DRAFT
CLINICAL REVIEW

Application Type	NDA
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Submission Code	000
Letter Date	06 December 2005
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Reviewer Name	Kristen K. Buck MD
Review Completion Date	
Established Name	Polyethylene Glycol 3350 Powder Laxative
(Proposed) Trade Name	MiraLAX OTC
Therapeutic Class	Laxative
Applicant	Braintree Laboratories, Inc.
Priority Designation	Standard
Formulation	Oral powder for solution
Dosing Regimen	17 grams once daily
Indication	Occasional Constipation
Intended Population	Adult population

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1.3.1 Brief Overview of Clinical Program

This application includes three clinical studies; 851-CR1, 851-CR3, and 851-ZCC. Study 851-CR1 was a Phase 3, double-blind, placebo-controlled, parallel group, multi-center study which compared MiraLAX 17 grams to placebo in daily dosing. 851-CR1 was a six month efficacy and safety study with 304 Intent-to-treat patients of which 75 were 65 years of age or older. Study 851-CR3 was a Phase 4, open-label, extended use, single treatment, multi-center study with MiraLAX 17 grams per day daily dosing. 851-CR3 was a twelve month safety study of chronic MiraLAX use with 311 Intent-to-treat patients of which 117 were 65 years of age or older. Study 851-ZCC was a Phase 4, randomized, open-label, parallel, multi-center study which compared MiraLAX 17 grams daily dosing to Zelnorm 6 mg twice daily dosing. Study 851-ZCC was a one month comparative safety and efficacy study with 237 Intent-to-treat patients of which 31 were 65 years of age or older.

1.3.2 Efficacy

1.3.3 Safety

The safety evaluation of MiraLAX OTC can be found in totality in the NDA 22-015 Safety Review performed by Dr. Karen Feibus, Division of Non-Prescription Drug Products.

1.3.4 Dosing Regimen and Administration

The sponsor's proposes that Over-the-counter MiraLAX should be dosed as 17 grams [redacted] of powder per day in 8 ounces of water, juice, soda, coffee, or tea for the treatment of occasional constipation in the adult population.

1.3.5 Drug-Drug Interactions

As noted in the original NDA 20-698 and on the prescription label, no drug-drug interactions have been demonstrated with MiraLAX.

Additionally, within this NDA (22-015), there were 44 patients in the MiraLAX treatment group in the 851-CR1 and 851-CR3 studies taking narrow therapeutic index drugs (NTI: warfarin, depakote, dilantin, lanoxin, synthroid, tegretol, and theophylline). Comparison of adverse event reports for these NTI patients against MiraLAX patients not taking these medicines reveals a slight, yet non-significant, higher overall frequency (78.6% versus 68.1%; NTI versus non-NTI patients) of adverse reports.

Medical Officer's Comments
These results in patients taking narrow therapeutic index drugs are to be expected since patients taking NTI drugs typically have underlying disease making adverse events and procedures more likely over the course of long term studies.

1.3.6 Special Populations

Pediatrics:

- The sponsor requested a deferral of all pediatric studies (ages birth to 16 years) to support the OTC MiraLAX NDA 22-015.
- [redacted]
- [redacted]

2 INTRODUCTION AND BACKGROUND

Constipation, generally defined as infrequent and difficult passage of stool, is one of the most common disorders suffered by Americans. It affects between two and twenty-seven percent of the population in Western countries. In the United States, it results in more than 2.5 million visits to physicians and 92,000 hospitalizations annually. Factors contributing to the development of constipation can include inadequate fiber in the diet, lack of exercise, neurological and systemic disorders and problems with colon, rectum, and/or intestinal function. Other contributing factors can include side effects from medication, particularly narcotic analgesics, antidepressants, antacids, antispasmodics, anticholinergics, antispasmodics, and blood pressure medications. Constipation is more likely to affect females than males and more likely to occur in older patients, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. Currently, the most widely accepted definition of constipation is the one established by the Rome II criteria which include:

> At least 12 weeks, which need not be consecutive, in the preceding 12 months of 2 or more of:
>
> - Straining in more than one quarter of defecations;
> - Lumpy or hard stools in more than one quarter of defecations;
> - Sensation of incomplete evacuation in more than one quarter of defecations;
> - Sensation of anorectal obstruction/blockage in more than one quarter of defecations;
> - Manual maneuvers to facilitate more than one quarter of defecations (e.g., digital evacuation, support of the pelvic floor; ***and/or***
> - Less than 3 defecations per week.
>
> Loose stools are not present, and there are insufficient criteria for irritable bowel syndrome (IBS).

The treatment of constipation depends on the cause, severity, and duration of symptoms, however; in most cases dietary (increasing dietary fiber to 20 – 35 grams per day) and lifestyle changes (increasing daily fluid intake and engaging in daily exercise) can help relieve constipation. For patients who have made lifestyle modifications and are still constipated, laxatives are the most commonly prescribed pharmacological interventions, of which there are four main types (bulk, osmotic, stimulant, and softener). Bulk-forming laxatives are generally considered the safest and most mild treatments but they are not always efficacious in relieving

constipation and can interfere with absorption of some medicines. Stool softening agents are also regarded as very safe yet also not always efficacious requiring one to three days of regular use to take effect. In patients unresponsive or intolerant to bulking agents or stool softeners, both osmotic and stimulant laxatives are very effective, but the latter must be avoided for long term use as they have a potential for adverse effects (exacerbation of other symptoms such as abdominal pain, bloating, or flatulence). Among the osmotic agents, lactulose is a synthetic disaccharide that is not absorbed by the small intestine but is readily metabolized by colonic bacteria. It has been shown to be effective for treating constipation, especially in the elderly. Intracolonic fermentation of lactulose is associated with production of gases and with colic, bloating, and flatulence. Furthermore, chronic ingestion of lactulose may induce changes in colonic bacterial metabolism

(Polyethylene glycol (PEG) 3350) is a mixture of non-absorbable, non-metabolized polymers of mean molecular weight 3350 (±10%) that act as pure osmotic agents. PEG has been available in prescription form as MiraLAX™(Polyethylene Glycol 3350, NF Powder for Solution) since February 1999. Prescription MiraLAX™ at a dose of 17 grams of powder per day in solution is indicated for the treatment of occasional constipation in the adult population, to be used for 2 weeks or less or as directed by a physician.

In this New Drug Application, the sponsor is proposing that prescription MiraLAX™ is an excellent drug candidate to switch to over-the-counter.

2.1 Product Information

MiraLAX OTC is composed of only one constituent, polyethylene glycol 3350 powder laxative. It is a laxative designed to act without the use of metabolizable or irritating substances.

2.2 Currently Available Treatment for Indications

Currently Approved Over-the-Counter Products

- **Bulk-forming laxatives** generally are considered the safest and most mild treatments but they are not always efficacious in relieving constipation and can interfere with absorption of some medicines. These laxatives, also known as fiber supplements, are taken with water. They absorb water in the intestine and make the stool softer. Brand names which usually are made from bran or psyllium include Metamucil®, Citrucel®, and Serutan®.

- **Stimulants** cause rhythmic muscle contractions in the intestines. Brand names include Correctol, Dulcolax®, Ex-Lax®, Purge®, and Senokot®. Studies suggest that phenolphthalein, an ingredient in some stimulant laxatives, might increase a person's risk for cancer. The Food and Drug Administration has proposed a ban on all over-

the-counter products containing phenolphthalein. Most laxative makers have replaced or plan to replace phenolphthalein with a safer ingredient.

- **Stool softeners** provide moisture to the stool. These laxatives are often recommended after childbirth or surgery. Products include Colace® and Surfak®.
- **Lubricants** grease the stool enabling it to move through the intestine more easily. Mineral oil and glycerin suppositories are the most common examples.
- **Saline laxatives** act like a sponge to draw water into the colon for easier passage of stool. Laxatives in this group include Milk of Magnesia®, Citrate of Magnesia®, and Haley's M-O®.
- **Osmotic Agents** draw water into the lumen into the lumen of the bowel and effectively increase the overall stool volume. These agents are made from nonabsorbable inorganic salts or sugars. Agents in this group include Magnesium citrate, Sodium citrate.
- **Enemas** empty the distal colon or rectum of retained solid material through mechanical distention of the bowel. Tap water or other osmotic, stimulant or irritative substances can be used.

Currently Approved Prescription Products

- *MiraLAX*® is indicated for the treatment of occasional constipation. It is a synthetic polyglycol that acts as an osmotic agent which causes water to be retained within the stool thereby softening it. The recommended dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by a physician) in 8 ounces of water, juice, soda, coffee, or tea. Two to four days may be required to produce a bowel movement. MiraLAX should be used for 2 weeks or less. Prolonged use of Miralax may result in electrolyte imbalance and dependence. Nausea, abdominal bloating, cramping and flatulence may occur. High doses may produce diarrhea.[1]

- *Zelnorm*® is indicated for the treatment of patients less than 65 years of age with chronic idiopathic constipation. The effectiveness of Zelnorm in patients over 65 years of age with chronic idiopathic constipation has not been established. Zelnorm is also indicated for the short term treatment of women with IBS whose primary bowel symptom is constipation. Zelnorm is a $5HT_4$ (serotonin type 4) agonist that acts as a promotility agent in the gastrointestinal tract by mimicking the natural effects of serotonin through normalization of impaired gut motility, inhibition of visceral sensitivity, and stimulation of intestinal secretion. The recommended dose is 6 mg by mouth twice daily. Diarrhea was the most common adverse event in placebo controlled trials and the prescribing information for Zelnorm carries a warning that hypovolemia, hypotension, and syncope may occur as well as ischemic colitis.

- *Amitiza*™ is indicated for the treatment of chronic idiopathic constipation in the adult population. It is a prostaglandin E_1 metabolite analogue that activates ClC-2 chloride channels on the apical membrane of the intestines thereby promoting a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. By increasing intestinal fluid secretion, Amitiza increases motility in the intestine and therefore increases passage of stool. The recommended dose is 24 mcg by mouth twice daily. Nausea was the most common adverse event in placebo controlled trials followed by diarrhea and headache.

2.3 Availability of Proposed Active Ingredient in the United States

Prescription MiraLAX™ has been widely available. The original NDA (NDA 20-698) for prescription MiraLAX™ was approved 18 February 1999. Braintree Laboratories, Inc. has been the owner and manufacturer of MiraLAX™ (NDA 20-698) throughout its drug development as well as the sponsor for this New Drug Application (NDA 22-015). The specifications for MiraLAX OTC are the same as the specifications for MiraLAX™. A generic formulation of MiraLAX™, Glycolax, is also available. Glycolax (ANDA 76-652) developed by Schwarz Pharma, was approved 02 July 2004.

2.4 Important Issues with Pharmacologically Related Products

Osmotic laxatives, used for the treatment of acute constipation or the prevention of chronic constipation, are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid. One such type of osmotic laxative is the nonabsorbable sugars and salts like Magnesium oxide. Magnesium oxide (milk of magnesia) is a commonly used nonabsorbable, osmotic salt laxative that is partially absorbed into the bloodstream and therefore poses a risk to some patients. It should not be used in large or frequent doses or for prolonged periods in patients with renal insufficiency or cardiac dysfunction due to the risk of hypermagnesemia. Sorbitol and lactulose are nonabsorbable, osmotic sugars that can be used to prevent or treat chronic constipation. These sugars are metabolized by colonic bacteria and therefore have the propensity to produce severe flatus and cramps.

High doses of osmotically active agents produce prompt bowel evacuation (purgation) within 1-3 hours. The rapid movement of water into the distal small bowel and colon leads to a high volume of liquid stool followed by rapid relief of constipation. The most commonly used **purgatives** are magnesium citrate and sodium phosphate. These hyperosmolar agents may lead to intravascular volume depletion and electrolyte fluctuations; hence they should not be used in patients who are frail, elderly, have renal insufficiency, or have significant cardiac disease.

Polyethylene Glycol; Electrolytes solutions containing polyethylene glycol (PEG) are used for complete colonic cleansing prior to gastrointestinal endoscopic procedures and off-label for the treatment of constipation and impaction. These balanced, isotonic solutions contain an inert, nonabsorbable, osmotically active sugar (PEG) with sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride. The solution is designed so that no significant intravascular

fluid or electrolyte shifts occur. Despite this design, however; sodium and fluid retention with edema occasionally occurs. Additionally, due to the rapid nature of administration, polyethylene glycol; electrolytes solutions may rarely pose a risk of GI perforation in patients that have pre-existing conditions that compromise the integrity of the bowel wall (e.g., diverticulitis or severe ulcerative colitis). Isolated and rare cases of serious adverse reactions to polyethylene glycol; electrolytes solution in elderly patients ≥ 60 years old have included upper GI bleeding from Mallory-Weiss Tear, esophageal perforation, asystole, as well as sudden dyspnea with pulmonary edema and a 'butterfly-like' infiltrate on chest x-ray after vomiting and aspirating the solution. Post-marketing analysis of the PEG-based colon preparations according to the Adverse Event Reporting System (AERS) revealed 5 fatalities, 5 seizures secondary to hyponatremia, one renal failure, and one ventricular fibrillation between 1996 and 2003. While

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- All four patients who developed nonfatal seizures developed hyponatremia (ranging from 110 to 116 mmoles/L), were hospitalized, and then recovered. Three of these four patients had documented normal pre-dosing sodium levels and the fourth patient did not have a documented sodium level. Another patient (a 51 year old male with a history of diabetes hypertension, and end stage renal disease developed seizures and subsequently died after receiving a PEG-based colon preparation product. This patient, who had a normal baseline sodium level, developed hyponatremia (sodium level was 122 mmoles/L). All five patients did not have a known history of seizures.

While the aforementioned AERS data reflects PEG-based colonic preparations instead of PEG as indicated for constipation, the risk of hyponatremia and seizures is still of significant concern. PEG preparations for either indication may be associated with diarrhea and with various amounts of concomitant fluid intake which could potentially contribute to electrolyte changes specifically hyponatremia and possibly seizures.

2.5 Pre-submission Regulatory Activity

Clinical studies performed to support the original NDA (NDA 20-698, approved 18 February 1999) established the safety and efficacy of prescription MiraLAX with a two week course of therapy.

The clinical development program for MiraLAX [redacted] was discussed at several meetings and through several communications with the Agency.

On 28 September 1999 the Agency and the sponsor (Braintree Laboratories, Inc.) met to discuss the sponsor's MiraLAX protocol for constipation [redacted] At this meeting, the Agency requested that a 6 month, double blind, placebo controlled study be performed as well as an extended treatment study (therapy for up to 1 year). The Agency also noted that the sponsor's development program should also include a sufficient number of elderly patients to assess safety and efficacy in this subpopulation. Study entry and efficacy success criteria were to be based on ROME constipation criteria. The Agency further agreed to modified entry criteria based on the Rome criteria as (on average, satisfactory stool less frequent than 3 per week and at least 1 other criteria; straining on toilet more than 25% of the time, feeling of incomplete

evacuation more than 25% of the time, hard stools more than 25% of the time). The Agency guided the sponsor in duration (6 months), adequacy of patient cohort (300 to 600 patients), and additional trials (12 month trials with at least 100 subjects). Additionally, the Agency guided the sponsor away from lactulose as a control therapy as lactulose is not approved for choric use and as the Agency recommends a double-blind, placebo-controlled trial. The Agency recommended that the primary efficacy endpoint be three or more satisfactory stools per week and the absence of the other Rome criteria.

The second meeting was held 6 September 2000 (concerning MiraLAX Rx to OTC switch). The Agency expressed serious safety concerns about the indiscriminate use of MiraLAX in several populations including the elderly, the renally-impaired, pregnant women, and patients with eating disorders (abuse potential). The Agency reflected back to the 28 September 1999 sponsor meeting noting that the sponsor would be required to conduct all non-completed pre-clinical studies to support their Rx-OTC switch (renal studies in animals, chronic oral toxicity studies of 6 months in rats, full battery of genotoxicity studies, reproductive toxicity, and two year carcinogenicity studies). The Agency agreed that an actual use study would be needed.

On 6 December 2002, the Agency provided the sponsor with correspondence to their Special Protocol Assessment for Protocol 851-CR3, Extended Use of MiraLAX Laxative in Constipated Patients. The Agency noted that the 851-CR3 protocol, an open-label study of MiraLAX, was not adequate unto itself to establish the long term safety of MiraLAX. However, in conjunction with safety data from Protocol 851-CR1 and CR1-2, it should be adequate. Additionally, the Agency noted the 12 month duration did meet the ICH E1A Guidance for assessing clinical safety for drugs intended for long term treatment of non-life threatening conditions. The Agency noted that the inclusion criteria should be the population that will receive the drug for the intended population, namely those who meet the criteria for *chronic constipation.*

On 21 May 2003, the Agency provided the sponsor with correspondence to their Special Protocol Assessment for Protocol 851-CR1, Extended Use of MiraLAX Laxative in Constipated Patients. The Agency agreed that the efficacy endpoint for this study protocol should be 3 or more bowel movements per week and the absence of any other Rome criteria.

On 09 July 2003 the sponsor and the Agency had a teleconference at the request of the sponsor to discuss the definition of success for Protocol 851-CR1. [redacted] Upon completion of the teleconference, an agreement was reached for the primary efficacy variable (3 or more satisfactory bowel movements and the absence of Rome criteria and no use of laxatives). The secondary efficacy variable was also agreed upon as (3 or greater satisfactory bowel movements a week and absence of all Rome criteria).

On 27 April 2005 the Agency provided correspondence to the sponsor's pre-meeting (type C) package in which they describe their intentions to submit an NDA for the switch of MiraLAX from Rx to OTC. The sponsor outlined their submission of studies including 851-CR1 (6 month, placebo controlled study), 851-CR3 (one year, open label), and 851-ZCC (one month, MiraLAX vs. Zelnorm) to support the safety and efficacy for an OTC switch for MiraLAX. The Agency

noted that the newly proposed clinical studies provided adequate clinical data for the MiraLAX OTC use in the adult population. The Agency expressed that there is not adequate safety or efficacy data in children especially those < 16 years of age and thus it is not appropriate to label this drug for OTC use in children. The label needs to reflect an absence of data in the pediatreic population. The label should address renally impaired subjects. The following should be communicated in the label for adult use [redacted] and "stop use and ask your doctor if you need to use a laxative for longer than one week". Additionally, the Agency noted that an actual use study would not be needed.

On 28 October 2005, the sponsor and their counsel [redacted] sent correspondence to the Agency which argued the statement [redacted] The sponsor/counsel argued [redacted] support by: (a) the clinical and experience data and information submitted with the MiraLAX switch application (b) consistent with FDA policy as set forth in its Manual of Policies and Procedures chapter regarding OTC drug review (MAPP 6020.5); and (c) consistent with the position taken by FDA with regard to a number of other products approved for OTC use through the NDA process. The sponsor notes that under MAPP 6020.5, it is NOT necessary for OTC drug products marketed under the authority of an approved NDA to conform to wording/labeling in OTC drug monographs for similar products. The sponsor cites previous approvals by the Agency such as Prilosec OTC which unlike the labeling for antacids marketed under the monograph, directs consumers that they [redacted]

Medical Officer's Comments:
As noted by the above sequence of events, the sponsor [redacted] after their original approval for "occasional constipation", NDA 20-698). It is unclear to the undersigned reviewer, after thorough investigation, what transpired that caused the sponsor [redacted] It appears [redacted] fact, an OTC indication has the durability of effect of the current MiraLAX prescription to rely upon and is only deficient on long term safety data. This NDA's efficacy review, therefore, appears to only augment the long term efficacy of NDA 20-698 in "occasional constipation" use.

2.6 Other Relevant Background Information

MiraLAX OTC has an involved drug development and regulatory history. MiraLAX laxative was derived from Braintree Laboratories' PEG-electrolyte lavage solutions (GoLYTELY® and NuLYTELY®). Utilizing the osmotic effect of PEG-3350 to increase the water content in the gastrointestinal tract, these drugs were designed to cleanse the gut prior to diagnostic examination by rapidly inducing a voluminous liquid stool. The PEG lavages were formulated with electrolytes to prevent net gain or loss of electrolytes from the resulting diarrhea.

Early laxative studies evaluated various formulations of PEG 3350 in combination with electrolytes. The first study (Braintree Protocol 851-P2A, MiraLAX NDA 20-698) tested several solutions based on the NuLYTELY formula on five constipated but otherwise normal outpatients in order to determine a final formulation and appropriate dose. Patients received doses of PEG with electrolytes ranging from 0 to 52 grams of PEG 3350 per day. Unexpectedly, analysis of the electrolyte content of the stool resulting from the study subjects revealed that all salts included in any formulation were avidly absorbed. Therefore, the study concluded that the laxative should be composed only of PEG 3350. Analysis of stool output with respect to dose of PEG revealed that a dose of approximately 17 grams PEG was most satisfactory, with diarrhea tending to occur at the highest dose test (52 grams).

Additional studies were performed using up to 252 grams of PEG in combination with electrolytes (NuLYTELY) and administered to normal volunteers over a period of a single day in several divided doses. The study subjects suffered no ill effects except moderate diarrhea. All electrolytes contained in the test solution were absorbed.

The marked difference in salt absorption between a gastrointestinal lavage process and a laxative effect using the same PEG electrolyte solution can presumably be attributed to intestinal absorptive processes which remain active but are overwhelmed by the very large volumes of solution ingested when gastrointestinal cleansing is desired. When lesser volumes are ingested, or the ingestion occurs slowly, the absorptive systems are better able to remove the electrolytes.

Given the aforementioned data, Braintree Laboratories believed that MiraLAX laxative would be an excellent drug candidate for a prescription to over-the-counter switch.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

MiraLAX (Polyethylene Glycol 3350, NF Powder For Solution), a synthetic polyglycol, is a water soluble, linear diol characterized by a repeating oxyethylene unit. Its CAS Number is 25322-68-3 and its CAS name is Poly(oxy-1-2-ethanediyl), *alpha*-hydro-*omega*-hydroxy. It has an average molecular weight of 3350. The actual molecular weight is not less than 90% and not greater than 110% of the nominal value. The chemical formula is:

$$HO(C_2H_4O)_{75}C_2H_4OH$$

3.2 Animal Pharmacology/Toxicology

The toxicology testing included in this New Drug Application included Segments I-III developmental and reproductive studies, genotoxicity studies according to ICH guidelines, renal function studies in rats and dogs, and two-year carcinogenicity studies in two rodent species.

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The doses selected for these studies were picked primarily on the basis of the "maximum practical dose" tenet. Considering the route and dosage form of administration in humans (oral, in solution) and the solubility of PEG 3350, it would not have been feasible in most studies to dose animals at the equivalent

No evidence of carcinogenicity, mutagenicity, or reproductive toxicity was obtained. These studies were all generally negative. Except for the expected soft stools and frequent defecation, no signs of toxicity were seen except for non-neoplastic findings in a carcinogenicity study in mice and in chronic toxicity studies in rats. In the carcinogenicity study in mice, non-neoplastic microscopic observations included test article-related increased incidence of renal amyloidosis in the 6 g/kg/day group females that died or were euthanized in extremis compared to the control group animals that died or were euthanized in extremis.

In 6 and 24 month studies in rats, there was evidence of kidney histological abnormalities. Functional changes, as assessed by renal function tests, were not evident in rats and were not sought in mice. All renal function tests were normal in rats. Lesions in rats consisted of tubular cytoplasmic vacuoles, tubular widening and tubular hyperplasia. They were not seen in a 3 month rat study but were first seen in the 6 month rat toxicity study and progressed in incidence and severity in the 24 month rat carcinogenicity study. There was no evidence of necrosis, inflammation or crystal formation. There was generally not evidence of alterations in renal function tests. The observed changes were consistent with those seen with other hyperosmotic agents are administered. They may in fact represent physiological adaptations to colonic water conservation in the presence of this largely non-absorbed osmotic burden. In light of the normal kidney function tests, perhaps the observed vacuoles may contain highly concentrated PEG solution, being readied for tubular secretion. No changes of a similar nature were seen in dogs treated for up to 9 months at 3g/kg/day or in mice receiving 6 g/kg/day for up to 2 years.

The NOEL for carcinogenicity was 6 g/kg/day for both males and females in rats and mice. This represents nearly 25-times higher than the dose on a per kg basis.

The pharmacokinetic studies across different species indicated that the animals were exposed to dose-related systemic levels of PEG 3350. Blood levels showed classical PK behavior, peaking several hours after dosing, and becoming nearly undetectable before the next dose. On repeated administration, the PK parameters did not change. Considering that the High Performance Liquid Chromatography (HPLC) tandem mass spectrometry (MS/MS) method that was developed and validated had a sensitivity of [redacted] in plasma, these studies assure that PEG 3350 is poorly absorbed and rapidly cleared. When comparisons are made across species, rats show the highest systemic levels. Even when these levels are taken into consideration, the kidney alterations in the rat appeared at levels of exposure that are attained without histologic changes in other non-human species. This may suggest that rats are uniquely sensitive to the effects of a PEG 3350 osmotic load.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data reviewed within NDA 22-015 include three studies: 851-CR1, 851-CR3, and 851-ZCC.

Study 851-CR1 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multi-center trial comparing MiraLAX 17 grams to placebo in daily dosing. 851-CR1 was a six month efficacy and safety study which included 304 Intent-to-treat patients of which 75 were 65 years of age or older.

Study 851-CR3 was a Phase 4, open-label, extended use, multi-center, single treatment study of MiraLAX 17 grams per day. 851-CR3 was a twelve month safety study of chronic MiraLAX use which included 311 Intent-to-treat patients, of which 117 were 65 years of age and older.

Study 851-ZCC was a Phase 4, randomized, open-label, parallel, multi-center trial comparing MiraLAX 17 grams daily dosing to Zelnorm 6 mg twice daily dosing. 851-ZCC was a one month safety and efficacy study.

4.2 Tables of Clinical Studies

Clinical Study Summary

Study (# Sites)	Study Start/ Finish	Design/ Blind	Study and Control Drugs	# Subj/arm (Entered/ Completed)	Patients M/F Age	Elderly	Treatment Duration	1° Efficacy[1] ML/control
851-CR1 (50)	08/20/03 12/20/04	Randomized Parallel/ Double blind	MiraLAX 17 g/day	204/127	46/258	75	6 months	52 %/11% p<0.001
			Placebo 17 g/day	100/43	53			
851-CR3 (50)	07/14/03 11/16/04	Single arm Open	MiraLAX 17 g/ day	311/184	63/248 57	117	12 months	57.9%[2]
851-ZCC (25)	06/09/04 10/08/04	Randomized/ Parallel/open	MiraLAX 17 g/day	120 (106/14)	24/213	31	1 month	50%/31% p=0.003
			Zelnorm (6 mg BID)	117 (97/20)	46			

Reviewer's table, modified from sponsor's Table 2.7.3-1, Section 2.7, Clinical Summary, page 4

1. Percent patients successfully treated: MiraLAX/Control
2. End of study for all enrolled patients

4.3 Review Strategy

The undersigned medical reviewer from the Division of Gastroenterology Products performed the efficacy review for this NDA 22-015 while the safety evaluation and review for MiraLAX OTC, NDA 22-015, was performed by Dr. Karen Feibus, Division of Non-Prescription Drug Products.

To compile an efficacy review, this medical officer thoroughly evaluated the sponsor's three studies which included: one well-controlled, double-blinded, placebo-controlled, 6-month study to assess efficacy, one 12-month, single-arm, open-label study to assess both safety and efficacy, and a one-month randomized, parallel, comparative efficacy trial versus Zelnorm.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted by the Agency for this New Drug Application. The undersigned medical officer selected 2 sites/protocol for DSI inspection. Sites with the highest number of patients per physician were selected for investigation. The Division of Scientific Investigations concluded that Braintree Laboratories, Inc. and their investigators adhered to the applicable statutory requirements and Food and Drug Administration regulations governing the conduct of clinical investigations and the protection of human subjects.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all three clinical trials were performed in compliance with Good Clinical Practices (GCP) and the International Conference on Harmonization (ICH). Braintree also noted that there was periodic including the archiving of essential documents. Each of the three clinical trials utilized appropriate informed consent procedures and had no apparent protocol violations.

4.6 Financial Disclosures

The sponsor provided and signed a copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the sponsor certified that no clinical investigator was the recipient of any significant payments of any other sorts.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication of this New Drug Application is for MiraLAX OTC 17 grams once daily for the treatment of occasional constipation in adults.

6.1.1 Methods

The efficacy evaluation for this New Drug Application was based upon a total three individual clinical trials; one double-blind, multi-center study that evaluated the safety and efficacy of 6 months of daily use of MiraLAX against placebo, one open-label, multi-center, extended use study which evaluated patient safety and exposure for up to one year of daily MiraLAX use, and one randomized, open-label, comparison study of the efficacy and safety of one month use of MiraLAX versus Zelnorm®.

The medical officer will perform a detailed, integrated review of the aforementioned studies.

6.1.2 General Discussion of Endpoints

As noted above, three unique clinical studies (851-CR1, 851-ZCC, and 851-CR3) were performed in support of this current application. Although all three studies utilized a modified ROME constipation definition for enrollment, due to the differing objectives and designs of the studies the efficacy endpoints used in each study were not the same.

Study 851-CR1: Primary Efficacy Endpoint

The primary efficacy endpoint comparing MiraLAX to placebo:

- was based on a binary outcome of overall treatment success (responder) or failure (non-responder) as defined below.

A treatment success (responder) was defined as:

A. Satisfactory stools greater or equal to 3 ***per*** week, and
B. 1 or fewer of the following additional ROME based criteria
    a. Straining in more than 25% of defecations
    b. Lumpy or hard stools in more than 25% of defecations
    c. Sensation of incomplete evacuation in more than 25% of defecations

This definition was further refined according to the following rules:

- Patients who received fewer than 8 weeks of active treatment for any reason were classified as an overall treatment failure.
- A successful treatment week was defined as ≥ 3 satisfactory bowel movements without the aid of rescue medication or prohibited laxative.
- A successful treatment week rate was defined as the ratio of successful treatment weeks to total number of weeks of actual treatment.
- Overall treatment success was defined as a 0.50 or greater rate of successful treatment weeks.
- Only days in which data has been reported were counted toward the success calculation for that particular week. Days with missing data were not included in any calculations.

Medical Officer's Comments:

As noted above, the primary endpoint for this study was agreed to in the Pre-NDA meeting and investigates the proportion of weekly responders. To the undersigned reviewer, this type of analysis appears [redacted] ***Without earlier efficacy endpoints (i.e., Week 1), the study design does not appear to appropriately capture and/or support the sponsor's proposed label claim*** [redacted] ***However, the undersigned reviewer will dissect out the daily and weekly bowel movement data as well as rely on the pre-established "approved" efficacy of the prescription MiraLAX data.***

Secondary Efficacy Endpoints:

The **secondary efficacy endpoints** included assessments of ROME definition for each treatment week and "super efficacy" (weeks where patients did not have *any* of the four ROME symptoms, without the aid of rescue medication or prohibited laxatives).

Study 851-CR3: Efficacy Endpoints

This study was specifically designed for the collection of long-term safety data collection in the extended use of MiraLAX. Supportive efficacy assessments were performed, however; throughout the duration of the study.

Global Efficacy Assessment (GEA):

Global Efficacy Assessment (GEA) responders are defined as patients that reported "completely relieved" or "considerably relieved" to the GEA question at each visit.

The GEA question was summarized for each visit (Visits 2-6) by the number and percentage of patients in each of the five response categories.

> *"Consider how you felt since your last visit in regard to your constipation, in particular, your overall well being, number of bowel movements, consistency and completeness of your bowel movements, and symptoms of straining. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms since your last visit (completely relieved, considerably relieved, somewhat relieved, unchanged, or worse)."*

Modified ROME Criteria Efficacy Assessment:

This endpoint was an assessment of a modified ROME definition for each treatment visit (Visit 2 through Visit 6). According to this definition, a successfully treated patient must report ≥ 3 satisfactory bowel movements with 1 or no additional ROME symptom criteria, without the aid of rescue medication or prohibited laxative, on their visit questionnaire.

Study 851-ZCC: Primary Efficacy Endpoint

The primary efficacy endpoint comparing MiraLAX to Zelnorm:

- was based on a binary outcome of overall treatment success (responder) or failure (non-responder) as defined below.

    1. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.
    2. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
        a. Straining in more than 25% of defecations
        b. Lumpy or hard stools in more than 25% of defecations
        c. Sensation of incomplete evacuation in more than 25% of defecations
    3. Patients who received fewer than 2 weeks of active treatment for any reason were classified as overall treatment failures.

This definition was further refined according to the following rules:

- Patients who received fewer than 2 weeks of active treatment for any reason were classified as an overall treatment failure.
- A successful treatment week rate was defined as the ratio of successful treatment weeks to total number of weeks of actual treatment.

- Overall treatment success was defined as a 0.50 or greater rate of successful treatment weeks.
- Only days in which data has been reported were counted toward the success calculation for that particular week. Days with missing data were not included in any calculations.

Medical Officer's Comments:
As noted above, the primary endpoint for this study was agreed to in the Pre-NDA meeting and compares the safety and efficacy of MiraLAX to Zelnorm, which was approved for chronic constipation. To the undersigned reviewer, Zelnorm is not the appropriate comparator against which to study MiraLAX for the proposed indication, "OTC use for occasional constipation." Zelnorm is neither approved for over-the-counter use, nor is it approved for occasional constipation.

6.1.3 Study Design

Medical Officer's Comments:
Given the difference in design, duration, and objectives of the three studies submitted in NDA (22-015) supporting the MiraLAX Rx to OTC switch; (851-CR1, 851-CR3, and 851-ZC), the undersigned medical officer will separately review, compare, and summarize each study design rather than analyze the combined data.

Study 851-CR1

Protocol 851-CR1 was a Phase 3, double blind, randomized, parallel, placebo-controlled, multi-center study that evaluated 6 month daily use of MiraLAX in normal, constipated, otherwise healthy adult outpatients. This study enrolled 304 adult patients (204 MiraLAX, 100 Placebo) of which 75 (51 MiraLAX, 24 Placebo) were ≥ 65 years of age. MiraLAX 17 grams per day or placebo were given daily to eligible patients with at least a 3 month history of constipation prior to entering the study. Additionally, patients had to have fewer than 3 satisfactory bowel movements per week with one or more of the ROME based criteria for constipation. Protocol 851-CR1 employed a 2 week baseline 'observation period' during which patients were instructed to stop laxative treatments prior to starting MiraLAX therapy. This study was intended to provide both safety and efficacy information associated with extended MiraLAX use. During this study, patients were asked to call into an Interactive Voice Response System (IVRS) each day to report their bowel movement (BM) experiences for that day and answered questions related to the study efficacy and safety criteria. The primary efficacy variable was based on a binary outcome of overall treatment success (responder) or failure (non-responder). A responder in this study was based upon modification of the ROME criteria where a successful treatment week was defined as a patient having 3 or more satisfactory bowel movements and one or fewer of the remaining ROME criteria without the use of rescue laxatives. Overall treatment success in Protocol 851-CR1 was defined as having a 50% or greater rate of successful treatment weeks throughout the trial.

For this trial, only days in which data had been reported were counted toward the success calculation for that particular week. Days with missing data were not included in any calculations.

Medical Officer Comments:
Beyond the issues involving the primary efficacy endpoint as previously discussed, the protocol for Study 851-CR1 was well-designed. Bias was appropriately minimized via randomization and blinding procedures. The treatment group size and duration were adequate. The dosing of MiraLAX 17 gram/day was previously established under NDA 20-698 (RX MiraLAX) and therefore appears acceptable. The protocol's inclusion and exclusion criteria were acceptable in that they properly excluded concomitant medications that are known to affect bowel habits, patients with inflammatory bowel disease, and IBS. The protocol also appropriately implemented a 14 day washout period of all other laxative treatments prior to MiraLAX dosing and also allowed for the use of bisacodyl as a rescue medication. Reasonable safety precautions were employed throughout the 6 month trial to ensure to well-being of the patients.

Study 851-CR3

Protocol 851-CR3 was a Phase 4, open-label, single treatment, multi-center study that evaluated 12 month daily use of MiraLAX in normal, constipated, otherwise healthy adult patients. This study enrolled 311 adult patients of which 117 were ≥ 65 years of age. MiraLAX 17 grams per day was given to eligible patients who had at least a 3 month history of constipation (when not taking laxatives) prior to entering the study. Additionally, patients had to have fewer than 3 satisfactory bowel movements per week with one or more of the ROME based criteria for constipation. This study's primary intention was to evaluate the safety of extended (chronic) use of MiraLAX, however; supportive efficacy assessments were performed throughout the duration of the study. The main efficacy variable was based on a responder analysis to a Global Efficacy Assessment (GEA) question. Responders of the GEA reported whether their overall symptomatology was "completely relieved" or "considerably relieved." Secondary efficacy analysis was based on overall treatment success (responder) or failure (non-responder). A responder in this study was based upon modification of the ROME criteria where a successful treatment week was defined as a patient having 3 or more satisfactory bowel movements and one or fewer of the remaining ROME criteria.

Medical Officer Comments:
The protocol for Study 851-CR3 was adequately designed for a single arm, open label study with the primary emphasis of long-term safety. The treatment group size was sufficient according to the ICH guidance. The dosing of MiraLAX 17 grams/day was previously established under NDA 20-698 (RX MiraLAX) and therefore appears acceptable. The protocol's inclusion and exclusion criteria was acceptable in that it properly excluded concomitant medications that are known to affect bowel habits, patients with inflammatory bowel disease, and IBS. Unlike protocol 851-CR1 which employed a 14 day washout period of all other laxative treatments prior to MiraLAX dosing, Protocol 851-CR3 did not have a pre-

study washout period. A two week washout period was not as important in this trial because the primary intention of this trial was to evaluate safety instead of efficacy. Additionally, given the length of this trial, a two week washout would not necessarily influence the durability of efficacy findings. Similar to protocol 851-CR1, however; this study appropriately allowed for the use of bisacodyl as a rescue medication. Reasonable safety precautions were also employed throughout the 12 month trial to ensure to well-being of the patients.

Study 851-ZCC

Protocol 851-ZCC was a randomized, Phase 4, open-label, parallel, multi-center study that compared the safety and efficacy of 1 month daily use of MiraLAX to Zelnorm in constipated, otherwise healthy, adult patients. This study enrolled 237 patients (120 MiraLAX, 117 Zelnorm) of which 31 (17 MiraLAX, 14 Zelnorm) were ≥ 65 years of age. An amendment was made to protocol 851-ZCC 14 July 2004 following an Advisory Committee which recommended the approval of Zelnorm for chronic constipation be limited to females under the age of 65. The protocol inclusion/exclusion criteria were modified to exclude patients who were elderly or male, however; male or elderly patients enrolled prior to the approval of this amendment were allowed to complete the study. MiraLAX 17g and Zelnorm 6 mg BID were given to eligible patients who had at least a 3 month history of constipation (when not taking laxatives) prior to entering the study. Additionally, patients had to have fewer than 3 satisfactory bowel movements per week with one or more of the ROME based criteria for constipation. This study was intended to compare and evaluate the safety and efficacy of MiraLAX laxative to Zelnorm in constipated, yet otherwise healthy adults. During this study, patients were asked to call into an Interactive Voice Response System (IVRS) each day to report their bowel movement (BM) experiences for that day and answered questions related to the study efficacy and safety criteria. The primary efficacy variable was based on a binary outcome of overall treatment success (responder) or failure (non-responder). A responder in this study was based upon modification of the ROME criteria where treatment success was defined as a patient having 3 or more satisfactory bowel movements and one or fewer of the remaining ROME criteria without the use of rescue laxatives. Overall treatment success in Protocol 851-ZCC was defined as having a 50% or greater rate of successful treatment weeks throughout the trial.

Medical Officer Comments:
Beyond the issues involving the primary efficacy endpoint as previously discussed, Study 851-ZCC was adequately designed. The treatment group sizes were acceptable, however; given that the inclusion/exclusion criteria were modified to exclude patients who were elderly or male, not enough elderly or male patients were enrolled in this study to allow for cross comparison with the other two studies. The dosing of MiraLAX 17 grams/day and Zelnorm 6 mg/BID were previously established and administered in accordance with approved labeling and dosages. The protocol's inclusion and exclusion criteria was acceptable in that it properly excluded concomitant medications that are known to affect bowel habits, patients with inflammatory bowel disease, and IBS. Similar to Protocol 851-CR3 yet unlike protocol 851-CR1, Protocol 851-CR3 did not employ a pre-study 14 day washout period of all other laxative treatments. Similar to protocol 851-CR1 and 851-CR3, this study appropriately

allowed for the use of bisacodyl as a rescue medication. Reasonable safety precautions were also employed throughout the 12 month trial to ensure to wellbeing of the patients.

6.1.4 Efficacy Findings

Medical Officer's Comments:
Although each of the three Braintree studies utilized the 'modified ROME criteria' as part of their constipation endpoints, due to the differing objectives and designs of the trials, the efficacy endpoints used in each study were not the same. It will not be possible, therefore; to perform direct efficacy comparisons across the three studies. The efficacy results will be summarized rather than combined.

Study Populations

All three clinical studies (851-CR1, 851-CR3, and 851-ZCC) enrolled constipated, yet otherwise healthy male and female adult outpatients. All enrolled patients had to provide a history of constipation based on "modified ROME" constipation criteria.

Table XX: Study Demographics

Variable	851-CR1	851-CR3	851-ZCC
Age (years)[1]			
Mean (SD)	53.5 (14.9)	56.9 (16.4)	46.5 (14.5)
≥65	75 (25%)	117 (38%)	31 (13%)
n	304	311	237
Gender			
Female	258 (85%)	248 (80%)	213 (90%)
Male	46 (15%)	63 (20%)	24 (10%)
Race			
Caucasian	255 (84%)	248 (80%)	151 (63.7%)
A. American	39 (12.8%)	49 (16%)	57 (24.1%)
Other	5 (1.6%)	4 (1%)	10 (4.2%)
Missing	5 (1.6%)	10 (3%)	19 (8.0%)
Weight (kg)			
Mean (SD)	74.8 (16.0)	77.3 (17.6)	76.4 (20.4)
Constipation Hx.			
(yrs) (SD)	23.1 (18.9)	17.9 (19.1)	17.5 (16.3)

Reviewer's table, modified from sponsor's Table 2.7.3-2, Section 2.7, Clinical Summary, page 8
1. Age is calculated using date of birth and screening visit (Visit 1) date.
SD = Standard deviation; kg = kilograms; A. American = African American

Medical Officer's Comments:

As noted above in Table XX, the demographics were by and large similar across all three clinical studies within this New Drug Application. There was a gender disparity favoring females (258/304, 85%; 248/311, 80%; 213/237, 90%) in studies CR1, CR3, and ZCC, respectively. As noted above, the greater disproportion of females in 851-ZCC was due to an amendment made to the protocol which recommended the approval of Zelnorm for chronic constipation be limited to females under the age of 65. The racial distribution was relatively similar across 851-CR1 and 851-CR3 with 84% and 80% Caucasian patients, and 12.8% and 16% African American patients, respectively. Study 851-ZCC had a more diverse patient population with 63.7% Caucasian patients and 24.1% African American patients. The sponsor noted that the age, gender, and racial characteristics of studies CR1 and CR3 generally reflect the overall demographics and national population distribution of constipation and that the percentage of African American patients was higher in study ZCC than the national average, which they attributed to the geographic location of the study centers. Despite these claims, epidemiological studies suggest, that constipation is more common in non-whites than whites[1] with a ratio as high as 1.3:1.[2] Prevalence estimates by gender support a female predominance supported by a ratio of 2.2:1.[2] Perhaps a more homogeneous patient population in general and across the three studies would have allowed for a more accurate efficacy analysis by gender and age and perhaps better estimated the intended market patient population for MiraLAX OTC.

Statistical Analytical Plan

Medical Officer's Comments:

The statistical analytical plans were outlined in each individual study report. As noted below, the statistical analytic plans for protocols 851-CR1 and 851-CR3 are very similar.

Protocol 851-CR1

The primary analysis was based upon and intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. All patients in this group had a determination of overall treatment success (responders). The primary efficacy analysis was on the primary efficacy endpoint of overall treatment success or failure rate determined for each patient. The primary analysis for the between treatment comparison used the Cochran-Mantel-Haenszel (CMH) statistic stratified by site with no covariate adjustment. The difference was the weighted difference of responder rates between the active treatment group and placebo group. The weight for each site was proportional to the number of patients in each treatment group. Exact p-value was used for this comparison and a 95% confidence interval for the difference in proportions was also obtained for the non-stratified population. Sites that recruited fewer than 24 ITT patients were pooled to form larger pseudo sites in order to maintain at least 24 ITT patients for each site in the CMH stratified analysis. To meet this requirement, pseudo sites were created by pooling individual sites within a pre-determined geographic region. The specifics of this pooling algorithm were defined prior to un-blinding the study data and included in a detailed statistical analysis plan. Secondary efficacy endpoints defined in terms of successful treatment rates were analyzed using analysis of variance with factors for treatment group, pooled-site, and interaction between treatment group and pooled-site.

Protocol 851-ZCC

The primary analysis group was based upon an intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. All patients in this group had a determination of overall treatment success (responders). The primary efficacy analysis was based on the primary efficacy endpoint of overall treatment success or failure determined for each patient. The primary analysis for the between treatment comparison used the Cochran-Mantel-Haenszel (CMH) statistic stratified by site with no covariate adjustment. The difference was the weighted difference of responder rates between the MiraLAX group and the Zelnorm group. The weight for each site was proportional to the number of patients in each treatment group. Sites that recruited less than 20 ITT patients were pooled to form larger pseudo sites in order to maintain at least 20 ITT patients for each site in the (CMH) stratified analysis. To meet this requirement, pseudo sites were created by pooling individual sites within a pre-determined geographic region. The specifics of this pooling algorithm were defined prior to un-blinding the study data and included in a detailed statistical analysis plan. Secondary efficacy endpoints defined in terms of successful treatment rates were analyzed using analysis of variance with factors for treatment group, pooled-site, and interaction between treatment group and pooled-site.

Protocol 851-CR3

Information on global efficacy assessment, adverse events, and laboratory results was pooled across all sites and descriptively summarized by visits. The incidence of adverse events was summarized by severity and relationship to study drug. The summary tables included incidence estimates for overall body systems as well as for individual events within each body system. Adverse events resulting in treatment modifications or discontinuation were identified. Any increase in incidence of adverse events across visits were estimated and identified; the major focus was a comparison in rates between the first 6 months of treatment versus the last 6 months of treatment. Results of laboratory tests were descriptively summarized based upon actual change from baseline for continuous assessments. In addition, shift tables were used to describe changes in lab tests between baseline and on treatment using normal range categories (low, normal, high). Global efficacy assessment categories were descriptively summarized by treatment visits. The major comparison was between the first and last six months of treatment. The primary analysis group was based upon an intent-to-treat (ITT) analysis and included all patients enrolled and receiving any treatment.

PRIMARY EFFICACY VARIABLE:

Protocol 851-CR1:

The primary efficacy variable for treatment response in protocol 851-CR1 was assessed on the basis of binary outcome of overall treatment success (responder) or failure (non-responder) where:

1. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.

2. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
    d. Straining in more than 25% of defecations
    e. Lumpy or hard stools in more than 25% of defecations
    f. Sensation of incomplete evacuation in more than 25% of defecations
3. Patients who received fewer than 8 weeks of active treatment for any reason were classified as overall treatment failures.

Table XX: Study 851-CR1Primary Efficacy Responder Analysis Number of Successfully Treated Patients

Responder[1]	MiraLAX n (%)	Placebo n (%)	All	95% CI[2]	p[3]	Δ MiraLAX and Placebo responder %
All Patients						
(n)	204	100	304			
Yes	106 (52.0%)	11 (11.0%)	117 (38.5%)	31.8, 50.2	<0.001	41 %
No	98 (48.0%)	89 (89.0%)	187 (61.5%)			

Reviewer's table, modified from sponsor's Table 2.7.3-3, Clinical Summary, page 9

1. A successful treatment week is defined as above text.
2. (CI): Confidence interval; difference between MiraLAX and Placebo is from Cochran-Mantel-Haenzsel-Test.
3. P-value for the difference between MiraLAX and Placebo is from a pooled site stratified Cochran-Mantel-Haenzsel-test.

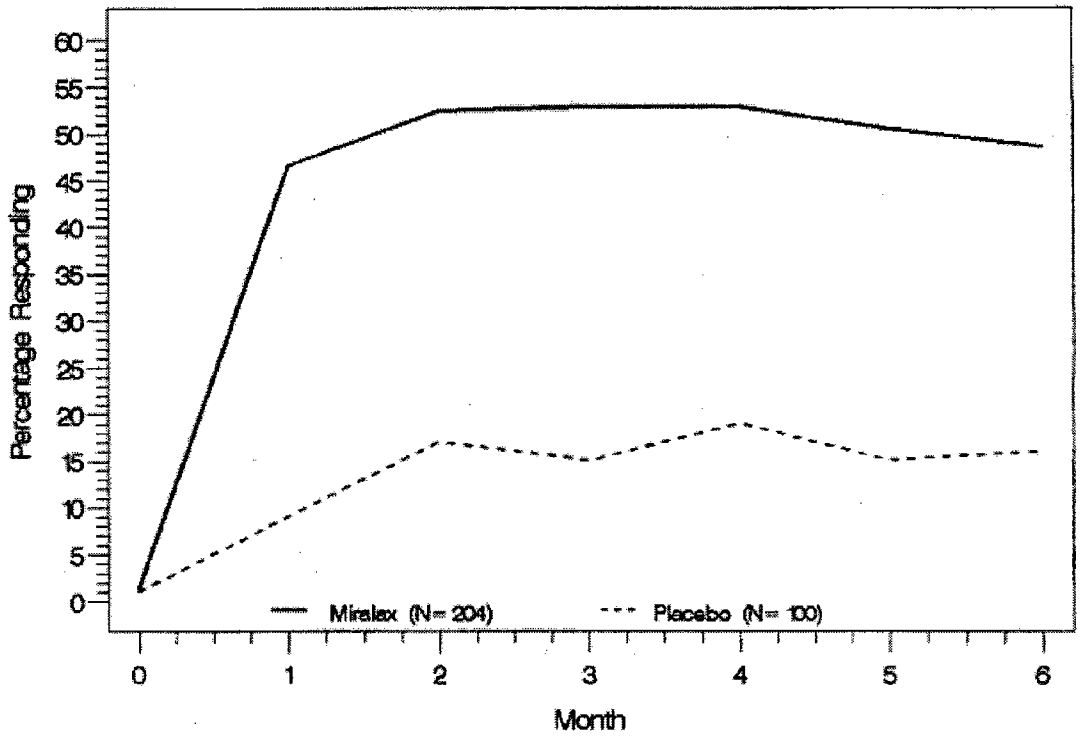
Medical Officer's Comments:

As noted in Table XX above, the primary responder analysis for the intent-to-treat (ITT) population in study 851-CR1 showed a statistically significant 41% difference in treatment response favoring MiraLAX over placebo. Given that the inclusion criteria for this study required patients to be constipated (have satisfactory stool less frequent than 3 per week), and have 1 or more of the additional ROME based criteria at entry; the 41% responder difference reflects a clinical relevance of approximately one bowel movement increase per week and no more than 1 ROME symptom criteria.

Appears This Way
On Original

The figure below reveals the proportion (as percent) of successfully treated patients responding to therapy by month for the primary efficacy measure. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative. At each month the difference was statistically significant ($p<0.001$).

Figure 1
Percentage of Patients Responding (Primary Efficacy) by Month
Intent-to-Treat Population



Sponsor's Figure taken from Protocol 851-CR1, page 33.

Medical Officer's Comments:

As shown graphically above in Figure 1, MiraLAX treatment resulted in a rapid increase in the number of successfully treated patients within the first month of therapy (up to 47%). The maximum response occurred by the second month (approximately 53%) and the response remained fairly level thereafter. The response to placebo was less impressive reaching about 9% the first month and remaining at a relatively lower level over the course of the study. The difference between MiraLAX and placebo was statistically significant ($p<0.001$) at all 6 study months. This study supports the durability of effect of MiraLAX for up to 6 months.

Early Efficacy of MiraLAX:

As shown above, MiraLAX appears to effectively relieve constipation by a statistically significant margin during months 1 through 6. The sponsor, however; seeks as part of their indication the statement that notes [redacted] Given that the endpoints were not designed to capture "time to event" data or early efficacy data (i.e. days, initial weeks), the undersigned medical officer extracted the stools/day and weekly bowel movement data below from the sponsor's submitted efficacy tables as to determine MiraLAX's initial efficacy.

Table XX: Study 851-CR1 Satisfactory Stools/Day (means)

	Satisfactory STOOLS/Day (mean)		
	MiraLAX	Placebo	P-Value
Week 1	0.56	0.36	<0.001
Week 2	0.78	0.37	<0.001
Week 3	0.84	0.46	<0.001
Week 4	0.87	0.43	<0.001
Week 5	0.94	0.44	<0.001
Week 6	0.93	0.48	<0.001
Week 7	0.95	0.50	<0.001
Week 8	0.96	0.50	<0.001

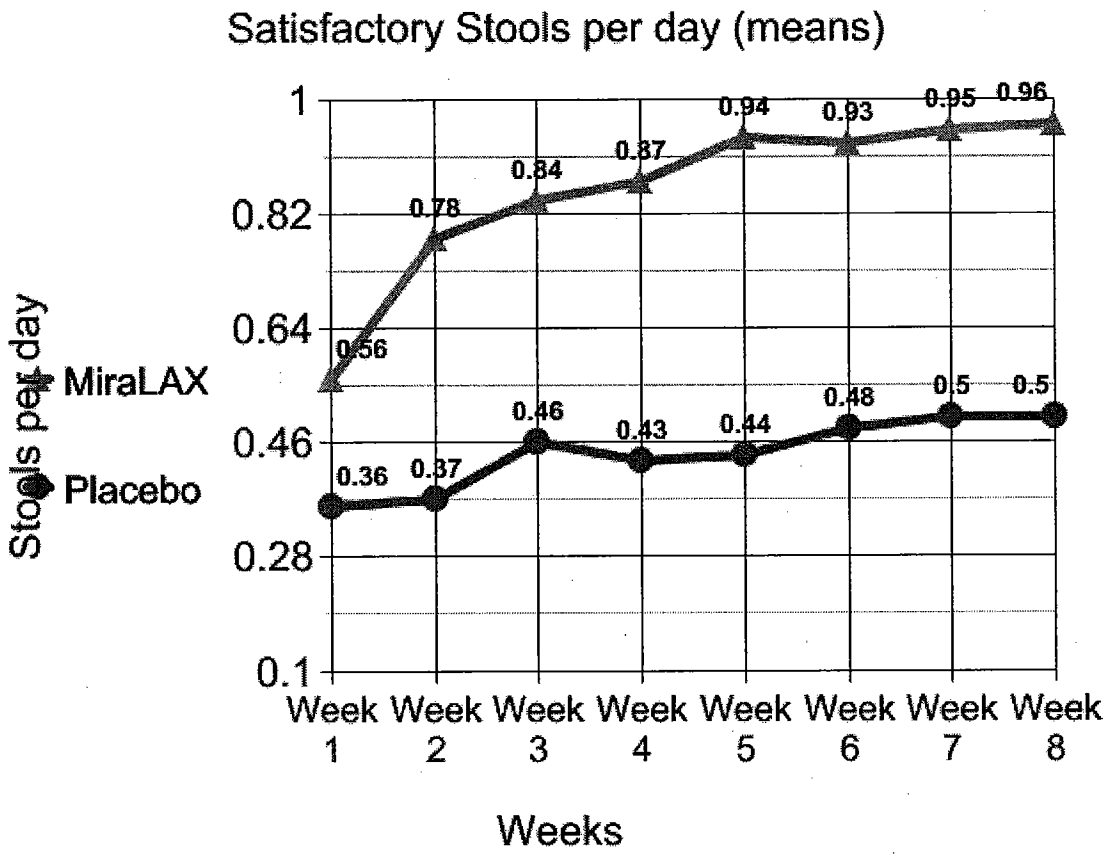
Reviewer's table, taken from Module 5, Volume 8.2, section 14

Medical Officer's Comments:
As noted above in Table XX above and Figure XX below, the number of satisfactory stools/day was statistically significant (p <0.001) for weeks 1 through 8 in favor of MiraLAX versus placebo.

At week one, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 0.56 BMs/day which equals 3.9 BMs/week or 1 BM every 1.8 days compared to placebo patients with 0.36 BMs/day which equals 2.5 BMs/week or 1 BM every 2.8 days.

At week two, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 0.78 BMs/day which equals 5.5 BMs/week or 1 BM every 1.3 days compared to placebo patients with 0.37 BMs/day which equals 2.6 BMs/week or 1 BM every 2.7 days.

Figure XX: Study 851-CR1 Satisfactory Stools/Day (means)



Protocol 851-ZCC:

The primary efficacy variable for treatment response was assessed on the basis of binary outcome of overall treatment success (responder) or failure (non-responder) where:

1. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.
2. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
    g. Straining in more than 25% of defecations
    h. Lumpy or hard stools in more than 25% of defecations
    i. Sensation of incomplete evacuation in more than 25% of defecations
3. Patients who received fewer than 2 weeks of active treatment for any reason were classified as overall treatment failures.

Table XX: Study 851-ZCC Primary Efficacy Responder Analysis Number of Successfully Treated Patients at 1 month

Responder	MiraLAX n (%)	Zelnorm n (%)	All	95% CI[1]	p[2]	Δ MiraLAX and Zelnorm responder %
All Patients						
(n)	120	117	237			
Yes	60 (50.0%)	36 (30.8%)	96 (40.5%)	7.0, 31.5	0.003	19.2 %
No	60 (50.0%)	81 (69.2%)	141 (59.5%)			

Reviewer's table, modified from sponsor's Table 2.7.3-8, Clinical Summary, page 14.

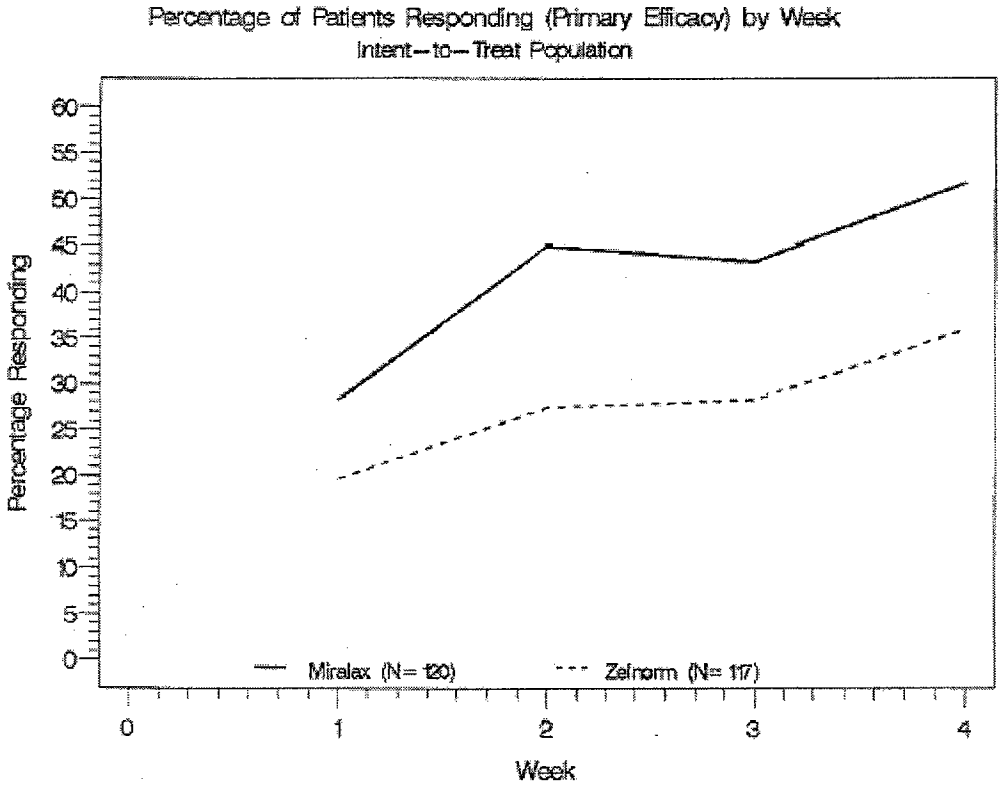
1. (CI): Confidence interval; difference between MiraLAX and Zelnorm is from Cochran-Mantel-Haenzsel-Test.
2. P-value for the difference between MiraLAX and Placebo is from a pooled site stratified Cochran-Mantel-Haenzsel-test.

Medical Officer's Comments:

As noted in Table XX above, the primary responder analysis for the intent-to-treat (ITT) population in study 851-ZCC showed a statistically significant 19.2% difference in treatment response favoring MiraLAX over Zelnorm (p = 0.003 at one month. Given that the inclusion criteria for this study required patients to be constipated (have satisfactory stool less frequent than 3 per week), and have 1 or more of the additional ROME based criteria at entry; the 19.2% responder difference reflects a clinical relevance of approximately one bowel movement increase per week and no more than 1 ROME symptom criteria. This study demonstrates that at one month, MiraLAX has superior efficacy in the responder analysis to Zelnorm; an approved and widely prescribed medicine for chronic constipation.

Figure XX below shows the proportion (as percent) of successfully treated patients, according to the primary efficacy definition, for each week of the study for both treatments. As noted below, MiraLAX treatment resulted in an increase in the number of successfully treated patients over the four weeks of therapy (to 50%). A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative. The difference in successfully treated patients between the MiraLAX and Zelnorm groups reached statistical significance by Week 2 and remained significant through Week 4 (p = 0.005, 0.0015, 0.015, respectively).

Figure XX: Study 851-ZCC Percentage of Patients Responding (Primary Efficacy) by Week (ITT-Population)



Early Efficacy of MiraLAX by Week:

As shown above, MiraLAX appears to be superior to Zelnorm by a statistically significant margin at weeks 2 through 4 of the one month trial. As discussed above, Zelnorm is approved for *chronic constipation* and may not have been the best active comparator against which to compare MiraLAX for an occasional constipation indication. In seeking an occasional constipation indication with MiraLAX, Braintree Laboratories notes that [redacted] Given that the endpoint(s) in study 851-ZCC were not designed to capture "time to event" data or early efficacy data (i.e. days), the undersigned medical officer extracted the weekly and daily bowel movement data from the sponsor's submitted efficacy tables as shown below, to determine MiraLAX's initial efficacy by week.

Table XX: Study 851-ZCC Satisfactory Stools/Day in Weeks 1 through 4 (means)

	Satisfactory STOOLS/DAY (mean)		
	MiraLAX	Zelnorm	P-value
Week 1	0.84	0.87	0.846
Week 2	1.16	0.92	**0.034**
Week 3	1.20	1.07	0.307
Week 4	1.35	0.98	**0.012**

Reviewer's table, taken from Module 5, Volume 9.2, section 14

Medical Officer's Comments:
As noted above in Table XX above, unlike the responder analysis, the number of satisfactory stools/day was statistically significant in favor of MiraLAX at week's 2 and 4 but not week's 1 or 3 versus Zelnorm. Regardless of statistical significance, during all four weeks, both MiraLAX and Zelnorm were clinically effective at relieving constipation.

At week 1, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 0.86 BMs/day which equals 5.9 BMs/week or 1 BM every 1.2 days compared to Zelnorm patients with 0.87 BMs/day which equals 6.1 BMs/week or 1 BM every 1.1 days.

At week 2, the outcome for MiraLAX translated into a clinically meaningful outcome as such: MiraLAX subjects had a mean of 1.16 BMs/day which equals 8.1 BMs/week or 1 BM every 0.86 days compared to placebo patients with 0.92 BMs/day which equals 6.4 BMs/week or 1 BM every 1.1 days.

Overall, the above data essentially translates into patients on both MiraLAX and Zelnorm having less than three bowel movements per week to approximately one bowel movement per day.

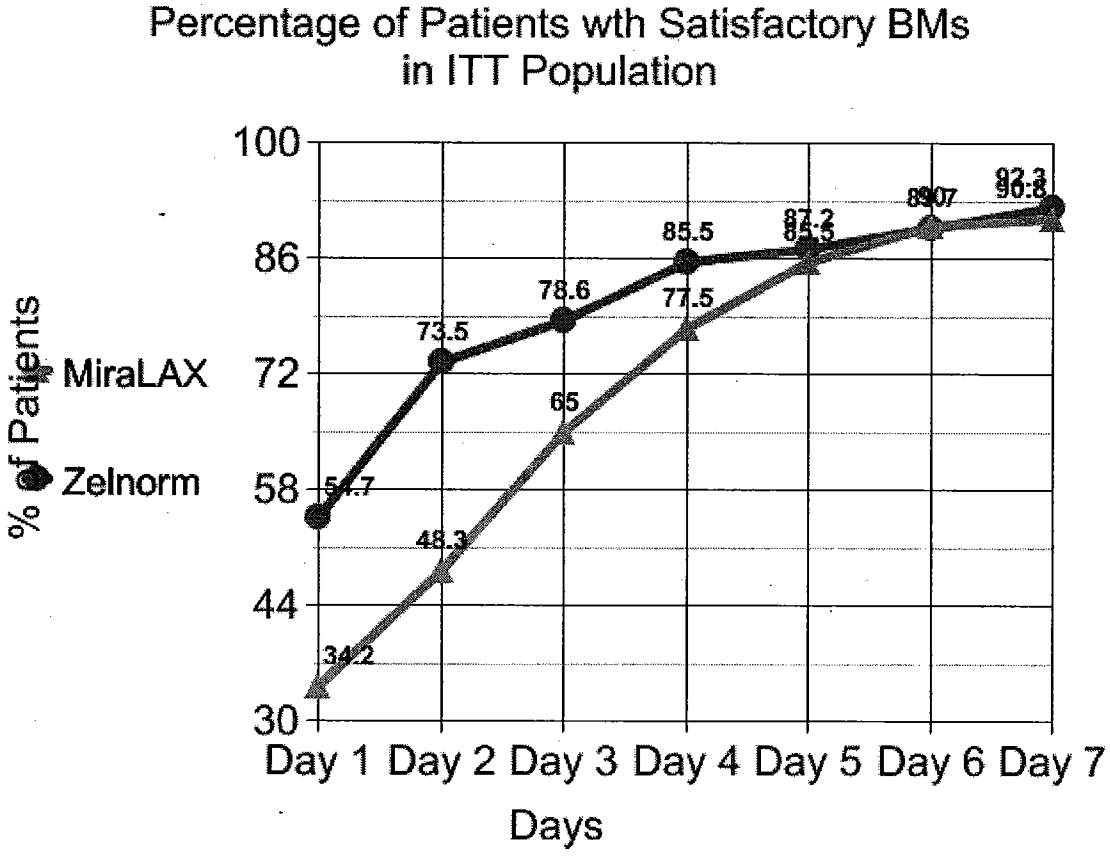
Early Efficacy of MiraLAX by Day:

The undersigned medical officer scrutinized the sponsor's data even further to examine the effects of MiraLAX on relief of constipation within the first 24 to 72 hours. Table XX and figure XX below show the percentage of patients with satisfactory bowel movements in the Intent-to-treat population on MiraLAX versus Zelnorm on Days 1 through 7 and on Day 28.

Table XX: Study 851-ZCC Percentage of Patients with Satisfactory BMs by DAY (means)

Day	MiraLAX (n = 120) N (%)	Zelnorm (n =117) N (%)	P- value
1	41 (34.2)	64 (54.7)	0.001
2	58 (48.3)	86 (73.5)	<0.001
3	78 (65.0)	92 (78.6)	0.020
4	93 (77.5)	100 (85.5)	0.115
5	103 (85.8)	102 (87.2)	0.762
6	108 (90.0)	105 (89.7)	0.948
7	109 (90.8)	108 (92.3)	0.648
28	116 (96.7)	114 (97.4)	0.727

Figure XX: Study 851-ZCC Percentage of Patients with Satisfactory BMs by DAY (means)



Medical Officer's Comments:

As noted above in Table XX and Figure XX, the percentage of patients with satisfactory bowel movements was higher in the Zelnorm cohort than the MiraLAX cohort, weeks 1 through 5, 7 and 28.

Protocol 851-CR3:

The primary efficacy variable for treatment response was assessed on the basis of binary outcome

Table XX: Global Efficacy Responder Analysis: Number and Percent of Successfully Treated Patients by Visit

Responder N (%)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
ITT by Visit[2]	250	217	203	185	180
Yes (success)	199 (80%)	177 (82%)	168 (83%)	163 (88%)	154 (85%)
No (failed)	51 (20%)	39 (18%)	35 (17%)	21 (11%)	21 (12%)
Missing	0	1 (0%)	0	1 (1%)	5 (3%)
ITT by Enrollment[3]	311	311	311	311	311
Yes (success)	199 (64%)	177 (57%)	168 (54%)	163 (52%)	154 (50%)
No (failed)	51 (16%)	39 (13%)	35 (11%)	21 (7%)	21 (7%)
Missing	0	1 (0.3%)	0	1 (0.3%)	5 (2%)

6.1.5 Clinical Microbiology

No microbiology information was included in this application.

6.1.6 Efficacy Conclusions

7 INTEGRATED REVIEW OF SAFETY

This section can be found in totality in the Safety Review by Dr. Karen Feibus, Division of Non-Prescription Drug Products.

7.1 Methods and Findings

7.1.1 Deaths

7.1.2 Other Serious Adverse Events

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

7.1.3.2 Adverse events associated with dropouts

7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events

7.1.5.4 Common adverse event tables

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

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7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.14 Human Reproduction and Pregnancy Data

7.1.15 Assessment of Effect on Growth

7.1.16 Overdose Experience

7.1.17 Post-marketing Experience

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

7.2.1.3 Extent of exposure (dose/duration)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.2 Post-marketing experience

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

8.3 Special Populations

8.4 Pediatrics

The safety and effectiveness of MiraLAX OTC in pediatric patients has not been established. The sponsor requested, and was granted a deferral of pediatric studies in this New Drug Application.

8.5 Advisory Committee Meeting

There was no Advisory Committee Meeting required for this New Drug Application.

8.6 Literature Review

8.7 Post-marketing Risk Management Plan

Comments regarding a Post-marketing Risk Management Plan can be found in the Safety Review by Dr. Karen Feibus, Division of Non-Prescription Drug Products.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

9.2 Recommendation on Regulatory Action

9.3 Recommendation on Post-marketing Actions

9.3.1 Risk Management Activity

Comments regarding a Post-marketing Risk Management Plan can be found in the Safety Review by Dr. Karen Feibus, Division of Non-Prescription Drug Products.

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

9.5 Comments to Applicant

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10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Review of Individual Study Reports

STUDY 851-CR1

Title: EXTENDED USE OF MIRALAX™ LAXATIVE IN CONSTIPATED PATIENTS, Braintree Protocol 851-CR1

10.1.2 Objectives

The objective of this study was to evaluate the safety and efficacy of extended (6 month) use of MiraLAX laxative as compared to placebo in constipated patients, including a subgroup of elderly patients.

Study Design

This was a double blind, placebo controlled, parallel group treatment study in which MiraLAX laxative or placebo (maltodextrin) was provided to patients in identically labeled single dose packets. Patients were instructed to mix the contents of one packet (approximately 17 g) with 8 oz. of juice or other beverage, and take once daily. Randomized patients were treated with study medication each day for up to 180 days.

Patients were allowed the use of bisacodyl 5 mg tablets as rescue medication and were instructed to take 10 mg of bisacodyl if they experienced severe discomfort due to their constipation, or if they had not had a BM in 4 days.

Male and female patients that met the protocol definition of constipation, but who were otherwise in generally good health, were enrolled. Of these patients, about 100 were expected to be 65 years of age or older. Enrolled study patients were instructed to stop all laxative treatments for a 14 day observation period. Three hundred and six patients met the study definition of constipation and were randomized to treatment by a computer generated randomization scheme. Three hundred and four patients remained in the Intent-to-Treat (ITT) analysis. Of the 304 ITT patients, 75 were 65 years of age or older.

Patients called into an IVRS (Interactive Voice Response System) each day to report their bowel movement (BM) experiences for that day and answer questions related to the study efficacy and safety criteria.

No safety, data monitoring, special steering, or evaluation committees were formed or met during the study period. Additionally, no interim analysis was performed.

Efficacy and Safety Variables

Patients called into the IVRS daily to report their BM experiences for that day. Following input of the patient identifiers and security code, the IVRS prompted the patient as follows:

- How many stools did you pass today?
- How many satisfactory stools did you pass today?
- Did you have to strain to pass your stool today?
- Were your stools lumpy or hard today?
- Were your bowel movements complete?
- Did you take any laxatives, including rescue med today?
- Please rate the amount of cramping you experienced today on a scale of 0 to 4 with 0 indicating no cramping and 4 indicating extreme cramping
- Please rate the amount of gas you had today on a scale of 0 to 4 with 0 indicating no gas and 4 indicating extreme gas.
- Did you have 3 or more large watery stools today?

Every 7 days the patient was given the following additional prompt to provide a global assessment of their constipation:

"In the past seven days, do you feel you have had adequate relief of your constipation?"

Primary Efficacy Endpoint

The primary efficacy endpoint:

- was assessed on the basis of a binary outcome of overall treatment success (responder) or failure (non-responder) as defined below.

A treatment success (responder) was defined as:

C. Satisfactory stools greater or equal to 3 per week, and
D. 1 or fewer of the following additional ROME based criteria
    a. Straining in more than 25% of defecations
    b. Lumpy or hard stools in more than 25% of defecations
    c. Sensation of incomplete evacuation in more than 25% of defecations

This definition was further refined according to the following rules:

- Patients who received fewer than 8 weeks of active treatment for any reason were classified as an overall treatment failure.
- A successful treatment week was defined as ≥ 3 satisfactory bowel movements without the aid of rescue medication or prohibited laxative.

- A successful treatment week rate was defined as the ratio of successful treatment weeks to total number of weeks of actual treatment.
- Overall treatment success was defined as a 0.50 or greater rate of successful treatment weeks.
- Only days in which data has been reported were counted toward the success calculation for that particular week. Days with missing data were not included in any calculations.

Secondary Efficacy Endpoints

- ROME Definition: A successful week was defined as not satisfying any 3 of 4 ROME constipation symptom criteria without the aid of rescue medication or prohibited laxative. Only days in which data was reported counted toward the endpoint calculation. The rate of successful treatment weeks was defined in the same manner as for the primary endpoint.
- Super Efficacy: A successful week was defined as not satisfying any of the four ROME constipation symptom criteria without the aid of rescue medication or prohibited laxative. The rate of successful treatment weeks was defined in the same manner as for the primary endpoint.
- A successful treatment week rate was also defined in terms of each individual ROME constipation symptom. A successful week was defined as not satisfying that constipation criterion without the aid of rescue medication or prohibited laxative. For this endpoint there was no requirement for a minimum number of treatment weeks. Otherwise, the rate of successful treatment weeks was defined in the same manner as for the secondary endpoint based on overall ROME criteria.
- A successful treatment week rate was also defined in terms of no use of rescue medication or prohibited laxative. A non-successful treatment week was any week for which either rescue medication or prohibited laxative was used.
- Only days in which data were reported counted toward the success calculation for that particular week. Missed days were treated as if no bowel movements occurred and no alternate laxative was used.

Statistical Methods:

The primary analysis was based upon and intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. All patients in this group had a determination of overall treatment success (responders). The primary efficacy analysis was on the primary efficacy endpoint of overall treatment success or failure rate determined for each patient.

The null hypothesis was: "There is no difference in the proportion of responders between MiraLAX and placebo." The alternative hypothesis is: "There is a difference in the proportion of responders between MiraLAX and placebo."

The primary analysis for the between treatment comparison used the Cochran-Mantel-Haenszel (CMH) statistic stratified by site with no covariate adjustment. The difference was the weighted difference of responder rates between the active treatment group and placebo group. The weight

for each site was proportional to the number of patients in each treatment group. Exact p-value was used for this comparison and a 95% confidence interval for the difference in proportions was also obtained for the non-stratified population. Sites that recruited fewer than 24 ITT patients were pooled to form larger pseudo sites in order to maintain at least 24 ITT patients for each site in the CMH stratified analysis. To meet this requirement, pseudo sites were created by pooling individual sites within a pre-determined geographic region. The specifics of this pooling algorithm were defined prior to un-blinding the study data and included in a detailed statistical analysis plan.

Secondary efficacy endpoints defined in terms of successful treatment rates were analyzed using analysis of variance (ANOVA) with factors for treatment group, pooled site, and interaction between treatment and pooled site. Selected secondary endpoints were also analyzed using survival analysis to evaluate time to event [treatment response (success) and duration of response (persistence)]. The time to treatment response was defined as the time since first dose until obtaining response criteria. The duration of response was defined as the time of first obtaining the response criteria until the first time of failure to obtain the response criteria. The differences in response curves for the two treatment groups were compared using a log rank test. The estimated time to event and the proportion of patients obtaining the event at 4, 8, 12, 16, and 24 weeks were based on the Kaplan-Meier product limit method.

More specifically:

Patients who are responders by Month (Figure 1):

A successful treatment for this endpoint was defined as a month (4 week period) with two or more successful weeks. A successful week is defined as a week with ≥ 3 satisfactory bowel movements with the presence of one or no additional ROME criteria without the aid of rescue medication. For the baseline two-week period, a patient must have one or two successful treatment weeks to satisfy this endpoint.

Not meeting ROME definition of constipation by Month:

Constipation for this study was defined as meeting greater than 1 of the 4 ROME criteria of constipation. Failure to meet 3 of the four criteria was considered to be absence of constipation. A successful treatment for this endpoint is defined as a month (4 week period) with two or more successful weeks. A successful week is a week in which three of the four ROME criteria are not satisfied.

Not meeting Super Efficacy by Month:

Super efficacy was defined as absence of all the four ROME symptoms without the aid of rescue medication for two or more weeks in a four week month.

For each of the above secondary endpoints, the number and percent of patients achieving the endpoint was calculated for each month of the study period and compared between the treatment

groups by a stratified CMH test controlling for the pooled-site. In addition, and exact 95% confidence interval for the difference in treatment response was obtained for the non-stratified population.

Mean Number of BM by Week, Mean Number of Satisfactory BM by Week, Mean Number of CSBM by Week:
For each of the three preceding endpoints, descriptive statistics for the mean number of bowel movements per week for each four month period was computed and the mean compared between the treatment groups by ANOVA with terms for treatment, pooled-site and their interaction. The average number of bowel movements per week for each four week period was computed for each patient initially and then from these patient averages the mean number of bowel movements for the treatment group was calculated.

Determination of Sample Size:

The sample size calculation was based upon the normal approximation to the binomial distribution. Using the results from a previous study (851-6) and taking into account potential laxative use, the overall treatment success for the placebo group was expected to be approximately 40%. An absolute increase of 20 percentage points in overall treatment success with MiraLAX over placebo (40 to 60%) was considered a clinically important improvement. Assuming a 40% placebo response rate for overall treatment success, based on a two-sided chi-squared test, a study size of 300 patients (200 on MiraLAX and 100 on placebo) was expected to have 90% power to detect a treatment difference of 20% at the two-sided significance level of 0.05.

Inclusion/Exclusion Criteria

Inclusion criteria: 306 male and female patients that met a definition of constipation, but were otherwise in generally good health, were enrolled. Of these patients, 76 were 65 years of age or older.

Constipation was defined based on modified ROME definition: on average, for greater than the preceding 3 months, when not taking laxatives, the patients had:

A. Satisfactory stool less frequent than 3 per week, and
B. 1 or more of the following additional ROME based criteria
    a. Straining in more than 25% of defecations
    b. Lumpy or hard stools in more than 25% of defecations
    c. Sensation of incomplete evacuation in more than 25% of defecations

Other inclusion criteria were:

- On average, fewer than 3 satisfactory BMs per week during the 14 day observation period.

- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so during the duration of study.
- Are otherwise in good health, as judged by a physical examination.
- In the investigator's judgment, patient is mentally competent to sign an instrument of informed consent

Exclusion criteria: Patients who met any of the following criteria were excluded from the study:

- Patients with heme positive stool at screening
- Patients with hypo- or hyperthyroidism as determined by history, or screening TSH results.
- Patients with known or suspected perforation or obstruction
- History of gastric retention, inflammatory bowel disease, bowel resection, or colostomy.
- Patients with a known history or organic cause for their constipation.
- Loose stools are present, and there is sufficient criteria for IBS:

  At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two or three features:
  a. Relieved with defecation; and/or
  b. Onset associated with a change in frequency of stool; and/or
  c. Onset associated with a change in form (appearance) of stool.
- Patients currently taking any of the following medications that are known to affect bowel habits:
  a. Antidiarrheals
  b. Antacids containing magnesium or aluminum salts
  c. Anticholinergics
  d. Antispasmodic agents
  e. Erythromycin and other macrolides
  f. Octreotide
  g. Lotronex, Zofran, or other 5-HT_3 antagonists
  h. Zelnorm, or other 5-HT_4 agonists
  i. Opioids/narcotic analgesics (occasional use of codeine is allowed if needed for a non-gastrointestinal indication)
  j. Prokinetics
  k. Serotonin re-uptake inhibitors or tricyclic antidepressants (allowable only if patient has been on a constant dose for one month prior to screening)
  l. Calcium antagonists (allowable only if patient has been on a constant dose for one month prior to screening)
- Patients who are breastfeeding, pregnant, or intend to become pregnant during the study.
- Female patients of childbearing potential who refuse a pregnancy test.

- Patients with a known allergy to corn or polyethylene glycol.
- Patients who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures.
- Patients who, within the past 30 days have participated in an investigational clinical study.

PROTOCOL AMENDMENT 1 (06/17/2003):

- ***IBS patients were excluded from participation in the study***
- ***patients with hypo- or hyperthyroidism based on baseline thyroid stimulating hormone levels were excluded from the study***
- ***patients may be discontinued prematurely based on usage of non-study laxatives or excluded medications (per exclusion criteria).***

PROTOCOL AMENDMENT 2 (09/29/2003):

- ***patients with heme positive stool at baseline were eligible if the result could be attributed to hemorrhoids or anal fissures***
- ***fiber and herbal laxatives are excluded medications and must be discontinued at screening***
- ***patients could not have undergone a colonoscopy within 30 days of their screening visit***
- ***patients that have had prior exposure to MiraLAX were ineligible for the study***
- ***Patients that missed 1 day of IVRS diary reporting were still eligible for randomization as long as the missed diary call did not occur on Day 14.***

Demography and Disease History

A total of 609 patients were screened and 304 were enrolled in this study at 50 centers. Of the 304 enrolled patients, 76 were elderly. Three hundred and four (304) patients received study medication and were included in the Intent-to-Treat treat analysis (75 elderly). The majority of enrollees in this study (258 or 85%) were female. Forty-six males were enrolled. The treatment groups were similar with respect to age, racial distribution, weight, and constipation history. The average age of study participants was about 53 years, ranging in age from 20 to 92 years of age. About 84% of study enrollees were Caucasian and 13% were African American, reflecting national racial population distribution. Study patients weighed on average of about 75 kg. There were no demographic related statistically significant differences between the treatment groups.

Table XX: Study Demographics

	MiraLAX			Placebo			
	All	Younger (<65 y)	Elderly (≥65y)	All	Younger (<65 y)	Elderly (≥65y)	p[1]
Age (years)[2] n Mean (SD)	204 53.1 (14.8)	153 46.6 (10.5)	51 72.7 (6.5)	100 54.4 (15.0)	76 48.4 (11.5)	24 73.5 (6.4)	0.46
Gender n (%) Female Male	175 (86) 29 (14)	144 (94) 9 (6)	31 (61) 20 (39)	83 (83) 17 (17)	70 (92) 6 (8)	13 (54) 11 (46)	0.56
Race n (%) Caucasian A.Amer. Other Missing	168 (82) 28 (14) 4 (2) 4 (2)	122 (80) 25 (16) 2 (1) 4 (3)	46 (90) 3 (6) 2 (4) 0	87 (87) 11 (11) 1 (1) 1 (1)	63 (83) 11 (14) 1 (1) 1 (1)	24 (100) 0 0 0	0.81
Ethnicity n (%) Hispanic Non-Hispanic	12 (5.9) 192 (94.1)	12 (8) 141 (92)	0 51 (100)	7 (7) 93 (93)	6 (8) 70 (92)	1 (4) 23 (96)	075
Weight (kg) Mean (SD)	74.7 (16.3)	74.5 (17.5)	75.1 (12.2)	75.1 (15.6)	73.4 (14.7)	80.3 (17.2)	0.65
Constipation Hx (yrs) Mean (SD)	23.4 (18.7)	21.1 (15.8)	30.2 (24.4)	22.6 (19.2)	20.4 (16.2)	29.5 (25.8)	0.66

Reviewer's Table, modified from Sponsor's Table CR1-3, Protocol 851-CR1, page 28

1. P-Value from CMH test controlling for pooled site for the categorical variables, and from an ANOVA with terms for pooled site and treatment for the continuous variables.
2. Age is calculated using date of birth and screening visit (Visit 1) date.

SD = Standard Deviation; kg = kilograms; A.Amer. = African American

Patient Disposition

One hundred-seventy (170) patients completed all 6 months of the study. The reasons for discontinuation are given below in Table XX.

Table XX: Reasons for Patient Discontinuation

	MiraLAX % (n)	Placebo % (n)
Completing Patients	62.3 (127)	43.0 (43)
Patients Discontinued	37.7 (77)	57.0 (57)
Reasons:		
Patient withdrew consent	18 (14)	25 (14)
Lack of efficacy	31 (24)	46 (26)
Non-compliance	12 (9)	12 (7)
Lost to follow-up	14 (11)	5 (3)
Adverse Event	25 (19)	12 (7)

Reviewer's Table, modified from sponsor's Table CR-1, Protocol 851-CR1, page 25

Patient withdrawals associated with MiraLAX or placebo treatment are shown above in Table XX. The MiraLAX group had approximately 20% more completing patients (62.3% vs. 43.0%) than did the placebo group (given there were nearly 3 times the amount of patients in the population), three times the percent of patients who were lost to follow-up and who suffered an adverse event. Not unexpected, there were a higher percentage of placebo patients who discontinued secondary due to withdrawing consent and lack of efficacy.

Three hundred and three (303) patients did not meet study inclusion/exclusion criteria or otherwise failed screening during the 14 day washout period. The reasons for screen failures are given below in Table XX.

Table XX: Reasons for Screen Failure:

Patients Failed Screen	n = 303
Reasons:	% (n)
Failed BM criteria	38 (115)
Failed inclusion criteria	24 (73)
Withdrew consent	13 (40)
Adverse Event	1 (1)
Non-compliance	24 (74)

Reviewer's Table, modified from sponsor's Table CR-2, Protocol 851-CR1, page 26

Compliance

Patients returned monthly to their study center where study drug and rescue medications were reviewed for treatment compliance. Patients were allowed use of rescue bisacodyl (10 mg) if they experienced severe constipation discomfort; however their study drug dose could not be increased above one packet.

Monthly compliance for each patient was calculated based on the number of packets of study medication returned at each study visit divided by the number of treatment days between visits (expressed as a percent). The monthly compliance values were then averaged to arrive at a single study compliance value for each patient. Overall, the mean compliance between treatment groups was similar ($p = 0.30$). MiraLAX patients were 88.9% (SD=17.9%) compliant and placebo patients were 86.3% (SD=18.4% compliant. Single-patient compliance generally exceeded 90% for both treatments throughout the entire study period.

10.1.3 Efficacy Results

Data Sets Analyzed:

All patients enrolled that received at least one dose of study medication were included for analysis. Two patients were enrolled (patients 108-008 and 112-020) but were withdrawn from the study prior to receiving study drug due to inappropriate enrollment (e.g. elevated baseline TSH results, received late) or due to severe non-compliance (no IVRS calls – patient lost to follow-up).

Analysis of Efficacy:

Overall, patients treated with MiraLAX achieved a statistically significant benefit ($p < 0.001$) over placebo in 11 of 12 primary and secondary efficacy measures.

Primary Efficacy Endpoint:

The primary efficacy variable for treatment response was assessed on the basis of binary outcome of overall treatment success (responder) or failure (non-responder) where:

4. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.
5. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
    j. Straining in more than 25% of defecations
    k. Lumpy or hard stools in more than 25% of defecations
    l. Sensation of incomplete evacuation in more than 25% of defecations
6. Patients who received fewer than 8 weeks of active treatment for any reason were classified as overall treatment failures.

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As indicated in Table XX below, the percentage of patients who responded successfully with MiraLAX was more than four times higher than with placebo; regardless of age, gender, or race.

Table XX: Primary Efficacy Responder Analysis; Number and Percent of Successfully Treated Patients

Responder[1]	MiraLAX n (%)	Placebo n (%)	All	95% CI[2]	p[3]
All Patients (n)	204	100	304		
Yes	106 **(52)**	11 **(11)**	117 **(39)**	31.8, 50.2	<0.001
No	98 (48)	89 (89)	187 (61)		
Elderly (≥ 65 y)	51	24	75		
Yes	30 **(59)**	3 **(13)**	33 **(44)**	27.4, 65.2	<0.001
No	21 (41)	21 (87)	42 (56)		
Non-Elderly (<65 y)	153	76	229		
Yes	76 **(50)**	8 **(11)**	84 **(37)**	28.6, 49.7	<0.001
No	77 (50)	68 (89)	145 (63)		
Males	29	17	46		
Yes	13 **(45)**	1 **(6)**	14 **(30)**	17.7, 60.2	0.007
No	16 (55)	16 (94)	32 (70)		
Females	175	83	258		
Yes	93 **(53)**	10 **(12)**	103 **(40)**	30.9, 51.3	<0.001
No	82 (47)	73 (88)	155 (60)		
Caucasian	172	88	260		
Yes	89 **(52)**	10 **(11)**	99 **(38)**	30.4, 50.4	<0.001
No	83 (48)	78 (89)	161 (62)		
Non-Caucasian	32	12	44		
Yes	17 **(53)**	1 **(8)**	18 **(41)**	21.5, 68.1	0.014
No	15 (47)	11(92)	26 (59)		

Reviewer's Table, modified from sponsor's Table CR1-4, Protocol 851-CR1, page 30

1. A successful treatment week is defined as ≥ 3 satisfactory bowel movements, with 1 or no additional ROME symptom criteria, and without the aid of rescue medication or prohibited laxative during the week. A responder must have at least a 0.50 rate of successful treatment weeks (based on number of actual treatment weeks. Days with missing data are not included in computing success. A patient with fewer than 8 weeks of data will be counted as a failure.
2. Confidence interval (CI) for the difference between MiraLAX and placebo is from a Cochran-Mantel-Haenzsel test or Fisher's Exact test (for race).
3. P-value for the difference between MiraLAX and placebo is from a pooled site stratified Cochran-Mantel- Haenzsel test or Fisher's Exact test (for race).

For this study, centers were pooled into eight geographic areas (composed of about 25 to 60 patients each) and individually analyzed for the primary efficacy variable. This analysis, shown below in Table XX, reveals that in all regions, placebo failed in 78% or more of patients. Of the geographic regions, Florida and Carolina had the lowest success rates for MiraLAX yet still showed an increase in responder status of 23 and 27 percent, respectively.

Table XX: Responder Analysis by Geographic Region

Region	Responder[1]	MiraLAX (N=204) n (%)	Placebo (N=100) n (%)	All (N=304) n (%)	95% CI[2]	p[2]
S West	Yes	24 (58)	2 (11)	26 (43)	27.6, 68.5	**<0.001**
	No	17 (42)	17 (89)	34 (57)		
E Coast	Yes	18 (56)	3 (21)	21 (46)	7.3, 62.3	0.052
	No	14 (44)	11 (79)	25 (54)		
FL	Yes	9 (38)	2 (15)	11 (30)	-5.4, 49.7	0.262
	No	15 (62)	11 (85)	26 (70)		
S East	Yes	13 (54)	0 (0)	13 (37)	34.2, 74.1	**0.002**
	No	11 (46)	11 (100)	22 (63)		
Carolina	Yes	9 (35)	1 (8)	10 (26)	3.6, 50.3	0.120
	No	17 (65)	12 (92)	29 (74)		
TX	Yes	9 (53)	1 (11)	10 (39)	10.5, 73.2	0.087
	No	8 (47)	8 (89)	16 (61)		
Midwest	Yes	10 (56)	2 (20)	12 (43)	1.8, 69.3	0.114
	No	8 (44)	8 (80)	16 (57)		
OH/IL	Yes	14 (64)	0 (0)	14 (42)	43.5, 83.7	**<0.001**
	No	8 (36)	11 (100)	19 (58)		

Reviewer's Table, modified from sponsor's Table CR1-4, Protocol 851-CR1, page 30

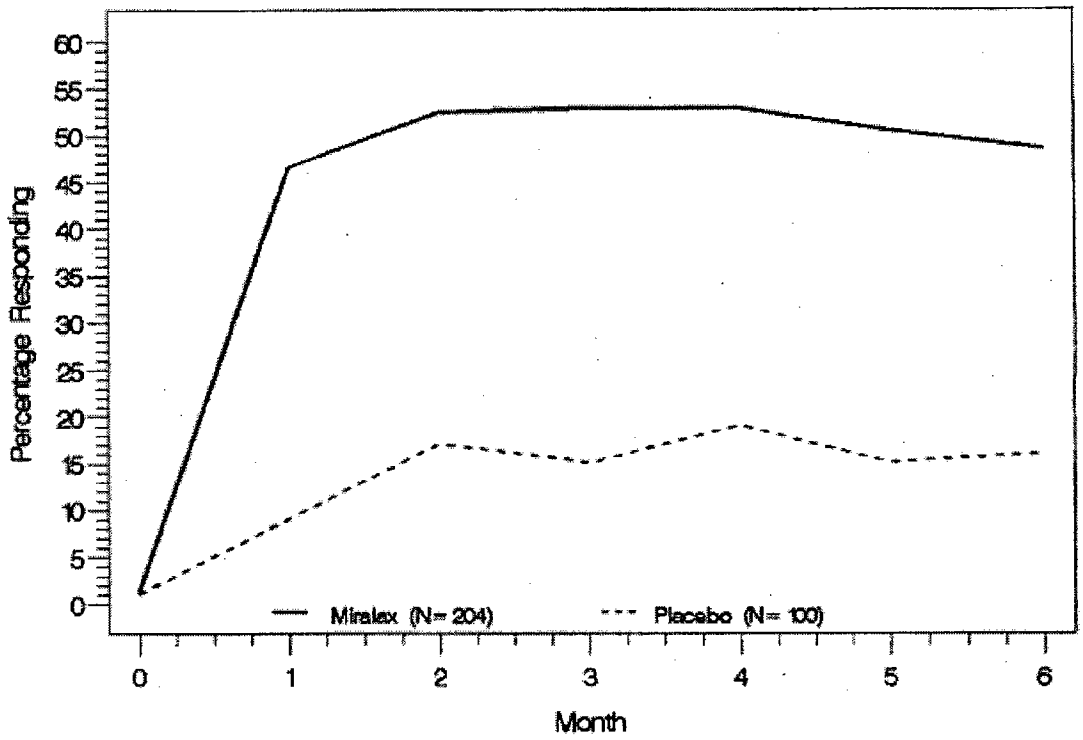
1. A successful treatment week is defined as ≥ 3 satisfactory bowel movements, with 1 or no additional ROME symptom criteria, and without the aid of rescue medication or prohibited laxative during the week. A responder must have at least a 0.50 rate of successful treatment weeks (based on number of actual treatment weeks. Days with missing data are not included in computing success. A patient with fewer than 8 weeks of data will be counted as a failure.
2. Confidence interval (CI) for the difference between MiraLAX and placebo is from a Cochran-Mantel-Haenzsel test or Fisher's Exact test LAX and placebo is from a Cochran-Mantel-Haenzsel test or Fisher's Exact test.

Figure 1 below shows the proportion (as percent) of successfully treated patients, according to the primary efficacy definition, for each month of the study for both treatments. MiraLAX treatment resulted in a rapid increase in the number of successfully treated patients within the first month of therapy (to about 47%). The maximum response occurred by the second month and the response then remained fairly level thereafter. The response to placebo was much less dramatic (about 9% in the first month) and remained at a low level over the course of the study. The difference between MiraLAX and placebo was statistically significant at all study months.

Figure XX: Percentage of Responders (Intent-to-Treat Population):

The figure below reveals the percent of patients responding to therapy by month for the primary efficacy measure. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative. At each month the difference was statistically significant ($p<0.001$).

Figure 1
Percentage of Patients Responding (Primary Efficacy) by Month
Intent-to-Treat Population



Sponsor's Figure taken from Protocol 851-CR1, page 33.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints included assessment of ROME definition for each treatment week and "super efficacy" (weeks where patients did not have *any* of the four ROME symptoms). These analyses are shown below in Table XX below for the ITT population where the number of successful treatment weeks according to each definition is displayed.

Table XX: Number of Successful Weeks; Secondary Endpoint Analyses

Responder Definition	MiraLAX	Placebo	All	p[1]
Mean Treatment Weeks	19.5	15.4	-	-
Primary Definition[2] Mean (SD) % of weeks	196 12.0 (9.8) **61.4**	95 3.4 (5.8) **21.8**	291 9.2 (9.6)	**<0.001**
ROME[3] Mean (SD) % of weeks	202 12.9 (10.0) **66.2**	100 3.8 (6.2) **24.4**	302 9.9 (9.9)	**<0.001**
Super Efficacy[4] (n) Mean (SD) % of weeks	196 9.2 (9.0) **47.3**	95 2.2 (4.7) **14.4**	291 6.9 (8.5)	**<0.001**

Reviewer's Table, modified from sponsor's Table CR1-6, Protocol 851-CR1, page 34

1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled site interaction.
2. ≥3 satisfactory bowel movements, with 1 or no additional ROME symptom criteria, and without the aid of rescue medication or prohibited laxative during the week.
3. ROME definition not met without aid of rescue medication.
4. No ROME symptom criteria met, without aid of rescue medication.

SD = Standard Deviation.

As graphically depicted above in Table XX, MiraLAX treated patients had approximately 4 times as many successful treatment weeks as placebo patients by any definition. There was fewer successful "super efficacy" treatment weeks for both therapies due to the more strict definition, however; even by this more rigorous definition, nearly 50% of the treatment weeks were successful for MiraLAX versus 14% for placebo.

Table XX below shows the number of successful treatment weeks for each of the four ROME symptom criteria. The table entries indicate weeks where the ROME constipation symptom was not met (i.e. a successful treatment week). The differences between MiraLAX and placebo in individual ROME symptoms were all statistically significant with the most dramatic differences occurring in straining (symptom 2) and hard stool (symptom 3).

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Table XX: Individual ROME Symptoms; Secondary Efficacy Analyses – Number of Successful Weeks

Responder Definition[2]	MiraLAX	Placebo	All	p[1]
Treatment Weeks	19.5	15.4	-	-
ROME #1 <3 Satis. BM (n) Mean (SD) % of weeks	202 13.5 (9.8) **68.9**	100 5.6 (7.4) **36.4**	302 10.9 (9.8)	<0.001
ROME #2 Strain >25% (n) Mean (SD) % of weeks	202 12.4 (9.9) **63.6**	100 3.1 (5.6) **20.1**	302 9.3 (9.8)	<0.001
ROME #3 Hard Stool >25% Mean (SD) % of weeks	202 14.3 (10.1) **73.3**	100 4.5 (6.8) **29.2**	302 11.1 (10.2)	<0.001
ROME #4 Incomplete >25% Mean (SD) % of weeks	202 10.6 (9.2) **54.4**	100 4.3 (6.7) **27.9**	302 8.5 (8.9)	<0.001

Reviewer's Table, modified from sponsor's Table CR1-7, Protocol 851-CR1, page 35
1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled-site interaction
2. Specific ROME symptom not met, without aid of rescue medication.

Table XX below shows the statistically significant differences between treatments in the total number of bowel movements (BM) per week as well as the number of "satisfactory BM" per week. MiraLAX patients achieved one bowel movement per day, which was nearly, double the number of "satisfactory BM" per week (about 5.4) as compared to placebo (about 2.7). This level of weekly "satisfactory BM" output for placebo meets the study definition of constipation (fewer than 3 satisfactory BM's per week).

As noted below, MiraLAX also performed much better than placebo in an analysis for "Complete, Spontaneous BM" (CSBM) (5.0 CSBM vs. 2.1 CSBM; MiraLAX vs. placebo, respectively). In this analysis, a successful CSBM was defined as a patient score for a BM as "complete" and occurring on a day in which no stimulant rescue laxative was taken. Similar to the "satisfactory BM" analysis discussed above, the placebo treated patients continued to meet the study definition of constipation.

Success for MiraLAX was also noted for MiraLAX in the patient "Global Assessment of Efficacy" (GEA) where patients taking MiraLAX noted that 64% of their treatment weeks were satisfactory as compared to 34% of placebo treatment weeks.

Interestingly, although MiraLAX-treated patients on average used fewer tablets of the rescue medication (2.8 mean tabs/wk vs. 3.9 tabs/wk, MiraLAX vs. placebo, respectively), this

difference was not statistically significant. Half of the MiraLAX study patients used a total of eight bisacodyl tablets or less over the six month treatment period and about 21% did not use any at all.

Table XX: Additional Secondary Efficacy Analyses:

Responder Definition[2]	MiraLAX	Placebo	All	p[1]
Mean BM/week (n) Mean (SD)	202 7.9 (4.5)	100 5.6 (5.5)	302 7.1 (5.0)	<0.001
Mean Satisfactory BM/wk (n) Mean (SD)	202 5.4 (3.6)	100 2.7 (2.1)	302 4.5 (4.0)	<0.001
Mean CSBM/wk[2] Mean (SD)	202 5.0 (4.2)	100 2.1 (2.7)	302 4.0 (4.0)	<0.001
Global Assess.[3] Mean weeks (SD) % weeks[4]	202 12.5 (8.9) 64.1	100 5.2 (7.1) 33.8	302 10.1 (9.0)	<0.001
Rescue Med Use Mean tabs/wk (SD)	198 2.8 (6.0)	97 3.9 (7.1)	295 3.2 (6.4)	0.138

Reviewer's Table, modified from sponsor's Table CR1-7, Protocol 851-CR1, page 35

1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled-site interaction
2. CSBM = Complete, Spontaneous BM, without aid of rescue medication
3. Number of weeks that patients indicated that they had adequate relief
4. Mean number of MiraLAX treatment weeks = 19.5; mean placebo weeks = 15.4.

SD = Standard Deviation

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Figure 2: Percentage of Successfully Treated Patients (ITT)

The figure below displays the percent of patients who did not meet the ROME definition of Constipation each month. According to this definition, a successful treatment week was defined as a patient reporting no more than 1 ROME symptom criterion, without the aid of rescue medication or prohibited laxative. The ROME symptoms for constipation are:

a. < 3 satisfactory bowel movements per week
b. Straining in more than 25% of defecations
c. Lumpy or hard stools in more than 25% of defecations
d. Sensation of incomplete evacuation in more that 25% of defecations

Treatment with MiraLAX resulted in a rapid increase in the number of successfully treated patients. The maximum response occurred by the second month and the response then remained fairly level thereafter. The differences between MiraLAX and placebo were statistically significant at each month ($p<0.001$). There was no evidence of tachyphylaxis associated with long term MiraLAX treatment.

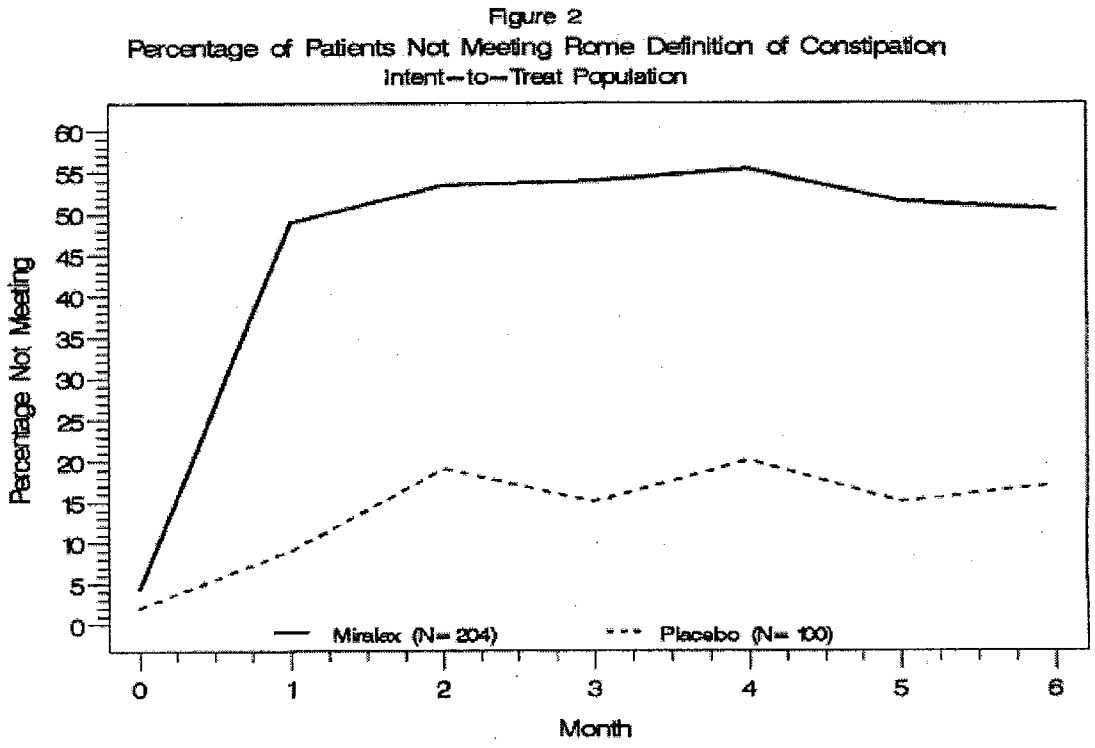
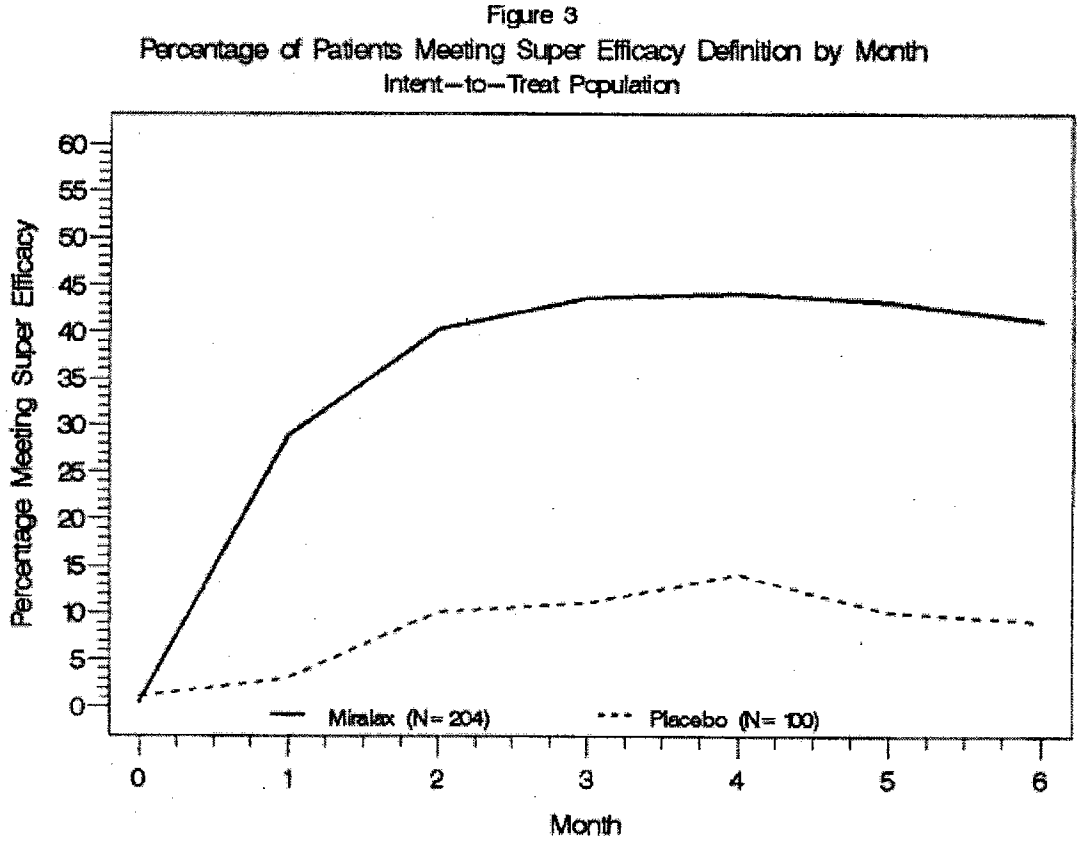


Figure 3: Percentage of Successfully Treated Patients (ITT)

The figure below displays the percent of patients who met the "super efficacy" definition by month. According to this definition, a successful treatment week was defined as a patient reporting none of the ROME symptom criteria (above), without the aid of rescue medication or prohibited laxative. Treatment with MiraLAX resulted in a rapid increase in the number of successfully treated patients by either definition within the first month of therapy and the maximum response occurred by month two remaining fairly level thereafter. The response to placebo was much less dramatic in the first month and remained at low levels over the course of the study. The difference between MiraLAX and placebo at each month was statistically significant ($p<0.001$). Similar to Figure 2 which described the percentage of successfully treated patients (not meeting the ROME criteria for constipation), Figure 3 reveals there was no evidence of tachyphylaxis associated with long term MiraLAX treatment.



10.1.4

Drug-Dose Response:

10.1.5 As shown below in Table XX, no significant changes in dose were observed over the course of the study for either the MiraLAX or placebo patients.

Table XX: Treatment Dose by Month

Study Month	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
MiraLAX						
N	172	158	146	135	135	127
Mean	16.4	16.2	16.2	16.2	16.2	16.2
SD	2.3	2.5	2.6	2.5	2.6	2.6
Placebo						
N	72	62	53	45	43	43
Mean	16.9	16.9	17.0	17.0	17.0	17.0
SD	1.0	1.1	0.0	0.0	0.0	0.0

Reviewer's Table, modified from sponsor's Table CR1-9, Protocol 851-CR1, page 41

10.1.6 **The table above indicates that there was no tachyphylaxis or increase in sensitivity (resulting in dose reduction) in continuing patients associated with MiraLAX use.**

10.1.7 Reviewer's summary and comments on Protocol 851-CR1

This multi-center study compared MiraLAX to placebo in a double-blinded, randomized trial of constipated adult-patients with at least a three month history of constipation by ROME criteria. Patients were randomized in a 2:1 ratio to either 17 grams of MiraLAX or placebo daily.

The total number of subjects in the Intent-To-Treat (ITT) population in this study (n = 304) was adequate for evaluation. Of the 304 treated subjects, 75 (24.7%) were elderly (≥ 65), 258 (85%) were female, and 84% were Caucasian. The MiraLAX and placebo treatment groups were similar with respect to age, racial distribution, weight, and constipation history. Patient compliance with study medication administration averaged about 88%.

The primary measure of efficacy used a binary outcome of overall treatment success (responder) or failure (non-responder) where overall treatment success was defined as a 0.50 or greater rate of successful treatment weeks to weeks of actual treatment. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative.

The primary responder analysis for the ITT population showed a highly statistically significant difference (41%; p<0.001) in successful patient treatment response between MiraLAX (52%) and placebo (11%) over the six month study period. The elderly subpopulation demonstrated similar statistically significant results in favor of MiraLAX with a 46% (p<0.001) difference in treatment response between MiraLAX (59%) and placebo (13%). Gender and race did not seem to influence the efficacy variables. Both males and females significantly improved on MiraLAX relative to placebo, similar to the general study population. The difference for males was (39%, p = 0.007) and the difference for females was (41%, p <0.001). Caucasian as well as Non-Caucasian subjects significantly improved on MiraLAX relative to placebo with response differences of (41%, p <0.001) and (45%, p = 0.014), respectively.

A secondary efficacy analysis for "super efficacy" was also performed. According to this definition of success, a successful treatment week was on where the patient had 3 or more satisfactory bowel movements and no other ROME symptoms, without the aid of rescue medication or prohibited laxatives. By this measure, MiraLAX treated patients experienced 47% of their treatment weeks as successful versus 14% of placebo patients (p<0.001). Another secondary efficacy analysis also revealed statistical significance in favor of MiraLAX. MiraLAX patients achieved on average one bowel movement per day, nearly double the number of "satisfactory BM" per week (about 5.4) as compared to placebo (about 2.7, p <0.001). The results are also mirrored in the "Global Assessment of Efficacy" where patients taking MiraLAX noted that 64% of their treatment weeks were satisfactory as compared to 34% of placebo treatment weeks (p<0.001).

STUDY 851-ZCC

Title: MiraLAX™ vs. ZELNORM® IN TREATMENT OF PATIENTS WITH CHRONIC CONSTIPATION

10.1.8 Objectives

The objective of this study was to evaluate the safety and efficacy of use of MiraLAX laxative as compared to Zelnorm in patients with constipation.

Study Design

This was an open-label, parallel treatment design study in which MiraLAX laxative (17 g QD) and Zelnorm (6 mg BID) were compared in randomized, constipated patients for up to 28 days. Patients were instructed to take their study drug according to the approved product label. Patients were also allowed the use of bisacodyl 5 mg tablets as rescue medication and were instructed to take 10 mg bisacodyl (2 tablets) if they experienced severe discomfort due to their constipation, or if they had not had a BM in 4 days.

Two-hundred thirty-nine male and female patients that met a definition of constipation and all other entry criteria were enrolled and randomized to treatment by a computer generated

randomization scheme. Two patients were randomized in error by study personnel and did not receive study medication, thus were not included in the Intent-t-Treat (ITT) population. Of the 237 ITT patients, 31 were 65 years of age or older.

Patients called into an Interactive Voice Response System (IVRS) each day to report their bowel movement (BM) experiences for that day and answered questions related to the study efficacy and safety criteria.

No safety, data monitoring, or special steering or evaluation committees were formed or met during the study period. Additionally, no interim analysis was performed.

Statistical Methods of Analysis:

The primary analysis group was based upon an intent-to-treat (ITT) analysis and included all patients randomized and receiving any treatment. All patients in this group had a determination of overall treatment success (responders). The primary efficacy analysis was based on the primary efficacy endpoint of overall treatment success or failure determined for each patient.

The primary analysis for the between treatment comparison used the Cochran-Mantel-Haenszel (CMH) statistic stratified by site with no covariate adjustment. The difference was the weighted difference of responder rates between the MiraLAX group and the Zelnorm group. The weight for each site was proportional to the number of patients in each treatment group. Sites that recruited less than 20 ITT patients were pooled to form larger pseudo sites in order to maintain at least 20 ITT patients for each site in the (CMH) stratified analysis. To meet this requirement, pseudo sites were created by pooling individual sites within a pre-determined geographic region. The specifics of this pooling algorithm were defined prior to un-blinding the study data and included in a detailed statistical analysis plan.

Secondary efficacy endpoints defined in terms of successful treatment rates were analyzed using analysis of variance with factors for treatment group, pooled-site, and interaction between treatment group and pooled-site.

Treatment emergent adverse event rates were descriptively presented by body system, preferred term, severity, and relationship to treatment for each treatment group. Differences in adverse event rates between treatment groups were assessed using Fishers Exact Test.

Determination of Sample Size

The sample size calculation was based upon the normal approximation to the binomial distribution. Using the results from a previous study in which Zelnorm was compared to placebo in female patients with constipation predominant IBS, and taking into account potential laxative use, the overall treatment success rate for the Zelnorm group was expected to be approximately 40%. An absolute increase of 20 percentage points in overall treatment success with MiraLAX over Zelnorm (40 to 60%) was considered a clinically important improvement. Assuming a 40% Zelnorm response rate for overall treatment success, based on a two-sided chi-squared test, a

study size of 240 patients (120 MiraLAX and 120 Zelnorm) will have 80% power to detect a treatment difference of 20% at the two-sided significance level of 0.05.

Inclusion/Exclusion Criteria

Two hundred thirty seven (237) male and female patients that met an historical definition of constipation, but were otherwise in generally good health, were enrolled. No pre-treatment observational period to evaluate constipation status was performed.

Constipation was defined based on modified ROME definition: on average, for greater than the preceding 3 months, when not taking laxatives, the patients had:

A. Satisfactory stool less frequent than 3 per week, and
B. 1 or more of the following additional ROME based criteria
    a. Straining in more than 25% of defecations
    b. Lumpy or hard stools in more than 25% of defecations
    c. Sensation of incomplete evacuation in more than 25% of defecations

Other **inclusion criteria** were:

- On average, fewer than 3 satisfactory BMs per week during the14 day observation period.
- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so during the duration of study.
- Are otherwise in good health, as judged by a physical examination.
- In the investigator's judgment, patient is mentally competent to sign an instrument of informed consent.

Exclusion criteria: Patients who met any of the following criteria were excluded from the study:

- Patients with heme positive stool at screening
- Patients with hypo- or hyperthyroidism as determined by medical history.
- Patients with severe renal impairment.
- Patients with moderate or severe hepatic impairment.
- Patients with known or suspected perforation or obstruction.
- History of gastric retention, inflammatory bowel disease, bowel resection, or colostomy.
- Patients with symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions.
- Patients with a known history or organic cause for their constipation.
- Patients currently taking any of the following medications that are know to affect bowel habits:

a. Anti-diarrheals
b. Antacids containing magnesium or aluminum salts
c. Anticholinergics
d. Antispasmodic agents
e. Erythromycin and other macrolides
f. Octreotide
g. Lotronex, Zofran, or other 5-HT_3 antagonists
h. Zelnorm, or other 5-HT_4 agonists
i. Opioids/narcotic analgesics (occasional use of codeine is allowed if needed for a non-gastrointestinal indication)
j. Prokinetics
k. Serotonin re-uptake inhibitors or tricyclic antidepressants (allowable only if patient has been on a constant dose for one month prior to screening)
l. Calcium antagonists (allowable only if patient has been on a constant dose for one month prior to screening)

- Patients who are breastfeeding, pregnant, or intend to become pregnant during the study.
- Female patients of childbearing potential who refuse a pregnancy test.
- Patients who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures.
- Patients who, within the past 30 days have participated in an investigational clinical study.
- Patients that have undergone a colonoscopy within 30 days of screening.
- Patients that are currently taking, or have previously been treated with MiraLAX or Zelnorm.

Medical Officer's Comment:
This protocol did not include the following exclusion criteria:

- *Loose stools are present, and there is sufficient criteria for IBS:*
  At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that two or three features:
  d. Relieved with defecation; and/or
  e. Onset associated with a change in frequency of stool; and/or
  f. Onset associated with a change in form (appearance) of stool.
- *Patients with a known allergy to corn or polyethylene glycol.*

Changes in the Study Plan

PROTOCOL AMENDMENT 1 (04/27/2004)

- ***Amendment 1 occurred prior to enrollment and addressed the following issues: Dose increases in medication were disallowed; reporting timeframes for adverse events and serious adverse events were added; guidelines for handling patients experiencing diarrhea were added; an accepted visit window for visit 2 was added; drug dispensation procedures were clarified; supporting information for planned statistical analyses was***

added; clarification was added that blood draws for laboratory analysis were not to performed.

PROTOCOL AMENDMENT 2 (06/10/2004)

- ***Amendment 2 occurred after commencement of enrollment and clarified a prior diagnosis of IBS were to be excluded from the study. This included patients with constipation predominant IBS.***

PROTOCOL AMENDMENT 3 (07/23/2004)

- ***Amendment 3 was implemented following the Agency's 14 July 2004 Advisory Committee which recommended that the approval of Zelnorm for chronic constipation be limited to females under the age of 65. The protocol inclusion criteria were modified to exclude patients who were elderly or male. Male or elderly patients enrolled prior to the approval of this amendment were allowed to complete the study.***

Demography and Disease History

A total of 237 patients were enrolled and received treatment (Intent-to-treat population; ITT) at a total of 25 centers. Of the 237 total patients, 31 were elderly. The majority of enrollees in this study were female (213, 90%). Twenty-four (10%) males were enrolled. The sponsor notes that this gender disparity is consistent with previous constipation studies and with the overall demographics of constipation. In addition, male patients were specifically excluded by protocol amendment 3. The average age of study participants was 46 years, ranging from 19 to 81 years of age. Elderly patients were specifically excluded following the approval of protocol amendment 3. The average duration of constipation reported by all patients was 17.5 years. About 64% of study enrollees were Caucasian, 24% were African American, and 13% were Hispanic or Latino ethnicity. The sponsor notes that the percentage of African American patients is higher than the national average, which can be attributed to the geographic location of study centers. Study patients weighed an average of about 76 kg. There were no demographic related, statistically significant differences between the treatment groups.

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Table XX: Study Demographics

	MiraLAX		Zelnorm		
	All	Younger (<65 y)	All	Younger (<65 y)	p[1]
Age (years)[2]					
n	120	103	117	103	0.75
Mean (SD)	46.1 (14.4)	42.2 (11.5)	46.9 (14.5)	43.5 (11.7)	
Gender n (%)					
Female	109 (91)	96 (93)	104 (89)	93 (90)	0.59
Male	11 (9)	7 (7)	13 (11)	10 (10)	
Race n (%)					
Caucasian	72 (60)	57(55)	79 (68)	66 (64)	
A.Amer.	31 (26)	29 (28)	26 (22)	25 (24)	0.766
Other	5 (4)	5 (5)	5 (4)	5 (4)	
Missing	12 (10)	12 (12)	7 (6)	7 (7)	
Ethnicity n (%)					
Hispanic	18 (15)	18 (17)	13 (11)	13 (13)	0.328
Non-Hispanic	102 (85)	85 (83)	103 (88)	89 (86)	
Missing	0	0	1 (1)	1 (1)	
Weight (kg)					
Mean (SD)	77.0 (14.2)	77.8 (23.6)	75.8 (18.3)	75.4 (18.4)	0.68
Constipation Hx (yrs)					
Mean (SD)	16.2 (14.2)	15.4 (13.6)	18.9 (18.2)	16.7 (15.6)	0.27

Reviewer's Table, modified from Sponsor's Table ZCC-2, Protocol 851-ZCC, page 25

1. P-Value from CMH test controlling for pooled site for the categorical variables, and from an ANOVA with terms for pooled site and treatment for the continuous variables.
2. Age is calculated using date of birth and screening visit (Visit 1) date.

SD = Standard Deviation; kg = kilograms; A.Amer. = African American

Patient Disposition

Of the 237 total patients who were enrolled and received treatment (ITT) in this study, 203 patients completed all 4 weeks of the study. The reasons for discontinuation are given below in Table XX.

Table XX: Reasons for Patient Discontinuation

	MiraLAX % (n)	Zelnorm% (n)
Completing Patients	106 (88.3)	97 (82.9)
Patients Discontinued	14 (11.7)	20 (17.1)
Reasons:		
Patient withdrew consent	6 (5.0)	7 (6.0)
Lack of efficacy	1 (0.8)	1 (0.9)
Non-compliance	4 (3.3)	4 (3.4)
Lost to follow-up	3 (2.5)	3 (2.6)
Adverse Event	0 (0)	5 (4.3)

Reviewer's Table, modified from sponsor's Table ZCC-1, Protocol 851-ZCC, page 23

As noted above in Table XX, the percentage of completing patients between the two subgroups (MiraLAX and Zelnorm) was similar. There were more patients discontinuing from the Zelnorm cohort (17.1%, MiraLAX versus Zelnorm, 11.7%), with Adverse Events having the largest discrepancy between the cohorts (4.3%, Zelnorm versus 0% for MiraLAX).

Compliance

Patients returned after 4 weeks to their study center where study drug and rescue medications were reviewed for treatment compliance. Patients were allowed use of rescue bisacodyl (10 mg) if they experienced severe constipation discomfort; however their study drug dose could not be increased.

Compliance for each patient was calculated based on the number of packets or tablets of study medication returned at each study visit divided by the number of treatment days between visits. Overall, treatment compliance was comparable between the two subgroups with 94% for MiraLAX and 91% for Zelnorm patients (based on drug accountability). Eight MiraLAX patients (7%) had a compliance level of less than 80%; Eighteen Zelnorm patients (15%) had a compliance level of less than 80%.

10.1.9 Efficacy Results

Data Sets Analyzed

All patients enrolled that received at least on dose of study medication were included in the analysis. Two patients (142-002 and 151-003) were randomized into the IVRS in error by the study coordinator. Neither patient was dispensed study medication; therefore they are not included in the analysis.

Primary Efficacy Endpoint

The primary efficacy variable for treatment response was assessed on the basis of binary outcome of overall treatment success (responder) or failure (non-responder) where:

1. Overall treatment success was defined as 0.50 or greater rate of successful treatment weeks to weeks of actual treatment.
2. A successful treatment week was defined as $\geq$ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative:
    m. Straining in more than 25% of defecations
    n. Lumpy or hard stools in more than 25% of defecations
    o. Sensation of incomplete evacuation in more than 25% of defecations
3. Patients who received fewer than 2 weeks of active treatment for any reason were classified as overall treatment failures.

As noted below in Table XX, overall, there was a statistically significant 19.2% difference (p = 0.003) in the overall treatment success (responder) for patients treated with MiraLAX compared to Zelnorm. There was also a statistically significant 15.6% difference (p = 0.032) in response favoring MiraLAX when analyzing non-elderly (<65 year old) patients.

Table XX: Primary Efficacy Responder Analysis: Number and Percent of Successfully Treated Patients

Responder	MiraLAX n (%)	Zelnorm n (%)	95% CI[1]	P[2]
All Patients (n)	120	117		
Yes	60 (50.0)	36 (30.8)	7.0, 31.5	**0.003**
No	60 (50.0)	81 (69.2)		
Non Elderly (<65 y)	103	103		
Yes	49 (47.6)	33 (32.0)	2.3, 28.7	**0.032**
No	54 (52.4)	70 (68.0)		

Reviewer's Table, modified from sponsor's Table ZCC-3, Protocol 851-ZCC, page 27

1. Confidence interval (CI) for the difference between MiraLAX and Zelnorm is from a Cochran-Mantel-Haenzsel test.
2. P-value for the difference between MiraLAX and Zelnorm is from a pooled site stratified Cochran-Mantel- Haenzsel test.

For this study, centers were pooled into 8 geographic areas (composed of about 20 to 45 patients each) and individually analyzed for the primary efficacy variable. This analysis, shown below in Table XX, reveals that in 7 of 8 geographic regions, MiraLAX had a better response than Zelnorm. Only in the region Carolinas was the favorable response for MiraLAX over Zelnorm statistically significant.

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Table XX: Responder Analysis by Geographic Region

Region	Responder	MiraLAX (N=120) n (%)	Zelnorm (N=117) n (%)	95% CI[1]	P[1]
West	Yes No	4 (36.4) 7 (63.6)	3 (23.1) 10 (76.9)	-23, 49.8	0.659
Atlantic	Yes No	7 (58.3) 5 (41.7)	2 (18.2) 9 (81.8)	4.1, 76.2	0.089
Florida	Yes No	3 (25.0) 9 (75.0)	4 (36.4) 7 (63.6)	-49, 26.2	0.667
Carolinas	Yes No	11 (50.0) 11 (50.0)	3 (14.3) 18 (63.6)	10.0, 61.4	**0.022**
Texas	Yes No	11 (55.0) 9 (45.0)	9 (45.0) 11 (55.0)	-21, 40.8	0.752
South/Midwest	Yes No	6 (40.0) 9 (60.0)	5(35.7) 9 (64.3)	-31, 39.6	1.000
Boston, MA	Yes No	10 (62.5) 6 (37.5)	5 (35.7) 10 (66.7	-4.5, 62.8	0.156
Anaheim, CA	Yes No	8 (66.7) 4 (33.3)	5 (41.7) 7 (58.3)	-14, 63.6	0.414

Reviewer's Table, modified from sponsor's Table ZCC-4, Protocol 851-ZCC, page 28

1. Confidence interval (CI) for the difference between MiraLAX and Zelnorm are from a Fisher's Exact test.

Figure 1 below shows the proportion (as percent) of successfully treated patients, according to the primary efficacy definition, for each week of the study for both treatments. As noted below, MiraLAX treatment resulted in an increase in the number of successfully treated patients over the four weeks of therapy (to 50%). The difference in successfully treated patients between the MiraLAX and Zelnorm groups reached statistical significance by Week 2 and remained significant through Week 4.

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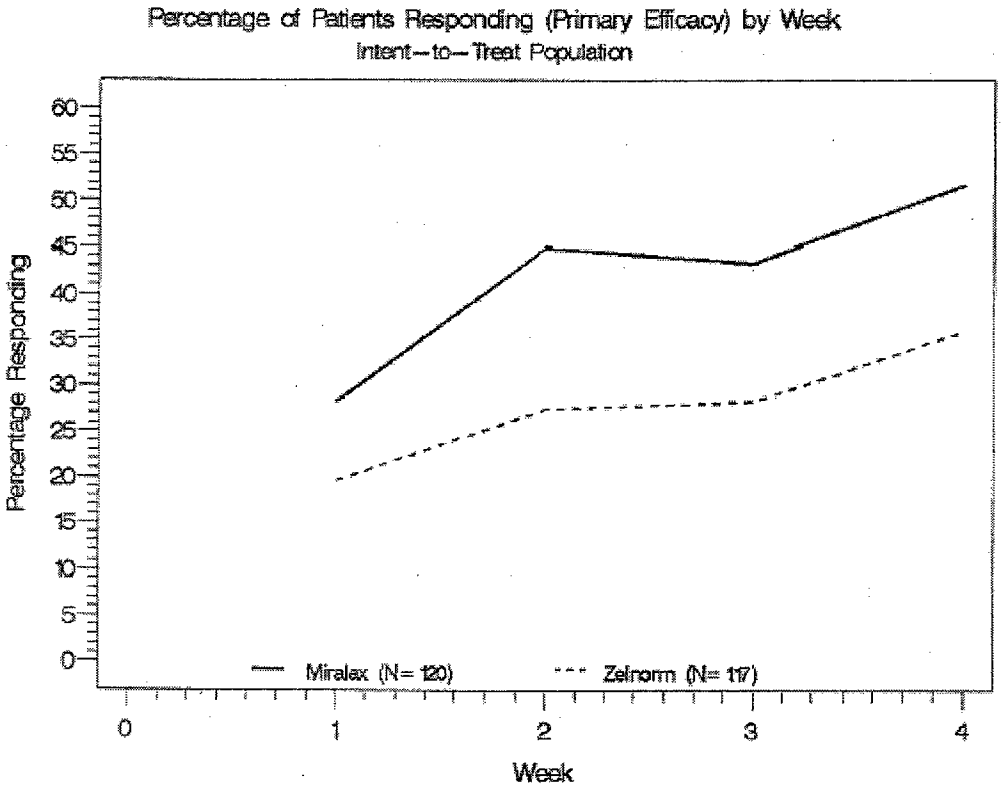
Figure 1: Percentage of Patients Responding (Primary Efficacy) by Week (ITT-Population)



The percent of patients responding to therapy by week for the primary efficacy measure is shown above. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME symptom criteria without the aid of rescue medication or prohibited laxative. A Weeks 2 through 4, the difference was statistically significant (p = 0.005, 0.0015, 0.015, respectively).

Secondary Efficacy Endpoints

Secondary efficacy endpoints included assessment of ROME Definition for each treatment week and Super Efficacy (weeks where patients do not meet any of the four ROME symptom criteria).

Table XX below demonstrates that the observed difference in efficacy seen in the primary efficacy endpoint persists for the analysis by ROME definition as well as when a definition of Super Efficacy is applied.

Table XX: Secondary Endpoint Analyses; Number of Successful Weeks

Responder Definition	MiraLAX n = 120	Zelnorm n = 117	P[1]
Primary Definition[2] Mean (SD)	1.79 (1.51)	1.19 (1.36)	**0.003**
ROME[3] Mean (SD)	1.84 (1.53)	1.28 (1.35)	**0.006**
Super Efficacy[4] Mean (SD)	1.09 (1.35)	0.71 (1.12)	**0.028**

Reviewer's Table, modified from sponsor's Table ZCC-5, Protocol 851-ZCC, page 30

1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled site interaction.
2. ≥3 satisfactory bowel movements, with 1 or no additional ROME symptom criteria, and without the aid of rescue medication or prohibited laxative during the week.
3. ROME definition not met without aid of rescue medication.
4. No ROME symptom criteria met, without aid of rescue medication.

SD = Standard Deviation.

As shown in the table above, the number of successful weeks when applying the primary responder definition was highly statistically significant (p=0.003) in favor of MiraLAX. This statistically significant success response persisted when both groups were analyzed using the clinically accepted ROME definition (p=0.006). Although there were fewer successful Super Efficacy treatment weeks for both therapies due to the more strict definition which required that a successful treatment week could have none of the four individual ROME constipation symptom criteria, there were still more successful treatment weeks in favor of MiraLAX. Table XX below indicates the number of successful treatment weeks for each of the four individual ROME symptom criteria. The table entries indicate weeks where the ROME constipation symptom was not met (i.e. a successful treatment week).

Table XX: Individual ROME Symptoms – Number of Successful Weeks

Responder Definition[2]	MiraLAX N = 120	Zelnorm N = 117	p[1]
ROME #1 <3 Satis. BM Mean (SD)	2.43 (1.6)	2.39 (1.5)	0.703
ROME #2 Strain >25% (n) Mean (SD)	1.78 (1.6)	1.37 (1.4)	0.065
ROME #3 Hard Stool >25% Mean (SD)	2.13 (1.5)	1.47 (1.4)	**0.001**
ROME #4 Incomplete >25% Mean (SD)	1.37 (1.6)	1.23 (1.4)	0.448

Reviewer's Table, modified from sponsor's Table CR1-7, Protocol 851-CR1, page 35

1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled-site interaction
2. Specific ROME symptom not met, without aid of rescue medication.

As shown above in Table XX, the difference in stool consistency (lumpy/hard stools) between MiraLAX and Zelnorm was statistically significant (p=0.001). The differences in BM frequency, incomplete evacuation, and straining all favored MiraLAX, however none were statistically significant.

Table XX: Additional Secondary Efficacy Analyses

Responder Definition[2]	MiraLAX	Zelnorm	p[1]
Mean BM/week (n) Mean (SD)	118 10.42 (7.7)	116 8.48 (4.9)	**0.019**
Mean Satisfactory BM/wk (n) Mean (SD)	118 7.09 (5.7)	116 5.84 (4.3)	0.072
Mean CSBM/wk[2] Mean (SD)	118 5.56 (5.2)	116 4.80 (4.2)	0.162
Global Assess.[3] Mean weeks (SD)	118 1.95 (1.4)	116 1.63 (1.3)	0.081
Rescue Med Use Mean tabs/wk (SD)	102 1.40 (3.4)	93 1.00 (2.3)	0.268

Reviewer's Table, modified from sponsor's Table ZCC-7, Protocol 851-ZCC, page 33
1. P-Value from an ANOVA with terms for treatment, pooled-site, and treatment by pooled-site interaction
2. CSBM = Complete, Spontaneous BM, without aid of rescue medication
3. Number of weeks that patients indicated that they had adequate relief

SD = Standard Deviation

Table XX above shows a statistically significant difference between MiraLAX and Zelnorm in the total number of bowel movements (BM) per week. The MiraLAX subgroup had a mean of 10.42 BM/week and the Zelnorm subgroup had a mean of 8.48 BM/week (p=0.019). As noted above, all other BM related measured favored MiraLAX; however these were not significantly significant. The number of rescue medication tablets used per week was not significantly different between treatment groups. Of importance though is that most MiraLAX patients who did not use rescue medication experienced a bowel movement within the first three days of treatment. Table XX below graphically depicts this cumulative incidence.

Table XX: Cumulative Percentage of Patients with BM in the First Treatment Week MiraLAX Patients with no Rescue Med Use

N	Day 1	Day 2	Day 3
96	54.2% (52)	78.1% (75)	89.6% (86)

Reviewer's Table, modified from sponsor's Table CR1-ZCC-8, Protocol 851-ZCC, page 33

As noted above in Table XX, approximately 90% of subjects taking MiraLAX had a BM within 3 days of treatment without the aid of rescue medication.

Figure 2 below shows the proportion (as percent) of successfully treated patients assessed by the ROME Definition for each week of the study for both treatments. According to this definition, a successful treatment week was defined as a patient reporting no more than 1 ROME symptom criterion, without the aid of rescue medication or prohibited laxative. The ROME symptoms for constipation are:

a. <3 satisfactory bowel movements per week
b. Straining in more than 25% of defecations
c. Lumpy or hard stools in more than 25% of defecations
d. Sensation of incomplete evacuation in more than 25% of defecations.

As evident in the figure below, MiraLAX treatment resulted in an increase in the number of successfully treated patients during the four week treatment period. A statistically significant difference favoring MiraLAX was achieved at Week 2 and persisted through Week 4 (p=0.011, 0.047, 0.022, respectively).

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Figure 2: Percentage of Patients Not Meeting Rome Definition of Constipation (ITT)

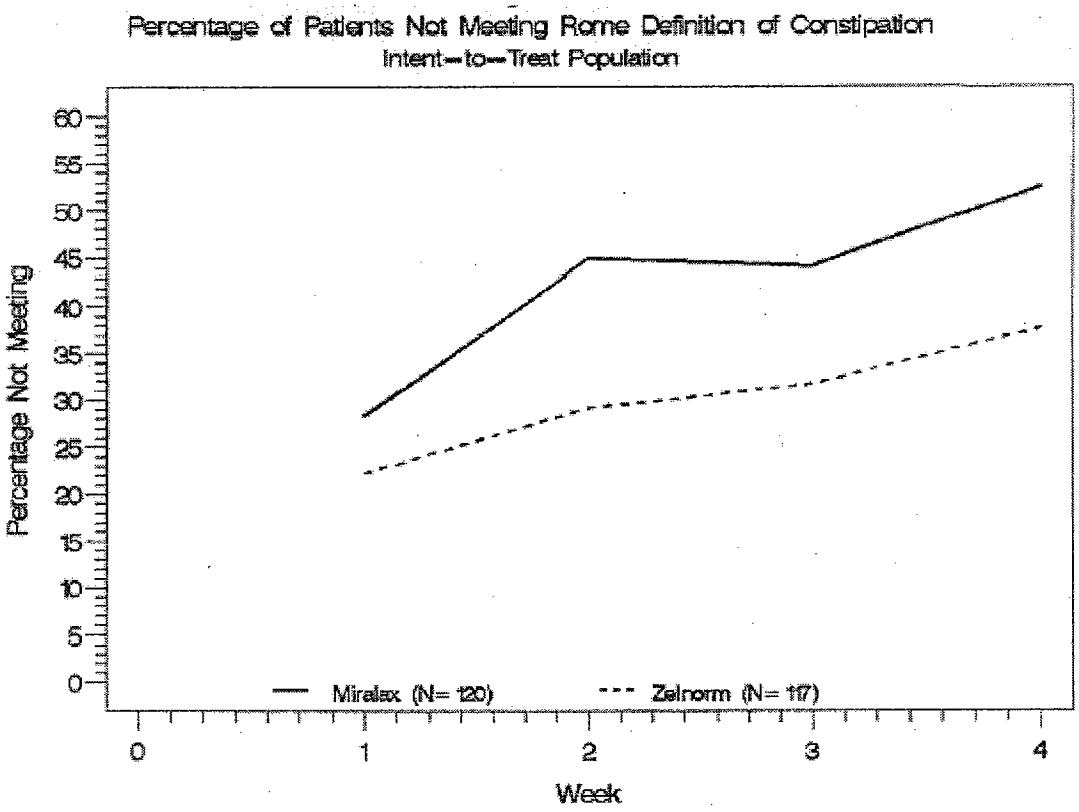

Figure 3 below shows the proportion (as percent) of successfully treated patients using the more stringent Super Efficacy definition. According to this definition, a successful treatment week was defined as a patient reporting no more than 1 ROME symptom criterion, without the aid of rescue medication or prohibited laxative. A statistically significant difference was seen for weeks 3 and 4 only (p=0.019 and p=0.023, respectively).

Figure 3: Percentage of Patients Not Meeting Super Efficacy Definition by Week (ITT)

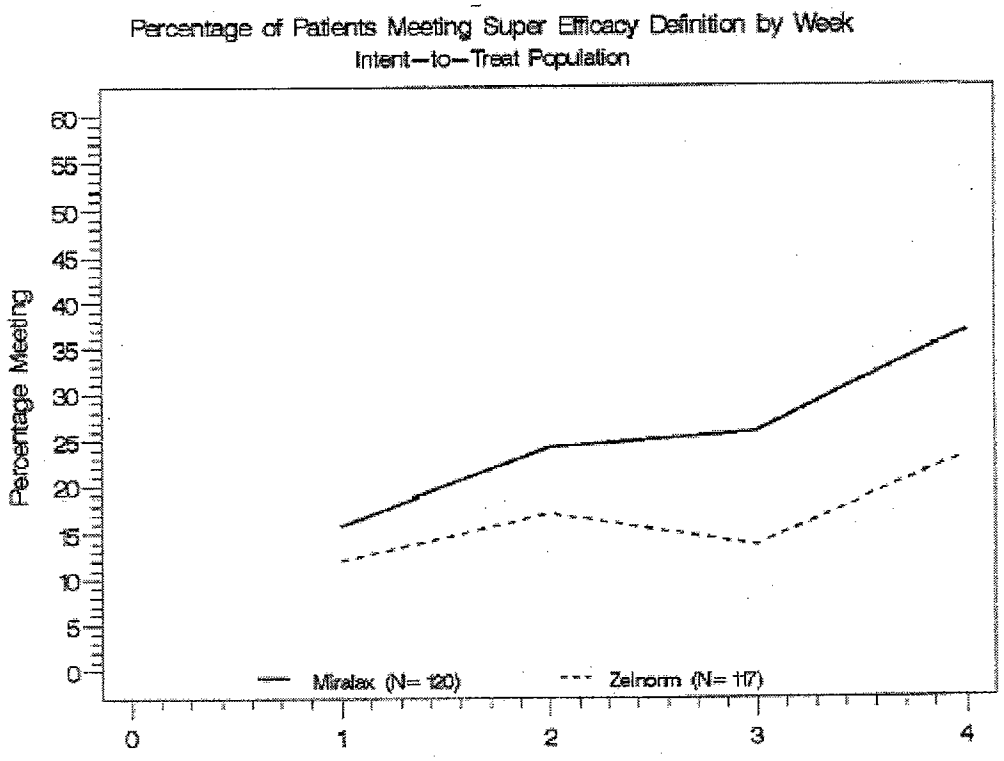

Table XX below is a summary of patient reported outcomes that were collected using the Patient Assessment of Constipation Symptoms (PAC-SYM) and Quality of Life (PAC-QOL) questionnaires administered at baseline and end of study. There was no baseline difference between groups in terms of patient reported Abdominal Symptoms, Rectal Symptoms, Stool Symptoms, or Overall using the PAC-SYM.

As noted below in Table XX, MiraLAX showed a statistically significant improvement over Zelnorm in the following end of study patient symptom questionnaire questions: stomach cramps, bowel movements that were too hard, and straining or squeezing to try to pass bowel movements. No patient reported measures were statistically significant in favor of Zelnorm.

Table XX: Patient Assessment of Constipation Symptom Questionnaire

Symptom[1] How severe have each of these symptoms been in the last two weeks?	MiraLAX mean[2](SD) n	Zelnorm mean (SD) n	p[3]
1. Discomfort in your abdomen?	0.81 (0.73) 108	0.88 (0.88) 105	0.822
2. Pain in your abdomen?	0.50 (0.74) 108	0.56 (0.84) 105	0.684
3. Bloating in your abdomen?	1.16 (0.96) 108	1.10 (1.03) 105	0.623
4. Stomach cramps?	0.69 (0.78) 108	0.93 (0.86) 105	**0.048**
5. Painful bowel movements?	0.50 (0.79) 108	0.58 (0.73) 105	0.361
6. Rectal burning during or after a bowel movement?	0.31 (0.66) 108	0.42 (0.76) 105	0.399
7. Rectal bleeding or tearing after a bowel movement?	0.10 (0.43) 108	0.12 (0.38) 105	0.976
8. Incomplete bowel movements, like you didn't finish?	1.26 (0.97) 108	1.43 (1.12) 105	0.133
9. Bowel movements that were too hard?	0.35 (0.73) 108	0.81 (0.93) 105	**<0.001**
10. Bowel movements that were too small?	1.22 (1.03) 108	1.14 (1.05) 105	0.885
11. Straining or squeezing to try to pass bowel movements?	0.86 (0.98) 108	1.24 (1.17) 105	**0.013**
12. Feeling like you had to pass a bowel movement but you couldn't (false alarm)?	0.75 (0.93) 108	1.00 (1.19) 105	0.103

Reviewer's Table, modified from sponsor's Table CR1-ZCC-9, Protocol 851-ZCC, page 39

1. Symptoms scored on a 0 to 4 scale: 0=Absent, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe
2. Means are based on non-missing items. (n) is based on patients completing the questionnaire.
3. P-value from an ANOVA with factors for treatment, pooled site, and their interaction.

With respect to the change in statues from baseline, MiraLAX revealed statistically significant improvement over Zelnorm in the Overall Mean, p=0.016, the Rectal Symptoms Mean, p=0.026, and the Stool Symptoms Mean, p=0.005. As noted below the Abdominal Symptoms Mean was not statistically significant, and no patient reported measures were statistically significant in favor of Zelnorm.

Differences in PAC-QOL scores between groups were not statistically different at baseline or at end of study.

Symptom[1]	MiraLAX	Zelnorm	p[3]
Change from Baseline to End of Study	mean[2](SD) n	mean (SD) n	-
Overall Mean (Items 1-12)	-1.13 (0.79) 107	-0.88 (0.74) 103	**0.016**
Abdominal Symptoms Mean (Items 1-4)	0.78 (0.85) 107	-0.74 (0.80) 103	0.655
Rectal Symptoms Mean (Items 5-7)	-0.90 (0.99) 107	-0.64 (0.77) 103	**0.026**
Stool Symptoms Mean (Items 8-12)	-1.54 (1.06) 107	-1.13 (0.73) 103	**0.005**

Reviewer's Table, modified from sponsor's Table CR1-ZCC-10, Protocol 851-ZCC, page 40

10.1.10 Reviewer's summary and comments on Protocol 851-ZCC

The total number of constipated subjects enrolled and treated in the Intent-To-Treat (ITT) population over a four week period was (n = 237). Of the 237 treated subjects, 120 patients were treated with MiraLAX. Thirty-one (31), 13.1% of the 237 total subjects were elderly (≥ 65 years of age), 213, 90% were female, and 64% were Caucasian. The average age of the study participants was 47 years. The sponsor noted that there were no other demographic related, statistically significant differences between the MiraLAX and Zelnorm treatment groups.

The primary efficacy analysis was based on a binary outcome of overall treatment success (responder) or failure (non-responder) where overall treatment success was defined as a 0.50 or greater rate of successful treatment weeks to weeks of actual treatment. A successful treatment week was defined as ≥ 3 satisfactory bowel movements with no more than 1 additional ROME constipation symptom criterion without the aid of rescue medication or prohibited laxative.

The primary responder analysis for the ITT population showed a statistically significant 19% difference (p=0.003) in successful patient treatment response favoring MiraLAX over Zelnorm. Thus, 50% of patients vs. 30.8% of Zelnorm patients were successfully treated over the 4 week study period, according to this definition. When analyzing only the non-elderly population for which Zelnorm is currently approved, the statistically significant effect persists (p=0.032), where 16% more MiraLAX patients were successfully treated (48% vs. 32%), MiraLAX vs. Zelnorm, respectively.

Some of the results from the secondary efficacy analyses also revealed statistical significance showing MiraLAX superiority. A review of individual treatment weeks showed that when using the study definitions of successful treatment based on the primary endpoint definition, and the clinically accepted ROME Definition, statistical significance was reached in favor of MiraLAX at Week 2 and continued through Week 4. When the Super Efficacy Definition was applied (no ROME criteria; the complete absence of constipation symptoms), MiraLAX achieved statistically significant superiority in response at Weeks 3 and 4. A review of the individual ROME symptom criteria by week (mean number of successful weeks) shows that the two main

factors contributing to the superior efficacy of MiraLAX are improved stool consistency (p=0.001) and straining (p=0.065). MiraLAX patients experienced a greater number of bowel movements (BMs) per week compared to Zelnorm (10.42 vs. 8.48, respectively, p=0.019) and most experienced a bowel movement within one to three days after starting treatment. In addition, BMs reported by the MiraLAX group were less lumpy/hard compared to those experienced by the Zelnorm group (31% difference, p=0.001).

Only certain patient reported constipation symptoms (PAC-SYM) at the end of the study supported the aforementioned results. Stool Symptoms (including consistency and straining) were statistically superior in favor of MiraLAX (p=0.02) with a corresponding difference of 20%. When analyzing the improvement from baseline, MiraLAX again revealed efficacy over Zelnorm with statistical significance in Stool Symptom, Rectal Symptom, and Overall Symptom measures.

Overall, while MiraLAX and Zelnorm are both approved for the treatment of constipation, this study demonstrated that MiraLAX is more effective than Zelnorm in treating constipation over a four week period.

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STUDY 851-CR3

Title: AN OPEN LABEL STUDY OF CHRONIC MIRALAX USE IN CONSTIPATED PATIENTS, Braintree Protocol 851-CR3

10.1.11 Objectives

The objective of this study was to evaluate the safety of extended (1 year) use of MiraLAX laxative in constipated patients, including a subgroup of elderly patients.

Study Design:

This was an open-label, Phase 4, single treatment, multi-center study in which normal, constipated patients were enrolled to receive MiraLAX laxative for up to 12 months. Patients were provided with MiraLAX in 527 gram bottles and instructed to dispense one capful of the contents (approximately 17 grams) of MiraLAX and mix with 8 oz. of juice or other beverage, and take once daily. Bisacodyl tablets (5mg) were allowed as rescue medication. Patients were instructed to take 10 mg of bisacodyl if they experienced severe discomfort due to their constipation, or did not have a bowel movement in 4 days.

Male and female patients that met the protocol definition of constipation, but who were otherwise in generally good health, were enrolled. Of these patients, about 100 were expected to be 65 years of age or older.

Patients returned to their study center at months 2, 4, 6, 9, and 12, where blood and urine samples were collected and adverse events were reviewed. During these visits, study drug and rescue medications were also reviewed for treatment compliance. At each follow-up visit, patients were queried for ROME criteria, and rated their overall improvement using a global efficacy scale.

No safety, data monitoring or special steering or evaluation committees were formed or met during the study period. No interim analysis was performed.

Three hundred and eleven patients were evaluated in up to 50 centers in this study. Of the 311 patients, 117 elderly patients ($\geq$ 65 years of age) were treated for up to one year, with at least 2 geriatric patients per study center.

Table XX is a tabulated version of the study procedures.

Table XX: Tabulated Study Procedures

Procedure	Visit 1 Day 0	Visit 2 Month 2	Visit 3 Month 4	Visit 4 Month 6	Visit 5 Month 9	Visit 6 Month 12
Informed Consent	X					
Medical History	X					
Physical Exam	X					X
Pregnancy Test (if female)	X					
Constipation Status	X	X	X	X	X	X
ConMed Review	X	X	X	X	X	X
Lab Testing	X	X	X	X	X	X
Instruct Patient	X	X	X	X	X	
Dispense Study Drug	X	X	X	X	X	
Study Drug Accountability		X	X	X	X	X
Dispense Rescue Medication	X					
Rescue Med Accountability		X	X	X	X	X
Global Efficacy Assessment		X	X	X	X	X
Assess Safety (AE review)		X	X	X	X	

Reviewer's Table, modified from sponsor's Tabulated Study Procedure Table, Final Study Report, Protocol 851-CR3, page 15

Statistical Methods:

Information on global efficacy assessment, adverse events, and laboratory results was pooled across all sites and descriptively summarized by visits. The incidence of adverse events was summarized by severity and relationship to study drug. The summary tables included incidence estimates for overall body systems as well as for individual events within each body system. Adverse events resulting in treatment modifications or discontinuation were identified. Any increase in incidence of adverse events across visits were estimated and identified; the major

focus was a comparison in rates between the first 6 months of treatment versus the last 6 months of treatment. Results of laboratory tests were descriptively summarized based upon actual change from baseline for continuous assessments. In addition, shift tables were used to describe changes in lab tests between baseline and on treatment using normal range categories (low, normal, high). Global efficacy assessment categories were descriptively summarized by treatment visits. The major comparison was between the first and last six months of treatment. The primary analysis group was based upon an intent-to-treat (ITT) analysis and included all patients enrolled and receiving any treatment.

Global Efficacy Assessment (GEA):

The GEA question is summarized for each visit (Visits 2-6) by the number and percentage of patients in each of the five response categories.

"Consider how you felt since your last visit in regard to your constipation, in particular, your overall well being, number of bowel movements, consistency and completeness of your bowel movements, and symptoms of straining."

"Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms since your last visit (completely relieved, considerably relieved, unchanged, or worse)."

GEA responders are defined as patients that report "completely relieved" or "considerably relieved" to the GEA question.

ROME Constipation Assessment:

At each follow-up time point (Visits 2-6), patients were asked the following question:

"Since your last visit, have you experience the following:

- Less than 3 satisfactory bowel movements per week
- Straining in more than 25% of your bowel movements
- Lumpy or hard stool more than 25% of the time
- Sensation of incomplete evacuation following more than 25% of your bowel movements"

The response to the constipation assessment is summarized for each criterion by the number and percentage of subjects who responded "YES" to each criterion.

Responder analysis (ROME criteria):

A constipation responder is defined as a patient that has had three or more satisfactory bowel movements per week and had not indicated, "YES" to more than 1 of the three remaining ROME criteria. Missing patient data for a specified visit was classified as "Missing" and not as non-responder for the specified visit.

The number and the percentage of responders at each visit are presented in a tabular form and illustrated graphically.

Determination of Sample Size:

In order to detect adverse events that may increase in frequency or severity over time, 300 patients will be enrolled and treated with MiraLAX for a period of 12 months. This number of patients is sufficient to estimate an adverse event rate o 5% with a precision of ±3.0% based upon a 95% confidence interval using a normal approximation to the binomial distribution. Lower adverse event rates will be estimated with greater precision (less than ±3.0%) and higher adverse event rates will be estimated with less precision (greater than ±3.0%). For example adverse event rates of 10% will be estimated with a precision of ±4.2% and adverse event rates of 20% will be estimated with a precision of 5.5%.

Inclusion Criteria:

Patients will be admitted to the study if they are in generally good health:

- Male or female adult patients that met a definition of constipation at least 18 years of age
- Constipation was defined based on modified ROME definition: on average, for greater than the preceding 3 months, when not taking laxatives,

  A. Satisfactory stool less frequent than 3 per week, and
  B. 1 or more of the following additional ROME based criteria
     a. Straining in more than 25% of defecations
     b. Lumpy or hard stools in more than 25% of defecations
     c. Sensation of incomplete evacuation in more than 25% of defecations

Other inclusion criteria were:

- Are otherwise in good health, as judged by a physical examination.
- If female and of childbearing potential, patient must be surgically sterilized or using oral contraceptives, depot contraceptives, intrauterine device, or testifies that she is monogamous with a vasectomized partner, or practices abstinence and will continue to do so during the duration of study.
- In the investigator's judgment, patient is mentally competent to sign an instrument of informed consent

Exclusion Criteria:

Patients who met any of the following criteria were excluded from the study:

- Patients with heme positive stool at baseline exam
- Patients with hypo- or hyperthyroidism as determined by history, or screening Thyroid Stimulating Hormone (TSH) results.
- Patients with known or suspected perforation or obstruction
- History of gastric retention, inflammatory bowel disease, bowel resection, or colostomy.
- Patients with a known history or organic cause for their constipation.
- Loose stools are present, and there is sufficient criteria for Irritable Bowel Syndrome (IBS):

  At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two or three features:
  a. Relieved with defecation; and/or
  b. Onset associated with a change in frequency of stool; and/or
  c. Onset associated with a change in form (appearance) of stool.
- Patients currently taking any of the following medications that are know to affect bowel habits:
  d. Antidiarrheals
  e. Antacids containing magnesium or aluminum salts
  f. Anticholinergics Antidiarrheals
  g. Antispasmodic agents
  h. Erythromycin and other macrolides
  i. Octreotide
  j. Lotronex, Zofran, or other 5-HT_3 antagonists
  k. Zelnorm, or other 5-HT_4 agonists
  l. Opioids/narcotic analgesics (occasional use of codeine is allowed if needed for a non-gastrointestinal indication)
  m. Prokinetics
  n. Serotonin re-uptake inhibitors or tricyclic antidepressants (allowable only if patient has been on a constant dose for one month prior to screening)
  p. Calcium antagonists (allowable only if patient has been on a constant dose for one month prior to screening)

- Patients who are breastfeeding, pregnant, or intend to become pregnant during the study.
- Female patients of childbearing potential who refuse a pregnancy test.
- Patients with a known allergy to corn or polyethylene glycol.
- Patients who, in the opinion of the investigator, should not be included in the study for any reason, including inability to follow study procedures.
- Patients who, within the past 30 days have participated in an investigational clinical study.

Changes in the Study Plan

PROTOCOL AMENDMENT 2: (06/17/2003)

- ***Use of non-study laxatives or excluded medications is prohibited. Study personnel must document each occurrence on the case report form. In cases of excessive use, the investigator may discontinue the patient from the study due to lack of efficacy or non-compliance.***

PROTOCOL AMENDMENT 1: (09/29/2003):

- ***Patients with heme positive stool that can be attributed to hemorrhoids or anal fissures are eligible for inclusion.***
- ***Fiber supplements and herbal laxatives must be discontinued at screening. Any restricted medication or supplement taken during the study must be listed as a Concomitant Medication and [redacted]/Braintree should be notified to assess the continuing inclusion of the patient.***

Patient Disposition

As noted above, this study was conducted in 50 different centers. A total of 335 patients enrolled with 311 patients included in the ITT population. Twenty-four patients did not meet study inclusion/exclusion criteria or otherwise failed screening. Three patients had a positive stool hemoccult and 21 had an abnormal TSH result upon baseline physical examination. Of the 311 ITT patients, 117 were ≥ to 65 years of age. One hundred and eighty four patients (59.2%) completed all 12 months of the study. The reasons for discontinuation are given below in Table XX.

Table XX: Reasons for Patient Discontinuation

Total Enrolled (n)	100 % (311)
Completing Patients	59% (184)
Patients Discontinued	41% (127)
Reasons:	
Patient withdrew consent	28% (35)
Lack of efficacy	10% (13)
Non-compliance	13% (16)
Lost to follow-up	31% (40)
Adverse Event	18% (23)

Reviewer's Table, modified from sponsor's Table CR3-1, Final Study Report, Protocol 851-CR3, page 22

As shown above, of the 311 enrolled patients, only 184 (59%) completed the study. One-hundred and twenty-seven (127, 41%) discontinued the study for various reasons including lack of efficacy (13, 10%), non-compliance (16, 13%), lost to follow-up (40, 31%) and adverse event (23, 18 %).

Demography and Disease History

As shown in Table XX below, the majority of patients (248, 80%) were female. Sixty-three of the total 311 enrolled patients (20%) were male. The sponsor notes that this gender disparity is consistent with previous constipation studies and with the overall demographics of constipation. The average age of study participants was 57 years, ranging from 19 to 95 years of age. Approximately 80% of the study enrollees were Caucasian and 16% were African American reflecting the national racial population distribution. The study population weighed an average of 77 kg.

Table XX: Study Demographics

Variable	All	Elderly (≥ 65 years)
Age (years)[1]		
n	311	117
Mean (SD)	56.9 (16.4)	73.9 (7.4)
Gender		
Female	248 (80%)	74 (63%)
Male	63 (20%)	43 (37%)
Race		
Caucasian	248 (80%)	105 (89%)
A. American	49 (16%)	9 (8%)
Other	4 (1%)	1 (1%)
Missing	10 (3%)	2 (2%)
Weight (kg)		
Mean (SD)	77.3 (17.6)	80.1 (20.1)
Constipation Hx		
years	17.9 (19.1)	21.9 (22.4)

Reviewer's Table, modified from sponsor's Table CR3-2, Final Study Report, Protocol 851-CR3, page 24
(1): Age is calculated using the date of birth and screening visit (Visit 1) date.
SD = standard deviation; kg = kilograms; A. American = African American

Measurements of Treatment Compliance

Patients returned to their study center every two or three months for follow-up visits, during which study drug and rescue medications were reviewed for treatment compliance. Patients were allowed use of rescue bisacodyl (10 mg) if they experience severe constipation discomfort; however their study drug dose could not be increased above 17 grams.

Compliance for each patient was calculated based on the number of bottles of study medication returned at each study visit divided by the number of treatment days between visits. The compliance values were then averaged to arrive at a single study compliance value for each patient. Overall, the mean treatment compliance for the study was 72.9% (SD=23.9%). Table XX above shows that following visit 2, study treatment compliance of continuing patients was about 80%.

Table XX: Study Medication Treatment Compliance by Visit – Continuing Patients

Compliance	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6/End of Study
Mean %	76.5%	79.4%	79.7%	80.0%	71.2%
SD	25.6	23.0	23.7	23.2	29.0
n	253	219	207	189	255

Reviewer's Table, modified from sponsor's Table CR3-3, Final Study Report, Protocol 851-CR3, page 26

Analysis of Efficacy Variables

This study was specifically designed for the collection of long-term safety data collection in the extended use of MiraLAX. Supportive efficacy assessments were performed, however; throughout the duration of the study.

Global Efficacy Assessment (GEA):

Global Efficacy Assessment (GEA) responders are defined as patients that reported "completely relieved" or "considerably relieved" to the GEA question at each visit.

The GEA question was summarized for each visit (Visits 2-6) by the number and percentage of patients in each of the five response categories.

> "*Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms since your last visit (completely relieved, considerably relieved, somewhat relieved, unchanged, or worse).*"

As shown below in Table XX, the responder analysis reveals that most of the treatment failures occurred prior to Visit 2. With respect to all enrolled patients (311), the proportion of responders remained relatively constant throughout the study period. At Visit 2 and thereafter, about 80% of participating patients reported a successful response to treatment at each subsequent visit. A similar pattern of treatment response (Table XX) was noted for elderly patients, male and female patients, and the non-Caucasian subgroups.

Table XX: Global Efficacy Responder Analysis: Number and Percent of Successfully Treated Patients by Visit

Responder N (%)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
All by Visit[2]	250	217	203	185	180
Yes	199 (80%)	177 (82%)	168 (83%)	163 (88%)	154 (85%)
No	51 (20%)	39 (18%)	35 (17%)	21 (11%)	21 (12%)
Missing	0	1 (0%)	0	1 (1%)	5 (3%)
All by Enroll[3]	311	311	311	311	311
Yes	199 (64%)	177 (57%)	168 (54%)	163 (52%)	154 (50%)
No	51 (16%)	39 (13%)	35 (11%)	21 (7%)	21 (7%)
Missing	0	1 (0.3%)	0	1 (0.3%)	5 (2%)
Elder by Visit[2]	98	98	85	82	79
Yes	86 (88%)	75 (84%)	76 (89%)	77 (94%)	74 (94%)
No	12 (12%)	13 (15%)	9 (11%)	4 (5%)	3 (4%)
Missing	0	1 (1%)	0	1 (1%)	2 (2%)
Elder Enroll[3]	117	117	117	117	117
Yes	86 (74%)	75 (64%)	76 (65%)	77 (66%)	74 (63%)
No	12 (10%)	13 (11%)	9 (8%)	4 (3%)	3 (3%)
Missing	0	1 (1%)	0	1 (1%)	2 (2%)
<65 by Visit[2]	152	128	118	103	101
Yes	113 (74%)	102 (80%)	92 (78%)	86 (83%)	80 (79%)
No	39 (26%)	26 (20%)	26 (22%)	17 (17%)	18 (18%)
Missing	0	0	0	0	3 (3%)
<65 by Enroll[3]	194	194	194	194	194
Yes	113 (58%)	102 (53%)	92 (47%)	86 (44%)	80 (41%)
No	39 (20%)	26 (13%)	26 (13%)	17 (9%)	18 (9%)
Missing	0	0	0	0	3 (2%)

Reviewer's Table, modified from sponsor's Table CR3-4A , Final Study Report, Protocol 851-CR3, page 25

(1) A responder is defined as a patient that reports "Completely Relieved" or "Considerably Relieved" to the Global Efficacy Assessment question.

(2) By Visit: Proportions calculated based on the actual number of patients completing each visit.

(3) By Enrolled: Proportions calculated based on patients initially enrolled (All=311, Elderly=117)

Table XX: Global Efficacy Responder Analysis: Number and Percent of Successfully Treated Patients by Visit

Responder[1] N (%)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Male by Visit[2]	53	43	41	38	35
Yes	42 (79%)	32 (8274	35 (85%)	33 (87%)	29 (83%)
No	11 (21%)	11 (26%)	6 (15%)	4 (10%)	5 (14%)
Missing	0	0	0	1 (3%)	1 (3%)
Male Enroll[3]	63	63	63	63	63
Yes	42 (67%)	32 (51%)	35 (56%)	33 (52%)	29 (46%)
No	11 (17%)	11 (17%)	6 (10%)	4 (6%)	5 (8%)
Missing	0	0	0	1 (2%)	1 (2%)
Female Visit[2]	197	174	162	147	145
Yes	157 (80%)	145 (83%)	133 (82%)	130 (88%)	125 (86%)
No	40 (1220	28 (16%)	29 (18%)	17 (12%)	16 (11%)
Missing	0	1 (1%)	0	0	4 (3%)
Female Enroll[3]	248	248	248	248	248
Yes	157 (63%)	145 (59%)	133 (54%)	130 (52%)	125 (50%)
No	40 (16%)	28 (11%)	29 (12%)	17 (7%)	16 (7%)
Missing	0	1 (0%)	0	0	4 (2%)
NonCaucasian by Visit[2]	42	36	33	29	29
Yes	33 (79%)	26 (72%)	24 (73%)	22 (76%)	22 (76%)
No	9 (21%)	10 (28%)	9 (27%)	7 (24%)	7 (24%)
Missing	0	0	0	0	0
NonCaucasian by Enroll[3]	53	53	53	53	53
Yes	33 (62%)	26 (49%)	24 (45%)	22 (42%)	22 (42%)
No	9 (17%)	10 (19%)	9 (17%)	7 (13%)	7 (13%)
Missing	0	0	0	0	0

Reviewer's Table, modified from sponsor's Table CR3-4B , Final Study Report, Protocol 851-CR3, page 27
(1) A responder is defined as a patient that reports "Completely Relieved" or "Considerably Relieved" to the Global Efficacy Assessment question.
(2) By Visit: Proportions calculated based on the actual number of patients completing each visit.
(3) By Enrolled: Proportions calculated based on patients initially enrolled (Male=63, Female=248)

Secondary Efficacy Endpoints

The secondary efficacy endpoint was an assessment of a modified ROME definition for each treatment visit. According to this definition, a successfully treated patient must report ≥ 3 satisfactory bowel movements with 1 or no additional ROME symptom criteria, without the aid of rescue medication or prohibited laxative, on their visit questionnaire.

This secondary analysis is shown below in Table XX for both the entire study population and elderly patients. In the table, the number of successful (denoted as "Yes") or failed (denoted as

"No") treatment visits according to the definition is displayed. Table XX below demonstrates that most of the treatment failures occurred early in the study and that treatment efficacy remained constant following Visit 2.

Table XX: Modified ROME Criteria Success Analysis: Number and Percent of Successfully Treated Patients by Visit

Responder[1] N (%)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
All by Visit[2]	253	220	207	191	184
Yes	215 (85%)	192 (87%)	181 (87%)	168 (88%)	169 (92%)
No	38 (15%)	28 (13%)	26 (13%)	23 (12%)	14 (8%)
Missing	0	0	0	0	1 (0%)
All by Enroll[3]	311	311	311	311	311
Yes	215 (69%)	192 (62%)	181 (58%)	168 (54%)	169 (54%)
No	38 (12%)	28 (9%)	26 (8%)	23 (7%)	14 (5%)
Missing	0	0	0	1 (2%)	1 (0%)
Elder by Visit[2]	99	99	87	84	81
Yes	90 (91%)	84 (93%)	80 (92%)	76 (90%)	77 (95%)
No	9 (9%)	6 (7%)	7 (8%)	8 (10%)	3 (4%)
Missing	0	0	0	0	1 (1%)
Elder Enroll[3]	117	117	117	117	117
Yes	90 (77%)	84 (72%)	80 (68%)	76 (65%)	77 (66%)
No	9 (8%)	6 (5%)	7 (6%)	8 (7%)	3 (3%)
Missing	0	0	0	0	1 (1%)

Reviewer's Table, modified from sponsor's Table CR3-5, Final Study Report, Protocol 851-CR3, page 28
(1) ≥3 satisfactory bowel movements, with 1 or no additional ROME symptom criteria
(2) By Visit: Proportions calculated based on the actual number of patients completing each visit
(3) By enrolled: Proportions calculated based on patients initially enrolled (All=311, Elderly=117)

Table XX below reveals that there was no substantial change in MiraLAX dose over the course of the study. There appears to be no evidence of tachyphylaxis or increased potency (increased sensitivity) to the drug resulting in dose reduction associated with MiraLAX treatment.

Table XX: Treatment Dose by Month

Study Month	Month 2	Month 4	Month 6	Month 9	Month 12
MiraLAX					
Mean (g)	16.3	16.0	15.8	15.7	15.3
SD	2.5	2.9	3.0	3.3	4.2
N	253	219	207	191	184

Reviewer's Table, modified from sponsor's Table CR3-6, Final Study Report, Protocol 851-CR3, page 29

10.1.12 Reviewer's summary and comments on Protocol 851-CR3

This open label, multi-center study evaluated MiraLAX in constipated adult patients with at least a three month history of constipation by ROME criteria prior to entering the study. Enrolled patients were treated with 17 grams of MiraLAX. Three hundred and eleven (311) patients were evaluated and treated, including one hundred and seventeen (117) elderly, for up to one year. One hundred and eighty four (184) patients completed all twelve months of treatment.

The primary measure of efficacy for this study was a "Global Efficacy Assessment" (GEA) made by the study patients at each visit. According to this self-assessment measure (dependent on the month of observation), 80-88% of patients (84%-94% of elderly) were rated as successfully treated during the course of the study. For patients that continued therapy beyond the second visit (about 2 months), 80% or more (84% of elderly) were rated as successfully treated.

Very similar results were obtained from the secondary efficacy measure which assessed the modified ROME constipation criteria at each study visit. The response to treatment was consistent over time and was seen in 85% to 92% of patients during the course of the study and in 91 to 95% of elderly. Analysis by gender or race did not alter these conclusions.

Patients treated with MiraLAX for up to 12 months achieved similar benefits to those previously reported in shorter studies.

10.2 Line-by-Line Labeling Review

Appears This Way
On Original

REFERENCES

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2. Am J Gastroenterology. 2004 Apr; 99(4): 750-9. Epidemiology of Constipation North America: a systematic review.

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/s/

Kristen Buck
7/27/2006 03:23:50 PM
MEDICAL OFFICER
Incomplete Medical Officer NDA review secondary to timing of resignation.