

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020698

STATISTICAL REVIEW(S)

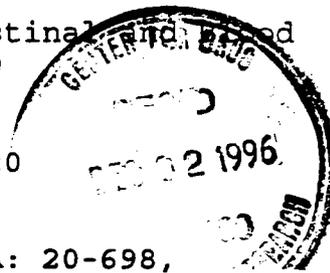
McNeil

Memorandum of Consultation

Date: DEC 2 1996

To: Stephen Fredd, M.D.
Director, Division of Gastrointestinal
Coagulation Drug Product, HFD-180

From: M. Al-Osh, Ph.D.
Mathematical Statistician/ HFD-720



Subject: Request for additional analyses for NDA: 20-698,
laxative (PEG-851)

I. Background:

This is in response to the medical officer, R. Prizont, M.D., request of November 27, 1996, and his E-mail on the same date, for testing whether there is a significant difference in the laxative response rate by race in Study 851-6 (Week Two). Dr. Prizont presented (see Attachment 1) in Table 4 efficacy data for Black patients centers 2 and 4 combined and for center 3 (separate) and in Table 5 presented similar data for White patients. Table 6 shows efficacy data combined from all centers (1, 2, 3 and 4) after excluding the Black patients in Center 3. A copy of Dr. Prizont's tables is given in Attachment 1.

II. Statistical Analyses:

Table 4 shows there are a total of 15 Black patients in Center 3 (7 on placebo and 8 on PEG 851). Comparison of the response rates in the two groups (2/7 vs 7/8) resulted in a p-value equal 0.0406 (Fisher's Exact test). The corresponding p-value for testing the difference in the response rates for centers 2 and 4 (combined) (3/5 vs 3/10) is 0.3287.

By combining data from centers 2, 3 and 4 in Table 4 and testing for efficacy for the Black patients for Week Two in these three centers for (5/12 vs. 10/18), the calculated p-value is 0.7104. Thus the laxative response rate is not statistically different from that of placebo in the Black patients in these three centers combined.

The corresponding comparison for the White patients in Table 5 show that the p-value centers 2 and 4 combined (13/28 vs 21/30) equals 0.1090. The analogous p-value for testing efficacy for the White patients in Center 3 (4/7 vs 7/10) is 0.6437. These comparisons show that the difference in response is not significant disregard of the centers analyzed (centers 2 and 4 combined, and center 3). Testing for efficacy for the White patients in the three centers combined (17/35 vs 28/40) resulted in a p-value equal 0.0975.

On combining centers 2, 3 and 4 and testing for efficacy by race based on the data of tables 4 and 5, the comparisons show that for Week Two the laxative response is not significantly different from that of placebo disregard of race (the p-values for Blacks and White are: 0.7104 and 0.0975, respectively, as stated above).

Now to test for difference in the response by race one can combine the data in tables 4 and 5 and compare placebo response and laxative response by race. The following table presents the results of these comparisons:

Table 1: Consistency of response rates (Blacks vs White) by treatment group; Study 851-6 (centers # 2, 3 and 4 combined)

	Blacks	White	p-value
Placebo	5/12 (42%)	17/35(49%)	0.7417
PEG 851	10/18 (56%)	28/40(70%)	0.3729

The results of the comparisons in Table 1 show there are no significant differences in placebo or the laxative responses by race for the patients of the three centers (# 2, 3, 4).

In a response to address the medical reviewer's inquiry whether the response rates vary by race in Center 3, this reviewer compared the placebo and the PEG 851-responses in this center (the data are combined from Dr. Prizont's table 4 and 5, see Attachment 1). The results of the comparisons are given Table 2:

Table 2: Consistency of response rates (Blacks vs White) by treatment group; Study 851-6 / Center 3

	Blacks	White	p-value
placebo	2/7 (29%)	4/7 (57%)	0.5921
PEG 851	7/8 (88%)	7/10(70%)	0.5882

Due to the small sample size the observed differences in Table 2 failed to reach statistical significant

In Table 6, Dr. Prizont requested testing for efficacy after excluding the Black patients in Center 3. The calculated p-value for this tables is 0.0247. This p-value is slightly smaller than that reported in Table 2 of the Statistical Review dated September 9, 1996, 0.028 which was based on excluding all patients of Center 3.

In conclusion, as most of the requested comparisons are based on small number of patients most of the observed differences did not reach statistical difference. On the other hand, even for the reported p-value (0.0406) for the medical officer's Table 4, the conclusion is not expected to be robust. As a result of this subgroup analyses in one center a shift in one patient will change the results due to the small number of patients in Table 4.

From this reviewer's perspective, the additional analysis of this consultation could not explain the higher efficacy results of center 3 compared to the other centers, as reported in Center-By-Center efficacy results, for Week One, Week Two and the two weeks combined, presented in Table 15, p.25 of the Statistical Review dated July 29, 1996 (see Attachment 2). The results of the comparison in Table 15, disregard of race, show that the p-values for Week Two for centers 1, 2, 3 and 4, respectively, are: 0.14, 0.39, 0.07 and 0.40.

/s/

11/29/96

M. Al-Osh, Ph.D.

Mathematical Statistician

Concur:

Dr. Huque

/s/

0 11/29/96

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CC:

Archival NDA 20-698

HFD-180

HFD-180/ Dr. Fredd

HFD-180/ Dr. Prizont

HFD-180/ Ms. McNeil

HFD-720/ Dr. Smith

HFD-720/ Dr. Huque

HFD-720/ Dr. Al-Osh

HFD-720/ Chron Copy

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This consultation consists of 4 pages of text and 2 attachments.

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Aloshm/x73092/Biom.III/Alosh/11/29/96

Attachment # 1

Medical Officer's Request for Analyses

Including Tables (#: 4, 5, and 6)

November 27, 1996

To: Dr. Mohamed Huque, Division of Biometrics

Subject: NDA 20-698. Request of Statistical Calculations

From: Dr. Robert Prizont, Medical Officer, DGCDP, ODE III

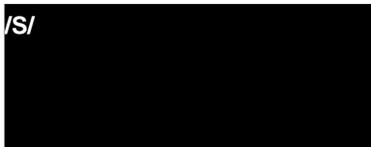
1. Trial 851-3. Statistician Reviewer Table 12, Page 22, July 29, 1996 review. Please, calculate rate of Success for first 10 days, 17 g PEG, considering success as subect/s who had ≥ 5 movements in 10 day period.

2. Trial 851-6. Calculate p-Value of comparison of % Success between PEG 851 and laxative shown in the enclosed MO Reviewer Table 6.

3. Trial 851-6. Calculate p-Value of comparison of % Successes between PEG 851 and placebo in black population of Center 3.

These calculations are needed for cob Tuesday December 3, 1996.

/s/



Dr. Robert Prizont

xc. Attachments are enclosed.

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crossed over to placebo treatment. Further examination of the data also shows that after the placebo treatment, placebo patients were no longer meeting the definition of constipation established in the study protocol, i.e., mean bm in placebo patients was 3.63 bm/week. In this sense, placebo was also effective in the relief of constipation.

The binary comparison of efficacy simply attempts to establish the proportion of patients who, after experimental therapy, no longer met the definition of constipation. This comparison perhaps appears more realistic, in view of the difficulties reported by Braintree in assessing with some sort of accuracy the number of stools and/or the stool output in outpatients during a 10 day period. This difficulty in assessing the exact number of stools has been reported in the gastroenterological literature (Ashraf W et al. An examination of the reliability of reported stool frequency in the diagnosis of idiopathic constipation. *A. J. of Gastroent.* 91:26-32, 1996). *As illustrated in the statistician Table 12, the binary comparison of success/failure, showed no significant difference in the relief of constipation between any of the PEG doses and placebo treatment.*

It should be noted that the statistician reviewer calculated the rate of success or failure by applying a definition of constipation distinct from the established in the study protocol. As recall, the 851-3 study protocol required a stool frequency of more than 3 bowel movements a week to be considered as no longer constipated. The footnote in the statistician Table 12 states that *"for the 10 (day)-treatment success is taken (defined) as ≥ 4 bowel movements"*. Thus, subjects who had more than 2 bowel movements per week were considered by the statistician reviewer no longer constipated and entered as therapy success in the efficacy rate estimate.

The statistician's use of less than 3 bowel movements per week to define constipation stems from discussions in our team meetings. This usage originated in a large study conducted around the greater London area in the 1960's (Connell AM et al. Variation in bowel habit in two population samples. *BMJ*, 2:1095-1099, 1965). This agency refers to this definition in section C of Federal Register, Proposed Establishment of Monographs for OTC Laxative, Vol. 40, Page 12904, 1975, and in *comments 44, OTC Laxative Tentative Final Monograph, Federal Register, Vol. 50, Page 2133, 1985* (in this comment, the agency defines constipation as *"no more than three evacuations per week"*). *It should be noted, however, that this agency does not have yet a firm and well established definition of constipation, because the final monograph version has not been concluded.* For instance, in other sections of the same OTC Laxative Tentative Final Monograph, Page 2127, the agency accepts the use of *"irregularity"* as synonymous of constipation, as taken from the Webster's New Collegiate Dictionary. Springfield, MA, 1979, and, in the Proposed Establishment of Monographs for OTC Laxative, the agency also defines constipation as *"infrequent, or difficult evacuation of the feces"*, taken from Dorland's Illustrated Medical Dictionary, Saunders Co. 1965.

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In order to adhere with the prospective protocol, I requested to the statistician reviewer, a repeat calculation of the proportion of therapy success (and failure) using a stool frequency of 5 bowel movements in the 10 day study period; this corresponds to a weekly stool frequency above the 3 bowel per week.

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Protocol Study 851-6. Vol. 3 and IND [REDACTED]

i. Study Protocol.

- *a. Note from the Reviewer.* Braintree submitted several protocols for study 851-6. I found a protocol for study 851-6 in IND [REDACTED]. This protocol was apparently the original prospective protocol submitted in April 2, 1991. This prospective protocol was again submitted to the DSI in early 1994 together with data from an interim analysis. This submission included a cover letter dated January 27, 1994 from the Braintree Vice President of New Product Development (Dr. M Cleveland), to Dr. Bette Barton, DSI/FDA. In his letter, Dr. Cleveland states that **this study was originally designed as a single center study (Dr. DiPalma) with enrollment by this center of 200 patients.** Because of the low enrollment in Dr. DiPalma site, three other centers were added, each responsible for enrolling 50 patients. At the time of this letter, the study was still ongoing.

The January 27, 1994 letter from Dr. Cleveland to Dr. Barton, IND [REDACTED] is included as Appendix 5 of this review.

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centers was the higher proportion of blacks, 45%, enrolled in this particular center (see my *Descriptive of Study 851-6*). In view of this higher proportion of blacks in this site, I proceeded to determine whether the rate of success/failure in the black population at Center #3 was comparable to the rate of success/failures to that of Centers #2 and #4 (as stated in my descriptive of demographics, Braintree did not submit any information on race demographics for Center #1). In the next MO Reviewer Table 4, I illustrate the proportion of success/failures in the black population at Center #3 and at Centers 2 + 4 for the Week 2 period, the only period revealing a significant superiority of the laxative 851 (at $p=0.018$).

MO Reviewer Table 4

Study 851-6. Week Two Rate of Successes for Blacks in Center 3 versus the Combined Rate of Successes for Blacks in Centers 2 & 4

Center/Investigator	Placebo	PEG 851	Drug With Therapeutic Gain
C2 + C4 (Dr. DeRidder and Dr. Koltz)	3/5 (60%)	3/10 (30%)	30% favors Placebo
C3 (Dr. Orlando)	2/7 (29%)	7/8 (88%)	59% favors PEG

In the following MO Reviewer Table 5, I display the rate of successes in the same Centers 2 + 4 and Center 3, but for the white population.

MO Reviewer Table 5

Study 851-6. Week Two Rate of Successes for Whites in Center 3 versus the Combined Rate of Successes for Whites in Centers 2 & 4

Center/Investigator	Placebo	PEG 851	Drug With Therapeutic Gain
C2 + C4 (Dr. DeRidder and Dr. Koltz)	13/28 (46%)	21/30 (70%)	24% favors PEG
C3 (Dr. Orlando)	4/7 (57%)	7/10 (70%)	13% favors PEG

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MO Reviewer Tables 4 and 5 reveal a marked difference in the Week 2 response to the PEG 851 and placebo administration by the white and black populations enrolled in Center 3. While the therapeutic gain for the PEG laxative is a modest 13% among whites, it rises to a very high therapeutic gain of almost 60% among blacks. This 60% PEG therapeutic gain among blacks observed in Center 3, appears to be due to a combination of a higher than expected therapeutic response to PEG 851, plus, a rather unusually low therapeutic response to the placebo administration. This very high therapeutic gain favorable to PEG 851 observed in the black population enrolled in Center 3, sharply contrasts with the therapeutic response to the PEG 851 and placebo exhibited by blacks in Centers 2 + 4. In these two centers, blacks administered either PEG 851 or placebo, revealed a Week 2 therapeutic response favorable to placebo, i.e., a therapeutic gain in the opposite direction from that observed in blacks enrolled in Center 3. Conspicuous, is the consistent therapeutic response to PEG 851 by the white population enrolled in the three centers.

The very high therapeutic response by the black population enrolled in Center 3 may provide a possible explanation to the statistically significant rate of PEG 851 success observed in Center 3, a statistical significance not replicated in the other three remaining enlisted centers. To test this possibility, I compared the Week 2 overall rate of success/failures for all centers with exclusion of the 15 black subjects enrolled in Center 3; this is illustrated in the following MO Table 6. ←

MO Reviewer Table 6

Study 851-6. Week 2 Rate of Successes After Exclusion of the Black Population Enrolled in Center 3

Experimental Drug	Success/Total Subjects	Therapeutic Gain; p-Value
Placebo	29/63 (46%)	20% Favors PEG 851
PEG 851	48/73 (66%)	p =

It is unclear the reason for the high responsiveness to the experimental PEG 851 treatment observed in the black subjects enrolled in Center 3. The large study conducted in the second National Health and Nutrition Examination Survey (NHANES II) revealed a higher prevalence of constipation among blacks, with fewer periodic and weekly bowel movements than the observed in the white population (Everhart JE et al. A longitudinal survey of self-reported bowel habits in the United States. Dig. Dis. and Sci., 34:1153-1162, 1989). This reviewer has not found published evidence linking ethnic groups in whom a functional disorder is more prevalent, i.e., idiopathic constipation, with higher responsiveness to a specific therapy. In this case, the high therapeutic responsiveness to PEG from

Attachment # 2

Table 15, Center-By-Center Efficacy Results, Study 851-6
 Extracted from Statistical Review, dated July 29, 1996

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.

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STATISTICAL REVIEW AND EVALUATION

SEP - 4 1995

(Addendum # 1)

Date: SEP 9 1996

NDA #: 20-698

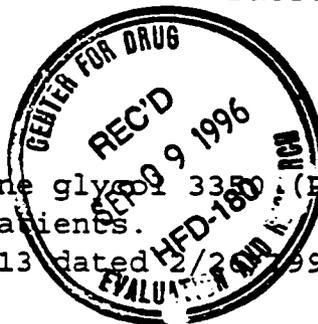
Sponsor: Braintree Laboratories, Inc.

Name of Drug: 851 laxative (Polyethylene glycol 3350 (PEG-3350))

Indication: Treatment of constipated patients.

Documents Reviewed: Vol. 1.1, 1.8 - 1.13 dated 2/2/96

Statistical Reviewer: M. Al-Osh, Ph.D.



I. Background:

The statistical evaluation for this NDA was presented in a statistical review, by this reviewer, dated 7/29/96 (to be called previous review). The findings of that review were discussed in a progress review meeting held on 8/1/96. The following two points emerged from discussing the efficacy results of the sponsor's second study (Study 851-6) during the meeting:

(A) The efficacy results by center and treatment period as presented in Table 15, p. 25, of the previous review showed that center # 3 had higher percentage for relief than those of other centers. Is there an explanation, whether in terms of randomization or other factors, for this result ?

(B) In carrying out the statistical analysis for this study an adjustment was made for the interim analysis but not for multiplicity of the periods analyzed. How would such an adjustment effect the efficacy results of the study ?

This reviewer's justification for not adjusting for multiplicity was discussed in the previous review and will be presented in Section II.B, p. 4, of this addendum. Also homogeneity of the efficacy results across the study centers was tested by using the Breslow-Day statistics in that review.

The purpose of this addendum is to address the multiplicity issue in light of Dr. Fredd's (Director of Gastrointestinal and Blood Product Division) recent comments about the efficacy endpoints. Also, in this addendum I present an analysis dealing with the randomization in center # 3 and center # 4. Finally I comment on testing for treatment by center interaction requested by R. Prizont, M.D., the medical reviewer.

II. Statistical Analysis

II.A. Randomization:

In this section I present the results of a statistical analysis aimed toward testing whether there is imbalance in the distribution of patients between the two treatment arms, and whether the observed patients allocation differs from that of random allocation. The analysis deals with center # 3 and center # 4 since they have the largest observed imbalance.

II.A.I. Randomization in Center # 3:

There are 34 patients enrolled in center # 3 (investigator: Roy Orlando, M.D., New Orleans), 18 patients were assigned to the laxative treatment and 14 patients to placebo. Attachment 1 shows the patients listing of all centers along with their treatment's allocation and Attachment 2 shows the sponsor's treatment allocation in center # 3.

Even though there is an agreement between the two treatment allocation lists for center # 3, some issues regarding the randomization for all centers are still present. First, it is not clear when the randomization schedules for all centers were done. There are no dates attached to these schedules and the sponsor did not specify when the treatment allocation occurred. Second, the sponsor did not explain the method of randomization. Was it done at the individual sites or was it done at the center? In addition, it is not clear whether the randomization was set in advance or it was carried sequentially, that is at the time when the patient enter the study.

Under the assumption of random allocation of patients to treatments one expects the number of patients in the various treatment arms (here laxative and placebo) to be similar and that there are no long runs of a single treatment allocation.

Concerning center # 3, a point was raised during the progress review meeting about the inequality of the number of patients in the two treatments (18 versus 14) and about the treatment allocation in this center. This reviewer conducted statistical tests for these two issues. The finding of the test dealing with the departure of the number of patients from equality in the two treatment arms was not significant ($p = 0.4778$). In testing for randomness of patient's allocation to treatments in center 3, the data showed that there are 17 runs of treatment allocations for the 32 patients of this center. Application of the Runs Test gave rise to a p-value of 0.2739, indicating that the departure from random allocation is not statistically significant.

II.A.II. Randomization in Center # 4:

R. Prizont, M.D., requested in a meeting on August 26, 1996, a testing for the patients allocation in center # 4 similar to those done for center # 3. The result for testing for departure from equality in the number of patients in the two treatment arms(14 versus 9) was not significant ($p = 0.2938$). Also, the observed patient allocation in center # 4 (12 runs) was not significantly different from that of random allocation ($p = 0.8104$). The observed imbalance in the patient allocation between the treatments was reduced by the number of withdrawals from this center. There were 3 withdrawals from the laxative treatment but none from the placebo. Examination of the case report forms, or a request to the sponsor, might explain this pattern of withdrawals.

II.B. Homogeneity of the Efficacy Results Across Centers:

For testing homogeneity of the efficacy results across the study centers this reviewer applied the Breslow-Day test to the patients classified by their relieved/ not relieved status. The p-value obtained from the application of this test to the 3

periods analyzed (see Table 15, p.25, previous review) were : 0.099, 0.837 and 0.426 for Week 1, Week 2 and the two weeks combined, respectively. Even though Week 1 p-value is 0.099 is small, it is still not significant. In a discussion with Dr. Huque, team leader in Division of Biometrics III, about interpreting the results of the Breslow-Day test, he expressed that, when the efficacy results of the various centers are in the same direction in a randomized trial, the above p-values are of no significance as an indication of non-homogeneity of the efficacy results and could arise by chance.

Another approach for testing homogeneity in the efficacy results across the study centers is to test for center by treatment interaction, as requested by R. Prizont, M.D., during the progress review meeting. This reviewer explained during the meeting that he had fitted statistical models (Analysis of Variance as well as Generalized Linear Model) which included an interaction term, but was not convinced about the findings of the analysis.

The following technical discussion aimed to explain this reviewer dissatisfaction with the fitted models. The fitted models explained only about 7% of the variation in the bowel movements frequency. This lack of fit can be attributed to presence of extreme outliers in the data or to the elimination of important covariates from the model. For Study 851-6 at least one outlier contributed a large amount to the total variation around the mean. The frequency of bowel movements for patient # 43 were: 21 and 42 for two weeks of treatments compared to 3.62 and 3.55 the mean bowel movements during the two weeks. Such outliers will influence estimates of the parameters. In addition, the fitted model is unstable when one deletes some outliers from the data. This is the reason for this reviewer's inclination not to include results based on poor fitted models.

Regardless of the goodness of fit for the Generalized Linear Model, the p-value for the treatment-by-center interaction were: 0.06, 0.32 and 0.16 for Week 1, Week 2 and the two weeks combined, respectively. This indicates, as per Breslow-Day test, a possibility of treatment by center interaction is in Week 1.

Singling out the results for the Week 1 can be attributed not only to the high efficacy results of center # 3 but also to the efficacy results of center # 1 which were in the opposite direction for Week 1 (see discussion following Table 15, p. 25, in the previous review).

With this 'no clear cut' result of testing for homogeneity of the efficacy results across the study centers, I present in Table 1 (P.8) efficacy results for all centers combined (the same as in Table 16, p.27, of the previous review). In addition I present in Table 2 (p.9) efficacy results for all centers except center # 3. In these tables an additional analysis based on ranks of the bowel movements frequency (Wilcoxon Rank Sum test) is also presented. The analysis of ranks is preferable to that of the mean when the data set has extreme outliers as in this study. A similar rank test was carried out when analyzing the sponsor first study (see Table 11, p.20, previous review).

II.C. Adjustment for Multiple Comparisons:

No adjustment for multiplicity of the periods analyzed was made in the previous statistical review since:

(i) Following a discussion with the medical officer, R. Prizont, M.D., Week 1 treatment was considered to be the primary period of analysis (see pp. 12-13 and Section II.B.II (iii) p. 14 of previous review), and

(ii) Study 851-6 protocol was not explicit about this multiplicity when the sponsor stated (p. 6-261) 'An overall analysis including both treatment weeks will be performed. In addition, each week of the two treatment weeks will be considered separately'.

However, following Dr. Fredd's comments during the progress review meeting on 8/1/96, that one might consider Week 1 efficacy as well as the cumulative effect of the two weeks combined, the multiplicity issue needs to be re-considered. In making adjustments for multiplicity it is known that for a given type I error rate, say α , and a number of endpoints analyzed, say k , the

derived 'nominal' value α' increases as the correlation (ρ) between the endpoints increases. That is to say, the conservatism of well-known Bonferroni correction increases as ρ increases [see e.g. Pocock, Geller and Tsiatis: *The Analysis of multiple Endpoints in Clinical Trials; Biometrics* 43, 487-498 (1987)].

In carrying out the multiplicity adjustment for study 851-6 one expects that the endpoints are highly correlated since Week 1 and Week 2 data are subsets of the two weeks data. The following matrix presents the estimated correlation coefficients for the three periods analyzed in Study 851-6.

Estimated correlation coefficients of the bowel movements frequency for the three periods analyzed in Study 851-6 (calculated from the sponsor's data)

	Week1	Week2	Week1+Week2
Week1	1.0	0.77	0.92
Week2		1.0	0.96
Week1+Week2			1.0

Having estimated the correlation between the endpoints, the approach I consider for multiplicity adjustment is based on calculating the overall level of significance (see Dubey: *Adjustment of p-values for multiplicities of intercorrelating symptoms; 1985*):

$$\alpha_{adj} = 1 - (1 - \alpha_{min})^m$$

where:

α_{adj} is the adjusted p-value for multiple comparison

α_{min} is the minimum p-value observed from the data

$m = k^{1-r_i}$, for $i=1,2,3$, with r_i being the average estimated correlation coefficients among the three endpoints analyzed shown above (i.e. 0.88).

The value of α_{adj} will be compared with the appropriate boundary for the interim analysis, $\alpha_2 = 0.018$ (see previous review) to determine significance of the results.

II.D. Final Efficacy Results:

Table 1 (p.8) shows the efficacy results for all study centers combined. The entries of this table are the same as those of Table 16 of the previous review after correcting two typographical errors related to the number of patients and mean number of bowel movements. In addition, Table 1 presents the results of the additional analysis for the frequency of bowel movements mentioned before (Pp.4-5), that is the Wilcoxon Rank Sum test.

Table 1 shows that the results of the ranks test are stronger than those based on comparing the mean bowel movements. This can be attributed mainly to an extreme outlier in placebo response. The frequency of bowel movements for patient # 43 (placebo) was 21, 42 and 63 for Week 1, Week 2 the two weeks combined, respectively. The advantage of using the rank test over that comparing the means is that it reduces the influence of extreme outliers on the comparison.

It can be seen from Table 1 that the adjustment for multiplicity did not change the conclusion based on adjustment for interim analysis alone. This is mainly due to the fact that only one of the calculated p-value is close to the α -boundary (.018). However, even the calculated p-value of 0.014 is still significant after the multiplicity adjustment due to the high correlation among the endpoints analyzed.

Table 2 (p.9) presents similar analyses to those of Table 1 after excluding center # 3 data from the analyses. The results of Table 2 are weaker than those of Table 1 and are not significant in most cases. Consequently one concludes that center 3 had a significant contribution to the overall observed efficacy results reported in Table 1.

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Table 1/ 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

Period/ Treatment	Mean Bowel Movement		p-value		% of success	p-value ^a
	n	\bar{X} (SE)	t-test	Ranks test		
I) Missing data are set =0 ^b						
Week 1						
laxative	81	4.049(.354)			63% (51/81)	
Placebo	70	3.129(.345)	.066	.0478	50% (35/70)	.109 (.138)
Week 2						
laxative	81	4.074(.362)			68% (55/81)	
Placebo	70	2.943(.610)	.114	.0009*	44% (31/70)	.003* (.005*)
Week 1 + Week 2 ^c						
laxative	81	8.123(.670)			60% (49/81)	
Placebo	70	6.071(.922)	.076	.0046*	44% (31/70)	.047 (.052)
II) Weeks with all 7 days missing data are deleted						
Week 1						
laxative	76	4.316(.356)			67% (51/76)	
Placebo	70	3.129(.345)	.018*	.0069*	50% (35/70)	.036 (.044)
Week 2						
laxative	72	4.583(.365)			76% (55/72)	
Placebo	65	3.169(.649)	.060	.0001*	48% (31/65)	.001* (.007)
Week 1 + Week 2 ^c						
laxative	76	8.658 (.670)			64% (49/76)	
Placebo	70	6.071 (.922)	.025	.0003*	44% (31/70)	.014* (.020)

* Significant p-value after adjustment for interim analysis ($\alpha_{adjusted} = .018$, see p. 26, previous review) and multiplicity .

^a Based on the χ^2 (Fisher's Exact) test

^b The missing data are as follows:

	control period	Week1	Week2	Week1+Week2
Laxative	1	6	10	6
placebo	0	0	5	0

Comparison of the number of withdrawals of laxative vs placebo are: 0.062, 0.575 and 0.062 for Week1, Week2 and week 1+ week 2, respectively, after excluding patient # 8 (laxative) since no data reported for this patient during the control period (see Attachment 1 for list of patients).

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

Table 2/ Reviewer's Analysis, Study 851-6
 Efficacy Results After Excluding Center # 3; Comparison of % of success and mean of bowel movements frequency for each treatment week and for the two weeks combined

Period/ Treatment	n	Mean B.M. \bar{X} (SE)	p-value t-test	Rank Sums	% of success	p-value ^a
I) Missing data for a week are set =0 ^b						
Week 1						
laxative	63	3.778(.390)			598 (37/63)	
Placebo	56	3.321(.410)	.422	.395	548 (30/56)	.571 (.584)
Week 26						
laxative	63	3.984(.425)			658 (41/63)	
Placebo	56	3.107(.748)	.311	.012 [*]	458 (25/56)	.025 (.028)
Week 1 + Week 2 ^c						
laxative	63	7.762(.770)			578 (36/63)	
Placebo	56	6.429(1.12)	.329	.075	468 (26/56)	.243 (.273)
II) Weeks with all 7 days missing data are deleted						
Week 1						
laxative	58	4.103(.396)			648 (37/58)	
Placebo	56	3.321(.410)	.173	.102	548 (30/56)	.268 (.342)
Week 2						
laxative	54	4.648(.434)			768 (41/54)	
Placebo	54	3.222(.772)	.111	.0001 [*]	468 (25/54)	.002 [*] (.002 [*])
Week 1 + Week 2 ^c						
laxative	58	8.431 (.775)			628 (36/58)	
Placebo	56	6.428 (1.12)	.145	.008 [*]	468 (26/56)	.094 (.132)

^a Significant p-value after adjustment for interim analysis (α adjusted = .018, see p.26 of previous review) and multiplicity.

^a Based on the χ^2 (Fisher's Exact) test

^b The missing data are as follows:

	Control period	Week1	Week2	Week1+Week2
Laxative	1	6	10	6
placebo	0	0	2	0

Comparison of the number of withdrawals of laxative vs placebo are: 0.059, 0.062 and 0.059 for week1, week2 and week 1+ 2, respectively, after excluding patient # 8 (laxative) since no data reported for this patient during the control period (see Attachment 1 for list of patients).

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

Following the first draft of this addendum, Dr. Prizont requested an analysis, similar to that of Table 1, for the patients who completed the study. In a meeting with Dr. Prizont on 8/26/96 we agreed to consider a patient completed Week 1 or Week 2 if he/she has efficacy data for at least 6 days during that week, and a patient completed weeks 1 and 2 if he/she completed both weeks. Table 3 (p.11) presents the results of the analysis of the completed patients.

The results of the analysis in Table 3 are similar to those of Table 1, Part II, in which weeks with missing data were deleted from the analysis. The difference between Table 1 (part II) and Table 3 analyses is in the definition of the missing data for a week. Table 1 analyses requires all 7 days data of the week to be missing whereas Table 3 analyses requires 2 days or more to be missing for the week to be considered as having missing data.

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cleansed with a non-PEG containing lavage (usually containing mannitol). The rectal effluent was analyzed for PEG and recoveries were almost 100%.

b. Metabolism: It was stated that there is no evidence of PEG 3350 being metabolized. However, no data was provided.

II. FORMULATIONS:

The drug product is supplied as a powder. It is composed entirely of PEG 3350. The PEG 3350 in 851 laxative is [REDACTED] material. The investigational formulations used in clinical trials and bio studies are listed in Appendix II.

III. ASSAY:

The PEG concentrations in urine and stool were measured by a [REDACTED] method which was originally developed by [REDACTED]. The firm stated that the sensitivity of this method is 50 µg/ml of PEG in urine, which is comparable to [REDACTED]. However, the [REDACTED] method has a drawback of being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. In addition, assay validation data is deficient. It lacks linearity, sensitivity, specificity, accuracy and precision information.

GENERAL COMMENTS:

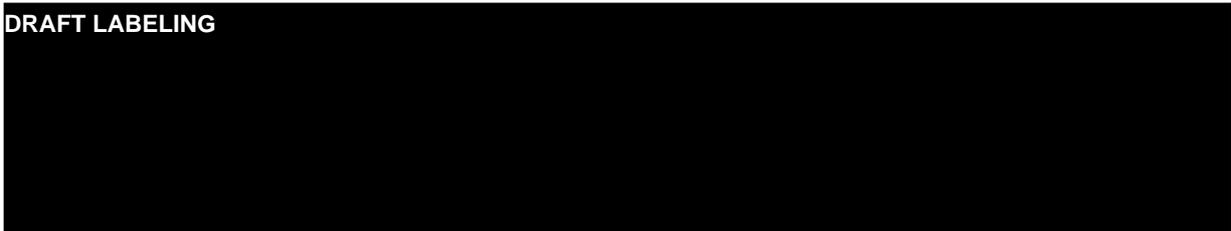
The following information has been requested to the firm on 12/19/96 and is waiting for a response.

1. The assay validation data for measuring PEG 3350 in urine and stool regarding linearity, sensitivity, specificity, accuracy and precision.

LABELING COMMENTS (to be sent to the firm):

1. The following proposed labeling, "851 Laxative is not absorbed from the gastrointestinal tract, has no effect on the active absorption or secretion of glucose or electrolytes and is not metabolized by the colonic flora." should be replaced by:

DRAFT LABELING



/S/ [Redacted]

12/30/96

Hae-Ryun Choi, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Lydia Kaus, Ph.D. 12/11/96

FT initialed by Lydia Kaus, Ph.D. /S/ [Redacted] 12/30/96

cc: NDA 20-698, HFD-180, HFD-870 (MChen, Kaus, Choi), HFD-870 (Chron, Drug, Reviewer),
HFD-340 (Viswanathan), HFD-205 (FOI).

APPENDIX I

IN-VITRO GAS PRODUCTION STUDY

Title: Hydrogen and methane production by fecal homogenates containing mannitol and polyethylene glycol.

Protocol No.: 851-1

Objective: To determine if hydrogen can be produced by fermentation of PEG.

Investigator and Site: [REDACTED]

Experimental Methods:

A 1:20 fecal homogenate was made by anaerobically homogenizing 10 g of normal human feces with 190 ml of phosphate buffered saline. Twenty ml of the homogenate was then added to each of three syringes. One syringe served as a negative control, 200 mg mannitol was added to the second as a positive control, and 2 g of PEG 3350 was added to the third. The three syringes were incubated at 37°C and the volume of gas produced was measured at 1, 3, 5 and 22 hours. Also the volume of methane was measured in the 22 hour sample.

Analytical Methods:

Hydrogen and methane gas concentrations were measured by [REDACTED] methods in 1983 by [REDACTED]. The assay conditions were:

Instrument: [REDACTED] equipped with a [REDACTED] valve and a [REDACTED] temperature: 100°C

Detector: [REDACTED] for hydrogen; [REDACTED] for methane.

The concentrations of hydrogen and methane were determined by comparison of [REDACTED]s of the unknowns to that of a series of standards consisting of dilutions of authentic hydrogen and methane. The reproducibility of the assays (C.V.) was about $\pm 5\%$. There is no information on linearity, sensitivity, specificity, or accuracy.

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Results:

The cumulative hydrogen and methane production in cc is provided below:

	<u>Hydrogen</u>				<u>Methane</u>
	<u>1 hr</u>	<u>3 hr</u>	<u>5 hr</u>	<u>22 hr</u>	<u>22 hr</u>
Control	0.18	0.17	0.16	0.11	0.0021
200 mg Mannitol	0.26	0.54	1.04	7.59	0.0042
2 g PEG 3350	0.10	0.11	0.10	0.13	0.0019

The PEG 3350 did not enhance production of either gas (0.13 and 0.0019 cc of hydrogen and methane produced in 22 hours, respectively) while the positive control, mannitol resulted in copious amounts of hydrogen (7.59 cc) at the same period of time. There was no significant methane production by fecal homogenate containing mannitol.

Comments:

- This study was previously submitted in approved NDAs 19-011 and 19-797.
- It should be noted that only one sample per each time point was measured; no replication of the data.

Conclusions: This in-vitro study showed that PEG-3350 was not fermented into hydrogen or methane by the colonic microflora in human feces.

Labeling Claim: "851 Laxative is not metabolized by the colonic flora."

Labeling Comments: The proposed labeling should be replaced by:

"In vitro study showed indirectly that PEG 3350 was not fermented into hydrogen or methane by the colonic microflora in human feces."

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DOSE FINDING STUDY

Title: Laxative effects of low dose SF-ELS

Protocol No.: 851-2a

Investigator and Site: 

Study Dates: 08/86 - 05/87

Objective: To evaluate the laxative effects of four doses of SF-ELS (NuLYTELY) in constipated but otherwise normal subjects. The SF-ELS solution contains electrolytes and PEG 3350.

Study Design:

This was a single-center, double blind, randomized, cross-over study comparing four daily SF-ELS doses ranging from 1/64 to 1/8 of the standard four liter bolus dose of SF-ELS (equivalent to 6 to 52 grams 3350). The composition of each dose is shown below:

Component	control	1/64	1/32	1/16	1/8
PEG 3350 (g)	0	6	13	26	52
NaCl (g)	0	0.18	0.35	0.70	1.40
NaHCO ₃ (g)	0	0.09	0.18	0.36	0.71
KCl (g)	0	0.02	0.05	0.09	0.18

The 1/64 dose was intended as an "ineffective" or placebo treatment.

Patients with a history of constipation (but otherwise healthy) were given 250 ml of a placebo daily for one week and asked to collect each stool. Patients were included in the study if they had 3 or fewer bowel movements and/or 300 or less grams of stool in the 7 day control period. Five female constipated subjects (mean age: 39 years) were enrolled and completed the study. Following a control period, subjects were randomized to a four period treatment schedule where they drank one of four possible daily doses of SF-ELS solution during each 7 day treatment period. Each dose was administered as a 250 ml solution. Each treatment period followed by 7 day washout.

Stool (both wet and dry weights) were collected. Each subject maintained a diary recording each bowel movement and subjective symptoms (stool consistency, passage, cramps and flatus). Except for the first stool, stool from each treatment week was pooled and analyzed for dry weight, sodium, potassium and chloride content as well as PEG. The first stool of each treatment period was analyzed

separately, however this data was added to the pooled data to calculate the weekly values. Lab values were obtained on the first and last day of each treatment period. These included hematology measurements, blood chemistry and a urine analysis.

Formulations:

Active: (per 2 liters):

- a. 1/8 dose: 420 g PEG 3350, 11.2 g NaCl, 5.72 g NaHCO₃, 1.48 g KCl, 14.5 g [REDACTED]
Lot # 86040x2
- b. 1/16 dose: 210 g PEG 3350, 5.6 g NaCl, 2.86 g NaHCO₃, 0.74 g KCl, 14.5 g [REDACTED]
Lot # 86040x3
- c. 1/32 dose: 105 g PEG 3350, 2.8 g NaCl, 1.43 g NaHCO₃, 0.37 g KCl, 14.5 g [REDACTED]
Lot # 86040x4
- d. 1/64 dose: 50 g PEG 3350, 1.4 g NaCl, 0.715 g NaHCO₃, 0.185 g KCl, 14.5 g [REDACTED]
Lot # 86040x5

Placebo: 14.5 g [REDACTED] per 2 liters, Lot # 86040x1

The test materials were manufactured by [REDACTED]

Data Analysis:

Stool weight and bowel movement frequency were analyzed by repeated measures analysis of variance. If a significant difference was found, differences between individual treatments were analyzed by [REDACTED] Test. Subject rating of stool consistency, passage, flatus and cramping/irritation are tabulated but not tested for significant differences. Comparison of laboratory values for treatment was by repeated measures analysis of variance. Calculated p values of $p \leq 0.05$ were considered statistically significant.

Results:

The primary efficacy variables evaluated were seven day stool weight and frequency.

The weekly wet stool output analyzed by repeated measures analysis of variance is given in the following table:

Table 1. Weekly Wet Stool Output (grams)

Daily Dose	Control	1/64	1/32	1/16	1/8
Mean	166.9	269.0	415.1	560.5	578.4
SD	65.6	151.3	195.6	188.0	299.4

$F = 4.24, df = 4, 20; p = 0.01$

Total stool output was significantly increased ($p=0.01$) as SF-ELS dose was increased.

Differences between treatments means are evaluated by [REDACTED] Test. The results showed that weekly stool output during the control period was not significantly different from the 1/64 dose. Weekly stool output between the 1/32, 1/16 and 1/8 doses were not significantly different from each other. However, stool output from the 1/32 dose was significantly different from the control. It was concluded that the minimum dose for the laxative purpose should be more than the 1/32 dose (13 g) and somewhat less than the 1/16 dose (26 g).

Similarly, the weekly dry stool output (grams) at different doses was evaluated and the results are given below:

Table 2. Weekly Dry Stool Output (grams)

Daily Dose	Control	1/64	1/32	1/16	1/8
Mean	51.1	82.2	111.8	141.2	145.1
SD	18.5	51.7	50.8	48.6	70.2

$F = 3.1, df = 4, 20; p = 0.04$

The dry stool output was significantly increased ($p=0.04$) as SF-ELS dose was increased.

The weekly stool water output (grams) was also evaluated similarly and the results are given in the following table:

Table 3. Weekly Stool Water Output (grams)

Daily Dose	Control	1/64	1/32	1/16	1/8
Mean	115.8	186.8	303.3	419.3	433.4
SD	49.4	103.6	149.2	154.0	232.4

$F = 4.33, df = 4, 20; p = 0.01$

The stool water output was significantly increased ($p=0.01$) as SF-ELS dose was increased.

The following table shows the weekly bowel movement frequency at different doses:

Table 4. Weekly Bowel Movement Frequency

Daily Dose	Control	1/64	1/32	1/16	1/8
Mean	1.8	2.8	4.4	5.4	5.4
SD	0.4	0.8	1.8	1.5	1.5

$F = 6.96, df = 4, 20; p < 0.001$

The weekly bowel movement frequency was significantly increased ($p < 0.001$) as the SF-ELS dose was increased.

Test for BM frequency showed a pattern identical to that for wet stool weight where the bowel movement frequencies resulting from the three larger SF-ELS doses (1/32, 1/16 and 1/8) were not significantly different from each other. Weekly stool output during the control period was not significantly different from the 1/64 dose. However, 1/64 dose was also not significantly different from the 1/32 dose. It was concluded that a reasonable laxative effect can be achieved using SF-ELS at somewhat more than the 1/32 dose, but less than 1/16 dose.

Mean weekly electrolyte outputs are shown in table 5 for sodium and in table 6 for potassium.

Table 5. Total Stool Sodium Excretion (mEq)

Daily Dose	Control	1/64	1/32	1/16	1/8
Total Na Input	0	28	56.9	113.8	227.5
Mean Na Output	21.8	28.7	30.6	35.2	32.9
SD of Output	16.5	23.7	12.7	15.1	5.3

F = 0.52, df = 4, 20; p = 0.72 (not significant)

Table 6. Total Stool Potassium Excretion (mEq)

Daily Dose	Control	1/64	1/32	1/16	1/8
Total K Input	0	2.2	4.4	8.75	17.5
Mean K Output	35.7	39.7	45.0	47.0	38.5
SD of Output	13.6	26.7	18.7	27.4	15.8

F = 0.24, df = 4, 20; not significant

There were no significant differences between the treatment doses with respect to stool electrolyte content. It was concluded that at low doses, the salts in the SF-ELS solution do not affect the stool electrolyte content.

Comments:

- The drug tested in this study was SF-ELS (Low Sodium Sulfate Free Polyethylene Glycol-Electrolyte Lavage, NuLYTELY®, approved as NDA 19-797) which is indicated for bowel cleansing prior to colonoscopy or barium enema x-ray examination. A single dose of SF-ELS contains 420 grams of PEG 3350 and electrolytes to be reconstituted with water to 4 liters. Four low doses of SF-ELS were evaluated for the laxative effect. This pilot study was to determine a final formulation and appropriate daily PEG 3350 dose for laxative use. The stool volume and frequency were significantly increased by increasing stool water content as the SF-ELS dose was increased. Analysis of stool output with respect to the amount of PEG ingested showed that a dose of approximately 17 g PEG would be the appropriate daily dose. The salts in the low doses of SF-ELS did not affect the stool electrolyte (sodium and potassium) content. The proposed formulation for laxative use would be composed of PEG 3350 only.

- This protocol was the subject of a meeting between Braintree and the Agency on 05/29/86.
- Stool was analyzed for PEG content. However, the firm stated that stool collection was insufficient to demonstrate recovery.

Conclusions:

- Stool volume and frequency were significantly increased as the SF-ELS dose was increased. The stool water content was also significantly increased.

Labeling Claim: "When ingested in solution it increases the stool volume and frequency by increasing stool water content."

Labeling Comments: The proposed labeling is acceptable.

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