

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

STATISTICAL REVIEW(S)

ADDENDUM TO THE STATISTICAL REVIEW

NDA#: 21-200 (response to an approvable letter)

SPONSOR: Novartis Pharmaceutical Corp.

DRUG: Zelmac (Tegaserod, 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate)

INDICATION: Treatment of _____ constipation in female patients with irritable bowel syndrome (IBS).

DOCUMENTS REVIEWED: document BM (letter date 4-25-01)

STATISTICAL REVIEWER: Sonia Castillo, Ph.D., HFD-715

This is an addendum to the statistical review dated April 27, 2001. Since the submission of the statistical review for NDA 21-200, the sponsor has provided information about the withdrawal period in response to a request made by the Division of Gastrointestinal and Anticoagulant Drug Products.

Following the double-blind treatment period, subjects entered a 4-week withdrawal period during which no study medication was given. The application initially included a brief discussion and graphs for the following ten withdrawal period comparisons:

- (1) Weekly proportion of patients with at least somewhat relief (used SGA of relief definition only)
- (2) Weekly proportion of patients with complete/considerable relief (used SGA of relief definition only)
- (3) Weekly change from baseline in score of SGA of abdominal discomfort/pain
- (4) Weekly change from baseline in score of SGA of bowel habit
- (5) Weekly change from baseline in score of SGA of satisfaction with bowel habit
- (6) Weekly responder rate for SGA of satisfaction with bowel habit (positive response, is a weekly score of at least "somewhat satisfied")
- (7) Weekly change from baseline in mean of daily abdominal discomfort/pain score
- (8) Weekly change from baseline in mean of daily bloating score
- (9) Weekly change from baseline in number of bowel movements
- (10) Weekly change from baseline in mean of daily stool consistency

According to the sponsor, the results for the above comparisons show that the tegaserod and placebo groups were not different during the withdrawal period. In addition, for both treatment groups, there was a loss of effect in the first withdrawal week, which continued to decline over the second and third weeks, and then stabilized over weeks 3 and 4.

The current response from the sponsor for the withdrawal period contains the tabular data used to generate the graphs, the same graphs as submitted previously, and no additional discussion for the ten comparisons. Further statistical comment is not necessary.

**APPEARS THIS WAY
ON ORIGINAL**

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DRUG CLASS: 1P

INDICATION: Treatment of _____ constipation in female patients with irritable bowel syndrome (IBS).

DOCUMENTS REVIEWED: Volumes 2.1, 2.3 to 2.16.

DATES: **Date received by Medical Division, HFD-180:** December 18, 2000
 User Fee Date: June 18, 2001

MEDICAL REVIEWER: Raymond Joseph, M.D., HFD-180

STATISTICAL REVIEWER: Sonia Castillo, Ph.D., HFD-715

**APPEARS THIS WAY
ON ORIGINAL**

Key words: clinical studies, NDA review, covariate.

Study HTFB 358: A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Tegaserod 12 mg/d and Placebo in Females with Constipation-predominant Irritable Bowel Syndrome (C-IBS)

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**APPEARS THIS WAY
ON ORIGINAL**

1 INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder having a broad range of symptom severity, from mild to severe and intractable symptoms. IBS is characterized by recurrent abdominal pain and discomfort associated with alterations in bowel habit. Changes in gastrointestinal motility, visceral perception, and psychosocial factors contribute to the overall symptom expression.

Tegaserod is a selective agonist at 5-HT₄ receptors. Activation of 5-HT₄ receptors is considered to be a trigger for the peristaltic reflex and motor activity of the entire gastrointestinal tract. The sponsor has investigated the effects of tegaserod on gut motility, intestinal secretion, and visceral sensitivity in healthy volunteers and in patients with constipation predominant IBS (C-IBS). From these investigations the sponsor has hypothesized that the enhancement of small bowel transit may relieve the symptoms of C-IBS.

This submission is a response to an approvable letter. The initial NDA submission for this product (February 14, 2000) consisted of three Phase 3 clinical trials (Study 301, Study 307, and Study 351). The statistical review resulted in the following:

- Study 351 used post-hoc exploratory analyses to demonstrate efficacy. The Division of Gastrointestinal and Anticoagulant Drug Products deemed Study 351 exploratory and not persuasive as evidence of efficacy.
- Study 307 did not demonstrate efficacy.
- Study 301 demonstrated efficacy only in female patients with C-IBS.

To gain marketing approval, the Division requested that the sponsor submit the results of a well-controlled, double-blind, randomized study of at least 300 female patients with C-IBS per study arm and of at least 12 weeks duration. The sponsor was to assess drug efficacy in this study with the endpoints used in Study 301 with the intention of replicating the results of Study 301.

This statistical review of the NDA for tegaserod evaluates the data intended to provide evidence of efficacy by replicating the results from Study 301 and support approval of the application. The review describes the study conduct, efficacy data collected, the sponsor's efficacy analyses and results, the statistical reviewer's evaluation of the studies and the sponsor's analyses, the statistical reviewer's efficacy analyses, comparison with Studies 301 and 307, and conclusion. Safety is not addressed in the statistical review but is assessed in the clinical review.

The sponsor has proposed the following indication for their product, Tegaserod:

Tegaserod maleate is indicated for the treatment _____ constipation in female patients with irritable bowel syndrome (IBS).

2 DESCRIPTION OF STUDIES

The sponsor submitted one Phase 3 study, Study 358. The primary objective of the study was to determine the efficacy of tegaserod 12 mg/d by comparison to placebo as measured by the Subject's Global Assessment (SGA) of relief. There were 25 secondary objectives including the determination of efficacy as measured by the weekly SGA of abdominal discomfort/pain, weekly SGA of bowel habit, and weekly SGA of satisfaction with bowel habit.

2.1 Study Design

This is a 20-week, prospective, double-blind, placebo-controlled, parallel group, multicenter study in female patients with constipation-predominant irritable bowel syndrome (C-IBS). The study consists

of a 4-week baseline period (no medication), a 12-week randomized double-blind treatment period with either tegaserod 12 mg/d, and then followed by a 4-week withdrawal period (no medication). This review does not address the withdrawal period. The target enrollment for entry into the randomized double-blind phase is 1528 intent to treat patients in approximately 135 centers. Table 2.1 presents an overview of the design of the Phase 3 study.

Table 2.1
Overview of Phase 3 Study 358

Study No.	No. of Centers in ITT [#] Population	Design*	Treatment Groups	ITT Sample Size (n)	ITT Subgroups (n): a) Male/Female b) White/Black/Oth
358	135	MC,R,DB, PC,PG	12 mg/d tegaserod placebo	767 752 Total – 1519	a) 0 / 1519 b) 1175 / 248 / 96

* MC: Multicenter; R: Randomized; DB: Double-blind; PC: Placebo control; PG: Parallel Group.

[#] ITT: intent-to-treat

Patients entered, via a touch-tone telephone data entry system, all baseline and post randomization information into the database. Following a 4-week baseline period, eligible patients were randomized, in equal allocation (764 patients per treatment group), to receive either placebo or 12 mg/d tegaserod. Eligible patients were female (non-pregnant and non-lactating) patients aged 18 years or older with constipation predominant irritable bowel syndrome (C-IBS). Following a 4-week baseline period, patients who met the following 5 criteria were randomized into the 12 week treatment period:

- had 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;
- had a mean stool consistency score of > 3.5 during the baseline period;
- had the SGA or relief of weeks –4, -3, -2, and –1 qualified for “non-response”, i.e., complete or considerable relief less than or equal to 50% of the weeks or at least somewhat relief less than 100% of the weeks during the baseline period;
- did not use disallowed medication affecting gastrointestinal motility and/or perception on more than 4 days during the baseline period.
- In addition, patients during the baseline period who failed to record at least 11 of 14 days of daily self assessments and/or both weekly assessments in the last 2 week of the baseline period or who used disallowed medication affecting GI motility and/or perception on more than 4 days during the baseline period were excluded from the double-blind treatment period.

Using the patients’ baseline assessments on the touch-tone telephone system, qualified patients were assigned a randomization number if they met the randomization criteria. Each center received one or more blocks of consecutive medication numbers. Patients were allocated the next available randomization number in each center via the touch-tone telephone system.

Patients took 6 mg tegaserod tablets b.i.d. or placebo tablets b.i.d. with water within 30 minutes prior to meals in the morning and evening. Concomitant laxative use was not allowed during the study, unless requirements for rescue use were met (i.e., no bowel movement for 4 consecutive days associated with highly bothersome abdominal discomfort/pain or bloating/distension). Bulk-forming agents were allowed provided they had been taken at constant doses for at least one month prior to study entry and if the dose remained stable during study. Patient clinical visits were monthly.

2.2 Efficacy Outcomes

The patient recorded all daily and weekly efficacy assessments via a touch-tone telephone data entry system. Four weekly assessments (Subject Global Assessments of relief, abdominal discomfort/pain, bowel habit, and satisfaction with bowel habit) and 5 daily (intensity of abdominal pain/discomfort,

intensity of bloating, frequency of bowel movements, average stool consistency, and straining) assessments were made by the patient throughout the duration of the study.

2.2.1 Subject Global Assessment (SGA) of Relief

Patients responded weekly to the following question:

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

Answers were: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse.

2.2.2 Subject Global Assessment of Abdominal Discomfort/Pain

Patients responded weekly to the following question:

How bothersome was your abdominal discomfort and pain over the past week?

Answers from a 7-point scale were: 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, and 6 = a very great deal.

2.2.3 Subject Global Assessment of Bowel Habit

Patients responded weekly to the following question:

How bothersome was your constipation over the past week?

Answers from a 7-point scale were: 0 = not at all, 1 = hardly, 2 = somewhat, 3 = moderately, 4 = a good deal, 5 = a great deal, and 6 = a very great deal.

2.2.4 Subject Global Assessment of Satisfaction with Bowel Habit

Patients responded weekly to the following question:

How satisfied were you with your bowel habits over the past week?

Answers from a 4-point scale were: 1 = very satisfied, 2 = somewhat satisfied, 3 = somewhat dissatisfied, 4 = very dissatisfied.

2.2.5 Daily Bowel Habit Information

Patients recorded on a daily basis the following bowel habit information:

- intensity of abdominal discomfort/pain (7-point scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe)
- intensity of abdominal bloating (7-point scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe)
- number of bowel movements (if the number of bowel movements was zero, the question on stool consistency was omitted)
- average daily stool consistency (7-point scale: 1 = watery, 2 = loose, 3 = somewhat loose, 4 = neither loose nor hard, 5 = somewhat hard, 6 = hard, 7 = very hard)
- episode of straining (1 = yes, 2 = no)

2.3 Protocol amendments

The one amendment made to the protocol, 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 301
- 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 end of study for all secondary weekly assessments instead of absolute scores.
- Added a weekly analysis for change from baseline for all secondary assessments.

2.4 Efficacy Analysis

All primary efficacy statistical tests were two-sided and performed at the 0.05 significance level. The intent-to-treat (ITT) population, defined as all patients randomized and treated, was the primary population. All analyses for the SGAs used the last 4 available weekly SGA responses in the post-randomization period or all weekly responses if fewer than 4 weekly scores were available. Primary analyses for the diary data used the daily scores obtained in the last 28 days post-randomization or all daily scores obtained in the diary if fewer than 28 days were available. Data were also analyzed for the primary analyses for two other populations: the per-protocol population and the completed population. This review will focus on the ITT population because it was the protocol specified population for efficacy analyses.

2.4.1 Sample Size

A total of 1528 patients (764 per treatment group) were planned to be randomized into the double blind portion of the study. Assuming 33% placebo response rate for the SGA of relief, based on a two-sided chi-squared test, a sample size of 764 per group was considered sufficient to detect an 8% treatment difference with 90% power at the 2-sided significance level of 0.05.

2.4.2 Background and demographic characteristics

The analysis of the demographic and disease background of IBS used the following protocol specified variables:

Demographic - Age, body weight, and race (white, black, other)
Any past/current medical conditions
Smoker

IBS disease background - Duration of main symptoms of IBS
Baseline values for all efficacy variables
Use of bulking agents during the last 28 days of the run-in period

In addition, an extra variable, not per protocol, was added for the analysis of IBS disease background:
Use of laxatives during the last 28 days of the run-in period

These variables were summarized by treatment. A t-test or chi-square test was performed to assess the baseline comparability between the two treatment groups.

2.4.3 Pooling of Centers for Analysis

Pooled centers were used in any Mantel-Haenszel test that was stratified by center. Centers were pooled to ensure the pooling criteria (treatment row totals ≥ 2 and response column totals ≥ 1) were fulfilled for the primary variable in all three of the following data sets: ITT population, PP population, and all completed patients:

- 2*2 tables were created for each center, with the two treatment groups as row headers and the response status for SGA of relief (yes/no) as column headers.
- Centers were sorted by center size and center number in ascending order. Centers with a treatment row total < 2 or a response column total < 1 were placed at the top, by center size and center number.
- Centers were pooled sequentially by the sorting order in the same country category until fulfilling the pooling criteria.

The sets of centers after pooling were used as strata in the analysis of the primary variable.

2.4.4 Primary Endpoint: Subject Global Assessment of Relief

The primary efficacy variable was response for SGA of relief (yes/no). The definition of responder was defined as follows:

- At least 50% of the SGAs with complete or considerable relief OR
All of the SGAs with at least somewhat relief (i.e. complete, considerable or somewhat)
- Number of days with laxative use during treatment period ≤ 5 and no laxative use during the last 28 days of treatment (with the exception of bulk-forming laxatives)

- Duration of exposure to study medication ≥ 28 days
- At least one post-baseline SGA of relief

Note that laxative use, duration of exposure to treatment, and missing SGA of relief data are accounted for in the definition of a responder for the new SGA of relief. For the remainder of this review, these three variables will be referred to as the accounting criteria.

The primary null hypothesis H_0 is:

There is no difference in proportion of responders for SGA of relief between tegaserod 12 mg and placebo.

Versus the alternative hypothesis H_1 :

There is a difference in proportion of responders for SGA of relief between tegaserod 12 mg and placebo.

For the primary efficacy analysis, the Mantel-Haenszel test stratifying by center was used to compare the tegaserod versus placebo at the 0.05 significance level. According to the protocol:

“If it is evident that the response for SGA of relief is confounded with some of the background variables, then non-parametric analysis of covariance described in Koch, G. et al may be performed as an exploratory analysis, using the background variable(s) as covariate(s). Other analyses, such as logistic regression analysis, may also be performed as appropriate.”

The primary efficacy variable was summarized by age group (<65 , ≥ 65 years) and by race (white, black, other). In addition, the sponsor provided various monthly (did not take laxative use into account) and five “supplemental” analyses for SGA of relief (4 of these 5 analyses did not take laxative use into account; and the longitudinal analysis was not as specified in the protocol). This review does not present these analyses because the Division has repeatedly requested the sponsor to take laxative use into account for all analyses from the double blind treatment period.

2.4.5 Secondary Endpoints

Twenty-five secondary efficacy variables were analyzed:

- (1) Change from baseline in mean score of SGA of abdominal discomfort/pain by month
- (2) Change from baseline in mean score of SGA of abdominal discomfort/pain at study end
- (3) Weekly change from baseline in score of SGA of abdominal discomfort/pain
- (4) Change from baseline in mean score of SGA of bowel habit by month
- (5) Change from baseline in mean score of SGA of bowel habit at study end
- (6) Weekly change from baseline in score of SGA of bowel habit
- (7) Change from baseline in mean score of SGA of satisfaction with bowel habit by month
- (8) Change from baseline in mean score of SGA of satisfaction with bowel habit at study end
- (9) Weekly change from baseline in score of SGA of satisfaction with bowel habit
- (10) Response for SGA of satisfaction with bowel habit by month (positive response, if the patient had at least “somewhat satisfied” in at least 50% of the assessments)
- (11) Response for SGA of satisfaction with bowel habit at study end
- (12) Weekly responder rate for SGA of satisfaction with bowel habit (positive response, if the weekly score was at least “somewhat satisfied”)
- (13) Weekly change from baseline in mean of daily abdominal discomfort/pain score
- (14) Change from baseline in mean of daily abdominal discomfort/pain at study end
- (15) Percent change from baseline to study end in number of days with significant pain
- (16) Percent change from baseline to study end in number of bowel movements.
- (17) Weekly change from baseline in mean of daily bloating score
- (18) Change from baseline in mean daily bloating score at study end
- (19) Percent change from baseline to study end in number of days with significant bloating
- (20) Weekly change from baseline in number of bowel movements
- (21) Percent change from baseline to study end in number of days without bowel movements
- (22) Weekly change from baseline in mean of daily stool consistency
- (23) Change from baseline in mean of daily stool consistency at study end
- (24) Percent change from baseline to study end in number of days with hard/very hard stool
- (25) Percent change from baseline to study end in number of days with straining

Between treatment comparison for the dichotomous variables was analyzed using the Mantel-Haenszel test stratified by center, and the numeric variables were analyzed using an Extended Mantel-Haenszel test stratified by center (using modified ridit scores). The tests used a two-sided significance level of 0.05.

Since the purpose of this study is to provide replication of the results in Study 301, analyses of the 25 secondary variables listed above are not presented in this review because of the following four reasons:

- SGA of abdominal discomfort/pain and SGA of bowel habit did not describe what qualified a patient as a responder, as was done for the patients in Study 301
- All the SGA variables listed above did not use the three accounting criteria (laxative use, duration of exposure to treatment, and missing SGA data) in the primary analyses as in Study 301
- All 25 variables did not take laxative use into account in the weekly and study end analyses
- For the mean change variables, no description of a clinically meaningful difference was presented

In addition, post-hoc analyses (not per protocol) of SGA of abdominal discomfort/pain, SGA of bowel habit, daily abdominal discomfort/pain score, and daily bloating score were analyzed monthly in terms of various improvement from baseline criteria. This review will not present any of these analyses because they did not take laxative use into account.

3 RESULTS OF STUDY 358

This section presents information about Study 358 and the sponsor's results and conclusions.

3.1 Patient and Study Site Information

3.1.1 Patient Enrollment and Disposition

Table 3.1 presents a summary of the patient enrollment and disposition. The number of randomized patients in the ITT population is 1519 patients (767 tegaserod and 752 placebo). Also, of the total 3177 patients enrolled, 1658 patients (47.8%) were not randomized.

Table 3.1
Study 358: Summary of Patient Enrollment and Disposition

Population	Total
Number of Patients Enrolled	3177
Number (%) of Patients Not Randomized	1658 (52.2)
Number of Patients Randomized	1519
Number of Patients in ITT Population	1519
Number (%) of Patients Who Completed Study*	1200 (79.0)
Number (%) of Patients Who Did Not Complete Study*	319 (21.0)
Reasons for Not Completing:	
Patient withdrawal of consent	116 (7.6)
Adverse Events	88 (5.8)
Lost to Follow-up	55 (3.6)
Unsatisfactory therapeutic effect	41 (2.7)
Abnormal lab values	9 (0.6)
Administrative problems	7 (0.5)
Protocol violation	2 (0.1)
Patient's condition no longer required drug	1 (0.1)

Source: Tables 7-1 and 7-2, Vol. 2.3, page 8-40; and Vol. 2.7, page 8-392.

* Percentage is with respect to the number of randomized patients.

Of the patients randomized to treatment, 21% of patients discontinued during the 12 week treatment period. The most common reasons for discontinuation were patient withdrawal of consent (7.6%) and adverse events (5.8%).

3.1.2 Number of Centers and Number of ITT Patients by Country

Table 3.2 presents the number of centers and the number patients in the intent to treat population for each state. There was one principal investigator at each center in each study. All centers were located in the United States. Per protocol, all centers were to randomize a minimum of 10 patients each. This was not achieved at all centers. Of the 127 centers in the ITT population, 59 centers (46.5%) randomized less than 10 patients each and 68 centers (53.5%) randomized at least 10 patients each.

Table 3.2
Number of Patients by State in the ITT Population

State	# of Centers	N	Number Randomized (n)		Center Size (Min, Max)
			Tegaserod	Placebo	
Alabama	4	37	19	18	(3, 16)
Arizona	3	20	11	9	(3, 10)
California	14	162	82	80	(2, 40)
Colorado	4	89	45	44	(20, 25)
Florida	16	137	69	68	(4, 16)
Georgia	3	44	21	23	(4, 25)
Illinois	7	107	54	53	(5, 28)
Indiana	3	28	15	13	(1, 16)
Iowa	1	16	8	8	16
Kansas	2	19	10	9	(3, 16)
Louisiana	2	31	16	15	(3, 28)
Massachusetts	2	24	12	12	(4, 20)
Maryland	3	47	23	24	(7, 32)
Michigan	3	24	12	12	(4, 11)
Montana	2	16	8	8	(6, 10)
North Carolina	7	142	71	71	(10, 27)
New Jersey	1	15	8	7	15
New Mexico	2	30	15	15	(6, 24)
New York	5	30	15	15	(2, 9)
Ohio	6	44	23	21	(3, 12)
Oklahoma	5	65	32	33	(8, 16)
Oregon	1	12	6	6	12
Pennsylvania	4	14	8	6	(3, 4)
Rhode Island	2	13	7	6	(4, 9)
Tennessee	6	112	56	56	(5, 35)
Texas	11	142	71	71	(2, 23)
Virginia	3	52	26	26	(7, 34)
Washington	4	44	23	21	(9, 12)
Wisconsin	1	3	1	2	3
Total	127	1519	767	752	

Source: Statistical Reviewer's listing.

3.1.3 Patient Demographics

Table 3.3 presents a summary of the patient demographics for the ITT population by treatment. All patients were female, the majority of patients were white (>75%), the majority of the patients were less than 65 years old (>96%), and the mean duration of IBS symptoms was about 16 years. Also, demographic variables were comparable between treatment groups.

Table 3.3
Study 358: Demographics and Baseline Characteristics for ITT Population

	Tegaserod N=767	Placebo N=752
Gender – n (%)		
Female	767 (100.0)	752 (100.0)
Race – n (%)		
White	589 (76.8)	586 (77.9)
Black	127 (16.6)	121 (16.1)
Other	51 (6.6)	45 (6.0)
Age (years) – n (%)		
< 65	744 (97.0)	725 (96.4)
≥ 65	23 (3.0)	27 (3.6)
Duration of IBS symptoms (months)		
Months: Mean (SD)	192.5 (145.8)	195.3 (154.7)
Years: Mean (SD)	16.0 (12.2)	16.3 (12.9)

Source: Table 7-3, Vol. 2.3, page 8-42.

3.2 Sponsor's Efficacy Results

All efficacy results are for the ITT population.

3.2.1 Primary Efficacy: Subject Global Assessment of Relief

The Subject Global Assessment (SGA) of relief definition of responder was: “completely relieved” or “considerably relieved” for at least 50% of the last 4 weeks of treatment, or at least “somewhat relieved” for all of the last 4 weeks of treatment. The responder rate also took into account laxative use, duration of treatment, and patients with no SGA assessments. Patients who did not meet all accounting criteria were classified as non-responders. The data were analyzed using a covariate adjusted Mantel-Haenszel statistic using baseline laxative use as the covariate and stratified by center.

The result for SGA of relief is presented in Table 3.4 and is as follows:

- The tegaserod treatment group had a larger responder rate compared to the placebo group. The treatment difference was 5.3%, which was statistically significant.

Table 3.4
Study 358: Subject Global Assessment of Relief

	Tegaserod	Placebo
Study 358 (N=1519)		
Responder Rate % (n)	43.5 (767)	38.8 (752)
Difference ¹	5.3	
p-value ²	0.033*	

Source: Table 9-1, Vol. 2.3, page 8-47.

¹ Difference is weighted by center size.

² p-value based on a covariate adjusted Mantel-Haenszel statistic using baseline laxative use as the covariate and stratified by center.

* Statistically significant at the 0.05 significance level.

The summary, not statistical analysis, of the primary efficacy variable by age group (<65, ≥65 years) and by race group (white, black, other) gave the following results:

- The responder rates for patients <65 years old and Caucasians were almost identical to those observed in the ITT population, since these subgroups made up the majority of the patient population.
- Only 3% of the patients in the study were ≥65 years old, not allowing for any meaningful comparisons in this subgroup.
- Approximately 16% of the patient population were black. Response rates were similar in the tegaserod (43.3%) and placebo groups (42.1%) among black patients.

3.3 Sponsor Conclusions

The sponsor concludes the following:

- Tegaserod 12 mg/d was effective in relieving overall IBS symptoms, and in improving abdominal discomfort and pain, bloating and altered bowel habits.

4 REVIEWER'S ANALYSES AND CONCLUSION

This section presents the reviewer's analyses, comparison of 3 studies (301, 307, 358), and conclusion. Analysis of the primary efficacy variable of SGA of relief uses a different pooling algorithm than is used by the sponsor. In addition, the analysis uses a Mantel-Haenszel statistic stratified by state with no covariable adjustment.

The sponsor used an algorithm for pooling centers to use sets of centers after pooling as the stratification variable in the Mantel-Haenszel efficacy analyses (see Section 2.4.2). In this algorithm, centers were pooled to ensure the pooling criteria (treatment row totals ≥ 2 and response column totals ≥ 1) were fulfilled.

This algorithm for pooling centers is not appropriate because it was based on the number of responders and non-responders for the primary efficacy variable after the blind was broken. Using the response column totals as a criterion for pooling after the blind is broken could potentially bias the results of the analyses. Given that a large number of centers did not recruit the protocol specified minimum of 10 ITT patients per center (see Section 3.1.3), the reviewer instead pooled all centers within a state and used state as the stratification variable in the Mantel-Haenszel analyses. The differences in responder rates are based on the weighted average of the responder rate. The weight for state k is proportional to $(1/n_{k1} + 1/n_{k2})^{-1}$, where n_{ki} is the number of patients in the i^{th} treatment group in state k .

4.1 Rationale for Not Using the Covariate Adjusted Primary Efficacy Analysis

The protocol states that: 1) the primary analysis for the between treatment comparison is the Mantel-Haenszel statistic stratified by center without covariate adjustment, and 2) a covariate adjusted Mantel-Haenszel statistic stratified by center may be performed as an *exploratory analysis* if it is evident that the response for SGA of relief is confounded with some of the background variables. These background variables, as listed in the protocol, are: duration of main symptoms of IBS, baseline values for all efficacy variables, and baseline use of bulking agents.

The sponsor does not present the protocol specified unadjusted analysis in the study report and instead presents the covariate (baseline laxative use) adjusted analysis. The protocol specified unadjusted analysis is presented in an appendix; which is shown in Table 4.1. The unadjusted analysis did not reach statistical significance ($p=0.059$).

Table 4.1
Study 358: Study 358: Sponsor's Analysis Stratifying by Center
Subject Global Assessment of Relief Unadjusted for Baseline Laxative Use

	SGA of Relief	
	Tegaserod	Placebo
Responder Rate % (n)	43.5 (767)	38.8 (752)
Difference ¹ (se)	4.8 (2.6)	
p-value ²	0.059	

Source: Appendix 5 Table 1-2, Vol. 2.7, page 8-166.

¹ Difference is the weighted difference of responder rates between the active treatment group and placebo group. The weights used are for each center and the weight for a center is proportional to the number of patients in each treatment group.

² Nominal p-value based on the Mantel-Haenszel test stratified by center.

A post-hoc search for a variable to serve as a covariate was done. Upon the examination of 15 baseline variables (consisting of both demographic and background variables) by the sponsor, use of laxative during baseline was the only baseline variable that had an imbalance between the two treatment groups ($p=0.011$). The sponsor justified the selection of baseline laxative use as the covariate based on it having a statistically significant difference between the treatment groups and it confounding the response to SGA of relief. The addition of baseline laxative use as a covariate to the analysis resulted in changing a non-significant primary efficacy result to a significant result ($p=0.033$). The sponsor's use of the term "confounding" is not appropriate in the context of randomized trials. Randomization assures that the tegaserod and placebo groups are roughly comparable on average. Any difference would occur entirely by chance and not in a systematic manner as implied when confounding occurs.

Baseline laxative use was not prespecified in the protocol as a background variable for consideration, yet the sponsor states in the study report that it is a clinically and statistically important factor to consider. The ICH E9 Document: Statistical Principles for Clinical Trials and the Koch, G. et al article cited by sponsor state the importance of specifying covariables in the protocol prior to unblinding the data. In addition, baseline laxative use was not cited as an important factor in the protocols for either Study 301 or 307.

Given the information above, the statistical reviewer does not consider the covariate adjusted analysis appropriate to demonstrate efficacy. Instead, the protocol specified primary analysis unadjusted for covariates is what should be used to demonstrate efficacy. The protocol specified analysis was performed first, gave a non-significant result, and thus used up all of the type I error (α). Once the additional analysis was performed, multiplicity became an issue, and adjusting the p-value for each test needed to be done to determine if either test was significant. Using Hochberg's step-up procedure, the adjusted p-values for the protocol specified and new analyses are both 0.059, neither of which is significant.

4.2 Primary Efficacy Analysis: Subject Global Assessment of Relief

The result for SGA of relief in the ITT population is presented in Table 4.2 and is as follows:

- The tegaserod treatment group had a larger responder rate compared to the placebo group. The treatment difference was 4.7%, which was not statistically significant.

Table 4.2
Study 358: Reviewer's Analysis Stratifying by State
Subject Global Assessment of Relief Unadjusted for Baseline Laxative Use

	SGA of Relief	
	Tegaserod	Placebo
Responder Rate % (n)	43.6 (767)	38.8 (752)
Difference ¹ (se)	4.7 (2.5)	
p-value ²	0.062	

Source: Statistical reviewer's table.

¹ Difference is the weighted difference of responder rates between the active treatment group and placebo group. The weights used are for each state and the weight for a state is proportional to the number of patients in each treatment group.

² p-value based on the Mantel-Haenszel test stratified by state.

Since the ITT population included about 17% black patients, the Medical Reviewer deemed that results for SGA of relief by race would be clinically relevant. The results for SGA of relief in a subgroup analysis by race are presented in Table 4.3 and are as follow:

- The tegaserod treatment group had a larger responder rate compared to the placebo group in white patients. The treatment difference was 5.2%, which was not statistically significant.

- The tegaserod treatment group had a larger responder rate compared to the placebo group in black patients. The treatment difference was 1.1%, which was not statistically significant.
- The tegaserod treatment group had a larger responder rate compared to the placebo group in patients who were neither White nor Black. The treatment difference was 6.5%, which was not statistically significant.

Table 4.3
Study 358: Subject Global Assessment of Relief by Race

	SGA of Relief	
	Tegaserod	Placebo
White (n=1175)		
Responder Rate % (n)	42.9 (589)	37.7 (586)
Unweighted Difference ¹	5.2	
p-value ²	0.073	
Black (n=248)		
Responder Rate % (n)	43.3 (127)	42.2 (121)
Unweighted Difference ¹	1.1	
p-value ²	0.406	
Other (n=96)		
Responder Rate % (n)	50.9 (51)	44.4 (45)
Unweighted Difference ¹	6.5	
p-value ²	0.513	

Source: Statistical reviewer's table.

¹ Difference is the unweighted difference of responder rates between the active treatment group and placebo group.

² p-value based on the Mantel-Haenszel test stratified by state.

4.1.2 Reviewer's Conclusions

Based on the SGA of relief, a treatment effect is not demonstrated for tegaserod 12 mg/d.

4.2 Comparison of Results for Studies 301, 307, and 358

This section presents the reviewer's comparison of the primary efficacy variable of SGA of relief results for Studies 301, 307, and 358. The ITT population analyses are presented.

4.2.1 Patient Distribution by Country

Table 4.4 presents the number of female patients by country for the three Phase 3 studies submitted to this application. The patients in Study 301 were primarily from Europe and South Africa (91.7%), in Study 307 the patients were primarily from the United States (67.9%), and in Study 358 the patients were all from the United States.

Table 4.4
Studies 301, 307, and 358: Number of Female Patients by Country

Country	Study 301 n (%)	Study 307 n (%)	Study 358 n (%)
United States	40 (8.3)	315 (67.9)	1519 (100.0)
Europe / South Africa	444 (91.7)	-	-
Europe / Canada	-	149 (32.1)	-
Total	484	464	1519

Source: Statistical reviewer's table.

**APPEARS THIS WAY
ON ORIGINAL**

4.2.2 Primary Efficacy: Subject Global Assessment of Relief

The results for SGA of relief in females from the three Phase 3 studies submitted to this application are presented in Table 4.5 and are as follow:

Study 301:

- Female patients had a higher response rate compared to the placebo group. The treatment difference was 12% in the 12 mg/d group, which was statistically significant.

Study 307:

- Female patients had a higher response rate compared to the placebo group. The treatment difference was 5% in the 4-12 mg/d titration group, which was not statistically significant.

Study 358:

- Female patients had a higher response rate compared to the placebo group. The treatment difference was 5% in the 12 mg/d group, which was not statistically significant.

Table 4.5
Studies 301, 307, and 358: Subject Global Assessment of Relief for Females

	12 mg/d or 4 to 12 mg/d Tegaserod	Placebo
Study 301 (n=484)		
Responder Rate % (n)	38.9 (244)	27.5 (240)
Difference (se) ¹	11.8 (4.3)	
p-value ^{3,4}	0.012*	
Study 307 (n=464)		
Responder Rate % (n)	42.7 (232)	37.5 (232)
Difference (se) ¹	4.8 (4.6)	
p-value ^{3,4}	0.570	
Study 358 (n=1519)		
Responder Rate % (n)	43.6 (767)	38.8 (752)
Difference (se) ²	4.7 (2.5)	
p-value ³	0.062	

Source: Statistical reviewer's table.

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 A weighted Difference is the weighted difference of responder rates between the active treatment group and placebo group. The weights used are for each state and the weight for a state is proportional to the number of patients in each treatment group.

³ Nominal p-value based on Mantel-Haenszel test stratified by country in Studies 301 and 307 and based on Mantel-Haenszel test stratified by state in Study 358.

⁴ p-value adjusted using Hochberg's multiple comparison procedure.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

Note: Six patients are not included in the ITT population of Study 307.

Three further observations about the three studies are as follow:

- The placebo response rate in Studies 307 and 358, which were predominately conducted in patients from the United States, are similar (37.5% and 38.8%, respectively) and larger than the placebo response rate in Study 301 which was primarily conducted in patients from Europe/S. Africa (27.5%).
- The difference in responder rates in Studies 307 and 358 were similar (4.8% and 4.7%, respectively) and less than half as large as the difference in responder rates in Study 307 (11.8%).
- The results of Study 307 are replicated in Study 358.

4.2.3 Reviewer's Conclusions for the Three Studies Submitted to the Application

In female patients, based on the SGA of Relief, a treatment effect is demonstrated in Study 301 but not replicated in Studies 307 and 358 for tegaserod 12 mg/d.

4.3 Reviewer's Overall Conclusion

From a statistical standpoint, the sponsor has provided three studies that are well controlled but not adequate to show evidence for efficacy in support of their proposed claim for treatment of _____ constipation in female patients with irritable bowel syndrome (IBS). The sponsor has provided one adequate and well-controlled study that shows a treatment effect in female patients with constipation predominant irritable bowel syndrome (based on a global assessment of relief that incorporates overall well-being, symptoms of abdominal discomfort and pain, and bowel habit). The remaining two studies do not replicate this result.

**APPEARS THIS WAY
ON ORIGINAL**

ADDENDUM TO THE STATISTICAL REVIEW

COPY AUG 8 2000

NDA#: 21-200

SPONSOR: Novartis Pharmaceutical Corp.

DRUG: Zelmac (Tegaserod, 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate)

INDICATION: Treatment of irritable bowel syndrome _____
constipation as their predominant symptoms.

STATISTICAL REVIEWER: Sonia Castillo, Ph.D., HFD-715

This is an addendum to the statistical review dated July 6, 2000. Since the submission of the statistical review for NDA 21-200, there have been further discussions within the Division of Gastrointestinal and Anticoagulant Drug Products and the Office of Biostatistics about what was presented and discussed in the Gastrointestinal Drugs Advisory Committee Meeting of June 26, 2000. Based on these discussions, some additional recommendations follow.

The initial statistical review stated that "... a treatment effect is demonstrated in female patients with constipation predominant irritable bowel syndrome (based on a global assessment of relief that incorporates overall well-being, symptoms of abdominal discomfort and pain, and bowel habit) in one study and supported in a post-hoc analysis of a second study but not replicated in a third study ..."

The phrase "supported in a post-hoc analysis of a second study" was used to describe what was done in study B351 to provide information useful in the design of studies B301 and B307. Since the aim of the post-hoc analysis of study B351 was to provide information useful in the design studies B301 and B307, I view this as being exploratory and as not being pivotal or providing replication of the study results seen in study B301. If study B351 were to be used to support study B301, then I would use the original protocol specified analyses. These protocol specified analyses do not give results that are favorable to either dose.

To further clarify my recommendation, the sponsor has provided one adequate and well-controlled study that demonstrates a treatment effect in female patients with constipation predominant irritable bowel syndrome (based on a global assessment of relief that incorporates overall well-being, symptoms of abdominal discomfort and pain, and bowel habit). The remaining two studies do not replicate this result.

Given that C-IBS is not a life threatening condition and is not a clearly classified condition, replication of efficacy in females would need to be demonstrated in another clinical study.

/S/ 8-8-00

Sonia Castillo, Ph.D.
Mathematical Statistician, HFD-715

Concur:

/S/ 8/8/00
Ed. Nevius, Ph.D.
Division Director

/S/ 8/8/00
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NDA 21-200
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HFD-715/File Copy/E. Nevius/M. Welch/T. Permutt/S. Castillo

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-200

JUL 6 2000

SPONSOR: Novartis Pharmaceutical Corp.

DRUG: Zelmac (Tegaserod, 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate)

DRUG CLASS: 1P

INDICATION: Treatment of irritable bowel syndrome _____
_____ constipation as their predominant symptoms.

DOCUMENTS REVIEWED: Volumes 1.1, 1.95, 1.157 to 1.186, and 1.200 to 1.211; and documents BZ (stamp date 4-3-00), BZ (stamp date 4-25-00), C (stamp date 4-10-00), BZ (stamp date 6-1-00), and BZ (stamp date 6-9-00).

DATES: **Date received by Medical Division, HFD-180:** February 14, 2000
 Date received by Division of Biometrics, HFD-715: March 6, 2000
 User Fee Date: August 9, 2000

MEDICAL REVIEWER: Raymond Joseph, M.D., HFD-180

STATISTICAL REVIEWER: Sonia Castillo, Ph.D., HFD-715

**APPEARS THIS WAY
ON ORIGINAL**

Studies HTFB 301 and HTFB 351: 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

AND

Study HTFB 307: A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of SDZ HTF 919 at Two Dose Regimens and Placebo in Subjects with Constipation-predominant Irritable Bowel Syndrome

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Table 2.1
Overview of Phase 3 Studies 301, 307, and 351

Study No.	No. of Centers in ITT [#] Population	Design*	Treatment Groups	ITT Sample Size (n)	ITT Subgroups (n): a) Male/Female b) White/Black/Oth
301	95	MC,MN,R,DB, PC,PG,DD	4 mg tegaserod 12 mg tegaserod placebo	299 294 288 <i>Total – 881</i>	a) 150 / 731 b) 863 / 7 / 11
307	67	MC,MN,R,DB, PC,PG, DT,DD	4 mg tegaserod 4 to 12 mg titration tegaserod placebo	282 275 284 <i>Total – 841</i>	a) 138 / 703 b) 760 / 46 / 35
351	49	MC,MN,R,DB, PC,PG,DD	4 mg tegaserod 12 mg tegaserod placebo	265 267 267 <i>Total – 799</i>	a) 102 / 697 b) 702 / 68 / 29

* MC: Multicenter; MN: Multinational; R: Randomized; DB: Double-blind; PC: Placebo control; PG: Parallel Group; DD: Double-dummy; DT: Dose Titration

[#] ITT: intent-to-treat

Studies 351 and 301 had identical study designs: following a 4 week baseline period, eligible patients were randomized, in equal allocation (231 patients per treatment group), to receive either placebo, 4 or 12 mg tegaserod. In Study 307, following a 4 week baseline period, eligible patients were randomized, in equal allocation (231 patients per treatment group), to receive either a fixed dose of 4 mg of tegaserod, a dose-titration regimen or placebo. The patients randomized to dose-titration received 4 mg of tegaserod and underwent dose titration to 12 mg at week 4 if the response on the SGA of relief was complete or considerable relief <50% of the time. Patients in the 4 mg and placebo groups underwent a mock dose titration at week 4.

Patients eligible for each study were male and female (non-pregnant and non-lactating) patients aged 18 years or older (≥ 12 years in Study 351) with constipation predominant irritable bowel syndrome (C-IBS). Following a 4-week baseline period, patients who had at least mild abdominal discomfort/pain (as determined by a mean score ≥ 35 mm on a 100 mm visual analogue scale) were randomized. In addition, patients were required to have at least 2 of 3 constipation symptoms (<3 bowel movements/week, hard/lumpy stools, straining with a bowel movement $\geq 25\%$ of the time). In addition, patients during the baseline period who failed to complete the daily diary cards or who used disallowed medication affecting GI motility and/or perception were excluded from the double-blind treatment period.

Patients took tegaserod at 4 mg/d, or 12 mg/d, or placebo tablets with water within 30 minutes prior to meals in the morning and evening. Concomitant laxative use was not allowed during the study, unless requirements for rescue use were met (i.e., no bowel movement for 4 consecutive days associated with bothersome abdominal discomfort/pain or bloating). Bulk-forming agents were allowed if used in constant doses for at least one month prior to study entry and were to be taken in constant doses throughout the study. Patient clinical visits were monthly.

2.2 Efficacy Outcomes

The patient recorded all efficacy assessments in a diary. Three weekly assessments (Subject Global Assessments (SGAs) of relief, abdominal discomfort/pain and bowel habit) and 4 daily (intensity of abdominal pain/discomfort, intensity of bloating, frequency of bowel movements and average stool consistency) assessments were made by the patient throughout the 16-week study duration.

2.2.1 Subject Global Assessment of Relief

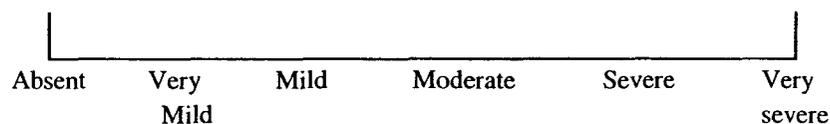
Patients responded weekly to the following question:

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

Answers were: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse.

2.2.2 Subject Global Assessment of Abdominal Discomfort/Pain

Efficacy was assessed weekly by a self-administered 100 mm visual analog scale (VAS) with verbal descriptors for abdominal discomfort/pain and for bowel habit. Patients placed a vertical mark on the line in response to the following question: *"How much of a problem was your abdominal discomfort/pain over the last week?"*



2.2.3 Subject Global Assessment of Bowel Habit

The SGA of bowel habit was self-administered weekly using the above VAS, in which patients responded to a similar question regarding their altered bowel habit. *"How much of a problem was your bowel habit over the last week?"*

2.2.4 Daily Bowel Habit Information

Patients recorded on a daily basis the following bowel habit information:

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

2.3 Protocol amendments

In the original protocol, there was one primary efficacy variable, the Subject Global Assessment (SGA) of abdominal discomfort/pain. Three protocol amendments were subsequently submitted. Discussed below are the 2 protocol amendments that pertain to changes in the statistical design.

The first amendment (dated 22-Aug-97 for 301, 4-Sept-97 for 307 and 351) was written prior to the start of all three studies. Its aim was to:

- introduce a second primary efficacy variable, the SGA of relief, and to adjust for the sample size accordingly (Holm's procedure was introduced, leading to an increase in sample size)
- introduced Holm's procedure to adjust for multiplicity
- The target enrollment for entry into the randomized double-blind phase of the study was increased from 591 ITT patients (in approximately 45 centers) to 693 ITT patients (in approximately 50 centers).

The sponsor's rationale for adding a second primary efficacy variable was based on the idea that both the SGA of relief and the SGA of abdominal discomfort/pain were considered clinically relevant variables in irritable bowel syndrome. The sponsor was not clear which of the two variables was more meaningful in evaluating IBS, so either variable was considered important.

The other amendment (12-Jul-99 for studies 301 and 307) was written prior to breaking the double-blind treatment code in studies 301 and 307 and after post-hoc analyses of study 351. Its aim was to:

- modify the definition of responder for the SGA of relief from a single criterion of “considerable or complete relief at least 50% of the time during the last 4 weeks on treatment” to include a second criterion of “OR somewhat, considerable, or complete relief for all of the last 4 weeks on treatment”
- introduce a modified primary efficacy analysis where SGA of relief became the only primary outcome measure
- eliminate SGA of abdominal discomfort/pain as a primary efficacy variable and keep it as a secondary variable
- introduce additional secondary efficacy variables
- apply Hochberg’s procedure for the multiple comparisons of the two tegaserod treatment groups versus placebo in the primary analysis

Study 351 was completed and analyzed first. The results of the protocol specified primary analyses were not statistically significant. This led to an exploratory analysis that resulted in a modification of the definition of a responder for the SGA of relief. Subsequent post-hoc analysis of study 351 that used the modified definition of a responder gave statistically significant results. The sponsor’s rationale for modifying the definition of a responder for the primary outcome measure was based on the low responder rates in both the tegaserod groups and the placebo group in study 351. According to the sponsor, the low responder rates in study 351 indicated that the definition of response for both the SGA of relief and the SGA of abdominal discomfort/pain was too stringent and therefore the response definition appeared to lack the sensitivity to detect a significant treatment effect.

The Division considered the change in definition of responder acceptable and requested that the study results be presented using both the original SGA of relief and the new SGA of relief. The reason for presenting both results is to see how the redefinition affected the original study results. In addition, the Division deemed that study 351 was not pivotal because the post-hoc analysis of study 351 was considered exploratory and led to a change in the protocols of studies 301 and 307.

The sponsor’s rationale for eliminating the SGA of abdominal discomfort/pain as a primary efficacy variable and retaining it as a secondary efficacy variable is that there are inherent problems with the use of the VAS, including the patient’s potential difficulties in translating her/his experiences to the scale and the difficulty in defining a response on the VAS.

2.4 Efficacy Analysis

All primary efficacy statistical tests are two-sided and performed at the 0.05 significance level. The intent-to-treat (ITT) population, defined as all patients randomized and treated, was the primary population. Endpoint for the SGAs refers to the last 4 available weekly SGA responses in the post-randomization period or all weekly responses if fewer than 4 weekly scores were available. Endpoint for the diary data refers to the daily scores as obtained in the last 28 days post-randomization or all daily scores obtained in the diary if fewer than 28 days were available. Data were also analyzed at endpoint for two other populations: the per-protocol population and the completers population. This review will focus on the ITT population only because it was the protocol specified population for the primary efficacy analyses.

2.4.1 Sample Size

The sample size calculation was specified in the original protocol and revised in an amendment to the following. A total of 693 eligible and randomized patients (231 per treatment group) were required for statistical analysis. The sample size was calculated under the assumption that the true difference in responder rate to SGAs of relief and abdominal discomfort/pain between a tegaserod dose group and

the placebo group was at least 15%; with a statistical power of 80% using a two-sided chi-squared test at a significance level of 0.0125 (after adjustment for multiple comparisons using Holm's procedure for two primary variables and two doses). The responder rate in the placebo group was assumed to be 30%. As a result of the changes to the statistical methodology in another protocol amendment, the significance level was raised to 0.025 (after adjustment for multiple comparisons using Hochberg's procedure for one primary variable and two doses). The sample size was not adapted to the new analysis plan.

2.4.2 Pooling of Centers for Analysis

Pooled centers were used in any Mantel-Haenszel test that was stratified by center. Centers were pooled to ensure the pooling criteria (treatment row totals ≥ 2 and response column totals ≥ 1) were fulfilled for both primary variables in all three of the following data sets: ITT population at endpoint, PP population at endpoint, and ITT population who completed the study:

- 3*2 tables were created for each center, with the three treatment groups as row headers and the response status for SGA of relief at endpoint (yes/no) as column headers.
- Centers were sorted by country, center size, and center number in ascending order. Centers with a treatment row total < 2 or a response column total < 1 were placed, by center size and center number, at the top of the respective country category.
- Centers were pooled sequentially by the sorting order in the same country category until fulfilling the pooling criteria.

The sets of centers after pooling were used as strata in the analysis of the primary variable. The response column criterion had to be fulfilled for each of the two pairwise treatment comparisons, i.e. for the tegaserod 4 mg and placebo, and for the tegaserod 12 mg and placebo comparisons.

2.4.3 Primary Endpoints

The new SGA of relief was the single protocol specified primary efficacy variable in studies 301 and 307. The original SGA of relief and the SGA of abdominal discomfort/pain were the two protocol specified primary efficacy variables in study 351. The new SGA of relief will also be presented for study 351.

2.4.3.1 Subject Global Assessment of Relief

The primary efficacy variable was response for new SGA of relief at endpoint (yes/no). The definition of responder at endpoint was defined as follows:

- At least 50% of the SGAs at endpoint with complete or considerable relief OR All of the SGAs at endpoint with at least somewhat relief (i.e. complete, considerable or somewhat)
- Number of days with laxative* use during treatment period ≤ 5 and no laxative* use during the last 28 days of treatment (* with the exception of bulk-forming laxatives)
- Duration of exposure to study medication ≥ 28 days
- At least one post-baseline SGA of relief

Note that laxative use, duration of exposure to treatment, and missing SGA of relief data are accounted for in the definition of a responder for the new SGA of relief. For the remainder of this review, these three variables will be referred to as the accounting criteria.

The two primary null hypotheses H_0 are:

There is no difference in proportion of responders for SGA of relief between tegaserod 4 mg and placebo.

There is no difference in proportion of responders for SGA of relief between tegaserod 12 mg and placebo.

Versus the two alternative hypotheses H_1 :

The proportions of responders for SGA of relief are not equal between tegaserod 4 mg and placebo.

The proportions of responders for SGA of relief are not equal between tegaserod 12 mg and placebo.

For the primary efficacy analysis, the Mantel-Haenszel test stratifying by center was used to compare the two doses of tegaserod versus placebo. The differences in responder rates (tegaserod-placebo) are based on the weighted average of the responder rate. The weight for center k is proportional to $(1/n_{k1} + 1/n_{k2})^{-1}$, where n_{ki} is the number of patients in the i -th treatment group in center k . To ensure the overall two-sided type I error ≤ 0.05 , Holm's multiple comparison procedure, adjusting for two primary variables (SGA of relief and SGA of abdominal discomfort/pain) and two tegaserod doses, was used in study 351, and Hochberg's multiple comparisons procedure, adjusting for 2 tegaserod doses, was used in studies 301 and 307.

2.4.4 Secondary Endpoints

Fifteen secondary efficacy variables were analyzed:

- (1) Response for original SGA of relief at endpoint (yes/no)
 - Responders for the original SGA of relief at the endpoint are patients who met the following criteria:
 - at least 50% of the SGAs at endpoint with complete or considerable relief and
 - the three accounting criteria as for the primary efficacy analysis
 - (2) Response for SGA of relief based on at least somewhat relief (yes/no)
 - Responders for SGA of relief at endpoint based on at least somewhat relief are patients who met the following criteria:
 - 100% of the SGAs at endpoint with somewhat, complete or considerable relief and
 - the three accounting criteria as for the primary efficacy variable
 - (3) Response for SGA of abdominal discomfort/pain (VAS) at the endpoint (yes/no): Responders for SGA of abdominal discomfort/pain at endpoint are patients who met the following criteria:
 - a ≥ 20 mm and $\geq 40\%$ reduction in mean VAS at endpoint compared to the baseline and
 - the three accounting criteria as for the primary efficacy variable
 - (4) Percent change from baseline to endpoint in mean VAS of SGAs of abdominal discomfort/pain.
 - (5) At least 2 categories improvement (categories are defined by 6 equally spaced intervals on SGA scale) from baseline to endpoint in mean VAS of SGA of abdominal discomfort/pain (yes/no)
 - (6) Response for SGA of bowel habit (VAS) at the endpoint (yes/no): A responder for SGA of bowel habit is a patient who met the following criteria:
 - a ≥ 20 mm and $\geq 40\%$ reduction in mean VAS at endpoint compared to baseline and
 - the three accounting criteria as for the primary efficacy variable
 - (7) Percent change from baseline to endpoint in mean VAS of SGAs of bowel habit.
 - (8) At least 2-category improvement from baseline to endpoint in mean VAS of SGA of bowel habit (yes/no).
 - Categories were defined in the same way as for variable (5).
- The following were normalized to 28 days:
- (9) - (11) Percent change from baseline to endpoint in number of days with: significant pain (pain score ≥ 2), significant bloating (bloating score ≥ 2), and no bowel movements.
 - (12) Percent change from baseline to endpoint in number of bowel movements.
 - (13) - (14) Percent of days at endpoint with: hard or very stools (stool consistency score of 6 or 7), and stool consistency between 3 and 5 (inclusive).
 - (15) Normalized bowel habit (yes/no) during the last 4 weeks of treatment: A patient had normalized bowel habit if the following four criteria were met:
 - No more than 25% of the last 4 weeks post-randomization with less than 3 bowel movements per week;
 - No more than 25% of the last 28 days of treatment with more than 3 bowel movements per day;
 - Median stool consistency score during last 28 days of treatment was between 3 and 5 (inclusive);
 - Duration of exposure to study medication ≥ 28 days.

All secondary variables were analyzed only for the ITT population for the following two comparisons: tegaserod 4 mg vs. placebo and tegaserod 12 mg vs. placebo. The dichotomous variables were analyzed using the Mantel-Haenszel test stratified by center, and the numeric variables were analyzed using an Extended Mantel-Haenszel test stratified by center (using modified ridit scores). The tests used a two-sided significance level of 0.05. Holm's multiple comparison procedure, adjusting for two tegaserod doses, was used for each secondary efficacy analysis in study 351. No multiple comparison procedure was used in studies 301 and 307.

Responder rates at endpoint not using the accounting criteria (calculated using the SGA response criterion only) for the original SGA of relief, new SGA of relief, SGA of abdominal discomfort/pain, and SGA of bowel habit were analyzed using the same statistical method as for the primary variable. In addition, monthly responder rates not using the accounting criteria for the original SGA of relief, new SGA of relief, and SGA of abdominal discomfort/pain were summarized by treatment in each study. This review will not present the responder rate analyses without accounting criteria.

2.4.5 Post-Hoc Analyses

In addition, the sponsor has presented post-hoc analyses for the primary efficacy variables pooled across all three studies, across studies 301 and 351, and across studies 301 and 307. Also, post-hoc analyses using the number of months (0, 1, 2, or 3 months) that a patient was a responder to SGA of relief without accounting for laxative use was presented by the sponsor. The results of these analyses will not be presented in this review. Section 4 presents comments by the reviewer about these analyses.

3 RESULTS OF STUDIES 301, 307, and 351

This section presents information about studies 301, 307, and 351, and the sponsor's results and conclusions.

3.1 Subject and Study Site Information

3.1.1 Patient Enrollment and Disposition

Table 3.1 presents a summary of the patient enrollment and disposition for each study. The number of randomized patients in the ITT population is as follows: study 301 has 881 patients, study 307 has 845 patients, and study 351 has 799 patients.

Table 3.1
Studies 301, 307, 351: Summary of Patient Enrollment and Disposition

Population	301	307	351
Number of Patients Enrolled	1122	1163	1093
Number of Patients Not Randomized	241 (21.5)	318 (27.3)	294 (26.9)
Number of Patients Randomized	881	845	799
Number of Patients in ITT Population	881	841	799
Number (%) of Patients Who Completed Study*	751 (85.2)	680 (80.5)	633 (79.2)
Number (%) of Patients Who Did Not Complete Study*	130 (14.8)	165 (19.5)	166 (20.8)
Reasons for Not Completing:			
Adverse Events	53 (6.0)	68 (8.0)	37 (4.6)
Unsatisfactory therapeutic effect	23 (2.6)	12 (1.4)	32 (4.0)
Patient withdrew consent	22 (2.5)	41 (4.9)	40 (5.0)
Protocol violation	16 (1.8)	6 (0.7)	16 (2.0)
Lost to Follow-up	14 (1.6)	29 (3.4)	38 (4.8)
Patient's condition no longer required drug	1 (0.1)	0	0
Death	1 (0.1)	0	0
Abnormal lab values	0	2 (0.2)	3 (0.4)
Administrative	0	7 (0.8)	0

Source: Tables 7-1 and 7-2, Vol. 1.168, page 48; Tables 7-1 and 7-2, pages 49 – 50, and Vol. 1.185, pages 047 - 048.

* Percentage is with respect to the number of randomized patients.

Of the patients randomized to treatment, 14.8%, 19.5%, and 20.8% of patients discontinued during the 12 week treatment period in studies 301, 307, and 351, respectively. In studies 301 and 307, the most

common reason for discontinuation was adverse events (6% and 8%), while for study 351 the most common reason for discontinuation was patient withdrawal of consent (5%). The frequency of patients who discontinued due to unsatisfactory therapeutic effect, protocol violation, and lost to follow-up were different across the three studies.

Table 3.2 presents the number of patients randomized into each treatment group for each study. As per protocol, patients were equally allocated to each treatment group.

Table 3.2
Number of Patients Randomized into Each Treatment Group

Study	4 mg	12 mg or 4 to 12 mg	Placebo	Total
301	299	294	288	881
307	283	277	285	845
351	265	267	267	799

Source: Statistical Reviewer's listing.

3.1.2 Patient Demographics

Table 3.3 presents a summary of the patient demographics for the ITT population. In all three studies there were more females (83% to 87%) than males (13% to 17%), the majority of patients were white (88% to 98%), the majority of the patients were less than 65 years old (89% to 93%), and the mean duration of IBS symptoms was 13.2 to 14.6 years. Also, in all three studies, demographic variables were comparable between treatment groups.

Table 3.3
Studies 301, 307, and 351: Demographics and Baseline Characteristics for ITT Population

	301 (N=881)	307 (N=841)	351 (N=799)
Gender – N (%)			
Male	150 (17.0)	138 (16.4)	102 (12.8)
Female	731 (83.0)	703 (83.6)	697 (87.2)
Race – N (%)			
White	863 (98.0)	760 (90.4)	702 (87.9)
Black	7 (0.8)	46 (5.5)	68 (8.5)
Other	11 (1.3)	35 (4.2)	29 (3.7)
Age (years) – N (%)			
< 65	787 (89.3)	750 (89.2)	744 (93.1)
≥ 65	94 (10.7)	91 (10.8)	55 (6.9)
Duration of IBS symptoms (months)			
Months: Mean (SD)	158.1 (147.6)	166.4 (120.0)	174.6 (120.0)
Years: Mean (SD)	13.2 (12.3)	13.9 (10.0)	14.6 (10.0)

Source: Table 7-3, Vol. 1.157, page 8-52; Table 7-3, Vol. 1.167, page 8-50; and Table 7-3, Vol. 1.162, page 8-44.

3.1.3 Number of Centers and Number of ITT Patients by Country

Table 3.4 presents the number of centers and the number patients in the intent to treat population for each country. There was one principal investigator at each center in each study. Study 301 was mainly conducted at European centers with some United States and South African centers, for a total of 95 centers. Study 307 was mainly conducted at United States centers in addition to European and Canadian centers, for a total of 67 centers. Study 351 was mainly conducted at United States centers with two Canadian centers, for a total of 49 centers.

Table 3.4
Number of Patients by Country in the ITT Population

Country	Study 301		Study 307		Study 351	
	# of Centers	N	# of Centers	N	# of Centers	N
Austria	3	51	-	-	-	-
Belgium	-	-	3	28	-	-
Canada	-	-	3	17	2	24
Finland	4	38	-	-	-	-
France	-	-	8	90	-	-
Germany	16	197	5	44	-	-
Italy	7	76	-	-	-	-
Netherlands	12	98	-	-	-	-
Portugal	2	7	-	-	-	-
South Africa	6	29	-	-	-	-
Spain	1	1	1	25	-	-
Switzerland	9	99	-	-	-	-
Turkey	6	49	-	-	-	-
United Kingdom	18	168	10	84	-	-
United States	11	68	37	553	47	775
Total	95	881	67	841	49	799

Source: Statistical Reviewer's listing.

3.2 Sponsor's Efficacy Results

The Division requested that the study results be presented using both the original SGA of relief and the new SGA of relief. All results are for the ITT population. In addition, the division deemed that study 351 was not pivotal because the post-hoc analyses are considered exploratory.

3.2.1 Primary Efficacy: Subject Global Assessment of Relief

The new Subject Global Assessment (SGA) of relief definition of responder was: "completely relieved" or "considerably relieved" for at least 50% of the last 4 weeks of treatment, or at least "somewhat relieved" for all of the last 4 weeks of treatment. The original SGA of relief definition of responder did not include the "somewhat relieved" component. The responder rate also took into account laxative use, duration of treatment, and patients with no SGA assessments. Patients who did not meet all accounting criteria were classified as non-responders. The responder rates and treatment differences for the original and new SGA of relief at endpoint are presented in Table 3.5 for studies 301, 307 and 351. Recall that the analyses for the new SGA of relief for study 351 are post-hoc.

The results using both the original definition and new definition of responder are presented to show the effect of changing the definition of responder on the treatment differences. The effect of adding the category "at least somewhat relieved 100% of the time at study endpoint" is that all responder rates increase. Except for the 4 mg group in study 351, all treatment differences also increased.

The following remarks pertain to the new definition of SGA of relief. The results for the original definition of SGA of relief are presented for completeness to compare the effect of changing the definition of responder. The results for all studies are presented in Table 1.2 and are as follow:

- In study 301, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 9% in the 4 mg group and 8% in the 12 mg group, both were statistically significant.

- In study 307, the 4 mg group had a similar response compared to the placebo group and the 4-12 titration group had a higher responder rate compared to the placebo group. The treatment difference was 0.8% in the 4 mg group and 6% in the 4-12 mg titration group, neither of which was statistically significant.
- In study 351, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 6% in the 4 mg group and 12% in the 12 mg group, of which only the 12 mg group was statistically significant.

A treatment effect is demonstrated in study 301 for both the 4 mg and 12 mg doses and supported by a post-hoc analysis of study 351 for the 12 mg dose but not replicated in study 307.

In addition, in study 307, 583 patients either titrated or mock-titrated, which is 69% of all randomized patients. The percentage of titrated or mock-titrated patients is greatest in the placebo group (73.3%) and similar between the tegaserod treatment groups (4 mg, 68.2% and 4 to 12 mg, 65.3%). The difference between the placebo group and the 4 to 12 mg group was statistically significant (p=0.039). The differences between the placebo group and the 4 mg group and between the two tegaserod groups were not statistically significant.

Table 3.5
Subject Global Assessment of Relief by Study

	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 301 (N=881)						
Responder Rate % (n)	27.8 (299)	26.2 (294)	20.5 (288)	38.8	38.4	30.2
Difference ¹ (se)	7.6 (3.5)	5.5 (3.5)		9.1 (3.8)	8.3 (3.9)	
p-value ²	0.028	0.116		0.018	0.033	
Adjusted p-value ³	0.056	0.116		0.033*	0.033*	
Study 307 (N=841)						
Responder Rate % (n)	25.5 (282)	26.5 (275)	28.2 (284)	38.3	42.2	37.0
Difference ¹ (se)	-3.0 (3.6)	-1.4 (3.8)		0.8 (4.0)	6.0 (4.1)	
p-value ²	0.422	0.703		0.837	0.142	
Adjusted p-value ³	0.703	0.703		0.837	0.284	
Study 351 (N=799)						
Responder Rate % (n)	29.4 (265)	26.2 (267)	22.1 (267)	38.9	45.7	33.3
Difference ¹ (se)	7.5 (3.8)	4.1 (3.7)		6.0 (4.1)	12.4 (4.2)	
p-value ²	0.050	0.266		0.157	0.004	
Adjusted p-value ³	0.200	0.370		0.157	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 center and the weight for a center is proportional to the number of patients in each treatment group.

² Nominal p-value based on the Mantel-Haenszel test stratified by center.

³ p-value adjusted using Hochberg's multiple comparison procedure adjusting for two doses in studies 301 and 307, or using Holm's multiple comparison procedure adjusting for two doses and co-primary efficacy variable of SGA of abdominal discomfort/pain in study 351.

* Statistically significant at the 0.05 significance level, using Hochberg's (301 and 307 for both definitions and 351 for the new definition of SGA of Relief) or Holm's (351 for the original definition of SGA of Relief) multiple comparison procedure.

Source: Tables 9-1 and 9-2, Vol.1.157, pages 8-58 and 8-59. / Tables 9-1 and 9-2, Vol.1.167, pages 8-56 and 8-57. / Tables 9-2 and 9-7, Vol.1.162 pages 8-52 and 8-62.

3.2.2 Secondary Efficacy: Subject Global Assessment of Abdominal Discomfort/Pain

The results for SGA of abdominal discomfort/pain in the ITT population for all studies are presented in Table 3.6 and are as follow:

- In study 301, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 7% in both the 4 mg group and the 12 mg group.
- In study 307, both treatment groups did not have higher responder rates compared to the placebo group. The treatment difference was -6% in the 4 mg group and -3% in the 4-12 mg titration group.

- In study 351, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 5% in the 4 mg group and 6% in the 12 mg group. Since pain is an important clinical component of IBS, it is not clear why the treatment difference for SGA of abdominal discomfort/pain is not significant in study 35, where SGA of abdominal discomfort/pain was a protocol specified primary efficacy variable.

Table 3.6
Subject Global Assessment of Abdominal Discomfort/Pain by Study

	4 mg	12 mg or 4 to 12 mg	Placebo
Study 301 (N=880)			
Responder Rate % (n)	29.8 (299)	29.9 (294)	22.6 (287)
Difference ¹	7.0	7.3	
p-value ²	0.055	0.044	
Study 307 (N=841)			
Responder Rate % (n)	25.5 (282)	27.6 (275)	30.6 (284)
Difference ¹	-5.5	-3.1	
p-value ²	0.141	0.411	
Study 351 (N=799)			
Responder Rate % (n)	23.4 (265)	25.1 (267)	18.7 (267)
Difference ¹	4.8	6.4	
p-value ²	0.185	0.075	
Adjusted p-value ³	0.370	0.225	

¹ Difference is the weighted difference of responder rates between the active treatment group and placebo group. The weights used are for each center and the weight for a center is proportional to the number of patients in each treatment group.

² Nominal p-value based on the Mantel-Haenszel test stratified by country.

³ Holm's multiple comparison procedure, adjusting for two doses and two primary variables, was used to determine whether a treatment difference was statistically significant at the significance level of 0.05.

Source: Table 9-8, Vol. 1.157, page 8-66; Table 9-9, Vol. 1.167, page 8-65; and Table 9-2, Vol. 1.162, page 8-52.

3.3 Sponsor Conclusions

The sponsor concludes the following:

- In study 301, tegaserod 12 mg/d was effective in relieving overall IBS symptoms and abdominal discomfort and pain.
- In study 307, the efficacy of tegaserod was not demonstrated. The lack of statistically meaningful differences observed at study endpoint between tegaserod and placebo may be related to the dose-titration study design.
- In study 351, the protocol specified primary and secondary efficacy variables showed consistent trends for a treatment effect for tegaserod compared to placebo. A post-hoc analysis in which the responder definition on SGA of relief was revised demonstrated clinically meaningful differences between the 12 mg/d tegaserod group and placebo.

4 REVIEWER'S COMMENTS ON STUDY DESIGN AND SPONSOR ANALYSES

1. All per protocol analyses of SGA of relief, SGA of abdominal discomfort/pain, bowel habit, and abdominal discomfort/pain need to take laxative use into account because the protocol specified definition of a responder takes laxative use into account. Consequently, the analyses presented by the sponsor that do not take laxative use into account in the definition of a responder are not consistent with the protocol specified definition of a responder.

2. The sponsor's scientific rationale for changing the co-primary efficacy variable of SGA of abdominal discomfort/pain to a secondary efficacy variable in protocol amendments for studies 301 and 307 is not clear. Changing SGA of abdominal discomfort/pain from a primary to secondary efficacy variable is of clinical concern because, per the medical reviewer, pain is an important clinical component of IBS. The following are three reasons found by the reviewer for the change:

- a. The sponsor stated in Volume 1.158 on page 8-356 that:

In addition, given the inherent problems with the VAS (both the patient's potential difficulties in translating her/his experiences to the scale and the difficulty in defining a responder), the SGA of abdominal discomfort/pain will be eliminated as a primary efficacy variable and instead be retained as a secondary efficacy variable. In study 351, the two primary efficacy variables (SGA of relief and SGA of abdominal discomfort/pain) had been highly correlated.
- b. During a sponsor meeting on May 8, 2000 to discuss the sponsor's Advisory Committee Briefing Package, the statistical reviewer requested the scientific rationale for reclassifying the co-primary efficacy variable of SGA of abdominal discomfort/pain to a secondary efficacy variable. The sponsor responded that the VAS measurement was no longer the norm in assessing pain or other outcomes.
- c. The sponsor stated that the results in study 351 for SGA of abdominal discomfort/pain were not statistically significant.

3. The sponsor developed an algorithm for pooling centers. In this algorithm, centers within a country were pooled to ensure that the pooling criteria (treatment row totals ≥ 2 and response column totals ≥ 1) were fulfilled for both primary variables in all three of the following data sets: ITT population at endpoint, Per Protocol population at endpoint, and ITT population who completed the study. Specifically:

- 3*2 tables were created for each center, with the three treatment groups as row headers and the response status for SGA of relief at endpoint (yes/no) as column headers.
- Centers were sorted by country, center size, and center number in ascending order. Centers with a treatment row total < 2 or a response column total < 1 were placed, by center size and center number, at the top of the respective country category.
- Centers were pooled sequentially by the sorting order in the same country category until fulfilling the pooling criteria.
- The response column criterion had to be fulfilled for each of the two pairwise treatment comparisons, i.e. for the tegaserod 4 mg and placebo, and for the tegaserod 12 mg and placebo comparisons.

The sets of centers after pooling were used as strata in the Mantel-Haenszel analysis of the primary efficacy variable.

This algorithm for pooling centers is not appropriate because it was based on the number of responders and non-responders for each primary efficacy variable after the blind was broken. Using the response column totals as a criterion for pooling after the blind is broken could potentially bias the results of the analyses. A preferable algorithm is one that pools centers within a country based on the total number of patients in the ITT population at that center until a minimum number of patients is achieved.

Given that a large number of centers did not recruit the minimum of 15 ITT patient per center (see item 8 below) and that the randomization list was generated by country, a better algorithm is to pool all centers within a country. The analyses would then be stratified by country. These analyses, stratified by country, will be addressed in section 5 of this review.

4. The sponsor's presentation of results pooled across studies 301, 307, and 351 are not appropriate. The following three pooled populations were considered at endpoint and at 1 month: 351/301, 351/301/307, and 301/307. Pooling these three studies is not appropriate because of the following reasons:

- a. The pooled analyses are not pre-specified in the protocol, are data driven, and are subject to bias. The protocol specified analysis of study 301 yielded favorable results for the 12 mg group and the post-hoc analysis of study 351 yielded favorable results for the 4 mg and 12 mg groups. Pooling these two studies with favorable results with the non-significant results of study 307 bias the pooled results in favor of the active treatment. Also, pooling artificially resolves the lack of statistical significance in study 307 by making it appear acceptable in the light of a positive overview
- b. Assuming pooling were reasonable to do, one is still left with only one pooled study and no second study to provide replication of the pooled study results.
- c. The design of the three studies is not the same. The number of protocol specified primary endpoints is not the same because study 351 had two primary efficacy variables, SGA of relief and SGA for discomfort/pain and studies 301 and 307 had one primary efficacy variable, SGA of relief. Also, the type of treatment groups is not the same for all three studies. Studies 301 and 351 had 4 mg, 12 mg, and placebo treatment groups while study 307 had 4 mg, 4 to 12 mg dose titration, and placebo treatment groups. As a consequence, the interpretation of the study results is different for the three studies. Study 307 tests a fixed dose and a titrated dose while studies 301 and 351 test two fixed doses. Also, pooling the 4 to 12 mg titration group with the 4 mg group for the month 1 analyses and then with the 12 mg group for the endpoint analyses is not appropriate because not all patients in the 4 to 12 mg titration group were at a constant dose.
- d. Pooling is not necessary because there is sufficient sample size in each study to give an adequate evaluation of the treatment effect on a per study basis (see item 6 below). Pooling gives a smaller p-value because of the larger sample size but the p-value is not interpretable because the decision to pool is data driven, as discussed in item a. above.

5. Participation in more than one Phase 3 study by the same principal investigator does not meet the assumption of having at least two independent studies to demonstrate efficacy. Of the 11 U.S. centers in study 301, 8 came from the U.S. centers in study 351 and three from the U.S. centers in study 307. Of the 41 U.S. centers in study 307, 9 came from the U.S. centers in study 351. Study 351 was completed before both studies 301 and 307 were completed. It was after study 351 was completed that the principal investigators participated in the other studies. The same is true for those principal investigators in study 307 who participated in study 301.

6. Studies 301 and 307 recruited more patients to the ITT population than was planned for in the protocol. Table 4.1 presents an overview of the sample size for studies 301 and 307. The original protocol, with one primary efficacy variable tested at two dose groups compared to placebo called for a total of 531 patients at approximately 45 centers in the ITT population. An amendment to the protocol, which increased the number of primary efficacy variables to two tested at two dose groups compared to placebo, called for a total of 693 patients at approximately 50 centers in the ITT population. Another protocol amendment, which changed the number of primary efficacy variables to one tested at two dose groups, made no adjustment to the sample size. The final number of patients in the ITT population for studies 301 and 307 were 881 patients at 95 centers and 835 patients at 66 centers, respectively. The sponsor gave no reason why the number of centers in both studies was increased.

The final sample size was over 40% larger than what was planned for in the original protocol, which also had one primary efficacy variable tested at two dose groups compared to placebo. In addition, the final sample size was over 20% larger than what was planned for in the first amendment, whose protocol had two primary efficacy variables tested at two dose groups compared to placebo. In response to a question from the reviewer about the over recruitment of patients, the sponsor responded (document BZ, stamp date 4-25-00) with the following:

There was no prospective decision to recruit and randomize more than 231 patients per study arm in each of these studies [301 and 307]. At the end of the enrollment phase in each of these studies, Novartis allowed patients who had entered the baseline phase of the study [who signed informed consent] to continue on through

randomization and complete the study because those patients had undergone diagnostic procedures, including endoscopy. It was therefore felt that patients completing the baseline should be allowed to complete the study. This resulted in an over-enrollment for each study; however, please note that this was not intentional.

The larger sample sizes result in an increase in the power of the statistical tests for the primary efficacy analyses.

Table 4.1
Sample Size Overview for Studies 301 and 307

	Study 301 N (n per group)	Study 307 N (n per group)
Original Protocol ITT Population Sample Size*	591 (197)	591 (197)
Number of Centers	45	45
Number of Primary Efficacy Variables	1	1
First Protocol Amendment ITT Population Sample Size*	693 (231)	693 (231)
Number of Centers	50	50
Number of Primary Efficacy Variables	2	2
Second Protocol Amendment ITT Population Sample Size*	693	693
Number of Centers	50	50
Number of Primary Efficacy Variables	1	1
ITT Population Sample Size at End of Study	881	835
Number of Centers	95	66
Sample Size at Study End Increase from Original Protocol	290	244
% Increase from Original Protocol	49.1%	41.3%
Sample Size at Study End Increase from First Amendment	188	142
% Increase from First Amendment	27.1%	20.5%

* Sample size calculations assumed a placebo responder rate of 0.30, an active treatment effect of 0.45 for both doses (resulting in a 0.15 difference in responder rates), 80% power, 0.05 significance level, and adjustment for multiple comparisons (two doses and number of efficacy variables) using either Holm's or Hochberg's procedure for multiple comparisons.

Source: Statistical Reviewer's listing.

7. Recruitment of the per protocol minimum number of patients at each study center for the ITT population in studies 301, 307, and 351 was not achieved at all centers. Per protocol, each study center was to recruit a minimum of 15 ITT patients up to a maximum of about 30 ITT patients. The proportion of centers that had at least 15 patients was 22% (21 of 95 centers), 39% (26 of 66 centers), and 51% (25 of 49 centers) for studies 301, 307, and 351, respectively.

5 REVIEWER'S ANALYSES AND CONCLUSIONS

This section presents the reviewer's overall and by-gender analyses for each study and conclusions. The by-gender analyses are presented because the medical reviewer considers them informative in assessing the effectiveness of tegaserod in each gender. Analyses of the primary efficacy variable of SGA of relief and secondary efficacy variable of SGA of abdominal discomfort/pain use a different pooling algorithm within a study and a different ITT population used by the sponsor.

The sponsor used an algorithm for pooling centers within a country to use center as a stratification variable in the primary and secondary efficacy analyses. Given that a large number of centers did not recruit the minimum of 15 ITT patient per center and that the randomization list was generated by country, the reviewer instead pooled all centers with a country and used country as a stratification variable in the primary and secondary efficacy analyses. Consequently, the differences in responder rates are based on the weighted average of the responder rate. The weight for country k is proportional to $(1/n_{k1} + 1/n_{k2})^{-1}$, where n_{ki} is the number of patients in the i -th treatment group in country k .

The ITT populations for studies 307 and 351 differ from the sponsor's ITT populations. In study 307, the reviewer's ITT population was of size 835 instead of size 841 because one — center with 6

randomized patients was removed from the ITT population. The center was removed because the sponsor suspended the investigator due to audit findings demonstrating significant departures from GCP (good clinical practice). In study 351, the reviewer's ITT population was of size 775 instead of size 799 because two — centers with 18 and 6 randomized patients were removed from the ITT population. Both — centers in the ITT population were removed from the ITT population because:

- The sponsor suspended one center's investigator because audit findings demonstrated significant departures from GCP. This was the same investigator that was removed from study 307.
- The other center had 6 randomized patients, which are not enough to include as the contribution from —

5.1 Overall Analyses

5.1.1 Primary Efficacy: Subject Global Assessment of Relief

The following remarks pertain to the new definition of SGA of relief. The results for the original definition of SGA of relief are presented for completeness to compare the effect of changing the definition of responder. The results in the ITT population for all studies are presented in Table 5.1 and are as follow:

- In study 301, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 9% in the both the 4 mg group and the 12 mg group, both were statistically significant.
- In study 307, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 1% in the 4 mg group and 5% in the 4-12 mg titration group, neither of which was statistically significant.
- In study 351, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 7% in the 4 mg group and 13% in the 12 mg group, of which only the 12 mg group was statistically significant.

Table 5.1
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 301 (N=881)						
Responder Rate % (n)	27.8 (299)	26.2 (294)	20.5 (288)	38.8	38.4	30.2
Difference (se) ¹	7.7 (3.5)	5.9 (3.5)		9.0 (3.8)	8.6 (3.9)	
p-value ²	0.029	0.092		0.020	0.028	
Adjusted p-value ³	0.058	0.092		0.028*	0.028*	
Study 307 (N=835)						
Responder Rate % (n)	25.7 (280)	26.7 (273)	28.0 (282)	38.2	42.1	36.9
Difference (se) ¹	-2.4 (3.7)	-1.2 (3.8)		1.2 (4.0)	5.4 (4.2)	
p-value ²	0.524	0.753		0.768	0.193	
Adjusted p-value ³	0.753	0.753		0.768	0.386	
Study 351 (N=775)						
Responder Rate % (n)	30.0 (257)	26.2 (259)	21.6 (259)	39.7	45.2	32.4
Difference (se) ¹	8.4 (3.8)	4.6 (3.7)		7.3 (4.2)	12.8 (4.2)	
p-value ²	0.035	0.257		0.099	0.004	
Adjusted p-value ³	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.

Note: Six patients are not included in the ITT population of study 307 and only United States centers are in the ITT population of study 351.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

5.1.2 Secondary Efficacy: Subject Global Assessment of Abdominal Discomfort/Pain

The results in the ITT population for all studies are presented in Table 5.2 and are as follow:

- In study 301, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 7% in the 4 mg group and 8% in the 12 mg group.
- In study 307, both treatment groups did not have higher responder rates compared to the placebo group. The treatment difference was -5% in the 4 mg group and -3% in the 4-12 mg titration group.
- In study 351, both treatment groups had higher responder rates compared to the placebo group. The treatment difference was 5% in both the 4 mg group and the 12 mg group.

Table 5.2
Subject Global Assessment of Abdominal Discomfort/Pain

	4 mg	12 mg or 4 to 12 mg	Placebo
Study 301 (N=880)			
Responder Rate % (n)	29.8 (299)	29.9 (294)	22.6 (287)
Difference (se) ¹	7.4 (3.6)	7.6 (3.6)	
p-value ²	0.041	0.038	
Study 307 (N=835)			
Responder Rate % (n)	25.7 (280)	27.8 (273)	30.5 (282)
Difference (se) ¹	-4.9 (3.8)	-2.5 (3.9)	
p-value ²	0.194	0.518	
Study 351 (N=775)			
Responder Rate % (n)	24.1 (257)	24.3 (259)	18.9 (259)
Difference (se) ¹	5.2 (3.6)	5.4 (3.6)	
p-value ²	0.164	0.165	
Adjusted p-value ³	0.492	0.492	

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 the Mantel-Haenszel test in studies 301 and 307 and based on Fisher's Exact test in study 351.

³ Holm's multiple comparison procedure, adjusting for two doses and co-primary efficacy variable of SGA of relief in study 351.

Note: Six patients are not included in the ITT population of study 307 and only United States centers are in the ITT population of study 351.

5.1.3 Reviewer's Conclusions for Overall Analyses

Based on the SGA of Relief, a treatment effect is demonstrated in study 301 for both the 4 mg and 12 mg doses and supported by a post-hoc analysis of study 351 for the 12 mg dose but not replicated in study 307.

5.2 Analyses by Gender

This section presents the reviewer's analyses of the primary efficacy variable of SGA of relief and secondary efficacy variable of SGA of abdominal discomfort/pain by gender for each study. The same ITT population as used in the alternative analyses presented above is used in the analyses by gender.

5.2.1 Patient Demographics and Baseline Characteristics by Gender

Table 5.3 presents a summary of patient demographics and baseline characteristics for the ITT population by gender. Approximately 15% of the patient population were male (ranged from 13% to 17%) and more than 86% of the patient population was Caucasian in the three studies. Males weighed more, were older, and had a shorter duration of disease compared to females in all studies. Duration of IBS was long-standing overall and the bowel and stool baseline variables show that the population was constipation predominant.

Table 5.3
Studies 301, 307, 351: Demographics and Baseline Characteristics by Gender

Demographic/Baseline variable	Study 301		Study 307		Study 351	
	Females (n=731)	Males (n=150)	Females (n=700)	Males (n=135)	Females (n=675)	Males (n=100)
Age (yrs)	45 ± 14	49 ± 14	44 ± 13	49 ± 14	42 ± 12	48 ± 13
Age ≥ 65 years	10%	16%	10%	16%	6%	14%
Race: Caucasian	98%	97%	90%	91%	87%	91%
Race: Black	1%	0%	6%	4%	9%	5%
Race: Other	1%	3%	4%	4%	4%	4%
Weight (kg)	65 ± 13	79 ± 12	68 ± 15	83 ± 15	69 ± 15	86 ± 17
Duration of IBS (months)	165 ± 150	127 ± 130	169 ± 150	151 ± 168	181 ± 161	135 ± 144
Abdominal discomfort/pain VAS score (mm)	61 ± 13	57 ± 12	62 ± 13	58 ± 12	64 ± 13	61 ± 10
Bowel habit VAS score (mm)	61 ± 14	56 ± 12	62 ± 14	58 ± 14	65 ± 14	62 ± 13
No. of days/28 days with significant ¹ discomfort/pain	23 ± 6	24 ± 6	24 ± 6	25 ± 6	24 ± 5	25 ± 6
No. of days/28 days with significant ¹ bloating	23 ± 7	23 ± 7	24 ± 6	23 ± 8	25 ± 5	23 ± 8
No. of days/28 days without bowel movements	13 ± 7	9 ± 8	12 ± 7	9 ± 7	14 ± 7	9 ± 8
No. of bowel movements/28 days	20 ± 14	28 ± 22	24 ± 19	30 ± 24	21 ± 16	32 ± 25
% of days ² with hard/very hard stools	29 ± 29	22 ± 27	30 ± 28	24 ± 25	32 ± 29	28 ± 26

Note: results are expressed as mean ± SD.

¹ Defined as at least mild (daily score ≥ 2 on a 6-point scale).

² Denominator is days with bowel movements.

Source: Statistical Reviewer's listing.

5.2.2 Primary Efficacy: Subject Global Assessment of Relief by Gender

The results for SGA of relief by gender in the ITT population is presented in Table 5.4. The results are based using the new definition of responder to SGA of relief and are as follow:

Study 301:

- Female patients in both treatment groups had higher response rates compared to the placebo group. The treatment difference was 10% in the 4 mg group and 12% in the 12 mg group, both were statistically significant.
- Male patients in both treatment groups did not have higher response rates compared to the placebo group. The treatment difference was 0.5% in the 4 mg group and -8% in the 12 mg group, neither of which was statistically significant.

Study 307:

- Female patients in both treatment groups had higher response rates compared to the placebo group. The treatment difference was 0.4% in the 4 mg group and 5% in the 4-12 mg titration group, neither of which was statistically significant.
- Male patients in both treatment groups had slightly higher response rates compared to the placebo group. The treatment difference was 0.1% in the 4 mg group and 5% in the 4-12 mg titration group, neither of which was statistically significant.

Study 351:

- Female patients in both treatment groups had higher response rates compared to the placebo group. The treatment difference was 9% in the 4 mg group and 15% in the 12 mg group, of which only the 12 mg group was statistically significant.
- Male patients in both treatment groups did not have higher response rates compared to the placebo group. The treatment difference was -2% in both the 4 mg group and 12 mg group, neither of which was statistically significant.

Table 5.4
Subject Global Assessment of Relief by Gender

	Male			Female		
	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
Study 301 (n_m=150, n_f=731)						
Responder Rate % (n)	44.2 (52)	36.0 (50)	43.8 (48)	37.6 (247)	38.9 (244)	27.5 (240)
Unadjusted Difference (se) ¹	0.4 (9.9)	-7.8 (9.9)		-	-	
Difference (se) ²	-	-		10.4 (4.2)	11.8 (4.3)	
p-value ³	0.433	0.555		0.013	0.006	
Adjusted p-value ⁴	0.555	0.555		0.013*	0.012*	
Study 307 (n_m=135, n_f=700)						
Responder Rate % (n)	34.1 (44)	39.0 (41)	34.0 (50)	39.0 (236)	42.7 (232)	37.5 (232)
Unadjusted Difference (se) ¹	0.1 (9.8)	5.0 (10.1)		-	-	
Difference (se) ²	-	-		0.4 (4.5)	4.8 (4.6)	
p-value ³	0.859	0.455		0.928	0.285	
Adjusted p-value ⁴	0.859	0.859		0.928	0.570	
Study 351 (n_m=100, n_f=675)						
Responder Rate % (n)	32.4 (37)	32.3 (31)	34.4 (32)	40.9 (220)	46.9 (228)	32.2 (227)
Difference (se) ²	-2.0 (11.4)	-2.1 (11.9)		8.7 (4.5)	14.7 (4.5)	
p-value ³	1.00	1.00		0.062	0.002	
Adjusted p-value ⁴	1.00	1.00		0.062	0.004*	

¹ A weighted difference is not calculated for males due to the small sample size within some countries, so the unadjusted difference is shown.

² 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.

³ 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.

⁴ p-value adjusted using Hochberg's multiple comparison procedure.

* Statistically significant at the 0.05 significance level, using Hochberg's multiple comparison procedure.

Note: Six patients are not included in the ITT population of study 307 and only United States centers are in the ITT population of study 351.

5.2.3 Secondary Efficacy: Subject Global Assessment of Abdominal Discomfort/Pain by Gender

The results for SGA of abdominal discomfort/pain by gender in the ITT population is presented in Table 5.5 and are as follow:

Study 301:

- Female patients in both treatment groups had higher response rates compared to the placebo group. The treatment difference was 9% in the 4 mg group and 10% in the 12 mg group.
- Male patients in both treatment groups did not have higher response rates compared to the placebo group. The treatment difference was -2% in the 4 mg group and -5% in the 12 mg group.

Study 307:

- Female patients in both treatment groups did not have higher response rates compared to the placebo group. The treatment difference was -5% in the 4 mg group and -1% in the 4-12 mg titration group.
- Male patients in both treatment groups did not have higher response rates compared to the placebo group. The treatment difference was -11% in the 4 mg group and -12% in the 4-12 mg titration group.

Study 351:

- Female patients in both treatment groups had higher response rates compared to the placebo group. The treatment difference was 5% in the 4 mg group and 7% in the 12 mg group.
- Male patients in the 4 mg group had a higher response rate compared to the placebo group and those in the 12 mg group had a lower response rate compared to the placebo group. The treatment difference was 8% in the 4 mg group and -6% in the 12 mg group.

Table 5.5
Subject Global Assessment of Abdominal Discomfort/Pain by Gender

	Male			Female		
	4 mg	12 mg or 4 to 12 mg	Placebo	4 mg	12 mg or 4 to 12 mg	Placebo
Study 301 (n_m=150, n_f=730)						
Responder Rate % (n)	26.9 (52)	24.0 (50)	29.2 (48)	30.4 (247)	31.1 (244)	21.3 (239)
Unadjusted Difference (se) ¹	-2.3 (9.0)	-5.2 (8.9)		-	-	
Difference (se) ²	-	-		9.2 (3.9)	9.8 (4.0)	
p-value ³	0.864	0.985		0.020	0.014	
Study 307 (n_m=135, n_f=700)						
Responder Rate % (n)	25.0 (44)	22.0 (41)	34.0 (50)	25.8 (236)	28.9 (232)	29.7 (232)
Unadjusted Difference (se) ¹	-11.0 (9.4)	-12.0 (9.3)		-	-	
Difference (se) ²	-	-		-4.5 (4.2)	-1.0 (4.2)	
p-value ³	0.606	0.451		0.273	0.808	
Study 351 (n_m=100, n_f=675)						
Responder Rate % (n)	29.7 (37)	16.1 (31)	21.9 (32)	23.2 (220)	25.4 (228)	18.5 (227)
Difference (se) ²	7.8 (10.5)	-5.8 (9.8)		4.7 (3.8)	6.9 (3.9)	
p-value ³	0.585	0.750		0.245	0.089	

¹ A weighted difference is not calculated for males due to the small sample size within some countries, so the unadjusted difference is shown.

² 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.

³ 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.

Note: Six patients are not included in the ITT population of study 307 and only United States centers are in the ITT population of study 351.

5.2.4 Reviewer's Conclusions for Analyses by Gender

In female patients, based on the SGA of Relief, a treatment effect is demonstrated in study 301 for both the 4 mg and 12 mg doses and supported by a post-hoc analysis of study 351 for the 12 mg dose but not replicated in study 307. No treatment effect is demonstrated in male patients. The active treatment was numerically worse than placebo in males, resulting in treatment differences of -8% in study 301 for the 12 mg group and -2% in study 351 for both the 4 mg and 12 mg groups. The lack of a treatment effect is possibly due to gender differences and/or the small number of male patients in each study. In addition, per the medical reviewer, the results for male and female patients may indicate a difference in the pathophysiology of C-IBS between genders.

6 RECOMMENDATION

From a statistical standpoint, the sponsor has provided studies that are well controlled but not adequate to show evidence for efficacy in support of their proposed claim for treatment of irritable bowel syndrome (IBS) constipation as their predominant symptoms.

Instead, a treatment effect is demonstrated in female patients with constipation predominant irritable bowel syndrome (based on a global assessment of relief that incorporates overall well-being, symptoms of abdominal discomfort and pain, and bowel habit) in one study and supported in a post-hoc analysis of a second study but not replicated in a third study. No treatment effect is demonstrated in male patients.

The following is a list of inadequacies:

1. Efficacy has not been adequately assessed in male patients with constipation predominant IBS.
2. The effect of treatment on abdominal pain has not been adequately assessed.

/S/

7-5-00

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Concur:

/S/

Ed Nevius, Ph.D.
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7-6-00

**APPEARS THIS WAY
ON ORIGINAL**

/S/

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7/5/00

cc:
NDA 21-200
HFD-180/Division Files/L. Talarico/H. Gallo-Torres/R. Joseph/P. Levine
HFD-715/File Copy/E. Nevius/M. Welch/T. Permutt/S. Castillo

S. Castillo/x71658/Microsoft Word/6/29/00
This review contains 22 pages of text and tables.