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URINE AND STOOL RECOVERY IN CONSTIPATED PATIENTS

Title: Recovery of PEG 3350 from constipated patients

Protocol No.: 851-2b

Investigator and Site: [redacted]

Study Dates: 11/93 - 2/95

Objectives: To evaluate the disposition of orally administered PEG 3350 in constipated individuals. This was done by measuring urine PEG 3350 excretion as well as recovery of PEG 3350 from stool.

Study Design: This is a Phase I, open-label study. Following a seven day qualification period, five (3 males and 2 females, mean age: 54.4 years) constipated but otherwise normal individuals were hospitalized for six days. Patients were selected if they were 18 years of age or older and could meet the criteria for constipation of less than or equal to 3 bowel movements per week and/or less than or equal to 300 grams of stool per week during an evaluation period. Each subject was administered a daily dose of 17 g PEG 3350 in 250 ml of [redacted] flavored water each day for the first two days of the study period (for a total of 34 grams) and placebo for the next four days. Study subjects were instructed to collect all stool and urine. No other markers were given. On the sixth day, the subjects were administered four to seven liters of lavage solution containing mannitol by stomach tube. The stool, lavage effluent and urine was analyzed for PEG 3350 to determine recovery. Hematology survey and general blood chemistry analysis were performed on the first and last of the treatment period.

Formulations:

- Active: 17 g PEG 3350 filled into individual vials as a powder, Lot # 2EX03, manufactured by [redacted]
- Placebo: [redacted]
- Mannitol

Assay Method:

Stool and urine were analyzed for PEG by a modification of the method [redacted]

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PEG 3350 in Stool: PEG 3350 concentrations in stool were measured by a [redacted] method. All samples and standards were prepared in triplicate. Stool specimens believed to be free of PEG and these specimens with added PEG, 2.0 g/L, were analyzed. In the assay procedure, 1.00 g of stool was mixed with 1.0 mL of PEG standard (2.0 g/L) instead of 1.0 mL of water.

PEG 3350 in Urine: PEG 3350 concentrations in urine was measured by a [redacted] method. All samples and standards were prepared in triplicate. Urine specimens believed to be free of PEG and these same specimens with added PEG were analyzed. 9.00 mL of urine and 1.00 mL PEG standard (2.0 and 5.0 g/l) were mixed to give urine samples with expected values of 0.2 and 0.5 g/L.

It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

Results:

The urine output (ml) and PEG recovery in urine during the 6-day treatment period are given below:

Subject	Volume (ml)	PEG (g)
1	6848	0
2	4678	0
3	4701	0
4	18228	0
5	8295	0
Mean	8550	0
SD	5622	0

No PEG was detected in the urine of any study subject for the 6 day treatment period.

The frequency of bowel movement (#BM), stool output (grams), and recovery (%) of PEG 3350 in stool during control and treatment period are given in the following table:

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	Control Period		Treatment Period				
Subject No.	#BM	Stool Weight (g)	#BM	Stool* Weight (g)	PEG% in Stool	PEG% in Lavage	Total PEG%
1	3	233.8	5	733.2	84.7	0.0	84.7
2	4	170.6	4	168.1	34.4	7.9	42.3
3	3	186.8	4	474.3	91.8	0.9	92.7
4	2	22.6	3	37.4	0.9	87.3	88.2
5	3	215.8	4	192.3	45.9	9.1	55.0
Mean	3	165.9	4	321.1	51.5	21.0	72.6
SD	0.7	83.8	0.7	280.1	37.5	37.3	22.5

*Stool weight values do not include lavage effluent.

More than 80% of PEG 3350 administered was recovered from the collected stool of three study subjects (#1, #3, and #4). Two study subjects (#2 and #5) had poor stool recovery (about 50%). It was stated that subject #5 had been unable to complete the lavage on day 6 which may contributed to the incomplete collection; no explanation for subject #2 was given.

Comments:

- Protocol violation: subject #2 had 4 bowel movements during the control period, this subject, therefore, cannot be considered as "constipated patient". This subject had a 42% PEG stool recovery.

- Since no PEG was detected in the urine of any subject, the firm claimed that the unrecovered PEG might remain either in the study subject's GI tract or that stool collection in these subjects might be incomplete.

- It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

- The firm stated that there is no assay method to detect PEG level in blood. However, DiPiro et al (1986) published an assay method capable of detecting 10 μg/ml of PEG 4000 in blood by using a gel permeation chromatography.

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Conclusions:

No PEG was detected in the urine. However, the recovery of PEG in collected stool was variable, ranged from 42% to 93% in the constipated patients.

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[redacted]

Assay:

Stool was analyzed for PEG by a modification of the method of [redacted] Chromium oxide was analyzed by a modification [redacted] 1969 and barium sulfate by a modification of the method [redacted] The plastic markers were counted following [redacted] of the collected stool.

PEG 3350 in Stool: PEG 3350 concentrations in stool was measured by a turbidimetric method. All samples and standards are prepared in triplicate. Stool specimens believed to be free of PEG and these specimens with added PEG, 2.0 g/L, were analyzed. In the assay procedure, 1.00 g of stool was mixed with 1.0 ml of PEG standard (2.0 g/L) instead of 1.0 ml of water. It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

Results:

The results of the analysis of the stool collections for the markers are given below.

Table 1. Percent Total Marker Recoveries

Subject	PEG	CrO_4	$BaSO_4$	[redacted]
1	[redacted]			
2[b]				
3[b]				
4[b]				
5				
Mean	65.3	75.2	55.4	78.3
SD	37.2	42.2	33.9	36.1

a Total recovery = 24
b Stools reported lost by patient on interview.

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STOOL RECOVERY OF NONABSORBABLE MARKERS IN CONSTIPATED PATIENTS

Title: Stool recovery of nonabsorbable markers in constipated patients.

Protocol No.: 851-2c

Investigator and Site: [redacted]

Study Dates: 2/95 - 6/95

Objectives: To evaluate the feasibility of outpatient stool collection studies in constipated patients using several different non-absorbable markers.

Study Design:

This is a single-dose study. Five (2 males and 3 females, mean age, 51.8 years) constipated but otherwise normal subjects were enrolled into the study, following a seven day qualification period. Study subjects were not hospitalized. Each study subject was administered four nonabsorbable markers on the first day of treatment. These were: 17 gram of PEG 3350 in 250 ml of [redacted] flavored water; [redacted] capsule (containing 24 plastic intestinal transit markers); 500 mg chromic oxide in a capsule; and 1 gram of barium sulfate in a capsule. Subjects were instructed to collect stools for the next 13 days. Study subjects were given laxative [redacted] starting dose 2 tablets each evening) sufficient to induce at least one bowel movement every two days. On day 13, patients were given a laxative bowel cleansing preparation which consisted of 20 mg bisacodyl followed by 10 oz magnesium citrate and were instructed to collect all effluent. The stool and final clean-out were analyzed for the markers.

[redacted]

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[redacted]

Assay:

Stool was analyzed for PEG by a modification of the method of [redacted] Chromium oxide was analyzed by a modification [redacted] 1969 and barium sulfate by a modification of the method [redacted] The plastic markers were counted following [redacted] of the collected stool.

PEG 3350 in Stool: PEG 3350 concentrations in stool was measured by a turbidimetric method. All samples and standards are prepared in triplicate. Stool specimens believed to be free of PEG and these specimens with added PEG, 2.0 g/L, were analyzed. In the assay procedure, 1.00 g of stool was mixed with 1.0 ml of PEG standard (2.0 g/L) instead of 1.0 ml of water. It should be noted that the assay method has a drawback being not specific; it doesn't distinguish PEG 3350 from the lower molecular weight PEGs such as PEG 400, PEG 1000, etc. The validation data provided is not satisfactory. It lacks linearity, sensitivity, accuracy and precision information.

Results:

The results of the analysis of the stool collections for the markers are given below.

Table 1. Percent Total Marker Recoveries

Subject	PEG	CrO_4	$BaSO_4$	[redacted]
1	[redacted]			
2[b]				
3[b]				
4[b]				
5				
Mean	65.3	75.2	55.4	78.3
SD	37.2	42.2	33.9	36.1

a Total recovery = 24
b Stools reported lost by patient on interview.

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APPENDIX II

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INACTIVE INGREDIENT GUIDE

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REFERENCES

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BIBIOGRAPHY

1. DiPiro JT, Michael KA, Clark BA, Dickson P, Vallner JJ, Bowden TA, Tedesco FJ: Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. Clin. Pharm. 5:153-155, 1986.

2. Brady CE, DiPalma JA, Morowski SG, Fordtran JS: Urinary excretion of polyethylene glycol 3350 and sulfate after gut lavage with a polyethylene glycol electrolyte lavage solution. Gastronenterology 90: 1914-1918, 1986.

3. Barker RWR and Ferrett J: Estimation of polyethyleneglycols in human urine for studies of intestinal absorption. J. Chromatogr. 273: 421-425, 1983.

4. Jackson PG, Lessof MH, Baker RWR, and Ferret J: Intestinal permeability in patients with eczema and food ellergy. Lancet June 13, 1981.

5. Schedl HP, Miller D, and White D: Use of polyethylene glycol and phenol red as unabsorbed indicators for intestinal absorption studies in man. Gut 7: 159-163, 1966.

6. Devrode G, and Soffie M: Colonic absorption in idiopathic constipation. Gastroenterology 64: 552-561, 1973.

7. Bo-Linn GW, Davis GR, Buddrus DJ, Morawski SG, Santa Ana C, and Fordtran JS: An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium. J. Clin. Invest. 73: 640-647, 1984.

8. Knutson L, Odlind B, and Hallgren R: A new technique for segmental jejunal perfusion in man. American J. of Gastroenterology 84 (10): 1278-1284, 1989.

9. Ingelfinger FJ: The kinetics of water absorption in the human intestine. Trans. Assoc. Am. Phys. 74: 195-206, 1961.

10. Dillard RL, Eastman H, and Fordran JS: Volume-flow relationship during the transport of fluid through the human small intestine. Gastroenterology 49 (1): 58-66, 1965.

11. Miller DL, and Schedl H: Total recovery studies of nonabsorbable indicators in the rat small intestine. Gastroenterology 58 (1): 40-46, 1970.

12. Fox JE, Bourdages R, and Beck IT: Effect of ethanol on glucose and water absorption in hamster jejunum in vivo. Digest. Diseases 23 (3): 193-195, 1978.

13. Schiller LR, Hogan RB, Morawski SG, Santa Ana CA, Bern MJ, Norgaard RP, Bo-Lin GW, and Fordtran JS: Studies of the prevalence and significance of radiolabeled bile acid

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malabsorption in a group of patients with idiopathic chronic diarrhea. Gastroenterology 92 (1): 151-160, 1987.

14. Ramirez JA, Emmett M, White MG, Fathi N, Santa Ana C, Morawski SG and Fortran JS: The absorption of dietary phosphate and calcium in hemodialysis patients. Kidney Int. 30: 753-759, 1986.

15. Sheikh MS, Santa Ana CA, Nicar MJ, Schiller LR, and Fortran JS: Gastrointestinal absorption of calcium from milk and calcium salts. N. Eng. J. Med. 317: 532-536, 1987.

16. Mai ML, Emmett M, Sheikh MS, Santa Ana CA, Schiller L, and Fortran JS: Calcium acetate, an effective phosphorus binder in patients with renal failure. Kidney International 36: 690-695, 1989.

17. Schiller RL, Santa Ana CA, Sheikh MS, Emmett M, and Fordtran JS: Effect of the time of administration of calcium acetate on phosphorus binding. New Eng. J. Med. 320: 1110-1113, 1989.

18. Sheikh MS, Maguire JA, Emmett M, Santa Ana CA, Nicar MJ, Schiller LR, and Fordtran JS: Reduction of dietary phosphate absorption by phosphorus binders: A theoretical, in vitro, and in vivo study. J. Clin. Invest. 83: 66-73, 1989.

19. Soergel KH and Hogan WJ: On the suitability of poorly absorbed markers as dilution indicators in the gastrointestinal tract. Gastroenterology 52 (6): 1056-1057, 1967.

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III. Summary/ Conclusion:

The efficacy results of study 851-6 for Week 2 treatment, and to a less extent, for the Week 1 and Week 2 combined, show that a significantly higher proportion of laxative patients got relief from constipation compared to those on placebo. Analysis of the frequency of bowel movements based on ranks supports these findings. But analysis based on comparison of the mean bowel movements failed, in general, to show significant results. This is due to extreme outliers in the data. Comparisons of the ranks of the bowel movements, which account for the outliers in the data, were significantly in favor of the laxative except for Week 1 when the missing data are set to 0.

However among the four centers, center # 3 contributes the most to the overall observed efficacy results (see Tables 1 and 2). In addition, as most of the missing values occurred in the laxative treatment arm, the overall efficacy results depends on the way of handling the missing values (see Tables 1 and 2).

The sponsor may be asked to explain the variation in the efficacy results of center # 3 and those of other centers and the variation in the missing values between the two treatments. The field investigation may also look into these issues.

/S/ [redacted] 9/4/96

M. Al-Osh, Ph.D.
Mathematical Statistician

Concur: /S/ [redacted]
Dr. Huque
Dr. Smith

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This review consists of 13 pages of texts and 2 attachments (6 pages).

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
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Attachment # 1

Data Listing / Study 851-6

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OBS	PATIENT	CENTER	DOSE	Contrat Wuk CWK	Wuk1 TWK1	Wuk2 TWK2	Wuks 1 & 2 TWK12
1	1	1.	1 ≡ Laxati[redacted]				
2	2	1.	1.				
3	3	1.	1.				
4	4	1.	2.				
5	5	1.	2.				
6	6	1.	1.				
7	7	1.	1.				
8	8	1.	1.				
9	9	1.	1.				
10	10	1.	2 ≡ placebo				
11	11	1.	1.				
12	12	1.	1.				
13	13	1.	1.				
14	14	1.	2.				
15	15	1.	2.				
16	16	1.	2.				
17	17	1.	2.				
18	18	1.	2.				
19	19	1.	1.				
20	20	1.	1.				
21	21	1.	1.				
22	22	1.	2.				
23	23	1.	1.				
24	24	1.	1.				
25	25	1.	1.				
26	26	1.	1.				
27	27	1.	2.				
28	28	1.	2.				
29	29	1.	2.				
30	30	1.	1.				
31	31	1.	1.				
32	32	1.	2.				
33	33	1.	1.				
34	34	1.	2.				
35	35	1.	2.				
36	36	1.	2.				
37	37	1.	2.				
38	38	1.	1.				
39	39	1.	2.				
40	40	1.	2.				
41	41	1.	2.				
42	42	1.	1.				
43	43	1.	2.				
44	44	1.	1.				
45	45	1.	1.				
46	46	1.	2.				
47	47	1.	2.				
48	101	2.	2.				
49	102	2.	1.				
50	103	2.	2.				
51	104	2.	1.				
52	105	2.	1.				
53	106	2.	1.				
54	107	2.	2.				
5	108	2.	1.				

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OBS	PATIENT	CENTER	DOSE	CWK Control	TWK1 Week 1	TWK2 Week 2	TWK12 Week 12
56	109	2.	1≡Lo2	[redacted]			
57	110	2.	2.				
58	111	2.	1.				
59	112	2.	1.				
60	113	2.	2≡plac				
61	114	2.	2.				
62	115	2.	2.				
63	116	2.	1.				
64	117	2.	2.				
65	118	2.	2.				
66	119	2.	2.				
67	120	2.	1.				
68	121	2.	2.				
69	122	2.	1.				
70	123	2.	2.				
71	124	2.	1.				
72	125	2.	1.				
73	126	2.	2.				
74	127	2.	1.				
75	128	2.	2.				
76	129	2.	1.				
77	130	2.	1.				
78	131	2.	2.				
79	132	2.	1.				
80	133	2.	1.				
81	134	2.	2.				
82	135	2.	1.				
83	136	2.	1.				
84	137	2.	2.				
85	138	2.	1.				
86	139	2.	2.				
87	140	2.	2.				
88	141	2.	2.				
89	142	2.	2.				
90	143	2.	2.				
91	144	2.	1.				
92	145	2.	1.				
93	146	2.	2.				
94	147	2.	1.				
95	148	2.	1.				
96	149	2.	2.				
97	150	2.	1.				
98	201	3.	1.				
99	202	3.	1.				
100	203	3.	1.				
101	204	3.	2.				
102	205	3.	1.				
103	206	3.	1.				
104	207	3.	2.				
105	208	3.	2.				
106	209	3.	2.				
107	210	3.	2.				
108	211	3.	2.				
109	212	3.	1.				
110	213	3.	2.				

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OBS	PATIENT	CENTER	DOSE	CWK Control	TWK1 Week 1	TWK2 Week 2	TWK12 Weeks 1 + 2
111	214	3.	1 = Low	[redacted]			
112	215	3.	1.				
113	216	3.	1.				
114	217	3.	2 = plac				
115	218	3.	2.				
116	219	3.	1.				
117	220	3.	2.				
118	221	3.	2.				
119	222	3.	1.				
120	223	3.	2.				
121	224	3.	1.				
122	225	3.	2.				
123	226	3.	1.				
124	227	3.	2.				
125	228	3.	1.				
126	229	3.	1.				
127	230	3.	1.				
128	231	3.	1.				
129	232	3.	1.				
130	301	4.	1.				
131	302	4.	2.				
132	303	4.	1.				
133	304	4.	2.				
134	305	4.	1.				
135	306	4.	1.				
136	307	4.	1.				
137	308	4.	1.				
138	309	4.	1.				
139	310	4.	2.				
140	311	4.	1.				
141	312	4.	2.				
142	313	4.	2.				
143	314	4.	1.				
144	315	4.	1.				
145	316	4.	2.				
146	317	4.	1.				
147	318	4.	1.				
148	319	4.	1.				
149	320	4.	1.				
150	321	4.	2.				
151	322	4.	2.				
152	323	4.	2.				

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Attachment # 2

Center #3 Treatment Allocations

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Patient Randomization Table
Braintree Protocol 851-6

Center: New Orleans (#3)
Investigator: Orlando

A = 17 gram 851
B = Placebo

Patient #	Drug
201	A
202	A
203	A
204	B
205	A
206	A
207	B
208	B
209	B
210	B
211	B
212	A
213	B
214	A
215	A
216	A
217	B
218	B
219	A
220	B
221	B
222	A
223	B
224	A
225	B

Patient #	Drug
226	A
227	B
228	A
229	A
230	A
231	A
232	A

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STATISTICAL REVIEW AND EVALUATION

Date: JUL 29 1996

NDA #: 20-698
Sponsor: Braintree Laboratories, Inc.
Name of Drug: 851 laxative (Polyethylene glycol 3350 (PEG-3350))
Indication: treatment of normal constipated patients.
Documents Reviewed: Vol. 1.1, 1.8 - 1.13 dated 2/26/1996
Statistical Reviewer: M. Al-Osh, Ph.D.

The issues in this review have been discussed with the Medical Officer R. Prizont, M.D.

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
REC'D
JUL 30 1996
HFD-160

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I. Introduction/Background

This review addresses the two pivotal studies (#851-3 and #851-6) which the sponsor has submitted for claiming safety and efficacy of a 17 gram dose of 851 Laxative in the treatment of occasional constipation. The sponsor has submitted also, in support of this claim, the efficacy results for two additional clinical studies #851-4 and #851-5. The sponsor's choice of the proposed dose was based on a Phase II study of 5 patients and, as the sponsor stated, on the efficacy results of studies #851-3 and #851-4, which were designed to evaluate the efficacy results of two doses (17 and 34 grams) against placebo in a cross-over design.

II. Description of The Pivotal Studies:

II.A. Study 851-3:

This was a single center, randomized, double blind, three way (4-sequence, 3-period) cross over study for comparing placebo, 17 grams and 34 grams dose of 851 laxative for the treatment of constipated but otherwise normal outpatients.

Following a seven day control period during which patients were given placebo daily, patients who experienced 3 or less bowel movements and/or produced 300 or less grams of stool during this period were enrolled in the study. A total of 50(3M/47F) patients were enrolled in the study.

The treatment phase of the study consisted of three 10-day periods. Patients were randomized to receive one of three possible treatments (placebo, 17 gram dose or 34 gram dose) during each period. At the completion of each treatment period patients were to be crossed over into an alternative treatment

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according to a randomization schedule. However, placebo was not given during the first treatment period. The sponsor claimed that constipated patients would be unwilling or unable to complete a 10-day placebo treatment following a seven day control period without a significant bowel movements. Thus, the conduct of the trial was not that of a genuine cross-over design which requires that every treatment precede any other treatment equal number of times.

The primary outcome variables were: stool output, bowel movement frequency and physician and patients overall effectiveness ratings.

The study protocol stated that only data from the last seven days of each treatment period will be analyzed. The sponsor reasoned that this will prevent residual effects from earlier laxative use from interfering with the study. Furthermore, the sponsor restricted his efficacy analysis (this reviewer assumes that this means the efficacy evaluable group) to include only patients who completed at least 4 days of the 10-day treatment period.

The protocol specified that a repeated measures ANOVA method as well as a Bonferroni t-test will be used to detect differences between treatments.

In addition to the analysis of the 7 days treatment specified in the protocol, the sponsor presented some analyses for the whole 10-day treatment period. The sponsor claimed that this analysis is in response to a suggestion made by Dr. Fredd, Director of the Gastrointestinal and Blood Products Division, during a meeting with the sponsor on 8/20/90. In this meeting, Dr. Fredd, suggested that the sponsor should reanalyze the study with primary endpoint being relief/no relief and further to demonstrate a response in the most severely affected patients based on baseline values. In addition, Dr. Fredd recommended that if an additional study is needed then baseline stool measurements should be taken and that frequency of bowel movements is sufficient as a single measurable endpoint.

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Therefore, based on these considerations, and a discussion with R. Prizont, M.D. the medical officer, this reviewer's evaluation and re-analyses focuses on the frequency of bowel movements as the primary endpoint. However, the sponsor's results for stool weight are included without any analysis for this variable.

II.A.I Sponsor's Results/ Study 851-3:

This section summarizes the sponsor's initial efficacy results and the sponsor's response to agency inquiry about the presence of a carry-over effect and the efficacy results for constipated patients with ≤2 bm during the control period. In this section, this reviewer also raises some key issues relevant to the sponsor's analyses and claimed results. Section IV deals with the reviewer's re-analyses and evaluation.

II.A.I.a. Initial Analysis:

Table 1 and 2 present, respectively, the sponsor's efficacy results for the stool frequency and stool weight, analyzed by repeated measures analysis of variance.

Table 1/ Sponsor results[a]
Mean daily Bowel Movement Frequency/ Study 851-3

	Placebo	17 grams	34 grams
Mean	0.45	0.54	0.82
SEM	0.04	0.05	0.09

P < 0.001 DF=2,76 F=10.8

[a] Sponsor's Table 3.5, vol.1.4.2, p.3-21

Table 2/ Sponsor's results[a]
Mean Daily Wet Stool Output (grams)/ Study 851-3

	Placebo	17 grams	34 grams
Mean	41.0	58.4	84.7
SEM	6.05	7.13	9.8

P < 0.001 DF=2,76 F=76.7

[a] Sponsor's Table 3.4, vol.1.4.2, p.3-21

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The sponsor concluded that the efficacy results for stool output and bowel movement frequency was highly significant as the 851 laxative dose was increased from placebo. The sponsor in particular stated, on p.3-21, that: "for both stool weight and frequency, the response to the 17 gram dose was not significantly different from the response to placebo but the response to the 34 gram dose was significantly different from the response to the 17 gram dose or placebo (LSD=12.17; $p<0.05$)", where 'LSD' means the least significant mean difference. But having this value as the LSD for the stool weight is not consistent with the sponsor's above statement that the response to the 17g dose was not significantly different from that of the placebo, since the difference in the treatment's responses is: 58.4 - 41.0= 17.4g. In addition, the sponsor's statement does not support the stool frequency efficacy claim for the 17 gram dose requested in this NDA.

However, in reporting Tables 1 and 2 results, the sponsor did not specify the type of study population analyzed (evaluable or the ITT group) or the number of patients analyzed. Furthermore, the sponsor's results shown above are different from those the sponsor reported in Table 3.1, vol. 1.4.2, p.3-5 (see Attachment 1, p.32).

II.A.I.b. Cross-Over Effect

The sponsor analyzed data on stool weight and bowel movement frequency to examine a possible "carry over" effect from previous treatment. The sponsor compared the mean stool weight and mean bowel movement frequency for each treatment across all treatment orders. The results of these comparisons are presented in Table 3 (p. 6).

Based on the results of this analysis the sponsor concluded that no cross-over effect was observed for bowel movement frequency except for placebo following the 34 gram dose in the 34g, 0, 17g treatment order. A cross-over effect from laxative treatment to placebo treatment would only tend to obscure the true efficacy of the laxative (by inflating the placebo response).