Table 3/ Sponsor's results[a]
Mean Daily Frequency Analysis of Cross-Over Effect/ Study 851/3

Treatment	Treatment orders 17g,p,34g	17g,34g,p	34g,p,17g	34g,17g,p	F (DF)	p-value
Placebo x(SE)	0.33(.17)	0.40(.06)	0.63(.06)	0.36(.05)	5.44 3,45	0.003
n	9	14	14	12		
17g x(SE)	0.51(.09)	0.52(.06)	0.72(.08)	0.53(.12)	1.47 3,43	0.23
n	8	15	13	11		
34g x(SE)	0.85(.26)	0.73(.14)	0.69(.08)	0.90(.24)	0.31 3,38	0.82
n	7	11	12	10		

[a] Sponsor Table 3.9, vol.1.4.2, p.3-27

As with the previous analysis, the sponsor did not specify the study population analyzed. However, from the above table one concludes that the number of patients analyzed in each treatment order was changing from one treatment to another. These changes are shown in the following table.

Table 4
Change in the number of patients analyzed
for cross over effect/ Study 851-3 [a]

Treatment Order	Treatment 17g	placebo	34 g
1	8	9	7
2	14	15	11
3	14	13	12
4	12	11	10

[a] Extracted from the sponsor's Table 3.9, vol 1.4.2, p.3-27

The sponsor did not explain as to how these changes in number of patients analyzed occurred, and did not address handling of missing data and the impact of missing data on the results. This reviewer will re-analyze the sponsor's data for cross-over effects in Section IV.A.II (p. 17).

II.A.I.c. Sponsor's Further Analysis:

Based on the results of the cross-over analysis, and on Dr. Fredd request, during the meeting held on 8/20/1990, as the sponsor claimed, the sponsor analyzed efficacy data for the first treatment period. The results of this analysis for comparing the mean daily of bowel movements is presented in Table 5.

Table 5/ sponsor's results
Comparison of mean daily of bowel movement frequency
First Treatment period/ Study 851-3 [a]

	17 grams	34 grams	p-value
mean(SE)	0.52(0.05)	0.80(0.09)	0.05

[a] Sponsor's table 3.11, vol 1.4.2, p.3-30.

The sponsor's efficacy results for patients with ≤ 2 bowel movements during the control period are presented Table 6.

Table 6/ Sponsor's results[a]
Comparison of 1st treatment period with placebo period
(Patients with ≤ 2 b.m. during the control period
(not constipated requires >3 b.m.)

Treatment period	Constipated	Not constipated
First (all doses)	12(39%)	19(61%)
Placebo	26(84%)	5(16%)

χ^2=11.5, p<0.001
[a] Sponsor's Table 3.12, vol .1.4.2, p.3-32

Taking into account that the application is for the 17 gram dose, the sponsor's comparisons in the last two tables are not relevant in this reviewer's opinion. In Table 5 comparison of the 17 gram response should have been made against that of the placebo (not that of 34 grams). Similarly the comparison in Table 6 should have been made for the 17 gram dose (not all doses). Furthermore, aside from the fact that the number of patients or the study population analyzed are not specified, the placebo efficacy response in the Table 6 is in error. According to this reviewer's analysis, the placebo response rate is 48% instead of the 16% listed above (see reviewer's analysis, Table 13, p. 22). Also the criteria for constipation used in Table 6 is not consistent with other criteria used to define constipation in this NDA. The following section presents this reviewer's comments concerning this study.

II.A.II Reviewer's Comments and Proposed Analysis/ Study 851-3:

In the following, this reviewer raises some issues about the design of the study and the clinical endpoints analyzed, and proposes ways of handling them. These propositions form the basis of this reviewer's re-analyses in Section IV (pp. 17-24).

i) Criteria for patient's enrollment: The criteria used for patients enrollment in this study differs from that of the second pivotal study (851-6). In study 851-3 patients with three or less bowel movements per week and /or less than 300 grams of stool per week were enrolled. But according to Dr. Fredd and the medical officer, Robert Prizont, M.D., the agency criteria for constipation is that a patient have less than 3 bowel movements per week. Consequently, patients with 3 bowel movements during the control period can not be considered constipated and should not have been included in the treatment period.

Among the 50 patients who enrolled in the study there were 17 patients with 3 bowel movements and 2 patients with 4 bowel movements during the one week control period. Having 19 (38%) patients out of 50 (the total study population) who do not meet the constipation criteria makes efficacy analysis based on the total study population inappropriate. To find out the affect of choosing this patients population on the efficacy results this reviewer carried out analysis for the total study population as well as for the subgroup of patients with < 3 bowel movements during the control period (see Tables 12-14, pp. 22-24, of this review). In this reviewer's assessment, the primary analysis should be that dealing only with constipated patients, i.e., 31 patients for this study.

ii) Study design and conduct: Even though the study design calls for distributing the patients among the three treatment arms (placebo, 17 g and 34 g), no patient was placed on placebo during the first treatment period. Thus, causing the cross-over design to be incomplete cross-over, and creating difficulties in handling carry-over effect. Also, unusually, there was no wash out period in between treatment periods. However, the sponsor

decided to analyze the last seven days of each treatment leaving the first 3 days to account for the possibility of carry-over effect. Clearly the above conduct of the trial, unnecessarily, complicates the analysis.

This reviewer will test for the presence of carry-over effect by using data from all patients as well as from the 31 constipated patients. The efficacy of the drug will be compared with that of placebo which have the least minimum carry-over effect. This is, in this reviewer assessment, the best one can do in the presence of contaminated placebo response.

iii) Primary endpoint and statistical methods for analysis:
Following Dr. Fredd's suggestion to the sponsor during the 8/20/90 meeting, this reviewer's analysis focuses, as discussed on page 3, on the binary endpoint (success/ failure) and to a less extent on the frequency of the mean bowel movements. In addition to the clinical preference for analysis of this binary endpoint there is also a statistical reasoning. It is known that the mean is influenced by outliers, but outliers (large number of bowel movements or diarrhea) in the presented NDA is viewed by the sponsor as treatment failure. The sponsor did not specify, however, the number of bowel movements in this case.

As the length of the study treatment period is 10 days, choice of the above binary endpoint requires one to decide on the number of bowel movements for a treatment to be considered successful. The sponsor did not deal with this issue since the analysis was based, as discussed, on the last 7 days of each treatment period. Section IV.A (p.17) presents results of analyses which refer to 3 periods:

a) the first 7 days of each of the 10-day treatment period, as suggested Dr. Fredd, Director of the Gastrointestinal and Blood Products Division, during a progress review meeting on July 2, 1996 (see Section IV.A.III.a, p. 19)

b) the last 7 days of each of the 10-treatment period to find out whether the sponsor's approach of handling the carry-over effect was effective, and

c) the entire 10-day treatment period. Here, this reviewer and in a consultation with the medical officer, R. Prizont, M.D., extrapolated the definition of constipation (<3 bowel movements per week, see p. 8) to < 4 bowel movements during the 10-day treatment.

II.B. Study Braintree 851-6:

This was a multi-center (4 centers) parallel design study aimed to evaluate the efficacy of a 17 gram dose of 851 laxative daily versus placebo in a blinded randomized trial. Subjects were enrolled after a 1 week qualification period during which they had less than 3 bowel movements. Qualified subjects were randomized to a 14 day treatment period on either placebo (dextrose) or 17 gram dose of 851 laxative. The primary outcome variable was stool frequency.

The number of patients to be enrolled in the study was not uniquely specified. The study protocol stated in one place 150 patients and in another place 200 patients. In a meeting between the sponsor and the GI Division on 3/9/94, the sponsor stated that about two thirds of the 200 patients have been enrolled, and based on the efficacy results available then, the sponsor requested to stop the trial. The study was terminated after enrolling 151 (20M/131F) patients based on the results of interim analyses (the sponsor did not specify how many analyses).

The original protocol was amended to include, based on the Agency request, among other things, a provision for an interim analysis after 50 patients from each treatment group have completed the protocol. The sponsor specified that the O'Brien and Fleming method [Biometrics 35: 549-556, 1979] will be used to maintain the level of significance ≤.05. But in the NDA submission the sponsor considered values of p ≤ .04 to be significant. In addition, the sponsor considered another boundary for the p-value, 0.05, when presented the results of the first interim analysis.

The sponsor analyzed the efficacy data for the first and second 7-day segments as well as for the entire 14 days treatment. These analyses were done for the evaluable and ITT groups. According to the sponsor's criteria, the evaluable group includes only patients who have completed at least 3 days in the first treatment week analysis and the ITT group includes all patients entering the treatment phase. In carrying out the analysis the sponsor defined treatment success as having more than three bowel movements per 7-day period, and treatment failure as having less than three bowel movements per 7-day period, but the sponsor did not specify how the case of 3 bowel movements would be handled.

II.B.I Sponsor's Results/ Study 851-6:

A summary of the sponsor's efficacy results along with this reviewer's comments about these results are presented in this section.

The sponsor pointed out that the efficacy analysis was based on 147 patients (4 patients were excluded; one for non-compliance, one was inadvertently re-enrolled and two patients were withdrawn by the investigator following abnormal baseline labs). In addition, the sponsor stated that only 131 of the 151 patients fully completed the protocol.

The sponsor presented what was called a comparison of the center-by-center efficacy results. This comparison displays the ratio of total number of successes (active drug and placebo combined) to the total number of failures for each center. A copy of the sponsor's comparison is presented in Attachment 2 (p.33).

The sponsor's approach for testing homogeneity of the treatment responses across the study centers does not achieve its purpose. Instead one might compares the response rates for the drug and placebo, or alternatively the odd-ratios, across the study centers. This reviewer's analysis for testing homogeneity across centers is given in Section IV.B.I, p. 25.

Table 7 summarizes the sponsor's efficacy results for the bowel movement frequency for the 'evaluable group' for each week of

treatment as well as for the 2 weeks combined.

Table 7/ Sponsor's results
Treatment Success Evaluable Data, By week
and for the 2 Weeks combined/ Study 851-6 [a]

	Week 1		Week 2		Week 1 and Week 2	
	Success	Fail	Success	Fail	Success	Fail
lax 851(n)	68.5% (50)	31.5%(23)	76.1% (54)	23.9%(17)	72.2%(104)	27.8%(40)
placebo(n)	50.7% (34)	49.3%(33)	48.4% (31)	51.6%(33)	49.6% (65)	50.4%(66)
	$p<0.04$, $X^2=4.59$, n=140		$p<0.001$, $\chi^2=11.01$, n=135		$p<0.001$, $X^2=13.85$, n=275	

[a] Compiled from the sponsor's Tables: 6.4 (p.6-22), 6.5 (p.6-24) and 6.6 (p.6-25)
Success was defined >3 BM and failure was defined <3 BM per week

Table 8 presents similar results to that of the Tables 7 for the ITT group.

Table 8/ Sponsor's results[a]
Treatment Success ITT Data, By week and for the 2 Weeks combined,

	Week 1		Week 2		Week 1 and Week 2	
	Success	Fail	Success	Fail	Success	Fail
lax 851(n)	63.3%(50)	36.7%(29)	68.3%(54)	31.6%(25)	65.8%(104)	34.2%(54)
placebo(n)	50% (34)	50%(34)	45.6% (31)	54.4%(37)	47.8% (65)	52.2%(71)
	$p>0.05$, $X^2=2.64$, n=147		$p<0.005$, $\chi^2=7.77$, n=147		$p<0.005$, $\chi^2=9.72$, n=294	

[a] Compiled from the sponsor's Tables: 6.7, 6.8 and 6.9 (p.6-27)
Success was defined >3 BM and failure was defined <3 BM per week

It can be seen from Tables 7 and 8 that the sponsor in analyzing the two weeks combined assigned two scores for each patient completed the first treatment week and entered the second, i.e. one for each week of treatment. By considering the patient/week as the unit of measurement one increases the number of patients analyzed and consequently reduces the standard errors of the estimates. This might lead to significant results even though the one week results might be not.

According to the medical officer, R. Prizont, M.D., the primary analysis should center on the efficacy results for the first week since a patient would not wait for more than a week to see the efficacy results of laxative treatment.

Also, for this reviewer, there is another factor which requires one to discriminate among the three periods (first week, second week and the two weeks combined) analyzed. It is reasonable to assume, if the treatment is effective, that after the first week of treatment some of the patients would no longer meet the definition of constipation at the start of the second week of treatment. Consequently, if efficacy is to be expressed in terms of relieve of constipation one should focus on first week data take those for the second week and the two weeks combined (without doubling the patients) as supportive.

Furthermore, there is a technical issue related to the sponsor's analysis. If one is looking for efficacy results at either week 1 or week 2 or both weeks combined, without discrimination, one needs to make an adjustment for multiple comparisons.

II.B.II Reviewer's Comments and Proposed Analysis/ Study 851-6

This section addresses several issues concerning data consistency, analysis methods and primary endpoint/period for analysis. Also, presented in the section this reviewer's approach to handling these issues when carrying the analyses in Section IV.B.III.

i) Inconsistency in the data: In addition to the inconsistency in the number of patients planned to enroll in the study, as discussed above, there is also inconsistency in the number of withdrawals from the study.

The original submission states that 7 patients were excluded (patients # 6, 133, 308, 309 for lack of compliance, patient 144 was re-enrollment to patient 114 and patients 207 and 217 were withdrawals by the investigator following abnormal baseline labs). This number of withdrawals changed later, based on the sponsor's request, to 4 patients. Thereafter, another change occurred when the sponsor presented a list of 10 withdrawals from this study in their supplement, dated May 9, 1996. The sponsor marked this list as 'interim analysis data not audited or confirmed'.

There are justifications, in this reviewer's judgement, to argue against the exclusion of some of these patients at least. For example, patient 144 supposed to be re-enrollment to patient 114, but there are efficacy data for both patients, 114 (placebo) and 144 (laxative), for the entire 14 days study period. So which patient should be included/ excluded ? Also, patients 207 and 217 were withdrawals by the investigator following abnormal baseline labs. But the study plan requires physical exam and lab work to be done during the qualification period, i.e., before the start of the treatment period. However, these two patients not only were enrolled but they have efficacy data for 4 and 7 days, respectively. Other patients (#6, 133, 308, 309) were withdrawn for lack of compliance, but the sponsor did not specify when this occurred.

It is assumed, in this reviewer's analysis in Section IV.B. (P.25), that a total enrollments of 200 patients was planned. The actual enrollment shown by the sponsor's data was 152 patients. There is no baseline data for patients #8, this leaves 151 patients for the Intent-to-Treat Analysis. No efficacy data were available for 6 patients (#'s: 6, 8, 130, 305, 308, 309) and all of these patients were randomized to the laxative treatment.

ii) Handling missing values: This reviewer's handling of the missing values is as follow:

(a) missing values for part of the treatment week (< 7 days) were assigned '0' bowel movement frequency and

(b) missing data for the whole treatment week (7 days) were handled by two ways; one assigning them 0 values as in (a) and the second deleting them from the analysis.

iii) Primary treatment period and endpoint for analysis: Following the discussion below Table 8 (p.12 of this review), efficacy data for the first week of treatment will be taken as the primary period for efficacy analysis. The choice of primary period for analysis cancel the need for adjustment for multiple comparisons needed when one look for efficacy at different periods as the sponsor did.

Following the same reasoning for Study 851-3 (see p.8 of this review) the percentage of success will be taken as the primary endpoint. A treatment success is taken as a patient having three bowel movements or more in a week.

iv) Number of Interim Analyses: The study protocol, as discussed, called for carrying out an interim analysis after 50 patients from each treatment group have completed the protocol. In addition, the sponsor terminated the trial based on the results of an interim analysis done when 151 patients completed the study. But, in a response to this reviewer's request about the number and results of previous interim analyses, the sponsor presented on May 9, 1996 results of an interim analysis based on actual enrolment of 119 patients, as the sponsor stated. However, the sponsor's accompanying patients data list shows a total of 127 patients.

It is not clear to this reviewer whether the sponsor conducted one interim analysis when 119, instead of 100, patients completed the trial, in addition to the final one, or 3 interim analyses were done when 100, 119, 127 in addition to the final one. This reviewer's statistical analysis assumes that two interim analyses were done, as the sponsor claimed. One when 119 patients completed the trial and the final one. This number of interim analyses will be used to calculate the α-boundaries in the following Section IV.B.II, p. 25.

III. Description of the Non-Pivotal Studies:

In addition to the two pivotal studies the sponsors submitted results for two non-pivotal studies (Study 851-4 and Study 851-5). A summary of these studies is given below.

III.A. Study 851-4:

This study was conducted in an elderly nursing home population with design similar to that Study #851-3. The study goal was to compare two doses (17g and 34g) of PEG and placebo. But when 4 of the first 5 patients enrolled developed diarrhea with the PEG, the study doses were decreased to 6 and 12 grams. The sponsor

stated that 35 (16M/19F) patients were enrolled and 17 completed the entire study protocol.

Primary outcome variables were stool frequency, but according to the sponsor stool collection proved very difficult, and therefore this study is presented only as an indication for an appropriate dose for elderly nursing home residents. In discussing the efficacy results the sponsor stated that no significant difference between the treatments could be determined, but in comparison to the control period the first treatment period resulted in a significant increase in both stool weight and frequency.

III.B. Study 851-5:

This study was designed to compare a single daily dose of laxative (17 grams) and placebo in constipated patients in a similar fashion to that of Study 851-6. Patients were enrolled in the study if they had less than 3 bowel movements during a week of placebo treatment or they were constipated in the opinion of the investigators. According to the sponsor 25 (1M/24F) patients were enrolled and 24 completed the study and that about half (13) of the enrolled patients had 3 or more bowel movements during the control period.

The sponsor compared the mean bowel movements frequency of the laxative treatment and the placebo and reported a p-value of 0.002 for the 14 day treatment period and a p-value of 0.25 for the first treatment period (this reviewer assumes the first week of treatment). The sponsor did not state the number of patients involved in each comparison.

IV. Reviewer's Evaluation and Comments:

This section presents the reviewer's evaluation and comments based on the re-analysis of the efficacy data for the pivotal studies 851-3 and 851-6. The statistical analysis takes into account some of the issues this reviewer raised about these studies in Section II and the way of handling them.

IV.A. Reviewer's Re-Analyses/ Study 851-3:

The re-analyses addresses the randomization of the trial, the carry-over effect, and the efficacy results.

IV.A.I. Randomization:

Following the control period, patients were distributed between two treatments (17g and 34g). The following table summarizes the treatment sequence which patients followed, along with number of patients in each treatment arm.

Table 9/ Reviewer's analysis, Study 851-3
Allocation of patients to treatment

Order	1st treatment	2nd treatment	3rd treatment	no. Patients
1	17 g dose	placebo	34 g dose	9
2	17 g dose	34 g dose	placebo	15
3	34 g dose	placebo	17 g dose	14
4	34 g dose	17 g dose	placebo	12

Table 9 shows that the number of patients in the four treatment sequences varies from 9 to 15 patients. It is not clear what causes this imbalance in the number of patients. Perhaps on-site investigation can clear this issue.

Ordering the patients by their chronological order showed runs of a single treatment. Having that, this reviewer addresses the following question: Are the patients who completed the control period randomly distributed between the two treatments (17g and 34g)? Are the patients who completed the first treatment randomly distributed between the two treatments for the second treatment period ?

Application of the run test to answer the above questions resulted in p-values 0.112 and 0.219 respectively. These p-values suggest that the deviations from random allocation of patients between the two treatments, following the control period and the first treatment, were not statistically significant.

IV.A.II. Analysis for Carry-Over Effects:

In order to test for carry-over effect this reviewer made the following assumption: If there is a carry-over effect it would be

from the laxative treatment to placebo, and that this carry-over effect is proportional to the laxative dose. Following this assumption, this reviewer test for carry-over effect consists of:

(i) comparing the mean of placebo response following the 17g and the 34g doses, for all patients as well after excluding patients with 3 or more bowel movements during the control period. However, excluding patients with 3 or more bowel movements during the control period reduces the size of the study. Consequently, a non-significant effect may be due to lack of power.

(ii) comparing the percentage of successes for the patients in part (i). However, this is not a planned analysis end point for the current trial, but the justification for this analysis was discussed in pages 3 and 8.

Table 10 presents this reviewer's analysis for testing for the presence of carry-over effect by comparing the placebo responses following the 17g and the 34g doses of 851 laxative.

Table 10/ Reviewer's Analysis, Study 851-3
Comparison of the mean bowel movements and the response rates for placebo treatment following two doses(17g and 34g) of laxative

Treat. Order	N.Pat	Mean(SE)	p-value[1]	% success [3]	p-value[2]
A) All patients					
i)10 days treatment					
17g, placebo	21	3.476 (0.382)		48% (10/21)	
34g, placebo	29	5.000 (0.479)	0.023	69% (20/29)	0.128
ii)Last 7 days treatment					
17g, placebo	21	1.809 (0.245)		5% (1/21)	
34g, placebo	29	2.793 (0.274)	0.014	21% (6/29)	0.215
B) Excluding patients base ≥ 3					
i)10 days treatment					
17g, placebo	13	3.231 (0.426)		46% (6/13)	
34g, placebo	18	3.889 (0.449)	0.313	50% (9/18)	0.833
ii)Last 7 days treatment					
17g, placebo	13	1.615 (0.241)		0% (0/13)	
34g, placebo	18	2.222 (0.275)	0.124	11%(2/18)	0.497

[1] p-value is based on the t test

[2] p-value is based on the χ^2 test, or continuity adjusted/Fisher's exact test when an expected cell frequency is less 5.

[3] For the 10-treatment success is taken as ≥ 4 b.m.

Part (A-i) of Table 10 shows that the mean bowel movement frequency for patients on placebo following the 34 grams is significantly higher than that following the 17 grams. This raises the possibility of over estimating the placebo response. Consequently, comparison of the treatment response with that of the placebo underestimates the efficacy of the treatment. On the other hand, comparison the percentage of success shows that the difference between the two placebo rates, even though it is about 20%, is not statistically significant. This might be due to the small sample size.

Part(A-ii) of Table 10 shows in comparison to part (A-i) that, approximately half of the placebo 10 days bowel movement frequency occurred during the first three days. In addition, it shows that placebo response following the 34g dose still significantly greater than that of the 17g dose. This indicates that comparison of the frequency of bowel movements of the laxative with that of placebo following a 34g dose is biased against the laxative treatment even if one analyzes data on the last 7 days of the 10-day treatment.

Part (B) of the Table 10 shows that the difference between the placebo responses, whether in terms of bowel movement frequency or percentage of success, are lower than those in part (A) indicating that most of the carry-over effect occurred in patients with ≥ 3 bowel movements at the base line.

IV.A.III. Efficacy Analysis:

IV.A.III.a. Analysis Requested by Dr. Fredd:

During a progress review meeting held on July 2, 1996, Dr. Fredd requested comparison of the mean bowel movements for all treatment and across all periods, disregarding the presence or absence of a carry over effect. Dr. Fredd requested also comparison of the corresponding percentage of success for the first 7 days out of each 10-day treatment period. Table 11(p. 20) presents the comparison's results for the means and percentage of success.

In judging the efficacy results of Table 11 one needs to make adjustments for multiple comparisons. The Duncan-Waller method

addresses comparison of the mean multiplicity by finding the least significant difference. According to this method there is no significant difference between the mean bowel movements of placebo and the 17g dose or between those of the 17g and 34g doses. But the mean bowel movements of the 34g dose is significantly higher than that of the placebo. Comparison of the mean bowel movements, or their ranks, gives the same conclusion as that of the Duncan-Waller grouping.

Table 11/ Reviewer's Analysis, Study 851-3
Comparison of the mean bowel movements and the response rates

Treatment	10days mean b.m.	p-value[1]	Duncan-Waller Grouping[2]	Wilcoxon Rank test p-value[3]	First 7 days % success	p-value[4]
placebo	4.360		A		68% (34/50)	
17g	5.592	0.023	A B	0.035	70% (35/50)	0.830
34g	6.620	0.003	B	0.010	76% (38/50)	0.373
17g vs. 34g		0.184		0.481		0.499

[1] p-value is based on the t-test
[2] Means with same letter are not significantly different; minimum significant difference = 1.3251.
[3] p-values based on the χ^2 approximation
[4] p-value is based on the χ^2 test, or continuity adjusted/Fisher's exact test when an expected cell frequency is less 5.

Table 11 shows also comparison of the percentage of success for the first 7 days of each of the 10-day treatment period. Here, the results of the comparison fail to show significant results for any two treatments compared, this might be due to small sample size.

The results of the comparisons in Table 11 should be interpreted with caution since efficacy data are contaminated by the carry-over effect. Testing for a carry-over effect from the laxative to placebo treatment was discussed in Section III.A.II. In the following section I present results of various comparisons aimed toward reducing the carry-over effect, since there is no simple method for evaluating treatment's efficacy when treatment response is contaminated by a carry over effect.

IV.A.III.b. Analysis in the Presence of Carry Over Effect:

In this section I present several analyses for evaluating the drug efficacy with the goal of minimizing the carry-over effect.

In order to estimate the placebo response which is free of the carry-over effect one needs to have placebo treatment which is not precedent by an active treatment. For the current trial only the control period meets this requirements. But, since the number of patients enrolled in the control period was not given, only the number of those who failed placebo treatment was given, one can not estimate the (true) placebo response. Having given this and the possibility of a carry-over effect from one dose to another dose of the active treatment the only alternative approach is to look for subsets of the data for which the carry over is minimum. There are several possibilities in this regard. Thus to eliminate the carry over effect from one dose to another of the active treatment, one might compare the response of the active treatment in first treatment period with that of the placebo in same arm. The placebo response, however, still contaminated. One can use the results of Table 10 (p.18) to reduce this contamination by excluding patients with 3 or more bowel movements during the control period. However, this reduces the size of the study, and consequently, non-significant difference in efficacy may be due to low power of the test.

Table 12 (p. 22)compares the first treatment efficacy results of 17g and 34g doses versus placebo in each treatment arm. This compares the response of the 17g dose versus that of placebo in orders 1 and 2 of Table 9, and compares the response of 34g dose against that of placebo in orders 3 and 4 of Table 9.

By comparing (i) and (ii) in Table 12 one can see that all treatment responses (frequency as well as success rate) for patients with < 3 bowel movements during the control period (part ii) are lower than their analogues when all 50 patients analyzed (part i). However, the magnitude of the difference between the laxative and placebo responses is similar for these two patient populations.

Table 12 shows that the mean bowel movements of the 17g dose is significantly higher than that of the placebo. But this is not the case for comparing the mean bowel movements 34g dose and placebo. This lack of significance might be attributed, however, to the different placebo responses used in the comparisons. Table 12 shows that the mean placebo response used in the 17g dose comparison is 3.625 bowel movements, which is numerically lower

than that used in the 34g dose comparison, 5.038 bowel movements.

Table 12/ Reviewer's Analysis, Study 851-3
Comparison of the mean bowel movements and % of success for the 1st treatment

Treatment	N.Pat	Mean(SE)	p-value[1]	% success [3]	p-value[2]
i)10 days treatment, all patients					
1st trt 17g	24	5.000 (0.442)		67% (16/24)	
placebo	24	3.625 (0.407)	0.023	46% (11/24)	0.146 (0.245)
1st trt 34g	26	6.846 (0.828)		73%(19/26)	
placebo	26	5.038 (0.495)	0.067	73%(19/26)	1.00 (0.755)
ii)10 days treatment, excluding patients base ≥ 3					
1st trt 17g,	15	4.267 (0.358)		53%(8/15)	
placebo	15	3.067 (0.317)	0.018	33%(5/15)	0.269(.462)
1st trt 34g,	16	6.187 (0.963)		63%(10/16)	
placebo	16	4.125 (0.515)	0.069	63%(10/16)	1.00(.715)

[1] p- value is based on the t-test
[2] p- value is based on χ^2(Fisher's Exact)test
[3] For the 10-treatment success is taken as ≥ 4 b.m.

To avoid the problem of comparing with two placebo responses Table 13 compares the laxative response rates with that of the placebo during the trial.

Table 13/ Reviewer's Analysis, Study 851-3
Comparison of the mean of bowel movements and % of success for the first treatment with those of all Placebo patients

Treatment	N.Pat	Mean(SE)	p-value[1]	% success [3]	p-value[2]
i)10 days treatment, all patients					
All placebo	50	4.360(0.335)		60% (30/50)	
1st trt 17g	24	5.000(0.442)	0.268	67% (16/24)	0.580(.619)
1st trt 34g	26	6.846(0.828)	0.009	73% (19/26)	0.258(.318)
ii)10 days treatment, excluding patients base ≥ 3					
All placebo	31	3.613(0.317)		48% (15/31)	
1st trt 17g	15	4.267(0.358)	0.215	53% (8/15)	0.753(1.00)
1st trt 34g	16	6.187(0.963)	0.020	63% (10/16)	0.358(.538)

[1] p- value is based on the t-test
[2] p- value is based on χ^2 (Fisher's Exact)test
[3] For the 10-treatment success is taken as ≥ 4 b.m.

The results of Table 13 shows that even though the 17g dose response (bowel movements and success rate) is numerically greater than that of the placebo, the difference is not statistically significant. This is because the combined placebo response of 4.36 bowel movements is greater than 3.625 which is the placebo response used for the 17g treatment sequence. Therefore, this analysis would be biased against the 17g dose. The mean bowel movements of the 34g dose is significantly higher than that of the placebo. This is because now the placebo mean response is reduced by combining two placebos of the two treatment sequences. The results of comparing the mean bowel movements after excluding patients with 3 or more bowel movements during the control period, part (ii) of Table 13, are similar to that of Part (i). The change in the level of significance can be attributed to the smaller sample size in (ii) in comparison to that in (i).

Table 13 shows also that the percentage of success for the 34g dose is not significantly different from that of placebo disregarding the population analyzed. Here the laxative response rate, for either dose, is not significantly different from that of placebo.

Since placebo response following the 17g dose is less contaminated than that following the 34g dose (see Table 10, p. 18), a reasonable way to reduce the effect of this contamination on the efficacy results is to compare the treatment response with that of placebo following the 17g dose only. Such comparison is useful for the efficacy analysis when patients with 3 or more bowel movements during the control period are excluded from the analysis.

Table 14 (p. 24) presents the efficacy results for the first 7 days of the 10-day treatment as well as for the total 10-day treatment. The analysis for the first 7 days of the 10-treatment period is made in response to Dr. Fredd's suggestion to calculate response rates for the first 7 days of the 10 days of treatment (see p. 19).

Table 14/ Reviewer's Analysis, Study 851-3
Comparison of mean of bowel movements and % of success for the 1st treatment (for all placebo following 17g dose)

Treat.	N.Pat	Mean(SE)	p-value[1]	% success [3]	p-value[2]
A)First 7 days treatment					
i)All patients					
placebo after 17g	21	2.571 (0.328)		57% (12/21)	
1st trt 17g	24	3.958 (0.392)	0.011(.048)	71% (17/24)	0.338(.369)
1st trt 34g	26	5.269 (0.705)	0.001(.026)	73% (19/26)	0.252(.355)
ii)Excluding base ≥ 3					
placebo after 17g	13	2.154 (0.355)		46% (6/13)	
1st trt 17g	15	3.267 (0.316)	0.027(.083)	60% (9/15)	0.464 (.705)
1st trt 34g	16	4.937 (0.951)	0.013(.027)	56% (9/16)	0.588(.715)
B)10 days treatment					
i)All patients					
placebo after 17g	21	3.476 (0.382)		48% (10/21)	
1st trt 17g	24	5.000 (0.442)	0.014(.286)	67% (16/24)	0.197(.237)
1st trt 34g	26	6.846 (0.828)	0.001(.0004)	73% (19/26)	0.074(.130)
ii)Excluding base ≥ 3					
placebo after 17g	13	3.231 (0.426)		46% (6/13)	
1st trt 17g	15	4.267 (0.358)	0.072(.710)	53% (8/15)	0.705 (1.00)
1st trt 34g	16	6.188 (0.968)	0.011(.178)	63% (10/16)	0.379(.467)

[1] p-values is based on the t-test (median 2-sample test, normal approximation)

[2] p-values is based on the test χ^2(Fisher Exact) test

[3] For the 10-treatment success is taken as ≥ 4 b.m.

The results of the comparison in Table 14 are similar whether one analyze data from the first 7 days of treatment or analyze data for the whole 10 days of treatment. The various comparisons show that the mean bowel movements for either dose is significantly higher than that of the placebo. In general, when one excludes patients with 3 bowel movements or more during the control period from the analysis the p-value increases from that for the total patients and the mean bowel movements for the 17g dose during the 10-day treatment period become not significant. Efficacy results in terms of the percentage of success are not significant disregard of the dose or the patients analyzed.

The results of Table 14 are consistent with those of previous analysis (see Tables 11-13), yet they are stronger since placebo response in Table 14 is lower, as a result of the carry-over effect, than those in Tables 11-13.

IV.B. Reviewer's Analysis/Study 851-6:

This analysis addresses the center-by-center efficacy results, adjustment for interim analyses and finally the efficacy results.

IV.B.I. Center-by-Center Efficacy Results:

Table 15 presents the center-by-center efficacy results for each week of treatment as well as for the two weeks of treatment combined.

Table 15/ Reviewer's Analysis, Study 851-6
Efficacy Results by Center and Treatment Period

Center	Treat	Week1	p-value[a]	Week2	p-value	Wk1&Wk2 [b]	p-value[a]
1	lax	52%(12/23)		70%(16/23)		57%(13/23)	
	Placebo	65%(15/23)	.37(.55)	43%(10/23)	.07(.14)	57%(13/23)	1.0(1.0)
2	lax	65%(17/26)		65%(17/26)		58%(15/26)	
	Placebo	46%(11/24)	.16(.25)	50%(12/24)	.27(.39)	42%(13/23)	.26(.40)
3	lax	78%(14/18)		78%(14/18)		72%(13/18)	
	Placebo	36%(5/14)	.02(.03)	43%(6/14)	.04(.07)	36%(5/14)	.04(.07)
4	lax	57%(8/14)		57%(8/14)		57%(8/14)	
	Placebo	44%(4/9)	.55(.68)	33%(3/9)	.27(.40)	33%(3/9)	.27(.40)
Breslow-Day test of homogeneity p-value		.099		.837		.426	

[a] Based on the χ^2 (Fisher exact) test

[b] Success (failure)is defined as having $\geq(<)$ 6 bowel movements during the 2 weeks.

Table 15 shows that the response rate for the 17g dose is consistently higher than that of placebo for all centers and periods analyzed, except for the first week of treatment in center 1. The difference in the efficacy results among centers was not significant according to the Breslow-Day test of homogeneity. Consequently, this reviewer's analysis considers efficacy data from all centers combined.

IV.B.II. Adjustment for Interim Analyses:

Based on the sponsor's information that two interim analyses (one at the enrollments of 119 patients and the final one) were done

the appropriate boundaries for the significance level at each of these two analyses, as well as that if the trial continued, are the following:

Appropriate Boundaries for stopping the trial under α =0.05 [a]

Analysis	n	O'Brien-Fleming	Pocock
1 (α_1)	119	.008	.038
2 (α_2)	151	.018	.019
3 (α_3)	200	.043	.017

[a] α-levels are computed by using EaSt Software for the binomial endpoint.

Thus to maintain the nominal 0.05 level, comparison of the percentage of success at the final (second) analysis should be done at the .018 by the O'Brien-Fleming significance level, and not at the .04 or .05 which the sponsor specified in different places (see p.10).

IV.B.III. Efficacy Results:

Table 16 (p.27) compares the efficacy results for the two endpoints: mean bowel movements and the percentage of success of 17g dose of laxative against that of placebo. The table shows comparisons for each week of treatment and for the two weeks combined. In addition, the two approaches, discussed in Section II.B.II(p.14) for handling all-week missing data are considered. In the first missing values are imputed as zero and in the second missing data are deleted from the analysis.

Table 16 shows that the efficacy results are greatly dependent on the way of the handling the missing values (compare entries of part I and II of the table). The magnitude of the response is influenced by the way of handling these missing values which mostly occurred in the laxative treatment. The change in the level of significance as a result of handling the missing values is driven by the change in the response as well as the change in the number of patients.

Table 16/ Reviewer's Analysis, Study 851-6
Comparison of % of success and mean of bowel movements frequency for each treatment week and for the weeks combined, ITT group

Period/ Treatment	Mean Bowel Movement n	$\bar{X}$ (SE)	p-value	% of success (3+ BM/S per wk)	p-value
I) Missing data for a week are set =0					
Week 1					
laxative	81	4.049(.354)		63%(51/81)	
Placebo	70	3.128(.345)	.066	50%(35/70)	.109(.138)
Week 2					
laxative	81	4.074(.362)		68%(55/81)	
Placebo	70	2.943(.610)	.114	44%(31/70)	.003(.005)
Week 1 + Week 2					
laxative	81	8.123(.670)		60%(49/81)	
Placebo	70	6.071(.922)	.076	44%(31/70)	.047(.052)
II) Weeks with missing data are deleted					
Week 1					
laxative	76	4.316(.356)		67%(51/76)	
Placebo	70	3.129(.345)	.018	50%(35/70)	.036(.044)
Week 2					
laxative	72	4.583(.365)		76%(55/72)	
Placebo	65	3.169(.649)	.060	48%(31/65)	.001(.007)
Week 1 + Week 2					
laxative	81	8.658 (.670)		60%(49/81)	
Placebo	70	7.711 (.922)	.025	44%(31/70)	.014(.020)

Taking into account the adjustment for interim analyses, the result of Table 16 shows that the laxative response rate for the second week is highly significant disregarding the method of handling the missing values. But for the first week of treatment the results remain significant only when the missing data are deleted from the analysis. Comparison of the mean bowel movements reaches the adjusted significance level (0.018) for the first week of treatment and only when the missing data are deleted from the analysis. The efficacy results of the two weeks combined fall, as expected, between those of the two weeks. The percentage of success of 17g dose response is significantly higher than that of the placebo. Also, the mean bowel movements shows a strong trend in favor of the laxative treatment compared to that of placebo, but the difference does not reach the significance level.

V. Subgroup / Safety Analysis:

Due to the small number of male patients in the pivotal studies (3 patients out 50 in Study 851-3 and 20 out of 151 patients in

Study 851-6) gender analysis is not practical in this NDA. Also since enrollment in the two studies was restricted to adult patients no statistical analysis for pediatric use is possible. There are some adverse events which include diarrhea and nausea, which the medical officer will address, but no deaths or serious adverse events was reported during the two trial.

VI. Overall Summary:

The sponsor submitted results of two studies in support of the claim that the 17g dose of 851 laxative is effective and safe for the treatment of constipated but otherwise normal patients. This reviewer's findings for the two studies are summarized below.

VI.A. Study 851-3

This is a 4-sequence 3-period incomplete cross over study aimed to compare the efficacy of two laxative doses (17g and 34g) with that of the placebo. Following a seven-day control period the study consists of a three 10-day treatment periods. A total of 50 patients were enrolled in the study. The primary outcome measures are stool output and bowel movements frequency. The design/ conduct of the study suffer from the following limitations:

i) About 38% (19/50) of the patients enrolled in the study do not meet the criteria of constipation (i.e. < 3 bowel movements per week).

ii) No patient were assigned to placebo treatment during the first treatment period. Thus, making the study design differs from the usual cross-over design in which every treatment (including placebo) precedes other treatments equal number of times for proper assessment and adjustment of first order carry-over effect. This unnecessary complicate the efficacy analysis for this study. In addition, the number of patients in the four treatment sequences varies from 9 to 15 patients. No explanation was given for this imbalance.

iii) Even though the sponsor expected at the design stage the possibility of a carry over effect, no allowance for a wash out period, to eliminate such carry-over effect was made. The sponsor's approach for handling this carry-over effect, by

analyzing the last 7 days of each of the 10-treatment period, was not effective (see Table 10, p. 18).

The finding of the analyses of this study are:

i) The magnitude of carry-over effect is proportional to the dose, that is the 34g dose have a higher carry over to placebo in the following period than the 17g dose.

ii) In the presence of the carry over effect it is difficult to evaluate the efficacy of the treatment accurately. However, the results of this reviewer's various analyses show that, in general, the mean bowel movements of the 34g dose is significantly greater than those of the placebo. But, the corresponding results for the 17g dose are not as strong as those of the 34g dose, and are analyses dependent. These results become less clear when one excludes the patients who did not meet the constipation criteria during the control period (< 3 bowel movements per week). Analysis of the binary end point success/ failure shows trend in favor of the laxative treatment but, in general, fail to reach the significance levels in the various analyses considered (Tables 13-14, pp. 22-24).

VI.B. Study 851-6:

This was a multi-center (4 centers) parallel design study aimed to evaluate the efficacy of a 17 gram dose of 851 laxative versus placebo. Following a one week control period, the study had a two-week treatment period. One hundred Fifty one patient were enrolled in the study. The primary outcome variable was stool frequency. This reviewer's comments about this study are:

i) There are inconsistencies about the number of patients enrolled, number of interim analyses, number of withdrawal from the study and the primary period analyzed.

ii) In addition to the inconsistency in the data mentioned above, there is inconsistency in the statistical methods concerning the adjustment for interim analysis. Also, no adjustment for the multiple comparisons was made when analyzing data for multiple time periods.

The results of the efficacy analysis of this study are:

i) Center-to-center variability in the efficacy results are not significant (see Table 15, p.24)

ii)Efficacy results are analyses driven and are not robust to the way of handling the missing values. This can be attributed to the fact that most of the missing data were for patients on the laxative treatment. Stronger efficacy results for the laxative treatment are obtained when the missing data are deleted from the analysis in comparison to imputing zero for these missing values.

iii)In contrast to the efficacy results of Study 851-3, here analysis of the percentage of success gives a stronger results than that of the mean bowel movements. The percentage of success of the 17g dose of laxative treatment for the second week of treatment is significantly higher than that of the placebo disregard of the way of handling the missing data. On the other hand, the mean bowel movements of the 17g dose of laxative for the second week of treatment is not significantly different from that of the placebo. Efficacy results for the first week of treatment are significant only when the percentage of success analyzed and when the missing data are deleted from the analysis. Efficacy results for the two-week treatment period fall in between those of the first and second weeks.

VII. Overall Summary/ Conclusion:

In study 851-3 the mean bowel movements of the 34g dose, and to lesser extent the 17g dose, of 851 laxative is significantly higher than that of placebo. But the results were not significant for the analysis of the percentage of success.

In contrast, for Study 851-6 the percentage of success of the 17g dose for the second week of treatment, was significantly higher than that of placebo, but the results were not significant when comparing the mean bowel movements. Results for the first week of treatment were mixed and depend on the way of handling the missing data.

/S/ [redacted] 7/22/96
M. Al-Osh, Ph.D.
Mathematical Statistician

Concur:
Dr. Huque /S/ [redacted] 7/22/96
Dr. Smith 7/26/96

This review consists of 31 pages of texts and 2 pages of attachments.

cc:
Archival NDA 20-698
HFD-180
HFD-180/ Dr. Fredd
HFD-180/ Dr. Prizont
HFD-180/ Ms. McNeil
HFD-344/ Dr. Lisook
HFD-720/ Dr. Smith
HFD-720/ Dr. Huque
HFD-720/ Dr. Al Osh
HFD-720/ Chron Copy
HFD-720/ File Copy

Aloshm/x73092/Biom.III/Alosh/7/10/96

Attachment # 1

Sponsor's Efficacy Results, Study 851-3

Table 3.1
Daily Wet Stool Output (grams) and BM Frequency
(Braintree Protocol #851-3)

	Placebo	17 grams	34 grams
Stool Output (daily grams)	41.9	59.8	87.8
BM Frequency (daily)	0.46	0.54	0.73

$p < 0.001$

Attachment # 2

Sponsor's Center-by-Center Efficacy Results, Study 851-6

Table 6.16
Treatment Success by Center
Evaluable Data
(Braintree Protocol 851-6)

Center	Week 1 S/F	Week 2 S/F	Total S/F
1	27/17	26/18	53/35
2	26/21	28/15	54/36
3	19/10	20/9	39/19
4	12/8	11/8	23/16
X^2	0.83	1.03	1.01
p	0.84	0.80	0.79

S = Success, F = Failure

Table 6.17
Treatment Success by Center
Intent-To-Treat
(Braintree Protocol 851-6)

Center	Week 1 S/F	Week 2 S/F	Total S/F
1	27/19	26/20	53/39
2	26/22	28/20	54/42
3	19/11	20/10	39/21
4	12/11	11/12	23/23
X^2	0.92	1.94	2.50
p	0.82	0.58	0.48

S = Success, F = Failure