued patients was only slightly higher than seen in Phase II and III studies. In this study, AEs contributed to the discontinuation of 67 out of 413 patients, the most common being g.i. symptoms although there was one case each of depression, weight increase, menorrhagia, joint pain, back pain and acne.

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**TABLE 35**  
**NDA 21-200**

**Disposition of Patients: Long-Term Studies**  
**(Database 4)**

	n=675 n (%)
Completed	262 (38.8)
Discontinued	413 (61.2)
Adverse event	67 ( 9.9)
Withdrawal of consent	61 ( 9.0)
Protocol violation	16 ( 2.4)
Treatment failure	72 (10.7)
Failure to return	46 ( 6.8)
Other	11 ( 1.6)
Administrative problem	140 (20.7)

**B. ADVERSE EVENTS**

In the Phase III studies the most frequently reported AEs were either g.i. symptoms which would be expected in patients with IBS (abdominal pain, diarrhea, nausea, flatulence, dyspepsia, constipation) or general disorders (head, back pain, infections of the upper respiratory tract or suggestive of influenza).

Diarrhea was the only adverse event that appeared more clearly frequent in the tegaserod group than the placebo group (11.7% vs 5.4%;  $p < 0.0001$ ).

In the Phase II studies similar AEs predominated. The frequencies were slightly higher, probably secondary to more frequent visits (every two weeks in study B251) and the longer duration (26 weeks in Study B202). The most frequent AE was abdominal pain (28% tegaserod vs 29% placebo) followed by diarrhea (28% vs 15%), headache (23% vs 25%), nausea (18% vs 21%), flatulence (16% vs 11%) and dizziness (11% vs 11%). Upper respiratory infections were reported more frequently in the tegaserod patients (9% vs 3%) but these differences were not observed in the Phase III studies.

The L-T studies showed AEs of similar frequencies and types as those observed in the Phase II and Phase III studies. However, 61% of L-T patients discontinued treatment.

**C. Severe Adverse Events**

The pooled Phase III trials showed a 26% incidence of at least one severe AE in the tegaserod group vs 23% of patients in the placebo group. AEs that the investigators suspected of possible-

relationship to the test medication included diarrhea (tegaserod 8.8%, placebo 2.5%), and abdominal pain (9.2% vs 6.9%).

In the pooled Phase II studies the overall reporting frequency (28% vs 27%) of severe AEs was comparable to that observed in the Phase III studies, with severe abdominal pain (10.2% vs 6.6%) the most frequently reported. Severe diarrhea was also more than four times as frequent in the tegaserod patients (8.5% vs 2.0%). In addition, suspected treatment-related diarrhea was twice as frequent in the Phase II study tegaserod patients as in the placebo patients (19% vs 9%).

In the L-T studies severe AEs were reported on a less frequent basis (15%) than in the Phase II or III studies. Severe diarrhea occurred in 1.5% of the patients and severe abdominal pain in 3.9% of the patients. The diarrhea was considered at least possibly drug related in 10% of the patients in these L-T studies.

#### **D. Deaths**

A single patient (B301/147/0001) in the tegaserod 4 mg per day group committed suicide after 36 days in the study. The patient had a 14 year history of mild hypertension and had received tricyclic antidepressant drug therapy. Her mother had also committed suicide. This event is not considered related to the tegaserod therapy.

#### **E. Serious Adverse Events**

In the pooled phase III studies the incidence of SAEs was 1.8% in the treatment group vs 1.6% in the placebo group. In the pooled phase II studies the incidence of SAEs was 1.9% and 3.3% respectively. As would be expected the long-term studies showed slightly increased levels of SAEs (4.1%). The distribution of SAEs per organ system is addressed next.

##### **1. GI Disorders**

Gastrointestinal disorders were the most frequent reported SAEs. These included mostly recognized symptoms of IBS such as g.i. complications associated with excessive straining at stool (hiatal hernia, diverticulitis, rectocele). Most of these were considered serious because patients were hospitalized for a diagnostic work up. There was a case of "gastritis" in an 18 y M (W352/1/017), diagnosed following 4 days of dyspnea and chest pain, after completing four repeated single dose (12 mg) tegaserod treatments in the food interaction study. This patient had nausea, dizziness, abdominal cramps and diarrhea that had followed each intake of the drug, he was discontinued from the study. Suspicion is strong that the drug was the cause of the g.i. symptoms and subsequent pain. Gastritis is a diagnosis that can only be made after histological evaluation. No endoscopic or pathological information are available to document this patient's "gastritis".

## 2. Cardiovascular Events

These events included:

<u>EVENT</u>	<u>COMMENT</u>
• MI and unstable angina	Not thought to be due to drug
• Fluid overload	This occurred in a renal dialysis patient that had refused dialysis

## 3. CNS Events

The CNS events were predominantly those of headache. There were four serious cases, two in the PL and two in the treatment group. None were considered due to test medication. A case of peripheral neuropathy was noted and this was thought to be due to a cervical hernia.

## 4. Endocrine Disorders

There was a benign thyroid nodule that was diagnosed approximately 6 mo after tegaserod treatment had begun; it was removed surgically four months later, not considered to be drug related. This patient completed the full 12 months of tegaserod treatment.

## 5. Female Reproductive Disorders

### a. Ovarian Cysts

#### i) Introduction

Molecular cysts, corpus luteum cysts and theca lutein cysts comprise the category of functional ovarian cysts. Of note, smokers have a two-fold increase in developing functional ovarian cysts. These cysts are all benign and usually do not cause symptoms or require surgical management. As summarized in Table 36, annual rate of hospitalization for functional ovarian cysts has been estimated to be as high as 500 per 100,000 women-years in the U.S.

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ON ORIGINAL**

**TABLE 36**

**Estimated Number of Annual Hospitalizations Among Women of  
Reproductive age in the United States**

<i>Group of Diagnosis</i>	<i>Hospitalizations*</i>
Pelvic inflammatory disease	287,343
Benign cysts of the ovary	190,548
Endometriosis	188,805
Menstrual disorders	182,988
Uterine leiomyomas	177,082
Prolapse/stress incontinence	101,907
Cervical intraepithelial neoplasia	60,320

\*Based on discharge diagnoses for women 15 through 45 years of age in nonmilitary hospitals averaged for the period 1988-1990.  
From P. Velebil et al. Rate of hospitalization for gynecologic disorders among reproductive-age women in the United States. *Obstet Gynecol* 86:764-769 (1995).

Little is known of the epidemiology of this condition. The most common functional cyst is the follicular cyst, which is rarely larger than 8 cm and usually diagnosed incidentally to a pelvic examination. When cysts rupture, they cause pain and peritoneal signs, but normally resolve in 4 to 8 weeks.

Corpus luteum cysts called a cyst when the diameter is greater than 3 cm are less common than follicular cysts and may also rupture resulting in hemoperitoneum and requiring surgical management. Patients on anticoagulant therapy are at particular risk for rupture.

Theca lutein cysts are the least common of function ovarian cysts. They are usually bilateral, may occur with pregnancy including molar pregnancies, may be quite large (up to 30 cm), are multicystic and regress spontaneously.

**ii) Medications Associated With Ovarian Cyst Formation  
(Table 37)**

**Ovarian cyst formation** is cited under the following brands:

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**TABLE 37**  
**NDA 21-200**

**Medications Associated With Ovarian Cysts Formation**

\*Avonex (Biogen)  
Clomid Tablets (Hoechst Marion Roussel)  
Copaxone for Injection (Teva Marion)  
Effexor XR Capsules (Wyeth-Ayerst)  
Fertinex for Injection (Serono)  
Follistim for Injection (Organon)  
\*Gonal-F for Injection (Serono)  
Humegon for Injection (Organon)  
Nolvadex Tablets (AstraZeneca)  
Pergonal for Injection (Serono)  
Profasi for Injection (Serono)  
Repronex for Intramuscular Injection (Ferring)  
Serophene Tablets (Serono)

\*= incidence >3%

**b. Ovarian Cysts and Tegaserod (Table 38)**

A total of 9 cases of ovarian cysts were reported as AEs both serious and non-serious. Eight of the nine cysts were in tegaserod-treated patients, one occurred in the PL group. Five cases of ovarian cysts required surgery from the tegaserod patients, none in the PL patients.

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**TABLE 38**  
**NDA 21-200**

**Ovarian Cysts in Clinical Trials with Tegaserod**

Case #	Brief Summary of Case	Surg.	Pathology	Remarks
<b>TEGASEROD</b>				
B209/11/39	50 y WF, 10y Hx Menometrorrhagia and ovarian cyst. Asymptomatic during study. Elective surg. after 334d of study participation	yes	"water cyst" benign	pre-existing condition; no worsening of condition
B209/26/6	45 y WF presented with pain. CT, US and BE inconclusive. Underwent bilateral sphingoophorectomy after 261 d of test med.	yes	No mention of cyst	No ovarian cyst on surgery. Multi- adhesions gut-ommentum L. pelvic WALL
B209/28/4	35 y F underwent hysterectomy and sphingoophorectomy after day 306 on test med.	yes	3.5 cm partly-luteinized follicle cyst	Functional ovarian cyst
B209/28/22	40 y WF with RLQ abdominal pain after 89 days on the study drug. No diagnostic tests performed; presumptively diagnosed with a ruptured ovarian cyst.	no	None	No documentation of cyst
B251/32/2	22 y WF diagnosed as polycystic ovary after 43 days of test med. No treatment or other information available.	no	None	Pending [need information on sonogram, size of cysts, irregular menses, etc.
B251/32/7	30 y WF found by gynecology consult to have ovarian cyst after 56 days of test med. No specific treatment given	no	None	? functional ovarian cyst
B307/721/2	37 y BF presented after 100 days of test med. with pain and a 2.7 cm RT ovarian cyst seen on CT scan 5 wk AFTER diagnosis went to OR for RT salpingoophorectomy lysis of adhesions and appendectomy.	yes	peritubal cyst with	No ovarian cyst on pathology report
B351/518/27	13 y WF with previous bilateral resections of ovarian cysts, presented after 87 d of test med with RT abdominal pain. She had laparoscopic resection of an RT ovarian cyst and appendix	yes	early acute appendicitis	Recurrent functional cysts in women who were near menarche
<b>PLACEBO</b>				
B301/163/10	23 y WF after 71 days of placebo treatment - abdominal pain , CT scan showed polycytic ovaries. Treated with oral contraceptive (Meloden)	no	None	Incidental finding

After excluding pre-existing cases and those where there was no documentation or inadequate documentation, there were 5 ovarian cysts in the tegaserod group (total n=1649) and one in the placebo group (total n=607). This represents an estimated frequency of 0.3% for tegaserod and 0.1% for placebo patients. The confidence intervals for these events in both tegaserod and placebo overlap and therefore do not show an statistically significant difference. (See Appendix 1 for full consultation from Obstetrics and Gynecology.)

Originally, there were 8 cases of "ovarian cyst" in the tegaserod groups and one in the placebo group. Upon further analyses of the data provided by Novartis the same incidence of ovarian cyst was quite small. However, the number of patients requiring abdominal surgery in the tegaserod group (5 of 8) was worrisome. The significance of this finding is unclear at present.

#### **6. General Disorders**

These included four cases of non-specific chest pain in tegaserod patients. Two of these cases were ascribed to anxiety, one to a shoulder disorder, one patient underwent cholecystectomy five days later.

#### **7. Hematology**

One patient had increasing anemia after 80 days of treatment, leading to an episode of syncope. The patient had similar episodes in the past. The investigator did not consider this event to be drug related, in addition, the study medication had been discontinued days before the event.

#### **8. Liver/Biliary Disorders**

The liver/biliary disorders consisted of three cases of cholelithiasis and one of biliary stasis. Two of these patients had clear antecedents of biliary tract disease. A third underwent a cholecystectomy which showed multiple gallstones and chronic cholecystitis with omental adhesions that the investigator thought was more likely to represent a long-standing chronic disorder and to have preceded the 12 weeks of study medication.

#### **9. Metabolic Disorders**

One patient was hospitalized for post-prandial hypoglycemia discovered on day 22 of test medication. The medication was stopped and subsequently as long as day 63 there was still evidence of persistent hypoglycemia. Since the low blood sugar lasted more than 2 months beyond the withdrawal of the tegaserod this event was probably unrelated to test medication.

#### **10. Psychiatric Disorders**

It is well established that psychiatric disorders are frequent in IBS patients. Serious psychiatric events were found in five tegaserod treated patients compared with one placebo patient. The investigators did not consider any of these episodes, consisting of insomnia, anxiety and depression to be drug related.

#### **11. Other Serious Adverse Events**

There were five cases of neoplasm diagnosed in the tegaserod patients during these studies. None of these were considered to have drug causality.

**12. Laboratory Data (Non-Serious)**

**a, Serum Chemistry**

The mean changes for both tegaserod and placebo groups for all the parameters were negligible and not clinically relevant; these abnormalities were rare and drug effect was not suspected.

**b. Liver Enzyme Changes (Table 40)**

**TABLE 40  
NDA 21-200**

**Number (%) of Patients With Notable Liver Enzyme Abnormalities  
(Key safety population)**

	Phase II		Phase III		Long-Term
	Tegaserod ~24 mg/d n=519	Placebo n=151	Tegaserod 4 or 12 mg/d n=1679	Placebo n=837	Open N=675
ALT ( $\geq 3 \times$ ULN)	5 (1.0)	1 (0.7)	6 (0.4)	2 (0.2)	5 (0.8)
AST ( $\geq 3 \times$ ULN)	3 (0.6)	0	1 (0.1)	1 (0.1)	1 (0.2)
Bilirubin ( $\geq 34.2 \mu\text{mol/L}$ )	0	1 (0.7)	8 (0.5)	3 (0.4)	2 (0.3)
Alkaline phosphatases ( $\geq 3 \times$ ULN)	0	0	0	0	0

ALT=alanine transaminase, AST=aspartate transaminase, and ULN=upper limit of normal.

The majority of patients had single transient elevated liver enzyme values. All but 12 patients with an elevated value showed subsequent values that returned spontaneously to the normal range. In 12 patients, values were elevated at the last visit but no subsequent follow-up was available.

**c. Hematology/Urinalysis**

Notable abnormalities were rare. Urinalysis showed negligible differences and similar frequencies of abnormal readings in both the tegaserod and the placebo treatment groups.

**12. EKGs**

With the reported side effects of other prokinetic agents in mind, special emphasis was given to recording and analyzing of EKGs in the clinical studies. The phase II data, however, did not raise any suspicion regarding cardiac abnormalities in over 500 patients with four EKGs per patient.

During the phase III and phase II studies, EKG was obtained at 1.5 to 2.5 h after the first and last doses of the study drug and during any additional visit scheduled when the patient reported

symptoms of unusual dizziness or fainting. ( $T_{max}$  of tegaserod is approximately 1 hour.) A summary of the QT interval data for the phase III and long-term patients is given in Table 41.

**TABLE 41**  
**Study B209**

**Summary of QTc Interval Data in Phase III Studies (Database)  
and Long-term Study B209**

Assessment Parameter	Phase 3 studies				Long-term <sup>4</sup>
	4 mg/d n=844	12 mg/d n=560	All tegaserod n=1679	Placebo n=837	All tegaserod n=675
Baseline (mean, SD, msec)	401 ± 23	399 ± 24	401 ± 24	399 ± 22	396 ± 22
Change from baseline, at endpoint, (mean, SD, msec)	1.6 ± 22.9	3.8 ± 21.2	2.1 ± 22.2	3.1 ± 22.7	-0.7 ± 20.1
Increase by 30 to 60 msec	163 (19.6)	107 (19.5)	308 (18.6)	155 (18.7)	66 (12.4)
Increase by >60 msec	5 (0.6)	7 (1.3)	15 (0.9)	7 (1.3)	4 (0.7)
At least one post first-dose interval borderline <sup>1</sup>	37 (4.4)	27 (4.9)	72 (4.3)	37 (4.4)	11 (2.1)
At least one post first-dose interval prolonged <sup>2</sup>	10 (1.2)	2 (0.4)	16 (1.0)	8 (1.0)	0
With >499 msec <sup>3</sup>	3 (0.4)	0	3 (0.2)	0	0
Normal at baseline to prolonged at least once during study <sup>2</sup>	3 (0.4)	2 (0.4)	7 (0.4)	5 (0.6)	0
Normal at baseline to borderline at least once during study <sup>1</sup>	32 (3.8)	20 (3.6)	59 (3.5)	33 (4.0)	9 (1.7)
Borderline at baseline to prolonged at least once	4 (0.5)	0	5 (0.3)	3 (0.4)	0

Numbers in parentheses represent the corresponding percentages.

1) Borderline: males  $\geq 430$  to  $\leq 450$  msec; females:  $\geq 450$  to  $\leq 470$  msec.  
2) Prolonged: males  $> 450$  msec; females  $> 470$  msec.  
3) Newly occurring QTc  $> 499$  msec.  
4) Includes study B209 (Long-Term) only.

The percentage of patients who had an increase from 30 to 60 msec and greater than 16 msec were similar in both tegaserod and the placebo groups. However, three patients in the tegaserod group vs 0 patients in the placebo group had a greater than 499 msec of prolongation.

In the phase III studies, the EKGs that were considered overall as newly abnormal or worsened were similar in the tegaserod group (11%) and the placebo group (10%); the corresponding proportion of patients in Phase II studies was 18% for tegaserod and 14% for placebo. In long-term studies overall EKG abnormalities were less frequent in the tegaserod than the control studies. The most frequently occurring ECG abnormalities in the phase III studies were changes in t-wave morphology, which was slightly higher in the tegaserod group compared to placebo (4.3% vs 3.5%).

Additional abnormalities seen in greater than 1% of the patients in the total tegaserod group included ST segment depression and first degree AV block. The ST segment depression was slightly higher in the tegaserod than with the placebo group (2.6% vs 1.4%). Discontinuations due to EKG abnormalities occurred at a similar incidences in the total tegaserod vs placebo groups.

#### 14. Vital signs

##### a. Blood pressure and pulse

Due to rare cases of hypotension in healthy subjects phase II and phase III paid close attention to the analyses of the effects of tegaserod on BP and pulse.

The following AEs were defined as being suggestive of orthostatic hypertension: dizziness, syncope, hypertension, hypotension postural, circulatory failure, blood pressure labile, and cardiovascular not otherwise specified.

In phase III studies the AEs suggestive of orthostatic hypertension were reported with similar frequency in the placebo and total tegaserod groups. The most common AE of this group was dizziness and had similar frequency in all the treatment groups. However, syncope was more frequent in the total tegaserod group compared with the placebo group (0.5% vs 0.1%)  $p=0.16$ .

Careful attention was paid to any AE suggestion of orthostatic hypotension (e.g. dizziness, syncope, etc.). In the tegaserod treatment group 0.4% with an AE suggestive of orthostatic hypotension were observed and 0.1% in the placebo group. The total discontinued from the study secondary to an orthostatic hypotension related AE was equal in both tegaserod and placebo groups (1%).

In general, patients with C-IBS using tegaserod of doses of ~ to 24 mg per day did not have:

- changes in systolic or diastolic pressure or pulse rate (supine or standing)
- higher frequency of notably abnormal low or high blood pressure or pulse rate values
- higher frequency of reduction in orthostatic blood pressure
- higher frequency of discontinuation due to AEs suggestive of orthostatic hypotension.

The data are consistent with preclinical data that suggested that therapeutic doses of tegaserod had no significant effects on the circulatory system.

## 15. Interactions

Clinical drug-drug interaction studies were done in healthy subjects whose demographic characteristics were close to those of the target IBS patient population.

### a. Theophylline (Study W359)

From the results of this study, tegaserod is not expected to alter the PKs of drugs metabolized by CYP1A2 such as theophylline.

### b. Dextromethorphan (Study 360)

This study, consisting of co-administration of tegaserod with dextromethorphan did not show changes in the PKs of either compound. From this study and other drug-drug interaction studies with tegaserod and dextromethorphan, tegaserod is not expected to change the PDs of drugs metabolized by CYP2D6.

### c. Digoxin (Study W252)

From the results of this study, there was evidence that the digoxin  $AUC_{2\infty}$  decreased by 14% and the  $C_{max}$  decreased by 16% with co-administration of tegaserod. This extent of change in digoxin concentration was thought to be unlikely to be of clinical relevance. There were no reported EKG changes with the co-administration of tegaserod and digoxin. Data suggest that dose adjustment of either drug is not needed when tegaserod is co-administered with digoxin.

### d. Warfarin (Study W362)

This study in healthy volunteers showed no evidence that warfarin PK data changed by co-administration of tegaserod. No effect on the measurement of prothrombin times was noted. The data suggest that dose adjustment of either drug is not needed when tegaserod is given together with warfarin.

### e. Oral contraceptive (Study W357)

In this study in healthy female subjects taking oral contraceptives and tegaserod concomitantly, there was no increased in ovulation based on the changes in progesterone concentrations and sex hormone binding globulins. Tegaserod is not expected to alter the risk of ovulation in women taking oral contraceptives.

## 16. Common Concomitant Medications

The number of patients in the total tegaserod group who used concomitant medications ranged from 18 with anti-hypertensives to 244 with oral contraceptives. The pattern of the AEs and

overall frequencies of AEs were in general similar between the total tegaserod and placebo groups irrespective of whether or not oral contraceptives, anti-depressants, or anti-secretory drugs were used. However, these studies were not designed to detect such interactions and therefore no conclusion can be drawn from these data regarding the influence of concomitant medication on the safety of tegaserod.

## XII. Further Comments

*With regards to the pharmacologic studies, due to a lack of a surrogate marker for motility agents in healthy volunteers, the minimum effective dose was not able to be established. However, the highest well tolerated dose was 58 mg per Kg per day. The dose ranges tested in the phase II and phase III studies (to 24 mg per day) were appropriate.*

*Due to the drug's plasma concentration profile and the fact that no active metabolites were produced a b.i.d. dose was necessary to insure sufficient plasma concentrations for the evening meal. In general, all symptomatology in IBS seems to increase in the post-prandial period. Finally, because of the interaction with food (food intake decreases tegaserod concentration by 50%) and the results from the PK studies at 30, 15, and 1 min. AC, dosage within a 30 min AC until immediately before a meal seems adequate.*

*With regards to the pre-clinical data, this reviewer's main concerns are:*

- *pre-clinical rat data regarding types of ovarian cysts*
- *pre-clinical (mice) data regarding hyperplasia and adenocarcinoma of the small intestinal epithelium.*

*These pre-clinical findings are of concern because of the occurrence of ovarian cysts among tegaserod treated patients in phase II and III studies, and the rarity of adenocarcinoma of the small intestine in both animals and humans. (See Pharmacology/toxicology review for additional clarification on these concerns.)*

*With regard to the clinical study designs this reviewer agrees with the choice to focus on the constipation-predominant IBS subgroup with inclusion criteria predicated on the Rome II criteria. The 12-week treatment dose design is adequate to show therapeutic effect in IBS. Although adolescent and geriatric patients were included in the phase III studies, the numbers were insufficient to arrive at firm conclusions. Likewise, with men (10 to 15% of the phase III patients) no firm conclusions on the efficacy of tegaserod in males are possible at this time. When results of analyses in men are examined separately in Studies 301, 307 and 351 there was no therapeutic gain (in comparison to PL).*

*Efficacy: from the review of the clinical evidence provided this reviewer concludes that Zelmac has shown a modicum of efficacy in the constipation-predominant IBS subset of patients. The*

*data are not compelling. Therapeutic gain vs placebo was demonstrated using the modified primary efficacy variable at endpoint. In support there is evidence of statistically significant improvement in multiple secondary efficacy variables. Of note, the more easily documented objective endpoint of number of bowel movements was improved in the two pivotal studies 301 and 351 for the 12 mg dose. However, although, therapeutic gain with the treatment drug (8 to 12% with the best scenario) is not very impressive, Zelmac is undoubtedly differentiated from placebo. This efficacy result is reasonably convincing because:*

- It is shown in a well designed, well controlled, multicenter trial (B301) and supported by a similarly designed study (B351).*
- The effect on the SGA of relief occurs at one week and is sustained throughout the 12-week period. This would be hard to explain with mere coincidence.*
- Results of Study 307 where tegaserod was not differentiated from placebo, cannot be explained. In this trial, an increase in placebo response (in comparison to other trials), was not accompanied by a corresponding increase in tegaserod response.*

*Safety: Zelmac is safe and well tolerated at the dosages studied. The main and statistically significant adverse event, diarrhea, is up to a certain extent, a logical consequence of the pharmacodynamic action of the drug. The diarrhea occurred early (first week) and was usually short-lived. It did not result in discontinuing treatment to any great extent (1.6% in phase III vs 0.5% among placebo-treated patients). Changes in other safety parameters (changes in laboratory values, vital signs, EKG changes and orthostatic changes) have not been borne out in the clinical studies. More information may be required regarding the rat and mice data.*

*Effects relative to ongoing female reproductivity and pregnancy outcomes in future generations has not been totally addressed. Ergo, there are insufficient data to suggest that Zelmac be administered during pregnancy. In addition, since Zelmac has been demonstrated in breast milk (animal models) use in breast feeding mothers is not recommended.*

### **XIII. Brief Summary of Benefits, Risks of the Proposed Formulation**

In the Integrated Summary of benefits and risks (vol. 210, pages 10-29) the applicant states that IBS is a common, chronic g.i. disorder with a spectrum of severity and different pathophysiology. Among IBS patients, there are marked variations in the predominant symptoms: pain/flatulence/bloating, diarrhea or constipation. Treatment of IBS is currently tailored to relief of the predominant symptoms. Fiber supplementation affords only partial relief to those with constipation-predominant symptoms. Antidepressants are used to treat those with more severe or refractory symptoms. Currently there are no prokinetic agents available that have

established efficacy in treatment of dysmotility of the lower gut. Chronic use of non-bulk laxatives is very unsatisfactory and additional therapeutic measures are needed.

- *What is claimed above is true and is partially why the application was granted an accelerated review. It is difficult to determine what percentage of the patients fit into the constipation-predominant IBS and care must be taken not to treat patients with mere chronic constipation but no associated abdominal pain with a drug designed for irritable bowel. There are a multitude of safe and ineffective medications to treat chronic constipation.*

The applicant contends that they have carried out similarly designed well-controlled phase III studies of Zelmac as a new pharmacological treatment that show consistent benefit for bothersome symptoms of constipation-predominant IBS throughout the treatment period of 12 weeks. With no proven existing therapies, Zelmac provides efficacy in relieving the bothersome IBS symptoms, pain, hard stools and decreased frequency of stooling. Of note, effects on pain (by itself) do not reach statistical significance in any study.

- *With regard to the three similar controlled studies, it appears that 301 was of good design. It was well-controlled (placebo) and yielded reasonable proof that the drug is efficacious. The second study (351) can be considered supportive. This trial was flawed because it used different primary endpoints, underwent significant changes in the definition of responder when unblinded. The third study (307), where tegaserod was not differentiated from placebo, adds nothing to the efficacy. The patients enrolled in this trial do contribute to characterization of the safety profile of the drug.*

*Of note, care must certainly be taken in any clinical study involving constipation where laxative use is not fully taken into account. Therefore this reviewer believes that SGAs of relief, etc., should - ideally - have been adjusted for laxative use.*

With respect to the safety of Zelmac the applicant states that 4 out of 5 of the most frequent adverse events (AE) were G.I. related, namely abdominal pain, diarrhea, nausea and flatulence. As the frequency for reports of abdominal pain, nausea and flatulence were similar for tegaserod and placebo, the majority of these reports were likely symptoms of IBS itself rather than a side effect of the treatment. This is supported by the investigator's assessment of the causality: the frequency of patients reporting drug related abdominal pain, flatulence or nausea was similar in the tegaserod and placebo groups. On the other hand, diarrhea was reported about twice as frequently with tegaserod 12 mg per day as placebo (12% vs 5%), and was suspected to be drug related three or four times more frequently with tegaserod than with placebo. In addition, in patients who alternated between constipation and diarrhea the incidence of diarrhea was 21%.

- *It seems that the applicant is downplaying the importance of diarrhea as this adverse event occurred in a significant number of patients, approximately 11%. Although it is stated that*

*the discontinuation rate was low, the discontinuation rate due to diarrhea with tegaserod was approximately three times that of placebo (1.6% vs 0.5%).*

*Another issue that needs to be addressed is the true incidence and significance of ovarian cyst formation and surgical intervention. If Zelmac is approved for marketing, a prospective study of sufficient cohort of patients starting treatment with Zelmac should be carried out to detect and investigate cases of ovarian cysts and/or other related adverse events. This investigation should include assessment of hormone profiles and the use of intravaginal ultrasound to demonstrate complete absence of ovarian cysts at baseline or document those instances where the patient has asymptomatic ovarian cysts. The trial should be of a duration enough to observe at least 4-6 menstrual cycles.*

#### **XIV. RECOMMENDATIONS FOR REGULATORY ACTION**

1. Based on my review of the evidence presented by the sponsor in NDA 21-200, I recommend approval of Zelmac for the treatment of constipation-predominant IBS females. This recommendation is based on results from Clinical Study No. 301, which are supported by results of Study No. 351.
2. The frequent problem of ZELMAC-induced diarrhea must be clearly recognized by Novartis, and the labeling revised to properly address it. In addition, precautions to be taken when prescribing ZELMAC should be clearly specified in the labeling (i.e., patients currently constipated). Instructions should be written as to how the problem should be handled.
3. The rare but potentially serious problem of ZELMAC-induced abdominal surgical intervention somehow associated with ovarian cysts must be clearly addressed in the labeling. To address the abdominal surgery-ovarian cysts issue, a post-marketing prospective study of sufficient number of patients on the recommended regimen of ZELMAC, 6 mg po b.i.d., should be a condition for approval.

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[ ]

In this reviewer's opinion no major issues remain unresolved. Labeling recommendations are given separately.

*/S/* *7/24/06*  
Raymond Joseph, M.D.

*Concur. July 24, 2000*  
*/S/ /S/ , M.D., Ph.D.*

- cc:
- NDA 21-200
- HFD-180
- HFD-180/LTalarico
- HFD-180/SAurecchia
- HFD-180/HGallo-Torres
- HFD-180/RJoseph
- HFD-103/Dr. F. Houn
- HFD-103/Dr. V. Raczkowski
- ~~HFD-181/PLevine~~
- HFD-180/JChoudary
- HFD-180/LZhou
- r/d 5/17/00 jgw
- f/t 7/7/00 jgw
- deg: 7/12/00
- N/21200006.0RJ

*/Sh-25-00*

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS  
MEDICAL OFFICER'S SAFETY UPDATE

NDA: 21-200

Sponsor: Novartis Pharmaceuticals Corporation  
East Hanover, New Jersey

Date Received: June 9, 2000

Drug: Zelmac™ (tegaserod) Tablets

Pharmacological Category: A partial agonist at Serotonin Type 4 (5-HT<sub>4</sub>) receptors

Proposed Indication: Treatment of Irritable Bowel Syndrome in Patients Who Identify  
Constipation as Their  
Predominant Symptom

Reviewer: Raymond Joseph, M.D.,

**APPEARS THIS WAY  
ON ORIGINAL**

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**APPEARS THIS WAY  
ON ORIGINAL**

**I. INTRODUCTION**

In the integrated summary of safety in NDA 21-200, it was concluded that tegaserod given to 2,665 IBS patients in therapeutic doses (4-12 mg/d) was, in general, a safe medication. Of the AEs seen in the Phase II and Phase III studies, only diarrhea was identified as being clearly more frequent with tegaserod than placebo. The frequency of the SAEs was low and similar for tegaserod and placebo patients in the Phase II and Phase III trials (1.8%).

Of interest, there was a higher percentage of abdominal and pelvic surgery in the tegaserod treatment groups vs the placebo group. This will be addressed later in this review.

The sponsor has submitted a safety update (SU). The cut-off date for this SU is 31 March 2000. The source of the data is shown in Table 1.

**TABLE 1  
NDA 21-200**

**Data Included in the 120 Day Safety Update**

<b>Source</b>	<b>Data Included in the Safety Update</b>
Studies ongoing on 31 October 1999, completed by 31 March 2000	All data
Studies ongoing on 31 October 1999, and still ongoing on 31 March 2000	SAEs reported between 1 November 1999, and 31 March 2000
Studies initiated since 31 October 1999	SAEs reported until 31 March 2000
SAE serious adverse event	

The studies included in this SU are listed in Table 2.

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**TABLE 2**  
**NDA 21-200**

**Studies Contributing Data to Safety Update**

Study	Patients/Aim/Design	Tegaserod Administration		Number of Patients		
		Dosage(s) mg/d	Duration	Tegaserod	Placebo	Total
<b>Studies ongoing 31 Oct 99, completed 31 Mar 00</b>						
B301-E-01 <sup>(1)</sup>	C-IBS open, single cohort extension to previous comparative study	titration 4-12	6 mo	508 <sup>(2)</sup>	-	508
B307-E-01 <sup>(1)</sup>	C-IBS open, single-cohort, extension to previous comparative study	titration 4-12	6 mo	157 <sup>(2)</sup>	-	157
<b>Studies ongoing 31 Oct 99, ongoing 31 Mar 00</b>						
		4	14 d	17	17	17
		4, 12	10 w	69	17	86
		1, 4	2 wk	30	30	30
		0.4, 1, 4	8 wk	465	155	620
<b>Studies initiated since 31 Oct 99, ongoing 31 Mar 00</b>						
B358	C-IBS females: safety and efficacy (DB, 2-arm, parallel group)	12	12 wk	764	764	1528
	C-IBS open, single cohort extension to previous phase II-III studies	titration 4-12	≥6 mo	40	-	40
	C-IBS mechanistic study into anorectal motor activity (DB, placebo-controlled cross-over)	12	14 d	12	12	12
IBS=irritable bowel syndrome    c=circa (approximately)    C-IBS=constipation-predominant IBS    DB=double-blind 1) patients originating from previous controlled studies						

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The total exposure is a product of the addition of two newly finished studies to the completed studies described in the original integrated summary of safety (ISS) (see Table 3).

**TABLE 3**  
**NDA 21-200**

**Summary of Exposure**  
**(tegaserod-treated subjects only)**

	ICH Guideline (EIA)	ISS	ISS + 120 day safety update	
		Patients Exposed	Patients With C-IBS <sup>1</sup>	Total Subjects Exposed <sup>2</sup>
Total number	500 - 1500	2662	2892	3737
Treated for $\geq 6$ months <sup>3</sup>	300 - 600	418	826	826
Treated for $\geq 12$ months <sup>3</sup>	$\geq 100$	185	187	187

(The statistical methods and definitions are the same as those utilized in the previously-submitted ISS.)

Patients in the two extension studies (301-E-01 and 307-E-01) were treated with either 4 mg/d, 12 mg/d or placebo for 3 months in the source studies. When consenting to enter the extension did so with 4 mg/d of tegaserod with the possibility of up-titration at subsequent visits. The majority (60-70%) of patients were titrated to the higher dosage. The visits were monthly and included a physical exam with vital signs and laboratory data with periodic ECGs and pregnancy tests.

The demographic data collected at entry into the source studies are shown in Table 4.

**TABLE 4**  
**Demographics and Baseline Characteristics**

		B301 Ext [n=508]	B307 Ext [n=157]
Sex n(%)	Male	84 (16.5)	23 (14.6)
	Female	424 (83.5)	134 (85.4)
Race n(%)	Caucasian	504 (99.2)	156 (99.4)
	Oriental	3 ( 0.6)	1 ( 0.6)
	Other	1 ( 0.2)	
Age (yr)	Mean (SD)	46.7 (13.8)	49.3 (14.5)
	Median	47	48
	Range	18-85	18-83
Age category n(%)	18-64	450 (88.6)	128 (81.5)
	$\geq 65$	58 (11.4)	29 (18.5)
Duration of IBS symptoms (yr)	Mean (SD)	14.2 (12.7)	12.0 (11.6)
	Median	10	0.67

The patients in these studies were approximately 84% female, 99% caucasian with a average age of 47.5 years. These reflect the patient studies 301 and —

The total exposure to tegaserod per duration of exposure is seen in Table 5.

**TABLE 5**  
**Total Exposure to Tegaserod**

Duration of Exposure	B301 and Extension		B307 and Extension	
	Tegaserod [n=336]	Placebo [n=172]	Tegaserod [n=102]	Placebo [n=55]
≥ 1 day	336	172	102	55
≥ 1 mo	336	165	102	49
≥ 2 mo	336	151	102	49
≥ 3 mo	334	145	102	48
≥ 4 mo	316	138	97	26
≥ 5 mo	289	128	92	46
≥ 6 mo	282	26	92	8
≥ 7 mo	268	1	87	2
≥ 8 mo	258	1	84	0
≥ 9 mo	57	1	12	0

Ex-placebo = patients who were on placebo during the previous Study 301 or 307.

The disposition of patients is shown in Table 6.

**TABLE 6**  
**Disposition of Patients**  
**Numbers of Patients (%)**

	B301 Ext	B307 Ext
Entered study	508 (100)	157 (100)
Completed study	386 (76.0)	131 (83.4)
Discontinued prematurely: Total for	122 (24.0)	26 (16.6)
adverse event	40 ( 7.9)	12 ( 7.6)
abnormal laboratory value	2 ( 0.4)	2 ( 0.6)
ECG abnormality	0	1 ( 0.6)
unsatisfactory therapeutic effect	34 ( 6.7)	2 ( 1.3)
subject's condition not requiring further treatment	4 ( 0.8)	0
pregnancy	1 ( 0.2)	0
protocol violation	7 ( 1.4)	1 ( 0.6)
consent withdrawn	23 ( 4.5)	5 ( 3.2)
lost to follow-up	11 ( 2.2)	2 ( 1.3)
administrative reasons	0	1 ( 0.6)

The total percent of patients discontinuing for safety reasons (adverse event, abnormal laboratory values) totaled 8.5% (B301-E-01) and 9.5% (B307-E-01). These percentages are slightly higher than those in the previous studies, but consistent with the longer duration.

## II. CLINICAL STUDIES SAFETY RESULTS

### A. B301-E-01

This was an open label, single cohort extension of Study 301. All patients started at the 4 mg/d dose level with the possibility of up-titration to 12 mg/d at a subsequent visit. A total of 508 patients were enrolled by March 31, 2000. The study was completed by 386 patients (117 on 4 mg/d and 269 on 12 mg/d). A summary of the demographics of this study were previously provided in Table 4.

#### 1. Adverse Events

The most frequently reported adverse events and severe events are listed in Table 7.

**TABLE 7**  
**Study B301-E-01**  
**Most Frequently ( $\geq 2\%$ ) Reported Adverse Events**  
**All Events and Severe Events: numbers of patients (%)**

Total number of tegaserod-treated patients		508 (100%)			
Total number of patients reported with AEs		388 (76.4%)		with severe AEs 161 (31.7%)	
Events:	All	Severe		All	Severe
Headache	152 (29.9)	48 (9.5)	Dizziness	18 (3.5)	3 (0.6)
Abdominal pain	86 (16.9)	40 (7.9)	Sinusitis	18 (3.5)	6 (1.2)
Diarrhea	74 (14.6)	22 (4.3)	Insomnia	16 (3.2)	3 (0.6)
Back pain	58 (11.6)	23 (4.5)	Accidental trauma	15 (3.0)	2 (0.4)
Flu-like symptoms	48 ( 9.5)	9 (1.8)	Tooth disorder	15 (3.0)	7 (1.4)
URT infection	35 ( 6.9)	4 (0.8)	Vomiting	15 (3.0)	8 (1.6)
Flatulence	34 ( 6.7)	13 (2.6)	Constipation	14 (2.8)	6 (1.2)
Dyspepsia	28 ( 5.5)	9 (1.8)	Depression	14 (2.8)	3 (0.6)
Coughing	27 ( 5.3)	2 (0.4)	Rhinitis	14 (2.8)	4 (0.8)
Nausea	23 ( 4.5)	12 (2.4)	Dysmenorrhea	13 (2.6)	6 (1.2)
Pain	23 ( 4.5)	9 (1.8)	Gastroenteritis	13 (2.6)	3 (0.6)
Bronchitis	22 ( 4.3)	3 (0.6)	Fatigue	12 (2.4)	4 (0.8)
Migraine	22 ( 4.3)	13 (2.6)	Allergy	11 (2.2)	5 (1.0)
Pharyngitis	19 ( 3.7)	2 (0.4)	Arthralgia	11 (2.2)	2 (0.4)
Arthropathy	18 ( 3.5)	5 (1.0)	Urinary Tract Infection	11 (2.2)	1 (0.2)

G-I = gastrointestinal  
URT = upper respiratory tract

Specific AEs of diarrhea and dizziness are addressed below.

#### i) Diarrhea

The frequency of diarrhea was increased two-fold during tegaserod treatment relative to placebo in the protocol II=III data in ISS. In 301-E-01, the frequency of diarrhea was 15% and was considered severe in 34% of these patients. Overall diarrhea was considered a severe AE in 4.3% and led to discontinuation in 3.5% of the patients.

## ii) Dizziness

There were 18 cases of dizziness (3.5%) which were considered severe in 3 (0.6%). There were no cases of syncope reported in 301-E-01, and no significant changes in vital signs especially orthostatic hypotension.

## 2) Serious Adverse Events

There were 16 serious adverse events (SAEs) in study 301-E-01. Of interest, **there were two cases of appendicitis**; one in a 44 y F, and one a 56 y F. These will be dealt with later in the review.

Adverse events that were associated with premature discontinuation in extension studies B301-E-01 and B307-E-01 are shown in Table 8.

**TABLE 8**  
**Adverse Events Associated With Premature Discontinuation**  
**(numbers of patients)**

Total number of patients discontinuing for AE Organ system/Event	B301-E-01 (n=508) 40	B307-E-01 (n=157) 13
Gastro-intestinal	29	10
diarrhea	18	8
abdominal pain	7	4
flatulence	3	0
irritable colon/colitis	2	1
nausea	2	0
constipation	0	2
dyspepsia	1	0
hemorrhoids	0	1
rectal hemorrhage	0	1
Central Nervous System	7	2
headache	3	1
dizziness	3	0
vasovagal attack (dizziness)	0	1
peripheral neuropathy	1	0
General	3	0
accidental trauma	1	0
influenza-like symptoms	2	0
Musculo-skeletal	3	0
back pain	3	0
Cardiovascular	2	0
angina pectoris	1	0
extrasystoles	1	0
Psychiatric	3	0
depression	2	0
insomnia	1	0
Metabolic	2	0
weight gain	2	0
Skin	2	0
eczema	2	0
increased sweating	1	0
Neoplasma	1	0
uterine sarcoma	1	0

Table 8 shows no new pattern of AEs related to discontinuation when compared with the Phase II and II studies.

### B. Study 307-E-01

This study was of similar design as 301-E-01.

#### 1. Adverse Events

The most frequently reported adverse events and severe events are shown in Table 9.

The type of AEs are similar to the ones seen in the Phase II and Phase III trials.

**TABLE 9**  
**Study B307-E-01**  
**Most Frequently ( $\geq 2\%$ ) Reported Adverse Events:**  
**All Events and Severe Events: Number of Patients (Percentage)**

Total number of tegaserod-treated patients		157 (100%)			
Total number of patients reported with AEs		121 (77.1)		with severe AEs 56 (35.7%)	
Events:	All	Severe		All	Severe
Headache	40 (25.5)	13 ( 8.3)	Dyspepsia	7 (4.5)	2 (1.3)
Diarrhea	37 (23.6)	19 (12.1)	Urinary Tract Infection	7 (4.5)	1 (0.6)
Abdominal Pain	32 (20.4)	13 ( 8.3)	Circulatory Disorder	6 (3.8)	1 (0.6)
Back Pain	19 (12.1)	5 ( 3.2)	Coughing	6 (3.8)	0
Flatulence	16 (10.2)	8 ( 5.1)	Migraine	6 (3.8)	3 (1.9)
Flu-like Symptoms	15 ( 9.6)	3 ( 1.9)	Fatigue	5 (3.2)	1 (0.6)
Pharyngitis	14 ( 8.9)	4 ( 2.6)	Gastritis	5 (3.2)	3 (1.9)
URT Infection	12 ( 7.6)	1 ( 0.6)	Tooth Disorder	5 (3.2)	1 (0.6)
Nausea	10 ( 6.4)	3 ( 1.9)	Depression	4 (2.6)	0
Rhinitis	9 ( 5.7)	0	Irritable Colon	4 (2.6)	1 (0.6)
Constipation	8 ( 5.1)	6 ( 3.8)	Micturition Frequency	4 (2.6)	2 (1.3)
Hemorrhoids	8 ( 5.1)	2 ( 1.3)	Pain	4 (2.6)	0
Insomnia	8 ( 5.1)	1 ( 0.6)	Sinusitis	4 (2.6)	0
Bronchitis	7 ( 4.5)	1 ( 0.6)	Tonsillitis	4 (2.6)	1 (0.6)
Dizziness	7 ( 4.5)	2 ( 1.3)			

URT = upper respiratory tract

As shown in Table 9 with comparison to Table 7 the essential profile of the AEs is similar to 301-E-01. Specific AEs of diarrhea and dizziness are addressed below.

#### i) Diarrhea

The frequencies of diarrhea were higher in Study 307-E-01 compared to 301-E-01 (24% vs 15% with 12.1% vs 4.3 considered serious and a discontinuation rate of 5.1% vs 3.5%).

**ii) Dizziness**

The incidence of dizziness was similar to 307-E-01. Likewise, there were no episodes of syncope or severe orthostatic hypotension.

**2) Serious Adverse Events**

There were six serious adverse events (SAEs) in Study 307-E-01. None were considered related to tegaserod treatment. There were no cases of acute appendicitis. Adverse events that were associated with premature discontinuation are shown previously in Table 8.

**C. Other Studies That Contributed to the Safety Update**

The other studies that contributed to the safety update are listed in Table 10.

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**TABLE 10**

**Additional Studies Contributing Data to Safety Update**

Study	Patients/Aim/Design	Tegaserod Administration		Number of Patients		
		Dosage(s) mg/d	Duration	Tegaserod	Placebo	Total
<b>Studies ongoing 31 Oct 99, ongoing 31 Mar 00</b>						
		4	14 d	17	17	17
		4, 12	10 w	69	17	86
		14	2 wk	30	30	30
		0.4, 1, 4	8 wk	465	155	620
<b>Studies initiated since 31 Oct 99, ongoing 31 Mar 00</b>						
B358	C-IBS females: safety and efficacy (DB, 2-arm, parallel group)	12	12 wk	764	764	1528
—	C-IBS open, single cohort extension to previous phase II-III studies	titration 4-12	≥6 mo	40	.	40
—	C-IBS mechanistic study into anorectal motor activity (DB, placebo-controlled cross-over)	12	14 d	12	12	12
Abbreviations as in Table 2						
1) patients originating from previous controlled studies						
2) all patients entering the extension periods at the end of the double-blind period began treatment at 4 mg/d with subsequent up-titration according to efficacy and tolerability						

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Of note, there was one additional case of acute appendicitis in a 34 y F in Study 358.

### III. OVERALL SUMMARY ON APPENDICITIS/LAPAROTOMIES (Table 11)

During the 120 day safety update period there were 3 cases of appendicitis.

- 1) 44y WF who received placebo for 3 months during the source study. She started on the stable dose of 4 mg/d on day 85 and on day 166 experienced abdominal pain with appendectomy performed on day 168. She was discharged from the hospital 3 days later. The investigator assessed that the event was not related to the study medication (Study 301-E-01).
- 2) 56y WF who received 12 mg/d tegaserod during the 3 month study, reduced to 4 mg/d on ending the extension period on day 85, increased to 12 mg/d on day 113. On day 224 she was hospitalized for abdominal pain and underwent appendectomy on day 326. She was discharged 2 days later. The investigator considered the event as unlikely to have been caused by tegaserod (Study 301-E-01).
- 3) 34y WF enrolled in Study 358 whose treatment is unknown (blinded). She underwent an appendectomy 23 days after starting study medication. The investigator considered the event as unrelated to the study medication.

In the Phase III trial there was a 13y WF with a right ovarian cyst and "early appendicitis". This brings the total cases of appendicitis in the entire safety database to four. The total number of laparotomies is 9 (ISS=6; SU=3).

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**TABLE 11**

**Laparotomies and Appendectomies in Tegaserod Treated Patients  
ISS and SU**

Source	Laparotomies [n=9]	Appendectomies [n=4]
ISS	<ol style="list-style-type: none"> <li>1. Previous history of ovarian cyst. Benign tumor found at surgery 12 mg/d</li> <li>2. 45 WF OR day 261 BSO. Path. adhesions 12 mg/d</li> <li>3. 37 BF abdominal pain day 100, Rt. S.O. Lysis of adhesions, appendectomy. Path.: 1 cm peritubal cyst, adhesions, normal appendix 12 mg/d</li> <li>4. 35 F ? history surg. day 306 Path.: 3.5 cm luteal cyst 12 mg/d</li> <li>5. 51 WF Abdominal pain on day 75 - cholecystectomy 12 mg/d</li> <li>6. 43 WF worsening symptoms dysmenorrhea, day 37 hysterectomy 12 mg/d</li> </ol>	<ol style="list-style-type: none"> <li>1. 13 WF past history ovarian cyst. Abdominal pain on day 87. Laparoscopic resection of a right ovarian cyst plus appendectomy. Path: Early appendicitis 12 mg/d</li> </ol>
SU	<ol style="list-style-type: none"> <li>1. 54 WF Abdominal pain day 2. Cholecystectomy. Blinded</li> <li>2. 43 WF abdominal pain day 154. Cholecystectomy 4 mg/d</li> <li>3. 58 WF increasing symptoms. Uterine prolapse. Hysterectomy on day 90 12 mg/d</li> </ol>	<ol style="list-style-type: none"> <li>1. 45 WF abdominal pain day 166 4 mg/d</li> <li>2. 56 WF abdominal pain day 224 12 mg/d</li> <li>3. 34 WF on day 23 of study medication had abdominal pain. Blinded</li> </ol>

In addition to these cases of appendicitis there were 3 laparotomy in the SU. two cases of cholecystectomy for pre-existing stones and one case of urogenital prolapse. None of these were thought by the investigators to be related to the tegaserod treatment. There was one case of appendicitis in a 34y WF on PL in the Phase III studies, and no laparotomies in the Placebo group (appendectomies: Tegaserod 4, placebo 1) (laparotomies: Tegaserod 9, placebo 0).

Calculating cases per patient year, the numbers are calculated assuming all patients had 12 weeks of exposure to drug and using all patients randomized to treatment.

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Appendectomies

Placebo = 0.0052 cases per year  
Zelmac = 0.0026 cases per year

Laparotomies

Placebo = 0 cases per year  
Zelmac = 0.0154 cases year

Although there may be one effect possibly related to the pro-motility effect of the tegaserod in hollow organs (a working hypothesis), no conclusions regarding cause-and-effect can be drawn at this time. Irregardless, lingering concerns remain regarding these appendicitis cases and laparotomies.

**IV. COMMENTARY**

In general, the results of safety, evaluations in this safety update are similar to the analyses and conclusions from the ISS. There are no findings of concern, as new data in this safety update do not indicate any newly evident tegaserod-induced toxicity.

Although no conclusions can be drawn, the concerns relating to the increases of laparotomy and appendectomy still require further observation.

**IV. REGULATORY RECOMMENDATIONS**

No additional recommendations for labeling are made on the basis of this 120 day safety update.

A  
/S/ 8/8/00  
Raymond Joseph, M.D.  
August 8, 2000  
A.D., Ph.D.

cc:  
NDA 21-200  
HFD-180  
HFD-180/LTalarico  
HFD-180/SAurecchia  
HFD-180/HGallo-Torres  
HFD-180/RJoseph  
HFD-181/PLevine  
HFD-180/JChoudary  
HFD-180/LZhou  
r/d 7/31/00 jgw  
f/t 8/8/00 jgw  
N/21200008.0RJ

Concur.  
/S/ 8-8-00  
/S/

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