

and proportion of successes or failures (for each treated subject, success represents ≥ 3 bowel movements/week).

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	R (SD)	t-test	Mann test		
I) Missing data are set to 0 ^b						
Week 1						
Laxative	81	4.049 (.354)			63% (51/81)	
Placebo	70	3.129 (.345)	.046	.0470	50% (35/70)	.109 (.128)
Week 2						
Laxative	81	4.074 (.342)			60% (52/83)	
Placebo	70	3.843 (.618)	.114	.0000*	44% (32/70)	.001* (.005*)
Week 1 + Week 2 ^c						
Laxative	81	4.123 (.470)			60% (49/81)	
Placebo	70	4.071 (.922)	.076	.0046*	44% (32/70)	.047 (.052)
II) Weeks with all 7 days missing data are deleted						
Week 1						
Laxative	76	4.116 (.356)			67% (51/76)	
Placebo	70	3.129 (.345)	.018*	.0069*	50% (35/70)	.026 (.044)
Week 2						
Laxative	71	4.583 (.365)			76% (55/72)	
Placebo	65	3.159 (.449)	.040	.0001*	40% (26/65)	.001* (.007)
Week 1 + Week 2 ^c						
Laxative	76	4.658 (.470)			64% (49/76)	
Placebo	70	4.071 (.922)	.025	.0001*	44% (32/70)	.014* (.020)

* Significant p-value after adjustment for interim analysis (α = .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	5	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.

According to the FDA statistician Intent-to-Treat (ITT) analysis, administration to constipated patients of 17 grams of 851 or placebo, for a period of one week, does not result in a significant difference between the two treatments in either, the proportion of success/failures or mean number of bowel movements. In contrast, the statistician reviewer ITT analysis does show a significantly higher proportion of successes in patients administered 17 grams of 851 during a second week of therapy (see September 9, 1996, FDA statistician final review). **This second week result, consistent with the second week results presented by Braintree, demonstrates 851 superiority even after of subjects randomized but prematurely withdrawn data are included with last-observation-carried-forward (LOCF), and an adjusted p-Value of 0.018.**

As seen in the content and footnotes shown in the statistician reviewer Table 1, there was an imbalance in the number of subjects prematurely discontinued from the trial. A greater number of subjects randomized to the laxative 851 were prematurely discontinued from the trial. Most of the subjects withdrawn early in the trial had ≤ 2 bm/week at the time of departure and are by protocol definition, treatment failures. Exclusion of these premature withdrawals could, therefore, favor the laxative group. The inclusion of all 151 randomized patients in the statistician ITT analysis attempts to correct for possible bias favorable to the laxative treatment group. To confirm this latter point, I requested the FDA statistician reviewer to further analyze the efficacy in subjects who *fully*

completed the two week study period (thus excluding *all withdrawals*). As seen in the next FDA statistician reviewer Table 3, the comparison of efficacy in completed patients turns the first week numerical superiority of the laxative into a statistically significant superiority (in mean number of bowel movements), and, in the second week period, it augments the statistical significance of the laxative 851 superiority in the proportion of successes

Table 3/ Reviewer's Analysis, Study 851-6/ Completed Patients *
 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 *
	n	\bar{X} (SE)	t-test	Ranks test		
Week 1						
laxative	73	4.479 (.358)			70% (51/73)	
Placebo	67	3.194 (.355)	.012*	.003*	51% (34/67)	.021 (.025)
Week 2						
laxative	69	4.739 (.370)			80% (55/69)	
Placebo	62	3.306 (.675)	.067	.0001*	50% (31/62)	.001* (<.001*)
Week 1 + Week 2 ^c						
laxative	69	9.304 (.685)			70% (48/69)	
Placebo	62	6.661 (1.015)	.034	.0002*	50% (31/62)	.022 (.032)

* Significant p-value after adjustment for interim analysis ($\alpha_{adjusted} = .010$, see p. 26, previous review) and multiplicity.

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

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

f. *Possible Center Interaction.* As stated in my description of the Protocol 851-6, this trial was initially designed as a single center study, located at the University of South Alabama. However, Dr. DiPalma, the principal investigator of this center was unable to recruit the prospectively planned 200 patients. Other centers were then enlisted. The next two enlisted centers were located at Detroit, MI (Dr. DeRidder), and at the University of Florida Medical School, in Jacksonville, FL (Dr. Koltz), The last two enlisted centers were at Tulane Medical School, New Orleans, LA (Dr. Orlando) and St. Louis University Medical School, St. Louis, MI. Apparently, the St. Luis center never initiated any enrollment and was removed from any analysis (*my information on sequence of center enlistment was obtained from IND* [redacted]).

In this NDA submission, Braintree reported Dr. DiPalma's site as Center #1, Dr. DeRidder's site as Center #2, Dr. Koltz's site as Center #4, and Dr. Orlando's site (the last center to be enlisted) as Center #3.

The center-by-center comparison of effectiveness, estimated by the statistician reviewer, revealed a marked difference in the rate of success between Center #3 and the other three centers. After the Week 1 of therapy, the centers with larger enrollment, Centers #1 and #2 (96 subjects enrolled), and the center with the

smallest enrollment, Center #4 (23 patients enrolled), revealed no differences in the proportion of successes between PEG 851 and placebo, i.e., $p=0.37$, 0.16 , and 0.55 , respectively (it should be noted that in Center #1, the numerical difference favored the placebo group, but this occurred in Week 1 only). In these three centers, the comparison of effectiveness for the Week 2 period or for the combined Week 1 + Week 2 periods, failed to show any significant differences between treatments, though numerical differences were largely in the 851 direction (see Table 15, Page 25, July 29, 1996 statistical review).

In contrast to the other three centers, Center #3 (32 patients enrolled), exhibited a significantly higher proportion of successes in the PEG 851 group for the Week 1 period ($p=0.02$), for the Week 2 ($p=0.04$), and for the combined Week 1 + Week 2 of therapy ($p=0.04$). An ITT of Centers #1, #2, #4 with exclusion of Center #3 renders any difference in effectiveness between 851 and placebo as not significant (as illustrated in the statistician reviewer Table 2, September 9, 1996 review),

The Statistician Reviewer Table 2, Page 9, September 9, 1996 statistical review is included as Appendix 6 of this review.

In an effort to find a possible cause for this marked difference in effectiveness observed in Center #3, I examined the characteristics of the patient population enrolled in this specific site. The only demographic distinction from the other 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 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 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 $p=0.018$).

APPEARS THIS WAY ON ORIGINAL

MO Reviewer Table 4

Study 851-6. Week Two Rate of Success for Blacks in Center 3 versus the Combined Rate of Success 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, $p=0.33^*$
C3 (Dr. Orlando)	2/7 (29%)	7/8 (88%)	59% favors PEG, $p=0.04$

* As calculated by the statistician reviewer, Dr. M. Al-Osh

In the following MO Reviewer Table 5, I display the rate of success 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

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 successes 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 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%)	$p = 0.024^*$ (significance was set at $p=0.018$)

* As calculated by the statistician reviewer, Dr. M. Al-Osh

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 blacks in Center 3, appears inconsistent and not typical, because the combined black population in other two centers, Centers 2 & 4, failed to respond to the PEG administration and rather, responded better to placebo treatment.

2. Adequacy.

(a) The protocol submitted for study 851-6 designated this trial as a "**double-blind**" controlled study (see 851-6 protocol, section *c. Study Design*, this review). Yet, the PEG and the placebo compositions contained components which provided them with different and distinguishable flavors. The placebo solution was contained a heap tablespoon (17 g) of sugar dextrose dissolved in a glass of water or juice (8 oz). In contrast, the PEG solution did not contain *any* sugar. The use of an experimental PEG solution devoid of the sugar flavor vs. a placebo control solution flavored with sugar dextrose, raises serious concerns about the blinding protection offered in this investigational pivotal trial. This lack of blinding protection, a rather fundamental element in the shield against bias, creates concerns about the adequacy of this trial, as well (Methodology of Clinical Drug Trials. Chapter 6, Single-blind and double-blind trials, Pages 65-72, Eds. Alain Spriet, T. Dupin-Spriet, P. Simon, 1993).

Braintree was informed by the DGCDP Director of the inappropriateness of conducting a pivotal trial between PEG and placebo, in which only the placebo is composed of sugar water. *During the March 9, 1994 meeting between Braintree and the DGCDP Director, one of the issues discussed was the design of Protocol 851-6, already ongoing. The Division Director commented then the following: "Dr. Fredd asked for clarification of the placebo composition. When the firm responded it was dextrose, Dr. Fredd surmised that people would know they were drinking sugar water, thus affecting the study blind"* (MEMORANDUM OF MEETING, Page 2, IND [REDACTED]). During this meeting and in the August 30, 1996 correspondence with DGCDP on this specific issue, Braintree justified the use of sugar water placebo to the lack of cross-over design of the study. This justification is not acceptable, at least to this reviewer. Certainly, it should be considered incorrect and inadequate, in a prospectively named double-blind cross-over study, to administer to the same subject, two different medications unmasked by different flavors. The same incorrectness and inadequacy applies to a parallel study. This is so, for in a clinical multicenter trial, there is always the latent possibility of leaks, e.g., PEG patient-to-Placebo patient interaction, plus, the added likelihood of patients on PEG or on Placebo, discussing medication characteristics with investigators. This latent possibility of leaks between patients and investigators requires, on the part of the sponsor, *appropriate methodologies or procedures in the design of the clinical trial, which would provide assurance that "use of adequate measures are taken to minimize bias", e.g., maximum protection of blinding.*

2. Other Controlled Trials.

- *Note from the Reviewer.* Braintree submitted information on two other controlled studies, 851-4 and 851-5. Both studies did not provide supportive efficacy for the laxative use of 17 grams PEG 851 for a period of one or two weeks. I will very briefly summarize the efficacy data submitted of these trials, and, if appropriate, comment on the presented results.

Trial 851-4

I. Brief Descriptive of Design, Patient Population and Results.

a. Brief Summary of Design and Population. This trial was conducted on a nursing home population composed of mostly elderly individuals and had as single center, Mobile, Al. The single Principal Investigator was Dr. J. DiPalma. According to Braintree, **the protocol design for study 851-4 "was identical to protocol 851-3", see Protocol for 851-3, this review** (the prospective protocol for 851-4 was not included in this NDA submission). Thus, this study had a cross-over design with an open one week placebo qualifying period and three consecutive 10 day periods in which patients were randomized to two ascending doses of PEG 851 or placebo (only periods 2 and 3).

Originally, the protocol called for enrollment of 50 constipated patients randomized to 17 g PEG and 34 g PEG.

The average age of the subjects enrolled in the study was 75.7 years (Page 4-22, Vol. 2 or Braintree 1.4.2) **After randomization to the first 5 patients to either the 17 g or 34 g PEG doses, four elderly subjects experienced Adverse Drug Reactions (ADR) manifested by excessive or profuse diarrhea. Braintree then changed the PEG doses to 6 g or 12 g PEG, respectively. This study was discontinued after enrollment of 35 consecutive subjects.**

b. Patient Disposition. As stated, 35 subjects were enrolled in this 851-4 study; only 17 subjects (49%) completed the trial. The following is the sponsor's list of patient discontinuations. Braintree Table 4.14 was taken from Page 4-40, Vol. 2. The abbreviation AOTE indicates Adverse On Therapy Experience.

APPEARS THIS WAY ON ORIGINAL

Table 4.14
Dropouts and Incompletions
Protocol 851-4

Patient	Treatment	Reason
1	34g	AOTE (diarrhea); see table 4.13.
2	34g	AOTE (diarrhea); see table 4.13.
4	17g	AOTE (diarrhea); see table 4.13.
5	17, 34g	AOTE (diarrhea); see table 4.13.
7	c, 6g	AOTE (MI); see table 4.12.
8	12g	Removed from study due to noncompliance.
11	placebo	Removed from nursing home by family.
15	p, 6g	Noncompliant and removed from nursing home.
16	6g	Discharged from facility.
19	6g	AOTE (CVA); see table 4.12.
22	placebo	Discharged from facility.
23	placebo	AOTE (diarrhea, vomiting); see table 4.13.
24	6g	Patient withdrew after impaction.
25	6g	AOTE (death); see table 4.12.
27	6g	Patient withdrew due to lack of efficacy.
28	6g	Discharged from facility.
31	12g	Patient withdrew due to lack of efficacy.
35	6g	AOTE (nausea and vomiting); see table 4.13.

c = control; p = placebo; 6g, 12g, 17g, 34g = dose of 851

c. *Efficacy.* Braintree showed the primary overall efficacy variables (stool weight and stool frequency in Braintree Tables 4.4 and 4.5. Braintree stated the following on the tables results:

"These tables show the mean daily stool output and mean daily bowel movement frequency for each 10 day treatment period for the 17 patients that completed the protocol. No significant difference between the treatments could be determined. This was due in part to the highly variable responses between individuals as well as to a substantial placebo response and difficulty in stool collection".

Table 4.4
Mean Daily Wet Stool Output (grams)
(Braintree Protocol #851-4)

	Placebo	6 grams ^(a)	12 grams ^(b)
Mean	39.2	30.9	47.3
SEM	7.18	6.91	9.14

p = 0.34 DF=2,32 F=1.11

(SEM = standard error of mean)

(a) includes first five patients dosed at 17g

(b) includes first five patients dosed at 34g

Table 4.5
Mean Daily Bowel Movement Frequency
(Braintree Protocol #851-4)

	Placebo	6 grams ^(a)	12 grams ^(b)
Mean	0.59	0.45	0.70
SEM	0.04	0.04	0.06

p = 0.24 DF=2,32 F=1.47
(SEM = standard error of mean)
(a) includes first five patients dosed at 17g
(b) includes first five patients dosed at 34g

ii. Reviewer Comments.

(1) The results for Braintree study 851-4 failed to show differences in primary efficacy variables between placebo and any of the tested PEG 851 doses. The only two patients (4 and 5) with the laxative PEG dose included in the proposed label, i.e., PEG 17 grams, developed diarrheal conditions serious enough as to warrant their premature discontinuation. The two other patients (1 and 2) who were administered the submitted alternative PEG dose proposed in the label, i.e., 34 grams, similarly developed diarrhea and had to be discontinued from the trial. Ten other patients randomized to PEG 6 grams (8 patients) or PEG 12 grams (2 patients) were prematurely discontinued and never completed the trial. In this regard, it is noteworthy the sponsor's presentation of primary efficacy in the completed 17 patients. An intent-to-treat (ITT) comparison would require inclusion of the 14 patients randomized to PEG doses who departed the trial prematurely, may of them because of ADRs. Such an ITT comparison would decrease, even further, the low PEG laxative efficacy observed in this controlled clinical investigation.

Trial 851-5.

I. Brief Descriptive of Design and Subject Population. The following brief descriptive summary was taken from Vol. 3, Braintree Vol. 1.4.3. Braintree descriptive states that this was a crossover, double-blind, single-center study undertaken by the sponsor to evaluate the efficacy of 17 grams PEG 851 vs. placebo. After one week of run-in on placebo to confirm the diagnosis of constipation, subjects were randomized to two consecutive study periods of 14 days (2 Weeks) each. The consecutive cross-over sequence for each patient was randomized as follows: "Order 1 = 17 g PEG (1st period), Placebo (2d period); "Order 2 was = Placebo (1st

period), 17 g PEG (2d period)". Placebo and PEG 851 were appropriately blinded by addition of Crystal Light^R citrus flavor to both solutions.

The Investigator responsible for this study, Dr. D. Flavin, enrolled 25 consecutive patients with the diagnosis of idiopathic constipation; 24 were women and 1 was a male subject. Twenty four patients completed the one month study. The average age was 47 years; all patients were of Caucasian origin.

According to Braintree, Page 5-23, Vol. 3, the HFD-180 Division Director requested as the relevant efficacy analysis, a comparison of 851 and placebo during the first study period, i.e., the first two weeks of experimental treatment. The following Braintree table shows the mean number of bowel movements during the first treatment period. Braintree Table 5.5 was cut and pasted from Page 5-23, Vol. 3. Braintree concluded the following: *"In this parallel analysis of the first treatment period a comparison of the daily bowel movement frequency of the 13 patients receiving placebo to the 12 receiving laxative did not demonstrate a statistically significant difference. This was most probably due to the small number of patients in each group as well as the large variation between individuals"*.

Table 5.5
Mean Daily Bowel Movement Frequency
First Treatment Period
(Braintree Protocol #851-5)

	Placebo	851
Mean	0.50	0.69
SEM	0.09	0.14

p = 0.25	DF=23	t=1.18
(SEM = standard error of mean)		

ii. Reviewer Comments.

(a) This reviewer concurs with Braintree in its conclusion of the primary efficacy results after the first two week period of experimental therapy. No difference in frequency of bowel movements was observed between 851 and the placebo.

An alternative assessment of the primary efficacy is the use of a binary estimation to frequency of bowel movements, i.e., success or failure. Failure would be considered as ≤ 2 bm/week while success would be ≥ 3 bm/week. A breakdown of the two week first study period into subperiods of one week each,

would further provide us the primary efficacy during the first and second week of treatment, separately. My examination of Braintree computerized patient tabulation of stool frequency for placebo subjects and for subjects randomized to 17 g PEG (Pages 5-80 and 5-81), enabled me the assessment of efficacy by proportion of success/failures in each treatment group. The following MO Reviewer Table 7 illustrates this efficacy comparison.

MO Reviewer Table 7

Study 851-5. Proportion of Treatment Success After the First and Second Week of Therapy in Subjects Randomized to PEG 851 or Placebo

Treatment Period	PEG 851	Placebo	Therapeutic Gain, p-Value
Week One	7/12 (58%)	8/13 (62%)	+ 4% favors Placebo
Week Two	9/12 (75%)	7/13 (53%)	+ 20% favors PEG, p=0.41 (Not Significant) *

* Fisher Exact Test, calculated by Dr. M. Al-Osh.

As seen in MO Reviewer Table 7, administration of 17 g PEG 851 to constipated subjects failed to reveal statistical superiority over placebo either after one week or two weeks of treatment.

(b) The customary definition of constipation, i.e., ≤ 3 bm/week, was not appropriately followed in the selection of subjects. Braintree states the following: ***"In practice, about half (13) of the enrolled study subjects had 3 or more bowel movements during the control period. These study subjects were enrolled at the discretion of the investigators because in the investigator's clinical experience they were in fact constipated (for example, a patient could have may bowel movements, but small pellet stools)"***.

E. SAFETY

- The following summary describes the relevant subsections from Braintree's submission of the overall safety section, "c. *Safety Summary*", Pages 121-143, Vol. 1 (Braintree Vol. 1.1).

1. Proportion of Subjects Exposed to PEG 851. Braintree stated that "A total of 201 subjects have ingested the drug on a daily basis in the primary clinical studies (Braintree Protocols 3 and 6) for 10 to 20 days. Including all the controlled clinical studies, a total of 286 constipated patients have taken the drug on a daily basis for up to 20 days. In the open label study (Braintree Protocol 851-4a) 131 patients were enrolled and seven have taken the drug on a daily basis for 5 years or more. In all over 200 hundred patient years of daily exposure to 851 have been evaluated".

2. Adverse On Therapy Experiences (AOTE). Braintree reported that "In the controlled clinical studies, there were 14 reported unexpected adverse on therapy experiences (AOTE), six were serious. The serious AOTEs included one death, one CVA and one MI. All of these 41 occurred in the nursing home population and were associated with pre-existing disease. All of the unexpected AOTEs were described by the investigators as unrelated to the study medication. The unexpected AOTEs are below in Table 37". Braintree Table 37, was cut-and-paste from Page 123, Vol. 1.

Table 37
Unexpected AOTES
851 Clinical Studies

Patient	Study	Age	Sex	Dose	AOTE and Comment
1	851-4	84	F	placebo	"Sore stomach".
7	851-4	81	F	c, 6 gran	<u>Myocardial infarction</u> ; med discontinued.
19	851-4	92	F	6 gran	<u>CVA</u> , seizure; med discontinued.
23	851-4	72	F	placebo	<u>Infection</u> ; urinary tract; med discontinued.
25	851-4	76	M	6 gran	<u>Death</u> ; no code patient
19	851-5	32	F	placebo	<u>Heartburn</u> , nausea; prescribed Tagamet and Pepcid. Dyspepsia resolved.
31	851-6	47	F	17 gran	<u>Muscle aches</u> ; Mild. Pre-existing complaint. Patient recovered.
107	851-6	31	F	placebo	<u>Headache</u> ; Severe. Also mild bodyache and forgetfulness noted. Patient recovered.
135	851-6	73	F	17 gran	<u>Dislocated Shoulder</u> ; Treated, recovered.
140	851-6	73	F	placebo	<u>Abdominal Pain, Cramping</u> ; Mild to severe. Patient withdrawn.
207	851-6	40	F	placebo	<u>Elevated liver function</u> ; preexisting condition. Patient withdrawn.
217	851-6	42	M	placebo	<u>Elevated liver function</u> ; preexisting condition. Patient withdrawn.
218	851-6	59	F	placebo	<u>Abdominal pain</u> ; Severe. Patient withdrew from study.
230	851-6	43	F	17 gran	<u>Syncope and Volume depletion</u> ; history of dizziness following phlebotomy. Treated and recovered.

c = control period; 6 gran = 6 gran dose; 17 gran = 17 gran dose

Braintree notes that "All of the unexpected AOTEs were described by the investigators as unrelated to the body medication and due to pre-existing disease".

In Table 38, Page 124, Vol. 1, Braintree illustrated the number of "expected" AOTEs. Braintree states that most of the expected AOTEs were constipation and diarrhea. Braintree notes that Study 851-4 (nursing home study) had the "larger number of reports of reduced efficacy (i.e., continuing constipation)". Braintree postulates that the reduced efficacy observed in subjects enrolled in Study 851-4 was due to the low doses of PEG, i.e., 6 g and 12 g, used in this study. Braintree also notes that Study 851-3 had more reports of diarrhea, associated to the use of the high dose., 34 g, used in this trial.

Table 38
Summary of Expected AOTES
All 851 Clinical Studies

Study	Bloat	Imp./ Const.	Cramp	Diarrhea	Rec. Irr.	Nausea
851-3 ⁽¹⁾	0	1	2	20	1	0
851-4 ⁽²⁾	0	38	0	5	0	4
851-5 ⁽³⁾	0	4	0	3	0	1
851-6 ⁽⁴⁾	1	0	1	3	0	4
Total	1	42	3	31	1	9

(1) Cross-over study of placebo, 17g 851 and 34g 851.

(2) Cross-over study of placebo, 6 g 851 and 12g 851.

(3) Cross-over study of placebo vs 17g 851.

(4) Parallel study of placebo vs 17g 851

Imp./Const. = impacted or constipated

Rec.Irr. = rectal irritation

In Table 39, Braintree listed the individual AOTEs for all "the controlled clinical studies and preclinical studies".

Braintree Table 39, Pages 126-127, Vol. 1, is included as Appendix 7 of this review.

I. Reviewer Comments.

(a) *Therapeutic Range.* The safety data presented by Braintree in Studies 851-3 and 851-4 reveal a rather narrow therapeutic range for the use of the PEG 851 laxative. As stated in the proposed Braintree label, the recommended PEG laxative dose is 17 g per day, i.e., the ingestion of one heap full tablespoon daily. According to the safety data from 851-3 illustrated in Braintree Table 39, the daily ingestion of two heap full tablespoons of 851 laxative, i.e., 34 g, led to development of diarrhea in 12 patients; in 10 of these patients the diarrhea was severe enough as to cause discontinuation of the 851 laxative administration. Added to these episodes in 851-3, are the AOTE events with the use of the 34 g, two heap full tablespoons of PEG, in nursing home patients (Study 851-4). The 34 g dose was discontinued from this trial, after the first 4 consecutive enrolled patients developed diarrhea.

On the other side of the spectrum are the reported 12 treatment failures encountered in nursing home patients randomized to 6 g or 12 g of the PEG laxative, i.e., half or two third full tablespoon daily dose. As observed in Braintree Table 39, these 12 patients had constipation severe enough as to required the use of rescue medication.

This small therapeutic range observed with use of PEG 851 as laxative, raises some concerns on the clinical benefit for the wide use in subjects with the functional complain of idiopathic constipation.

(b) Unexpected Serious AE. There were two deaths, both in the nursing home study. Patient 7, shown in Braintree Table 37 as discontinued after the first PEG dose due to a MI, expired shortly after discontinuation of the laxative. She was an 81 y female with aphasia and paraplegia. The PI thought her death was unrelated to the use of the laxative.

The many discontinuations which occurred in the nursing home study and the narrow therapeutic range observed with the use of the 851 laxative, creates concerns of its use in elderly individuals, i.e., over 70 y old. These elderly subjects often have associated medical conditions and are more labile to sudden water or electrolyte changes due to moderate or severe diarrheas. This caution also would apply to the pediatric population of infants and young adolescents.

F. SUMMARY AND RECOMMENDATIONS FOR REGULATORY ACTIONS.

- In this NDA, Braintree proposes the use of PEG 851, an non-absorbable osmotic drug, for treatment of subjects with occasional constipation. The proposed label states that 17 g dissolved in 240 ml of water or juice should induce bowel movements 24 h to 48 h after ingestion.
- In support of the proposed indication, Braintree submitted two pivotal studies, (a) a randomized, crossover, double-blind, single center study conducted under Protocol 851-3 and (b) a parallel, placebo-controlled conducted in four centers under Protocol 851-6. Protocol 851-6 was also prospectively established as randomized and double-blind.

With the agreement by the sponsor, constipation or failure to relieve constipation was defined as less than 3 bowel movements per week and success in relieving constipation as equal or greater than 3 bowel movements per week.

- **Study 851-3, a single center study, randomized 51 constipated patients to a first period (10 days) of PEG therapy only, 17 g or 34 g. Subsequently, and without washout interval, subjects were randomized to a second or third periods of placebo or the alternate PEG dose. As a result of this design, contamination of the placebo by PEG or contamination of the low PEG dose by the high PEG dose, was likely. Adjustment of this probable carry-over effect by comparison of primary efficacy of the first 10 day period showed no significant difference between the proportion of successes in all subjects treated with PEG 17 g or PEG 34 g and placebo ($p=0.15$ and $p=1.0$, respectively). There was, however, a numerical difference between PEG 17 g and placebo, favorable to PEG 17 g. During this study, Braintree conducted an interim analysis, not reported in this submission (see Reviewer Comments section, Study 851-3, this review).**
- **Study 851-6 enrolled 151 subjects randomized to placebo or PEG 17 g. There was a reported interim analysis in the mid-trial and the sponsor stopped the trial after a second look at the results, before completing the prospectively established 200 subject sample size. In view of these interim looks, the reviewer statistician adjusted the significance to $p=0.018$. Comparison in the Intent-To-Treat population for Week 1 of therapy on these constipated subjects resulted in no significant difference in successes between PEG 17 g and placebo. The comparison between PEG 17 g and placebo for Week 2 of treatment did show a significant superiority of the PEG 17 g over placebo.** The blinding protection designed for this study was deficient; placebo was a sugar water solution. The same sugar, i.e., dextrose, was not part of the PEG solution.
- The sponsor conducted two other controlled studies, 851-4 and 851-5. Study 851-4 was a nursing home study with elderly patients. Only 5 subjects were enrolled on PEG 17 g or 34 g. These subjects were discontinued after development of diarrhea. The dose was reduced to PEG 6 g or 12g. No significant superiority was detected between PEG and placebo. Study 851-5 was a crossover study. The first period before the crossover lasted one month and failed to show any differences between PEG and placebo.

In view of the discussed efficacy results, I conclude the following:

1. Not to recommend approval of the present NDA submission, i.e., use of PEG 17 g as laxative for occasional constipation. **My decision is based on the lack of substantial evidence of effectiveness, i.e., lack of replication in demonstrating superiority as a laxative by the PEG over placebo. Of the two pivotal studies submitted, only one study, 851-6, showed a significant**

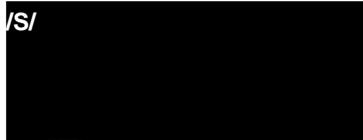
superiority of the PEG in only one of the two weeks investigated, i.e., week two. The only other controlled study in which the PEG laxative was administered to constipated subjects in the proposed laxative dose of 17g, and in which subjects completed the trial, Study 851-5, showed no significant difference in the laxative effect between the PEG and placebo.

As aforementioned in this section, both pivotal studies had serious deficiencies in design and problems in adequacy. Study 851-3 was a crossover study without any washout period between High dose PEG and Low dose PEG, or, between any PEG dose and placebo. Study 851-6 had sugar water as placebo and, thus, could not be considered a blinded study.

2. In spite of the deficiencies discussed in Study 851-6, and in view that after all the adjustments specified by the reviewer statistician the results observed in Week 2 remained highly significant in favor of the PEG 17 g laxative, this reviewer will accept Study 851-6 as one of the pivotal studies needed for the process of approval. Therefore, this reviewer would recommend the conduction of one additional adequate and well-controlled trial, to replicate and confirm the PEG efficacy observed in Study 851-6.

The narrow therapeutic range observed in this submission, between the proposed dose and a low dose, i.e., 6g-12g, or higher doses, i.e., 34g, raises concern on the PEG safety for its use as laxative in the elderly or pediatric population.

/s/



Robert Prizont, M.D.

cc:

NDA 20-698
HFD-180
HFD-180/SFredd
HFD-180/RPrizont
HFD-180/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/13/96 jgw
MED\N20698612.0RP

12/26/96

/s/



APPEARS THIS WAY ON ORIGINAL

APPENDIX 1
Minutes of 45 Day Filing Meeting

APPENDIX 2
Randomization Plan for Study 851-3

Table 3.2
Patient Randomization Table
Braintree Protocol #3
(Wisconsin)

Treatment Groups:

- A = Placebo
- B = 17 grams 851
- C = 34 grams 851

Pt#	Treat 1	Treat 2	Treat 3	Pt#	Treat 1	Treat 2	Treat 3
1	C	A	B	26	C	A	B
2	C	A	B	27	B	C	A
3	C	B	A	28	C	A	B
4	C	B	A	29	B	C	A
5	B	C	A	30	B	C	A
6	C	B	A	31	C	A	B
7	C	A	B	32	B	C	A
8	C	B	A	33	C	A	B
9	B	C	A	34	C	B	A
10	C	B	A	35	C	B	A
11	B	C	A	36	B	C	A
12	C	B	A	37	B	A	C
13	B	A	C	38	C	A	B
14	B	A	C	39	C	B	A
15	B	A	C	40	B	A	C
16	B	A	C	41	B	A	C
17	B	C	A	42	B	C	A
18	C	B	A	43	C	B	A
19	C	A	B	44	B	C	A
20	C	A	B	45	C	A	B
21	B	A	C	46	B	A	C
22	C	B	A	47	C	A	B
23	B	C	A	48	B	C	A
24	B	C	A	49	C	A	B
25	C	A	B	50	B	C	A
				51	C	A	B

Note: The table includes 51 entries because patient 7 was not entered into treatment, therefore a 51st patient was enrolled (see table 3.21, page 3-51).

243
24
48

APPENDIX 3
Minutes of Meeting Between Braintree and Division Director, November 5, 1987

**4 pages Redacted
Trade Secret/
Confidential Commercial**

APPENDIX 7
Braintree Table 39, Vol. 1, Safety of Braintree Laxative Trials

**5 pages Redacted
Draft Labeling**

APPENDIX 4
Braintree Investigational Plan for Study 851-3

4. Investigational Plan

Protocol Cover Sheet
851-3

Study Phase: III

Name of Drug: 851 Laxative

Active Ingredients: Polyethylene Glycol 3350

Dosage: 17 or 34 grams/day Route of Administration: Oral

Patient Population: Qualified constipated volunteer

Structure: Randomized, double blind cross-over

Duration of Study: 6 weeks

Drug Exposure: 20 days

Multicenter: No

Blinding: Double - all bottles labeled identically. Taste masked.

Method of Patient Assignment: Randomized

Patients with a history of constipation (but otherwise healthy) were given placebo 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.

Concurrent Control: Placebo

Total Sample size: 50

Primary Efficacy Variables: Stool output
Bowel movement frequency
Physician and patient ratings

Adverse Reactions: Elicited and volunteered

Plan for Data Analysis: yes (no interim analysis performed)

APPENDIX 5

January 27, 1994 from Dr. Cleveland (Braintree) to Dr. Barton, from IND [REDACTED]

**1 page Redacted
Trade Secret/
Confidential Commercial**

APPENDIX 6
Statistician Reviewer Table 2, from Statistical Review, September 1996

Patient	Study	Drug	Table 15 (cont.) AOTEs and Comment
517	851-4	c.p,6g	<u>Constipated</u> ; treated with enemas.
618	851-4	c.p,6,12g	<u>Constipated</u> ; treated with enemas.
20	851-4	control	<u>Constipated</u> ; treated with enemas.
22	851-4	c.p	<u>Constipated</u> ; treated with enemas.
23	851-4	control	<u>Constipated</u> ; treated with enemas.
23	851-4	placebo	<u>Diarrhea, nausea, vomiting</u> ; infection treated with antibiotics.
724	851-4	6 gran	<u>Impacted</u> ; treated with enemas.
28	851-4	control	<u>Nausea, vomiting</u> ; patient recovered.
828	851-4	12 gran	<u>Constipated</u> ; treated with enemas.
429	851-4	c,12	<u>Constipated</u> ; treated with enemas.
1030	851-4	c,12	<u>Constipated</u> ; treated with enemas.
1131	851-4	c,6,12	<u>Constipated</u> ; treated with enemas.
1232	851-4	c,6	<u>Constipated</u> ; treated with enemas.
1333	851-4	c,6,12	<u>Constipated</u> ; treated with enemas.
1434	851-4	c,12	<u>Constipated</u> ; treated with enemas.
35	851-4	control	<u>Constipated</u> ; treated with enemas.
35	851-4	6 gran	<u>Nausea</u> ; secondary to metastatic neoplasia. Med discontinued.
4	851-5	17 gran	<u>Nausea</u> ; flatus and weakness. Patient stopped med; recovered.
14	851-5	control	<u>Impacted</u> ; self disimpacted
14	851-5	17 gran	<u>Impacted</u> ; self disimpacted (moved to next treatment phase - placebo; later withdrew from study).
18	851-5	17 gran	<u>Loose, watery stool</u> ; Patient stopped med. Recovered.
19	851-5	17 gran	<u>Diarrhea</u> ; Mild, related to above. Recovered.
20	851-5	17 gran	<u>Loose stools</u> ; Mild nausea, dizziness, weakness. Recovered.
21	851-5	control	<u>Impacted</u> ; took laxative, self disimpacted.
21	851-5	placebo	<u>Impacted</u> ; took laxative, self disimpacted.
3	851-6	17 gran	<u>Nausea</u> ; Mild. Patient recovered.
6	851-6	17 gran	<u>Nausea</u> ; Mild. Patient withdrew from study.
11	851-6	17 gran	<u>Nausea and Cramping</u> ; Mild. Patient withdrew from study.
43	851-6	placebo	<u>Diarrhea</u> ; Also, hemorrhoid pain due to diarrhea. AOTEs noted in diary.
106	851-6	17 gran	<u>Bloating</u> ; Mild, recovered.
145	851-6	17 gran	<u>Diarrhea</u> ; Protocol definition.
205	851-6	17 gran	<u>Dry mouth, Nausea</u> ; Mild. Recovered.
206	851-6	17 gran	<u>Diarrhea</u> ; Moderate. Attributed to peppers. Recovered.

* control period; p = placebo