

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

MEDICAL REVIEW(S)

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS
MEDICAL OFFICER'S REVIEW**

NDA: 21-200/N-000AZ

Sponsor: Novartis PharmaG Basel, Switzerland

Date Submitted: December 15, 2000

Drug: Zelnorm™ (tegaserod)

Pharmacologic Category: A partial agonist at the serotonin type 4
5-HT₄ Receptors

Formulation/Route of Administration: Tablets/Oral Administration

Proposed Indication: Treatment of Constipation-predominate
Irritable Bowel Syndrome (C-IBS) in female
patients

Material Submitted/Reviewed: Vol. 3-17 (Efficacy and Safety Results
Study B358), Pertinent other Information
and Literature and (Expert Reviews)

Reviewer: Raymond E. Joseph M.D., F.A.C.P.
F.A.C.G.

Executive Summary

The original submission included three, Phase III studies. Efficacy, without post-hoc analysis, was demonstrated in one (B301), but not in another study (B307), containing a dose escalation component (4 to 12 mg/drug). In addition, the efficacy of the test medication in these Phase III studies was observed only in female patients. Due to these incomplete results the FDA requested an additional well controlled, randomized, double blind, multi-center Phase III study in American, female patients with C-IBS utilizing the same Rome II criteria for irritable bowel syndrome (C-IBS) used in the previous studies. Application of the Rome criteria allows a positive diagnosis of irritable bowel syndrome to be made with a modicum of confidence.

The subject of this review is an appraisal of the results of the aforementioned requested study (B358). This trial included 1,519 female patients with C-IBS. There were 135 U.S. centers which randomized the subjects in a double-blind manner to either 6 mg b.i.d. tegaserod or placebo for 12 weeks followed by a 4-week withdrawal period. The patients were selected on the basis of the Rome I criteria, and had to fulfill 2 of 3 constipation criteria (>3 BMs/wk, straining or hard stool). A touch tone telephone system (Q-tone) was used for data entry.

The primary efficacy variable was the Subject's Global Assessment (SGA) of Relief which encompassed abdominal pain, bowel function and overall well-being. Other weekly efficacy variables were SGA of abdominal discomfort/pain and SGA of satisfaction with bowel habit. Daily diary symptom variables including number and consistency of daily stools were also assessed.

Tegaserod demonstrated significant ($p < 0.05$) improvements in scores for SGA of Relief supported by significant improvements in bowel-related secondary variable assessments.

Tegaserod produced early improvement in cardinal C-IBS symptoms without evidence of a rebound effect. The drug was well tolerated with similar AEs and SAEs profile to placebo.

Based on the totality of evidence, approval of tegaserod, 6 mg b.i.d., for the treatment of female patients with C-IBS is recommended.

Lingering concerns remain with regards to effects of the drug on biliary tract motility, and its possible role in abdominal surgery, especially cholecystectomy. With the information at hand, it is not known if these concerns are valid because, all in all, the number of patients in whom untoward observations have been made, is small. However, adding tegaserod to the physician's armamentarium to treat IBS is an important public health contribution. Phase IV studies in patients with and without gallstones and a large epidemiology study to assess the true incidence of biliary tract disease are recommended to better inform prescribers and patients and thereby optimize the use of this drug in C-IBS female patients.

**APPEARS THIS WAY
ON ORIGINAL**

INTRODUCTION/BACKGROUND:

The sponsor submitted NDA (21-200) on February 11, 2000 for the use of tegaserod (HTF 919) Zelnac™ 4mg and 12 mg oral tablets per day, in the treatment of patients with constipation-predominate irritable bowel syndrome (C-IBS). This new molecular entity submission was a fast tract review by R. E. Joseph M.D. and finalized on July 25, 2000. The Recommendations for Regulatory Action were:

- Approval for the treatment of C-IBS in females
- The frequent problem of tegaserod-induced diarrhea must be clearly recognized by Novartis, and the labeling revised to properly address it. In addition, precautions to be taken when prescribing tegaserod should be clearly specified in the labeling (i.e., patients currently _____). Instructions should be written as to how the problem should be handled.
- The rare but potentially serious problem of tegaserod-induced abdominal surgical intervention must be clearly addressed in the labeling. A post-marketing prospective study of sufficient number of patients on the recommended regimen of tegaserod, 6mg po b.i.d., should be a condition for approval.

[_____]
The recommendation was for an American study for females with C-IBS.

In summary, the original submission included three Phase III studies. Efficacy, without post-hoc analysis, was demonstrated in one study (B 301), but not in another study (B307) containing a dose escalation component (4-to-12mg/drug). In addition, the efficacy of the test medication in these Phase III studies was observed only in female patients. It was due to these incomplete results that FDA requested an additional well controlled, randomized, double blind, multi-center Phase III study in American, female patients with C-IBS utilizing the same Rome II criteria for irritable bowel syndrome (C-IBS) used in the previous studies. Application of the Rome criteria allows a positive diagnosis of irritable bowel syndrome to be made with a modicum of confidence.

Irritable bowel syndrome represents a constellation of symptoms: a recurrent or chronic abdominal pain that is associated with defecation and a chronically altered bowel habit. There is neither a cure for irritable bowel syndrome, nor a universal, efficacious treatment for this life altering, non-progressive disease. Many of the currently approved therapeutic modalities are considered "possibly effective".

Tegaserod appeared to be safe and well tolerated at the doses previously studied (4mg/d and 12mg/d). All drugs induce undesirable or adverse effects; in the tegaserod treated patients concerns remained for both the true incidence of gynecologic, biliary, other intra- abdominal pathology, and the need and timing of abdominal or pelvic surgical intervention.

The sponsor subsequently submitted results of B358, the subject of this review. In the interim, tegaserod had a trade name change from Zelmac™ to Zelnorm™.

Study B358 was a randomized, multi-centered, double blind, 2-arm, parallel-group, placebo-controlled trial of tegaserod in female patients with C-IBS. The trial was conducted exclusively in the United States of America.

The sponsor, at the Advisory Committee Meeting (6/2000), proposed the following indication for tegaserod:

Tegaserod maleate is indicated for the treatment of abdominal pain, discomfort, and constipation in female patients with irritable bowel syndrome.

Study B358

At (135) centers in the U.S., one thousand five hundred nineteen patients diagnosed with C-IBS were randomized (767 tegaserod 12mg/d, 752 placebo). The randomization method proposed in the protocol and achieved in the clinical trial was deemed acceptable to achieve comparability.

The study consisted of a screening period, a 4-week baseline period (no medication), a 12-week randomized double-blind treatment period with either placebo or tegaserod 12mg/d, followed by a 4-week withdrawal period (no medication). The first patient was enrolled November 17, 1999, the last patient completed the study August 25, 2000.

This study differed from previous Phase III studies by:

- Composed of females only
- Aforementioned, Study B358 was conducted entirely in the U.S.
- Used a touch-tone electronic diary (——— developed by ———) instead of the standard paper diary used for data collection

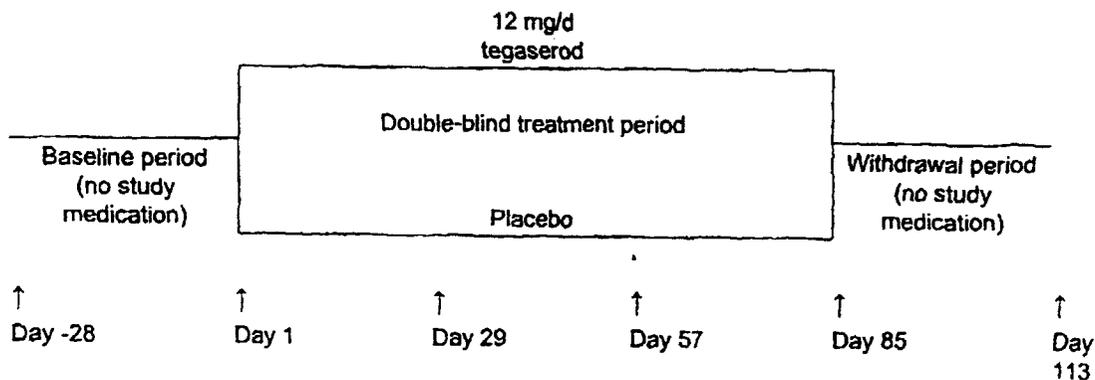
- Included a stool consistency criterion that did not allow randomization of a patient if her mean stool consistency score was < 3.5, prior to randomization, in addition to an abdominal discomfort/pain criterion used in the other studies.
- Employed an ordinal scale for weekly secondary efficacy variables as opposed to a visual analogue scale.
- Included a 4-week non-treatment withdrawal period after the double-blind treatment period.

The study design from the sponsor's submitted material is illustrated in Fig. 1.

[Scanned]

Figure 1

Study B358 Design



The target enrollment was 1528 intent-to-treat (ITT) female patients with C-IBS in approximately 135 U.S. centers. Each center was expected to randomize a minimum of 10 patients.

[From the sponsor's clinical report]

The primary efficacy variable was the subject's Global Assessment (SGA) of relief, collected weekly. The SGA of relief assessed the patient's relief of overall IBS symptoms: overall well being, abdominal discomfort/pain and altered bowel habit.

Secondary efficacy variables include: SGA of abdominal discomfort/pain (weekly), SGA of bowel habit (weekly), satisfaction with bowel habit (weekly), and daily assessments of abdominal discomfort/pain, abdominal bloating, number of bowel movements, stool consistency and straining at defecation

These patient self-assessments were performed throughout the baseline, double blind and withdrawal periods.

Reviewer Comment

Test medication was shipped to 135 centers. Of these only 127 randomized patients, and notably 50% of these centers randomized less than the minimum 10 patients per center that was specified in the protocol.

Scanned inclusion/exclusion criteria from the clinical report

The main criteria for inclusion (assessed on Day -28) were:

1. Female patients 18 years and older.
2. Patients met the definition of IBS as defined by their responses to the questionnaire below adapted from Drossman To qualify, patients must have met all three criteria based on the IBS Questionnaire as described below:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

IBS Questionnaire

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

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

Patients who were on stable treatment with a daily fiber supplementation or bulking agents might be enrolled provided that:

- they had the symptoms mentioned above (Inclusion criterion #2) while on treatment
- the administration schedule was intended to be maintained throughout the study and the patient had been on bulking therapy for at least 3 months.

4. Endoscopic/Radiologic bowel evaluation in order to rule out cancer, inflammatory bowel disease or other structural disease.
 - For patients 50 years of age and less: a flexible sigmoidoscopy (or colonoscopy) within 5 years and after the onset of IBS symptoms
 - For patients older than 50 years: a colonoscopy or flexible sigmoidoscopy plus double-contrast barium enema within 5 years and after the onset of IBS symptoms
 - For patients with guaiac positive stool: if obvious hemorrhoidal bleeding was excluded, a colonoscopy or flexible sigmoidoscopy plus double-contrast barium enema was required unless there had been a normal colonoscopy or flexible sigmoidoscopy plus double-contrast barium enema in the past year.
5. Ability to communicate well with the investigator and to comply with the requirements of the entire study, including an understanding of how to use the touch-tone telephone electronic diary.
6. Written informed consent to participate and a willingness to participate in the entire study.

**APPEARS THIS WAY
ON ORIGINAL**

[Note]: Treatment assignment and blinding were handled in a similar fashion to the previous Phase III studies (B351, B301 and B307).

Reviewer Comments

- The study had unambiguous inclusion criteria, and there were no systematic differences between the study population and the target population.
- With IBS there is uncertainty at which degree of severity or for what constellation of symptoms treatment might be most beneficial; a specific group of participants likely to respond cannot easily be selected. This is certainly true, however the criteria in this study are adequate, even though the true severity of the disease, at the time of entrance to the study, is difficult to ascertain. Pain level was to least moderate.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

[Scanned from the clinical report]

Exclusion criteria

The main criteria for exclusion (assessed on Day -28) were:

1. Significant diarrhea associated with C-IBS, ie, over the three months preceding Day -28 at least 25% of the days or occasions
 - loose or watery stools and/or
 - more than 3 bowel movements per day associated with urgency.
2. Evidence of any structural abnormality of the gastrointestinal tract or diseases/conditions that affect bowel transit.
3. Planned use of drugs or agents from Day -28 onward that could affect gastrointestinal motility and/or perception.
4. Evidence of cathartic colon or a history of laxative use, that in the investigator's opinion was consistent with severe laxative dependence such that the patient was likely to require or use laxatives during the study.
5. Current or recent history (within 12 months) of drug or alcohol abuse.
6. Clinical evidence of significant cardiovascular, respiratory, renal, hepatic, gastrointestinal, hematologic, neurologic, psychiatric or of any disease that may interfere with the patient successfully completing the trial.
7. Other clinically relevant intercurrent medical conditions that interfere with the objectives of the study.
8. Symptoms of a significant clinical illness in the preceding two weeks.

**APPEARS THIS WAY
ON ORIGINAL**

9. Existence of surgical or medical conditions which interfere with the absorption, distribution, metabolism and excretion of the study drug.
10. Pregnant or breast feeding women, or fertile women who were not surgically sterile (via hysterectomy, bilateral oophorectomy or bilateral tubal ligation) or not > 1 year post-menopausal or who were not using or complying with a medically approved method of contraception at the time of study entry.
11. Participation in other clinical trials within 1 month prior to Day -28, in which investigational or commercially available drugs was tested.
12. Previous participation in any clinical trial with tegaserod.
13. A positive HIV serology (test was not mandatory).

**APPEARS THIS WAY
ON ORIGINAL**

[Scanned from the clinical report]

Exclusion Criteria For Entry into Double-blind Treatment Period

Additional exclusion criteria were assessed on Day 1. A patient was not randomized if any of the following applied:

1. Failure to have recorded at least 11 of 14 days of daily self assessments and/or both weekly self-assessments in the last 2 weeks of the baseline period.
2. A mean score for the daily assessment of abdominal discomfort/pain of ≤ 1.5 on a 7 point scale (0-6) during the baseline period
3. A mean stool consistency score of ≤ 3.5 during the baseline period
4. The SGA of relief of Weeks -4, -3, -2 and -1 qualified for "response", ie, complete or considerable relief $\geq 50\%$ of the weeks or at least somewhat relief 100% of the weeks.
5. Use of disallowed medication affecting gastrointestinal motility and/or perception (ie, laxatives, prokinetics, antidiarrheals, antispasmodic) on more than four days during the baseline period.
6. Inability or unwillingness to follow directions or unable to understand how to use the telephone data entry system.

The investigator was informed of the patient's eligibility to continue into the double-blind treatment period regarding exclusion criteria 1-4 above by the telephone data entry system.

**APPEARS THIS WAY
ON ORIGINAL**

Prohibited concomitant medication

The following concomitant medications were prohibited after Day -28:

- Laxatives including stool softeners; however, patients experiencing significant constipation could use a laxative as rescue medication if needed
- Antidiarrheals (in case of significant diarrhea, loperamide could be used if needed)
- Antacids containing magnesium or aluminum salts
- Anticholinergics
- Antispasmodic agents
- Erythromycin and other macrolides
- Octreotide
- Ondansetron or other 5-HT₃ antagonists
- Opioids/narcotic analgesics; occasional use of codeine containing analgesics was allowed if needed for a non-gastrointestinal indication
- Prokinetics
- Serotonin re-uptake inhibitors or tricyclic antidepressants (allowed if constant doses for at least one month prior to Day -28)
- Calcium antagonists (allowed if constant doses for at least one month before Day -28).

Concomitant medications other than non-bulk forming laxatives were entered on the Prior and concomitant medication CRF. Start and end dates were not collected, except for laxatives. Laxatives were entered on the Laxative log CRF.

[Note]:

As in the previous Phase III trials, bulk forming agents, calcium antagonists, tricyclic antidepressants and serotonin re-uptake inhibitors were permitted provided they had been taken at constant doses for at least one month prior to Day-28 and if the dose had remained stable during the trial.

Patients receiving a stable dose of bulking agents were instructed to continue using the same dose of this agent during the study. Patients were **not** allowed to change their diet at anytime during the study.

In order to evaluate compliance, the investigator noted the number of tablets dispensed. He/she was subsequently required to comment in the case report forms (CRF) on any patients who were < 75% compliant.

Below is the sequence of evaluations and procedures. (Figure 2)

Study B358
Schedule of Evaluations and Procedures scanned from the sponsor's submission.

EVALUATION	Visit: Day:	Screening ¹	Baseline	Double-blind treatment				Withdrawal ²
		1	2	3	4	5	6	telephone
			-28	1	29	57	85	113
Informed Consent		X						
Endoscopic/radiologic procedures ³		X						
Inclusion/Exclusion		X	X	X				
Demography/ background information			X					
Past/current medical conditions			X					
Physical examination			X				X ⁹	
Vital signs ⁴			X				X ⁹	
ECG evaluation ⁵			X				X ⁹	
Pregnancy test			X	X ⁸	X	X ⁸	X ⁹	
Laboratory evaluations ⁶			X		X		X ⁹	
Comments			X	X	X	X	X ⁹	
Randomization ⁷				X				
Dispensing of study medication				X	X	X		
End of baseline				X				
End of double-blind treatment period							X ⁹	
End of withdrawal period								X ¹⁰
Study medication label page				X	X	X		
Efficacy variables/touch-tone telephone diary				← Daily and weekly patient assessments →				
Prior/concomitant medication				← Update as necessary →				
Laxative log				← Update as necessary →				
Adverse events assessment				← Update as necessary →				
Comments				← Update as necessary →				
1. Screening was conducted within 4 weeks of Day -28; this visit could be combined with Day -28 visit if patient was eligible to enter the baseline period. 2. Follow-up by telephone to assess adverse events and concomitant medication. A follow-up visit was scheduled if necessary for safety reasons. 3. If needed, these procedures were performed at least 3 days prior to Day -28 visit 4. Sitting blood pressure and pulse; weight were also recorded. 5. A second original or good copy of ECG tracing was collected. 6. Including hematology, serum chemistry profile and urinalysis; stool for occult blood on Day -28 7. In order to be randomized, patients had to fulfill baseline criteria as assessed by touch-tone telephone electronic data system; investigator was informed of patient's eligibility. 8. Urine pregnancy test on Days 1 and 57 9. Or at time of discontinuation from double-blind treatment 10. Or 4 weeks after premature discontinuation from double-blind treatment								

Figure 2.

APPEARS THIS WAY
ON ORIGINAL

[Note]: The patients phone recorded their responses consisting of 5 assessments of symptoms daily and 4 additional assessments weekly.

Protocol amendments

One protocol amendment, dated September 21, 2000, made the following changes in the statistical design:

- Modified the primary efficacy variable/analysis so that it is identical to what was used in tegaserod Study B 301 and B307.
- Added all patients who completed the study as an additional analysis population.
- Modified per protocol population criteria.
- Added several supplemental analyses for SGA of relief assessment.
- Change from baseline in scores was to be analyzed by month and at the end of study for all secondary weekly assessments instead of absolute scores.
- Added a weekly analysis for change from baseline for all secondary assessments.

Reviewer Comments

- The aforementioned protocol revisions to modify the statistical analyses were acceptable.
- As previously stated the inclusion/exclusion criteria for study **B358** were acceptable. The addition of "stool consistency" to the pre-randomization criteria better defined the proposed study population, i.e. patients with constipation (**C-IBS**). This reviewer would prefer a stool consistency score >5 (*somewhat hard*) rather than the >3.5 (between *somewhat loose* and *neither loose nor hard*) that was adopted in protocol B358. Also, the abdominal pain criteria for exclusion (pain <1.5) allows entry into the trial of patients with mild abdominal pain.
- The study population was not overly restrictive allowing the formation of a subset that approximates the C-IBS population in the community.
- The length of the study (12 week double-blind treatment phase) was suitable for a demonstration of therapeutic differences between the treatment arms.

- The 12mg/d dose of tegaserod demonstrated the most ‘consistent’ results in the previous Phase III studies (B351, B301, B307) without increases in the adverse events, i.e. efficacy similar to the 4mg/d dose.
- I fervently agree with the use of a touch-tone data retrieval system preferably to using the paper diary. First, it is more reliable, and second it has the benefit of ensuring that the patient’s responses are recorded at the specified interval.
- The addition of a *withdrawal phase* in study **B358** had the capacity to aid in demonstrating efficacy, durability and possible rebound effect/s related to the test medication.

Perhaps, more useful data would have been obtained with a randomized, double blind withdrawal design. Nonetheless, the data observed in Study **B358** revealed **no** significant differences between treatment groups, for any of the efficacy variables, during the 4-week withdrawal period. That is the loss of an effect was the same for both groups during week one and two, and then stabilized over withdrawal weeks three and four. Additional evidence of drug effect was not clearly demonstrated during the withdrawal phase.

**APPEARS THIS WAY
ON ORIGINAL**

I. Efficacy B358

1. The Primary Efficacy Variable (*scanned material*).

The primary efficacy parameter was the Subject's Global Assessment (SGA) of relief. Patients responded weekly to the following question by touch-tone telephone:

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

Possible answers were:

- completely relieved,
- considerably relieved,
- somewhat relieved,
- unchanged,
- worse.

As per protocol Amendment 1 (21-Sept-00), Responders are those who fulfill the following criteria:

- a) Patients who answered completely relieved or considerably relieved at least 50% of the weeks at endpoint or at least somewhat relieved (ie, completely, considerably or somewhat relieved) 100% of the weeks at endpoint
- b) ≤ 5 days with no laxative use during treatment period and no laxative use during the last 28 days (with the exception of bulk-forming laxatives)
- c) ≥ 28 days duration of exposure to study medication
- d) At least one SGA of relief assessment during treatment period

Otherwise, the patient is considered to be a nonresponder. This amendment added adjustment criteria b and c above, so that the primary efficacy variable would be identical to that used in previous tegaserod phase 3 studies B301 and B307.

2. Secondary Efficacy Variables

The secondary efficacy parameters were assessed daily and weekly via the touch-tone phone system. The following table demonstrates the timing, questions and responses.

Study B358

Table 1

Scanned chart of Secondary Efficacy Parameters

Efficacy Variable	Frequency	Question	Response Scale
SGA of abdominal discomfort/pain	Weekly	"How bothersome was your abdominal discomfort and pain over the past week?"	0= not at all 1= hardly 2= somewhat 3 = moderately 4= a good deal 5= a great deal 6= a very great deal
SGA of bowel habit	Weekly	"How bothersome was your constipation over the past week?"	0= not at all 1= hardly 2= somewhat 3 = moderately 4= a good deal 5= a great deal 6= a very great deal
SGA of satisfaction with bowel habit	Weekly	"How satisfied were you with your bowel habits over the past week?"	1= very satisfied 2= somewhat satisfied 3= somewhat dissatisfied 4= very dissatisfied
Abdominal discomfort/pain	Daily	"How intense was your abdominal discomfort and pain today?"	0= none 1= very mild 2= mild 3= moderate 4= moderately severe 5= severe 6= very severe
Bloating	Daily	"How intense was your abdominal bloating today?"	0= none 1= very mild 2= mild 3= moderate 4= moderately severe 5= severe 6= very severe
Stool frequency	Daily	"How many bowel movements did you have today?"	Number of bowel movements
Stool consistency ¹	Daily	"Please rate your average stool consistency today"	1 = watery 2 = loose 3 = somewhat loose 4 = neither loose nor hard 5 = somewhat hard 6 = hard 7 = very hard
Straining	Daily	"Did you strain during or while trying to have a bowel movement today?"	1= yes 2= no

¹ if the answer to number of bowel movements was zero, the question on stool consistency was omitted.

Patient Disposition:

- A total of 3,177 patients were screened for participation in the study.
- There were 1,658 (52.2%) patients enrolled, but not randomized. It has not escaped my attention that this is a large number of non-randomized patients. The following table lists the reasons for the discontinuations.

*[Scanned] Table 2***Study B358 - Number of patients who discontinued prematurely during baseline period by principle reason of discontinuation**

Reason	N = 1658
Unacceptable past medical history/concomitant diagnosis	51 (3.1%)
Intercurrent medical event	7 (0.4%)
Unacceptable laboratory values	16 (1.0%)
Unacceptable test procedure values	24 (1.4%)
Did not meet — randomization criteria	
< 11/14 days diary entry	402 (24.2%)
did not meet mean stool consistency criterion	196 (11.8%)
<2 weekly questions answered	184 (11.1%)
did not meet abdominal discomfort/pain criterion	38 (2.3%)
Weekly relief criteria not met	5 (0.3%)
Unacceptable use of excluded medications	43 (2.6%)
Subject withdrew consent	564 (34%)
Unknown	30 (1.8%)
Other	209 (12.6%)
Note: there may be more than one reason for an individual patient.	

The most prevalent reason for premature discontinuation other than “withdrawn consent” was noncompliance with the touch-tone telephone diary. The demographic characteristics of the discontinued group were similar to the treatment group.

- 1,519 patients (tegaserod n=767, placebo n=752) were randomized. Rightfully, all of the 1,519 patients were included in both the intent-to-treat and the safety analyzable populations.
- 1,410 (tegaserod n=712, placebo n=689) proceeded through the trial into the withdrawal period.

Patient disposition by treatment for all randomized patients is displayed in the scanned table 3 below.

Table 3
Study B358

Patient disposition	Tegaserod 12 mg/d n (%)	Placebo n (%)	Total n (%)
Randomized into double-blind period	767 (100)	752 (100)	1519 (100)
Completed the double-blind treatment period	609 (79.4)	591 (78.6)	1200 (79.0)
Discontinued double blind period prematurely	158 (20.6)	161 (21.4)	319 (21.0)
Safety analyzable population	767 (100)	752 (100)	1519 (100)
Per Protocol population	658 (84.5)	628 (83.5)	1276 (84.0)

The reasons for discontinuation from double-blind treatment period are in the scanned table 4 below.

Table 4
Study B358

Reason for discontinuation	Tegaserod 12 mg/d N=767 n (%)	Placebo N=752 n (%)	Total N=1519 n (%)
Total	158 (20.6)	161 (21.4)	319 (21.0)
Adverse event	52 (6.8)	36 (4.8)	88 (5.8)
Abnormal laboratory values	4 (0.5)	5 (0.7)	9 (0.6)
Unsatisfactory therapeutic effect	15 (2.0)	26 (3.5)	41 (2.7)
Patient's condition no longer required study drug	0 (0.0)	1 (0.1)	1 (0.1)
Protocol violation	1 (0.1)	1 (0.1)	2 (0.1)
Subject withdrew consent	56 (7.3)	60 (8.0)	116 (7.6)
Lost to follow-up	26 (3.4)	29 (3.9)	55 (3.6)
Administrative problems	4 (0.5)	3 (0.4)	7 (0.5)

Reviewer Comments

- In general, the numbers of patients and the reasons for discontinuation were similar between the tegaserod and placebo treatment groups.

Demographics

Table 5

The following table illustrates the Baseline Demographics of B 358

Demographic Variable	Category/ summary statistics	Tegaserod 12 mg/d N=767	Placebo N=752	P-value
Age group	< 65	744 (97.0)	725 (96.4)	0.518
	≥ 65	23 (3.0)	27 (3.6)	
	≥ 75	3 (0.4)	2 (0.3)	
Age (years)	Mean	41.5	41.0	0.331
	SD	10.8	11.7	
Gender	Female	767 (100)	752 (100)	
Race	Caucasian	589 (76.8)	586 (77.9)	0.538
	Black	127 (16.6)	121 (16.1)	
	Oriental	3 (0.4)	2 (0.3)	
	Other	48 (6.3)	43 (5.7)	
Smoker	Yes	127 (16.6)	148 (19.7)	0.114
Weight (kg)	Mean	70.7	70.0	0.345
	SD	15.4	13.9	
Duration of IBS symptoms (months)	Mean	192.5	195.3	0.719
	Median	168	168	
	SD	145.8	154.7	

- There were no significant differences in potentially confounding variables- such as age, sex and race or other protocol specified variables- between the treatment groups.
- In the baseline population 77% were Caucasian, 16.3% were Black and only 3% were > 65 years.
With this number of Blacks; some idea of efficacy and safety in this race might be possible. Data regarding racial differences in irritable bowel syndrome are sparse (tegaserod vs placebo) response rates for Blacks (43.3% and 42.1%) i.e. no demonstrated efficacy in Black females.
- The mean duration of the patient's irritable bowel syndrome was approximately 16 years for both treatment arms. Patients with a long duration of disease are, in general, more recalcitrant to therapeutic intervention, and have a higher degree of psycho-

social dysfunction. Therefore, adding to the difficulty of establishing robust efficacy data. **Thus, even modest efficacy data in this patient population could be clinically meaningful.**

- A confounding variable- **laxative use**- was the only demographic variable for which there was a statistically significant imbalance at baseline. This imbalance does not seem to favor the drug because patients taking laxatives may be “sicker” than those patients who are not taking the laxatives.
- Primary care centers evaluated 71% of the patients, 27% were evaluated at secondary centers, and only 2% came from tertiary centers.

Generally, the patients seen at tertiary centers are ones who have been treated with a wide array of medicinal options, and have undergone an increased number of diagnostic tests. Therefore, the chances of an alternative diagnosis to irritable bowel syndrome would be less likely in this group. Also, their clinically relevant response to ‘first line’ therapy is less likely.

The following is a *scanned* sponsor’s table 6 of **bulking agents** and **laxative use**.

Table 6

	Tegaserod 12 mg/d N=767	Placebo N=752	P-value
Bulking agents	91 (11.9%)	88 (11.7%)	0.922
Laxatives and cathartics	115 (15.0%)	80 (10.6%)	0.011*

*statistically significant at the two-sided significance level of 0.05.

[Note]: In the treatment groups, the SGA of abdominal discomfort/pain, bowel-habit, and satisfaction with bowel habit were all of a similar degree of severity at baseline.

[Note]: the above difference in laxative use was not seen during the 12-week double-blind treatment period. This difference in laxative (more use in tegaserod patients) use was again seen in the withdrawal period.

This is illustrated in the following *scanned* table.

Table 7
Study B358
Laxative Use

Study period	Tegaserod 12 mg/d (N=767)		Placebo (N=752)	
	n	%	n	%
Double-blind treatment period (any use)	145	(18.9)	144	(19.1)
Last 28 days of double-blind treatment (any use)	91	(11.9)	82	(10.9)
>5 days use over entire double-blind treatment	26	(3.4)	23	(3.1)
Withdrawal period (any use)	164	(24.7)	109	(17.3)

[Note]: This difference in laxative use during the withdrawal period might suggest a gastrointestinal, prokinetic response enacted by the test medication during the double-blind treatment period of observation. It is not known if tegaserod's greater efficacy over placebo was influenced by the amount of laxative taken, not as a "confounder factor" but as indicating the need for an anti-constipation medication. [M. Camilleri: Management of Irritable Bowel Syndrome. Gastroenterology 120: 652-668 (2001)].

Efficacy Results Study B 358

The following *scanned* table from the "clinical section" of the submission demonstrates the results of the primary efficacy variable analyses both with and without adjustments to the SGA of relief.

Table 8
Study B358
SGA of RELIEF

Adjustment factor applied	Responder rate		
	Tegaserod 12 mg/d (N=767)	Placebo (N=752)	Difference (p value)
None (unadjusted)	48.3%	41.7%	6.5 (0.010*)
No SGAs available ¹	47.5%	41%	6.5 (0.009*)
No SGAs available and duration < 28 days ²	45.8%	40%	5.9 (0.018*)
Primary efficacy variable definition ³	43.5%	38.8%	5.3 (0.033*)
No SGAs available, duration < 28 days, laxative intake			

* Statistically significant at the two-sided significance level of 0.05.

¹ This analysis represented the primary efficacy variable prior to Protocol Amendment No. 1.

² No laxative adjustment factor applied.

³ All 3 adjustments applied according to the primary variable definition.

[Note]: With the substantial imbalance in laxative use during baseline, a covariant analysis was performed (See table below). And this calculation demonstrated a p-value equal to the significant (0.033) seen in the table above. Generally, adding more “unplanned analyses” increases the risk of finding statistically significant differences purely by chance. However, the protocol (Vol. 5, p.38) states that “if it is evident that the response for SGA of Relief is confounded with some of the background variables”, then an exploratory analysis using the background variable(s) as covariate(s) would be performed. [This will be discussed further in a separate biostatistics review.][See table 9].

**Table 9
Study B358**

Impact of selection of covariables on the analysis results of SGA of relief

Covariable adjustment	p-value
Adjusting laxative use during baseline	0.033
Without covariable adjustment	0.0599

Reviewer comment

- Truly, the imbalance of laxative use at baseline would be a clinically relevant factor, and needs to be accounted for in the final analysis. From a statistical viewpoint, this covariant analysis appears exploratory, however the use of the covariant analysis remains clinically relevant.

[Note]: None of the following secondary efficacy variables were adjusted for laxative use etc.

Nonetheless, daily bloating scores along with bowel-related assessments (stool frequency, straining and stool consistency) showed both significant early and sustained relief.

**APPEARS THIS WAY
ON ORIGINAL**

Table 10
Secondary Variables from Daily Diary Assessments

Scanned Table

Efficacy variable	Tegaserod 12 mg/d	Placebo	P value
Mean change from baseline in daily abdominal discomfort/pain score	-1.63	-1.53	0.134
Mean percent change from baseline in number of days with significant abdominal discomfort/pain	-28.4%	-26.0%	0.196
Mean change from baseline in daily bloating score	-1.59	-1.47	0.036*
Mean percent change from baseline in number of days with significant bloating	-23.6%	-20.7%	0.086
Mean percent change from baseline in number of bowel movements	104.7%	68.6%	<0.001*
Mean percent change from baseline in number of days with no bowel movements	-30.4%	-22.8%	<0.001*
Mean change from baseline in daily stool consistency score	-0.91	-0.62	<0.001*
Mean percent change from baseline in number of days with hard or very hard stool ¹	-55.9%	-43.7%	0.002*
Mean percent change from baseline in number of days with straining	-19.9%	-11.9%	<0.001*

¹ Denominator is the number of days with a bowel movement within the 28-day interval.

* Statistically significant at the two-sided significance level of 0.05.

Reviewer comment

- The most consistent results were related to the number of bowel movements, stool consistency, straining, and the mean number of days without a bowel movement, or days with hard or very hard stools.

With tegaserod, the therapeutic gains over placebo for all of the secondary parameters of efficacy were all statistically significant at a 0.002 p-value or less. Similar statistically significant differences in these secondary variable endpoints were observed in the previously reviewed Phase III studies (B351, B301, B307).

Figure 3 demonstrates the side by side comparisons for the primary efficacy variable in all 4 Phase III trials

Figure 3

Complete or Considerable Relief by Week

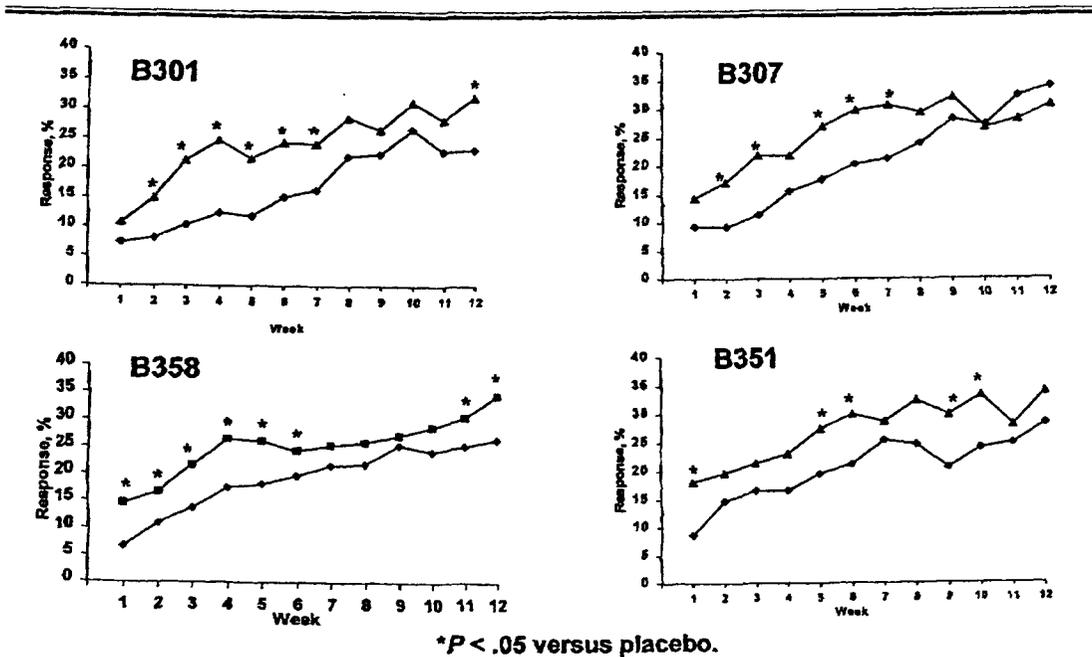
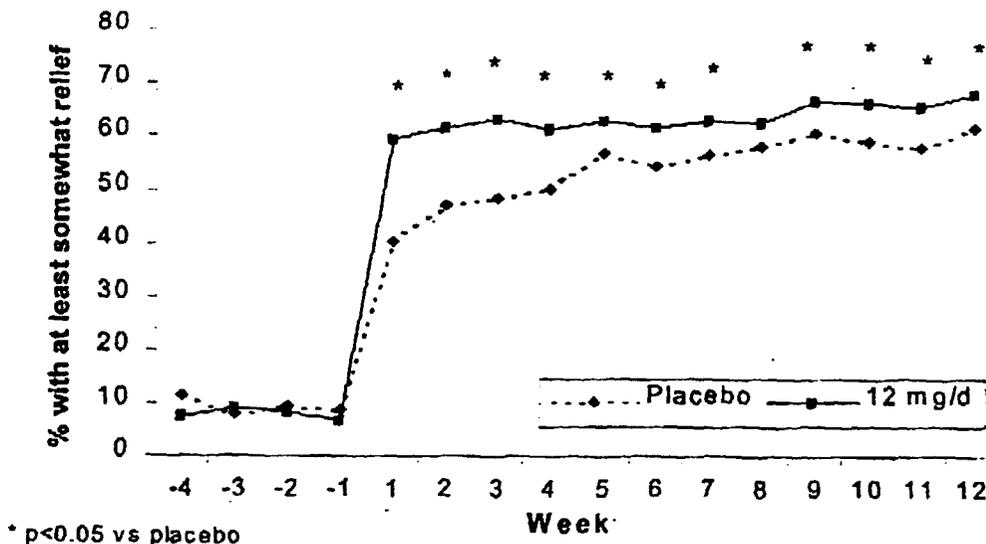


Figure 4 demonstrates the weekly responses via phone data entry of 'somewhat relief' for SGA of Relief during the 12- week treatment period.

Figure 4
B358

Weekly percentage of patients with at least somewhat relief



Additional Reviewer Comments

As seen Fig. 3 – the shape and size of the % of ‘responders’ in the line graph are similar for all studies, during the early months. Also, at the end of the double-blind period (12 weeks) the tegaserod and placebo responder lines are not coming closer together, but on the contrary are moving apart in the three positive trials (301,351 and 358).

The type of data for B358 displayed in figure 4 cannot be interpreted on a weekly basis, because the definition of a responder (primary efficacy variable) for ‘somewhat relief’ was actually a positive response for an entire 4-week period. Nonetheless, the Fig suggests sustained effects.

II. Safety

Safety analyzable population: This consisted of All randomized patients who received at least one dose of study medication and underwent at least one post-baseline safety assessment.

- There were **no deaths** in study **B358**.
- Fourteen of the 1,519 patients (**0.9%**) reported a total of **19 serious adverse events (SAE)** [9-tegaserod, 5-placebo group (1.2%) and (0.7%) respectively]. None of these SAEs were suspected by the investigators to be related to the test medication. In the tegaserod group four patients were discontinued while in the double-blind treatment period, and one was discontinued from the placebo group.
- There were **84 patients (5.5%)** who discontinued for **adverse events (AE)**. [49 of 767 with tegaserod (**6.4%**) and 35 of 756 with placebo (**4.7%**)] The **p value was NS**. [Table 11 AEs leading to discontinuations.]

Reviewer Comments Regarding Changes in Laboratory Parameters

- Only 5 patients discontinued the study because of abnormal laboratory values (3 patients - tegaserod, 2 patients - placebo).

- No clinically relevant changes were seen in mean values for hematology or biochemistry parameters in either of the treatment groups.
- Slight fluctuations in urine - blood, protein and glucose levels were noted in both treatment groups. The investigators did not think that these fluctuations were clinically relevant. The reviewer agrees with this assessment.

Changes in Vital Signs and Routine Physical Exam

- According to the sponsor, there were no clinically important or statistically significant changes in the vital signs or physical examination measurements in study 358.

Study B358

Table 11

Scanned Table of Adverse Events Leading to Discontinuation

	Tegaserod 12 mg/d (N=767)		Placebo (N=752)	
	n	(%)	n	(%)
Total patients with AEs leading to discontinuation	49	(6.4)	35	(4.7)
Diarrhea	12	(1.6)	0	(0.0)
Abdominal pain	11	(1.4)	4	(0.5)
Headache	10	(1.3)	6	(0.8)
Nausea	6	(0.8)	8	(1.1)
Flatulence	6	(0.8)	4	(0.5)
Dizziness	4	(0.5)	1	(0.1)
Dyspepsia	2	(0.3)	1	(0.1)
Vomiting	2	(0.3)	1	(0.1)
Arthropathy	2	(0.3)	0	(0.0)
Pain	2	(0.3)	0	(0.0)
Breast pain female	1	(0.1)	1	(0.1)
Chest Pain	1	(0.1)	1	(0.1)
Cramps	1	(0.1)	1	(0.1)
Dyspnea	1	(0.1)	1	(0.1)
Fecal incontinence	1	(0.1)	1	(0.1)
Palpitation	1	(0.1)	1	(0.1)
Paraesthesia	1	(0.1)	1	(0.1)
Vaginitis	1	(0.1)	1	(0.1)
Fatigue	0	(0.0)	3	(0.4)
Rash	0	(0.0)	3	(0.4)

**APPEARS THIS WAY
ON ORIGINAL**

The most frequent adverse events and the proportions of patients in the tegaserod treatment group experiencing these AEs were:

- Headache-9%
- Nausea-7%
- Abdominal pain-6%
- Diarrhea-6%
- Flatulence-6%

[Note]: These adverse events were similar to the “adverse events pattern” from previous Phase III tegaserod trials. Only diarrhea was significantly different from placebo.

**APPEARS THIS WAY
ON ORIGINAL**

Additional Reviewer Comments

- No clinically relevant changes were observed in vital signs or the ECG evaluations in either treatment group.
- The frequency of patients with prolongations of the QT_c interval was the same in both treatment groups. No ventricular tachycardia was observed.
- No conclusions were possible from analyses of adverse events reported during the withdrawal phase. [There is an addendum to the statistical review regarding the data from the withdrawal phase.]

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

III. Safety Areas of Special Interest to the Reviewer:
(i.e.concerns that derive from the earlier Phase III studies)

There are various issues that have derived from the evaluation of the data in a stepwise fashion over the last approximately 15 months. Some remained, but most decreased in clinical relevance and veracity (numbered 1 through 4).

1. Abdominal and Pelvic Surgery in Study B358

Table 12

Treatment	Tegaserod	Placebo
Abdominal or Pelvic Surgery	7	4
Laparoscopic Cholecystectomy	4	0
Appendectomy	1	0

More abdominal surgeries were performed in the tegaserod group especially laparoscopic cholecystectomies. However, this difference in incidences did not reach statistical significance.

'Inappropriate cholecystectomy' for nonspecific dyspeptic symptoms (as in IBS) is undoubtedly a common occurrence in the United States especially in the era of laparoscopic surgery. But, whether these imbalances are chance occurrences or whether tegaserod is playing a role, whatever minor, is not really known.

The effect of 5-HT₄ receptor activity on gallbladder, ductular or ampullary motility has not been studied.

Additional information related to the laparoscopic cholecystectomy patients in B358 is given in Table 13. This table shows only the laparoscopic cholecystectomies in study B358 that occurred during the actual timeframe of the study i.e. 85 days. In all the patients, the reason for the surgical intervention was abdominal pain. The patients in the tegaserod arm of the study received 12mg/drug of the drug and the event occurred in this 12-week interval of trial duration. The placebo event occurred @ 156 days after trial completion (see reviewer's comments).

Study B358- Laparoscopic Cholecystectomies

Table 13

Patient #/ age	Rx	Previous stones	Pain	Dx.	O.R. reason & day	Findin g	Related to Drug ?
358/52/15 (30) years	12mg/d	INA	Yes	US- GBS	Pain/ GBS (58)	INA	-
358/17/48 (38) years	12mg/d	INA	Yes	Abn. HIDA	INA (74)	Fibrosis/ adhesion	Poss. ^ Motility?
358/122/4 (37) years	12mg/d	Yes	Yes	US- GBS	Pain/ GBS (61)	Two gallston es/ fibrosis	^ motility/ symptoms ?
358/23/29 (54) years	12mg/d	Yes	Yes	US- GBS	Pain/ GBS	INA	Poss. ^ Motility
358/112/22 (31) years	Placebo	INA	Yes	INA	Pain ? (221)	INA	221 days/ not valid

INA = information not available

GBS = gallbladder stones

HIDA = nuclear medicine scan of the gallbladder

Reviewer Comments:

In the reviewer's opinion, in two of the above described surgical cases drug involvement can not be eliminated with certainty (/17/48 and /23/29).

Today, approximately 20 million Americans have gallstones, and more than 700,000 cholecystectomies are performed annually in the United States. [Sum, L.P. in Tadmada Yamada et al. Textbook of Gastroenterology, chapter 99, p. 2258, 1999]

With the incidence of cholelithiasis for adult American females conservatively 10-to-15 per cent, and the incidence of irritable bowel syndrome for this population possibly 15-to-20 per cent, the potential for a public health problem becomes evident.

[Note]: The populations of patients with C-IBS and gallstone disease are essentially the same (i. e. forty- year old, fertile females).

The first laparoscopic cholecystectomy was performed in France in 1987. Since then, there has been an increase in the number of cholecystectomies performed. [Escarce J.J. JAMA 1995-Vol 273, No 20 p. 1581-1585].

There is a suggestion of increased incidence of cholesterol cholelithiasis in patients with slow colonic transit. [Linzi, A. Gastroenterology 2000;119: 806-815]

This “increased incidence” and “lowered threshold” for cholecystectomy can not explain the uneven distribution of cholecystectomies seen in the two treatment arms of study B358. Whether the 4 to 0 incidence of cholecystectomies (the one placebo case occurred 156 days after the last dose) is significant or not is irrelevant because the study was not powered to detect such changes. This unequal distribution does evoke a concern. Whether this is a valid concern is not known.

Similar small qualitative differences were seen for abdominal, including appendectomies and pelvic non-elective surgeries. Serotonin (5-HT₄) receptors are known to exist throughout the tubular G. I. tract including the appendix, and to a questionable degree in the ovary and uterus. Their presence in or effect on gallbladder and bile duct motility remains unstudied.

Theoretically, enhanced gallbladder contractions might increase the possibility of “silent stones” becoming symptomatic (by traveling through the cystic into the common bile duct) or enhanced gallbladder contraction could mimic an episode of biliary pain in the absence of gallstones.

Notably, the incidence of silent gallstones is markedly increased in an elderly population as is the problem of constipation. Only 3.5% of the patients in study B358 were >65 years; more experience in the elderly is needed.

Biliary dyskinesia or non-synchronous changes in the sphincter of Oddi pressure are other possible pathophysiologic mechanisms that might simulate biliary colic.

2. Ovarian cysts

Ovarian cysts are not an issue. There were two instances of ovarian cysts in study B358, one in each treatment group. In the original NDA 21-200, after utilizing further evaluation of material supplied by the sponsor and a gynecologic consultation, ovarian cysts per se did **not** appear to be a valid concern.

**APPEARS THIS WAY
ON ORIGINAL**

3. Syncope

Syncope did not appear to be an issue either. Only one case was reported, and it occurred in the placebo treatment arm. This is in marked contrast to the episodes of syncope seen in the previous Phase III studies (9-1, tegaserod versus placebo). There were no significant changes seen in blood pressure or ECG's and no sudden deaths.

**APPEARS THIS WAY
ON ORIGINAL**

4. Diarrhea

Diarrhea is an issue. This ADVERSE EVENT, probably the result of an exaggeration of the pharmacologic effect, occurred in 41 of 767 tegaserod patients (5.4%), and in 13 of 752 placebo patients (1.7%). Tegaserod was the cause of discontinuation in 12 patients which represented 1.6%. This was higher than the 0% seen in the placebo arm of the trial.

In general, tegaserod treatment was associated with an increased frequency of diarrhea, predominantly in the first weeks of treatment. The diarrhea was mild and usually stopped promptly with discontinuation of the medication. Most patients were able to re-start the drug and finish the clinical trial.

**APPEARS THIS WAY
ON ORIGINAL**

Sponsor's conclusions:

In study B358, tegaserod 12mg/d was effective in relieving overall irritable bowel syndrome symptoms, and in improving abdominal pain, bloating and altered bowel habits (stool frequency, consistency, and straining). Tegaserod treatment had an early onset of action starting in week one. Results for the primary efficacy variable, the SGA of relief, were consistent with the secondary variables. Tegaserod treatment was well tolerated.

Additional Reviewer Comments

Currently, we are in a state of emerging science with regard to functional gastrointestinal diseases. I believe that the pathophysiology of irritable bowel syndrome is evolving from being considered solely a disorder of motility, to one that is distinguished by dysregulation of brain-gut function, manifest by gut motor hypo or hyper-reactivity and/or enhanced visceral sensitivity to a variety of stimuli. The tools to evaluate the effects of drugs in IBS are also evolving. The Rome criteria are not completely adequate in defining the IBS study population.

Utilizing the "totality of the evidence" approach, tegaserod demonstrates efficacy which although modest using the primary parameter of efficacy, is undeniably sustained for at least 12 weeks, the duration of the clinical trials. These findings in IBS patients who have experienced symptoms for an average of 10 to 16 years, are clinically meaningful. Although the data are not compelling, Zelnorm is undoubtedly differentiated from placebo. Results in study B301, part of the original NDA submission, were supported by study B358 (therapeutic difference of 5.3%). Importantly, in all trials, the bowel-related secondary variable endpoints (stool frequency, straining and stool consistency) all significantly improved within the first week of therapy. Improvement was then maintained throughout the treatment period without evidence of a rebound effect during the withdrawal period. Approximately three quarters of the responders at the first month were responders at the end of the treatment period suggesting that if a patient is going to respond to test medication, this response is quick (within the first 4 weeks). Also importantly, bloating scores improved significantly (there currently are no approved medications to treat this very important symptom to the IBS patient - bloating).

All in all, tegaserod was well tolerated, and had an acceptable safety profile compared to older gastrointestinal-prokinetic agents. The main and statistically significant adverse event, diarrhea, is a logical consequence of the pharmacodynamic action of the drug. The diarrhea occurred early (first week) and was usually short-lived with drug discontinuation. It did not result in withdrawal from treatment to any great extent (1.6% vs 0% for placebo). However, concerns remain regarding the need for

abdominal surgery particularly cholecystectomy. Table 14 depicts the reviewer's "special safety issues" addressed in detail in the primary review of NDA 21-200 and in the review of the present supplement.

Table 14
Special safety

	TEGASEROD (n=2,446)	PLACEBO (n=1,589)
Abdominal Surgery	16 (0.7%)	2 (0.1%)
Cholecystectomy	5	0
'Ovarian Cysts'	8	1
Actual	3	0
Non-	5	1
Appendectomy	1	0
Other	1	0
Syncope	8 (0.3%)	1 (0.1%)
Diarrhea	237	58
Discontinuations	39 (1.6%)	4 (0.3%)

Appendices:

- I. Slides from the June 5, 2001 Executive Pre-decision Briefing presentation.
- II. Handouts from the June 5, 2001 aforementioned meeting.

**APPEARS THIS WAY
ON ORIGINAL**

Recommendations for Regulatory Action

Based on my review of the evidence presented by the sponsor in NDA 21-200, and in agreement with my recommendation in my primary review of this NDA, I recommend that Zelnorm™ continue to be made approvable for the treatment of constipation-predominant IBS in females. Approval of the drug is contingent to the sponsor agreeing to carry out Post Marketing studies to further clarify the lingering safety concerns regarding a higher incidence of abdominal surgeries that might be associated with the use of tegaserod in women with C-IBS, especially cholecystectomies.

To further strengthening the labeling and adequately inform the practitioner regarding the best use of the drug, the following studies should be performed:

[

]

[

]

- A prospective study of sufficient number of patients on the recommended regimen of tegaserod, 6 mg po b.i.d., to assess the true rate of cholecystectomies in female patients being treated with the drug.

Raymond E. Joseph M.D., F.A.C.P., F.A.C.G.

cc:

HFD-180/LTalarico

HFD-180/HGallo-Torres

HFD-180/RJoseph

HFD-181/CPerry

**APPEARS THIS WAY
ON ORIGINAL**

Appendix I

Full set of slide presentation by Dr. Joseph at the June 5, 2001 Upper Management Briefing.

**APPEARS THIS WAY
ON ORIGINAL**

ZELNORM
(tegaserod)

Upper Management
Briefing
June 5, 2001
R. E. Joseph M.D., F.A.C.P.,
F.A.C.G.
Medical Officer

Introduction

Tegaserod is a aminoguanidin-indole (NME)

A partial agonist of the 5 - HT₄ receptor

- no 5 - HT₃ activity
- no dopamine receptor activity

Irritable Bowel Syndrome

Chronic or recurrent GI symptoms

- lower abdominal pain/discomfort
- altered bowel habits
- bloating

Not explained by structural or biochemical abnormalities

**APPEARS THIS WAY
ON ORIGINAL**

⋮

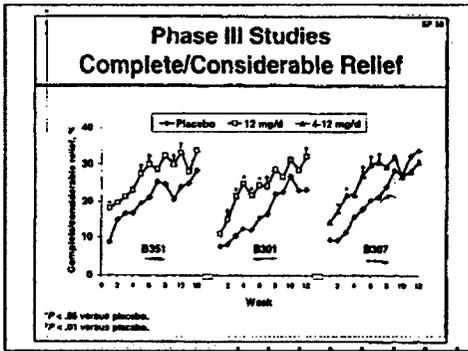
Prevalence in US

- IBS	15-20%
- Dyspepsia	8%
- GE reflux	7%
- Asthma	4%
- Diabetes	3%

- ⋮
- ### Irritable Bowel
- Klein's 1988 / Schuster's 1998 paper
 - Only the Lotronex trials showed efficacy in females with D-IBS
 - Tools to assess IBS are evolving - era of 'emerging science' 'Rome criteria'
 - Most patients have a long history of non-progressive disease /QOL
 - Currently there are **no** prokinetic drugs approved for the treatment of C-IBS

- ⋮
- ### Efficacy NDA 21-200
- (301) D-B, mostly European [n=881]
92 centers delta=11.8% p<0.01
 - (351) D-B, US [n=799] 52 centers -
(post-hoc) delta=12.8% p=0.004
 - (307) US [n=841] 79 centers
delta=5.4% p=0.19
- In all three trials: ■
- demographic and B-L characteristics similar
 - 12 mg/d statistically significantly better early compared to PL
 - relief supported by multiple secondary efficacy endpoints *

APPEARS THIS WAY
ON ORIGINAL



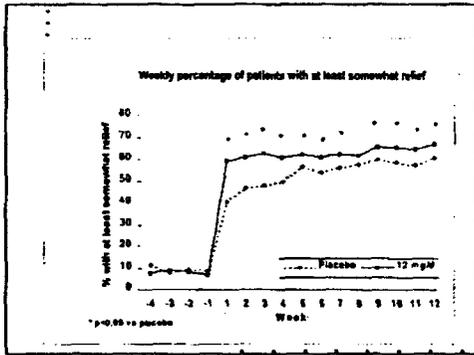
**Long-Term Efficacy
B 209 [n=579]**

- 12-month study (53%) completed [dose titration q month for 12 months]
- 80% titrated to 12 mg/d (4 to 12 mg/d)
- 62% reported 'complete or considerable' relief of the overall G.I. symptoms

**Efficacy B358
[n=1,519]**

- 135 U.S. centers
- 16 year history of disease / 78% Caucasian
- 767 TEGA 12mg/d 752 PL
- Design: screening/4 week baseline/12 week treatment/4 week withdrawal
- Responders: TEGA 44%
PL 39%
- Therapeutic Gain: 5%
 - (p=0.03 - covariable adjustment)
 - (p=0.06 - unadjusted)

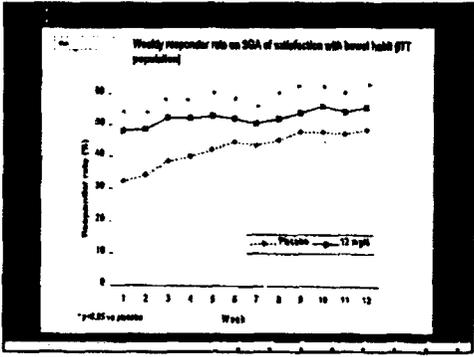
**APPEARS THIS WAY
ON ORIGINAL**



Study B358
Major Secondary Efficacy Parameters

- SGA satisfaction with bowel habit (p=0.007)
- Number of bowel movements (p<0.001)
- Stool consistency score (p<0.001)
- Daily bloating score (p=0.036)

11



APPEARS THIS WAY
ON ORIGINAL

Risks

- In general, well tolerated
- No QT_c prolongation unlike older prokinetics
- Manageable diarrhea
- AEs / SAEs: similar overall frequency to PL
- Biliary tract dysmotility ?

**Approve with
Recommendations for
Post-Marketing Studies:**

- Biliary motility in patients



**APPEARS THIS WAY
ON ORIGINAL**

Appendix II.

**APPEARS THIS WAY
ON ORIGINAL**

Appendix II.

Materials presented by Dr. R. Joseph to the Upper Management
Briefing of Tuesday, June 5, 2001

- Discontinuations in Study B358
- Definition of responders in the clinical trials
- Scales used for Efficacy Variables

UPDATES

(Individual Patients in all studies)

- Table 5. Abdominal and pelvic surgery
- Abdominal Surgery: open-label, L-T studies
: open label, Phase IV studies
- Pelvic Surgery: Double-blind studies
: Open-label, L-T studies
- Table 6. Cholecystectomies and pancreatic disorders

From Aug. 11, 2000 Approvable Letter

- Requirements for Approval
- Phase IV Commitments

Question to the June 5, 2001 UMB

**Study B358 - Number of patients who discontinued prematurely during
baseline period by principle reason of discontinuation**

Reason	N = 1658
Unacceptable past medical history/concomitant diagnosis	51 (3.1%)
Intercurrent medical event	7 (0.4%)
Unacceptable laboratory values	16 (1.0%)
Unacceptable test procedure values	24 (1.4%)
Did not meet — randomization criteria	
< 11/14 days diary entry	402 (24.2%)
did not meet mean stool consistency criterion	196 (11.8%)
<2 weekly questions answered	184 (11.1%)
did not meet abdominal discomfort/pain criterion	38 (2.3%)
Weekly relief criteria not met	5 (0.3%)
Unacceptable use of excluded medications	43 (2.6%)
Subject withdrew consent	564 (34%)
Unknown	30 (1.8%)
Other	209 (12.6%)
Note: there may be more than one reason for an individual patient.	

APPEARS THIS WAY
ON ORIGINAL

The primary efficacy parameter was the Subject's Global Assessment (SGA) of relief. Patients responded weekly to the following question by touch-tone telephone:

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

Possible answers were:

- completely relieved,
- considerably relieved,
- somewhat relieved,
- unchanged,
- worse.

As per protocol Amendment 1 (21-Sept-00), Responders are those who fulfill the following criteria:

- a) Patients who answered completely relieved or considerably relieved at least 50% of the weeks at endpoint or at least somewhat relieved (ie, completely, considerably or somewhat relieved) 100% of the weeks at endpoint
- b) ≤ 5 days with no laxative use during treatment period and no laxative use during the last 28 days (with the exception of bulk-forming laxatives)
- c) ≥ 28 days duration of exposure to study medication
- d) At least one SGA of relief assessment during treatment period

Otherwise, the patient is considered to be a nonresponder. This amendment added adjustment criteria b and c above, so that the primary efficacy variable would be identical to that used in previous tegaserod phase 3 studies B301 and B307.

APPEARS THIS WAY
ON ORIGINAL

Efficacy Variable	Frequency	Question	Response Scale
SGA of abdominal discomfort/pain	Weekly	"How bothersome was your abdominal discomfort and pain over the past week?"	0= not at all 1= hardly 2= somewhat 3 = moderately 4= a good deal 5= a great deal 6= a very great deal
SGA of bowel habit	Weekly	"How bothersome was your constipation over the past week?"	0= not at all 1= hardly 2= somewhat 3 = moderately 4= a good deal 5= a great deal 6= a very great deal
SGA of satisfaction with bowel habit	Weekly	"How satisfied were you with your bowel habits over the past week?"	1= very satisfied 2= somewhat satisfied 3= somewhat dissatisfied 4= very dissatisfied
Abdominal discomfort/pain	Daily	"How intense was your abdominal discomfort and pain today?"	0= none 1= very mild 2= mild 3= moderate 4= moderately severe 5= severe 6= very severe
Bloating	Daily	"How intense was your abdominal bloating today?"	0= none 1= very mild 2= mild 3= moderate 4= moderately severe 5= severe 6= very severe
Stool frequency	Daily	"How many bowel movements did you have today?"	Number of bowel movements
Stool consistency ¹	Daily	"Please rate your average stool consistency today"	1 = watery 2 = loose 3 = somewhat loose 4 = neither loose nor hard 5 = somewhat hard 6 = hard 7 = very hard
Straining	Daily	"Did you strain during or while trying to have a bowel movement today?"	1= yes 2= no

¹ if the answer to number of bowel movements was zero, the question on stool consistency was omitted.

APPEARS THIS WAY
ON ORIGINAL

**Table 5. Abdominal and pelvic surgery in individual patients in all studies.
Updated Table 5-19.4. from December 2000 ISS update**

Organ system/ adverse event	Age, Sex	Dose (mg/d)	Study/ Subject No.	Surgical procedure/ Comments	Day of sur- gery ¹	Vol # and Page
Abdominal surgery: double-blind studies						
Appendicitis	34F	Placebo	301/209/13	Appendectomy (ruptured appendix)	75	
Perforated cecum	27F	Placebo	351/518/19	Cececctomy with resection of distal ileum; surgery 123 days after last dose	207	
Fatty liver	31F	Placebo	358/112/22	Laparoscopic cholecystectomy after study; discontinued study due to fatty liver	221	
Subileus; Incarcerated hernia	42F	1	251/42/7	Herniotomy; symptoms during baseline	18	
Pancreatic cyst	71F	4	301/112/9	Exploratory laparotomy with removal of benign cyst; no gallstones	36	
Gallbladder dysfunction	51F	12	351/524/1	Laparoscopic cholecystectomy; RUQ pain	51	
Cholelithiasis	54F	12	358/23/29	Laparoscopic cholecystectomy; RUQ pain during baseline, ultrasound Day 2: gallstones	38	
Cholelithiasis	30F	12	358/52/15	Laparoscopic cholecystectomy; symptoms (back pain) during baseline	64	
Appendicitis	34F	12	358/132/8	Appendectomy	23	
Gallbladder dysfunction	38F	12	358/17/48	Laparoscopic cholecystectomy; history of chronic RUQ pain	71	
Cholelithiasis	37F	12	358/122/4	Laparoscopic cholecystectomy, elective surgery	61	
Esophagitis	33F	12	358/75/7	Hiatal hernia repair, elective surgery	70	
Abdominal surgery: open-label, long-term studies						
Ileus; small bowel obstruction	58F	12	209/28/6	Lysis of adhesions and reduction of "internal hernia;" prior history of hysterectomy and prior history of small bowel obstruction	183	
Cholelithiasis	68F	12	209/21/6	Laparoscopic cholecystectomy; epigastric and back pain	351	
Abdominal wall hernia	43F	12	307E1/759/1	Surgical repair of abdominal wall hernia	180	
Appendicitis	56F	12	301E1/155/3	Appendectomy	226	
Appendicitis	44F	4	301E1/114/1 9	Appendectomy	168	
Cholecystitis	43F	4	301E1/172/1	Laparoscopic cholecystectomy	155	
Gallbladder dysfunction ²	35F	12	209/24/13	Laparoscopic cholecystectomy; stomach discomfort and nausea	172	
Cholelithiasis; Biliary fistula ²	49F	4	209/28/31	Laparoscopic cholecystectomy, appendectomy; postoperative drainage of biloma; presented with chest pain	130	

Organ system/ adverse event	Age, Sex	Dose (mg/d)	Study/ Subject No.	Surgical procedure/ Comments	Day of sur- gery ¹	Vol # and Page
Abdominal surgery: open-label phase 4 studies						
Abdominal pain, jaundice, cholelithiasis ²	73M	12	— 29/1	ERCP with papillotomy, history of cholelithiasis	37	
Pelvic surgery: double-blind studies						
Uterine leiomyoma	43F	Placebo	358/61/23	Elective tubal ligation; laparotomy to repair tear in uterine wall, removal of fibroids, lysis of adhesions; prior history of myomectomy	89	
Tubal ligation	35F	Placebo	251/18/1	Elective tubal ligation and retropubic urethropexy	85	
Uterine leiomyoma	43F	Placebo	358/43/4	Hysterectomy and bilateral salpingo-oophorectomy; symptoms during baseline	80	
Endometriosis	36F	Placebo	358/64/4	Exploratory laparoscopy with lysis of adhesions; endometriosis	60	
Dysmenorrhea and menorrhagia	43F	4	307/792/7	Hysterectomy; prior history of dysmenorrhea and menorrhagia; multiple prior pelvic surgeries	37	
Peritubal cyst ³	37F	12	307/721/2	R-salpingo-oophorectomy, lysis of adhesions, appendectomy	143	
Ovarian cyst, appendicitis ³	13F	12	351/518/27	Appendectomy and removal of R ovarian cyst. Prior history of ovarian cyst surgery.	89	
Rt adnexa with cystic enlargement & adhesions	43F	12	358/76/24	Laparoscopy and subsequent laparotomy: bilateral salpingo- oophorectomy, lysis of adhesions and appendectomy. Symptoms during baseline with planned elective procedure	4	
Pelvic surgery: open-label, long-term studies						
Hysterectomy	31F	4	204/2/8	Hysterectomy; elective procedure; history of irregular menses	75	
Cystadeno- fibroma ³	50F	12	209/11/39	R oophorectomy; elective procedure	334	
Pelvic adhesions ³	46F	12	209/26/6	Bilateral salpingo-oophorectomy with lysis of adhesions and bladder repair for stress incontinence; history of hysterectomy	258	
Uterine adenomyosis; ovarian cyst ³	36F	12	209/28/4	Hysterectomy and bilateral salpingo-oophorectomy	306	
Uterine sarcoma	36F	4	301E1/114/1 3	Hysterectomy	212	
Fibroid uterus	50F	4	301E1/157/5	Hysterectomy, bladder neck suspension; elective surgery	83	
Urogenital prolapse	58F	12	307E1/749/3 9	Cystopexy	190	

¹ From start of study drug² New cases since December 2000 ISS update³ Adverse event from Table 5-19.3 of December 2000 ISS update

Table 6. Cholecystectomies and pancreatic disorders in individual patients in all studies.

Event	Age, Sex, (wt)	Dose (mg/d)	Study/ Subject No.	Comments	Day of surgery ¹	Prior biliary history ²	Presence of gallstones	Abnormal LFTs	Relationship with study drug	Completed study
Double-blind, placebo controlled studies										
Cholecystectomy	31F (158 lbs)	Placebo	358/112/22	Diagnosis of fatty liver; cholecystectomy 158 days after study	221	Yes	Yes	Yes	No	No
Cholecystectomy	51F (226 lbs)	12	351/524/1	Severe RUQ pain; normal ultrasound; abnormal HIDA scan	51	No	No	No	No	Yes
Cholecystectomy	38F (160 lbs)	12	358/17/48	Chronic RUQ pain with normal ultrasound 1 year prior to study; Day 48: Ultrasound normal; Biliary scan - reduced contractility	71	Yes	No	No	No	No
Cholecystectomy	54F (115 lbs)	12	358/23/29	RUQ pain during baseline; Day 2 ultrasound: gallstones	38	Yes	Yes	No	No	Yes
Cholecystectomy	30F (140 lbs)	12	358/52/15	History of chronic back pain with symptoms during baseline; Day 30 ultrasound: gallstones	64	Yes	Yes	Yes	No	No
Cholecystectomy	37F (142 lbs)	12	358/122/4	Cholelithiasis by ultrasound 1 year prior to study, deferred surgery at that time	61	Yes	Yes	No	No	Yes
Long-term open-label studies										
Cholecystectomy	68F (118 lbs)	12	209/21/6	Epigastric and back pain; Day 346 ultrasound: cholelithiasis; Cholecystectomy 13 days after completed study	351	No	Yes	Yes	Yes	Yes
Cholecystectomy	43F (112 lbs)	4	301E01/172/1	Diagnosis of cholecystitis. Prior history of cholelithiasis	155	Yes	Yes	No	No	Yes
Cholecystectomy ³	35F (208 lbs)	12	209/24/13	History of chronic stomach discomfort and nausea; normal ultrasound prior to study; Day 154 biliary scan with reduced ejection fraction. Persistent symptoms post-surgery	172	Yes	No	No	No	No

Event	Age, Sex, (wt)	Dose (mg/d)	Study/ Subject No.	Comments	Day of surgery ¹	Prior biliary history ²	Presence of gallstones	Abnormal LFTs	Relationship with study drug	Completed study
Cholecystectomy ³	49F (180 lbs)	4	209/28/31	Presented with chest pain; cardiac workup negative. Ultrasound showed gallstones; Underwent cholecystectomy with postoperative biloma requiring biliary stent for drainage	130	No	Yes	No	No	No
Phase 4 open-label studies										
ERCP with papillotomy ³	73M (167 lbs)	12	—/29/1	Present with abdominal pain and jaundice. Underwent ERCP with papillotomy. Ultrasound showed cholelithiasis 1 year prior	37	Yes	Yes	Yes	No	Yes
Other cases										
Pancreatitis	39F	Placebo	358/123/30	Abdominal pain	69	No	No	No	Yes	No
Pancreatic cyst	71F	4	301/112/9	Laparotomy with removal of benign cyst; no history of gallstones	36	No	No	No	No	Yes

¹ From start of study drug

² Symptoms attributed to gallbladder disease

³ New cases since December 2000 ISS update

**APPEARS THIS WAY
 ON ORIGINAL**

Before this application may be approved, however, it will be necessary for you to address concerns about the efficacy and safety of this drug, as follows:

1. Submit the results of a well-controlled, double-blind, randomized study of at least 300 persons per study arm and of at least 12 weeks duration. Assess drug efficacy in this study with the endpoints used in Study B301 entitled, "A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at two dose levels and placebo in subjects with constipation-predominant irritable bowel syndrome."
2. Provide safety data from the study requested above and from any additional studies for which safety data has not been previously submitted.
3. Submit the results of a study of the $5HT_4$ -receptor status of human appendix and non-gastrointestinal abdominal and pelvic organs compared to human intestinal samples.

APPEARS THIS WAY
ON ORIGINAL

We remind you of the following Phase 4 commitments agreed to in your August 3, 2000, submission:

1. A long-term (one year) maintenance study conducted in the U.S. in women with constipation-predominant IBS,
- []
3. An epidemiological study of a sufficient number of women administered the recommended regimen of tegaserod hydrogen maleate 6 mg b.i.d., to address concerns about the risk of laparotomies, ovarian cysts, and appendicitis.

APPEARS THIS WAY
ON ORIGINAL

**UPPER MANAGEMENT BRIEFING
(June 5, 2001)**

- 1) **What is the group's opinion of the efficacy of the drug?**
- 2) **Is there a safety signal with this drug?
If so, what is it?**
- 3) **What is the group's opinion re Risk/Benefit ratio?**
- 4) **Has the sponsor fulfilled the requirements stipulated in the
approvable letter of August 11, 2000.**

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Raymond Joseph
6/8/01 03:42:59 PM
MEDICAL OFFICER

Hugo Gallo Torres
6/8/01 04:22:17 PM
MEDICAL OFFICER

Signed for Lilia Talarico, .M.D., Division,s Director

The Medical Team Leader, Dr. Hugo E. Gallo-Torres, agrees with t
he Recommendations for Regulatory Action formulated by The Medical O
fficer Reviewer, Dr. RaymondJoseph..

**APPEARS THIS WAY
ON ORIGINAL**